NICE National Institute for Health and Care Excellence

Highly Specialised Technology Evaluation

Cerliponase alfa for treating neuronal ceroid lipofuscinosis type 2 [ID943]

Evaluation Report

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

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Cerliponase alfa for treating neuronal ceroid lipofuscinosis type 2 [ID943]

Contents:

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

Pre-meeting briefing

Cerliponase alfa for treating neuronal ceroid lipofuscinosis type 2 [ID943]

This slide set is the pre-meeting briefing for this appraisal. It has been prepared by the technical team with input from the committee lead team and the committee chair. It is sent to the appraisal committee before the committee meeting as part of the committee papers. It summarises:

- the key evidence and views submitted by the company, the consultees and their nominated clinical experts and patient experts and
- the Evidence Review Group (ERG) report

It highlights key issues for discussion at the first appraisal committee meeting and should be read with the full supporting documents for this appraisal

Please note that this document includes information from the ERG before the company has checked the ERG report for factual inaccuracies

The lead team may use, or amend, some of these slides for their presentation at the Committee meeting

1

Key issues for consideration

Clinical effectiveness

- The trials include a population of children aged >3 with mild-to-moderate disease and 'stable' seizures. Does the committee consider that this evidence is generalisable to the wider population included in the marketing authorisation?
- How is the screening tool developed to support early diagnosis likely to be used in practice?
- The company developed the CLN2 clinical rating scale focussing on motor and language domains (excluding seizures and vision loss). Is this appropriate?
- The evidence for the comparator is from a retrospective natural history study.
  - Is it generalisable to the population in England?
  - Which method to estimate the mean decline in the natural history control is most plausible?
- Do the trials suggest that cerliponase alfa is effective in treating CLN2 disease?
  - In the short term? In the long term (biological plausibility)?
  - Is early (week 16) or late stabilisation (week 96) possible with treatment?
- There are non-neurological aspects of the disease that may not be treated by cerliponase alfa (for example, vision loss). What is the committee's view on the burden of disease relating to this?
- What is the impact of treatment on mortality? How should the impact of neurological progression (after 96 weeks/no late stabilisation) and extra-neurological progression on mortality, and impact of other-disease-related mortality be considered?
- What is the committee's consideration of the use of cerliponase alfa in asymptomatic or pre-symptomatic patients (siblings)?

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Key issues for consideration

Cost-effectiveness

- Does the model fully capture disease progression in patients treated with cerliponase alfa?
  - Are the assumptions around disease stabilisation appropriate?
  - Has mortality been appropriately incorporated? Should neurological progression, extra-neurological progression and other-disease-related mortality be considered?
- The model incorporates the assumption that patients will be diagnosed in an earlier health state in the future. Is this realistic?
- Which utility values are most appropriate?
- Is it appropriate to include care and sibling disutility? If so, for what length if time is this appropriate?
- Patients stop receiving treatment with cerliponase alfa when they reach health state 7. Is this stopping rule appropriate?
- The base case uses discounting rates of 1.5% for costs and benefits (deviation from reference case) because the company considers that the beneficial impact of the treatment is expected to be substantial and sustained over a very long period. What is the committee's view?
- Which scenarios presented reflect the committee's preferred assumptions?

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Key issues for consideration

Health-related quality of life and other considerations

- What outcomes are important to patients?
- Does cerliponase alfa improve quality of life? Has this been adequately captured?
  - For patients?
  - For carers?
  - For siblings?
- Are there any elements of the administration of cerliponase alfa that need consideration?

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Disease background

- Neuronal ceroid lipofuscinosis type 2 (CLN2), is a rare genetic disease caused by the deficiency of an enzyme called tripeptidyl peptidase1 (TPP1)
- A deficiency of TPP1 results in abnormal storage of proteins and lipids in neurons and other cells, prevent the cells from functioning as they should
- CLN2 is characterised clinically by a decline of mental and other capacities, epilepsy, and vision loss
- Symptoms in children with CLN2 start typically arise between ages of 2-4 (late infantile-onset) and can then progress rapidly with the onset of seizures, decline in speech, loss of mobility, involuntary muscle spasms, pain, progressive dementia, and eventual loss of vision, requirement of gastronomy feeding, and early death
- Life expectancy is around 6 to 13 years; average 10 years
- It is estimated that in the UK, around 3 to 6 children are diagnosed each year and currently around 30 to 50 children are living with the condition

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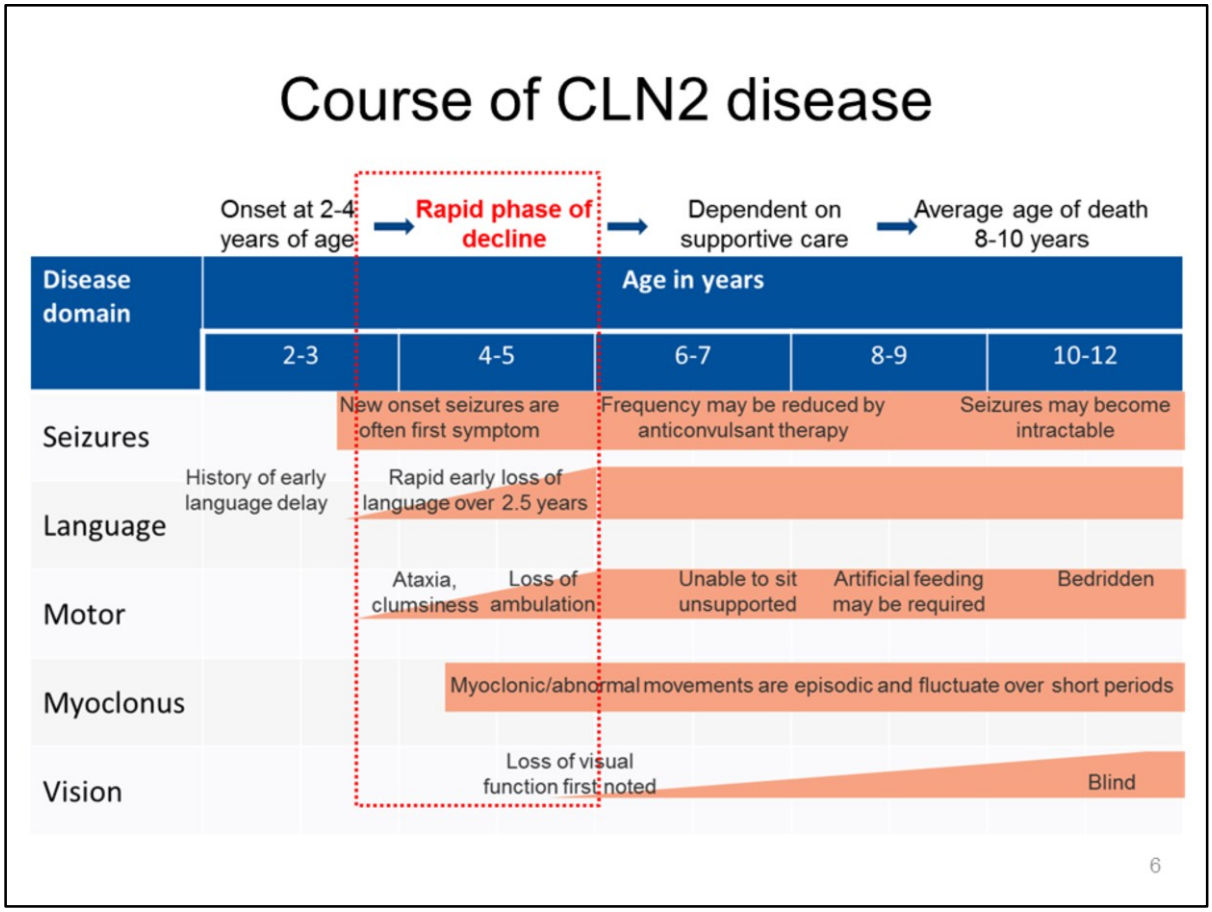
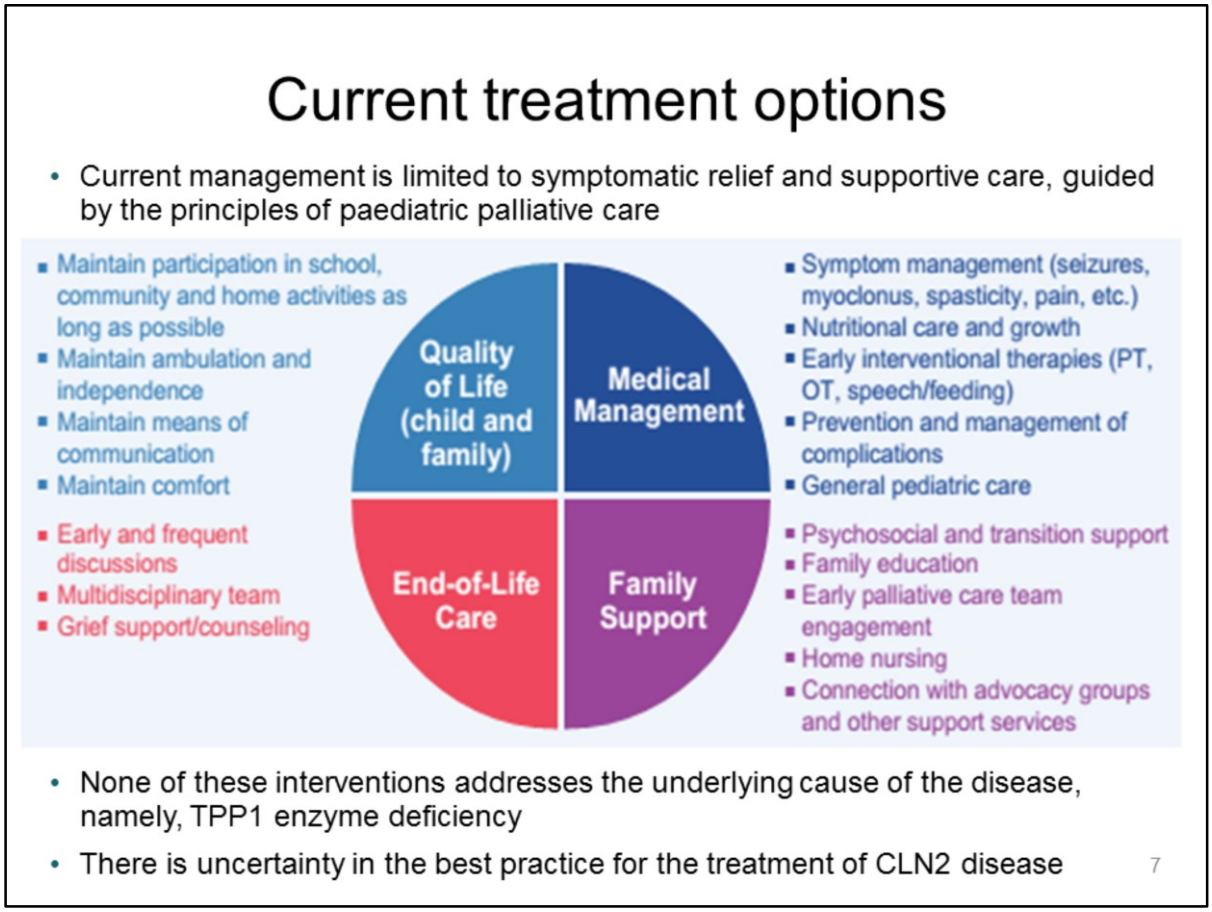
The exact prevalence of CLN2 is unknown.

The ERG has highlighted that while death usually occurs due to complications arising from neurological degeneration, the expression of TPP1 is not limited to the CNS and untreated accumulation of ceroid lipofuscin may lead to pancreatic, intestinal, cardiac, and hepatic pathologies and impairment.



Source: company submission Figure B1, page 39.

The rapid progression of the disease means that by the age of 6 years, most will be completely dependent on families and carers for all of their daily needs. They will lose their ability to swallow and need a feeding tube and their arms and legs may become stiff. Some children get frequent chest infections.



There is no clearly defined clinical pathway for CLN2 disease. Due to the low clinical awareness of the disease and non-specific initial symptoms there can often be a delay in clinical diagnosis. Nickel et al. reported an average delay of 21 months from the onset of symptoms to diagnosis. Williams et al. noted that a delay of 2-3 years between symptom onset and diagnosis is common.

Cerliponase alfa

authorised under 'exceptional circumstances'

Marketing authorisation	Indicated for the treatment of neuronal ceroid lipofuscinosis type 2 (CLN2) disease, also known as tripeptidyl peptidase 1 (TPP1) deficiency
Mechanism of action	A recombinant human tripeptidyl peptidase 1 which is an enzyme replacement therapy
Administration & dose	Cerliponase alfa is supplied as a sterile solution (30 mg/ml) for intracerebroventricular (ICV) infusion to the cerebrospinal fluid (CSF). The ICV access device must be implanted prior to the first infusion. The recommended dose of cerliponase alfa for children over the age of 2 is 300mg administered every other week, given by ICV over approximately 4.5 hours
List price	The price of a pack of cerliponase alfa (consisting of two 150mg vials) is £20,107.00
Treatment course length	Lifetime treatment duration, subject to clinical judgement

Source: Company submission

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Source P14/15 company submission

Cerliponase alfa has been launched in the UK and is currently available to a limited number of patients receiving free drug via the expanded access programme and participation in an ongoing clinical trial.

Cerliponase alfa is delivered via intra-cerebro-ventricular infusions (into the brain ventricles) that last for 4 hours. Up until now it has been given at Great Ormond Street Hospital, on day ward. A clinical expert stated that if approved cerliponase alfa may be delivered in specialist hospitals under the care of specialists in inherited metabolic disorders supported by a neurosurgical team. The company anticipate these to be Great Ormond Street Hospital, and the Royal Manchester Children's Hospital. In the future, it is possible that the drug may be delivered in local hospital (with appropriate support) or potentially home setting by qualified staff as for other enzyme replacement therapies. The ERG note that the plausibility of such a change to service provision is uncertain, and may be associated with an increased risk of infection.

Decision problem

	Final Scope
Population	People with a confirmed diagnosis of CLN2
Intervention	Cerliponase alfa
Comparator	Established clinical management without cerliponase alfa
Outcomes	• Symptoms of CLN2 (vision, seizures, myoclonus, dystonia, spasming, pain and feeding) • Disease progression (Hamburg scale, CLN2 rating scale, Weill Cornell LINCL score) • Need for medical care • Mortality • Adverse effects of treatment • HRQoL (patients and carers)

ERG comment:

- The clinical evidence from the company submission is derived from a narrower population of children aged >3 with mild-to-moderate disease and 'stable' seizures, who therefore may not represent the total NHS patient population.

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Source: Table A1 company submission

Patient perspective

Impact of disease - patients

- Children with CLN2 disease are born seemingly healthy and develop normally for the first few years of life.
  - Rapid progression of disease means that by the age of 6, most will be completely dependent on families and carers for all of their daily needs
  - Losing their ability to swallow and need a feeding tube; arms and legs may become stiff and some children get frequent chest infections
  - Progressive dementia; and death usually occurs between the ages of 6 and 12 years dependent on the levels and standard of care received
- Complete control of seizures is not always possible with anticonvulsants being necessary from early in the disease process
- Myoclonic jerks are common interfering with sleep and adding distress to both children and families
- Multiple medications required to manage symptoms; support is needed for progressive difficulties with swallowing, constipation, hydration, respiratory function, oral secretions, sleep disturbance and visual impairment
- Children will be required to be fitted with a gastrostomy

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Patient perspective

Impact of disease - carers

- CLN2 disease deprives the patient of a functional life from early childhood
  - devastating impact on quality of life of parents and families
  - *'A daily routine which involves administering medication, feeding, positioning, changing, suctioning and maintaining airways, hydration and stimulation creates pressures on families'*
- A UK/German study demonstrated the wide-ranging physical, emotional, psychological, financial, educational and social challenges of caring for and living with a child with CLN2 disease
  - Seizures mean children need to be monitored at night → sleep deprivation
  - 24/7 1:1 care means being unable to work and provide financially
  - Carers physical health is impacted as they have to carry increasingly heavy children resulting in back problems
  - Healthy siblings struggle to process and adjust; ensuring a normal childhood is a challenge
  - Many family relationships breakdown
  - Life revolves around appointments, '*simple pleasures are out of reach', 'running on empty', 'there are times when they just want to be their mum or a dad and not their doctor or nurse'*
- Quality of life for carers is considerably lower in the severe disease stage than the bereaved stage; the early stage and declining stages of CLN2 disease fell between the two extremes

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Reference for quality of life of carers study: 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

Patient perspective

Diagnosis and current treatment

- Children with CLN2 disease are born seemingly healthy and develop normally for the first few years of life
- Due to the rarity of CLN2 disease it can take 2 years from onset of symptoms to receive a diagnosis, meaning:
  - the condition may already have significantly deteriorated,
  - It's a battle to find the right medical care and manage progression of disease
- Earlier diagnosis will enable families to make informed choices about future children or younger children currently not showing symptoms
- Critical to develop a mechanism within the NHS to deliver an earlier diagnosis for families, specifically around the early manifestation of symptoms such as language/motor delay and seizures
- No available NHS treatments for CLN2 disease so there is a significant unmet need. Current standard of care centres on appropriate and effective symptom management
- CLN2 disease is excluded from the NHS specification for LSD centres, leading to inequalities in access to specific expertise and information
- Holistic support for parents, siblings and wider family members is vital to build resilient family networks

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Diagnosis is done by enzyme tests and follow up genetic testing.

Patient perspective
Cerliponase alfa

- All families are unanimous as to the invaluable benefit of treatment
  - Stabilises disease and allows motor skills and other developmental levels to be maintained
  - Allows children to retain critical life skills, and continue to interact and stay happy, enables engagement with school, including mainstream schools
  - No adverse effects reported in follow-up with families
  - Subsequent positive impact on the emotional well-being of parents

Child diagnosed at 4.5, started treatment in Jan 2017:
'Maintained level of mobility', with *'very limited amount of intervention'*
'Brighter, happier, much more alert', *'responsive'*, *'greater awareness'* where previously *'agitated'*
'We have started to go out again as a family, far more tolerant of new environments'

Sibling with no symptoms on sibling trial
not showing any symptoms and reaching normal developmental milestones

- Potential disadvantages:
  - Treatment does not help with vision loss
  - Travelling for treatment every 2 weeks - emotional and financial strain
  - Sibling trial being run in Germany, in process of being initiated at GOSH
- Treatment will benefit those who are diagnosed as early as possible, where rapid treatment response disease progression can be delayed

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Clinical expert comments

- Cerliponase alfa is a step-change in the management of CLN2
- The main aim of treatment is to prevent disease progression and to stabilise disease process. A significant response would be: maintained developmental skills (motor, language and cognitive) for at least six months from initiation of treatment, when deteriorating function would be expected without disease modifying therapy
- Amongst the children receiving treatment so far, the rate of expected disease progression based on motor and language skills has slowed significantly. Children continue to have epileptic seizures and may still have shortened lives, but if progressive neurodisability can be prevented, delayed or slowed down, the consequent problems (for example swallowing difficulties and necessity for tube feeding, aspiration pneumonia and spinal scoliosis) may be mitigated, and life-expectancy could be increased.
- Visual impairment is an important clinical factor not modified by treatment
  - hugely important to quality of life
- Treatment is more effective before the onset of symptoms or at early stages of disease
- After 1st year of treatment with cerliponase alfa there has been no further loss of skills in any of the patients
  - Benefit on medium and long term quality of life and survival is unknown

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Clinical expert comments

- Infusions are well tolerated with minimal adverse effects
- Catheter blockage and infection are the main predictable adverse events with potentially increased risks of both if the treatment is delivered outside major centres of expertise
- What investment would be needed to introduce cerliponase alfa?
  - A diagnostic pathway early in the course of disease
  - Specialist multidisciplinary teams with expertise in delivery of cerebro-ventricular infusions of enzyme replacement therapy and the management of symptoms of CLN2 disease
  - Psychological and emotional support for families attempting to make decisions regarding initiation of therapy
  - Care pathway and agreed protocol/guideline for long term monitoring of patients for response to therapy, adverse events, and emerging extra-CNS disease
  - Long term monitoring of cardiac, pancreatic and gut function should be put in place
- Need for an ethical framework for decision making regarding eligibility criteria for treatment
- A managed access agreement with clear starting and stopping rules which is in use already will be formalised
- There are benefits difficult to measure using the QALY: these include the retained ability to communicate and enjoy their environment in patients with limited mobility and speech.

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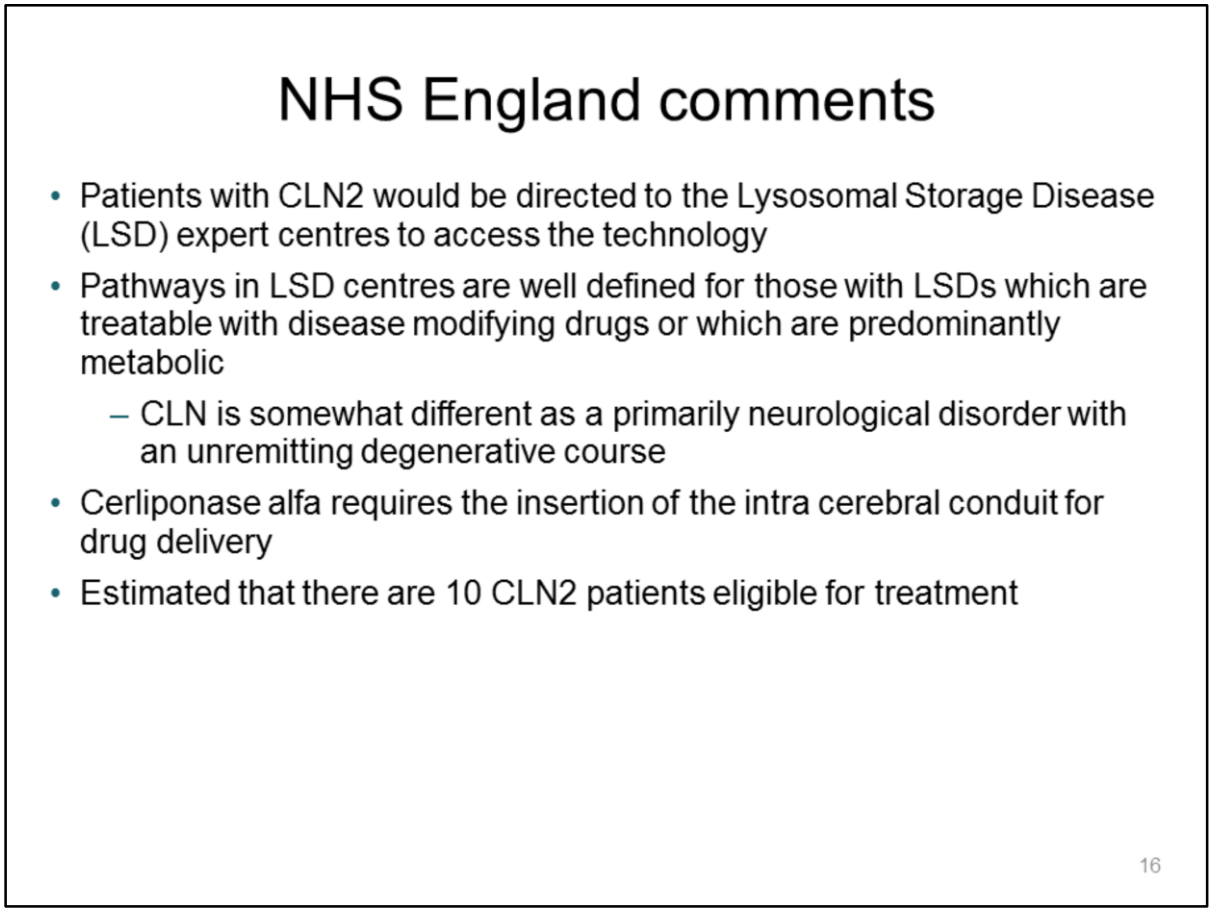

A clinical expert noted that not all patients are currently referred as it is felt that very little additional help can be offered to the patients in such centres.

Clinical effectiveness evidence

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Clinical evidence summary (1)

No RCTs

Trial name	Type	Location, duration and numbers enrolled	Primary outcome(s)
190-201 **Pivotal study**	Phase 1/2, open-label, including dose escalation phase	• United States, Germany, Italy, United Kingdom • 48 weeks • 23 patients (aged 3 to 16) • 1 drop out	• Adapted CLN2 rating scale • Safety
190-202 **Ongoing**	Extension to study 190-201	• Up to 240 weeks • 23 patients	• Motor and language changes • Safety

- Patients with late-infantile CLN2
  - Mild to moderate disease documented by a two-domain score of 3- 6 on motor and language domains of the Hamburg Scale, with a score of at least 1 in each of these two domains
- Cerliponase alfa administered by ICV at 300mg every two weeks
- Data is available up to a total of 70 weeks (48 weeks in Study 190-201 and 25 weeks in Study 190-202) for all efficacy and safety end points
- Data is available for 96 weeks of treatment for the primary efficacy endpoint – projected end is 15th December 2020
- Comparison with natural history data, from study 190-901

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Secondary outcomes included MRI measures and quality of life.

Clinical evidence summary (2)

Study name	Type	Location, duration and numbers enrolled	Primary outcome(s)
190-901	Natural history study, retrospective	• Germany, Italy (DEM-CHILD database) • 41 untreated patients (of which 23 were used in the 1:1 matched analysis of Study 190-201/202)	• Change in motor and language subscales of the CLN2 disease rating scale
190-502 **Unpublished**	Expanded access scheme for patients who could not participate in the trial, open label	• UK • 5 patients (≥2 years of age)	• Safety and tolerability
190-203 **Unpublished** anticipated completion date Dec 2022	Phase 2, open label	• Younger siblings of participants in 190-201 (≤17 years) • Up to 5 patients • 96 weeks • No data reported	• Adverse events • Change in the 0–6 point Motor/Language (ML) score on the Hamburg CLN2 rating scale • Immunogenicity

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CLN2 clinical rating scale

Primary outcome in key trials

- Used in clinical trials; adapted from Hamburg and Weill Cornell scales
- The company considers that motor and language function best track the early and rapid progression of disease, and other features of the disease included in the total Hamburg and Weill Cornell scales could reduce the sensitivity of the scale to disease progression
  - seizures, myoclonus, feeding are dependent on care and could confound measurement of disease progression
  - vision loss occurs later in disease and is slower to progress
- The similarity of the Hamburg and Weill Cornell scales allows for data collected using either scale to be combined to quantify clinical progression with motor function and language function each evaluated on a scale of 0-3, giving a total combined score between 0-6
- The smallest possible change on the summary motor-language score of 1 point is clinically meaningful by design, as the rating scales represent changes in milestone activities in children that clinicians familiar with treating children with CLN2 disease are trained to assess and that parents/ caregivers recognise
- For example, a 1-point drop in the motor item between a rating of 3 and 2 is the difference between a child who can walk normally and one who falls often

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The company stated that the Hamburg and Weill Cornell scales are well-established validated disease-specific instruments have been used in expert centres over many years to evaluate the severity and quantify the progression of CLN2 disease. While the Hamburg scale assesses motor function (walking ability), language, visual function and grand-mal seizures, the Weill Cornell scale assesses gait (walking ability), language, myoclonus (motor function abnormalities) and feeding/swallowing. Within each domain of both scales, normal function is given a score of 3, a just noticeable abnormality is given a score of 2, a severe abnormality is given a score of 1, and a complete loss of function is given a score of 0. The total score for each scale thus ranges from 0-12.

This CLN2 clinical rating scale of motor and language function has been adapted from the Hamburg and Weill Cornell scales and has been used in the study of natural history of CLN2 disease to date. In addition to prospective assessments by the clinician, the scale also allowed for retrospective assessment by the clinician based, not only on clinical records, but on reliable recordings and observations made by the patient's family.

The full Hamburg and Weill Cornell CLN2 rating scales were also evaluated as secondary endpoints, providing scores on the additional domains of vision, seizures, myoclonus and feeding.

CLN2 clinical rating scale (2)

CLN2 clinical rating scale used in cerliponase alfa Study 190-201		
Motor	3	Grossly normal gait
	2	Abnormal gait; independent ≥ 10 steps; Frequent falls, obvious clumsiness
	1	No unaided walking or crawling only
	0	Immobile, mostly bedridden
Language	3	Grossly normal
	2	Has become recognisably abnormal (worse than the individual maximum)
	1	Hardly understandable
	0	Unintelligible or no language

Language score is measured relative to best achieved

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The wording was adapted slightly from that in the motor and language domains used in the collection of natural history in the DEM-CHILD database in collaboration with the authors of the original Hamburg scale in order to allow standardisation in a multi-site setting.

CLN2 clinical rating scale
ERG comments

- European Medicines Agency (EMA) ad-hoc experts meeting confirmed that the CLN2 clinical rating scale was acceptable as a primary outcome at least in the short term context of study 190-201/202
- Reservations were noted that focusing on motor and language domains prevented a more comprehensive evaluation of patients' clinical situation
- The omission of vision and seizures from the original Hamburg/Weill Cornell scales and not assessing cognitive and developmental aspects was raised by experts as a limitation of the primary efficacy analyses
- Additionally, the ERG highlighted that while death usually occurs due to complications arising from neurological degeneration, the expression of TPP1 is not limited to the CNS
  - untreated accumulation of ceroid lipofuscin may lead to pancreatic, intestinal, cardiac, and hepatic pathologies and impairment
  - the European public assessment report (EPAR) for cerliponase alfa emphasised the importance of close monitoring of cardiac events

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Study 190-201/202

ERG comments

- Baseline CLN2 scores reflect the trial inclusion criteria of mild-to-moderate disease (CLN2 score of 3 - 6 points). However, since the decision problem includes all CLN2 patients, the trial population is unlikely to be representative of all patients in England and Wales
- The company expects to diagnose and treat patients much earlier (80% of participants with CLN2 score 5 or 6) than that reflected in the trial (16% of participants with CLN2 score 5 or 6)
- Patients were required to have stable seizures and therefore these findings may not be applicable to those without stabilisation of seizures
- The ERG agreed that assessment of CLN2 disease requires clinical judgement and that it was appropriate for data from the CLN2 clinical rating scale to be the primary outcome.
  - However, it is important to note that the use of subjective outcomes in the context of a single arm trial is associated with a high risk of bias.

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The largest systematic review of meta-epidemiological studies found that a lack of blinding of outcome assessors was associated with on average a 36% over-estimation of treatment effects.

Study 190-901: Natural history study

- Patients in the 190-201/202 studies were matched to the 190-901 population using a 1:1 matching algorithm. This matched trial patients based on their CLN2 clinical rating scale score and age within 12 months
  - 22 of 78 patients in the natural history study were matched for the 48 weeks analyses
  - Data on 8 further patients became available for subsequent analyses
- Baseline analysis indicated that the first CLN2 symptoms commonly manifest around 3 years of age, unprovoked seizures and language difficulties are most common, and diagnosis is at ~5 years age, nearly 2 years from onset of symptoms
- Disease progression at the time of diagnosis is variable, with Hamburg Motor-Language scale scores most commonly in the 2-4 range
- Analysis of the rate of decline of the CLN2 clinical rating scale confirmed the rapid progression of disease
  - Mean points lost per 48 weeks: 2.09 (estimated using first and last points methods)
- The time taken to lose 2 points on the CLN2 clinical rating scale at different stages of disease was also estimated in the 190-901 population, as an alternative way to measure the rate of decline
  - the mean time for a 2-point decline was less than a year for all categories except for people in the category with CLN2 scores of 5 & 4
  - The rate of decline estimated from the slope analysis (2.09 points per 48 weeks) would predict about 10.6 months for each 2-point residence period, so there is good agreement between methodologies

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Source (age of diagnosis) table C27 company submission and page 135 CS

The company also conducted a one-to-one matching of Study 190-901 control cohort to Study 190-201 patients; 22 patients were matched for the 48 week analysis.

Study 190-901: Natural history study
ERG comments (1)

- There are differences between the baseline CLN2 rating scores between the matched natural history (NH) population and the source population:
  - 2 patients were matched to NH with a score of 6 at or prior to diagnosis, however the study 190-901 supplement report shows there were no patients with a score of 6 at or prior to diagnosis
  - 10 patients were matched with a score of 3, however there were only 4 patients in this cohort with a score of 3 at diagnosis
- This may mean trial patients' CLN2 rating scale scores were not being compared against the same outcome in the natural history population, but against estimated or imputed outcome data
- The origin of the study 190-901 data is unclear, ERG unable to replicate analyses
- Fewer females in 190-901 (23%) compared to 190-201/202 (59%)
- NH patients had a lower vision score on average (median 2.0 vs 3.0)
  - Worse vision indicates more advanced disease (potential bias)

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Potential explanations may include: trial patients were matched with imputed NH data at suitable time points; or the NH patients were not assessed using the Hamburg CLN2 scale at the times stated in the CSR, with scores assigned retrospectively (rather than being generated through imputation).

There is no evidence of a difference in disease presentation or course between sexes.

Different vision scores indicate systematic differences between the two groups. A median 1-point difference between the cerliponase alfa and NH matched groups suggests the latter group may be more progressed overall, which could inflate the apparent efficacy of cerliponase alfa.

Study 190-901: Natural history study

ERG comments (2)

- Estimates of mean decline in the natural history controls varied depending on the statistical method used
  - The more sophisticated mixed effects models of repeated measures data resulted in a substantially lower estimate of mean decline (autoregressive variance: 1.29 points, 95% CI 1.03 to 1.54, unstructured variance: 1.46 points, 95% CI 1.12, 1.79) than those used in the main analyses (2.09 points, 95% CI 1.79 to 2.40)
  - ERG judged that the estimates from the mixed effects model were likely to have greater validity because it made better use of the data reported over time
  - In addition, these estimates were similar to analyses of a matched (CLN2 score, age and genotype) sample of the natural history controls that found a decline of 1.9 points at 48 weeks and 2.8 points at 96 weeks (a decline of approximately 1.4 points/48 weeks)
- Estimates of CLN2 rating score decline appeared to be sensitive to the stage of the disease and the duration of observation, as estimates varied widely.
  - This casts uncertainty upon the company's comparison of treatment effectiveness against a 2-point annual drop, particularly given the subjectivity of the CLN2 rating scale as being representative of the natural history of the disease.

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Clinical effectiveness – primary outcome results

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Summary of analyses

A number of analyses were carried out on the primary endpoint, including:

- a responder analysis (the percentage of patients with a less than 2-point decline per 48 weeks),
- a 'survival analysis' (the time taken to achieve a 2-point scale score change) and
- a 'slope analysis' (the rate of decline in score per 48 weeks)

Results are presented relative to fixed natural history controls with a mean rate of decline of 2.0 points per 48 weeks.

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Responder analysis
Study 190-201; 48 weeks

- Response defined as absence of an unreversed two-point decline by Week 48, based on the mean rate of decline in the natural history control group
  - 87% patients had a response (i.e. a 1-point decline or better), which significantly exceeded the expected untreated rate of 50% (95% CI 66%, 97%; p = 0.0002)
  - CLN2 score was stabilised in 65% of cerliponase alfa patients (i.e. no change or an improvement in score)

Baseline CLN2 clinical rating scale score

Change in CLN2 clinical rating scale score	6	5	4	3	2	1	Total
2							
1				2			2 (8%)
0	2	1	2	5	2	1	13 (57%)
-1		1	2	2			5 (22%)
-2			1	2			3 (13%)
Total	2 (9%)	2 (9%)	5 (22%)	11 (48%)	2 (9%)	1 (4%)	23 (100%)

65%

87%

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For the individual motor and language domains, a responder is defined as a subject who did not lose a point in that domain at time of last assessment. Of the twenty patients (87%) in the ITT population who met the definition of responder, eighteen (78%) and 16 (70%) met the definition of a responder on the language and motor domains, respectively.

Additionally, fifteen (65%) of the 23 treated patients had no unreversed single point loss (either stable or improved) as measured by the ML scale during the treatment period.

Responder analysis
Study 190-201/202; 96 weeks

- Response defined as absence of an unreversed 2-point decline in CLN2 score by Week 96
  - Results unchanged
  - [redacted] responded compared to a response rate of 50% predicted in untreated patients (p = 0.0002)
- The company stated that the expected rate of decline in ML score over a 48-week period is 2 points in a natural history population. Translating the rate of decline over 96 weeks, the expected loss is ~4 points for a natural history population – a conservative comparison
- [redacted] met the definition of a responder on the motor domain at Week 97, and [redacted] met the definition of a responder on the language domain at Week 97
  - The company stated that the relatively stable ML scores, even past a 96 week period, support the durability of treatment effect
- [redacted] had no clinical progression of disease (defined as an unreversed single point loss as measured by the CLN2 scale at Week 96
  - This exceeds the untreated responder rate of 25% ([redacted])

ERG comment:

- The company reports that [redacted] of cerliponase alfa patients experienced no change or an improvement in score at week 48 but this reduced at week 96
  - The number of patients at week 96 with no decline was either [redacted] [redacted] [redacted] (different figures in the CS and CSR)

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For individual motor and language domains, a responder is defined as a subject who did not lose a point in that domain at time of last assessment

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Change in ML score and CLN2 total score

Study 190-201/202; 96 weeks

- At Week 96, [redacted] showed no clinical progression on the CLN2 scale, and of these patients [redacted] showed an overall improvement
- [redacted] lost a single point and [redacted], all of which occurred during Study 190-201
- The graphs show change in ML score (A) and CLN2 total score (B) from baseline (cerliponase v natural history)

Figure redacted: academic-in-confidence

Figure redacted: academic-in-confidence

- At Weeks 48 and 96, the mean decline from baseline in the ML score was 0.5 and 2.8 for untreated patients and [redacted]; mean decline from baseline in the CLN2 total score was 2.8 and 4.3 for untreated patients and [redacted]

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Source figure C10 company submission

ML score only includes motor and language domains, CLN2 total score includes all domains: motor, language, vision, and seizures

ERG comments

Change in CLN2 clinical rating scale

- ERG extracted mean CLN2 scores from study 190-201/2012

Follow up time (weeks)	CLN2 score (ML): Mean (SD)	Absence of unreversed decline from baseline: n (%)	Absence of unreversed 2-point decline from baseline: n (%)	Decline in CLN2 points per 48 weeks: mean (SD)
Baseline	3.48 (1.20)	N/A	N/A	N/A
16	3.04 (1.33)	14 (57)	22 (96)	NR
48	3.13 (1.36)	15 (65)	20 (87)	0.40 (0.81)
96	[redacted]	[redacted]	[redacted]	[redacted]
Last follow up	[redacted]	[redacted]	[redacted]	[redacted]

- Decline in CLN2 scores for cerliponase alfa patients slows over time as shown both in the mean rate of decline and mean CLN2 score
- Fewer patients experience no decline in the later periods, therefore caution is needed when interpreting the long-term benefits
- The data on the number of patients not experiencing reductions in CLN2 score at 96 weeks was reported inconsistently between different sections of the company submission
  - [redacted] patients appeared to experience no unreversed declines, rather than [redacted] (at w96)

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In contradiction to the assumption of disease stabilisation, slope analyses suggest on average patients receiving cerliponase alfa continue to experience further declines in CLN2 score after week 96

[redacted]

Early vs. late Stabilisers

- Those who experienced no further unreversed declines after 16 weeks were classified by the company as 'early stabilisers'
  - In the model, early stabilisers were assumed by the company to experience no further decline in CLN2 score after 16 weeks
- Patients experiencing any unreversed point decline after 16 weeks were classified as 'late stabilisers'
  - Assumed by the company to experience no further decline after 96 weeks
- However, the ERG highlighted several concerns with this:
  - Post-hoc categories; could be sampling error rather than genuine reflection of patterns of response
  - 96 weeks follow up insufficient to make long terms judgements on stabilisation
  - Some patients classified as early stabilisers had fluctuations in CLN2 score suggesting disease may not be stable
  - Plotting the mean CLN2 score for 'late stabilisers' suggests late stabilisation unlikely as there is a trend of decreasing scores from week 48 to week 96*
- The ERG consider that in contradiction to the assumption of disease stabilisation, [redacted]
- [redacted]

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*see figure 1 ERG report

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Time-to-event analysis

Study 190-201/202: Time to first event

- After adjusting for baseline ML score, age, genotype and sex, compared to treated subjects, natural history patients were [redacted] times more likely to have experienced an unreversed 2-point decline in the ML score ([redacted])

Figure redacted: academic-in-confidence

- Similar results were found for the motor ([redacted]) and language ([redacted]) domains separately

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Source: adapted from figure C12 in the company submission

Graphs examining the decline in motor and language scores individually can be seen in figure C12 of the company submission

Slope analysis

Study 190-201/202

- The rate of decline in the CLN2 clinical rating scale, scaled to a 48 week time period, was conducted as an additional analysis of the primary endpoint.
- At 48 week follow up, the mean rate of decline was 0.40 points per 48 weeks in the treatment group
- From week 48 to 96 weeks follow up, the mean (median) rate of decline in the treated population is [redacted] points per each period of 48 weeks
  - Both statistically significant improvements in the rate of decline when compared with a population rate of decline in untreated patients of 2.0 points per 48 weeks
- Using the same method of slope analysis, the mean rate of decline in the Study 190-901 natural history population was 2.09 points per 48 weeks.

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Source (table): Table C34 company submission

Clinical effectiveness – secondary endpoints results

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Hamburg scale

Study 190-201/202

Change from baseline analysis on Hamburg 0-9 and 0-12

- CLN2 clinical rating scale only includes motor and language domains. The table below shows the mean baseline, 48-week endpoint and change for this scale and including other domains of the Hamburg rating scale
- The company stated that this demonstrates a durable treatment effect and broad-based stabilisation of the disease over time that is not domain specific

Domains included	Motor Language	Motor Language Vision	Motor Language Vision Seizures
Possible score range	0-6	0-9	0-12
BL mean (SD)	3.5 (1.20)	6.3 (1.34)	8.0 (1.83)
Week 49 mean (SD)	3.0 (1.33)	5.7 (1.58)	7.8 (2.07)
Week 49 mean (SD) change from BL	-0.4 (0.79)	-0.7 (1.03)	-0.2 (1.94)
Week 97 mean (SD)	[redacted]	[redacted]	[redacted]
Week 97 mean (SD) change from BL	[redacted]	[redacted]	[redacted]
*BL = baseline measurement			

Source: Table C24 company submission

AIC marking to be checked with company

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Hamburg scale

Domains

	Seizures				Vision			
	Natural history controls		Cerliponase alfa		Natural history controls		Cerliponase alfa	
	Mean (SD)	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)	N
Baseline	[redacted]							
W 49	[redacted]							
Week 97	[redacted]							

	Motor				Language			
	Natural history controls		Cerliponase alfa		Natural history controls		Cerliponase alfa	
Baseline	[redacted]							
W 49	[redacted]							
Week 97	[redacted]							

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Source: adapted from Table 7 ERG report

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ERG comment

Hamburg scale

- Improvement in seizure domain does not necessarily reflect a halt in the deterioration of seizures
  - Seizure domain of the Hamburg reflects only the frequency of tonic-clonic seizures, and does not take into account the activity of other movement disorders
- Decline in the vision domain was slower than that observed in the natural history group. However:
  - Vision scores were higher ([redacted] points) in the cerliponase alfa group at baseline potentially limiting comparability with the NH group
  - Assessment of vision on the Hamburg scale requires a certain level of motor function (e.g. grabbing objects) therefore declines in the motor domain inevitably impact on assessment of the visual domain
  - Company conclusions regarding long term declines in progression of vision loss lack biological plausibility

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MRI cranial imaging

Study 190-201/202

- MRI cranial imaging measures whole brain volume, volume of cerebrospinal fluid (CSF), volume of total cortical grey matter, total white matter volume, and whole brain apparent diffusion coefficient
- No comparative data from the natural history cohort available on MRI outcomes

Measure	Change (SD) at 48 weeks	Change (SD) at 96 weeks
Cerebrospinal fluid (CSF)	3.6% (SD 15.30)	
Volume of total cortical grey matter	-9.7% (SD 8.08)	[redacted]
Total white matter volume	-4.2% (SD 9.58)	
Volume of whole brain	-4.4% (SD 8.46)	[redacted]

- The company stated that up to 48 weeks the losses observed in cortical grey and whole brain volumes were less than seen in longitudinal MRI studies
- [redacted]

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*for the ITT population

The ERG stated that it was unclear how long after 97 weeks the last observation was, and whether this halt in decline of grey matter loss will be maintained in later follow up periods.

AIC marking to be clarified by company (response due 2nd of Jan)

HRQoL measures

Literature search

- One study was identified that reported on EQ-5D administered to care givers
  - Not considered sufficient for the cost-effectiveness analysis
  - Can be considered in cost-consequences analysis of carers
- A total of 7 (22%), reported moderate or severe pain, and 9 (29%) reported moderate or severe depression and anxiety
- No clear patterns by disease stage emerged
- Qualitative survey found that average number of hours of sleep was 5.38

Population	Utility Score	Utility Score (SD) age/gender matched control
England	0.775	0.890
Germany	0.870	0.953

Source: Ballinger 2016 (ICON study)

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HRQoL measures

Study 190-201/202

- HRQL was assessed in Study 190-201 using the PedsQL Parent Report for Toddlers, the PedsQL Family Impact Module and a CLN2 disease-based QoL instrument
- Scores range from 0-100, with a higher score indicating better function
- There was a broad-based improvement in all HRQL assessments, with mean increases in the total score for each questionnaire, which ranged from 4.3% to 10.9%.

Instrument	Mean (SD) at baseline	Mean (SD) at 49 weeks	Mean (SD) at 97 weeks
PedsQL Parent Report for Toddlers	60.7 (12.80)	63.3 (15.23)	[redacted]
PedsQL Family Impact Module	61.4 (14.27)	65.1 (15.46)	[redacted]
CLN2 disease-based QoL	74.2 (13.82)	81.9 (11.10)	[redacted]

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Source: adapted from tables C20, C25 and C26

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EQ-5D-5L

Study 190-202

- Only assessed in 190-202
- Baseline is defined as the first observation upon transitioning from Study 190-201 to Study 190-202
- Of the 23 subjects with data at baseline and Week 97, no change or more favourable scores were seen for most patients
  - [redacted]
  - [redacted]
  - [redacted]
  - [redacted]
  - [redacted]
- The EQ VAS score shows a slight downward trend, with a mean decline of [redacted]

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ERG comments

HRQoL

- PedsQL and the CLN2QL scales show an initial improvement in quality of life reported by parents, however scores decline between weeks 49 & 97

PedsQL Parent report for toddlers

- Baseline to week 49 there was a mean improvement of [redacted] points
- [redacted]
- Family impact module: baseline to week 49 there was a [redacted] point increase. However, from week 49 to week 97 there was a decline [redacted]

CLN2QL

- Scores for the CLN2 disease-based instrument improved by [redacted] points from baseline to week 49 but from week 49 to 97 scores declined [redacted]
- Unclear what a clinically meaningful difference is when using this scale, however changes in CLN2QL score reflect that of PedsQL

EQ-5D-5L

- No change for most patients when comparing baseline to week 97
- No data at week 49 therefore it is unclear whether a similar decline from week 49 to 97 is also observed when using this scale

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Mortality

- The company assume patients with CLN2 can die from either disease-related mortality, infection related mortality, and other-cause mortality (age-related)

ERG comment:

- Assuming patients receiving cerliponase alfa experience general population mortality is inappropriate
- Three potential reasons why patients receiving cerliponase alfa are likely to experience shorter life expectancy than assumed by company:
  1. *Neurological progression:* Assuming all patients on cerliponase alfa stabilise after 96 weeks (late stabilisers) is overly optimistic
  2. *Extra-neurological progression:* There may be serious implications for patient morbidity and mortality associated with cardiac, pancreatic, and hepatic impairment unless ERT is administered systemically. This unrelated to neurological progression, therefore represents an additional mortality risk
  3. *Other-disease-related mortality:* Evidence from the related Batten's disease sub-type CLN3 shows that the actual cause of death for a substantial proportion of CLN3 patients was either pneumonia or infection, therefore not related to either neurological failure or extra-neurological pathology

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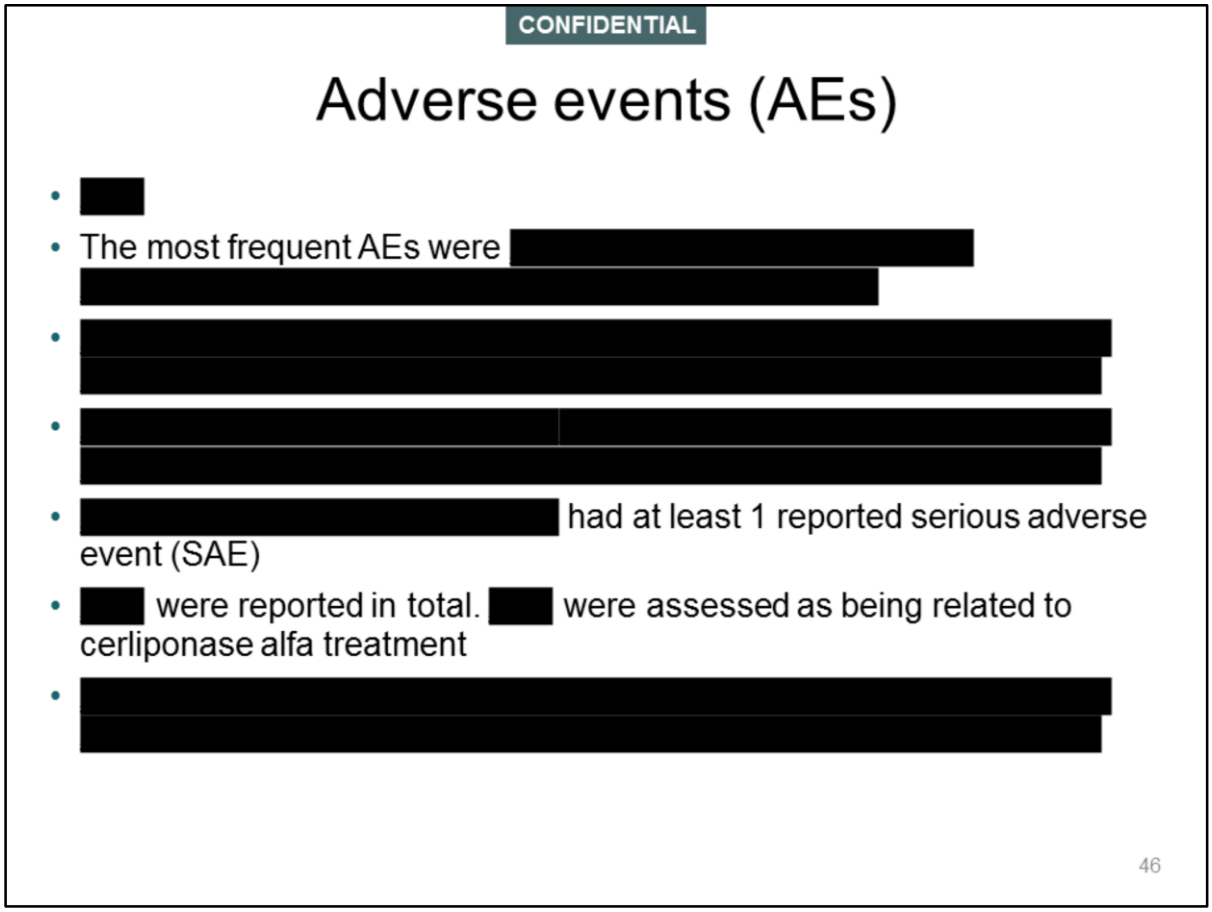
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Adverse events (AEs)
[redacted]
The most frequent AEs were [redacted]
[redacted]
[redacted]
[redacted] had at least 1 reported serious adverse event (SAE)
[redacted] were reported in total. [redacted] were assessed as being related to cerliponase alfa treatment
[redacted]
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ERG comment

Adverse events

- Hypersensitivity judged by EMA to be the most relevant safety concern related to cerliponase alfa
  - Although most hypersensitivity reactions appeared manageable (e.g. with antihistamines, antipyretics, steroids) life threatening anaphylactic reactions from cerliponase alfa cannot yet be excluded
- [redacted] patients experienced [redacted] cardiovascular adverse events
  - At baseline [redacted] had normal ECG readings; however, [redacted] of patients experienced ECG abnormalities post-baseline
  - No clear patterns of myocardial damage have been identified except 2 patients with suspected left ventricular hypertrophy
    - Hypotension was reported 8 hours after receiving cerliponase alfa infusion suggesting this may be related to receiving the treatment

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Cost-effectiveness evidence

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De novo cost-effectiveness analysis

Aspect	Details
Analytical method	Multi-state Markov model
Model perspectives	Base case: Healthcare system (NHS and Personal Social Services [PSS]) Additional scenario: Societal
Cycle length	2 weeks
Discounting	1.5% costs and benefits Additional scenarios: 3.5% costs and benefits, 1.5% for benefits, 3.5% for costs
Time horizon	Lifetime (95 years from the start of the model)
Patient population	Patients with a confirmed diagnosis of CLN2 disease
Health states	10 health states based on the CLN2 clinical rating score and other clinical key characteristics
Comparator	Standard of care

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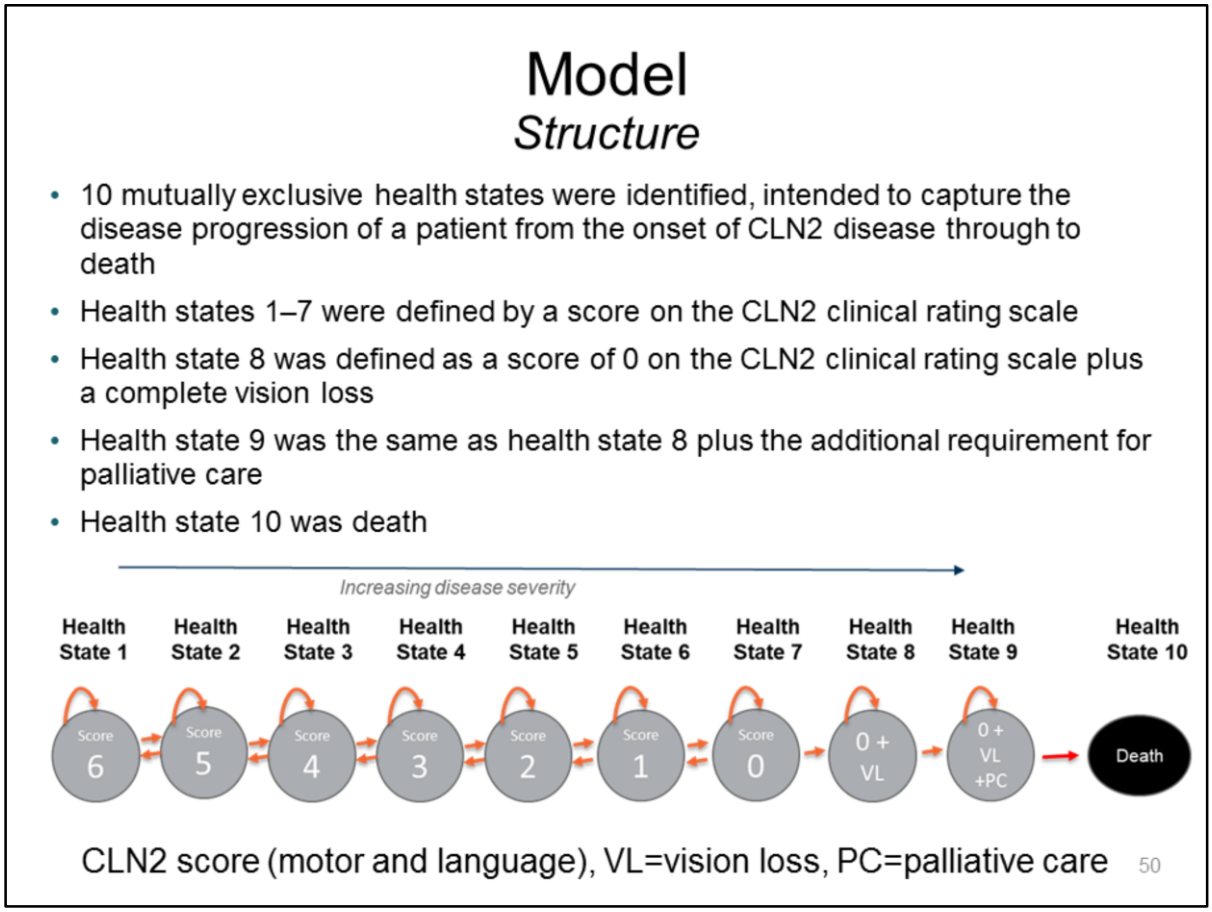
That company stated that given the beneficial impact of the treatment is expected to be substantial and sustained over a very long period, a discount rate of 1.5% has been used in the base case.



Source (figure): Adapted from figure D20 company submission

At model entry, the cohort is distributed across the health states according to the expected population that will receive treatment for CLN2 disease. At each cycle patients can either remain in the same health state, progress to a more severe health state or improve and move to a less severe health state, with the exception that once patients reach health state 8, they can no longer return to a previous health state. The health states and their defining characteristics were validated by clinical experts.

ERG comments
Model

- While the model accurately represent disease progression in the standard care arm it fails to adequately account for a number of elements of disease progression in patients treated with cerliponase alfa:
  - Some patients progress through the 'memoryless' model too quickly
  - The model structure does not account for the progressive vision loss
  - Extra-neurological progression symptoms are not accommodated for in the model, its impact on HRQoL should be considered
    - A lack of long-term data makes this difficult
- Using a discount rate of 1.5% applied in the model is not reasonable, given the reference case states 1.5% is only appropriate when:
  - Treatment restores individuals, who would otherwise die or have a very severely impaired life, to full or near full health, and when this is sustained over a very long period
  - No clinical evidence to suggest that cerliponase alfa is restorative
  - Reference case discount rate of 3.5% should be applied

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Model

Treatment effectiveness

- Treatment effectiveness was estimated using the CLN2 clinical rating scale scores
  - Transition probabilities for patients receiving cerliponase alfa were based on the 190-201/202 study
  - Transitions probabilities for patients receiving standard care were based on patient level data from the 190-901 study (natural history study)
  - Data were not available on the transition probabilities in the final health states (7, 8 and 9) as no patients progressed beyond health state 7 in Study 190-201/202. The transition probabilities and utilities for health states 7 to 9 were, therefore, based on expert opinion, and the same in both arms
  - When patients have reached health state 8 (CLN2 score of 0) they can no longer improve their health. Probabilities are based on average time taken to lose vision, require palliative care, and die, once palliative care is required
- To account for the symptom load not captured by the CLN2 clinical rating scale, it was assumed that each health state was associated with additional symptoms including epilepsy, disease-related distress, dystonia, myoclonus, vision loss and the requirement of a feeding tube

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Model

Transition probabilities

- Patients receiving cerliponase alfa transition through the model using the transition probabilities calculated from the study 190-201/202 data (until week 16)
  - [redacted] of the patients in the trial experienced no further disease progression (after 16 weeks, and
  - [redacted] of the patients in the trial experienced a decline of 1 point on the CLN2 clinical rating scale between 16 weeks and 96 weeks
- Model assumes that after 16 weeks, [redacted] of patients in the cerliponase alfa arm will continue to remain in the health state that they are in, and [redacted] of patients will decline at a rate of 1 health state per 80 weeks, up to 96 weeks. After 96 weeks, this cohort will be assumed to have stabilised, and will remain in the health state that they are in for the remainder of the time horizon.
- The model does this by splitting up the cohort into cohorts called 'early stabilisers' and 'late stabilisers' – in the early stabiliser cohort, the probability of remaining in a health state is 1, and in the late stabiliser cohort, the probability of remaining in a health state is 1 after 96 weeks.
- Patients stop receiving treatment when they reach health state 7 (CLN2 score =0) and switch to standard care utilities and transition probabilities

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The company stated that approach was validated by clinical experts. Please see tables D11-D14, pages 202-204 for the transition probabilities.

Health states were grouped together when calculating transition probabilities (1&2, 3-5, 6&7) – grouping was done with similar health states at similar stages of disease progression. However, different costs and utilities were still applied according to health state.

ERG comment
Transition probabilities

- Transition probabilities used for cerliponase alfa patients, in the first 16 weeks of the model, were based on the first 24 weeks of data (not 16 as stated by the company)
  - Inconsistency with the clinical data
  - While these transition probabilities are only applied for a short period of time, the assumption of stability after this period means that they are an important determinant of the total costs and QALY
- Although the treatment stopping rule was validated by clinical experts, the ERG is concerned a proportion of patients may continue to receive treatment after progressing to health state 7
  - Some parents and carers value extension of life more than quality of life and are likely to request therapy to continue as long as possible

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ERG comment

Stabilisation assumptions

- The early and late stabiliser distinction was not established a priori
  - No way of substantiating if these categories are a genuine reflection of different responses to cerliponase alfa
- By assuming stabilisation, the model implicitly assumes that these values for utilities and costs, which are relevant for ~4- to 5-year-olds, will still be appropriate for patients when they are in early, mid and late adulthood
- The assumption that all patients stabilise after 96 weeks is the single most important assumption in the economic model. The company draw upon clinical expertise, evidence from other disease areas in which ERT is used and the short-term evidence provided by the 190-201/202 trial, to justify this assumption. However:
  - Limited evidence from study 190-201/202 that all patients stabilise
  - The number which stabilise falls as follow up lengthens
  - IPD data reported in the 190-202 interim CSR shows [redacted] a further decline in CLN2 rating scale after 96 weeks
  - New (focal and/or generalised) epileptiform activity in [redacted] of patients suggests disease progression had not halted

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Mortality

- Three types of mortality were modelled – disease related mortality, infection related mortality, and age related mortality
  - Disease related mortality depends on time in palliative state
- The probability of transitioning to death from health state 9 is assumed constant, and an exponential function with a mean of 52 weeks was fitted and used to derive this transitional probability
  - Patients cannot die of disease-related causes in earlier states (0-8); validated by experts
- Infection related mortality is assumed to be 0 as no infections in the trials had led to a patient death

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ERG comments

Mortality

- Assuming patients experience general population mortality is reasonable for the standard care arm, but inappropriate in the cerliponase alfa arm:
  - Neurological progression, extra-neurological progression and other-disease-related mortality, are not directly attributable to progression of the disease and should be accounted for in the modelling

Neurological progression:

- Significant uncertainty regarding the assumption that patients experience no further disease progression after 96 weeks
- Any relaxation of this assumption will lead to a reduced life expectancy for cerliponase alfa patients

Extra-neurological progression:

- Pre-clinical studies indicated there may be serious implications for patient morbidity and mortality associated with cardiac, pancreatic, and hepatic impairment unless ERT is administered systemically
- Importantly the morbidity and mortality consequences of extra-neurological disease pathology will be unrelated to neurological progression and therefore, represent an additional mortality risk

Other-disease-related mortality

- Evidence from the related Batten's disease sub-type CLN3 shows that the actual cause of death for a substantial proportion of CLN3 patients was either pneumonia or infection, therefore not related to either neurological failure or extra-neurological pathology

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ERG exploration – Mortality

Scenario	Incremental costs (£)	Incremental QALYs	ICER	Threshold	Incremental undiscounted QALYs
No stabilisation (disease-related mortality)					
Cerliponase Alfa	[redacted]	11.81	[redacted]	£150,075	15.01
Standard Care	N/A	N/A	N/A	N/A	N/A
Extra neurological mortality					
Cerliponase Alfa	[redacted]	13.14	[redacted]	£154,282	15.43
Standard Care	N/A	N/A	N/A	N/A	N/A
Neurodisability-related mortality					
Cerliponase Alfa	[redacted]	29.19	[redacted]	£300,000	47.61
Standard Care	N/A	N/A	N/A	N/A	N/A
No stabilisation + Extra neurological mortality + Neurodisability-related mortality					
Cerliponase Alfa	[redacted]	9.14	[redacted]	£104,014	10.40
Standard Care	N/A	N/A	N/A	N/A	N/A

Mortality is an important driver in the model

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Model

Starting population

- Distribution across the different health states at model entry is based on the population expected to receive treatment for CLN2 disease in the UK
- It incorporates the assumption that patients will be diagnosed in an earlier health state in the future
- The starting age of all patients in the model of 4.8 years and is derived from Study 190-201 patient baseline characteristics

Health state	Base-case model	Based on patients in 190-901 born after 2000
Health state 1	40%	[redacted]
Health state 2	40%	[redacted]
Health state 3	10%	[redacted]
Health state 4	5%	[redacted]
Health state 5	5%	[redacted]
Health state 6	0%	[redacted]
Health state 7	0%	[redacted]
Health state 8	0%	[redacted]
Health state 9	0%	[redacted]

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Source: Table D15 company submission

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ERG comment

Model population

- The distribution of patients at the initiation of treatment is one of the most important drivers of cost-effectiveness, because cerliponase alfa is not restorative and can only stabilise/slow progression
- Assuming that patients would be diagnosed in an earlier health state in the future, means that there are more patients in the less severe health states than we would expect to see based on current diagnostic practice
- To justify this assumption the company stated that they would be implementing a campaign to improve awareness by:
  - [redacted]
- The impact of such a programme is highly uncertain
- The company is assuming significant improvements in diagnosis which is unreasonable

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Health-related quality of life

Proxy estimation

- The base case uses utility values collected during the utility study conducted by BioMarin in 2017
  - A vignette was produced for each health state, and separate vignettes were produced to describe patient experience in the two treatment arms of the model
  - Vignettes were sent to 8 clinical experts, who were asked to complete the EQ-5D-5L questionnaire as a proxy for patients that would be experiencing the description given in the vignettes
- The EQ-5D-5L values were mapped to EQ-5D-3L values
- The company stated that utility values from the data collected in studies 190-201/202 (limited amounts of EQ-5D-5L and PedsQL data) were not used in the model, due to the small sample size of values and the fact that utility values could not be obtained for all of the health states in the model
  - Scenario analysis mapping PedsQL to EQ-5D were also provided

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Vignettes found in 17.10 of the appendices.

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Utility values

Health state	Cerliponase alfa	Standard care
Health state 1	[redacted]	[redacted]
Health state 2	[redacted]	[redacted]
Health state 3	[redacted]	[redacted]
Health state 4	[redacted]	[redacted]
Health state 5	[redacted]	[redacted]
Health state 6	[redacted]	[redacted]
Health state 7	[redacted]	[redacted]
Health state 8	[redacted]	[redacted]
Health state 9	[redacted]	[redacted]
Health state 10 (death)	[redacted]	[redacted]

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Source: table D17 company submission

Utility values from utility study, after mapping EQ-5D-5L to EQ-5D-3L

Caregivers

- The Delphi panel described was used to determine the number of caregivers required for each health state in the model, and the proportion of that care that would be provided by family caregivers, and non-family caregivers
  - Caregiver costs were applied only to the proportion of the care provided by non-family caregivers
  - Proportion of family vs. non-family caregivers the same across treatments
  - Same proportion of family caregiving in health state 8 and 9
- Caregiver disutility was included in the model (see next slide)
- Additional disutility was added to the model to represent the impact on quality of life felt by siblings unaffected directly by CLN2 disease
  - applied across all but the first two health states, in line with guidance from clinical experts
  - a -0.09 decrement is applied to the midpoint of the remaining seven health states to the average number of unaffected siblings in a family with CLN2 disease; value obtained from a report on the challenges of living with and caring for a child affected by CLN2 disease

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Caregiver and sibling disutility

Health state	Caregiver disutility	Sibling disutility
1	-0.02	0.000
2	-0.025	0.000
3	-0.027	-0.023
4	-0.054	-0.045
5	-0.081	-0.068
6	-0.108	-0.090
7	-0.135	-0.113
8	-0.162	-0.135
9	-0.189	-0.158

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Source: adapted from table D9 and D10

Caregiver disutility in health states 1 and 2 are estimated by clinical experts.

The midpoint (health state 7) sibling disutility was obtained from a report on the challenges of living with and caring for a child affected by CLN2 disease (ref 13 company submission- ICON study)

ERG comment

Health-related quality of life

- The ERG is not concerned with the use of negative utilities per se, given the severity of the disability experienced by patients
  - Unmapped EQ-5D-5L values from the utility study show higher utility values with fewer negative health states, therefore they may be a better reflection of QoL experienced by CLN2 patients
- The ERG is concerned that the vignettes imply significant additional benefits of treatment with cerliponase alfa over and above the effects on disease progression. Specifically, the vignettes imply that cerliponase alfa improves seizure control, improves control of dystonia and myoclonus and delays the need for a feeding tube. However, minimal evidence was presented to support these implied benefits
- HRQoL data from study 190-201/202 can be used for validation of the elicited values used in the base-case
  - Vignettes appear to be underestimating the utilities, with the degree of underestimation increasing as the patient moves up health states*
- Assuming near perfect health in health state 1 is inappropriate as patients will have some symptom load at diagnosis
- Utility values applied in less severe health states are very high, which is a concern where disease stabilisation is assumed, as there is no modelled age-related decline in utility due to disability and comorbidities
- The accrual of disutilities from carers and siblings continues for too long

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HRQoL data collected from the 190-201/202 studies was not used in the company's base-case analysis, because utility values could not be obtained for all of the health states in the model and because the data were only available for patients receiving cerliponase alfa.

*The reason for this difference is not clear, but it may be because PedsQL is bound at zero

PedsQL aligns much better with the unmapped EQ-5D-5L. This may suggest that the mapping of the elicited EQ-5D-5L to the EQ-5D-3L has led to an overestimation of the impact of CLN2 on HRQoL

The company included only the most common study drug-related AEs in the model, and did not include the grade 3/4 AEs, which is a common criterion for selection of Aes. However, this is unlikely to have a large impact on the appraisal given the frequency of grade 3/4 AEs

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Adverse event disutility and proportions

Adverse event	Disutility	Time adverse event experienced for (days)	Annual occurrences of adverse events	Total annual disutility from adverse event
Pyrexia	-0.11	[redacted]	[redacted]	[redacted]
Hypersensitivity	-0.03	1	[redacted]	[redacted]
Headache	-0.12	1	[redacted]	[redacted]
Vomiting	-0.05	1	[redacted]	[redacted]
Infection	-0.2	N/A	N/A	N/A

Pyrexia	Hypersensitivity	Headache	Vomiting
[redacted]	[redacted]	[redacted]	[redacted]

- Focus on most frequent adverse events rather than the most severe
- An infection rate of 0.45% for each performed ICV infusion is assumed
- No treatment-related AEs are applied for standard care

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Source: table D7 company submission

Adverse event disutilities were sourced from the literature for the cerliponase alfa related adverse events reported during study 190-201/202 and applied to the cerliponase alfa arm of the model

ERG comment:

- The ERG considers that the company's approach to modelling AE's was generally appropriate
- The ERG is concerned that the company's focus is on the most frequent events rather than the most severe
- There's a number of serious adverse events that were not included in the company's base-case analysis
- The impact of this omission is, however, likely to be small given the infrequency of grades III and IV events

Treatment cost

Cost element	Value
Treatment costs	
Cost per 150mg vial	£10,053.50
Number of vials required per dose	2
Adherence rate	99.74%
Cost per dose	£20,055.18
Administration costs	
One-off insertion cost (ICV)	£9,518.70
Replacement cost	£4,387.99
Proportion of infusions that lead to an infection	0.45%
Proportion of infections that require a replacement	62%
Number of replacements per year	0.07254
Annual replacement cost applied in model	£318.30
Infusion costs	
Infusion cost (per infusion)	£466.00

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Source: tables D22 and D23

Health state costs

- Health state costs based on costs of specialist clinicians, nurses, GPs, Community paediatrician, Speech/language therapist, Physiotherapist, Family Support Worker, Opthalmologist, Health Visitor, Occupational therapist, Caregiver costs, Critical care bed days, Hospitalisation days, Palliative care, Educational Support, and Family and caregiver productivity losses
- Values used for appointments per year in each health state were obtained from the Delphi panel
- Whenever subsequent appointments were found to have a different cost to the first appointments, later years included costs of subsequent appointments.

Health state	Cost per year (1st year)	Cost per year (after 1st year)
1	£8,148.92	£7,666.92
2	£8,148.92	£7,666.92
3	£9,802.66	£9,320.66
4	£23,209.07	£22,727.07
5	£24,742.12	£24,260.12
6	£32,282.66	£31,800.66
7	£31,552.55	£31,070.55
8	£31,821.54	£31,339.54
9	£21,940.12	£21,940.12

Source tables D25 and D26 company submission

ERG comment
Resources and costs

- Administration cost:
  - Unit costs appear to be generally appropriate and the assumption that no additional training would be needed is reasonable
  - Replacement ICV is costed at paediatric prices, cost of ICV replacement is higher in adults, but this change makes little difference to the ICER
- Additional monitoring costs associated with treatment should be included in the model given the assumption of life-long treatment for responders
- Health state costs:
  - Insensitive to changes in cost estimates because of the large QALY gains arising due to assumed disease stability and continued survival
  - If these two assumptions were to be relaxed the treatment cost may become less of a factor in determining the likely cost-effectiveness, and greater weight may be given to the other cost items
- Important cost items relating to progressive symptoms were excluded
- The dosing of the majority of the therapies used to provide symptomatic relief was based on bodyweight, however the weight of patients was assumed not to change after age 18
  - Lacks face validity and is unnecessary given weight data availability

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Dosing was based on the assumption that all children started treatment > 3 years old (reflecting the trial) and received two vials of cerliponase alfa. Children under the age of 1 would only require a dose consisting of one vial. However, it does not seem likely that this dose will be applied until wide-scale genetic testing is in place and children are diagnosed significantly earlier.

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Company base case results

	Cerliponase Alfa	Standard Care	Incremental		ICER (£/QALY)
	Cost (£)	Cost (£)	Cost (£)	QALY	
Probabilistic	[redacted]	149,944	[redacted]	30.42	[redacted]
Deterministic	[redacted]	149,829	[redacted]	30.42	[redacted]

ERG comment:

- The company model included calculation errors
  - Correcting for these errors increased the ICER by about 0.3% from [redacted] to [redacted] per QALY

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Source: Table D36 company submission. See page 116 ERG report for calculation errors.

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Company alternative base case results

- Applying differential discount rates (1.5% for benefits and 3.5% for costs)

Treatment	Total costs (£)	Total LYG	Total QALYs	Inc costs (£)	Inc LYG	Inc QALY	ICER (£)
Standard care	149,829	4.97	-0.97	N/A	N/A	N/A	N/A
Cerliponase alfa	[redacted]	45.01	29.45	[redacted]	40.04	30.42	[redacted]

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Source: Table D37 company submission

The company states that discounting health benefits at a lower rate than costs will take into account any potential increase in the future value of health effects.

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Company scenario analysis

Scenario	Scenario info	ICER (£)
Base case	Company base case ICER (corrected)*	[redacted]
1	Starting population of patients evenly split across health states 1-2	[redacted]
2	All starting population starts in health state 1	[redacted]
3	Using PedsQL utility values from the trial, mapped to EQ-5D, with the assumption of the same utility values across both arms of the treatment	[redacted]
4	Utility values for cerliponase alfa arm assumed to be the same as the SoC arm, from the utility study	[redacted]
5	Patients stop receiving cerliponase alfa treatment at health state 6	[redacted]
6	Patients do not stop receiving cerliponase alfa treatment until death	[redacted]
7	No caregiver or sibling disutility is applied in the model, for the cerliponase alfa arm	[redacted]

Source: Company submission tables D47 to D56

*ERG corrected see slide 70

Company scenario analyses

Scenario	Change(s) made to model	ICER
Scenario 8	Discount rate of 3.5% for costs and benefits	[redacted]
Scenario 9	Discount rate of 3.5% for costs, 1.5% for benefits	[redacted]
Scenario 10	Reduced price, due to price evolution and PPRS rebate	[redacted]
Scenario 11	Time horizon of 75 years	[redacted]
Scenario 12	Societal perspective used	[redacted]
Scenario 13	Optimistic scenario - All starting population starts in health states 1-2, no caregiver or sibling disutility applied to the cerliponase alfa arm, 50% reduction in progressive symptoms, differential discount rate	[redacted]
Scenario 14	Pessimistic scenario - Utility values for cerliponase alfa arm assumed to be the same as the standard care arm, from the utility study, discount rate of 3.5% for costs and benefits	[redacted]

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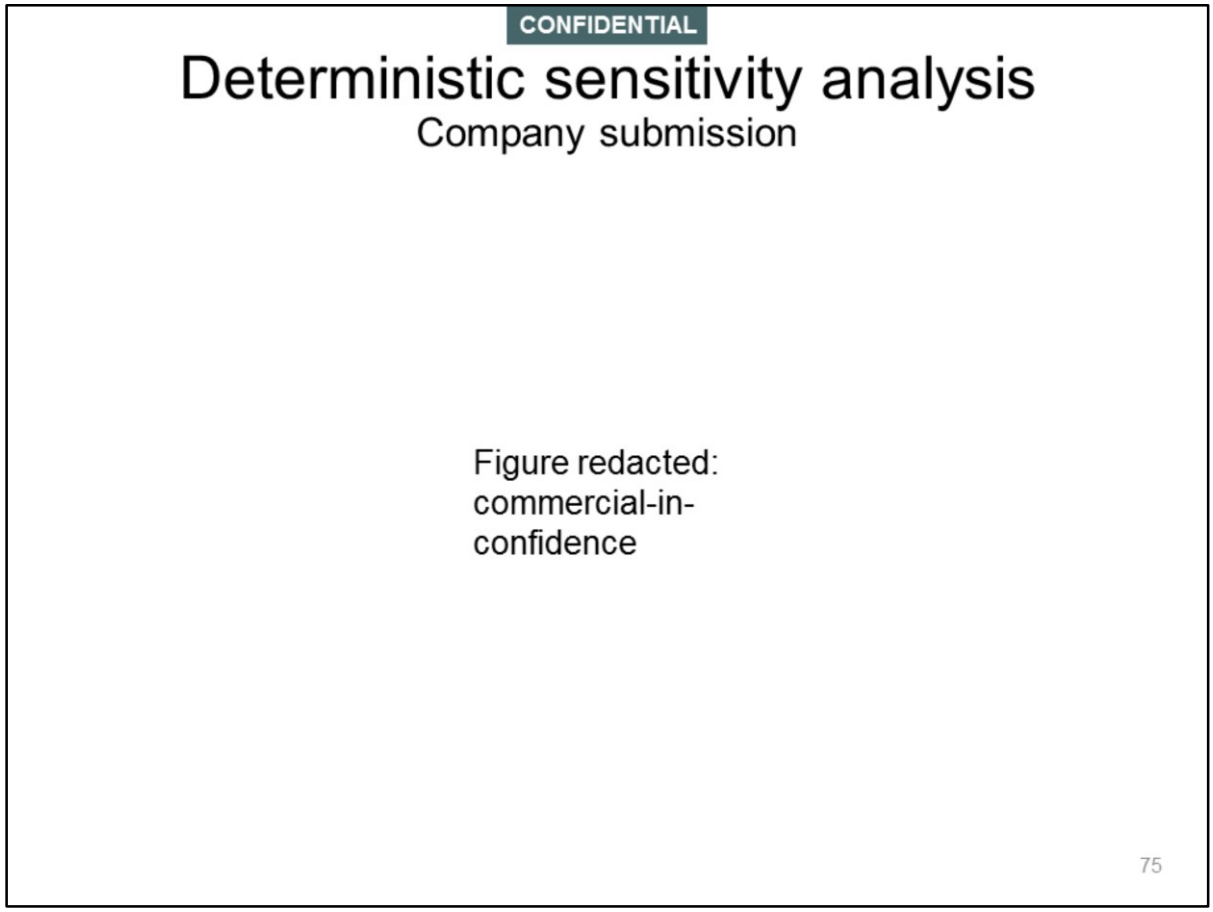
Additional scenarios

ERG requests at the clarification stage

PFC #	Scenario	ICER (£/QALY)
-	Company base-case (corrected)	[redacted]
B3	Cycle length of 8 weeks	[redacted]
B7	Starting population based on 190-201 population at baseline	[redacted]
B7	Starting population based on 190-201 population at screening	[redacted]
B10	Utility values for HS1 reduced by 10%	[redacted]
B10	Utility values decrease over time (age adjustment)	[redacted]
B12	EQ-5D-5L values from utility study used in model	[redacted]
B17	5% of patients in the cerliponase arm do not stabilise, life table mortality doubled, QoL decreases due to loss of vision	[redacted]
B19	Patients split into early and late stabilisers at 26 weeks	[redacted]
B21	Adult-equivalent health state costs used in HS1	[redacted]
B27	Removal of educational support, speech and language therapy and ophthalmologist costs in HS7 to HS9	[redacted]

Source: Table 41 ERG report

Scenario B17: The ERG requested a scenario relaxing the assumptions that all cerliponase alfa patients stabilise at week 96 and experience no further impact to mortality or vision symptoms. The company addressed this by assuming that 5% of cerliponase alfa patients did not stabilise, by gradually increasing general population mortality after stabilisation at 96 weeks (double at the age of 20 and four-fold by the age of 40), and applying a vision loss-associated reduction in utility of 13% after the age of 20. The ERG considered that the company remained very optimistic in these assumptions, specifically with regard to stabilisation and long-term mortality.



Source: Figure D24 company submission

Parameters included in the DSA were: HS utility values, carer and sibling disutility values, disutility values associated with infections and progressive symptoms, drug cost and infection frequency of cerliponase alfa, unit costs, mean number of siblings, frequency of appointments, and frequency of progressive symptoms. The company varied each parameter value by ±15%.

The parameters with the largest influence on the ICER were the drug cost and the health state utility values for cerliponase alfa.

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Subgroup analysis

- Analysis of a subgroup of asymptomatic and pre-symptomatic siblings with confirmed CLN2 disease was undertaken
- The assumption was made that if patients are asymptomatic and pre-symptomatic, then all patients will start in health state 1

Treatment arm	Total costs (£)	Total LYG	Total QALY	Δ costs (£)	Δ LYG	Δ QALY	ICER (£/ QALYs)
Standard care	152,985	5.36	-0.61	N/A	N/A	N/A	N/A
Cerliponase alfa	[redacted]	45.56	37.55	[redacted]	40.20	38.16	[redacted]

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Source: Table D58 company submission

Costs associated with each treatment arm are similar to those in the base-case; however, more QALYs are accrued by cerliponase alfa patients due to patients entering the model in a less severe health state and therefore are stabilised in less severe health state at the end of the trial period. As a result, cerliponase alfa is substantially more cost-effective in this subgroup, though the ICER still remains significantly above the threshold.

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ERG scenario analysis (1)

- Alternative starting populations based on the 190-901 cohort were explored. The cohort was restricted to patients born after 2000, as genetic testing for CLN2 was developed in the late 1990s.
  - A second scenario restricted to a CLN2 score of 2+ [redacted]

	Total costs	Total QALYs	Inc costs	Inc QALYs	ICER
1: Patient distribution in 190-901 trial					
Cerliponase alfa	[redacted]	17.38	[redacted]	18.79	[redacted]
Standard care	£143,004	-1.41	N/A	N/A	N/A
2: Patient distribution in 190-901 trial, restricted to CLN2 score of 2+					
Cerliponase alfa	[redacted]	18.11	[redacted]	19.51	[redacted]
Standard care	£145,156	-1.40	N/A	N/A	N/A

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Source: table 44 ERG report

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ERG scenario analysis (2)

The ERG extracted IPD from graphs in the CSRs and recreated transition probabilities for early (to week 16) and late responders (week 17 to 96)

Health state	Baseline to Week 16		Week 17 to Week 96	
	Probability of decline	Probability of improvement	Probability of decline	Probability of improvement
1 and 2	[redacted]	[redacted]	[redacted]	[redacted]
3 to 5	[redacted]	[redacted]		
6	[redacted]	[redacted]		

	Total costs	Total QALYs	Inc costs	Inc QALYs	ICER
3: ERG estimated transition probabilities for cerliponase alfa					
Cerliponase alfa	[redacted]	29.28	[redacted]	30.24	[redacted]
Standard care	£151,608	-0.96	N/A	N/A	N/A

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Source: Tables 45 and 46 ERG report

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ERG scenario analysis (3)

Two scenarios are presented relaxing this assumption of disease stabilisation

1. No late stabilisation, patients continue to progress after week 96
2. No disease stabilisation, disease progression continues indefinitely

	Total costs	Total QALYs	Inc costs	Inc QALYs	ICER
4: Disease stabilisation for early stabilisers on cerliponase alfa					
Cerliponase alfa	[redacted]	23.55	[redacted]	24.51	[redacted]
Standard care	£151,608	-0.96	N/A	N/A	N/A
5: No disease stabilisation					
Cerliponase alfa	[redacted]	10.85	[redacted]	11.81	[redacted]
Standard care	£151,608	-0.96	N/A	N/A	N/A

Source: Table 48 ERG report

Scenario 4: “late stabilisers” were assumed to continue experiencing disease progression after Week 96 in this scenario, with the rate of progression after this point defined by the transition probabilities used to model progression between 17 weeks and 96 weeks

Scenario 5: In this case, transition probabilities for Week 16 to Week 96 were estimated based on the dataset of all patients, and were applied beyond Week 96 for all patients.

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ERG scenario analysis (4)

- ERG concern that there is a significant risk that patients receiving cerliponase alfa will experience significantly shorter life expectancy than predicted by the company model. This is a result of both the impact of:
  - neurological disability,
  - and the effects of extra-neurological disease pathology.

	Total costs	Total QALYs	Inc costs	Inc QALYs	ICER
6: Extra-neurological mortality					
Cerliponase alfa	[redacted]	12.18	[redacted]	13.14	[redacted]
Standard care	£151,608	-0.96	N/A	N/A	N/A
7: Neurodisability-related mortality					
Cerliponase alfa	[redacted]	28.23	[redacted]	29.19	[redacted]
Standard care	£151,475	-0.96	N/A	N/A	N/A

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Source: Table 51 company submission

Modelling: mortality impact of neurological disability: a multiplier was applied to the general population mortality already included in the model.

Modelling: mortality impact of extra-neurological pathology: The impact of extra-neurological disease is subject to high degree of uncertainty as there is no long-term data available upon which to base assumptions and minimal evidence in untreated patients. The ERG's approach therefore focused on using evidence of extra-neurological pathology in the CLN3 subtype.

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ERG scenario analysis (5)

- Scenario assuming that cerliponase alfa would not slow the rate of vision loss in CLN2 patients. This was incorporated into health states 1-6 (for the proportion of patients estimated to have complete vision loss) by including:
  - The relative decrement in utility was estimated as 13%
  - A one of cost of blindness of £4,077 was applied (inflated from 2005 costs)

	Total costs	Total QALYs	Inc costs	Inc QALYs	ICER
8: Vision loss in cerliponase alfa patients					
Cerliponase alfa	[redacted]	25.64	[redacted]	26.61	[redacted]
Standard care	£151,608	-0.96	N/A	N/A	N/A

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Source: Table 52 ERG report

To account the effects of vision loss the ERG scenario incorporated a disutility and additional costs. These were applied to the proportion of cerliponase alfa patients in health states 1 to 6 who were estimated to have complete vision loss.

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ERG scenario analysis (6)

	Total costs	Total QALYs	Inc costs	Inc QALYs	ICER
9: EQ-5L-5L					
Cerliponase alfa	[redacted]	32.36	[redacted]	32.55	[redacted]
Standard care	£151,608	-0.20	N/A	N/A	N/A
10: Peds-QL					
Cerliponase alfa	[redacted]	33.15	[redacted]	32.12	[redacted]
Standard care	£151,608	1.03	N/A	N/A	N/A
11: Age-adjusted utilities					
Cerliponase alfa	[redacted]	27.50	[redacted]	28.46	[redacted]
Standard care	£151,608	-0.96	N/A	N/A	N/A
12: Removed carer and sibling disutility after 30 years					
Cerliponase alfa	[redacted]	30.20	[redacted]	31.17	[redacted]
Standard care	£151,608	-0.96	N/A	N/A	N/A
13: Same utility values in each arm					
Cerliponase alfa	[redacted]	26.49	[redacted]	27.45	[redacted]
Standard care	£151,608	-0.96	N/A	N/A	N/A

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Source: Table 53 ERG report

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ERG scenario analysis (7)

The ERG considered that there were some important cost items that were not included in the company analysis that had the potential to impact on the cost-effectiveness of cerliponase alfa

	Total costs	Total QALYs	Inc costs	Inc QALYs	ICER
14: Additional ECG cost					
Cerliponase alfa	[redacted]	29.24	[redacted]	30.20	[redacted]
Standard care	£151,608	-0.96	N/A	N/A	N/A
15: Psychiatric support					
Cerliponase alfa	[redacted]	29.24	[redacted]	30.20	[redacted]
Standard care	£151,608	-0.96	N/A	N/A	N/A
16: Residential care					
Cerliponase alfa	[redacted]	29.90	[redacted]	30.86	[redacted]
Standard care	£151,608	-0.96	N/A	N/A	N/A

Source: Table 54 ERG report

An additional cost of ECG (£494) has been applied to patients on treatment every six months and to the proportion of patients with heart disorders requiring an ECG every infusion. The proportion of patients requiring an ECG with each infusion was estimated from the clinical trial data, where [redacted]

The cost of paediatric and psychological support (£242)was applied every quarter

The cost of £43,810 (PSSRU young adult with severe brain injuries) was applied to 50% of patients over the age of 18. The ERG also removed the carer and sibling disutility for the proportion of patients in residential care.

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ERG scenario analysis (8)

- The company applied a discount rate of 1.5% for costs and outcomes
- The ERG preferred to apply the reference case discounting rates of 3.5% for both costs and outcomes

	Total costs	Total QALYs	Inc costs	Inc QALYs	ICER
17: Discounting costs and QALYs at 3.5%					
Cerliponase alfa	[redacted]	17.27	[redacted]	18.12	[redacted]
Standard care	£142,486	-0.84	N/A	N/A	N/A

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Source: Table 55 ERG report

ERG preferred base-case

The ERG's preferred base-case combines a number of the changes to the company base-case:

1. Starting population based on the 190-901 cohort;
2. ERG-calculated transition probabilities for cerliponase alfa patients;
3. No long-term disease stabilisation for cerliponase alfa patients;
4. Includes extra-neurological and neuro-disability-related mortality;
5. All patients go blind over time, and incur related support costs and disutility;
6. Utilities are the same for both treatment arms using EQ-5D-3L data
7. Age-adjusted utilities are applied;
8. Carer and sibling disutility are removed after 30 years;
9. Additional resource use items are included (ECG, psychiatric support, residential care);
10. Discount rate of 3.5% for costs and benefits

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ERG preferred base-case

	Total costs	Total QALYs	Inc costs	Inc QALYs	ICER
ERG-preferred base-case analysis					
Cerliponase alfa	[redacted]	2.02	[redacted]	3.32	[redacted]
Standard care	£135,549	-1.30	N/A	N/A	N/A

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Source: Table 56 ERG report

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Scenario analysis

On ERG preferred base-case

Scenario	Scenario info	ICER (£)
Base case	ERG preferred base-case	[redacted]
1	Partial stabilisation on cerliponase alfa (early stabilisers only)	[redacted]
2	No extra-neurological related mortality	[redacted]
3	Different utility values in each arm (EQ-5D-3L)	[redacted]
4	PedsQL for HRQoL	[redacted]
5	Stopping rule – no discontinuation of cerliponase alfa	[redacted]
6	Discounting at 1.5%	[redacted]
7	Optimistic base-case analysis - partial stabilisation, no cardiac mortality and HRQoL benefit for cerliponase alfa	[redacted]

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Source: Table 57 ERG report

The ERG acknowledges that some of these assumptions in its preferred base case are speculative. To further explore the impact of these assumptions the ERG therefore carried out further scenario analyses using the ERG base-case.

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Subgroup analysis

ERG approach

	Total costs	Total QALYs	Inc costs	Inc QALYs	ICER
ERG corrected company base-case: asymptomatic and pre-symptomatic subgroup					
Cerliponase alfa	[redacted]	37.29	[redacted]	37.89	[redacted]
Standard care	£155,422	-0.60	N/A	N/A	N/A
ERG-preferred base-case: asymptomatic and pre-symptomatic subgroup					
Cerliponase alfa	[redacted]	7.52	[redacted]	8.00	[redacted]
Standard care	£145,065	-0.48	N/A	N/A	N/A
Optimistic base-case analysis: asymptomatic and pre-symptomatic subgroup					
Cerliponase alfa	[redacted]	15.53	[redacted]	16.01	[redacted]
Standard care	£145,065	-0.48	N/A	N/A	N/A

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Source: Table 58 ERG report

QALY weighting

- For ICERs above £100,000 per QALY, recommendations must take into account the magnitude of the QALY gain and the additional QALY weight that would be needed to fall below £100,000 per QALY
- To apply the QALY weight, there must be compelling evidence that the treatment offers significant QALY gains
- In the company base case incremental undiscounted QALYs: 50.52
- ERG preferred base case incremental undiscounted QALYs: 4.19
- ERG most optimistic scenario incremental undiscounted QALYS: 21.15

Lifetime inc QALYs gained	Weight
Less than or equal to 10	1
11–29	Between 1 and 3 (using equal inc)
Greater than or equal to 30	3

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Budget Impact

- There are currently an estimated 34 patients in England was CLN2 disease, and it was assumed that [redacted] of these patients ([redacted]) would be eligible for treatment, in line with the market authorisation
- Based on the advice provided by clinical and patient experts consulted by the company, there are five estimated patients diagnosed per year, of which [redacted] ([redacted])would be eligible for treatment with cerliponase alfa

Cost	Year 1	Year 2	Year 3	Year 4	Year 5
Treatment cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Health state	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Progressive symptoms	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cumulative total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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Source: table D61 company submission

Impact of the technology beyond direct health benefits

- The introduction of cerliponase alfa could have a positive beneficial impact on the following non-health domains:
  - The emotional and psychological impact of caring for an affected child caregivers;
  - Family and social relationships, including the impact on non-affected siblings;
  - The education and social interaction of the affected child; and
  - Family finances
- Reduced expenditure incurred by government departments which provide support for families affected by CLN2 disease
- Costs borne by patients not reimbursed by the NHS
  - Transportation and accommodation when receiving specialist care
  - Home adaptations
  - Lost income

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Expected that the introduction of cerliponase alfa would reduce the expenditure currently incurred by the Department of Work and Pensions, the Department of Communities and Local Government and local County Councils.

If children stabilise on treatment, cerliponase alfa would be increasing the probability of patients reaching a working age and obtained a job. This employment would increase the mental wellbeing of patients with CLN2 disease, and would contribute to society through taxation, but this was not modelled due to limited data.

The benefit of cerliponase alfa is in delaying disease progression. It is likely that this would reduce home adaptation costs and wheelchair costs that would be associated with the later stages of CLN2 disease, which patients would experience with standard care.

Innovation

- The company stated that cerliponase alfa will represent a step-change in the management of CLN2 disease because:
  - It is the first approved pharmacological treatment; the first ERT administered to into the CNS via ICV
  - It is expected to restore TPP1 enzyme activity in the brain, addressing the underlying cause of the disease
  - It is approved for use in all ages
  - It is the first treatment option to have a positive impact on motor and language function

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Highly Specialised Technology Evaluation

Cerliponase alfa for treating neuronal ceroid lipofuscinosis type 2

Final scope

Remit/evaluation objective

To evaluate the benefits and costs of cerliponase alfa within its licensed indication for treating neuronal ceroid lipofuscinosis type 2 for national commissioning by NHS England.

Background

Neuronal ceroid lipofuscinosis type 2 (CLN2) is a rare genetic disease caused by the deficiency of an enzyme called tripeptidyl peptidase1 (TPP1). CLN2 is one form of neuronal ceroid lipofuscinosis (NCL), also known as Batten disease. CLN2 disease is inherited as an autosomal recessive disorder, which means that both chromosome copies carry mutations in the CLN2 gene, and both parents are unaffected carriers.[1] A deficiency of TPP1 results in abnormal storage of proteins and lipids in neurons and other cells. Accumulation of these proteins and lipids prevent the cells from functioning as they should.

CLN2 is characterised clinically by a decline of mental and other capacities, epilepsy, and vision loss through retinal degeneration, and histopathologically by intracellular accumulation of ceroid lipofuscin in the neuronal cells of the brain and retina.[2] Symptoms in children with CLN2 start to arise in the second year of life and can then progress rapidly with the onset of seizures, decline in speech, loss of mobility, involuntary muscle spasms and later on, visual impairment leading to blindness. Ultimately the child will become totally dependent on families and carers for all of their needs. Life expectancy is around 6 to 13 years.

The exact prevalence and incidence of CLN2 is unknown. It is estimated that in the UK, around 3 to 6 children are diagnosed each year and currently around 30 to 50 children are living with the condition.[1]

Currently there is no cure or life extending options available. Current clinical management options focus on symptom control, monitoring and prevention of complications, and palliative care. Management aims to maintain function as long as possible and to improve quality of life. This involves a multidisciplinary and multiagency team to control symptoms and complications such as, malnutrition, gastroesophageal reflux, pneumonia, anxiety, Parkinsonian symptoms and dystonia, through medication and physical therapy. Children often receive multiple medications and clinicians need to balance symptom control with the adverse effects and treatment interactions.

The technology

Cerliponase alfa (Brineura, BioMarin) is a recombinant human tripeptidyl peptidase 1 which is an enzyme replacement therapy. It is administered by intracerebroventricular infusion every 2 weeks.

Cerliponase alfa has a marketing authorisation in the UK for, "the treatment of neuronal ceroid lipofuscinosis type 2 (CLN2) disease, also known as tripeptidyl peptidase 1 (TPP1) deficiency". It has been studied in patients with a confirmed diagnosis of CLN2, with a 2-domain score of 3 to 6 on motor and language domains of the Hamburg Scale and a score of at least 1 in each of these domains.

Intervention(s)	Cerliponase alfa
Population(s)	People with a confirmed diagnosis of CLN2
Comparators	Established clinical management without cerliponase alfa (including a multidisciplinary and multiagency approach to manage the symptoms and complications associated with CLN2)
Outcomes	The outcome measures to be considered include: • symptoms of CLN2 (including visual function, seizures, myoclonus, dystonia, spasming, pain and feeding) • disease progression (including quantitative measure such as the Hamburg scale, CLN2 rating scale, and the Weill Cornell LINCL score) • need for medical care (including hospitalisation, emergency care and primary and secondary care appointments, and concomitant medication) • mortality • adverse effects of treatment (including immune response and effects and complications related to treatment administration) • health-related quality of life (for patients and carers, and including impact on families such as social and mental health and impact on siblings)
Nature of the condition	• disease morbidity and patient clinical disability with current standard of care • impact of the disease on carer's quality of life

	• extent and nature of current treatment options
Impact of the new technology	• overall magnitude of health benefits to patients and, when relevant, carers • heterogeneity of health benefits within the population • robustness of the current evidence and the contribution the guidance might make to strengthen it • treatment continuation rules (if relevant)
Value for Money	• cost effectiveness using incremental cost per quality-adjusted life year • patient access schemes and other commercial agreements • the nature and extent of the resources needed to enable the new technology to be used
Impact of the technology beyond direct health benefits	• whether there are significant benefits other than health • whether a substantial proportion of the costs (savings) or benefits are incurred outside of the NHS and personal and social services • the potential for long-term benefits to the NHS of research and innovation • the impact of the technology on the overall delivery of the specialised service • staffing and infrastructure requirements, including training and planning for expertise.
Other considerations	If appropriate, the evaluation should include consideration of the costs and implications of changes in service delivery for CLN2, but will not make recommendations on service provisions. If the evidence allows, the following subgroup should be considered: • based on disease progression • pre-symptomatic siblings with confirmed CLN2 • asymptomatic siblings with confirmed CLN2 Guidance will only be issued in accordance with the marketing authorisation.

	Guidance will take into account any Managed Access Arrangements.
Related NICE recommendations and NICE Pathways	None
Related National Policy	NHS England Manual for prescribed specialised services, service 71: lysosomal storage disorder service (adults and children), November 2012. http://www.england.nhs.uk/wp-content/uploads/2012/12/pss-manual.pdf NHS England Standard Contract for Lysosomal Storage Disorders Service (Children), 2013. http://www.england.nhs.uk/wp-content/uploads/2013/06/e06-lyso-stor-dis-child.pdf

References

1. CLN2 disease, late infantile. Batten Disease Family Association. Accessed September 2016.
2. Neuronal Ceroid Lipofuscinosis. Orphanet. Accessed September 2016.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Highly Specialised Technology Evaluation

Cerliponase alfa for treating neuronal ceroid lipofuscinosis type 2 [ID943]

Matrix of consultees and commentators

Consultees	**Commentators (no right to submit or appeal)**
Company • BioMarin (cerliponase alfa) Patient/carer groups • Batten Disease Family Association Professional groups • Royal College of Physicians Others • Department of Health • NHS England • Birmingham Children's Hospital NHS Foundation Trust Lysosomal Storage Disorders Unit • Welsh Government	General • All Wales Therapeutics and Toxicology Centre • British National Formulary • Department of Health, Social Services and Public Safety for Northern Ireland • Healthcare Improvement Scotland • Wales Neurological Alliance • Welsh Health Specialised Services Committee Comparator companies • None Relevant research groups • None Associated Public Health Groups • None

NICE is committed to promoting equality, eliminating unlawful discrimination and fostering good relations between people who share a protected characteristic and those who do not. Please let us know if we have missed any important organisations from the lists in the matrix, and which organisations we should include that have a particular focus on relevant equality issues.

PTO FOR DEFINITIONS OF CONSULTEES AND COMMENTATORS

Definitions:

Consultees

Organisations that accept an invitation to participate in the appraisal; the company that markets the technology; national professional organisations; national patient organisations; the Department of Health and the Welsh Government and relevant NHS organisations in England.

The company that markets the technology is invited to make an evidence submission, respond to consultations, nominate clinical experts and has the right to appeal against the Final Appraisal Determination (FAD).

All non company consultees are invited to submit a statement[1], respond to consultations, nominate clinical or patient experts and have the right to appeal against the Final Appraisal Determination (FAD).

Commentators

Organisations that engage in the appraisal process but that are not asked to prepare an evidence submission or statement, are able to respond to consultations and they receive the FAD for information only, without right of appeal. These organisations are: companies that market comparator technologies; Healthcare Improvement Scotland; related research groups where appropriate (for example, the Medical Research Council [MRC], National Cancer Research Institute); other groups (for example, the NHS Confederation, NHS Alliance and NHS Commercial Medicines Unit, and the British National Formulary.

All non company commentators are invited to nominate clinical or patient experts.

[1] Non company consultees are invited to submit statements relevant to the group they are representing.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Highly Specialised Technologies Evaluation Programme

Cerliponase alfa for the treatment of neuronal ceroid lipofuscinosis type 2 (CLN2) [ID943]

Submission of evidence by BioMarin Europe Limited

3rd October 2017

Contents

List of tables and figures

Glossary of terms

Term	Definition
ADC	Apparent diffusion coefficient
AED	Anti-Epileptic Drugs
ADL	Activities of daily living
BDFA	UK Batten Disease Family Association
BMN 190	Investigational name of cerliponase alfa
BOI	Burden of illness
BDSRA	US Batten Disease Science and Research Association
CADTH	Canadian Agency for Drugs and Technologies in Health
CDSR	Cochrane database of systematic reviews
CHQ	Child Health Questionnaire
CI	Confidence interval
CEA	Cost effectiveness analysis
CHO	Chinese Hamster Ovary
CLN2	Neuronal Ceroid Lipofuscinosis Type 2
Cr	Creatine
CSF	Cerebrospinal fluid
DARE	Database of abstracts of reviews of effects
DWI	Diffusion-weighted MR imaging
EEG	Electroencephalogram
EMA	European Medicines Agency
EPAR	European Public Assessment Report
ERT	Enzyme Replacement Therapy
EQ-5D	EuroQol 5 domain instrument of health outcomes
EQ-VAS	EuroQol 5 visual analogue scale
ER	Emergency room
EU	European Union
HRQL	Health-related quality of life
HTA	Health technology assessment
ICGA	Indocyanine green angiography
ICV	Intracerebroventicular infusion
ITQoL	Infant-Toddler quality of life instrument
JNCL	Juvenile neuronal ceroid lipofuscinosis
K-M	Kaplan-Meier
LINCL	Late infantile neuronal ceroid lipofuscinosis
LSD	Lysosomal storage disorder
MAA	Managed Access Agreement
ML	Motor-Language
MLV	Motor-Language-Vision
MPS	Mucopolysaccharide disease
MRI	Magnetic resonance imaging
mRNA	Messenger ribonucleic acid
n	Numerator within studies
N	Denominator (population) within studies
NAA	N-acetylaspartate
NCL	Neuronal ceroid lipofuscinosis
NHS	National Health Service
NHS EED	NHS economic evaluation database
NICE	National Institute for Health and Care Excellence
NORD	National Organization for Rare Disorders

NR	Not reported
OCT	Optical Coherence Tomography
PedsQOL	Pediatric Quality of Life instrument
PIND	Progressive intellectual and neurological deterioration
PRO	Patient reported outcomes
PT	Preferred Term
QoL	Quality of life
rhTPP1	Recombinant form of human tripeptidyl peptidase-1
SD	Standard deviation
SDO	Stable Dosing Only
SDP	Stable Dosing Period
SE	Standard error
SF-36	36 item Short Form Survey
SOC	System Organ Class
TPP 1	Tripeptidyl peptidase I
USA	United States of America
WCMC	Weill Cornell Medical College

Executive Summary

Nature of the condition

Neuronal ceroid lipofuscinosis (NCL) type 2 (a form of Batten disease, hereinafter referred to as 'CLN2 disease') is an ultra-rare, inherited neurodegenerative disease that has a rapid and predictable course of progression from presentation in late infancy to death by early adolescence (section 6.1).

The condition is caused by pathogenic variants/mutations in the *CLN2 (TPP1)* gene that lead to a functional deficiency of the lysosomal enzyme tripeptidyl peptidase 1 TPP1. TPP1 deficiency is associated with an accumulation of abnormal material (ceroid lipofuscin) in neuronal, glial and retinal cells. Functional deficiency of TPP1 causes CLN2 disease, resulting in neurodegeneration, loss of neurological function and early death around the age of 10 years (section 2.2).

Classic late-infantile phenotype CLN2 disease usually manifests in late infancy (age 2-4 years) with unprovoked seizures and/or ataxia, and can be preceded by a history of early language delay. The disease has a predictable and rapid course of physical, neurologic and mental decline, irrespective of ethnicity or gender. It is characterised by swift loss of motor function and language ability, ataxia, movement disorders (myoclonus, dystonia and chorea), progressive dementia, and eventual loss of vision and ability to swallow (section 6.1).

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. Limb spasticity, truncal hypotonia and loss of head control lead to complete loss of independent mobility between the ages of 4 and 6 years, such that most affected children are unable to sit unsupported, are wheelchair-bound and require gastrostomy feeding by the age of 6. Seizures can become intractable and resistant to treatment with patients suffering significant myoclonus and pain. The majority of children with CLN2 disease become bedridden and blind, and die between the age of 8 years and early adolescence(section 6.1).

CLN2 disease deprives the patient of a functional life from early childhood; consequently, it has a devastating impact on the quality of life of parents, caregivers and families (section 7.1).

CLN2 disease is an exceptionally rare condition, with estimated prevalence of 0.7 per million population and incidence of 0.5 per 100,000 live births based on literature reports. It is estimated that approximately 4-6 children are

diagnosed with CLN2 disease each year in England, with a total of approximately 25-30 children currently affected in England (section 6.2).

Extent and nature of current treatment options

Diagnosis of CLN2 disease is based on laboratory testing following clinical suspicion. CLN2 disease can be definitively diagnosed either through demonstration of deficient TPP1 activity or through identification of causative mutations in each allele of the *CLN2 (TPP1)* gene (section 8.2). In practice, most clinicians would make the decision to start treatment on the basis of the blood enzyme test, with the genetic test confirmatory only. Diagnosis is delayed by an average of 2 years from onset of symptoms due to low clinical awareness of the disease.

Cerliponase alfa is the only treatment licensed or otherwise approved to treat CLN2 disease or the underlying cause of CLN2 disease. Current management is, therefore, limited to symptomatic relief and supportive care only, guided by the principles of paediatric palliative care (section 8.3).

Management goals and strategies fall under four broad themes: Medical management of the child; quality of life of the child and family; family support; and end-of-life care. Due to the progressive nature of CLN2 disease, the goals of care evolve over time. In the early stages, the overarching aim is to maintain function and involvement in mainstream activities as long as possible. As the disease progresses, the symptoms become more difficult to control, and patients are also at greater risk of new complications (such as pressure sores due to immobility and risk of aspiration of food due to swallowing difficulties). The therapeutic goal thus evolves to maintaining quality of life despite the loss of function. In the later stages of disease, increasing levels of multidisciplinary support are required for the patient, parents and family and discussion of end of life care involves planning and decision-making (section 8.3).

A wide range of drugs and other interventions are used to manage CLN2 symptoms and palliation, including seizures, dystonia, pain, secretions, gastrointestinal symptoms, mood changes, difficulty sleeping and problems associated with lack of mobility, vision and communication.

None of these interventions addresses the underlying cause of the disease, namely, TPP1 enzyme deficiency as a result of the defective genetic mutation(s).

The technology

Cerliponase alfa (brand name: BRINEURA®) is an enzyme-replacement therapy (ERT) indicated for the treatment of patients with NCL Type 2 (CLN2

disease). It is the first and only technology licensed to treat CLN2 disease in the EU and in the USA and represents an entirely new treatment option for patients with this ultra- rare, rapidly progressing, fatal condition. It is also the first enzyme replacement therapy delivered directly to the brain.

Cerliponase alfa is a recombinant form of human TPP1 (rhTPP1), a lysosomal enzyme, produced in mammalian Chinese Hamster Ovary (CHO) cells. The technology 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 (rhTPP1) cleaves tripeptides from the N-terminus of target proteins, and is expected to restore the deficient TPP1 activity in the brain caused by the genetic mutation (sections 2.1 and 2.2).

Cerliponase alfa is supplied as a sterile solution (30 mg/ml) for intracerebroventricular (ICV) infusion to the cerebrospinal fluid (CSF). Vials are supplied for single use only and need to be stored frozen at -20˚C. Each vial contains 150mg of cerliponase alfa in 5ml of solution. A 5ml excipient ICV solution without active ingredient is also administered to aid with the complete infusion of the cerliponase alfa. The recommended dose of cerliponase alfa for children over the age of 2 is 300mg administered every other week (section 2.3).

The price of a pack of cerliponase alfa (consisting of 2 150mg vials) is £20,107.00 excluding VAT.

Impact of cerliponase alfa

The safety and efficacy of cerliponase alfa has been assessed in two phase 3 studies: an open label, dose escalation clinical study (190-201) and a long-term extension study (190-202) in a total of 24 patients with CLN2 disease.

A total of 24 patients, aged 3 to 8 years, were treated with cerliponase alfa 300mg every other week. All 23 subjects who completed 48 weeks of treatment in study 190-201 continued to the 190-202 extension study. Study 190-202 is ongoing, with treatment being administered for a period of up to 240 weeks. For the purposes of this NICE submission, efficacy data on the primary outcome and safety data are available on all patients for 96 weeks of treatment, with data up to 120 weeks of treatment also available for some study outcomes in some patients.

Studies 190-201/190-202 used the aggregate of the motor and language domains of the CLN2 scale as the primary means to assess disease progression. Motor and language function are contained in the Hamburg and Weil-Cornell scales, two well-established and validated disease-specific measures of CLN2 disease progression; motor and language function are the

two domains that best track the rapid disease progression. Each domain encompasses scores of 3 (grossly normal) to 0 (profoundly impaired), for a total possible score of 6, with unit decrements representing milestone events in the loss of previously-attained functions of ambulation and speech. Each unit represents a clinically meaningful change for patients.

Efficacy evaluation

The treatment effect of cerliponase alfa was demonstrated by comparing progression of disease in the cerliponase alfa-treated patients in studies 190-201/190-202 with that of a natural history cohort of untreated 190-901 patients that satisfied the inclusion criteria for studies 190-201/190-202 and were matched to treated patients.

Results from the 190 -901 natural history control group demonstrate that CLN2 disease is a rapidly progressive neurodegenerative disease with predictable decline in motor and language function with an estimated mean rate of decline in the CLN2 score of 2 points per 48 weeks, equivalent to a complete loss of motor and language function in 3 years.

Responder analysis

The primary analysis of the primary efficacy endpoint in the pivotal study 190-201 was a response-based analysis. 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 300mg infusion). On the primary responder analysis:

- 87% (20/23) of patients receiving cerliponase alfa for 48 weeks had a less than 2-point decline in CLN2 clinical rating scale score, the average decline in natural history controls who matched the pivotal trial inclusion criteria[30]. This response rate significantly exceeded the expected rate of 50% for untreated patients (95% CI 66%, 97%; p = 0.0002); and

- The CLN2 scale score was stabilised in 65% (15 of 23) of patients who had no change or an improvement in score, indicating no loss of function. This significantly exceeded the predicted stabilisation rate of 25% in untreated patients (p <0.0001).

- The majority of declines took place in the initial 16 weeks of treatment, and most patients show stabilisation in the following weeks. No patient had a greater than 1 unreversed point decline after week 16.

Updated responder analyses from the long-term extension study 190-202 support the enduring treatment effect of cerliponase alfa. [redacted]

[redacted]

[redacted]

Rate of decline (slopes analysis)

The rate of decline in the CLN2 clinical rating scale, scaled to a 48 week time period, was conducted as an additional analysis of the primary endpoint. At the completion of Study 190-201, the mean rate of decline for CLN2 patients treated with cerliponase alfa was 0.40 points per 48 weeks, a statistically significant improvement when compared with a population rate of decline in untreated natural history patients of 2.0 points per 48 weeks ($p<0.0001$). Using the same method of slope analysis, the mean rate of decline in the Study 190-901 natural history population, which included patients who conformed to the key eligibility criteria for Study 190-201, was 2.09 points per 48 weeks.

As at the last interim analysis for Study 190-201/202 (1st November 2016 cut off), the mean (SD) rate of decline per 48 weeks during the 300mg dosing period was statistically significant in treated patients [redacted]. This compares favourably to the mean rate of decline of 0.40 observed in Study 190-201 at Week 48 and demonstrates broad-based stabilisation of CLN2 disease with treatment with cerliponase alfa, with majority of patients not seeing any additional decline after the initial 48 weeks of treatment.

Secondary efficacy endpoints

96 week results from Study 190-201/202 demonstrate a durable treatment effect and a broad-based stabilisation of disease over time that is not a function of a domain-specific treatment effect The benefits of cerliponase alfa were observed across all functional domains of the Hamburg scale, including vision and seizures in addition to motor and language function irrespective of the stage of disease at the time of treatment initiation. Crucially, the stabilisation of disease as evidenced by the score for all four domains was also seen when comparing the mean change from baseline score for cerliponase alfa-treated patients with all evaluable patients in the matched natural history control population.

Quality of Life

The clinical relevance of reducing the decline in function is supported by an improvement in health-related quality of life (HRQL) assessments, with mean increases from baseline in the total score of up to 10%, depending upon the instrument used. All HRQL assessments were carried out on the ITT population (n=23).

The CLN2 QoL instrument score shows a mean (SD) increase of 8.1 (14.33) points from study baseline to last observation in Study 190-201, an improvement of approximately 10.9%. [redacted]

[redacted]

Higher scores are indicative of improved quality of life; the results suggest that quality of life was stabilised in patients treated with cerliponase alfa.

Safety and tolerability profile

The mean (SD) exposure to cerliponase alfa was 117.0 (32.91) weeks for all doses (range 0.1 – 161.0) and 114.6 (30.26) weeks during the 300mg dosing period (range 0.1 – 144.9 weeks). All subjects in the efficacy population received at least 96 weeks of treatment at the 300mg dose.

Cerliponase alfa treatment was generally well-tolerated, with an acceptable safety profile in this population of patients with significant disease burden that is similar to that of other ERTs.

Consistent with the severity of the disease and a paediatric population, all 24 subjects reported at least 1 adverse event (AE) while on study treatment. There have been no deaths, treatment-related withdrawals or study discontinuations due to an AE in Study 190-201/202 (section 9.7.1).

[redacted]

[redacted]

[redacted]

[redacted]

Impact on the NHS – costs and health effects (QALYs)

The manufacturer developed a de novo economic model and cost-consequence analysis to estimate the impact of treatment with cerliponase alfa in terms of costs and effects (QALYs) on CLN2 patients, comparing established clinical management without cerliponase alfa (the "standard of care strategy") with cerliponase alfa + standard of care (the "cerliponase alfa strategy"). The analysis is conducted from an NHS/PSS perspective and consists of a lifetime time horizon (section 12.1).

The model is a Markov structure with 9 health states plus death and a 2 week cycle length. The starting population for the model is based on the expected

population of patients that would be treated with cerliponase alfa. In the base case scenario, CLN2 patients receiving standard medical care generated 4.97 Life Years and -0.97 QALYs during their lifetime (section 12.5.6). If treated with cerliponase alfa as an add-on therapy to standard care, these numbers increased to 45.01 life years and 29.45 QALYs, resulting in health gains of 40.04 Life Years and 30.42 QALYs, respectively (benefits discounted at 1.5%). Treatment with cerliponase alfa resulted in a mean lifetime costs of [redacted], a difference of [redacted](costs discounted at 1.5%) (section 12.5.6). Not treating CLN2 patients with ERT resulted in an average cost of £149,829 over a patient's lifetime. In the base case, the incremental cost-effectiveness ratio was [redacted] per QALY versus standard care. An alternative base case, where the where a discount rate of 1.5% was applied for benefits, and 3.5% was applied for costs, provided an ICER of [redacted] per QALY versus standard care. Scenario analyses provided ICERs in the range of[redacted] to [redacted] per QALY versus standard of care.

One-way and multi-way sensitivity analyses show that the most important parameters in the model affecting the model outcomes are the drug cost and the starting population in the model (sections 12.5.11 and 12.5.14). Choice of perspective and caregiver disutility had a minimal impact on the modelled outcomes.

Value for money

There are 34 known CLN2 patients in England. Assuming that [redacted] of these patients were to receive treatment with cerliponase alfa in the first year, and [redacted] out of the 5 patients newly diagnosed in this period with CLN2 disease were to receive treatment with cerliponase alfa, the total budget impact in year 1 (2018) would be [redacted] to treat [redacted] patients (sections 13.2 and 13.7). If [redacted] new CLN2 patients are born each year and [redacted] of all newborn patients are initiated on ERT at diagnosis, the total number of patients receiving treatment in year 5 (2022) would be approximately [redacted]. The total (undiscounted) budget impact in year 5 is consequently estimated to be [redacted]

Impact of the technology beyond direct health benefits

CLN2 disease has a significant impact on patients, caregivers and their families outside of the NHS/PSS, particularly in terms of financial difficulties, education, employment and socialisation. By stabilising disease measured by the domains of motor and language function, as well as number of grad-mal seizures and vision, it is anticipated that patients treated with cerliponase alfa could remain in education for longer and/or require less educational support. It is expected that the primary caregiver could stay in employment for longer, and be less dependent upon financial or welfare support. In turn, this is

expected to improve the lives of siblings and lead to better socialisation for patients, their caregivers and families (section 14.1).

It is further anticipated that treatment with cerliponase alfa will result in cost savings to the following three government departments or budgets: Education, Welfare and Local Government (section 14.2).

The costs of caring for a child or children affected by CLN2 disease, which are not reimbursed by the NHS/PSS, are considerable (section 14.3). Because of the rapid decline in function, motor and language skills in CLN2 patients, a large number of ordinary everyday objects need to be adapted for use, often at considerable cost of the caregiver/family. These include adaptations of bed, home and car, cost of specialist lightweight electric wheelchairs and other specialist equipment to aid mobility (section 14.3). These costs could no longer be required for patients stabilised on treatment.

The impact of the technology on the delivery of the specialised service

UK centres are participating in the ongoing clinical trials for cerliponase alfa (190-202, 190-203 and 190-502), continuing to develop and expand UK specialist knowledge of this very rare, life-limiting condition.

BioMarin is committed to investing in further research in this area. As part of its commitment to US and European regulators, the manufacturer is planning an observational study that will collect further clinical data on patients treated with cerliponase alfa over a 10-year period. In addition, BioMarin is in the process of setting up a disease awareness and early diagnosis campaign, designed to provide early gene testing which will shorten the time to diagnosis of both late-infantile CLN2 disease and other forms of epilepsy with paediatric onset.

Conclusions

In summary, all analyses performed comparing the Study 201/202 population treated with cerliponase alfa 300mg every other week to natural history controls show strong, clinically and statistically significant results in favour of treated subjects. These results were confirmed to be robust by multiple sensitivity analyses, which varied the methods of analysis and the criteria used to match natural history and treated patients. Results based on matching were similar to unmatched analyses and each analysis supported the underlying primary analysis.

The treatment effect of cerliponase alfa was shown to be durable, with stable or even improved outcomes in the subjects treated with 300 mg every other week for up to 136 weeks, versus steady and almost uniformly progressive

clinical decline in the natural history population The broad-based stabilization of CLN2 disease rating scores in patients on treatment with cerliponase alfa will provide them with the opportunity to gain new milestones and enable them and their families have as close to normal lives as possible.

The cost-effectiveness analysis found cerliponase alfa to offer significant benefits to patients. The effect of treatment with cerliponase alfa was shown to provide gains to life years and QALYs, and reduced the time spent in more severe stages of disease progression. Scenario analyses tested a wide range of assumptions employed in the base case analysis, including progression rates, starting populations, and utility values; the majority of scenario analyses demonstrated similar conclusions as the base case analysis.

Section A – Decision Problem

Section A describes the decision problem, the technology, ongoing studies, regulatory information and equality issues. A (draft) summary of product characteristics (SPC), a (draft) assessment report produced by the regulatory authorities (for example, the European Public Assessment Report [EPAR] should be provided.

- Cerliponase alfa (Brineura™) is the first and only technology licensed for the treatment of Neuronal Ceroid Lipofuscinosis (NCL) type 2 (a form of Batten disease, hereinafter referred to as 'CLN2 disease').
- CLN2 disease is an ultra-rare, inherited neurodegenerative disease that has a rapid and predictable course of progression from presentation in late infancy to death by early adolescence.
- CLN2 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.
- Cerliponase alfa is a recombinant form of human TPP1, an enzyme replacement therapy for TPP1. It is the only approved treatment that targets the underlying cause of CLN2 disease.
- Cerliponase alfa is supplied as a sterile solution (30 mg/ml) for intracerebroventricular (ICV) infusion to the cerebrospinal fluid (CSF). Each vial contains 150mg of cerliponase alfa in 5ml of solution. A 5ml excipient ICV solution without active ingredient is also administered to aid with the complete infusion of the cerliponase alfa.
- Cerliponase alfa is administered at a dose of 300mg every other week through an implanted ICV reservoir and catheter to deliver the treatment directly to cells in the brain, which are the primary cells affected by CLN2 disease.
- The safety and efficacy of cerliponase alfa has been assessed in two Phase 1/2 clinical trials: an open label, dose escalation study (190-201) and a long-term extension study (190-202). A total of 24 patients with CLN2 disease, aged 3 to 8 years, were treated with cerliponase alfa 300mg every other week.

- All 23 subjects who completed 48 weeks of treatment in study 190-201 continued treatment in study 190-202. 190-202 is ongoing. Efficacy and safety data are available up to 96 weeks of treatment for all patients the purposes of this submission to NICE.
- The treatment effect of cerliponase alfa was demonstrated by comparing the progression of disease in the cerliponase alfa-treated patients in studies 190-201/190-202 with that of a natural history cohort of 49 untreated patients that satisfied the inclusion criteria for studies 190-201/190-202.
- The treatment effect was maintained irrespective of the criteria for matching the population, all comparative assessments supporting the efficacy of cerliponase alfa.

1 Statement of the decision problem

The decision problem is specified in the final scope issued by NICE. The decision problem states the key parameters that should be addressed by the information in the evidence submission. All statements should be evidence based and directly relevant to the decision problem.

Table A1. Statement of the decision problem

	Final scope issued by NICE	Variation from scope in the submission	Rationale for variation from scope
Population	People with a confirmed diagnosis of CLN2	None	Not applicable
Intervention	Cerliponase alfa	None	Not applicable
Comparator(s)	Established clinical management without cerliponase alfa (including a multidisciplinary and multiagency approach to manage the symptoms and complications associated with CLN2).	None	Not applicable
Outcomes	The outcome measures to be considered include: symptoms of CLN2 (including visual function, seizures, myoclonus, dystonia, spasming, pain and feeding); disease progression (including quantitative measure such as the Hamburg scale, CLN2 rating scale, and the Weill Cornell LINCL score); need for medical care (including hospitalisation, emergency care and primary and secondary care appointments, and concomitant medication); mortality; adverse effects of treatment (including immune response and effects and complications related to treatment administration); health-related quality of life (for patients and carers, and including impact on families such as social and mental health and impact on siblings).	None.	Not applicable.
Subgroups to be considered	If the evidence allows, the following subgroups should be considered: based on disease progression; pre-symptomatic siblings with confirmed CLN2; and asymptomatic siblings with confirmed CLN2.	None	Asymptomatic and pre-symptomatic siblings with confirmed CLN2 will be considered as part of the economic evaluation.
Nature of the condition	Disease morbidity and patient clinical disability with current standard of care; impact of the disease on carer's quality of life; extent and nature of current treatment options.	None	Not applicable
Cost to the NHS and PSS, and Value for Money	Cost effectiveness using incremental cost per quality-adjusted life year; patient access schemes and other commercial agreements; the nature and extent	None	Not applicable

	of the resources needed to enable the new technology to be used.		
Impact of the technology beyond direct health benefits, and on the delivery of the specialised service	Whether there are significant benefits other than health; whether a substantial proportion of the costs (savings) or benefits are incurred outside of the NHS and personal and social services; the potential for long-term benefits to the NHS of research and innovation; staffing and infrastructure requirements.	None.	Not applicable.
Special considerations, including issues related to equality	If appropriate, the evaluation should include consideration of the costs and implications of changes in service delivery for CLN2, but will not make recommendations on service provisions. Guidance will only be issued in accordance with the marketing authorisation.	None.	Not applicable.

2 Description of technology under assessment

2.1 Give the brand name, approved name and when appropriate, therapeutic class.

Brand name: Brineura™

Approved generic name: Cerliponase alfa

Therapeutic class/ATC code: A16AB

2.2 What is the principal mechanism of action of the technology?

Cerliponase alfa is a recombinant form of human tripeptidyl peptidase-1 (rhTPP1), a lysosomal enzyme, produced in mammalian Chinese Hamster Ovary (CHO) cells.[1]

Cerliponase alfa is an enzyme replacement therapy (ERT) indicated for the treatment of neuronal ceroid lipofuscinosis (NCL) Type 2, otherwise known as CLN2 disease or tripeptidyl peptidase 1 (TTP1) deficiency.[1] CLN2 a type of NCL that is caused by pathogenic variants/mutations in each *CLN2 (TPP1)* gene and associated with functional deficiency of tripeptidyl peptidase 1 (TPP1).[1]

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 childhood.

2.3 Please complete the table below.

Table A2. Dosing Information of technology being evaluated[1]

Pharmaceutical formulation	Cerliponase alfa is supplied as a sterile solution (30 mg/ml) for intracerebroventricular (ICV) infusion in single use vials, which need to be stored frozen at -20˚C. Each ml of solution contains 30mg of cerliponase alfa. Each vial contains 150mg of cerliponase alfa in 5ml of solution. A 5ml excipient ICV solution without active ingredient is also administered to aid with the

	complete infusion of the cerliponase alfa. Each vial of excipient solution contains 44mg of sodium in 5ml of solution. Each vial of cerliponase alfa and ICV solution is intended for single use only.
Method of administration	Cerliponase alfa is administered to the cerebrospinal fluid (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. Cerliponase alfa must only be administered by a trained healthcare professional knowledgeable in ICV administration in a healthcare setting. 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.
Doses	The recommended dose is 300mg cerliponase alfa. Lower doses are recommended in patients less than 2 years of age.
Dosing frequency	The treatment is administered every other week, given by ICV infusion over approximately 4.5 hours.
Average length of a course of treatment	As cerliponase alfa is an enzyme-replacement therapy (ERT), it is expected that patients with CLN2 disease would be treated with it for the duration of their lives, subject to clinical judgement and/or the application of any protocols or criteria that would lead to a decision to discontinue treatment.
Anticipated average interval between courses of treatments	Not applicable.
Anticipated number of repeat courses of treatments	Not applicable.

Dose adjustments	No dose adjustments are anticipated.

3 Regulatory information

3.1 Does the technology have a UK marketing authorisation for the indication detailed in the submission? If so, give the date on which authorisation was received. If not, state the currently regulatory status, with relevant dates (for example, date of application and/or expected approval dates).

A European marketing authorisation for Brineura (cerliponase alfa) for the treatment of patients with CLN2 disease, also known as tripeptidyl peptidase 1 (TPP1) deficiency or NCL Type 2, was granted on 30th May 2017.

3.2 If the technology has not been launched, please supply the anticipated date of availability in the UK.

Cerliponase afa has been launched in the UK and is currently available to a limited number of patients receiving free drug via the expanded access programme and participation in an ongoing clinical trial. It is anticipated that cerliponase alfa will become readily available for all eligible patients as soon as NICE positive guidance is confirmed

3.3 Does the technology have regulatory approval outside the UK? If so, please provide details.

Cerliponase alfa has regulatory approval inthe European Union (EMA centralised approval) and in the United States of America (FDA approval). Cerliponase alfa has orphan drug designation in both regulatory approvals.

3.4 If the technology has been launched in the UK provide information on the use in England.

Cerliponase alfa is not routinely available in England. Clinicians submitted a request to treat a CLN2 patient via the Clinically Critically Urgent process but unfortunately the interim NHS England Commissioning position was to wait till completion of the NICE assessment.

4 Ongoing studies

4.1 Provide details of all completed and ongoing studies on the technology from which additional evidence relevant to the decision problem is likely to be available in the next 12 months.

Study 190-201 is the pivotal study and has completed. Study 190-201 is a Phase 1/2, multi-centre, open-label, dose-escalation study to evaluate safety, tolerability, pharmacokinetics, and efficacy of ICV BMN190 (the investigational name for cerliponase alfa) in patients with late-infantile CLN2 disease. The study included a dose escalation phase in a subset of patients to establish a maximally tolerated dose. Treatment was given for a period of 48 weeks.

The primary efficacy endpoint for Study 190-201 was the adapted CLN2 rating scale (in particular the score on the six-point motor-language scale [ML scale]).

The treatment effect of cerliponase alfa was demonstrated by comparing progression of disease on the CLN2 clinical rating scale in 23 patients aged ≥ 3 years old receiving cerliponase alfa 300mg every two weeks in Study 190-201 with that of untreated patients in a natural history study of comparable patients (Study 190-901 (see below).

In the primary responder analysis of the Intent-To-Treat (ITT) population:

- the CLN2 clinical rating scale score was stabilised, indicating no decline in motor or language function, in 65% (15 out of 23) of patients receiving cerliponase alfa, with either no change or an improvement in CLN2 rating scale score at 48 weeks;
- 87% (20 of 23) of patients receiving cerliponase alfa for 48 weeks had a response, (defined as a less than a 2-point decline, which is the average decline in matched natural history controls), with disease progression significantly slower than that expected in untreated patients (p=0.002).

Study 190-202 is a multi-centre, international extension study to Study 190-201 to evaluate the long-term efficacy and safety of cerliponase alfa over for a period of up to 240 weeks. All enrolled patients are receiving treatment with a 300mg dose of cerliponase alfa.

Study 190-202 is still ongoing. Data is available up to a total of 70 weeks (48 weeks in Study 190-201 and 25 weeks in Study 190-202, interim data cut-off of 15 October 2015) for all efficacy and safety endpoints. Data is available for 96 weeks of treatment (48 weeks in Study 190-201 and 48 weeks in Study 190-202, interim data cut off of 1 November 2016) for the primary efficacy

endpoint. The projected last study visit for Study 190-202 is 15 December 2020.

The most recent interim analysis of Studies 190-201/190-202 reaffirms the benefits of cerliponase alfa treatment observed in Study 190-201 alone. The benefit of cerliponase alfa was seen relative to matched natural history controls irrespective of the stage of disease at the time of treatment initiation and across all functional domains of the CLN2 rating scale, including vision and seizures in addition to motor and language function.

The clinical relevance of slowing the decline in function is supported by a broad-based improvement in QoL assessments, with mean increases from baseline in the total score for each questionnaire, which ranged from 4.3% to 10.9%. The clinical and HRQoL benefits of treatment with cerliponase alfa have been maintained for up to 97 weeks.

Clinical Study Reports (CSRs) for Study 190-201 (final) and 190-202 (interim) are available.

Study 190-901 is a retrospective, non-interventional analysis of the natural history of a control cohort of untreated patients with CLN2 disease in the independent DEM-CHILD registry. The cohort was selected by applying filters to match the eligibility criteria of subjects used in Study 190-201. The purpose of the 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 mean (SD, median) rate of decline in CLN2 clinical rating scale score for the untreated patient population analysed in Study 190-901 (n=41), expressed as points lost for each 48-week period, was 2.09 (95% CI 1.79, 2.40). This rate of decline is very similar to that reported in natural history studies in the literature and greater than the 2.0 point decline per 48 weeks, which was the conservative estimate used in the primary analysis for Study 190-201/190-202.

In addition, Study 190-203, a Phase 2 open-label study, is being conducted to assess safety, tolerability and disease progression in younger siblings of children enrolled in Study 190-201. In this study, cerliponase alfa will be administered by ICV infusion at a dosage of 300 mg every other week for 96 weeks. The study will enrol up to 5 subjects, each with a sibling who was enrolled in Study 190-201. Interim data from Study 190-203 is expected to be available once the study has completed (expected in December 2022).

Cerliponase alfa is currently being made available to treat an additional five (5) patients in the UK as part of an expanded access programme (190-502). The objectives of the 190-502 programme are:

- To provide access to cerliponase alfa to patients with CLN2 disease who cannot participate in a clinical trial; and
- To collect additional information on the safety and tolerability of cerliponase alfa administration in patients with CLN2 disease.

The 190-502 programme is not collecting efficacy outcomes data and is now a closed program. UK patients treated on the program are currently receiving free drug during the NICE assessment.

4.2 If the technology is, or is planned to be, subject to any other form of assessment in the UK, please give details of the assessment, organisation and expected timescale.

The Sponsor is in discussion in Wales on treatment for a new patient and will consider a submission to the Scottish Medicines Consortium (SMC) for review sometime in 2018. The timescales for this assessment are not yet known.

5 Equality

NICE is committed to promoting equality of opportunity and eliminating unlawful discrimination on the grounds of age, disability, gender reassignment, race, religion or belief, sex, and sexual orientation, and to comply fully with legal obligations on equality and human rights.

Equality issues require special attention because of NICE's duties to have due regard to the need to eliminate unlawful discrimination, promote equality and foster good relations between people with a characteristic protected by the equalities legislation and others.

Any issues relating to equality that are relevant to the technology under evaluation should be described.

Further details on equality may be found on the NICE website (http://www.nice.org.uk/aboutnice/howwework/niceequalityscheme.jsp).

5.1 Please let us know if you think that this evaluation:

- could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/will be licensed;
- could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;
- could lead to recommendations that have any adverse impact on people with a particular disability or disabilities

The Sponsor has not identified any issues relating to equity or equality that are relevant to this evaluation, other than to reiterate that CLN2 is a ultra-rare, multi-systemic and life-limiting disease for which there are no current treatment options other than management of symptoms and palliative care.

Given the rapidly progressing nature of CLN2 disease, the accompanying loss of function across all domains, deteriorating HRQL 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.

Most patients with CLN2 disease suffer from a range of disabilities and morbidity; treatment with cerliponase alfa has been shown to stabilise the disease in these patients, thereby reducing and/or delaying the burden of morbidity and disability in these patients and reducing burden on their families.

5.2 How will the submission address these issues and any equality issues raised in the scope?

Not applicable.

Section B – Nature of the condition

6 Disease morbidity

CLN2 disease is an ultra-rare, inherited neurodegenerative disease that has a rapid and predictable course of progression from presentation in late infancy to death by early adolescence.

- CLN2 disease usually manifests in late-infantile children (age 2-4 years) with the onset of seizures, typically in combination with a history of early language delay.
- CLN2 has a predictable, rapid course of physical, neurologic and mental decline that has been observed in cohorts of patients irrespective of gender or ethnicity.
- Disease progression is rapid, leading to the loss of language and walking ability, movement disorders (myoclonus, dystonia, and chorea), pain, progressive dementia, and eventual loss of vision, requirement of gastronomy feeding, and early death.
- Most children with CLN2 disease become bedridden and blind, and die between the age of 8 years and early adolescence, average mortality is 10 years old.
- CLN2 disease is an exceptionally rare condition, with estimated prevalence of 0.7 per million population and incidence of 0.5 per 100,000 live births based on literature reports.

6.1 Provide a brief overview of the disease or condition for which the technology is being considered in the scope issued by NICE. Include details of the underlying course of the disease, the disease morbidity and mortality, and the specific patients' need the technology addresses.

CLN2 disease is an ultra-rare, severe, neurodegenerative disease that is uniformly fatal in childhood. It is an inherited autosomal recessive condition caused by pathogenic variants/mutations in the *CLN2 (TPP1)* gene that lead to a functional deficiency of the lysosomal enzyme tripeptidyl peptidase 1 (TPP1)[2-4] 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.[2, 4, 5]

CLN2 disease is one of a group of diseases called neuronal ceroid lipofuscinoses (NCLs) that are all characterised by the accumulation of ceroid lipofuscin in neurones and other cells. To date, 13 different genes associated with NCLs have been identified.[2, 5]

CLN2 disease usually manifests in late infancy (age 2-4 years) with unprovoked seizures and/ or ataxia, often with a history of early language delay.[4, 6-8] Late infantile-onset CLN2 disease accounts for the vast majority (>95%) of patients in large cohorts of CLN2 disease/ TPP1 deficiency.[9, 10]

Late infantile-onset CLN2 disease has a predictable and rapid course, with rapid loss of motor function and language ability,[3, 4, 6] ataxia, movement disorders (myoclonus, dystonia and chorea), progressive dementia, and eventual loss of vision[3, 8, 11] and the ability to swallow.[8, 11] The rapid and early clinical decline is most evident in motor and language functions, starting at approximately 3 years of age and progressing to essentially no remaining motor and language function after approximately 2.5 years.[7, 8] Seizures, which can be generalised tonic-clonic, partial, myoclonic or absence seizures,[3, 11, 12] often become resistant to treatment. [11]

The majority of children with CLN2 disease become bedridden and blind, and die between the age of 8 years and early adolescence[7].[3, 8, 11, 12]

Course of disease

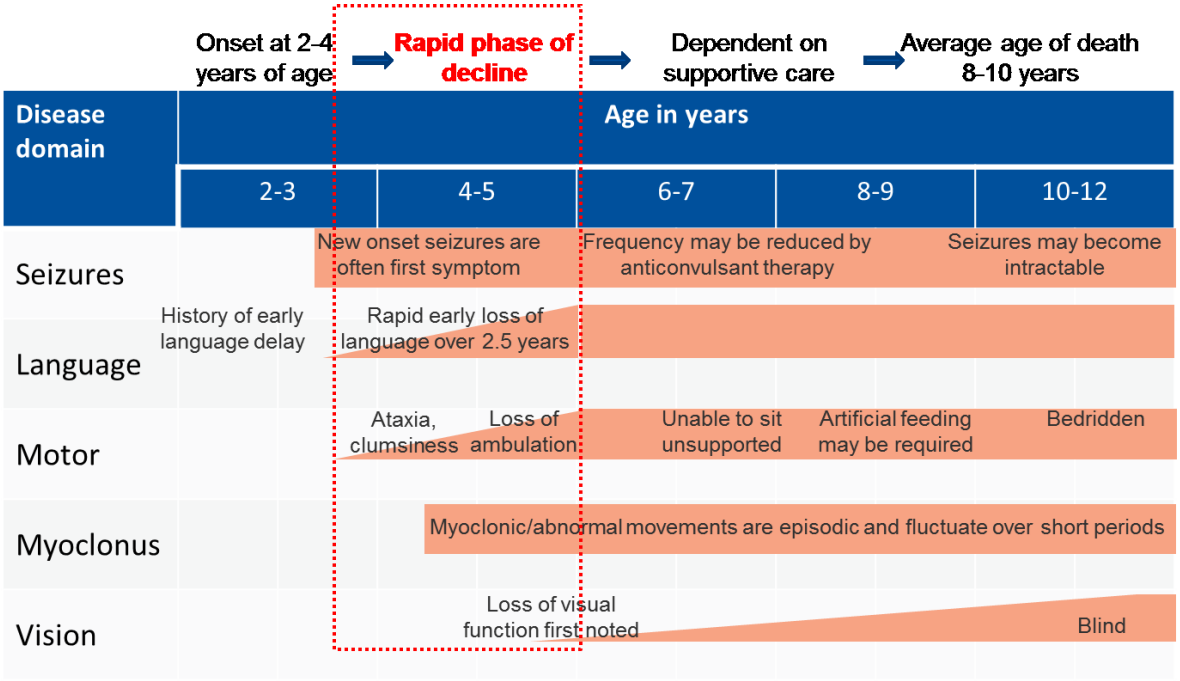
Based on studies and reviews that have been undertaken,[3, 6-8, 11] a very consistent and predictable time course of disease can be described:

- Seizures and ataxia occur around the age of 2-4 years, and can 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.
- 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.
- Whilst losing motor function and speech from the age of 4 patients will start to suffer myoclonus, dystonia and severe spasticity causing pain and distress.
- A decline in visual ability can occur from the age of about 4 years, when progressive psychomotor disturbances have already become obvious, leading to blindness within about 3 years. The decline in vision is slower than the decline in motor and language ability.

- Most children lose the ability to swallow, which may lead to the use of nutritional support through a nasogastric or gastrostomy tube.

The typical course of CLN2 disease is illustrated in Figure B1.

Figure B1. Typical course of CLN2 disease



As can be seen in

Figure B1, CLN2 disease is considered to be a disease of childhood dementia which remains undetected for the initial years of life and then suddenly manifests and deprives the patient of a functional life from early childhood. This consequently, has a devastating impact on the quality of life of parents, caregivers and families.[13] This impact is described in more detail in section 7.1.

A number of publications have described aspects of the time-course of disease progression in cohorts of patients with CLN2 disease of late infantile onset.[4, 6-8, 12, 14] The level of detail of reporting on different features of the natural history varies considerably between publications; however, there is remarkable consistency between publications on the timing of onset of symptoms, and it is clear that CLN2 disease has a predictable and rapid course of decline, irrespective of ethnicity or gender.

Evaluation of clinical progression in CLN2 disease

Hamburg and Weill Cornell scales

Two well-established validated disease-specific instruments have been used in expert centres over many years to evaluate the severity and quantify the progression of CLN2 disease:

- The Hamburg Scale, which was developed to enable a quantitative description of the course of CLN2 disease of late infantile onset over a number of years[8]
- The Weill Cornell scale, which was developed with a view to use in the evaluation of a novel therapeutic strategy being developed at the time.[4]

Figure B2 shows these rating scales side-by-side. Both scales were designed to be administered by healthcare professionals familiar with children with CLN2 disease, and in their full original forms each measures 4 single-item domains. Both scales measure 'walking and talking', which represent two key areas of function impacted during the rapid decline phase in CLN2 disease, and there is clearly commonality between the motor/gait and language items of the Hamburg and Weill Cornell scales. However, the other two items in each scale measure different aspects of disease. While the Hamburg scale assesses motor function (walking ability), language, visual function and grand-mal seizures, the Weill Cornell scale assesses gait (walking ability), language, myoclonus (motor function abnormalities) and feeding/swallowing. Within each domain of both scales, normal function is given a score of 3, a just noticeable abnormality is given a score of 2, a severe abnormality is given a score of 1, and a complete loss of function is given a score of 0. The total score for each scale thus ranges from 0-12.

Motor function (walking ability) and language function are the two items that best track the early and rapid progression of CLN2 disease,[8] and the most relevant domains to consider when evaluating the initial clinical progression of CLN2 disease. Other features of the disease included in the total Hamburg and Weill Cornell scales could reduce the sensitivity of progression:

- Although seizures present early in the course of the disease and continue to present through often reducing in the latter stage of disease, their severity and frequency could be affected by the use of various anti-epileptic drugs (AEDs)[8]
- Loss of vision usually occurs later in the course of the disease[8], and there is a central and retinal component to the manifestation of disease
- [redacted],[7]

- [redacted] [7]

[redacted]

Figure B2. Comparison of the Weill Cornell and Hamburg Scales

Hamburg Scale[8]		
Motor	3	Walks normally
	2	Frequent falls, obvious clumsiness
	1	No unaided walking or crawling only
	0	Immobile, mostly bedridden
Language	3	Normal (individual maximum)
	2	Has become recognisably abnormal
	1	Hardly understandable
	0	Unintelligible or no language
Visual	3	Recognises desirable object, grabs at it
	2	Grabbing for objects uncoordinated
	1	Reacts to light
	0	No reaction to visual stimuli
Seizures	3	No seizure in 3 months
	2	1-2 seizures in 3 months
	1	1 seizure per month
	0	>1 seizure per month

Weill Cornell Scale[4]		
Gait	3	Normal
	2	Abnormal* but able to ambulate independently
	1	Abnormal* requiring assistance
	0	Non-ambulatory
Language	3	Normal
	2	Abnormal speech with abnormal articulation or decreased vocabulary
	1	Barely understandable with severe dysarthria or very few meaningful words
	0	Unintelligible words or no speech
Myoclonus	3	None of myoclonus, chorea/tremor/athetosis, and upgoing toes
	2	One of myoclonus, chorea/tremor/athetosis, and upgoing toes
	1	Two of myoclonus, chorea/tremor/athetosis, and upgoing toes
	0	Myoclonus and chorea/tremor/athetosis, and upgoing toes
Feeding	3	No swallowing dysfunction
	2	Mild swallowing dysfunction
	1	Moderate swallowing dysfunction
	0	Gastrostomy tube-dependent

*(spastic or bradykinetic or ataxic)

The CLN2 clinical rating scale of motor and language function

The similarity of the Hamburg and Weill Cornell scales in terms of domains of gross motor function (Hamburg motor domain and Weill Cornell gait domain) and language function that are evaluated using a similar scoring system allows for data collected using either the Hamburg or the Weill Cornell scale to be combined to quantify clinical progression with motor function and language function each evaluated on a scale of 0-3, giving a total combined score between 0-6.

This CLN2 clinical rating scale of motor and language function has been adapted from the Hamburg and Weill Cornell scales and has been used in the study of natural history of CLN2 disease to date[6, 7].. In addition to prospective assessments by the clinician, the scale also allowed for retrospective assessment by the clinician based, not only on clinical records, but on reliable recordings and observations made by the patient's family. The steps in the scale therefore correspond to clinical milestone events that can be recalled in a very specific manner and accurately dated by parents/ guardians with reference to diaries, videos, notes, family photos, birthdays, holidays etc. [redacted].

The smallest possible change on the summary motor-language score of 1 point is clinically meaningful by design, as the rating scales represent changes in milestone activities in children that clinicians familiar with treating children with CLN2 disease are trained to assess and that parents/ caregivers recognise.

For example, a 1-point drop in the motor item between a rating of 3 and 2 is the difference between a child who can walk normally and one who falls often. Another 1-point drop would be a child who could no longer walk at least 10 metres, but can still move by some self-process (e.g. crawling). Similarly, clinically meaningful levels are present in the language item ratings: a 1-point drop in the language item between 3 and 2 is the difference between a child whose speech is normal for their age and one whose speech is clearly abnormal. Another 1-point drop would be a child who can barely be understood. Scores of 0 on either item indicate a complete loss of function.

Analysis examining the relationship between the CLN2 clinical rating scale and QoL measures has also validated the clinical meaningfulness of a 1 point change in the CLN2 clinical rating scale. Mixed effects regression analysis of CLN2 clinical rating scale and PedsQL data from Study 201/202 showed that a 1 point drop in the CLN2 clinical rating scale related to a 5.06 point drop in

the PedsQL. This 5.06 point drop is larger than the 4.5 point MCID for the PedsQL that has been established by Varni et al.[17]

Quantification of clinical progression

[redacted]

For most of the patients with longitudinal data (n=48), the entire course of the progression of disease from a score of 6 to a score of 0 was captured with evaluations at three month intervals, whereas for some patients (n=20) scores were only known over a narrower range.[4] The rate of decline was estimated for each patient by calculating the slope of the line drawn between the onset and end of decline for patients with a complete course of disease (last measurement of 6 and first measurement of 0), or between the first observation and last observation for patients with measurements over an incomplete range.[7]

Table B1 shows the results:

- [redacted]
- [redacted]
- [redacted]

Table B1. Rate of decline of combined motor and language scores (units/year) for longitudinal data[7]

Annualised slope (units/year)	All (n=[redacted])	6 to 0 (n=[redacted])	6 to 1 (n=[redacted])	5 to 1 (n=[redacted])
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Range (min, max)	[redacted]	[redacted]	[redacted]	[redacted]
Quartiles (25th, median, 75th)	[redacted]	[redacted]	[redacted]	[redacted]

6.2 Please provide the number of patients in England who will be covered by this particular therapeutic indication in the marketing authorisation each year, and provide the source of data.

The exact prevalence and incidence of CLN2 disease is unknown. It is an exceptionally rare condition, with estimated worldwide prevalence of 0.75 per million population and incidence of 0.5 per 100,000 live births based on literature reports.[3, 14, 18]

Williams, 2011[18] reported that the prevalence of CLN2 disease in the United Kingdom was 0.31+ per million of population, with a birth incidence of 0.78 per 100,000 live births.

Table B2 presents the data on prevalence and birth incidence of CLN2 disease available in published literature. The 2011 estimates provided by Williams[18] have been provided after consultation with local experts to maximise precision, but details of the methodology used are not provided.

Table B2. 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[18]	A Schulz, 2008^
West Germany	-	0.46	Moore et al, 2008[14]	Claussen, 1992
UK	0.31+	0.78	Williams, 2011[18]	Verity et al, 2010 and others
Portugal	0.15	-	Williams, 2011[18]	G Ribeiro, 2008^
Denmark	0.54	-	Williams, 2011[18]	J Ostergaard, 2008^
Sweden	0.43	-	Williams, 2011[18]	Uvebrant and Hagberg 1997
Norway	-	0.51	KSJ Systematic Review in development	Augestad, 2006

Czech Republic	-	0.36	Poupetova et al, 2010[19]	-
Netherlands	-	0.15	Moore et al, 2008[14]	Taschner et al., 1999
Italy	-	0.36	Moore et al, 2008[14]	Cardona and Rosati.1995
Canada (Newfoundland)	-	9	Moore et al, 2008[14]	-
Oman	-	4.9	Al-Maawali et al, 2012[20]	-
Argentina	0.1	-	Williams, 2011[18]	Noher de Halac, 2008^
May include variant cases of late infantile NCL, especially for birth incidence, as many studies precede availability of molecular diagnostic tests ^Personal communication				

The range seen in the literature is thus 0.1-0.75 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.[3]

Based on the estimated worldwide prevalence of 0.75 per million population, incidence of 0.5 per 100,000 live births, a total UK population of 53 million people, and 663,157 live births per annum in England and Wales, it is estimated that the number of CLN2 prevalent patients would be in the order of 40, with an estimated 4 new patients born with CLN2 disease per year.

In England, clinical and patient expert data shows that approximately 4 to 5 children are diagnosed each year and currently around 30 to 40 children are living with the condition. A recent survey conducted by the Batten Disease Family Association with expert physicians has identified 34 patients with CLN2 disease in England.

6.3 Please provide information about the life expectancy of people with the disease in England and provide the source of data.

The majority of children with CLN2 disease become bedridden and blind, and die between the age of 8 years and early adolescence[7, 3, 8, 11, 12].

Data which are available for patients with late infantile onset CLN2 disease are shown in Table B3, and these show an average age of death between 8 and 12 years, with few patients surviving into teenage years.

[redacted]

Table B3. Age of death for patients with late infantile onset CLN2 disease

Author, year	Age (years) at death	Comment
[redacted]	[redacted]	[redacted]
Moore et al., 2008[14]	Median: 8.6 Range: 4.0-12.9	Median (range) for 27/28 patients who died during the study
Steinfeld et al., 2002[8]	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[10]	Median: 9 SD: 2.45	Median and SD calculated for the 22 patients with late infantile onset who were dead at time of report. Publication reports 'lifespan >8.3±2.8' for 43 patients (including those still alive).

7 Impact of the disease on quality of life

CLN2 disease deprives the patient of a functional life from early childhood, which has a devastating impact on the quality of life of parents, caregivers and families.

- A systematic literature review did not identify any published information on the burden of CLN2 disease on patients, caregivers and families, or its impact on quality of life.
- In a comparison of the HRQoL of patients with CLN2 disease and the US general population using the Infant Toddler Quality of Life (ITQoL) instrument, CLN2 patients had much lower HRQL scores than the general population. The differences in mean score were clinically meaningful on most domains (including growth and development, physical abilities, temperament and moods, general behaviour and parental emotional impact).
- A study of the burden of CLN2 disease in 19 families in the UK and Germany demonstrated the wide-ranging physical, emotional, psychological, financial, educational and social challenges of caring for and living with a child with CLN2 disease.
- 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 5 hours per night;
    - Disease stage had an impact on caregiver burden.
    - Quality of life was considerably lower in the severe disease stage than the bereaved stage; the early stage and declining stages of CLN2 disease fell between the two extremes.
    - Caregivers reported significantly lower life satisfaction, lower happiness with their partner, on average 73.45 more caring hours per week and an average of 1.32 fewer hours sleeping per night, compared with parents of a non-sick or disabled child of the same age.
    - When measured by EQ-5D, the quality of life of caregivers of CLN2 disease patients was reduced by 0.12 points, compared to an age and gender-matched cohort in the general population.

- In the cerliponase alfa clinical trials, HRQoL was assessed using the PedsQL Generic Core Scale and Family Impact Modules, CLN2 disease-based QoL instrument and, in 190-202 only, the ED-5D-5L QoL instrument:

- The CLN2 disease-based instrument score shows a mean (SD) increase of 8.1 (14.33) points from study baseline to last observation in Study 190-201, an improvement of approximately 10.9%. [redacted].
- [redacted].

- Cerliponase alfa is the first and only technology licensed that targets the underlying cause of CLN2 disease.
- Cerliponase alfa can stabilise or slow the otherwise rapid and predictable decline measured by the CLN2 clinical rating scale allowing children to maintain motor and language function and the opportunity to gain new developmental skills and milestones. This clinical benefit is associated with improvements in the quality of life of patients, parents, caregivers and families.

7.1 Describe the impact of the condition on the quality of life of patients, their families and carers. This should include any information on the impact of the condition on physical health, emotional wellbeing and everyday life (including ability to work, schooling, relationships and social functioning).

As was shown in Figure B1, CLN2 disease exhibits a predictable and rapid course of decline which deprives the patient of a functional life from early childhood. The majority of children with CLN2 disease become bedridden and blind, and die between the age of 8 years and early adolescence.[7] Consequently, this disease has a devastating impact on the quality of life of patients, as well as parents, caregivers and families.[13]

Systematic literature review and review of patient organisation websites did not identify any information on the burden of CLN2 disease on patients, caregivers and families, or specifically on quality of life. Eleven key opinion leaders provided information on the nature of resources used in the management of CLN2 patients and some attempted to quantify those

resources. In addition, the manufacturer has undertaken analysis to investigate the correlation of severity of disease as measured by the Weill Cornell Medical College (WCMC) CLN2 clinical rating scale and health related quality of life (HRQL)[16] and the impact of CLN2 disease on caregivers and families in the UK and Germany.[13]

Finally, some information on the burden of NCL disease on families was reported in a needs assessment conducted by the Batten Disease Support and Research Association in the US and Canada.[21]

Impact of CLN2 disease on Health-Related Quality of Life

[redacted]

[redacted]

Table B4. [redacted]

Table redacted: academic in confidence

Impact of CLN2 disease on caregivers and families

A study of the burden of CLN2 disease in a survey of 19 families in the UK and Germany based on home surveys and focus groups 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.[13] This impact included:

- **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 change 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 carryng affected patients, anxiety/depression and exhaustion were all reported, as well as difficulties in looking after one's own health while caring for an affected child.[13]

  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 5 hours per night.[13]

- **Impact on family relationships**

  A few families reported an impact on their family relationships, with some family members distancing themselves since the child's diagnosis, while other families became closer. An impact on siblings was also reported, with some reporting that was difficult for the unaffected sibling to understand what was wrong with the affected sibling. Caregivers also reported finding it difficult to share time and attention between children; unaffected siblings were reported to display frustration and feelings of being left out. The support families experienced varied: one caregiver reported being very isolated, but other families said they had help from friends and family.[13]

- **Financial impact**

  Families described the financial impact of caring for a child with CLN2 disease, which included giving up work to care or being unable to return to work, having time off from work, additional expenses, 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 for a few years.[13]

  Secondary caregivers of patients with CLN2 disease reported a similar work impact as caregivers of cancer patients. The financial burden of CLN2 was severe and mainly driven by loss or reduced employment-related income as well as the necessity to self-fund healthcare needs of their child, including care equipment and adaptations to home and car.[13]

  A survey in the US and Canada of parents of patients with NCL, a third of whom had CLN2 disease, reported qualitatively very similar findings.[21]

- **Education**

  Education is important, particularly as an exercise that is both socialising and stimulating for children affected with CLN2 disease. All the affected children from the families participating in the manufacturer-commissioned survey/focus groups are 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.[13] However, many caregivers had experienced considerable difficulties and frustrations in getting access to the special needs schools or the support the child needed to manage mainstream school during the period when they did not have a clear diagnosis, even though the children had clearly needed specialist support.[13]

- **Social impact and isolation**

  The support received by families varies considerably – some reported felling isolated, while others derived a lot of support. The support received ranged from lack of family support and extreme loneliness, to receiving help from extended family, friends, schools and church 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.[13]

Some families reported opting for selective terminations when they found out their pregnancy was affected by CLN2 disease and having other siblings genetically tested. 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 a similar situation, and a few caregivers reported a change in their outlook on life and learning not to worry and be appreciative of life.[13]

Quality of life for family was assessed using EQ-5D-5L, the PedsQL Parent Report for Toddlers total score and the PedsQL family impact module (PedsQL-FIM) instruments. Disease stage (early/decline, severe and deceased) had an impact on caregiver burden: caregivers of children in the severe stage of CLN2 reported a greater number of hours caring and less sleep than both caregivers of children in the early/decline stage and of children who have deceased. Overall happiness reduced with disease stage, but life satisfaction was broadly similar across stages. Quality of life was considerably lower in the severe disease stage than the bereaved stage; the early stage and declining stages fell between the two extremes. PedsQL-FIM domain scores were lowest for families with a child in the severe 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, lower happiness with their partner, on average 73.45 more caring hours per week and on average 1.32 fewer hours sleeping per night, compared with parents with a non-sick or disabled child of the same age. These differences were all in the same direction when compared with parents who care for a sick or disabled child, although only statistically significant for hours sleep per night ($p<0.01$).[13]

7.2 Describe the impact that the technology will have on patients, their families and carers. This should include both short-term and long-term effects and any wider societal benefits (including productivity and contribution to society). Please also include any available information on a potential disproportionate impact on the quality or quantity of life of particular group(s) of patients, and their families or carers.

Enzyme replacement therapy (ERT) is standard of care for lysosomal storage disorders whose primary manifestations are predominantly peripheral. CLN2 disease requires direct administration of enzyme replacement to the CNS due

to the blood brain barrier that limits biodistribution of large molecules to the brain. The Sponsor has developed cerliponase alfa, a recombinant human TPP1 for the treatment of CLN2 disease.

Cerliponase alfa is the only licensed treatment that targets the underlying cause of CLN2 disease. Cerliponase alfa is an enzyme replacement therapy for the lysosomal enzyme TPP1, which is functionally deficient in CLN2 disease due to mutations in the *CLN2 (TPP1)* gene.

As ERT given directly to the central nervous system (CNS), cerliponase alfa is shown to restore TPP1 enzyme activity in the brain. As with other lysosomal storage disorders, correction of enzyme activity leads to cell survival and clinical stabilisation. It is therefore expected that treatment with cerliponase alfa will reduce the progressive, pathologic accumulation of lysosomal storage material, and improve signs and symptoms of the disease, stabilising the otherwise rapid and predictable decline measured by the CLN2 clinical rating scale allowing children to maintain motor and language function. As demonstrated by the clinical trial data presented in section 9.6.1, halting or slowing the decline of the CLN2 clinical rating scale score is clinically meaningful and is associated with improvement in the quality of life of patients, parents and families[16, 22]. This can allow children with the disease to maintain function potentially gain future development milestones and thus has a 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 with CLN2. Earlier treatment (of children/babies) is expected to lead to greater outcomes as patients may stabilise and never show the classic manifestation of disease thus developing similar to other children, gaining development milestones. Longer term registry data and the continuation of the 190-202 trial will follow patients over the next years and hopefully support these inferred outcomes.

8 Extent and nature of current treatment options

Diagnosis of CLN2 disease takes an average of 2 years from onset of symptoms due to their non-specific nature and low clinical awareness of the disease. Significant loss of function can occur between onset of symptoms and diagnosis. Current management is limited to symptomatic relief and supportive care.

- Diagnosis is based on laboratory testing following clinical suspicion. CLN2 disease can be definitively diagnosed either through demonstration of

deficient TPP1 activity or through identification of causative mutations in each allele of the *CLN2 (TPP1)* gene.

- There are currently no treatments licensed or otherwise approved to treat CLN2 disease or the underlying cause of CLN2 disease. Current management is limited to symptomatic relief and supportive care only, guided by the principles of paediatric palliative care.
- Management goals and strategies fall under four broad themes: Medical management of the child; quality of life of the child and family; family support; and end-of-life care. Due to the progressive nature of CLN2 disease, the goals of care evolve over time.
- A wide range of drugs and other interventions are used to manage CLN2 symptoms and palliation. These are used alongside non-pharmacological interventions including nutrition management, physiotherapy, speech and language therapy.
- None of these interventions addresses the underlying cause of the disease, namely, the defective genetic mutation(s), for which there is an urgent and unmet clinical need.
- Cerliponase alfa, an enzyme replacement therapy (ERT), is an innovative technology and represents a step-change in the management of CLN2 disease.
- Cerliponase alfa is the first pharmacological treatment approved for the treatment of CLN2 disease and the first treatment option (pharmacological or otherwise) that addresses the underlying biological cause of this severe, rapidly progressing and life-limiting disease.
- The goal of ERT is to restore the deficient TPP1 enzyme activity in the brain, reduce the accumulation of lysosomal storage material, restore cellular function and ultimately stabilise or slow the progression of disease.

8.1 Give details of any relevant NICE, NHS England or other national guidance or expert guidelines for the condition for which the technology is being used. Specify whether the guidance identifies any subgroups and make any recommendations for their treatment.

There are currently no NICE, NHS England or other national guidelines or guidance in place for the management of CLN2 disease.

In 2015, twenty-four disease experts (healthcare professionals and patient advocates) from 8 countries completed a survey comprising questions on CLN2 disease management and a subset met to discuss management practices. Their work, which has been presented[23] and recently published,[24] represents an important first step towards development of consensus-based expert professional management guidelines for CLN2 disease.

Management goals and strategies are consistent among these experts globally, and are guided by the principles of paediatric palliative care. Goals and interventions evolve as the disease progresses, with a shift in focus from maintenance of function early in the disease to maintenance of quality of life in the latter stages of disease. A multidisciplinary approach is critical for optimal patient care.[24] Further details about the global experts' approach to managing patients with CLN2 disease are presented in section 8.2.

8.2 Describe the clinical pathway of care that includes the proposed use of the technology.

Diagnosis of CLN2 disease

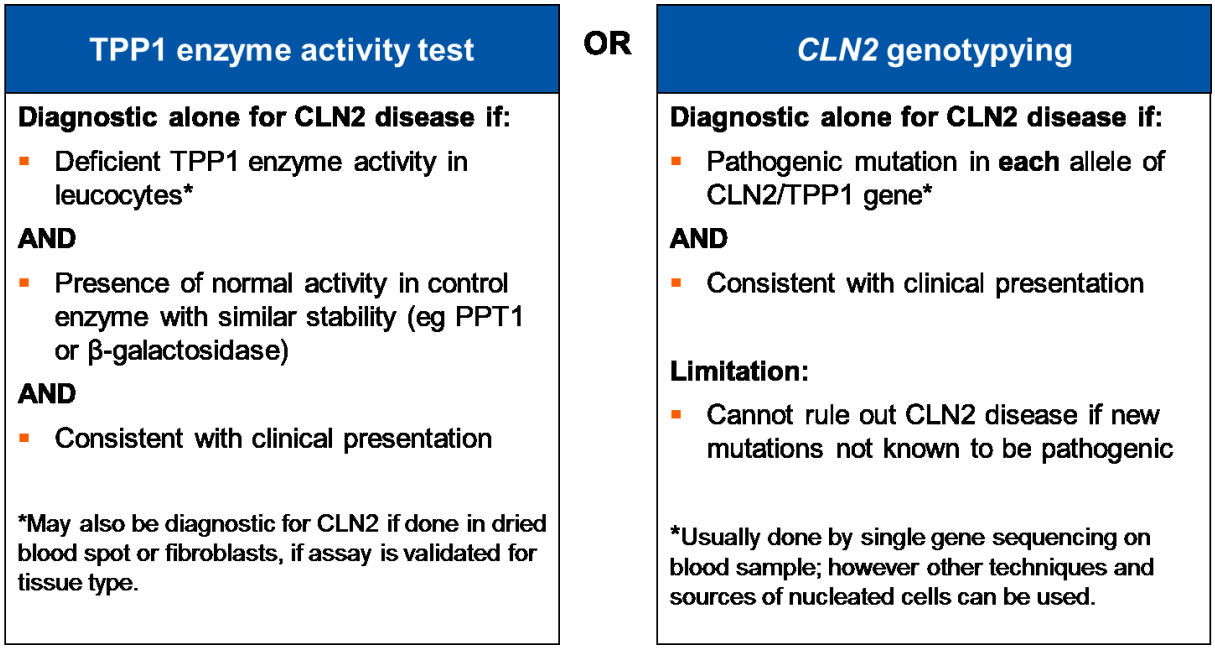
Early diagnosis of CLN2 disease is critical to ensure optimal care for patients and families but is challenging primarily due to a lack of disease awareness and the non-specificity of initial presenting symptoms. The diagnostic workup of isolated language delay in an otherwise "normal" toddler is limited 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 be misinterpreted as side effects of anticonvulsive medication initially.[24]

A delay of 2 to 3 years between symptom onset and diagnosis is common, and some children may appropriately be referred for speech therapy or have treatment for epilepsy prior to diagnosis. Most patients are diagnosed at approximately 5 years of age when substantial loss of function has already occurred. Timely diagnosis facilitates early initiation of disease-specific care, reduces the risk of inappropriate medications and enables families to make informed decisions as early as possible regarding the goals of care and family planning.[24] It is anticipated that greater awareness will result in earlier diagnosis, [redacted].

Diagnosis of CLN2 disease is based on laboratory testing following clinical suspicion.[25] CLN2 disease can be definitively diagnosed either through demonstration of deficient TPP1 activity or through identification of causative

mutations in each allele of the *CLN2 (TPP1)* gene, as shown in Figure B3.[25] 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 1 mutation or a variant of unknown significance. For this reason, an international expert panel stated that the gold standard diagnosis was the demonstration of both deficient TPP1 activity and identification of causative mutations in each allele of the *TPP1/CLN2* gene.[25]

Figure B3. Diagnosis of CLN2 disease



Management of CLN2 disease

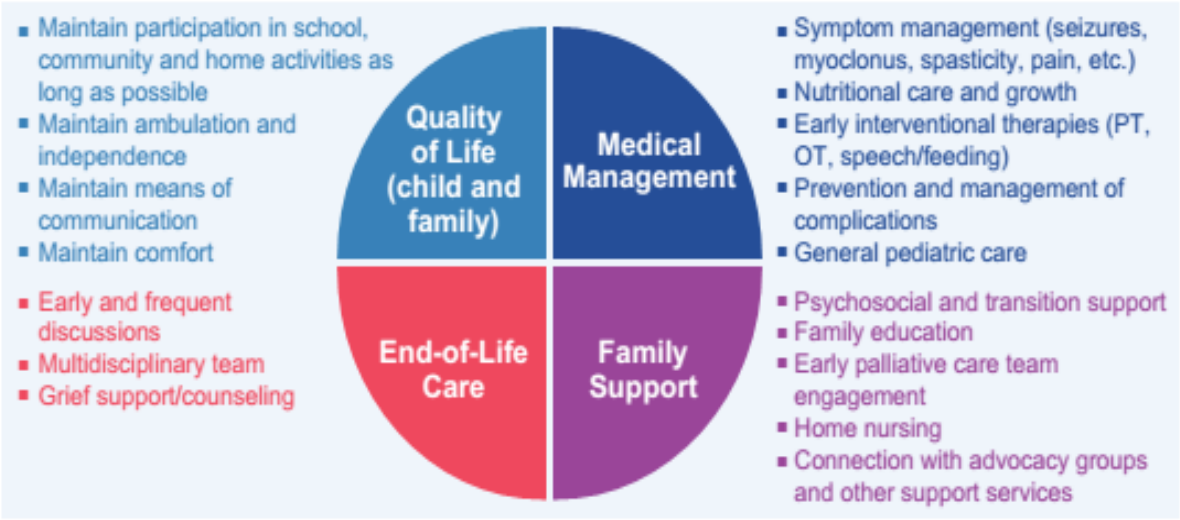
Apart from cerliponase alfa, there are no treatments licensed or otherwise approved to treat CLN2 disease. In the absence of treatments that target the underlying cause of CLN2 disease, current management is limited to symptomatic relief and supportive care. Management goals and strategies are consistent among experts globally, and are guided by the principles of paediatric palliative care.[23, 24] These management strategies have recently been published.[24]

Experts share common goals in CLN2 disease management that go well beyond medical management of the patient and extend to the support of the family beyond the life of the affected child.[23, 24] These can be considered under four main themes as laid out in Figure B4.

- Medical management of the child
- Quality of life of the child and family
- Family support

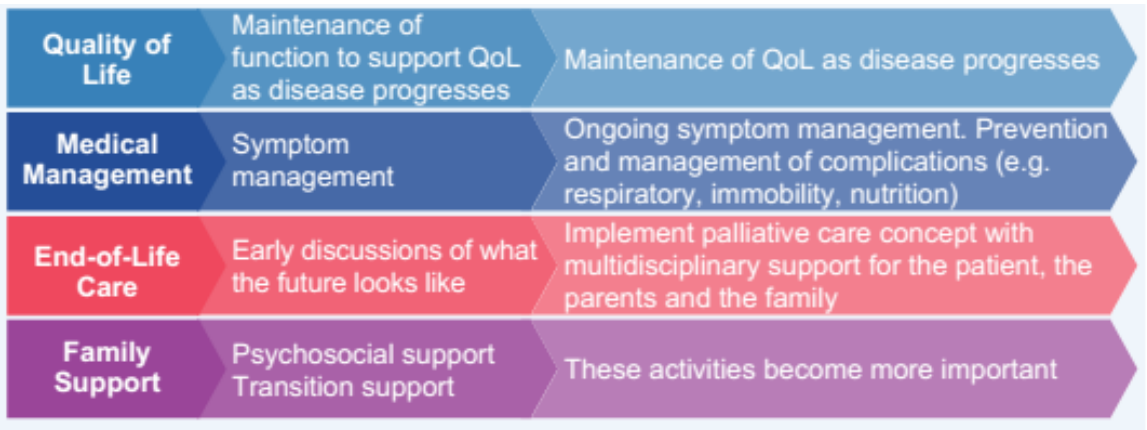
- End-of-life care.

Figure B4. A palliative care framework for the management of CLN2 disease[23, 24]



Due to the progressive nature of CLN2 disease, the goals of care evolve over time, as illustrated in Figure B5.[23] In the early stages of disease, the overarching aim is to maintain function and involvement in mainstream activities as long as possible. As the disease progresses, the symptoms become more difficult to control, and patients are also at greater risk of new complications such as pressure sores due to immobility and risk of aspiration of food due to swallowing difficulties. The therapeutic goal thus evolves to maintaining quality of life despite the loss of function. In the later stages of disease, increasing levels of multidisciplinary support are required for the patient, parents and family and discussion of end of life care involves planning and decision-making.[23, 24]

Figure B5. The evolving goals of care linked to disease progression



The multidisciplinary nature of care in CLN2 Disease

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 care professionals who are involved in the care of their patients as shown in Table B5.[23, 24] In many cases, there is also the need for one parent to give full-time commitment as a caregiver.[13, 21] There are also many adaptations needed to cope with a disabled child.[13, 21] This is explained in more detail in section 7.1 and section 10.1.1.

Table B5. Professions involved in the care of CLN2 patients and families[23, 24]

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

Pharmacological interventions

A wide range of drugs are used in the management of CLN2 symptoms and palliation. None of these drugs address or have an impact on the underlying cause of the disease, namely, the defective genetic mutation(s). In the majority of patients, multiple antiepileptic drugs and muscle relaxants are used for the treatment of seizures and movement disorders. It is also common to use analgesic medication for pain of different origins, and inhaled anti-muscarinic drugs to reduce secretions. These are 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.[13]

Further details on the management of specific symptoms (including seizures, movement disorders, pain management, gastrointestinal, nutrition and secretion management; ophthalmological interventions; occupational, speech and language therapy) are presented in Appendix 1, Section 17.1.

Use of cerliponase alfa

Once cerliponase alfa becomes routinely available, it is expected that clinicians would choose to prescribe it immediately following diagnosis, given the rapidly progressing nature of the disease and its devastating consequences.

As noted in section 7.2, cerliponase alfa is an ERT administered directly into the CNS. As such, it has been shown to restore TPP1 enzyme activity in the brain, addressing the underlying cause of the disease and reducing the progressive, pathologic accumulation of lysosomal storage materialin the brain and body so as to stabilise the rapid and predictable decline in motor and language function described in section 6.1. Relative to natural history patients, treated patients were also seen to have improvement in domains beyond motor and language function, with improvements in the seizure, and vision domains. As demonstrated by the clinical trial data presented in section 9.6.1, halting or slowing the decline of the CLN2 clinical rating scale score is associated with improvement in the quality of life of patients, parents and families.[16, 22] This enables children with CLN2 disease to maintain function and reach important new developmental milestones, and thus has a significant positive impact on the lives of patients, parents, caregivers and families.

8.3 Describe any issues relating to current clinical practice, including any uncertainty about best practice.

Delay from symptom onset to diagnosis

Difficulties in diagnosis, resulting in a delay from onset of symptoms to diagnosis and treatment, is a particular problem in clinical practice. As noted in section 8.2, diagnosis of CLN2 disease is based on laboratory testing following clinical suspicion.[25] Due to the low clinical awareness of the disease and non-specific initial symptoms there can often be a delay in clinical suspicion and diagnosis.[23-25]

Nickel et al.[6] reported an average delay of 21 months from the onset of symptoms to diagnosis. Williams et al.[24] noted that a delay of 2-3 years between symptom onset and diagnosis is common.

- The delay from onset to diagnosis reported by Perez-Poyato et al. (excluding a patient genetically screened because of a sibling with the disease) was from 0.5 to over 5 years, with a median of 2.3 years.[12]
- A survey of NCL experts indicated that the mean time from onset of symptoms to diagnosis of CLN2 disease was over 20 months and that in all patients diagnosis took more than 1 year from symptom onset.[25]
- The average age of diagnosis is thought to between 4 and 5 years of age, by which time the disease has progressed substantially and significant loss of function has occurred.[6, 24]

The prolonged use of a number of AEDs without early genetic testing can also result in delays in diagnosis, as well as the time taken for referral to an appropriate specialist. Once patients have been referred to a specialist in NCL diseases, diagnosis is rapid.[25]

[redacted]

Rarity of disease

The biggest issue concerning clinical practice is the rarity of CLN2 disease and the highly-specialised nature of the care and management required. This means that only a small number of very specialised centres - and healthcare professionals - have experience in managing such a rare condition.

Uncertainty in best practice

There is no real uncertainty about best practice in the management of CLN2 disease, either in the UK or elsewhere. International management strategies and practice are very similar, as the international consensus referred to in section 8.1 demonstrate.[24] Any variations in care that exist can be addressed by concentrating care in a small number of specialist centres, where specialist expertise and the full multi-disciplinary team is available.

[redacted]

8.4 Describe the new pathway of care incorporating the new technology that would exist following national commissioning by NHS England.

The introduction of cerliponase alfa will enable patients to have a standardised and centralised access to multi-disciplinary and specialist care within the existing Lysosomal Storage Disorder (LSD) network leading to better care and improved outcomes for patients. Currently, access to specialist care across England is patchy and highly variable, leading to sub-optimal outcomes for many patients and their families.

8.5 Discuss whether and how you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits, and whether and how the technology is a 'step-change' in the management of the condition.

Cerliponase alfa is a highly innovative, breakthrough technology which, once it becomes routinely available, will represent a step-change in the management of CLN2 disease.

CLN2 disease is a rapidly-progressing, life-limiting disorder causing extensive morbidity and a rapid loss of function, reduced quality of life and early mortality. There are currently no available treatment options specifically to treat CLN2 and none that correct the underlying biological cause of the condition. As noted in section 8.2 above, current care is symptomatic only. The available management options consist of supportive or palliative care, which includes both medication and other interventions to relieve symptoms, maintain function and health-related quality of life. CLN2 disease therefore represents a significant unmet medical need.

The main innovation of associated with cerliponase alfa is the ICV route of delivery. As this is the first protein/ERT delivered via infusion directly to the brain, UK clinicians have suggested that this paves the way for the future treatment of other neurological conditions, which not been possible before now due to the difficulties associated with crossing the blood-brain barrier.

In addition to the ICV route of administration, cerliponase alfa is an innovative technology and represents a step-change in the management of CLN2 because:

- It is the first and only treatment approved for the treatment of CLN2 disease
- It is approved for use in CLN2 in patients of all ages;
- It is the first and only treatment option (pharmacological or otherwise) that addresses the underlying biological cause of this severe, rapidly-progressing and life-limiting disease. Cerliponase alfa is an ERT; the goal of ERT in CLN2 is to restore the deficient TPP1 enzyme activity in the brain, reduce the accumulation of lysosomal storage material, restore cellular function and ultimately stabilise or slow the progression of disease.
- It is the first and only treatment option to have a positive impact on motor and language function in CLN2 in clinical trials, stabilising or halting the rate of decline as measured by the CLN2 clinical rating scale in [redacted]% of patients [redacted] in Study 190-201/202 up to 96 weeks of treatment.[22, 26, 27]

8.6 Describe any changes to the way current services are organised or delivered as a result of introducing the technology.

The introduction of cerliponase alfa will enable patients have a standardised and centralised access to multi-disciplinary and specialist care within the existing LSD network leading to better care and improved outcomes for patients. Currently, access to specialist care across England is patchy and highly variable, leading to sub-optimal outcomes for many patients and their families.

There are several particular requirements associated with the administration of cerliponase alfa that must be adhered to:

- Cerliponase alfa can only be administered by the ICV route and by a healthcare knowledgeable in ICV administration[1];
- Creating the port/ICV access will constitute a surgical procedure in its own right – this must be done prior to the first infusion;
- Treatment involves infusions administered every two weeks directly to the brain in a hospital setting;
- The complete infusion, including cerliponase alfa and the required ICV solution, is given over a period of approximately 4.5 hours[1];
- Pre-treatment of patients with antihistamines with or without antipyretics is recommended 30 to 60 minutes prior to the start of infusion[1];

Very few specialist centres are able to administer treatment and/or provide ongoing care for patients with CLN2 disease because the condition is so rare.

Centres also need to be experienced in the administration of ERT, because of the potential for infusion-related aderse events (AEs). However, it should be possible to accommodate these requirements within the existing LSD service.

As such, BioMarin does not anticipate any changes to the way in which current LSD services are organised or delivered as a result of introducing cerliponase alfa. Proposed expert reference centres are currently considered to be Great Ormond Street Hospital and Manchester Childrens Hospital.

8.7 Describe any additional tests or investigations needed for selecting or monitoring patients, or particular administration requirements, associated with using this technology that are over and above usual clinical practice.

No additional tests or investigations are needed for selecting or monitoring patients, over and above that which is required for the administration of ERTs generally.

Cerliponase alfa administration differs from other ERTs only in that there is the need to create the infusion port/ICV access prior to first infusion, and aseptic technique must be strictly observed during preparation and administration of the infusion.[1]

8.8 Describe any additional facilities, technologies or infrastructure that need to be used alongside the technology under evaluation for the claimed benefits to be realised.

Cerliponase alfa and the ICV solutions are supplied and stored frozen at -20C. Both the cerliponase alfa and ICV solution vials must be thawed at room temperature for approximately 60 minutes prior to infusion. Once completely thawed, the solutions must be used immediately (see sections 4.2, 6.3 and 6.4 of the SmPC).[1]

8.9 Describe any tests, investigations, interventions, facilities or technologies that would no longer be needed with using this technology.

Not applicable.

Section C – Impact of the new technology

9 Published and unpublished clinical evidence

Section C requires sponsors to present published and unpublished clinical evidence for their technology.

All statements should be evidence-based and directly relevant to the scope. Reasons for deviating from the scope should be clearly stated and explained.

This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal' section 5.2 available from www.nice.org.uk/guidance/ta.

9.1 Identification of studies

Published studies

9.1.1 Describe the strategies used to retrieve relevant clinical data from the published literature. Exact details of the search strategy used should be provided in the appendix.

A comprehensive search was conducted to identify all published studies of any therapy used for the treatment of patients with CLN2 disease or TPP1 deficiency. Four strategic approaches were used:

- A search of the published literature via electronic databases conducted on 23rd January 2017:
  - MEDLINE, including MEDLINE Daily, MEDLINE In-Process and Epub via Ovid SP
  - Embase via Ovid SP
  - The Cochrane Library Databases via the Wiley Online Platform
    - Cochrane Database of Systematic Reviews (CDSR)
    - Cochrane Central Register of Controlled Trials (CENTRAL)
    - Database of Abstracts of Reviews of Effects (DARE)

- A manual search of congress proceedings from the last two years, conducted in February 2017:
  - International Conference on Neuronal Ceroid Lipofuscinosis (2016)
  - WORLD Symposium (2015, 2016)
  - International Child Neurology Congress (2016)
  - Society for the Study of Inborn Errors of Metabolism Meeting (2016)
- Manual checking of reference lists of all relevant systematic literature reviews (SLRs) and (network) meta-analyses identified in the course of the review
- A manual search of the European Medicines Agency (EMA) website for European public assessment reports (EPAR) of relevant treatments, conducted on 23rd August 2017

Full details of each of these search strategies are provided in the appendix, section 17.2.

Following the systematic review, a supplementary search was run in the internal BioMarin database in August 2017 to identify any relevant published records which became available after the systematic searches were run. The results of this search are presented in section 9.6.1.

Unpublished studies

9.1.2 Describe the strategies used to retrieve relevant clinical data from unpublished sources.

An additional search using the World Health Organization International Clinical Trials Registry Platform (WHO ICTRP) was conducted on 13th February 2017 to identify any unpublished studies of patients with CLN2 disease or TPP1 deficiency. Relevant studies were cross-checked against the results from the database searches (Section 9.1.1) to avoid duplication of included studies.

9.2 Study selection

Published studies

9.2.1 Complete table C1 to describe the inclusion and exclusion criteria used to select studies from the published literature. Suggested headings are listed in the table below. Other headings should be used if necessary.

Before conducting the literature searches, eligibility criteria were defined for the inclusion and exclusion of results. These criteria are presented in Table C1.

Table C1. Selection criteria used for published studies

Domain	Inclusion criteria	Exclusion criteria	Justification
Population	Patients with any variant of CLN2 disease or TPP1 deficiency	Individuals without any variant of CLN2 disease or TPP1 deficiency	This is the patient population relevant to the NICE decision problem for this submission.
Interventions	Any intervention	There were no limits regarding interventions.	Due to the lack of existing treatments, a broad approach with regards to both intervention and comparator was adopted.
Comparators	Any or none	There were no limits regarding comparators.	
Outcomes	Any efficacy or safety outcomes	Studies where outcomes were not reported separately for the population of interest	These outcomes encompass the clinical outcomes specified as relevant in the NICE decision problem for this submission.
Study design	Any of the following: RCTs Interventional non-RCTs, including single-arm clinical trials and non-randomised comparative studies Observational studies Retrospective studies Case reports and case series Registries	Any other study design, which included: Economic evaluations Editorials, notes, comments or letters Narrative or non-systematic literature reviews	The study designs specified as eligible for inclusion were those considered most likely to report relevant data for this SLR.

Other considerations	Articles published in or after 1997 including patients diagnosed in or after Studies with full texts in the English language Human patients	Articles published prior to 1997 or including only patients diagnosed prior to 1997 with no subsequent genetic or enzymatic confirmation Studies with full texts not in the English language Studies in non-human patients only	The loci of CLN2 mutations and their involvement with TPP1 was not discovered until 1997 and so diagnoses before this date could not reliably be confirmed as CLN2 without subsequent genetic or enzymatic analysis.[28, 29] Therefore, a cut-off date of 1997 was applied, in order to be sure that all identified results referred to the patient population of interest. The review team also did not have the linguistic capability to review non-English language articles; however, studies were not limited to those conducted in specific geographical locations. Additionally, studies on non-human subjects were not considered relevant to the decision problem.

ABBREVIATIONS: CLN2: neuronal ceroid lipofuscinosis type 2; RCT: randomised controlled trial; TPP1: tripeptidyl-peptidase 1.

9.2.2 Report the numbers of published studies included and excluded at each stage in an appropriate format.

The results of the literature searches are presented in a PRISMA diagram in Figure C. Briefly, the electronic database searches identified a total of 2,471 records. After screening of titles and abstracts, 182 relevant citations were selected. Following a detailed evaluation of the full texts of these articles, 19 records were identified that met the review inclusion criteria.[30-48] 44 records were identified through supplementary searches, of which 14 met the inclusion criteria [49-52]. In total 33 publications reporting on 16 unique studies were ultimately included in the review. No RCTs were identified however 5 non-RCTs were included (from 21 publications)[41-45, 47, 48, 51-63] and the majority of evidence was identified in the form of 11 case studies (from 12 publications).

Unpublished studies

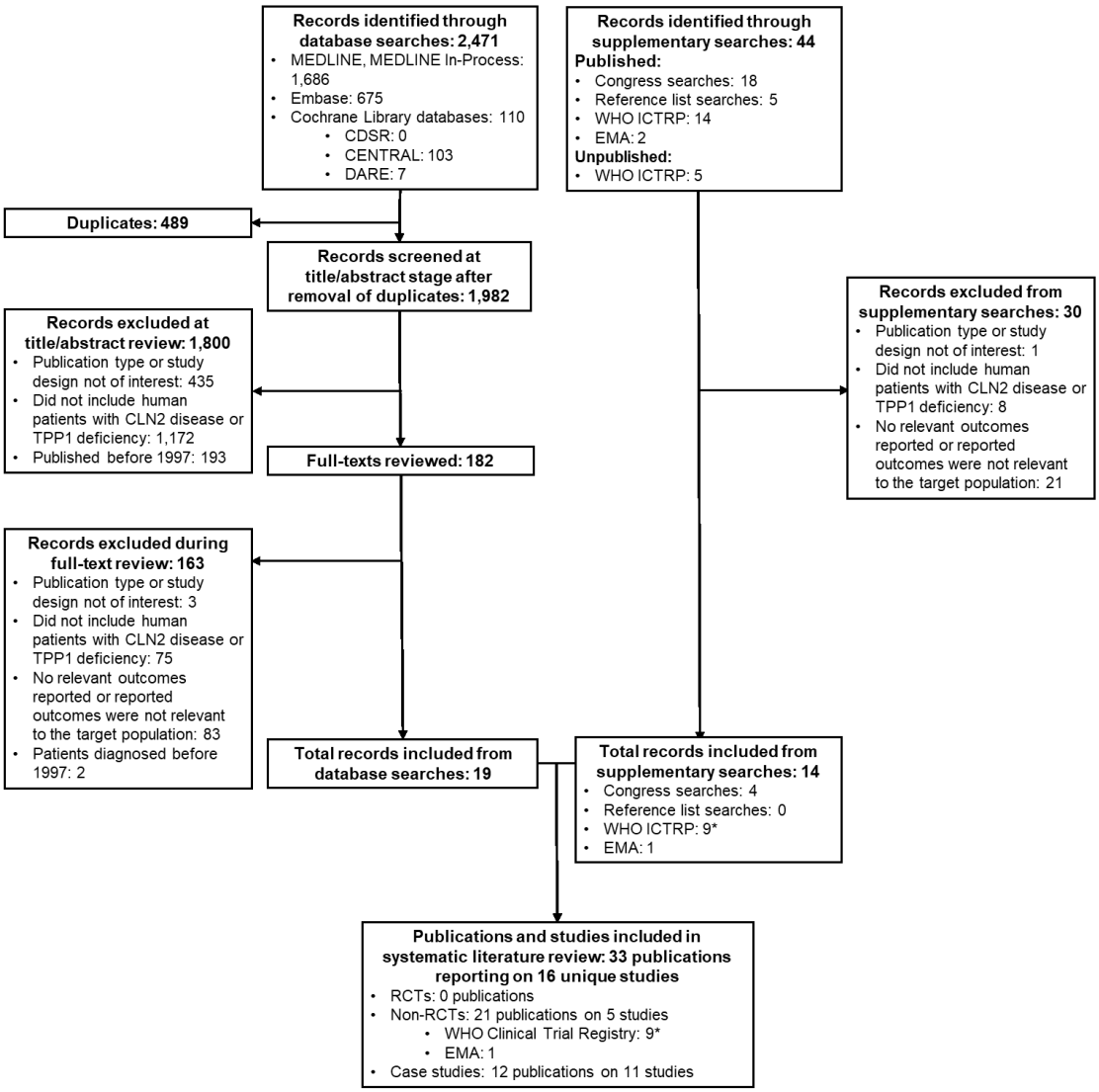
9.2.3 Complete table C2 to describe the inclusion and exclusion criteria used to select studies from the unpublished literature. Suggested headings are listed in the table below. Other headings should be used if necessary.

The eligibility criteria used for the screening of published studies were also used to screen unpublished studies. For full details of the eligibility criteria, please refer to Table C1 in section 9.2.1.

9.2.4 Report the numbers of unpublished studies included and excluded at each stage in an appropriate format.

44 records identified through supplementary searches included 5 unpublished records reporting on 4 unique studies.[59-63] However, as no relevant outcomes were reported, these studies were ultimately excluded from the review.

Figure C6. PRISMA flow diagram of clinical SLR



*The nine studies included from WHO ICTRP provided supplementary data to three non-RCT publications.

ABBREVIATIONS: CLN2: neuronal ceroid lipofuscinosis type 2; RCT: randomised controlled trial; TPP1: tripeptidyl-peptidase 1; WHO ICTRP: World Health Organization International Clinical Trials Registry Platform.

9.3 Complete list of relevant studies

The sponsor should provide a PDF copy of all studies included in the submission. For unpublished studies for which a manuscript is not available,

provide a structured abstract about future journal publication. If a structured abstract is not available, the sponsor must provide a statement from the authors to verify the data provided.

9.3.1 Provide details of all published and unpublished studies identified using the selection criteria described in tables C1 and C2.

Details of the 16 published studies that met all of the pre-defined inclusion criteria of this review were collected and are reported in Table C2. Due to differences in the methods of diagnosis for suspected CLN2 patients in the literature, studies on patients with genetically or enzymatically confirmed CLN2 disease (n=13) are presented separately to those studies that are based solely on a clinical definition of LINCL (n=3).

The five records reporting on 4 unique unpublished trials that were identified during the searches of the WHO ICTRP could not be associated with any published results and therefore failed to meet the inclusion criteria of this review. However, due to their relevance to the decision problem, the unpublished studies that were associated with (expected) data were recorded separately (Table C3). Considering their particular relevance to this submission, the methodology of the ongoing trials of cerliponase alfa (Study 190-502 and 190-203) are presented in more detail in section 9.4.1; the other two unpublished studies do not investigate cerliponase alfa and so are not described further in this submission.

Table C2. List of relevant published studies

Primary study reference	Study type	Study name (acronym)	Population	Treatment	Comparator	Results reported	Supplementary reference(s)
BioMarin studies							
CLN2 disease							
Schulz 2016a[51]	Interventional study	Study 190-201 EUCTR2012-005430-11-GB NCT01907087	Patients with CLN2 disease (3–16 years of age)	Cerliponase alfa	N/A	Safety, tolerability, pharmacokinetic, and efficacy	NCT01907087[64] EUCTR2012-005430-11-GB[65] Schulz 2016b[52] Schulz 2016c[47] Schulz 2016d[48]
Schulz 2016a[51]	Interventional study	Study 190-202 EUCTR2014-003480-37-GB NCT02	Patients with CLN2 disease (3–16 years of age)	Cerliponase alfa	N/A	Safety and efficacy	NCT02485899[54] EUCTR2014-003480-37-GB[53] Schulz 2016b[52] Schulz 2016c[47] Schulz 2016d[48]

Primary study reference	Study type	Study name (acronym)	Population	Treatment	Comparator	Results reported	Supplementary reference(s)
		485899					
Non-BioMarin studies							
CLN2 disease							
Barisic 2003[30]	Case study	N/A	1 patient with CLN2 disease	Valproic acid and clobazam, supplemented with lamotrigine	N/A	Effectiveness	N/A
				L-Dopa/Carbidopa and tetrahydrobiopterin (in addition to antiepileptic drugs)	N/A	Effectiveness	
				Trihexyphenidyl	N/A	Effectiveness	
Eto 2016[49]	Case study	N/A	1 patient with CLN2 disease	Intraventricular enzyme replacement therapy	N/A	Effectiveness	N/A
Johannsen 2016[37]	Case study	N/A	2 patients with CLN2 disease	Valproate (and ethosuximide)	N/A	Safety	N/A
				Fluid replacement, analgesia, antipyresis, antiepileptics, sedation, baclofen, dantrolene, trihexphenidyl, and bromocriptine	N/A	Effectiveness	
Le 2012[31]	Case study	N/A	1 patient with CLN2 disease	Ketogenic diet	N/A	Effectiveness	N/A
				Vagal nerve stimulator	N/A	Effectiveness	

Primary study reference	Study type	Study name (acronym)	Population	Treatment	Comparator	Results reported	Supplementary reference(s)
				Carbidopa-levodopa therapy	N/A	Effectiveness, safety	
Lehwald 2016[41]	Observational study	NCT01966757 IRB 13-00376	16 children with CLN2 disease	Exogenous melatonin	N/A	Perceived benefit	NCT01966757[55]
Lorenz 2002[32]	Case study	N/A	2 patients with CLN2 disease*	Oxcarbazepine	N/A	Effectiveness, safety	Lorenz 2004[33]
				Baclofen / tetrazepam	N/A		
				Delta 9-THC	N/A		
				Piracetam / zonisamide	N/A		
				Valproic acid	N/A		
				Dopa	N/A		
				Meperidine	N/A		
Mohamed 2015[35]	Retrospective chart review	N/A	1 patient with CLN2 disease	Antiepileptic drugs (not specified)	N/A	Effectiveness	N/A
Ravi 2016[50]	Case series	N/A	6 patients with CLN2 disease*	Ketogenic diet	N/A	Tolerance	N/A
Selden 2013[42]	Single-arm, interventional phase 1 study	NCT00337636	4 patients with CLN disease	Human central nervous system stem cells (with immunosuppression post-surgery)	N/A	Safety and preliminary efficacy	NCT00337636[56]
Worgall 2008[43]	Single-arm, interventional	NCT00151216	10 children with CLN2	Adeno-associated virus serotype 2 vector	Data from 4 independent	Safety and preliminary	NCT00151216[57] Crystal et al.

Primary study reference	Study type	Study name (acronym)	Population	Treatment	Comparator	Results reported	Supplementary reference(s)
	phase 1 study	0401007010	disease	expressing human CLN2 cDNA	patients with LINCL as untreated control group (plus, 12 patients from a study published by Steinfeld et al. (2002))	efficacy	(2004)[44] Souweidane et al. (2010)[45] NCT01161576[58]
Yuza 2005[40]	Case study	N/A	1 patient with CLN2 disease	Bone marrow transplant	N/A	Effectiveness	N/A
LINCL							
Rubenstein 2005[36]	Retrospective chart review	N/A	1 patient with LINCL	Ketogenic diet	N/A	Efficacy	N/A
Veneselli 2001[39]	Case series	N/A	5 patients with LINCL	Adrenocorticotropic hormone	N/A	Effectiveness	N/A
Yamada 2002[38]	Case study	N/A	1 patient with LINCL (Jansky-Bielschowsky disease)	Valproic acid, clonazepam, diazepam	N/A	Effectiveness	N/A

ABBREVIATIONS: CLN2: genetically/enzymatically confirmed neuronal ceroid lipofuscinosis type 2; LINCL: clinically confirmed late infantile neuronal ceroid lipofuscinosis; N/A: not applicable.

*The diagnosis of CLN2 disease was not genetically or enzymatically confirmed.

Table C3. List of relevant unpublished studies

Primary study reference	Study name (acronym)	Population	Treatment	Comparator	Results to be reported	Supplementary reference(s)
CLN2 disease						
NCT02963350[59]	Study 190-502	Patients with CLN2 disease (≥2 years of age)	Cerliponase alfa	N/A	Safety and tolerability	N/A
NCT02678689[62]	Study 190-203 EUCTR2015-000891-85-DE	Patients with CLN2 disease (≤17 years of age)	Cerliponase alfa	N/A	Safety, tolerability, and efficacy	EUCTR2015-000891-85-DE[63]
NCT01414985[60]	1005011054	Patients with CLN2 disease (3–18 years of age)	Adeno-associated virus serotype rh. 10 vector expressing human CLN2 cDNA	N/A	Safety and efficacy	N/A
NCT01238315[61]	CL-N03-NCL	Patients with CLN1 or CLN2 disease (6 months to 6 years of age)	Human central nervous system stem cells	N/A	Safety and preliminary efficacy	N/A

ABBREVIATIONS: CLN1: genetically/enzymatically confirmed neuronal ceroid lipofuscinosis type 1; CLN2: genetically/enzymatically confirmed neuronal ceroid lipofuscinosis type 2.

BioMarin database search

Following the systematic review, a limited search was undertaken to identify any relevant articles which became available since the date the searches were run. Two additional records published after the search date were identified. Details of these two publications, that met all of the pre-defined inclusion criteria of this review were collected and are reported in Table C4.

Cherukiri 2017

Cherukuri et al. (2017) report on the immunogenicity of cerliponase alfa in patients with CLN2 treated as part of Study 190-201 (see section 9.4). The anti-drug antibody response in patients was analysed over the course of the treatment period and correlated with safety and efficacy outcome results. As a result, no association between anti-drug antibody formation and hypersensitivity adverse events or changes in the CLN2 clinical rating score could be detected.[66]

Specchio 2017

Specchio et al. (2017) aimed to identify early clinical, MRI, and EEG characteristics of CLN2 disease through a retrospective clinical chart review of 14 patients with CLN2 disease. Early photosensitivity (e.g. a photoparoxysmal response at low intermittent photic stimulation frequencies, as revealed by EEG) was described as a hallmark of CLN2 disease, especially if accompanied by delayed speech, ataxia, or MRI abnormalities, and suggested to be used in the early diagnosis of CLN2 disease. Of the 14 patients, all were treated with antiepileptic drugs and 10 of these (70%) were receiving valproic acid which the authors acknowledged may have affected the patients' response to intermittent photic stimulation.[67]

Table C4. List of additional relevant published studies from BioMarin database search

Primary study reference	Study type	Study name (acronym)	Population	Treatment	Comparator	Results reported	Supplementary reference(s)
BioMarin studies							
Cherukuri 2017[66]	Interventional study	Study 190-201 EUCTR2012-005430-11-GB NCT01907087	Patients with CLN2 disease (3–16 years of age)	Cerliponase alfa	N/A	Time course of the anti-drug antibody response and correlations of immunogenicity with safety and with efficacy.	NCT01907087[64] EUCTR2012-005430-11-GB[65] Schulz 2016a[51] Schulz 2016b[52] Schulz 2016c[47] Schulz 2016d[48]
Non-BioMarin studies							
Specchio 2017[67]	Retrospective clinical chart review of a series of patients	N/A	Patients with CLN2 disease	NR	N/A	AEDs received by patients, clinical, MRI, and EEG findings were reviewed.	Specchio 2016

ABBREVIATIONS: AEDs: antiepileptic drugs; CLN2: genetically/enzymatically confirmed neuronal ceroid lipofuscinosis type 2; EEG: electroencephalograph; MRI: magnetic resonance imaging; N/A: not applicable; NR: not reported.

9.3.2 State the rationale behind excluding any of the published studies listed in tables C3 and C4.

None of the published studies which met the inclusion criteria were excluded. Unpublished studies (Table C3) for which no results have been reported were excluded from this review on the basis of insufficient data.

9.4 Summary of methodology of relevant studies

9.4.1 Describe the study design and methodology for each of the published and unpublished studies using tables C5 and C6 as appropriate. A separate table should be completed for each study.

Published studies

A description of the design and methodology of each of the included, published observational and interventional studies considered most relevant to this submission, is provided below. Due to the lack of information on the methodology of the 11 case studies, it was not possible to provide detailed descriptions of these studies.

For each of the described studies, a critical appraisal can be found in section 9.5. Details of the outcomes and adverse events reported by each study are described in section 9.6 and section 9.7, respectively.

Please note that equivalent information for the other studies identified by the SLR, but not considered relevant to this submission, is provided in Appendix 3, section 17.3.

BioMarin studies

In addition to Study 190-201 (Table C5) and Study 190-202 (Table C6), the search for published studies on the EMA website further identified Study 190-901.[68] Although this study did not meet the eligibility criteria for inclusion in the SLR as it collected natural history data from treatment naïve patients with CLN2 disease, considering its relevance to this submission a description of the design and methodology of Study 190-901 is also provided below (Table C7).

Study 190-201

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 (Table C5). The study aimed to evaluate safety, efficacy, and

pharmacokinetics of the therapy and after its completion in November 2015, participants were enrolled in an extension study (Study 190-202, Table C6) for long-term follow-up.[51]

Table C5. Summary of methodology for Study 190-201

Study name	Study 190-201; Schulz 2016a[51]; EUCTR2012-005430-11-GB[65]; NCT01907087[64]
Objective	• To evaluate safety and tolerability of cerliponase alfa in the treatment of patients with CLN2 disease • To evaluate effectiveness of cerliponase alfa using the CLN2 clinical rating score, in comparison with natural history data • To evaluate the impact of treatment with cerliponase alfa on brain atrophy, and to determine immunogenicity
Location	United States, Germany, Italy, United Kingdom
Design	Interventional study (open-label, phase 1/2)
Duration of study	48 weeks
Patient population	Children with confirmed CLN2 disease treated with the study intervention and compared to a natural history control group
Sample size	24 were enrolled and received treatment however 23 of these patients completed the trial (one patient withdrew from the study after receiving a single dose of cerliponase alfa)
Inclusion criteria	• Diagnosis of CLN2 determined by TPP1 enzyme activity (dried blood spot) available at study entry. If no genotype information is available, blood will be collected for CLN2 gene analysis at baseline. In addition, blood for TPP1 enzyme activity (dried blood spot) will be collected at baseline to be analysed centrally • Mild to moderate disease documented by a two-domain score of 3- 6 on motor and language domains of the Hamburg Scale, with a score of at least 1 in each of these two domains • Written informed consent from parent or legal guardian and assent from subject, if appropriate • The ability to comply with protocol requirements, in the opinion of the investigator • Seizures are stable in the judgement of the investigator

Exclusion criteria	• Less than 3 years old at enrolment • 16 years old or older at enrolment • Another inherited neurologic disease, e.g. other forms of CLN or seizures unrelated to CLN2 (patients with febrile seizures may be eligible) • Another neurological illness that may have caused cognitive decline (e.g., trauma, meningitis, haemorrhage) before study entry • Patients who require ventilation support, except for non-invasive support at night • Patients who have received stem cell, gene therapy, or ERT for CLN2 • Contraindications for neurosurgery (e.g., congenital heart disease, severe respiratory impairment, or clotting abnormalities) • Contraindications for MRI scans (e.g., cardiac pacemaker, metal fragment or chip in the eye, aneurysm clip in the brain) • Patients with generalized motor status epilepticus within 4 weeks before the First Dose visit, taking care that status epilepticus is on clinical examination and not only EEG (enrollment may be postponed) • Severe infection (e.g., pneumonia, pyelonephritis, or meningitis) within 4 weeks before the First Dose visit (enrollment may be postponed) • Patients prone to complications from intraventricular drug administration, including patients with hydrocephalus or ventricular shunts • Patients with known hypersensitivity to any of the components of cerliponase alfa • Patients who have received any investigational medication 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 • Patients who have a medical condition or extenuating circumstance that, in the opinion of

	the investigator, might compromise the subject's ability to comply with the protocol requirements or compromise the subject's wellbeing, safety, or clinical interpretability • Patients who have 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 • Pregnancy any time during the study
Intervention(s) (n = 23 completed*) and comparator(s) (n = 41)	Intervention: Cerliponase alfa The study included a dose escalation phase in a subset of patients to establish a maximally tolerated dose. Comparator: Natural history cohort (Study 190-901)
Baseline differences	NR
How were participants followed-up (for example, through pro-active follow-up or passively). Duration of follow-up, participants lost to follow-up	Study participants were followed up in a separate extension study (Study 190-202).
Statistical tests	Treatment effect was assessed using a Fisher exact test. This was a conservative estimate of the within-subject change based on review of subjects from natural history databases.[68] Slopes (the rate of decline in the CLN2 disease rating scale in points per 48 weeks) were compared both for treated patients in Study 190-201/202 and for untreated patients in the overall 190-901 population using a two-sample t-test, with adjustment to accommodate unequal variances.[26]
Primary outcomes (including scoring methods and timings of assessments)	• To evaluate the safety of every other week infusions of cerliponase alfa based on: vital signs, physical examination, electrocardiogram tests, clinical laboratory tests, adverse events, concomitant medications, immunogenicity tests. Time frame: 48 weeks • Vital signs, adverse events, concomitant

	medications: Screening, Baseline, Weeks 1 to 49. Physical examination: Screening, Baseline, Weeks 1 to 49. Electrocardiogram tests: Baseline, Weeks 1, 24 and 49 Clinical laboratory tests: Baseline, Weeks 1, 5, 9, 13, 17, 21, 25, 29, 33, 37, 41, 45, 49 Immunogenicity tests: Baseline, Weeks 1, 5, 9, 13, 17, 21, 25, 29, 33, 37, 41, 45, 49 • To evaluate the efficacy of every other week infusions of cerliponase alfa by monitoring changes in clinical measures as measured by the CLN2 disease rating scale. Time frame: 48 weeks • Screening, baseline, Weeks 1, 5, 9, 13, 17, 21, 25, 29, 33, 37, 41, 45, 49
Secondary outcomes (including scoring methods and timings of assessments)	• To evaluate the efficacy of every other week infusions of cerliponase alfa by monitoring changes in clinical measures as measured by MRI. Time frame: 1 year • Screening, Baseline, every 8 weeks during Dose Escalation Period, Weeks 1, 9, 17, 33, 49 • To determine the PK parameters of infused cerliponase alfa in subjects with CLN2. Time frame: 48 weeks

ABBREVIATIONS: CLN2: genetically/enzymatically confirmed neuronal ceroid lipofuscinosis type 2; EEG: electroencephalogram; ERT: enzyme replacement therapy; MRI: magnetic resonance imaging; N/A: not applicable; NR: not reported; PK: pharmacokinetics; TPP1: tripeptidyl-peptidase 1.

*One enrolled patient had a single dose and withdrew consent due to inability to comply with study procedures.

Study 190-202

The phase 2 extension Study 190-202 was designed as a long-term follow-up to Study 190-201 (Table C5), allowing patients from Study 190-201 to continue treatment with cerliponase alfa. Study 190-202 assesses long-term safety and efficacy and has an expected completion date of December 2021 (Table C6).[51]

Table C6. Summary of methodology for Study 190-202

Study name	Study 190-202; Schulz 2016a[51]; EUCTR2014-003480-37-GB[53]; NCT02485899[54]
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 (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 complete the Study 190-201 with the option to continue to receive continued cerliponase alfa treatment. The Study 190-202 is an open label extension protocol to assess long-term safety and efficacy.
Location	United States, Germany, Italy, United Kingdom
Design	Interventional study (phase 2) This study is designed as an open-label extension to Study 190-201.
Duration of study	Up to 240 weeks
Patient population	Children with confirmed CLN2 disease treated with the study intervention and compared to a natural history control group.
Sample size	23
Inclusion criteria	• Patients must have completed 48 weeks in Study 190-201 • 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 written assent (if required) and have written informed consent, signed by a legally authorized representative, after the nature of the study has been explained, and prior to performance of research-related procedures • 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 • 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
Exclusion criteria	• Patients who have had a loss of 3 or more points in the combined motor and language components of the Hamburg CLN2 rating scale between Baseline of Study 190-201 and the Study Completion visit in Study 190-201 and

	would not benefit from enrolling in the study in the Investigator's discretion • Patients with a score of 0 points on the combined motor and language components of the Hamburg CLN2 rating scale • Pregnant or breastfeeding patients, at Baseline, or planning to become pregnant (self or partner) at any time during the study • Patients who have use any investigational agent prior to completion of all scheduled study assessments • Patients with a concurrent disease or condition that would interfere with study participation, or pose a safety risk, as determined by the Investigator • 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
Intervention(s) (n = 23) and comparator(s) (n = 0)	Intervention: Cerliponase alfa Comparator: N/A
Baseline differences	NR
How were participants followed-up (for example, through pro-active follow-up or passively). Duration of follow-up, participants lost to follow-up	NR
Statistical tests	Slopes (the rate of decline in the CLN2 disease rating scale in points per 48 weeks) were compared both for treated patients in Study 190-201/202 and for untreated patients in the overall 190-901 population using a two-sample t-test, with adjustment to accommodate unequal variances.[22]
Primary outcomes (including scoring methods and timings of assessments)	• Long term safety as assessed by analysis of adverse events. Time frame: up to 240 weeks • Long term safety of cerliponase alfa administered to subjects with CLN2 disease via an implanted ICV reservoir and cannula as

	assessed by analysis of adverse events • Motor and language changes. Time frame: up to 240 weeks • Change in motor and language subscales of the CLN2 disease rating scale in patients with CLN2 following administration of 300 mg every other week of cerliponase alfa
Secondary outcomes (including scoring methods and timings of assessments)	• Quantitative Assessment of MRI. Time frame: up to 240 weeks • Changes in quantitative assessment of MRI • CLN2 Disease Scale Score. Time frame: up to 240 weeks • Changes in the CLN2 disease scale total score • Quality of Life Changes. Time frame: up to 240 weeks • Changes in the quality of life with long-term use of cerliponase alfa

ABBREVIATIONS: CLN2: genetically/enzymatically confirmed neuronal ceroid lipofuscinosis type 2; ICV: intracerebroventricular; MRI: magnetic resonance imaging; N/A: not applicable; NR: not reported.

Study 190-901

Study 190-901 was designed as a natural history study, retrospectively analysing disease progression in untreated patients with CLN2 disease (as collected in the DEM-CHILD database) in order to support the assessment of efficacy outcomes in Study 190-201/202.[68, 69]

Table C7. Summary of methodology for Study 190-901

Study name	Study 190-901[68, 69]
Objective	To analyse data from natural history patients with CLN2 disease in order 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	Germany, Italy
Design	Observational natural history study (retrospective database review)
Duration of study	NR
Patient population	Untreated patients with CLN2 disease included in the DEM-CHILD database
Sample size	41 (of which 23 were used in the 1:1 matched analysis of Study 190-201/202)

Inclusion criteria	The following filters were applied to the patients in the DEM-CHILD databse, matching key eligibility criteria for Study 190-201: • 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
Exclusion criteria	NR
Intervention(s) and comparator(s)	N/A
Baseline differences	NR
How were participants followed-up (for example, through pro-active follow-up or passively). Duration of follow-up, participants lost to follow-up	NR
Statistical tests	Slopes (the rate of decline in the CLN2 disease rating scale in points per 48 weeks) were compared both for treated patients in Study 190-201/202 and for untreated patients in the overall 190-901 population using a two-sample t-test, with adjustment to accommodate unequal variances.[22] Matching of untreated patients from Study 190-901 and patients treated with cerliponase alfa from Study 190-201/202 was based on: • CLN2 clinical rating scale score identical to that at the 300mg baseline; and • Closest match for age within 12 months.
Primary outcomes (including scoring methods and timings of assessments)	Change in motor and language subscales of the CLN2 disease rating scale, including slope (the rate of decline in the CLN2 disease rating scale in points per 48 weeks) and 2-point residence time. Outcomes were analysed in comparison with 1:1-matched treated patient from Study 190-201/202.
Secondary outcomes (including scoring methods	NR

and timings of assessments)	

ABBREVIATIONS: CLN2: genetically/enzymatically confirmed neuronal ceroid lipofuscinosis type 2; N/A: not applicable; NR: not reported.

**This information has been reported in BioMarin Data on File.

Unpublished studies

The methodology for each of the unpublished cerliponase alfa studies, as identified through the WHO ICTRP, are presented below.

Study 190-502

The expanded access Study 190-502 is 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 (Table C8).

Table C8. Summary of methodology for Study 190-502

Study name	Study 190-502; NCT02963350[59]
Objective	To provide access to cerliponase alfa to patients with CLN2 disease who cannot participate in a clinical trial. To collect additional information on the safety and tolerability of cerliponase alfa administration in patients with CLN2 disease.
Location	United States, Germany, Italy, United Kingdom
Design	Expanded Access (open-label)
Duration of study	NR
Patient population	Children with clinically CLN2 disease
Sample size	NR
Inclusion criteria	• Diagnosed with CLN2 disease as confirmed by deficient TPP1 enzyme activity in leukocytes or molecular analysis by identifying 2 known pathogenic mutations. If enzyme analysis is performed by dried blood spot, diagnosis must be confirmed with molecular testing • Age ≥2 old at the time of informed consent • Patients 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 written assent (if required) and have written informed consent, signed by a legally authorized representative, after the nature of the program

	has been explained, and prior to any program assessments • If sexually active, patients must be willing to use 2 forms of acceptable methods of contraception while participating in the program • If female of childbearing potential, must have a negative pregnancy test at Baseline and be willing to have additional pregnancy tests during the program • Patients willing and able to comply with all program procedures
Exclusion criteria	• Another inherited neurologic disease, e.g., other forms of CLN or seizures unrelated to TPPI deficiency/CLN2 disease (patients with febrile seizures may be eligible) • Patients who received stem cell, gene therapy, or ERT for CLN2 disease • Contraindications for neurosurgery (e.g., congenital heart disease, severe respiratory impairment, or clotting abnormalities) • Contraindications for MRI scans (e.g., cardiac pacemaker, metal fragment or chip in the eye, aneurysm clip in the brain) • Episode of generalized motor status epilepticus within 4 weeks before the first infusion • Presence of ventricular abnormality (hydrocephalus, malformation) • Presence of ventricular shunt • Patients with known hypersensitivity to any of the components of cerliponase alfa • Patients currently enrolled or previously enrolled in a clinical study with cerliponase alfa • Use of any investigational product or investigational medical device within 30 days prior to Baseline, or requirement for any investigational agent prior to completion of all scheduled program assessments • Patients who have travel plans that may interfere with dosing regimen, scheduled

	program visits and safety monitoring • Patients with a medical condition or extenuating circumstance that, in the opinion of the physician, might compromise the patient's ability to comply with the protocol required testing or procedures or compromise the patient's wellbeing, safety, or clinical interpretability • Pregnancy any time during the program; a female patient judged by the physician to be of childbearing potential will be tested for pregnancy • A CLN2 combined motor/language score of less than 1 (apply to US only) • Asymptomatic (symptomatic is defined as having any evidence of neurological involvement attributed to CLN2 disease irrespective of the CLN2 score, including clinical signs and symptoms of disease such as seizures, ataxia, language delay or other developmental delays) (apply to US only)
Intervention(s) (n = 0) and comparator(s) (n = 0)	Intervention: Cerliponase alfa Comparator: N/A
Baseline differences	NR
How were participants followed-up (for example, through pro-active follow-up or passively). Duration of follow-up, participants lost to follow-up	NR
Statistical tests	NR
Primary outcomes (including scoring methods and timings of assessments)	NR
Secondary outcomes (including scoring methods and timings of assessments)	NR

ABBREVIATIONS: CLN2: genetically/enzymatically confirmed neuronal ceroid lipofuscinosis type 2; ERT: enzyme replacement therapy; MRI: magnetic resonance imaging; N/A: not applicable; NR: not reported; TPP1: tripeptidyl-peptidase 1.

Study 190-203

Study 190-203 is a phase 2 open-label study, with an anticipated completion date of December 2022. The study aims to evaluate the safety, tolerability, and efficacy of cerliponase alfa in CLN2 patients compared to untreated historical controls (Table C9).

Table C9. Summary of methodology for Study 190-203

Study name	Study 190-203; NCT02678689[62]
Objective	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. To assess disease progression in CLN2 patients treated with cerliponase alfa compared to natural history data from untreated historical controls.
Location	United States, Germany, United Kingdom
Design	Interventional study (open-label, phase 2)
Duration of study	Up to 96 weeks
Patient population	Children with confirmed CLN2 disease treated with the study intervention and compared to a natural history control group.
Sample size	NR
Inclusion criteria	• Diagnosis of CLN2 disease as determined by TPP1 enzyme activity (dried blood spot) in the fibroblasts and leukocytes available at Screening • Quantitative clinical assessment of the Hamburg motor-language aggregate score 3-6 at Screening on CLN2 disease motor-language scale, as defined in the Ratings Assessment Guideline • Age <18 years of age at the time of informed consent • Written informed consent from parent or legal guardian and assent form subject, if appropriate • Ability to comply with protocol required assessments (ICV implantation, drug administration, laboratory sample collection, EEG, ECG, MRI, etc.) • 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
Exclusion criteria	• 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) • Presence of another neurological illness that may have caused cognitive decline (e.g., trauma, meningitis, haemorrhage) or interference with disease rating (autism) before Screening • Presence of percutaneous feeding tube placement prior to enrolment • Has received stem cell, gene therapy, or ERT • Presence of contraindications for neurosurgery (e.g., congenital heart disease, severe respiratory impairment, or clotting abnormalities) • Presence of contraindications for MRI scans (e.g., cardiac pacemaker, metal fragment or chip in the eye, aneurysm clip in the brain) • Episode of generalized motor status epilepticus within 4 weeks before the First Dose visit • Severe infection (e.g., pneumonia, pyelonephritis, or meningitis) within 4 weeks before the First Dose visit (enrolment may be postponed) • Presence of ventricular abnormality (hydrocephalus, malformation) • Presence of ventricular shunt • Has known hypersensitivity to any of the components of cerliponase alfa • 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

	• 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 • Pregnancy any time during the study; a female subject judged by the investigator to be of childbearing potential will be tested for pregnancy
Intervention(s) (n = 0) and comparator(s) (n = 0)	Intervention: Cerliponase alfa Comparator: N/A
Baseline differences	NR
How were participants followed-up (for example, through pro-active follow-up or passively). Duration of follow-up, participants lost to follow-up	NR
Statistical tests	NR
Primary outcomes (including scoring methods and timings of assessments)	• Incidence and severity of adverse events as assessed by CTCAE v 4.0. Time frame: up to 96 weeks • Change in the 0–6 point Motor/Language (ML) score on the Hamburg CLN2 rating scale. Time frame: up to 96 weeks • Immunogenicity of cerliponase alfa in CSF and serum. Time frame: up to 96 weeks
Secondary outcomes (including scoring methods and timings of assessments)	• Change in the total Hamburg CLN2 rating scale. Time frame: up to 96 weeks • Change in clinical laboratory tests. Time frame: up to 96 weeks • Change in CSF laboratory parameters. Time frame: up to 96 weeks • Vital signs. Time frame: up to 96 weeks • Physical examination. Time frame: up to 96 weeks. • Neurological examinations. Time frame: up to

	96 weeks • 12-Lead ECG. Time frame: up to 96 weeks • Change in Brain Volumes as Assessed by Cranial MRI. Time frame: up to 96 weeks • Incidence of and change in abnormalities in standard awake EEG. Time frame: up to 96 weeks • Assess time to disease manifestation for asymptomatic patients. Time frame: up to 96 weeks

ABBREVIATIONS: CLN2: genetically/enzymatically confirmed neuronal ceroid lipofuscinosis type 2; CSF: cerebrospinal fluid; CTCAE: Common Terminology Criteria for Adverse Events; ECG: electrocardiogram; EEG: electroencephalogram; ERT: enzyme replacement therapy; ICV: intracerebroventricular; MRI: magnetic resonance imaging; N/A: not applicable; NR: not reported; TPP1: tripeptidyl-peptidase 1.

9.4.2 Provide details on data from any single study that have been drawn from more than one source (for example a poster and unpublished report) and/or when trials are linked this should be made clear (for example, an open-label extension to randomised controlled trial).

Study 190-201 is the primary study evaluating the effect of cerliponase alfa treatment on CLN2 patients for a period of up to 48 weeks. The data for this study is derived from a final Clinical Study Report (CSR).[26] The results were also presented in poster form at the 12th Annual WORLD Symposium in San Diego, California in 2016.[52]

Study 190-202 is the extension study of Study 190-201 and is still ongoing. All subjects who completed 48 weeks of cerliponase alfa treatment in Study 190-201 were enrolled in Study 190-202.

Pooled outcomes data from both studies up to a total of 96 weeks of treatment is derived from an interim CSR dated 8 August 2017 (data cut-off 1 November 2016).[22] Although interim efficacy and safety data from Studies 190-201/202 have been presented at several conferences and congresses throughout 2016 and 2017, the interim CSR contains the most up-to-date and most complete dataset so far, and is therefore the primary source of evidence for the purposes of this submission.

The case study by Lorenz (2002) (Table C2) was followed up by a case study of an additional patient with CLN2 disease by the same author (Lorenz 2004).[32, 33]

The description of the observational study by Lehwald et al. (2016) (Appendix 3, section 17.3) includes additional information from the relevant entry in the clinical trials registry (NCT01966757).[41, 55] Similarly, the description of the interventional study by Selden et al. (2013) (Appendix 3, section 17.3) also includes further information from the relevant entry in the clinical trials registry (NCT00337636).[42, 56]

The publication of the interventional study by Worgall et al. (2008) (Appendix 3, section 17.3) was complemented by data from two identified publications on the study methodology by Crystal et al. (2004) and Souweidane et al. (2010), as well as information from the relevant entry in the clinical trials registry (NCT00151216).[43-45, 57]

Study 190-202 (Table C6) is designed as a long-term extension to Study 190-201 (Table C5) and siblings of participants from the initial study have the opportunity to enrol in a separate Study 190-203 (Table C9).[51]

9.4.3 Highlight any differences between patient populations and methodology in all included studies.

Twenty-four patients were enrolled into Study 190-201 and comprised the Enrolled Population and Safety Population for evaluation purposes. Twenty-three patients received more than one dose of cerliponase alfa and comprised the ITT Population. All 23 patients in the ITT Population also completed 48 weeks of treatment in Study 190-201 and so were enrolled into the long-term extension study 190-202. Thus, the Safety and ITT Populations for Studies 190-201 and 190-202 are the same subjects.

The untreated patient population of the retrospective Study 190-901 was selected based on key eligibility criteria from Study 190-201/202, the two study populations were consequently similar with respect to key prognostic variables (i.e. age, genotype, CLN2 clinical rating score).

Study 190-202 followed the same methodology and design as Study 190-201, with the exception that EQ-5D-5L was assessed as an additional HRQL measure in Study 190-202, but not in Study 190-201.

The other included studies display substantial variation in regard to methodology and population, due to the range of study types and interventions, which precludes any comparison between the different study groups. Furthermore, many of the case studies did not report essential information such as eligibility criteria and baseline characteristics, rendering a summary of differences between the patient populations difficult. This reflects the lack of evidence available for treatments of CLN2 disease.

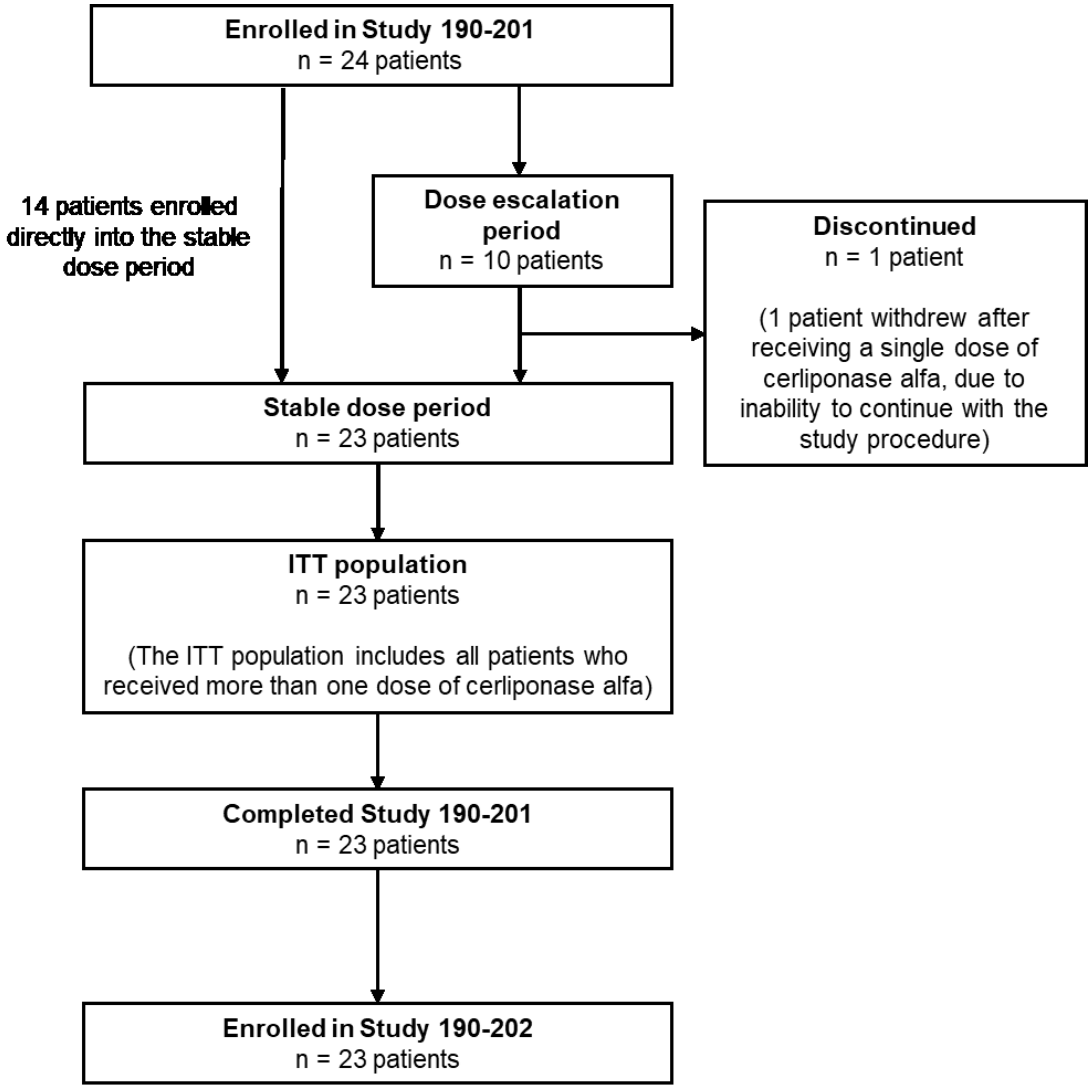
9.4.4 Provide details of any subgroup analyses that were undertaken in the studies included in section 9.4.1. Specify the rationale and state whether these analyses were pre-planned or post-hoc.

No analyses were undertaken to evaluate the treatment effect of cerliponase alfa in any sub-group. However, sub-group analyses are presented in the economic evaluation.

9.4.5 If applicable, provide details of the numbers of patients who were eligible to enter the study(s), randomised, and allocated to each treatment in an appropriate format.

Twenty-four subjects were enrolled in Study 190-201 and had an ICV access device implanted. They comprise the Safety Population. Ten subjects were enrolled in one of three cohorts in the dose escalation period and 14 patients were enrolled directly in the stable dose period. One subject (1287-1007) received a single dose of study drug (300mg) in the third dose escalation cohort and then withdrew due to inability to continue with study procedures. The ITT Population is defined as study subjects who received more than one dose of cerliponase alfa (n=23). These 23 patients all completed Study 190-201 and subsequently transitioned to Study 190-202 (Figure C7). At the time of the most recent data cut-off (1st November 2016), all 23 subjects who completed 48 weeks of treatment in Study 190-201, had at least 48 weeks of additional treatment in Study 190-202 (hence 96 weeks of data on indicated dose).

Figure C7: CONSORT flow diagram for Study 190-201/202



ABBREVIATIONS: ITT: intent-to-treat.

Populations for Sensitivity Analyses:

- *Efficacy Population (n=21):* ITT subjects, but excluding 2 subjects who enrolled with a baseline ML scale score of 6 (the maximum score) and who showed no decline in their ML scale score with 300 mg BMN 190 during Study 190-201 or Study 190-202. These 2 subjects were excluded because the analysis of the rate of decline presupposes that the subject has, in fact, entered the period of clinical decline; subjects who achieve the maximum score on the ML scale and do not decline from that score during the study are assumed not to yet be in the period of clinical decline.
    - Subset of efficacy population (n=18): includes only subjects with a 300-mg baseline ML score of 3, 4, or 5.

- *Enrolled Population (n=24):* all subjects who provided informed consent for 190-201
    - Subset of enrolled population (n=22): includes the single dose subject (with imputed 4-point loss over 48 weeks in Study 190-201), but excludes the 2 subjects with stable ML scores of 6.

The disposition of subjects enrolled in Studies 190-201/202 is provided in Table C10.

Table C10. Study 190-201/202 Subject Disposition (Enrolled Population)

Category	Overall (n = 24)
Subjects Enrolled in Study 190-201[a]	24 (100%)
Subjects Treated in Study 190-201	24 (100%)
Subjects who Completed Study 190-201	23 (96%)
Subjects who Enrolled in Study 190-202	23 (96%)
Subjects who Completed the 190-202 Study	0
Subjects who Discontinued from the Study 190-201	1 (4%)
Primary reason for study discontinuation:	
Withdrawal by Subject	1 (4%)
Subjects who Discontinued from Study 190-202	0
Subjects Evaluable for Safety[b]	24 (100%)
Subjects Evaluable for ITT Analysis[c]	23 (96%)
Subjects Evaluable for Efficacy Analysis[d]	21 (88%)

Note: The analysis of Study 190-202 incorporates final data from parent study, 190-201. The analyses for this interim clinical study report includes data from all Study 190-202 visits up to 1 November 2016 (190-202 interim data cutoff date) in addition to all visits from Study 190-201 through study completion and database lock (190 201 complete data set).

[a] The total number of subjects enrolled were used as denominators.

[b] The safety evaluable population included all subjects who received at least one dose of BMN 190.

[c] The ITT population included all subjects who received at least one dose of BMN 190 and reported any efficacy results, but excluded subject 1287-1007 who withdrew from Cohort 3 after a single infusion.

[d] The Efficacy population included all subjects in the ITT population, but excluded 2 subjects who started 300 mg dosing with an ML scale score of 6 and who saw no decline in that score over the course of the study.

Source: Interim CSR 190-201/202.[22]

9.4.6 If applicable provide details of and the rationale for, patients that were lost to follow-up or withdrew from the studies.

One patient withdrew from Study 190-201 after receiving a single dose of cerliponase alfa due to an inability to comply with study procedures. No other subjects withdrew from either Study 190-201 or Study 190-202. No patients were lost to follow-up.

9.5 Critical appraisal of relevant studies

9.5.1 Complete a separate quality assessment table for each study. A suggested format for the quality assessment results is shown in tables C7 and C8.

Critical appraisals of included studies considered most relevant to this submission are provided below. Descriptions of the methodology for each of the individual studies can be found in section 9.4. Further details of the outcomes and adverse events reported by each study are described in section 9.6 and section 9.7, respectively.

Please note that critical appraisals for the other studies identified by the SLR are provided in Appendix 3, section 17.3.

BioMarin studies

Study 190-201

Table C11. Critical appraisal of Study 190-201

Study name	Study 190-201; Schulz 2016a[51]; NCT01907087[47, 48, 52, 64]	
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 section 6.1. 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, in order 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 confidence interval and p values) are the results?	Yes	Results were accompanied by the description of confidence intervals and p values where applicable and were otherwise comprised of mean values with standard deviation.

ABBREVIATIONS: N/A: not applicable.

Adapted from Critical Appraisal Skills Programme (CASP): Making sense of evidence; 12 questions to help you make sense of a cohort study.

Study 190-202

Table C12. Critical appraisal of Study 190-202

Study name	Study 190-202; Schulz 2016a[51]; NCT02485899[47, 48, 52, 54]	
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, in order 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?	N/A	Study 190-202 is still on-going.
How precise (for example, in terms of confidence interval and p values) are the results?	Yes	Results were accompanied by the description of confidence intervals and p values where applicable and were otherwise comprised of mean values with standard deviation.

ABBREVIATIONS: N/A: not applicable.

Adapted from Critical Appraisal Skills Programme (CASP): Making sense of evidence; 12 questions to help you make sense of a cohort study.

Study 190-901

Table C13. Critical appraisal of Study 190-901

Study name	Study 190-901[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 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 natural history 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 was performed, in order 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?	N/A	Study 190-901 was a natural history study based on a retrospective database review.
How precise (for example, in terms of confidence interval and	Yes	Results were accompanied by the description of confidence intervals and p values where applicable and were otherwise comprised of mean values with standard deviation.

p values) are the results?		

ABBREVIATIONS: N/A: not applicable.

Adapted from Critical Appraisal Skills Programme (CASP): Making sense of evidence; 12 questions to help you make sense of a cohort study.

9.6 Results of the relevant studies

In the pivotal clinical trial, Study 190-201, the CLN2 clinical rating scale scores reflected stabilisation of disease in 65% of patients receiving cerliponase alfa for 48 weeks and significant slowing of progression versus natural history control data in 87% of patients (p=0.002). This treatment benefit was maintained in all 23 patients enrolled in the ongoing extension study, 190-202, after 96 weeks of treatment with cerliponase alfa, supporting an assumption of stabilisation across all patients.

- The CLN2 clinical rating scale is adapted from two well-established and validated disease-specific instruments, the Hamburg and Weill Cornell scales. These scales have been used over many years to describe and quantify the progression of CLN2 disease.
- The CLN2 clinical rating scale measures motor and language function, the two domains that best track the rapid progression phase of disease, on a scale of 3 (normal) to 0 (complete loss of function).
- Each 1 point decrement represents loss of previously attained developmental milestones in motor function and speech and represents a clinically meaningful change in quality of life. Natural history data shows an average rate of decline greater than 2 points per 48 weeks in a cohort of untreated CLN2 patients who match the inclusion criteria for Study 190-201.
- The treatment effect of cerliponase alfa was demonstrated by comparing progression of disease on the CLN2 clinical rating scale in 23 patients aged ≥ 3 years old receiving cerliponase alfa 300mg every two weeks in an open label clinical study with that of untreated patients in a natural history study of comparable patients.
- Cerliponase alfa provides clinical benefit irrespective of the stage of disease at the time of treatment initiation:

- 87% (20/23) of patients had a response (i.e. a 1-point decline on the CLN2 clinical rating scale or better), which significantly exceeded the expected rate of 50% for untreated patients (95% CI 66%, 97%; p = 0.0002);
- The CLN2 clinical rating scale score was stabilised in 65% (15 of 23) of patients, who had no change or an improvement in score from baseline, which significantly exceeded the predicted rate of 25% for untreated patients (p <0.0001).
- The majority of decline in CLN2 rating scale scores took place in the initial 16 weeks of treatment, and most patients showing

stabilisation in the following weeks. No patient had a greater than 1 unreversed point decline after week 16.

- The benefit of cerliponase alfa was seen relative to matched natural history controls. Study 190-201/190-202 is ongoing and the benefits of cerliponase alfa were maintained at the Week 96 analysis. At Week 96, [redacted] subjects had stabilised, with no clinical progression of disease [redacted].
- In total, [redacted] treated subjects continued to have better outcomes at 96 weeks than the expected 2-point loss in a natural history population over a 48-week period. [redacted], translating this rate of decline over 96 weeks, the expected loss is ~4 points for a natural history population, making the relative stability of the scores for the patients treated with cerliponase alfa even more noteworthy.
- The benefit of cerliponase alfa was seen relative to matched natural history controls and across all functional domains of the Hamburg scale, including motor and language function, vision and seizures.
- The clinical relevance of stabilising the decline in function is supported by improvements in quality of life assessments of both patients and caregivers.

9.6.1 Complete a results table for each study with all relevant outcome measures pertinent to the decision problem. A suggested format is given in table C9.

9.6.1.1 Introduction to efficacy results for Study 190-201 and Study 190-202

Efficacy results in this section are presented for two different populations:

- The ITT population (n=23) is the primary efficacy population and includes all study subjects who received any amount of study drug and reported any efficacy results, but excludes one subject who withdrew from the study after a single infusion of study drug.
- The efficacy population (n=21) includes all subjects in the ITT population, but excludes two subjects who had a baseline ML scale score of 6 and who showed no decline in that score over the duration of the study. These patients are excluded only because they were never observed to be in decline, therefore conservatively are not included in the calculation of slopes for rates of decline.

The results are presented relative to the two baselines:

- Results presented in reference to the “study baseline” sets baseline as the last observation preceding the first infusion of *any dose* of BMN 190.
- Results presented in reference to the “300mg baseline” set baseline as the last observation preceding the first infusion of *300mg* BMN 190. For Cohort 1 and Cohort 2 subjects, the 300mg baseline was the last assessment before their first 300 mg dose of BMN 190 in the Dose Escalation Period; for Cohort 3 and SDO subjects, the 300 mg baseline and study baseline are identical.

9.6.1.2 Instruments and measurements used to assess efficacy

Primary efficacy variable - CLN2 clinical rating scale

The primary efficacy endpoint in Study 190-201 and Study 190-202 was the CLN2 clinical rating scale, which measures motor function and language function each on a scale of 0-3 with a total combined score range 0-6 (also known as the ML scale), as shown in Table C14. The wording was adapted slightly from that in the motor and language domains used in the collection of natural history in the DEM-CHILD database in collaboration with the authors of the original Hamburg scale in order to allow standardisation in a multi-site setting.

This measure was chosen as being sensitive to changes in the progression of disease. As discussed in section 6.1:

- Motor function and language function are the domains that best track the early and rapid progression of CLN2 disease
- Items that fluctuate or can be dependent on care (seizures, myoclonus, feeding) could confound measurement of disease progression
- Vision loss occurs later in disease and is slower to progress than motor and language problems.

Table C14. CLN2 clinical rating scale of motor and language function

CLN2 clinical rating scale used in cerliponase alfa Study 190-201		
Motor	3	Grossly normal gait
	2	Abnormal gait; independent ≥ 10 steps; Frequent falls, obvious clumsiness
	1	No unaided walking or crawling only
	0	Immobile, mostly bedridden
Language	3	Grossly normal
	2	Has become recognisably abnormal (worse than the individual

		maximum)
	1	Hardly understandable
	0	Unintelligible or no language

The CLN2 clinical rating scale was evaluated at baseline for the 300mg stable dose treatment period, every 8 weeks during the studies, and at study completion. The primary endpoint was the change in the ML scale at 48 weeks compared to the change in natural history controls.

Ratings took place at the same time in the study visit, preferably in the morning before procedures and/or infusion took place. A number of steps were undertaken to ensure the consistency of measurement before study ratings took place and these are summarised in Appendix 4, section 17.4.

Analyses on the primary endpoint

A number of analyses were carried out on the primary endpoint, including a responder analysis (the percentage of patients with a less than 2-point decline per 48 weeks), a 'survival analysis' (the time taken to achieve a 2-point scale score change) and a 'slope analysis' (the rate of decline in score per 48 weeks).

Secondary efficacy variables

The full Hamburg and Weill Cornell CLN2 rating scales were also evaluated as secondary endpoints, providing scores on the additional domains of vision, seizures, myoclonus and feeding.

Measurements obtained from magnetic resonance imaging (MRI) were secondary efficacy variables to evaluate the effect of treatment on brain atrophy compared to natural history. MRI was performed at baseline for the 300mg stable dose period and at weeks 9, 25 and 49 in Study 190-201 and at 24-week intervals and at study completion in Study 190-202.

Exploratory efficacy variables

A number of variables were evaluated to explore the impact of treatment on age-appropriate developmental milestones and quality of life.

- *Denver II Developmental Screening Test (www.DenverII.com)*

  This test was designed to monitor the development of infants and preschool-aged children. The test covers four general functions: personal social (such as smiling), fine motor adaptive (such as grasping and drawing), language (such as combining words), and gross motor (such as walking). The scale reflects what percentage of a certain age group is able to perform a certain task. The test was

considered appropriate for the developmental age of the subject population.

- *PedsQL™ Measurement Model for Pediatric Quality of Life Inventory (www.pedsql.org)*

  The PedsQL™ Generic Core Scales are designed to measure Quality of Life in children and adolescents. The assessments are brief, practical, and developmentally appropriate. The instrument is responsive to clinical change over time.[70] The four parent reports cover the ages from 1-12 months, 13-24 months, 2-4 years, and 5-7 years, and include questions regarding physical, emotional, and social functioning, with school functioning where applicable.

  The Parent Family Impact Module of the PedsQL™ was also assessed. This includes questions related to physical, emotional, social and cognitive function, communication, worry, daily activities and family relationships.

- *CLN2 Disease-based QOL Instrument*

  The CLN2 Disease-based QOL questionnaire is a novel instrument that was designed by the Sponsor as a disease-specific health related module for the PedsQL™. The instrument was designed based on an evaluation of CLN2 family feedback from two focus groups performed by the Sponsor, one in Europe and one in the US. Focus groups were queried on common and impactful consequences of disease. Results were compiled and formatted to be used as an add-on module to the PedsQL™.

  Each of the PedsQL™ instruments comprises multiple modules. Each module is scored separately, and a total score across the multiple modules is also calculated. Possible scores, for individual modules and total score, range from 0 to 100, where 0 is the least favourable score and 100 is the most favourable score.

These variables were evaluated at baseline for the 300mg stable dose period, every 24 weeks for the Denver II developmental screening test, every 12 weeks for the quality of life measures and at study completion.

Efficacy results are presented in this section 9.6.1. Safety and tolerability outcomes are presented in section 9.7.

9.6.1.3 Efficacy Outcomes Study 190-201

The primary efficacy endpoint, the adapted CLN2 rating scale (in particular the score on the motor-language scale [ML scale]) for Study 190-201, was assessed by several methods of analysis. Primary efficacy outcomes are summarised in Table C15.

Table C15. Primary Efficacy Outcomes for Study 190-201

Study name		**Study 190-201**
Size of study groups	**Treatment**	Cerliponase alfa
	Control	None
Study duration	**Time unit**	48 weeks
Type of analysis	**Intention-to - treat/per protocol**	ITT (n=23)
Primary efficacy outcome (primary analysis)	**Name**	Response on CLN2 rating scale
	Unit	Response defined as the absence of an unreversed two-point decline or score of zero in CLN2 score by Week 48
Effect size	**Value**	20/23 patients (87%)
	95% CI	66%, 97%
Statistical test	**Type**	
	p value	0.0002
Primary efficacy outcomes (Responder analysis – motor domain)	**Name**	Proportion of subjects responding on the Motor Domain Score
	Unit	Absence of 1-point Decline Motor Domain Score
Effect size	**Value**	16/23 (70%)
	95% CI	NA
Statistical test	**Type**	
	p value	
Primary efficacy outcomes (Responder analysis)	**Name**	Proportion of subjects responding on the Language Domain Score
	Unit	Absence of One-Point Decline on Language Domain Score
Effect size	**Value**	18/23 (78%)
	95% CI	
Statistical test	**Type**	
	p value	
Primary efficacy outcomes (Responder analysis)	**Name**	Proportion of subjects with no change or an improved score on the CLN2 rating scale
	Unit	No unreversed single point loss (either stable or improved) as measured by the CLN2 scale
Effect size	**Value**	15/23 (65%)
	95% CI	
Statistical test	**Type**	
	p value	<0.0001
Primary efficacy outcome (additional slopes analysis)	**Name**	Rate of decline in the CLN2 clinical rating scale
	Unit	Points over 48 weeks
Effect size	**Mean**	0.40 (0.809)
	Median	0.00

	Min, Maz	-0.88, 2.02
	95%CI	0.05, 0.75
Statistical test	**Type**	
	p value	<0.0001
Comments		Secondary and exploratory endpoints were not measured statistically and are presented descriptively in the text below.

SOURCE: Clinical Study Report 190-201.[26]

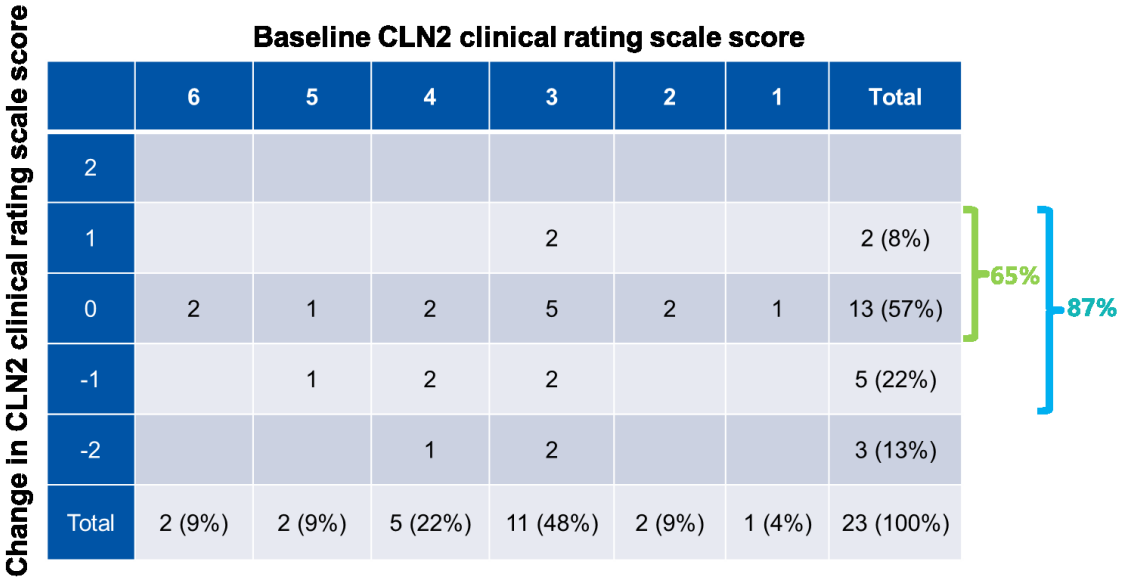
Primary endpoint - Responder Analysis

The primary analysis is a responder analysis based on the ITT population. 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). Results are presented relative to fixed natural history controls with a mean rate of decline of 2.0 points per 48 weeks.

Figure C8 shows the distribution of change in CLN2 clinical rating scale score over the 48-week stable dose treatment period in Study 190-201 by baseline score. The analysis showed that the study met the primary efficacy endpoint:

- 87% (20/23) of patients had a response (i.e. a 1-point decline or better), which significantly exceeded the expected untreated rate of 50% (95% CI 66%, 97%; p = 0.0002).
- 13% (3/23) of patients did not have a responder (i.e. presence of decline)
- The score was stabilised in 65% (15 of 23) of patients, who had no change or an improvement in score, which significantly exceeded the predicted rate of 25% (p <0.0001).

Figure C8. Change in CLN2 clinical rating scale score over 48 weeks (Study 190-201)[71]



Change in CLN2 clinical rating scale score	Baseline CLN2 clinical rating scale score						
	6	5	4	3	2	1	Total
2							
1				2			2 (8%)
0	2	1	2	5	2	1	13 (57%)
-1		1	2	2			5 (22%)
-2			1	2			3 (13%)
Total	2 (9%)	2 (9%)	5 (22%)	11 (48%)	2 (9%)	1 (4%)	23 (100%)

For the individual motor and language domains, a responder is defined as a subject who did not lose a point in that domain at time of last assessment.

Responder rates for the ML scale and separate motor and language domain scores for the ITT population during the 300mg dosing period are listed in Table C16.

Of the twenty subjects (87%) in the ITT population who met the definition of responder, eighteen subjects (78%) and 16 subjects (70%) met the definition of a responder on the language and motor domains, respectively.

Table C16. Responder Analysis: Proportion of Subjects with an Absence of One-Point Decline on Motor, One-Point Decline on Language and Two-point Declines or Score of 0 in ML Scale Score, ITT Population, 300 mg Dosing Period (Study 190-201)

Responder	Yes	No
Absence of 2-point Decline ML Scale Score	20 (87%)	3 (13%)
Absence of 1-point Decline Motor Domain Score	16 (70%)	7 (30%)
Absence of 1-point Decline Language Domain Score	18 (78%)	5 (22%)

SOURCE: Clinical Study Report 190-201[26]

The response to treatment was also analysed as the proportion of subjects that did not have a single unreversed ML scale point decline. Fifteen (65%) of the 23 treated patients had no unreversed single point loss (either stable or improved) as measured by the ML scale during the treatment period. Thus, the responder rate for the untreated population that has an unreversed single point drop is assumed to be 25%. The estimated treated responder rate of

65% significantly exceeds the expected untreated responder rate of 25% ($p < 0.0001$), as shown in Table C17.

Table C17. Responder Analysis: Proportion of Subjects without an Unreversed One-point Decline in ML Scale Score at 48 Weeks, ITT Population, 300mg Dosing Period (Study 190-201)

Outcome	190-201 (n=23)	95% Confidence Interval	1-sided p-value
Response (Absence of decline)	15 (65%)	(43%, 84%)	<0.0001
Non-Response (Presence of decline)	8 (35%)		

A 'response' is defined as the absence of an unreversed one-point decline in the 0-to-6 point CLN2 score at 48 weeks.

Inference is by an exact binomial test of the null hypothesis H0: Prob(response) <= 0.25 vs. the alternative hypothesis H1: Prob(response) > 0.25, where Prob(response) denotes the population probability of a response. The confidence interval is an exact interval.

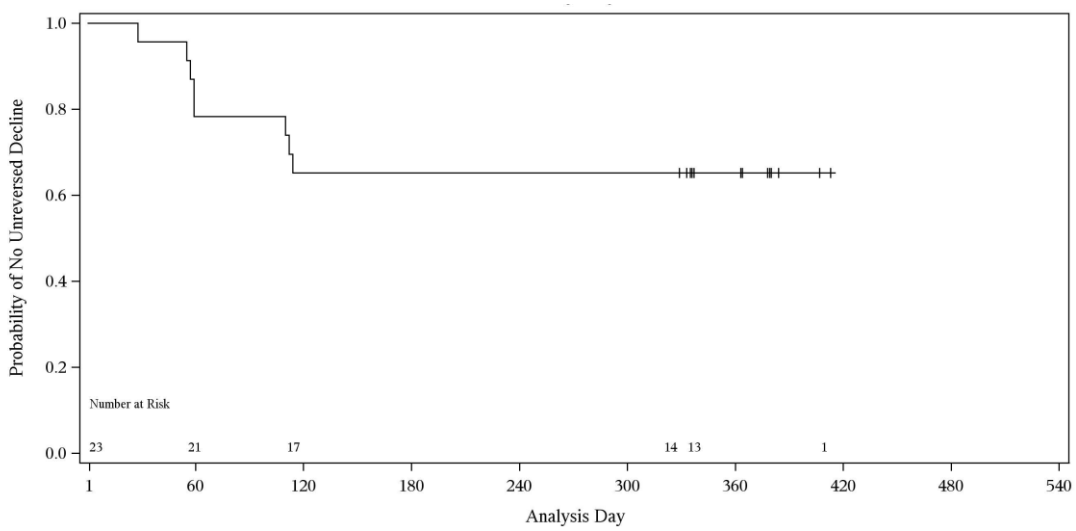
The table considers CLN2 assessments through Day 340 (relative to first 300 mg infusion).

SOURCE: Clinical Study Report 190-201[26]

Primary Endpoint - Time to Event Analysis

An additional efficacy analysis was performed to examine time to event analyses for change from 300mg baseline for the ML scale in the ITT population. An “unreversed decline” is a decline relative to the 300mg baseline value that had not subsequently returned to the 300 mg baseline value at the last observed assessment. The temporal relationship to the first unreversed decline in the CLN2 motor-language scale is depicted in the Kaplan-Meier analysis for the ITT population during the 300mg dosing period in Figure C9.

Figure C9. Time to First Unreversed Decline in ML Scale: Kaplan-Meier Estimation, ITT Population, 300 mg Dosing Period (Study 190-201)



Analysis Day 1 is the date of the first 300mg infusion.

SOURCE: Clinical Study Report 190-201[26]

Eight of 23 subjects experienced an unreversed point drop during the 300 mg dosing period on study; the remaining 15 subjects were stable or improved over the full duration of 300 mg treatment. All 8 subjects who experienced an unreversed point drop did so during the first 16 weeks on study; after that time point, only 3 of the 8 subjects experienced a second unreversed point decline. The remaining 5 subjects stabilised after losing a first point on the ML scale. The initial susceptibility to decline appears to describe a time to the maximal effect for the treatment. Once maximal effect is achieved, there was very little progression observed in ML scores over the course of the study indicating stabilisation after day 120.[26]

Primary endpoint - Slopes analysis

The rate of decline in the CLN2 clinical rating scale, scaled to a 48 week time period, was conducted as an additional analysis of the primary endpoint. The results are shown in Table C18. The mean rate of decline was 0.40 points per 48 weeks.[26] This was a statistically significant improvement when compared with a population rate of decline in untreated natural history patients of 2.0 points per 48 weeks ($p<.0001$). It is important to note that, using the same method of slope analysis, the mean rate of decline in the Study 190-901 natural history population, which included patients who conformed to the key eligibility criteria for Study 190-201, was 2.09 points per 48 weeks.

Table C18. Rate of decline of CLN2 clinical rating scale at 48 weeks (Study 190-201)

Rate of decline (Points per 48 weeks)	Study 190-201 (n=23)
Mean (SD)	0.40 (0.809)
Median	0.00
Min, Max	-0.88, 2.02
95% CI	0.05, 0.75
p vs fixed natural history (mean 2.0)	<0.0001

SOURCE: Clinical Study Report 190-201[26]

Sensitivity analyses on the primary endpoint are presented in the Study 190-201 CSR.

Secondary Endpoints Study 190-201

Change from baseline analysis on Hamburg 0-9 and 0-12

As previously discussed, the mean (SD) change at 48 weeks for the CLN2 clinical rating scale including only motor and language domains (primary endpoint) was -0.4 (0.84) points.

Table C19 shows the mean baseline, 48-week endpoint and change for this scale and for evaluations including other domains of the Hamburg rating scale. When the vision domain was added in (total score 0-9), the mean (SD) change was -0.7 (1.07) points, indicating a similarly small rate of decline for vision. Similarly, the mean (SD) change for the total Hamburg score (which also includes seizures, total score 0-12) was - 0.2 (2.01) points. This suggests an improvement in the seizure domain score during treatment. The addition of vision and seizure domains illustrates that the stabilisation of the clinical decline in CLN2 is broad-based and not a function of domain-specific therapeutic effect.

Table C19. Change in clinical rating including other domains of Hamburg rating scale at 48 weeks (Study 190-201)

Domains included	Motor Language	Motor Language Vision	Motor Language Vision Seizures
Possible score	0-6	0-9	0-12

range			
Baseline mean (SD)	3.5 (1.20)	6.3 (1.34)	8.0 (1.83)
Endpoint mean (SD)	3.1 (1.41)	5.7 (1.72)	7.8 (2.21)
Change mean (SD)	-0.4 (0.84)	-0.7 (1.07)	-0.2 (2.01)

SOURCE: Clinical Study Report 190-201[26]

MRI Cranial Imaging

The secondary efficacy endpoint was MRI cranial imaging, which measured whole brain volume, volume of cerebrospinal fluid (CSF), volume of total cortical grey matter, total white matter volume, and whole brain apparent diffusion coefficient (as assessed by MRI evaluation).

At the end of Study 190-201, the mean percentage changes in volume of whole brain, white matter, grey matter and CSF were -4.4% (SD 8.46), -4.2% (SD 9.58), -9.7 (SD 8.08) and 3.6 (SD 15.30), respectively, for the ITT population. While the increase in CSF and decrease in grey matter are consistent with CLN2 disease, there were only small mean changes and there was considerable variability in the population both at the starting point and after treatment, which makes any changes difficult to interpret. Comparison of the change from baseline in cortical grey matter volume of -9.7% in cerliponase-treated patients compared with -14.5% reported in untreated patients (n=6) over the course of 1 year suggests that cerliponase alfa may attenuate cortical grey matter volume loss.[72]

Exploratory Efficacy Endpoints Study 190-201

Denver II developmental screening test

The Denver II developmental screening test revealed universal developmental delay as expected in this population. At study baseline, all 23 subjects tested received an overall interpretation of “suspect”. At study completion, there was no change: of the 22 subjects evaluated, all 22 (100%) were classified as “suspect”.[26] A review of the by-subject listings shows no clear trends or patterns in change in the number of cautions or delays in either the gross motor or language scales between study baseline and the end of the 190-201 study.

HRQL measures

HRQL was assessed in Study 201 using the PedsQL Parent Report for Toddlers, the PedsQL Family Impact Module and a CLN2 disease-based QoL instrument. Scores on all instruments range from 0 to 100, with higher scores

relating to better function. The mean (SD) at baseline, at the end of Study 190-201 after 48 weeks' treatment with cerliponase alfa, and the change from baseline to week 48 are shown in Table C20. There was a broad-based improvement in all HRQL assessments, with mean increases in the total score for each questionnaire, which ranged from 4.3% to 10.9%.

Table C20. Scores of HRQL measures (Study 190-201)

Instrument	Mean (SD) at baseline	Mean (SD) at 48 weeks	Change	% Change
PedsQL Parent Report for Toddlers	60.7 (12.80)	63.3 (15.23)	2.6 (12.16)	4.3%
PedsQL Family Impact Module	61.4 (14.27)	65.1 (15.46)	3.7 (19.04)	6.0%
CLN2 disease-based QoL	74.2 (13.82)	81.9 (11.10)	8.1 (14.33)	10.9%

SOURCE: Clinical Study Report 190-201[26]

9.6.1.4 Study 190-202 results

For Study 190-202, descriptive summaries of the interim analyses only are available at the present time.

Introduction to results

Study 190-202 is an ongoing extension study of Study 190-201, with treatment scheduled to endure up to a maximum of 240 weeks (48 weeks of treatment in Study 190-201 and up to 192 weeks of treatment in Study 190-202).

Given the small sample size in these studies, interim efficacy and safety results comprise pooled data from the complete dataset of Study 190-201 were pooled across all sites and summarised with data from Study 190-202 up to the 1 November 2016 interim data cutoff date. All summaries are descriptive only. Selected efficacy results were evaluated by site on an exploratory basis.

The most recent interim analyses include data from all Study 190-202 visits up to 1 November 2016 (190-202 interim data cutoff date) in addition to all visits from Study 190-201 through study completion and database lock (190-201 complete data set).

The interim CSR presents efficacy and safety data up to 96 weeks of treatment. As of 1 November 2016, all subjects who completed 48 weeks of treatment in Study 190-201 had at least 48 weeks of additional treatment in Study 190-202; therefore, Week 96 of Study 190-201/202 (Week 48 of Study 190-202) was used for the primary efficacy analysis to ensure all subjects had maximal and equal time on study medication. Kaplan-Meier analysis of responder rates and analyses of slopes use the full 190-201 / 190-202 study duration.[22]

Primary Endpoint: Change in CLN2 clinical rating scale score (Study 190-201/202)

Table C21 summarises the distribution of 300mg CLN2 clinical rating scale scores at the time of last assessment (data cut off of 1 November 2016). In total, the mean (min, max) treatment duration at the 300 mg dose was 114.6 (0.1, 144.9) weeks for the combined Study 190-201/ 190-202.

[redacted]

Here, a positive change from baseline denotes an improvement in clinical status, and a negative change from baseline is a worsening in clinical status. These additional efficacy data for the primary analyses based on approximately 12 months of additional data after completion of Study 190-201 continue to show substantial stabilisation of disease progression with cerliponase alfa treatment.

Table C21. CLN2 clinical rating scale (Motor, Language) score at Baseline and at Last Assessment, 300mg dosing period (Study 190-201/202, ITT Population)

	Overall (n = 23)
300 mg Baseline, ML Scale	
6	2 (9%)
5	2 (9%)
4	5 (22%)
3	11 (48%)
2	2 (9%)
1	1 (4%)
0	0
Week 48 300 mg Assessment, ML Scale	
6	2 (9%)
5	1 (4%)
4	5 (22%)

	Overall (n = 23)
3	7 (30%)
2	5 (22%)
1	3 (13%)
0	1 (4%)*
Change from 300 mg Baseline to Week 48 300 mg Assessment, ML Scale	
3 (Improvement)	0
2	0
1	2 (9%)
0 (No change)	13 (57%)
-1	5 (22%)
-2	3 (13%)
-3 (Decline)	0
Week 96 300 mg Assessment, ML Scale	
6	[redacted]
5	[redacted]
4	[redacted]
3	[redacted]
2	[redacted]
1	[redacted]
0	[redacted]
Change from 300 mg Baseline to Week 96 300 mg Assessment, ML Scale	
3 (Improvement)	[redacted]
2	[redacted]
1	[redacted]
0 (No change)	[redacted]
-1	[redacted]
-2	[redacted]
-3 (Decline)	[redacted]

SOURCE: Interim Clinical Study Report for 190-202.[22]

[redacted]

At Week 96, [redacted] showed no clinical progression on the CLN2 clinical rating scale during the 300 mg treatment period. Of the [redacted] subjects with no clinical progression, [redacted] showed an overall improvement.[22]

[redacted] showed some clinical progression [redacted] lost a single point and [redacted], all of which occurred during Study 190-201. In total, [redacted] treated subjects continue to have better outcomes than the expected 2-point loss in a natural history population over a 48-week period.[22] In light of the additional exposure after completion of Study 190-201,

[redacted], suggesting continued durability of treatment effect. Furthermore, translating this rate of decline over 96 weeks, the expected loss is ~4 points for a natural history population, making the relative stability of the scores for the patients treated with cerliponase alfa even more noteworthy (see Figure C10).

Figure C10. Mean Change from 300 mg Baseline in the ML Score and CLN2 Total Score for the Overall Efficacy Population (n = 23) and Untreated Natural History Patients (n=42) by Study Week (Study 190-201/202) [74]

Figure redacted; academic in confidence

Figure C10 shows the ML score change from baseline (Panel A) and CLN2 total score change from baseline (Panel B) for the efficacy population (solid blue line) and untreated natural history patients (dashed red line). At Weeks 48 and 96, the mean decline from baseline in the ML score was, respectively, 0.5 and 2.8 for untreated patients and [redacted]. At Weeks 48 and 96, the mean decline from baseline in the CLN2 total score was, respectively, 2.8 and 4.3 for untreated patients and [redacted] in the efficacy population.

The 6-point CLN2 scale comprises 2 3-point scales: motor and language. The individual contribution of these two domains to the total scale score are presented in Appendix 17.5. Changes in the full 12-point scale score, which includes the vision and seizure domains, was a secondary endpoint and the results are presented below.

Primary Endpoint: Responder Analysis

A responder analysis (defined as absence of an unreversed 2-point decline or score of 0 in CLN2 score by Week 96 (Study Day 679 relative to first 300mg infusion in Study 190-201) was performed in the ITT population, as well as in the subset of subjects who had a 300mg baseline motor-language score that was between 3-5. Responder analyses were also produced for motor and language scores separately (defined as absence of an unreversed 1 point decline) over 96 Weeks in the ITT population.

As at 1 November 2016, the result of the responder analysis was unchanged since previous data cutoffs; [redacted] subjects responded compared to a response rate of 50% predicted in untreated patients (p = 0.0002) (Table C22). Note that the expected response rate for an untreated natural history population is ~50% for a 48-week period of follow-up and less than 50% for an 96-week period of follow-up. The expected rate of decline in ML score over a 48-week period is 2 points in a natural history population. Translating the rate of decline over 96 weeks, the expected loss is ~4 points for a natural history population. Thus, this analysis represents a conservative method of comparison between the treated and untreated populations and supports the enduring treatment effect of cerliponase alfa in this patient population.

Table C22. Responder Analysis (Primary Endpoint): Proportion of Subjects without an Unreversed 2-point Decline or Score of 0 in ML Scale Score at 96 Weeks, 300 mg Dosing Period (Study 190-201/202, ITT Population)

Outcomes	190-202 (n=23)	95% Confidence interval	1-sided p-value
Response (absence of decline)	[redacted]	[redacted]	[redacted]

Non-Response (presence of Decline)	[redacted]	[redacted]	[redacted]

A 'response' is defined as the absence of an unreversed 2-point decline or score of 0 in ML score at 80 weeks.
An unreversed 2-point decline or score of 0 is any decline of 2 points or more that had not reverted 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 reverted to > 0 at the last recorded observation.
Inference is by an exact binomial test of the null hypothesis H0: Prob(response) <= 0.50 vs. the alternative hypothesis H1 : Prob(response) > 0.50, where Prob(response) denotes the population probability of a response. The confidence interval is an exact interval.
The table considers CLN2 assessments through Day 679 (relative to first 300 mg infusion in Study 190-201).
SOURCE: Interim Clinical Study Report 190-210/202.[22]

[redacted] met the definition of a responder on the motor domain at Week 97, and [redacted] met the definition of a responder on the language domain at Week 97. The relatively stable ML scores, even past a 96-week period, support the durability of treatment effect.

[redacted] of the 23 treated subjects had no clinical progression of disease (defined as an unreversed single point loss as measured by the CLN2 scale at Week 96 (Study Day 679 relative to first 300 mg infusion). The responder rate of [redacted] significantly exceeds the untreated responder rate of 25% [redacted], as shown in Table C23.

Table C23. Proportion of Subjects without an Unreversed 1-point Decline in CLN2 Scale Score at 96 Weeks, 300 mg Dosing Period (Study 190-201/202, ITT Population)

Outcome	N =23 (%)	95% CI Absence of an unreversed 1-Point Decline	p-value
Response (Absence of decline)	[redacted]	[redacted]	[redacted]
Non-Response (Presence of decline)	[redacted]		

SOURCE: Interim Clinical Study Report 190-210/202.[22]

Responder rates for the separate motor and language domain scores for the ITT population during the 300mg dosing period are provided in Appendix 17.5.

Primary Endpoint: Time to Event Analyses

A Kaplan-Meier analysis was performed on the ITT population to examine the timing at which subjects had unreversed declines of 2 points or ML score of 0 (unresponsive to treatment). The analysis is similar to the primary endpoint and graphs the response (or lack of response) rate as a function of time on study (Figure C11). The probability of a 2-point unreversed decline by Week 97 was [redacted], which is similar to the finding of the primary responder

analysis. Similar analyses in the efficacy population (n = 21) confirm that a 2-point loss was a rare event.

Figure C11. Time to First Unreversed 2-Point Decline or Score of 0 in ML Score using Kaplan-Meier Estimation (ITT Population, 300 mg dosing period, Study 190-201/202)

Figure redacted: academic in confidence

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 reverted back to > 0 at last recorded observation.
Analysis Day 1 is the day of the first 300 mg infusion in Study 190-201.
SOURCE: Interim Clinical Study Report 190-201/202.[22]

Figure C12 shows the Time to First Event for the treated population vs. untreated natural history patients on the ML, motor, and language domains. After adjusting for baseline ML score, age, genotype and sex, compared to treated subjects, natural history patients were [redacted] times more likely to have experienced an unreversed 2-point decline in the ML score ([redacted]) (Panel A), [redacted] times more likely to have experienced an unreversed 2-point decline in the motor score ([redacted]) (Panel B), and [redacted] times more likely to have experienced an unreversed 2-point decline in the language score ([redacted]) (Panel C) than patients treated with cerliponase alfa in Studies 190-201/202. [74]

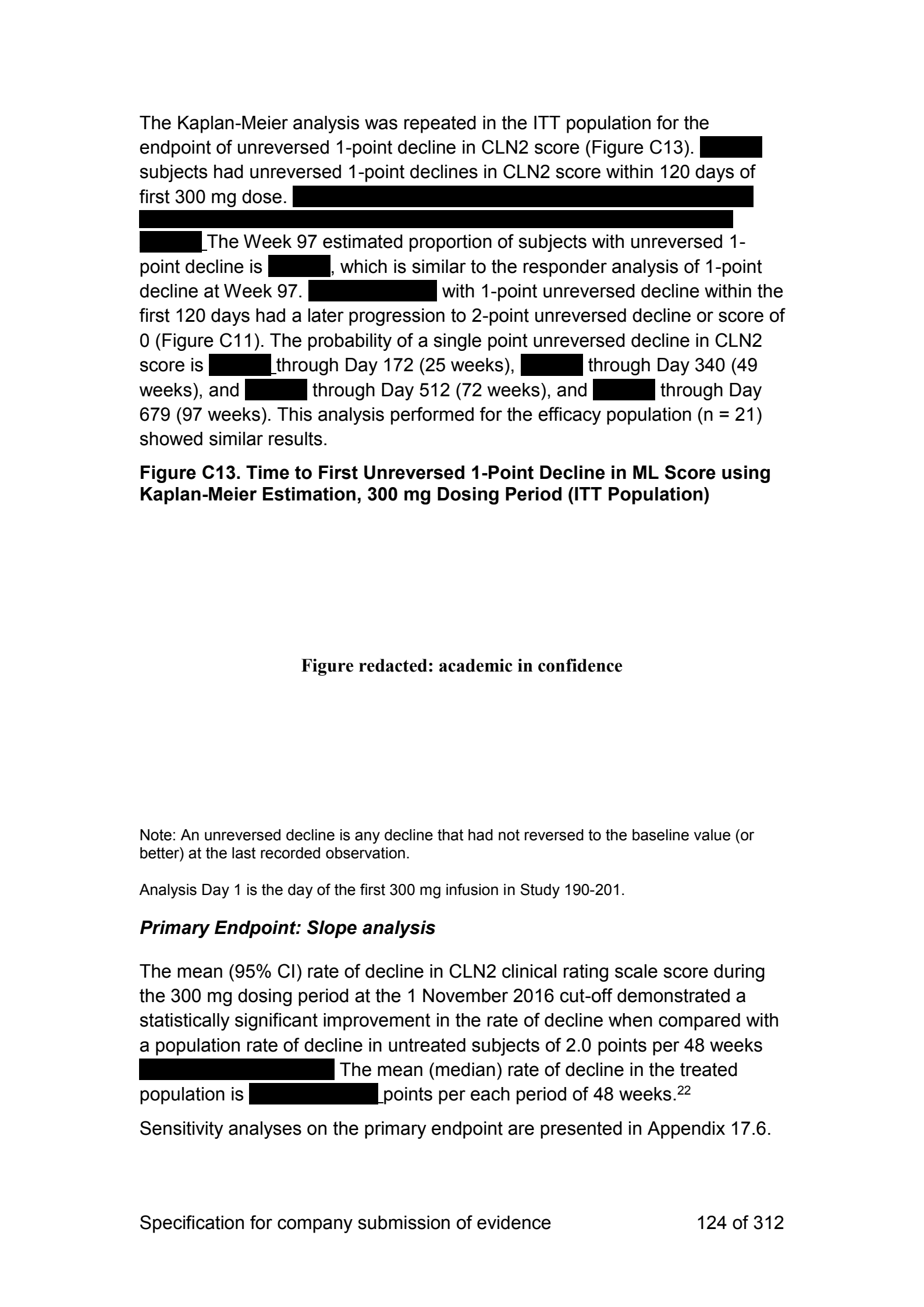
Figure C12. Time to First Event for the treated population vs. untreated natural history patients on the ML, motor, and language domains using

Kaplan-Meier Estimation (ITT Population vs. natural history patients, 300 mg dosing period, Study 190-201/202)

Figure redacted: academic in confidence

The Kaplan-Meier analysis was repeated in the ITT population for the endpoint of unreversed 1-point decline in CLN2 score (Figure C13). [redacted] subjects had unreversed 1-point declines in CLN2 score within 120 days of first 300 mg dose. [redacted] The Week 97 estimated proportion of subjects with unreversed 1-point decline is [redacted], which is similar to the responder analysis of 1-point decline at Week 97. [redacted] with 1-point unreversed decline within the first 120 days had a later progression to 2-point unreversed decline or score of 0 (Figure C11). The probability of a single point unreversed decline in CLN2 score is [redacted] through Day 172 (25 weeks), [redacted] through Day 340 (49 weeks), and [redacted] through Day 512 (72 weeks), and [redacted] through Day 679 (97 weeks). This analysis performed for the efficacy population (n = 21) showed similar results.

Figure C13. Time to First Unreversed 1-Point Decline in ML Score using Kaplan-Meier Estimation, 300 mg Dosing Period (ITT Population)



Note: An unreversed decline is any decline that had not reversed to the baseline value (or better) at the last recorded observation.

Analysis Day 1 is the day of the first 300 mg infusion in Study 190-201.

Primary Endpoint: Slope analysis

The mean (95% CI) rate of decline in CLN2 clinical rating scale score during the 300 mg dosing period at the 1 November 2016 cut-off demonstrated a statistically significant improvement in the rate of decline when compared with a population rate of decline in untreated subjects of 2.0 points per 48 weeks [redacted] The mean (median) rate of decline in the treated population is [redacted] points per each period of 48 weeks.[22]

Sensitivity analyses on the primary endpoint are presented in Appendix 17.6.

Secondary Endpoints: Study 190-202

Change from baseline analysis on Hamburg 0-9 and 0-12

Results from the extension study demonstrate a durable treatment effect and a broad-based stabilisation of disease over time that is not a function of a domain-specific treatment effect (see Table C24). Although the inclusion of the vision domain in the analysis leads to a small increase in clinical decline (mean change from 300 mg baseline was -0.7 points by Week 49 [redacted] when compared to the ML scale alone (mean change from baseline was -0.4 points by Week 49, [redacted] still represents stabilisation of disease and is mitigated by the improvement in the seizure domain score during the 300mg treatment period.[22]

Table C24. Change in clinical rating scale score including other domains of Hamburg rating scale (Study 190-201/202, ITT population)

Domains included	**Motor Language**	**Motor Language Vision**	**Motor Language Vision Seizures**
Total score available	6	9	12
300mg Baseline mean (SD) score	3.5 (1.20)	6.3 (1.34)	8.0 (1.83)
Week 49 mean (SD)	3.0 (1.33)	5.7 (1.58)	7.8 (2.07)
Week 49 mean (SD) change from Baseline	-0.4 (0.79)	-0.7 (1.03)	-0.2 (1.94)
Week 97 mean (SD)	[redacted]	[redacted]	[redacted]
Week 97 mean (SD) change from Baseline	[redacted]	[redacted]	[redacted]
Last observation (SD)	[redacted]	[redacted]	[redacted]
Last observation mean (SD) change from Baseline	[redacted]	[redacted]	[redacted]

SOURCE: Clinical Study Report 190-202[22]

[redacted] all domains can also be seen by comparing the mean change from baseline score for cerliponase alfa-treated patients with all evaluable patients in the matched natural history control population for ratings that include vision (

Figure C14) and vision and seizures (Figure C15) in addition to motor and language.

Figure C14. Mean change from baseline in score for motor, language and vision domains in cerliponase alfa-treated patients versus natural history control group

Figure redacted: academic in confidence

SOURCE: ISE updated submitted to the FDA on 16th November 2016. Figure 2.2.6[73]

Figure C15. Mean change from baseline in score for motor, language, vision and seizure domains in cerliponase alfa-treated patients versus natural history control group

Figure redacted: academic in confidence

SOURCE: ISE updated submitted to the FDA on16th November 2016. Figure 2.3.6.[73]

Change from baseline on MRI measures

On the secondary efficacy endpoint (MRI evaluation of brain volume and diffusion), at the end of Study 190-201 (Week 49), there was a mean (SD) absolute change in whole brain volume of -4.4% (8.46) in the ITT population. At Week 97 in Study 190-201/202, there was a mean (SD) absolute change in whole brain volume of [redacted]. At the last observation prior to the data cut, there was a mean (SD) absolute change in whole brain volume of [redacted].[22]

The conclusions of MRI data summarised to 48 weeks were that losses were observed in cortical grey and whole brain volumes that were less than seen in longitudinal MRI studies. [redacted][74]

Figure C16: Change in Total Cortical Gray Matter Volume as Measured by MRI during treatment on cerliponase alfa

Figure redacted: academic in confidence

SOURCE: Schulz et al. (2017). Manuscript on file.[74]

Exploratory Endpoints: Study 190-202

All evaluations were carried out on the ITT population (n=23).

Denver II developmental screening test
At study completion in Study 190-201, of the 22 subjects (96%) evaluated, all [redacted] were classified as "suspect." Over the entire Study 190-201/202 dosing period, [redacted] with a Denver II test at Week 97 were classified as "suspect," with no change in this interpretation from study baseline to Week 97.[22]

PedsQL Parent Report for Toddlers
The PedsQL Parent Report for Toddlers total PedsQL score showed a mean (SD) increase of [redacted] points from study baseline to last

observation in Study 190-201, an improvement of approximately [redacted] As of the interim data cutoff date (1 November 2016), [redacted] with a PedsQL assessment at Week 97 showed a mean (SD) change of [redacted] points from study baseline to Week 25 (see Table C25).[22]

Table C25. PedsQL: Generic Core Scale, Parent Report for Toddlers and Family Impact Module, by Nominal Timepoint (Study 190-201/202, ITT Population, Entire Dosing Period)

	Parent Report for Toddlers Module (n = 23)	Family Impact Module (n = 23)
Total Score		
Study Baseline		
N	23	23
Mean (SD)	60.7 (12.80)	61.4 (14.27)
Median	59.5	62.0
Min, Max	40.5, 81.9	38.0, 92.4
Week 49		
N	23	23
Mean (SD)	63.3 (15.23)	65.1 (15.46)
Median	61.9	64.1
Min, Max	39.3, 95.2	41.3, 95.7
Change from Study Baseline to Week 49		
N	23	23
Mean (SD)	2.6 (12.16)	3.7 (19.04)
Median	2.4	7.6
Min, Max	-17.9, 35.7	-32.6, 34.8
Week 97		
N	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
Median	[redacted]	[redacted]
Min, Max	[redacted]	[redacted]
Change from Study Baseline to Week 97		
N	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]

	Parent Report for Toddlers Module (n = 23)	Family Impact Module (n = 23)
Median	[redacted]	[redacted]
Min, Max	[redacted]	[redacted]

PedsQL scores have possible range of 0-100, inclusive, where 0 is the least favorable score and 100 is the most favorable score.
Psychosocial Health Summary is a summary across the Emotional, Social, and School Functioning scales.
[a] Baseline is defined as the last measurement prior to first infusion.
Report:
Source: Interim Clinical Study Report 190-202[22]

The PedsQL Family Impact Module total score shows a mean (SD) increase of [redacted] points from study baseline to last observation in Study 190-201, an improvement of approximately [redacted]. At Week 97, [redacted] with a PedsQL Family Impact Module score in Study 190-202 showed a mean (SD) decrease of [redacted] points from study baseline to Week 97 (see Table C25).[22]

The CLN2 disease-based instrument score shows a mean (SD) increase of [redacted] points from study baseline to last observation in Study 190-201, an improvement of approximately [redacted]. At Week 97, [redacted] with a score on the CLN2 Disease-based QoL instrument at that timepoint showed a mean (SD) increase of [redacted] points from study baseline to Week 97.

These results are consistent with the stabilisation of disease progression seen with ML scale scores (see Table C26).[22]

Table C26. CLN2 Disease-based QoL, by Nominal Timepoint (Study 190-201/202, ITT Population, Entire Dosing Period)

	Overall (n = 23)
Total Score	
Study Baseline	
N	22
Mean (SD)	74.2 (13.82)
Median	73.5
Min, Max	40.0, 99.0
Total Score	
Week 49	
N	23
Mean (SD)	81.9 (11.10)
Median	82.0
Min, Max	55.4, 99.0
Change from Study Baseline to Week 49	
N	22
Mean (SD)	8.1 (14.33)
Median	8.5
Min, Max	-13.4, 33.0
Week 97	
N	[redacted]

	Overall (n = 23)
Mean (SD)	[redacted]
Median	[redacted]
Min, Max	[redacted]
Change from Study Baseline to Week 97	
N	[redacted]
Mean (SD)	[redacted]
Median	[redacted]
Min, Max	[redacted]

CLN disease-based QoL scores have possible range of 0-100, inclusive, where 0 is the least favorable score and 100 is the most favorable score.
[a] Baseline is defined as the last measurement prior to first infusion.

SOURCE: Interim Clinical Study Report 190-202[22]

EQ-5D-5L

The ED-5D-5L QoL instrument was assessed in Study 190-202 only; baseline is defined as the first observation upon transitioning from Study 190-201 to Study 190-202.

Of the 23 subjects with data at baseline and Week 97, no change or more favourable scores were seen for most subjects ([redacted]).[22]

The EQ Visual Analogue Score (VAS) has a possible range of 0-100, inclusive, where 0 is the least favourable score and 100 is the most favourable score. The EQ VAS score shows a slight downward trend, with a mean decline of [redacted] from the time of Study 190-201/190-202 transition (n = 21) to Week 97 (n = 21).[22]

Preliminary assessment suggests there is not a precipitous drop in either the descriptive or VAS scores, and these results are generally consistent with the stabilisation seen in CLN2 scores.

9.6.1.5 Study 190-901 natural history study

Purpose and design of natural history analysis

The cerliponase alfa clinical development programme included a comparison to matched natural history controls. The purpose of the 190-901 natural history 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 natural history study 190-901 included patients from the DEM-CHILD cohort, from participating sites in Germany and Italy. These patients were matched to the Study 190-201 inclusion criteria using filters.

The 190-901 study 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 190-901 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 Hamburg CLN2 disease rating scale (and confirmed by the WCMC combined gait-language rating scale).

Eligibility criteria for 190-901 natural history analysis

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 Hamburg Motor-Language scale score.

A number of filters were applied to the 58 patients in order to align or match subjects with the patient population in Study 190-201, 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 Study 190-201.

Study 190-901 patient selection and characteristics

Of the 74 patients in the DEM-CHILD database for the 2 European centres, 41 (33 from Hamburg and 8 from Verona) conformed to the eligibility criteria for Study 190-201 indicated in section 9.4.1 and were included in the evaluable natural history control population for the purpose of the Week 48 analysis in Study 190-201 (data on an additional 8 patients became available for subsequent analyses).

Table C27 shows demographic characteristics of the 190-901 patients in the 48 week analysis. The early age of onset of disease and later diagnosis are entirely consistent with those in published studies. These demographic characteristics were not available for all patients in the database.

Table C27. Demographic characteristics of natural history patients (Study 190-901)

	Age (years)		
	Mean (SD)	**Median**	**Range**
Age at first clinical sign (n=32)[a]	2.98 (0.75)	3.0	1.5, 4.5
Age at diagnosis (n=32)[a]	4.98 (1.41)	4.8	2.9, 9.8
SOURCE: CSR 190-901 Supplemental Report 1st May 2016.[69] Adapted from table 8.3			

[a] Information on age at first clinical sign and at diagnosis was only available for 32 of the 41 patients included in the matched cohort.

Study 190-901 results - 48 weeks

Analysis of the baseline condition of the 41 patients in the evaluable natural history population found that the first CLN2 symptoms were commonly manifest around 3 years of age. Overall, the most common initial signs or symptoms of CLN2 disease were unprovoked seizures and language difficulties.

Currently, there is latency from the first observed sign or symptom to age of first diagnosis. Patients tend to be diagnosed just before their 5th birthday, nearly 2 years from the onset of symptoms, and this varies little between sites. Disease progression at the time of diagnosis is variable, with Hamburg Motor-Language scale scores most commonly in the 2-4 range.

- ***Rate of decline of CLN2 disease rating scale score***

Analysis of the rate of decline of the CLN2 clinical rating scale confirmed the rapid progression of disease reported in the publications on the natural history discussed previously[6].

The rate of decline of the CLN2 disease rating scale score expressed as points lost for each 48-week period to standardise with Study 190-201 treatment is shown in Table C28.

Table C28. Rate of decline of the CLN2 disease rating scale score in Study 190-901 (48 weeks)

Rate of decline (Points per 48 weeks)*	**Natural history population (n=41)**

Mean (SD)	2.09 (0.966)
Median	1.87
25th, 75th percentile	1.36, 2.80
Min, Max	0.45, 4.27
95% CI	1.79, 2.40
* Using line connecting first point-last point, but similar results were given by regression analysis of points between and including first and last points (Mean 2.09, SD 0.988).	
SOURCE: CSR 190-901 supplemental report 1st May 2016.[69]	

The slope of 2.09 points per 48 weeks is very similar to that reported in the natural history studies by Steinfeld et al.[8] and Nickel et al.[6] discussed in section 6.1 and greater than the 2.0 points per 48 weeks, which was the conservative estimate used in the primary analysis of Study 190-201.

- ***Estimation of 2-point residence time***

The time taken to lose 2 points on the CLN2 clinical rating scale at different stages of disease was also estimated in the 190-901 population, as an alternative way to measure the rate of decline. The time spent in months in each 2-point scale pair (5 & 4, 4 & 3, 3 & 2, 2 & 1) was estimated using assumptions that model the entrance and exit for each category. For a given 2-point scale score pair, residence time was defined as the time difference between when a patient first recorded the higher score of the pair and when the patient first recorded a score 2 points (or more) lower. A given patient can contribute data to more than one category, depending on the range of scores over which observations are available. The results are shown in Table C29.

Table C29. Time elapsed over 2 points in CLN2 disease rating scale in 190-901 natural history population

Pairs of CLN2 disease rating scale scores	**N**	**2-point residence time (months)**	
		Mean (SD)	**Median**
5 & 4	31	13.9 (11.39)	14
4 & 3	34	11.4 (10.19)	9
3 & 2	36	6.4 (6.01)	6
2 & 1	34	8.4 (8.16)	6
SOURCE: CSR 190-901 supplemental report 1st May 2016.[69]			

The rate of decline estimated from the slope analysis (2.09 points per 48 weeks) would predict about 10.6 months for each 2-point residence period, so there is good agreement between methodologies. However, it appears that the decline is more rapid in the middle stages of disease. The mean time for a 2-point decline was actually less than a year for all categories except the 5 &

4 category.

Comparison of CLN2 disease progression Study 190-201/202 and Study 190-901 patients

Descriptive analyses of the change from baseline in the CLN2 clinical rating scale were subsequently performed on all evaluable patients (N=49) up to the last data cut-off for Study 190-202. Baseline in the 190-901 analysis was defined based on the first CLN2 clinical rating scale score < 6 for patients.

After 48 weeks, the 190-901 mean (SD) baseline had declined by 2.1 (1.09) points, whereas the 190-201 treated subjects had only a 0.4 (0.79) point decline. As can be seen in Figure C17, the mean CLN2 clinical rating scale score continued to decline in 901, whereas there was no further decline in the Study 190-201/202 population from 48 weeks up to Week 97 and beyond, although there were a smaller number of data points at these later time points.

Figure C17. Mean change from baseline in CLN2 clinical rating scale score in cerliponase alfa-treated patients versus natural history control group

Figure redacted: academic in confidence

9.6.1.6 One-to-one matching of Study 190-901 control cohort to Study 190-201 patient

For the comparison of CLN2 patients treated with cerliponase alfa in Study 190-201/202 to the 190-901 natural history population, the primary analysis was based on a 1:1 matching algorithm. Each patient in Study 190-201 was

matched to a patient in the 190-901 natural history control population for their CLN2 clinical rating scale score and age within 12 months.

This method of matching was specified prior to performing any efficacy analyses and was designed to allocate the maximal number of Study 190-201 subjects to a unique 190-901 patient (no sharing). The follow-up assessments for Study 190-901 patients were included up to the longest duration that is less than or equal to the full 300mg dosing duration of the matched 190-201/202 patient. The goal of this methodology was 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.

Statistical Analysis

The primary efficacy measure was the change in CLN2 clinical rating scale score from baseline. The primary analysis was a comparison of the treatment effect of cerliponase alfa to the predicted mean decline of 2.0 points per 48 weeks in the matched natural history population. A sample size of 22 was estimated to have 90% power to detect a reduction to a decline of 0.5 points per 48 weeks compared with a natural history decline of 2.0 points per 48 weeks with $\alpha=0.05$. Analyses were performed on the treatment period starting from the baseline for the 300mg stable dose period. The base case analyses were on the ITT population.

Treatment effect was assessed by comparing the number of patients who did not experience an unreversed 2-point decline by week 48 in Study 201 with that in matched 190-901 controls using a Fisher exact test. This was a conservative estimate of the within-subject change based on review of subjects from natural history databases.

For this analysis, the proportion of subjects who did not experience an unreversed 2-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 Kaplan-Meier estimates (e.g. time to unreversed 2-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 treated patients in Study 190-201/202 and for untreated patients in the overall 190-901 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).

Baseline characteristics of matched patients (N=22)

One Study 190-201 subject could not be matched because the subject's closest match had an age difference of 21 months. The ITT population for these 1:1 matching analyses thus has an n=22. The baseline characteristics for the matched populations for the 48 week analysis are shown in Table C30.

Table C30. Baseline characteristics for 1:1 matched subjects

	Study 190-901 (n=22)	**Study 190-201/202 (n=22)**
Age at Enrolment in 190-201 (years)		
Mean (SD)	4.7 (0.77)	4.7 (0.93)
Median	4.7	4.7
Min, Max	3.5, 6.8	3.6, 7.7
Sex		
F	5 (23%)	13 (59%)
M	16 (73%)	9 (41%)
Missing	1 (5%)	0
Baseline CLN2 disease rating score		
6	2 (9%)	2 (9%)
5	2 (9%)	2 (9%)
4	5 (23%)	5 (23%)
3	10 (45%)	10 (45%)
2	2 (9%)	2 (9%)
1	1 (5%)	1 (5%)
Source: SCE 12th May 2016 Table 2.7.3.3.2.1.1, which cites ISE Table 0.1		

Proportion of patients without unreversed decline of 2 points

As for the primary analysis, the treatment effect was analysed considering the patients who did not experience an unreversed decline of 2 points in the 1:1 matched populations. The results are shown in Table C31 for the 48-week analysis. In the Study 190-201/202 population [redacted] did not experience an unreversed 2-point decline compared to 45% (10/22) in the matched 190-901 population. The estimated difference in proportion was [redacted].

Table C31. Primary analysis for 1:1 matched controls at 48 weeks

Outcome at 48 weeks	**Study 190-201/202 (n=22)**	**Matched 190-901 control (n=22)**	**Rate difference**	**2 sided p-value**
Absence of unreversed 2-point decline (positive)	[redacted]	10 (45%)	[redacted]	[redacted]
Presence of unreversed 2-point decline (negative)	[redacted]	12 (55%)		

Source: SCE dated 12th May 2016 Table 2.7.3.3.2.2.1, which cites ISE Table 3.1.1

The updated analysis at time of last data cut-off compared the proportion of patients with a rate of decline < or ≥ 2 points per 48 weeks in the 1:1 matched populations and is shown in Table C32. It can be seen that the benefit of cerliponase alfa was maintained.

Table C32. Analysis of treatment effect in 1:1 matched controls at last data cut-off (3rd June 2016) for Study 201/202 and last data transfer (11th August 2016) (Study 190-901)

Outcome at last data cut-off (June 2016)	Study 201/202 (n=22)	Matched 901 control (n=22)	Rate difference	2 sided p-value
Rate of decline < 2 points per 48 weeks (Positive)	[redacted]	10 (45%)	[redacted]	[redacted]
Rate of decline ≥2 points per 48 weeks (Negative)	[redacted]	12 (55%)		

Source: Response to FDA request for information dated 31st October 2016, Table 1 which cites updated ISE Table 3.1.1

Time to event analysis

A Kaplan-Meier (time to event) analysis was performed to examine the timing at which patients had an unreversed 2-point decline using all the data available from Study 190-201 and Study 190-202 and 1:1 matched control data up to the same duration, where available, and is shown in Figure C18. The graph for Study 190-201/202 is flat beyond 48 weeks (Analysis Day 340), whereas most patients in the natural history control had experienced a 2-point decline by 450 days.

Figure C18. Time to first unreversed 2-point decline for 1:1 matched controls

Figure redacted: academic in confidence

Source: ISE update submitted to FDA on 16th November 2016[73]: Figure 3.2.2

The hazard ratio was estimated using a Cox proportional hazards model, adjusting for baseline CLN2 clinical rating scale score, gender, and age. The hazard ratio for this analysis at the time of the October 2015 cut-off was [redacted], with 95% confidence intervals of ([redacted]). Thus at any time in the study period 190-901 patients were ten times more likely to experience an unreversed 2-point decline than the treated Study 190-201/202 patients.

Slope analysis

The rate of decline of the CLN2 clinical rating scale per 48-week time period was as described in section 9.6.1.1.1.3 using all the data available from Study 190-201/202 and 1:1 matched 190-901 controls up to the same duration. The results are shown in Table C33. The mean rate of decline in treated patients was only [redacted] per 48 weeks compared to 2.06 points per 48 weeks in matched untreated controls. [redacted]

Table C33. Rate of decline for 1:1 matched controls at 48 weeks

Rate of Decline (Points/48 weeks)	Study 201/202 (n=22)	Matched 901 controls (n=22)	Difference	2 sided p-value
N	22	22		
Mean (SD)	[redacted]	2.06 (1.379)	[redacted]	[redacted]
(SE)	[redacted]		[redacted]	
Median	[redacted]	2.36		
25th, 75th Percentile	[redacted]	1.02, 3.20		
Min, Max	[redacted]	0.00, 4.98		
95% CI	[redacted]	1.45, 2.68	[redacted]	
Source: SCE dated 12th May 2016 Table 2.7.3.3.2.4.1, which cites ISE Table 1.1.3				

The updated analysis at time of last data cut-off showed that the difference in rate of decline between treated patients and natural history controls was maintained (see Table C34).

Table C34. Rate of decline for 1:1 matched controls at last data cut-off (3rd June, 2016)

Rate of Decline (Points/48 weeks)	Study 190-201/202 (n=22)	Matched 190-901 controls (n=22)	Difference	2 sided p-value
N	22	22		
Mean (SD)	[redacted]	2.00 (1.392)	[redacted]	[redacted]
(SE)				
Median	[redacted]	2.14		
25th, 75th Percentile		0.93, 3.20		
Min, Max	[redacted]	0.00, 4.98		
95% CI	[redacted]	1.38, 2.62	[redacted]	
Source: Response to FDA request for information dated 31st October 2016, Table 2 which cites updated ISE Table 1.1.3				

9.6.2 Justify the inclusion of outcomes in table C9 from any analyses other than intention-to-treat.

All outcomes are reported in the ITT population (n=23). Where relevant, some outcomes are also presented for the efficacy population (n=21). The efficacy population excluded 2 subjects from the ITT population who had 300mg baseline ML scores of 6 and who continued to show no decline on study as of Week 97 (data cutoff 1 November 2016).

9.7 Adverse events

In section 9.7 the sponsor is required to provide information on the adverse events experienced with the technology being evaluated in relation to the scope.

For example, post-marketing surveillance data may demonstrate that the technology shows a relative lack of adverse events commonly associated with the comparator.

Overall, cerliponase alfa at a dose of 300mg administered by ICV infusion every 14 days was generally well tolerated and has an acceptable safety profile in this population of patients with significant disease burden.

- As of the data cutoff date for the interim CSR for Study 190-202 (1 November 2016), the mean (SD) exposure to cerliponase alfa was 117.0 (32.91) weeks for all doses (range 0.1-161.0) and 114.6 (30.26) weeks during the 300mg dosing period (range 0.1-144.9 weeks).
- [redacted].
- The most frequent AEs by preferred term (PT) were [redacted]. All of these AEs are consistent with the nature of CLN2 disease, the paediatric population, and administration of an ERT.
- [redacted].
- [redacted] had one or more treatment-related AEs. [redacted].
- [redacted] had at least 1 reported serious adverse event (SAE) during the entire dosing period.
- [redacted] were reported in total. [redacted] were assessed as being related to cerliponase alfa treatment ([redacted] in Study 190-201 and [redacted] in Study 190-202). [redacted].

9.7.1 Using the previous instructions in sections 9.1 to 9.6, provide details of the identification of studies on adverse events, study selection, study methodologies, critical appraisal and results.

Adverse event data were identified using the search strategy for clinical evidence from published and unpublished trials, as described in section 9.1 and Appendix 2, section 17.2.

9.7.2 Provide details of all important adverse events reported for each study. A suggested format is shown in table C10.

Overview of drug exposure in Study 190-201/202

The safety and tolerability of cerliponase alfa was evaluated in the safety population (N = 24), which comprised all subjects who had an ICV access device implanted in Study 190-201. Data were pooled with data from Study

190-202 and is reported for the entire period of treatment in Study 190-201 and up to the data cutoff (1 November 2016) for Study 190-202.[22]

[redacted]. The remaining 23 patients completed the 48-week treatment period in Study 190-201 and continued to receive treatment in Study 190-202.

At the time of data cut-off, a total of 1,420 infusions had been administered, of which 1,391 were at the licensed dose of 300mg.[22] This includes 616 total infusions (587 infusions at 300 mg) administered in Study 190-201 and 804 infusions at 300 mg administered in Study 190-202.

Summary of AEs in Study 190-201/202

Consistent with the severity of the disease and a paediatric population, [redacted] (Table C35). [redacted]

A total of [redacted] experienced SAEs; of these, [redacted] experienced SAEs considered related to cerliponase alfa. [redacted] experienced an AE assessed as related to cerliponase alfa.

Table C35. Overall Summary of Adverse Events (Safety Population, Entire Dosing Period)

Adverse Event Category	Number of Subjects (%) (n=24)
Any AE	[redacted]
Any study drug-related AE[a]	[redacted]
Any SAE	[redacted]
Any study drug-related SAE[a]	[redacted]
AE leading to study discontinuation	[redacted]
AE leading to permanent discontinuation of study drug	[redacted]
Death	[redacted]

AE, adverse event; SAE, serious adverse event
a AEs that were classified by the investigator as related to study drug
Mapping was based on MedDRA version 18.1
SOURCE: Interim Clinical Study Report 190-202.[22]

Common AEs

[redacted]

[redacted] The reported AEs also have to be interpreted in the context of an open-label study.

[redacted] experienced an AE that was assessed as being related to cerliponase alfa treatment. [redacted]

Convulsion AEs (seizure and epilepsy) are to be expected in a condition in which almost all patients have seizures reported at study baseline. Those AEs reported to be related to study drug were managed medically; they did not lead to modification of study drug dose or withdrawal from the study.

Hypersensitivity events were usually characterised by pyrexia. Some patients also experienced vomiting, pleocytosis (increased white blood cell count in CSF), and/or irritability. No association was found between serum anti-drug antibody (ADA) titer and incidence or severity of hypersensitivity AEs. Hypersensitivity events were generally mild and resolved with administration of antipyretics, antihistamines and/or glucocorticosteroids. These adverse reactions did not interfere with cerliponase alfa treatment. Pre-treatment of patients with antihistamines with or without antipyretics 30 to 60 minutes prior to the start of infusion is recommended.[22]

[redacted].[22]

Table C36 presents AEs occurring in ≥ 20% of subjects by System Organ Class (SOC) and Preferred Term (PT).

Table C36. Adverse Events Occurring in ≥ 20% of Subjects by System Organ Class and Preferred Term (Safety Population, Entire Dosing Period)

	Overall (n = 24)
Subjects with at Least 1 Reported AE	[redacted]
Gastrointestinal disorders	[redacted]
Vomiting	[redacted]

	Overall (n = 24)
Constipation	[redacted]
Diarrhoea	[redacted]
Dysphagia	[redacted]
General disorder and administration site conditions	[redacted]
Pyrexia	[redacted]
Gait disturbance	[redacted]
Immune system disorder	[redacted]
Hypersensitivity	[redacted]
Infections and infestations	[redacted]
Upper respiratory tract infection	[redacted]
Nasopharyngitis	[redacted]
Gastroenteritis	[redacted]
Pharyngitis	[redacted]
Rhinitis	[redacted]
Viral infection	[redacted]
Tonsillitis	[redacted]
Injury, poisoning, and procedural complications	[redacted]
Fall	[redacted]
Head injury	[redacted]
Nervous system disorders	[redacted]
Seizure	[redacted]
Epilepsy	[redacted]
Myoclonus	[redacted]
Tremor	[redacted]

	Overall (n = 24)
Dystonia	[redacted]
Generalised tonic-clonic seizure	[redacted]
Extensor plantar response	[redacted]
Petit mal epilepsy	[redacted]
Product issues	[redacted]
Needle issue	[redacted]
Psychiatric disorders	[redacted]
Insomnia	[redacted]
Respiratory, thoracic, and mediastinal disorders	[redacted]
Cough	[redacted]

AE, adverse event

Subjects who experience more than 1 AE within a given MedDRA system organ class or preferred term were counted once within that system organ class or preferred term. Mapping was based on MedDRA version 18.1.

Source: Interim Clinical Study Report 190-202.[22]

Serious AEs in Study 190-201/202

[redacted] during the entire dosing period. A total of [redacted].

[redacted]

[redacted].[22]

Drug-related SAEs

[redacted].[22]

Device-related SAEs

Hypersensitivity AEs were expected to occur with BMN 190 treatment, as with any biologic agent. [redacted].

[redacted][22]

Device-related AEs

[redacted]

9.7.3 Provide a brief overview of the safety of the technology in relation to the scope.

As of the data cutoff date for the interim CSR for Study 190-202 (1 November 2016), the mean (SD) exposure to cerliponase alfa was [redacted] weeks for all doses [redacted] and [redacted] weeks during the 300mg dosing period [redacted].[22]

Overall, cerliponase alfa at a dose of 300 mg every 14 days administered by ICV infusion was generally well tolerated and has an acceptable safety profile in this population of subjects with significant disease burden.

Interim safety results, inclusive of all AEs reported in both the 190-201 and 190-202 studies, are as follows:

[redacted]

Epilepsy is a hallmark of CLN2 disease. Medical history of convulsion (i.e., seizures and epilepsy) was reported in [redacted] subjects, thus a sizeable number of AEs of convulsion was expected during Study 190-201/ 190-202. A small subset of all convulsion AEs were reported to be related to study drug [redacted] these AEs were managed medically and did not warrant modification of study drug dose or termination from the study. None of the [redacted] were judged to be related to study drug.[22]

The most common hypersensitivity AE by PT was hypersensitivity, occurring in [redacted] and usually characterised by pyrexia. No association was found between serum anti-drug antibody (ADA) titer and incidence or severity of hypersensitivity AEs. Hypersensitivity events were medically managed with antipyretics, antibiotics, antihistamines and/or steroids in all subjects.[22]

[redacted]

Overall, the data from the 190-201/ 190-202 studies demonstrate an acceptable safety profile for long-term administration of cerliponase alfa in patients with CLN2 disease.

9.8 Evidence synthesis and meta-analysis

When more than one study is available and the methodology is comparable, a meta-analysis should be considered.

Section 9.8 should be read in conjunction with the 'Guide to the Methods of Technology Appraisal', available from www.nice.org.uk/guidance/ta

9.8.1 Describe the technique used for evidence synthesis and/or meta-analysis. Include a rationale for the studies selected, details of the methodology used and the results of the analysis.

Outcomes from the primary study, Study 190-201, and its long-term extension, Study 190-202, have been pooled using a variety of statistical analyses and methods. Further details on these analyses are provided in the interim CSR for Study 190-202. Beyond that, no other evidence synthesis or meta-analysis has been undertaken, other than a focus on the relevant populations for analysis as below.

Evidence synthesis is driven by the complexity of the disease and ethical concerns in subjecting patients with CLN2 to a clinical study. The Study 190-201 pivotal study duration was limited to 48 weeks duration due to ethical concerns. However, in this study, statistical significance was met on the primary outcome measure. As with other ERTs, secondary and tertiary outcomes can take much longer to develop – typically 2-3 years.

All of the patients who completed 48 weeks of treatment in Study 190-201 (n=23) continue to be studied in the Study 190-202 extension study, for a total treatment period of up to 240 weeks. All subjects have received at least 96 weeks of treatment so far.

As both Study 190-201 and Study 190-202 are open-label, non-comparative studies, the longitudinal natural history 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 reanalysed to focus on a population that matched the population enrolled in Study 190-201 in order to ensure a representative and relevant natural history cohort/control for comparison.

9.8.2 If evidence synthesis is not considered appropriate, give a rationale and provide a qualitative review. The review should summarise the overall results of the individual studies with reference to their critical appraisal.

Not applicable.

9.9 Interpretation of clinical evidence

9.9.1 Provide a statement of principal findings from the clinical evidence highlighting the clinical benefit and any risks relating to adverse events from the technology. Please also include the Number

Needed to Treat (NNT) and Number Needed to Harm (NNH) and how these results were calculated.

Study 190-202 interim efficacy results include pooled data from the complete dataset from Study 190-201 and interim data from Study 190-202 up to the 01 November 2016 data cutoff date.

The primary efficacy endpoint (the adapted CLN2 ML rating scale) was assessed by several methods of analysis and was based on the ITT population. As of the data cut-off, all subjects who completed 48 weeks of treatment in Study 190-201 had at least 48 weeks of additional treatment in Study 190-202; therefore, Week 96 of Study 190-201/202 (Week 48 of Study 190-202) was used for the primary efficacy analysis to ensure all subjects had maximal and equal time on study medication.

The primary efficacy analysis was a responder performed to determine the proportion of responders on the CLN2 clinical rating scale. The responder rate was 87% (20 of 23 treated subjects), which significantly exceeded the expected (conservative) untreated rate of 50% ($p = 0.0002$). The response rate over a treatment period of ≥ 96 weeks is expected to be much less than 50%. Likewise, the responder rate for an unreversed single point drop (no change or improvement on treatment) was [redacted], which significantly exceeded the predicted (conservative) rate of 25% ([redacted]). Motor and language domains were evaluated individually, and the treatment response was observed in both subscales.

In total, 20 of 23 (87%) treated subjects had better outcomes than the expected 2-point loss in an untreated population. This proportion of subjects with less than 2-point decline is unchanged between the initial 48-week 190-201 study and the 96-week time point in the combined 190-201/ 190-202 studies, suggesting durability of treatment effect.This support the persective that over time patients achieve stabilisation of disease, with some obtaining stabilization earlier than others. The variation in time to stabilization is as a result of the amount of time to remove existing waste storage material in the lysosomes of brain cells, as supported by the last MRI analysis

Time-to-event (TTE) analysis demonstrated that 8 subjects had an unreversed 1-point decline early (during the first 120 days of 300 mg dosing). Four of these 8 subjects progressed further to an unreversed 2-point decline. In addition, there were 5 subjects who had an unreversed 1-point decline later (after the first 120 days of 300 mg dosing) and none of these subjects had further decline beyond 1 point.

The slopes analysis presents the results in Study 190-201 / 190-202 as a rate of decline per 48 weeks as compared to the natural history population. There was a statistically significant reduction ($p < 0.0001$) in the rate of decline on the ML scale for the ITT population when compared with a population rate of decline in untreated natural history patients over at least 96 weeks (up to 145 weeks in Study 190-201/ 190-202). [redacted] For the untreated natural history patients, the mean rate of decline was estimated to be 2.0 points per 48 weeks on the ML scale.

On the primary efficacy variable, all analyses performed comparing the Study 201/202 population treated with cerliponase alfa 300mg every other week to natural history controls show strong, statistically significant results in favour of treated subjects. These results were confirmed to be robust by multiple sensitivity analyses, which varied the populations being examined, the methods of analysis and the criteria used to match natural history and treated patients. Results based on matching were similar to unmatched analyses and each analysis supported the underlying primary analysis. The treatment effect of cerliponase alfa was shown to be durable, with stable or even improved outcomes in the subjects treated with 300mg every other week for between 48-113 weeks, versus steady and almost uniformly progressive clinical decline in the natural history population.

[redacted]
weeks of treatment, showing a stabilisation in volume measurements in that period and suggesting that stabilisation in the loss of cortical grey matter volume occurs, but detection is delayed in relation to clinical scores.

The clinical findings were supported by quality of life outcomes. [redacted].

9.9.2 Provide a summary of the strengths and limitations of the clinical-evidence base of the technology.

Strengths

- Study 190-201/202 is the largest clinical study of an internvetional treatment for patients with CLN2 disease, providing long-term efficacy and safety data of up to 240 weeks. Although the study is still ongoing, data on all evaluable patients (n=23) is available for all outcomes for at least 96 weeks of treatment.

- The patients included in the 190-201/202 study have been recruited largely from US and European sites and are representative of CLN2 patients seen in UK clinical practice. The baseline characteristics of the study patients are also very similar to those seen in the natural history population.

- In addition, a well established independent longitudinal study of natural history funded by the EU FP7 grant as the DEMCHILD patient cohort with similar clinical endpoints allowed matching of patients and a stronger understanding of disease progression

- A wide variety of analyses have been evaluated on the primary endpoint of ordinal change in CLN2 clinical rating scale ML score from baseline, including survival, slope (rate of decline) and responder analyses. Sensitivity analyses have also been conducted on the primary endpoint. All of these analyses demonstrate the robustness of the main conclusions.

- Although the 190-201/202 has no comparator arm for ethical and practical reasons, the manufacturer used natural history controls for comparative purposes and conducted a matched cohort comparison with natural history patients who matched the clinical trial patients by CLN2 clinical rating scale score and age.

Limitations

- Study 190-201/202 is a non-randomised clinical trial, with no comparator arm and including only a small number of patients (n=24 were randomised to treatment). The lack of a comparator arm is as a result of the ethical and practical considerations of ICV insertion in patients receiving placebo.However, CLN2 disease is an extremely rare, life-limiting condition for which there was no pharmacological

treatment approved for use, prior to cerliponase alfa. Consequently, these limitations in study design and methodology, coupled with the small number of patients, are inevitable features of undertaking a clinical trial for an active treatment for patients with such a rare disease.

9.9.3 Provide a brief statement on the relevance of the evidence base to the scope. This should focus on the claimed patient- and specialised service-benefits described in the scope.

The clinical development programme for cerliponase alfa provides evidence of clinical benefit in the form of stabilisation of disease progression and health-related quality of life for CLN2 patients of all ages and across all stages of disease, irrespective of baseline CLN2 clinical rating scale ML score and patient genotype.

In Study 190-201, 20 of 23 (87%) treated subjects had better outcomes than the expected 2-point loss in an untreated population over 48 weeks of treatment. These benefits have been sustained over at least 96 weeks of treatment in Study 190-201/202, suggesting that cerliponase alfa stabilises disease progression and has a durable, long-term effect.

The clinical relevance of stabilising the decline in function is supported by an improvement in HRQL assessments, with mean increases from baseline in the total score of up to 10%, depending upon the instrument used.

Cerliponase alfa is a highly innovative, breakthrough technology which, once it becomes routinely available, will represent a step-change in the management of CLN2 disease.

The introduction of cerliponase alfa will enable patients have a standardised and centralised access to multi-disciplinary and specialist care within the existing Lysosomal Storage Disorder (LSD) network leading to better care and improved outcomes for patients. Currently, access to specialist care across England is patchy and highly variable, leading to sub-optimal outcomes for many patients and their families.

9.9.4 Identify any factors that may influence the external validity of study results to patients in routine clinical practice.

As stated above, limitations in study design and methodology (open-label, no comparator arm), coupled with the small number of patients, are inevitable features of undertaking a clinical trial for an active treatment for patients with

such a rare disease. Study 190-201/202 includes the largest number of patients with CLN2 disease who are receiving an active intervention in a clinical trial setting.

The patients included in the 190-201/202 study have been recruited largely from US and European sites and are representative of CLN2 patients seen in UK clinical practice. The baseline characteristics of the study patients are also very similar to those seen in the natural history population.

BioMarin is not aware of any other factors that may influence the external validity of the study results in routine clinical practice.

9.9.5 Based on external validity factors identified in 9.9.4 describe any criteria that would be used in clinical practice to select patients for whom the technology would be suitable.

Not applicable.

10 Measurement and valuation of health effects

Patient experience

10.1.1 Please outline the aspects of the condition that most affect patients' quality of life.

In the early stages of disease, the overarching aim of symptom management is to maintain function and involvement in mainstream activities as long as possible. As the disease progresses, the symptoms become more difficult to control, and patients are also at greater risk of new complications such as pressure sores due to immobility and risk of aspiration of food due to swallowing difficulties.[4, 8] The therapeutic goal thus evolves to maintaining quality of life despite the loss of function. In the later stages of disease, increasing levels of multidisciplinary support are required for the patient, parents and family and discussion of end of life care involves planning and decision-making.[23, 24]

CLN2 leads to a large and broad-ranging reduction in health-related quality of life (HRQL) of patients compared with the general population with the exception of family cohesion.[16]b CLN2 disease has a wide-ranging and severe impact on caregivers, siblings and families, with personal and financial adjustment needed as one parent often needs to give full-time commitment to care-giving.[13, 21]

Further details have been presented in section 7.

10.1.2 Please describe how a patient's health-related quality of life (HRQL) is likely to change over the course of the condition.

As has been previously described in section 6.1 and section 7, CLN2 is a rapidly progressing neurodegenerative disease, and so the patient's health-related quality of life (HRQL) deteriorates as the disease progresses and the infant becomes older.

HRQL data derived from clinical trials

10.1.3 If HRQL data were collected in the clinical trials identified in section 9 (Impact of the new technology), please comment on whether the HRQL data are consistent with the reference case.

HRQL was assessed in Studies 190-201 and 190-202 as an exploratory endpoint using the following instruments:

- PedsQL – Including Parent Report for Toddlers Module and a Family impact Module
- A CLN2 disease-specific QoL instrument.

Scores on these instruments range from 0 to 100, with higher scores relating to better function.

In addition, in Study 190-202 only, HRQL was also assessed using the EQ-5D-5L instrument. This is composed of 2 parts: a descriptive system that assesses 5 levels of perceived problems (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) in 5 dimensions and the EQ visual analogue scale (EQ VAS) assessment for overall health.

The results of these exploratory endpoints are presented in section 9.6.1.2 (Study 190-201) and section 9.6.1.3 (Study 190-202).

A utility study was conducted by BioMarin in 2017, in order to obtain utility values for the health states in the cost-effectiveness model.[75] Further details are provided in section 12.2.1 and section 10.1.10.

Mapping

10.1.4 If mapping was used to transform any of the utilities or quality-of-life data in clinical trials, please provide the following information.

- Which tool was mapped from and onto what other tool? For example, SF-36 to EQ-5D.
- Details of the methodology used.
- Details of validation of the mapping technique.

No mapping was carried out as a planned analysis of the HRQL data collected during Study 190-201/202. An exploratory mapping of the PedsQL data to EQ-5D-3L utility scores, using the algorithm described in Khan et al. (2014),[76] was conducted in order to provide data for a scenario analysis of the cost-effectiveness model. Please see section 12.4.1 for further details.

HRQL studies

10.1.5 Please provide a systematic search of HRQL data. Consider published and unpublished studies, including any original research commissioned for this technology. Provide the rationale for terms used in the search strategy and any inclusion and exclusion criteria used. The search strategy used should be provided in appendix 17.1.

Given the very small body of evidence surrounding CLN2 disease and TPP1 deficiency, a broad scope was used for the single SLR which aimed to identify all literature published since database inception on the health-related quality of life (HRQL), all economic evaluations and studies presenting cost and resource use data (CRU) for patients with CLN2 disease or TPP1 deficiency and/or their carers. Six strategic approaches were taken to identify this evidence:

- A search of the following electronic databases:
  - MEDLINE, including MEDLINE Daily, MEDLINE In-Process and Epub via Ovid SP
  - The Cochrane Library Databases via the Wiley Online Platform
    - The Heath Technology Assessment Database (HTA)
    - The NHS Economic Evaluation Database (NHS-EED)
  - Embase via Ovid SP
- A manual search of congress proceedings from the last two years:
  - International Conference on Neuronal Ceroid Lipofuscinosis (2016)
  - WORLD Symposium (2015, 2016)
  - International Child Neurology Congress (2016)
  - Society for the Study of Inborn Errors of Metabolism Meeting (2016)
  - International Society for Pharmacoeconomics and outcomes research (European meetings in 2015, 2016)
- Manual checking of reference lists of all relevant SLRs and (network) meta-analyses identified in the course of the review
- A search of HTA body websites for relevant, previous health technology assessment submissions
  - National Institute of Health and Care Excellence (NICE)
  - All Wales Medical Strategy Group (AWMSG)
  - Scottish Medical Consortium (SMC)
- A search of the WHO ICTRP for trials focusing on CLN2 disease or TPP1 deficiency was conducted to identify unpublished trials. Relevant trials

were cross-checked against the results obtained from the five other strategic approaches to ensure no duplication or incorrect classification of studies.

- For the HRQL data only: searching of online databases of health state utility values
  - The Cost-effectiveness Analysis (CEA) Registry, managed by Tufts Medical Center
  - The University of Sheffield Health Utilities Database
  - The EQ-5D Publications Database

Full details of each of these search strategies are provided in Appendix 8, section 17.8. The eligibility criteria for these reviews are provided in section 11.1.2.

Following the systematic review, a supplementary search was run in the internal BioMarin database in August 2017 to identify any relevant published records which became available after the systematic searches were run.

10.1.6 Provide details of the studies in which HRQL is measured. Include the following, but note that the list is not exhaustive.

- Population in which health effects were measured.
- Information on recruitment.
- Interventions and comparators.
- Sample size.
- Response rates.
- Description of health states.
- Adverse events.
- Appropriateness of health states given condition and treatment pathway.
- Method of elicitation.
- Method of valuation.
- Mapping.
- Uncertainty around values.
- Consistency with reference case.
- Results with confidence intervals.

One study was identified that reported on health-related quality of life in families of children with CLN2 disease (Table C37). In this study, Ballinger et al. (2016) administered a survey to caregivers and adult siblings of (self-

reported) CLN2 patients from 19 different families in the United Kingdom and Germany (as well as countries bordering Germany). Caregivers reported generally lower health-related quality of life compared to matched controls in the general population (as measured by EQ-5D), with the main negative influences being pain, depression and anxiety.[77]

Table C37. Study characteristics and data extracted from included health state utility studies

Study	Description of population and recruitment method	Country	Sample size and response rate	Intervention and comparator	Description of health states and adverse events	Methods of elicitation and valuation	Results	Appropriateness of study for cost-consequence evaluation
Ballinger 2016[77] (ICON Study)	Caregivers and adult siblings (aged ≥18 years) or child siblings (aged 6–17) of patients with CLN2 disease (self-reported) who were residents in the UK, Germany or countries bordering Germany (specific countries not specified) who were	UK, Germany or countries bordering Germany (specific countries not specified).	<u>UK</u> Families n=9 Individuals n=17 • Primary caregiver n=9* • Secondary caregiver n=5 • Sibling n=3 <u>Germany</u> Families n=10 Individuals n=16 • Primary caregiver n=10 • Secondary caregiver	N/A	Health states and adverse events were not reported.	EQ-5D-5L was completed in paper format by each respondent. Summary scores were derived according to recommended procedures. Qualitative surveys were conducted face-to-face at family homes or quiet rooms in hospital. Audio recordings were transcribed	<u>EQ-5D scores:</u> **Pop-ulation** / **Utility Score (SD)** England: 0.775 Age/ gender matched control: 0.890 Germany: 0.870 Age/ gender matched control: 0.953 By EQ-5D caregivers reported at least some problems across all domains except 'self-care'. A total of 7 (22%), reported moderate or severe	<u>Consistency with reference case:</u> The qualitative results are not consistent with the reference case. The utility values reported are consistent with the reference case in as far as the use of the EQ-5D-5L instrument and this was completed directly by carers, however it was not clear whether a certain health state was valued or the tariff used to determine the utility values,

Study	Description of population and recruitment method	Country	Sample size and response rate	Intervention and comparator	Description of health states and adverse events	Methods of elicitation and valuation	Results	Appropriateness of study for cost-consequence evaluation
	sufficiently fluent in English or German and able to provide written informed consent (aged ≥16 in UK or ≥18 in Germany) or informed assent with caregiver written consent (child siblings aged 6–15). Any caregivers or siblings who were participating or who had		n=5** • Sibling n=1 Response rate was not reported. *Both the mother and father in one family classified themselves as the primary caregiver. **Primary or secondary status was missing from one participant so they were classified as secondary, as			verbatim and thematic analysis was conducted to identify emerging themes.	pain, and 9 (29%) reported moderate or severe depression and anxiety. Caregivers of deceased children still reported at least slight problems with depression or anxiety (n=6, 60%), and pain (n=5, 50%). No clear patterns by disease stage emerged. <u>Qualitative survey results:</u> Of 28 parents of a child with CLN2 disease, the average number of hours of sleep per night was reported as just 5.38. They	therefore this may not reflect the preferences of the UK general public. <u>Appropriateness for cost-consequence model:</u> The EQ-5D scores are relevant to the cost-consequence model as the UK value can be applied to the caregiver health state. The qualitative data on the effect of disrupted sleep are less appropriate for the model as it

Study	Description of population and recruitment method	Country	Sample size and response rate	Intervention and comparator	Description of health states and adverse events	Methods of elicitation and valuation	Results	Appropriateness of study for cost-consequence evaluation
	participated in any clinical trial for CLN2 disease were excluded. These individuals were enrolled in a mixed-methods survey.		their spouse had indicated themselves as the primary caregiver.				reported that this disrupted sleep resulted in: feeling tired/weary all the time, being "grumpy" with their partner, worsened ability to concentrate at work and difficulty remembering things.	was not quantitatively determined.

ABBREVIATIONS: CLN2: genetically/enzymatically confirmed neuronal ceroid lipofuscinosis type 2; EQ-5D-5L: EuroQol 5 dimensions 5 levels questionnaire; SD: standard deviation.

10.1.7 Please highlight any key differences between the values derived from the literature search and those reported in or mapped from the clinical trials.

The only HRQL study identified in the literature search was the Ballinger et al. (2016) study. This study reported on HRQL of relatives and caregivers of children with CLN2 disease, as opposed to the patients themselves. As such the values derived from the literature search were not sufficient for the cost-effectiveness analysis.

Adverse events

10.1.8 Please describe how adverse events have an impact on HRQL.

Adverse events are understood to have a temporary impact on HRQL, and are typically resolved by infusion adjustments and treatment with antihistamines and antipyretics. Further details of the adverse events experienced by patients receiving cerliponase alfa in Study 190-201/202 are provided in section 9.7. The effect of adverse events on HRQL is accounted for in the cost-effectiveness model, and is detailed in section 12.1.7.

Quality-of-life data used in cost-effectiveness analysis

10.1.9 Please summarise the values you have chosen for your cost-effectiveness analysis in the following table. Justify the choice of utility values, giving consideration to the reference case.

The base case of the cost-effectiveness analysis uses utility values collected during the utility study conducted by BioMarin in 2017.[75] This study provided utility values for all of the health states in the cost-effectiveness model, for both patients receiving cerliponase alfa and on standard of care. Further details are provided in section 12.2.1 and section 10.1.10.

The utility values used for the base case cost-effectiveness analysis are shown in Table C38.

Table C38. Values used for cost-effectiveness analysis

Health state	Cerliponase alfa	Standard care
Health state 1	[redacted]	[redacted]
Health state 2	[redacted]	[redacted]
Health state 3	[redacted]	[redacted]
Health state 4	[redacted]	[redacted]
Health state 5	[redacted]	[redacted]
Health state 6	[redacted]	[redacted]
Health state 7	[redacted]	[redacted]
Health state 8	[redacted]	[redacted]
Health state 9	[redacted]	[redacted]
Health state 10 (death)	[redacted]	[redacted]

Please note that the cost-effectiveness model includes a scenario analysis using utility scores derived from an exploratory mapping of the PedsQL data collected during Study 190-201/202 to EQ-5D-3L via the algorithm described in Khan et al. (2014).[76] Please see section 12.4.1 for further details.

10.1.10 If clinical experts assessed the applicability of values available or estimated any values, please provide the following details[1]:

- the criteria for selecting the experts
- the number of experts approached
- the number of experts who participated
- declaration of potential conflict(s) of interest from each expert or medical speciality whose opinion was sought
- the background information provided and its consistency with the totality of the evidence provided in the submission
- the method used to collect the opinions
- the medium used to collect opinions (for example, was information gathered by direct interview, telephone interview or self-administered questionnaire?)
- the questions asked

[1] Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee.

- whether iteration was used in the collation of opinions and if so, how it was used (for example, the Delphi technique).

A utility study was conducted by BioMarin in July 2017 to inform the utility values used in the base case of the cost-effectiveness analysis.[75] The study employed an indirect elicitation method using proxy-reporting via clinicians and is described below, with further details provided in sections 12.2.1 and 10.1.10.

Eight international clinical experts working in three different treatment centres (in the UK, Germany and Italy), were selected for this study. Experts were identified based on their experience with cerliponase alfa and treatment of patients with CLN2 disease.

Two brief descriptions – vignettes – were prepared for each of the nine health states of the cost-effectiveness analysis, one describing a patient at a given health state being treated with cerliponase alfa and one describing an equivalent patient being treated with standard of care (18 vignettes were developed in total). The vignettes described the most common combination of motor and language domain scores that gave the relevant CLN2 clinical rating scale score for that health state. Additional details of vision loss and the requirement of palliative care were also included in the vignettes for health states 8 and 9, as per the health state definitions. The vignettes were validated by a clinical expert with experience of CLN2 disease and cerliponase alfa (please see section 12.2.5 for further details), to ensure that they were realistic and representative of the reality of the patient experience at different stages of disease progression. Details of other progressive symptoms (epilepsy, reported distress, dystonia, myoclonus, and the requirement of a feeding tube) were included in the vignettes as deemed appropriate by the clinical expert. The vignettes can be found in full in the appendices (section 17.10).

Prior to completion of the questionnaire, brief background information about the economic model, and the use of utility values within the economic model was presented to the participants via teleconference. The vignettes were then sent to the eight clinical experts, who were asked to complete an online version of the EQ-5D-5L questionnaire (prepared in the online software Typeform and validated by EuroQoL prior to use), as a proxy for patients that would be experiencing the description given in the vignettes. The EQ-5D-5L values were mapped to EQ-5D-5L values to obtain the utility values used in the model, in line with NICE preferences.[78, 79]

The values obtained from the utility study, to be used in the cost-effectiveness model, were then presented to the clinical experts, who confirmed that these results represented clinical reality.

10.1.11 Please define what a patient experiences in the health states in terms of HRQL. Is it constant or does it cover potential variances?

A description of patient experience in each of the health states in the economic model is provided in the vignettes that were prepared for each health state and as mentioned above validated by a clinical expert. The vignettes can be found in full in the appendices (section 17.10).

10.1.12 Were any health effects identified in the literature or clinical trials excluded from the analysis? If so, why were they excluded?

No health effects identified in the literature or clinical trials were excluded from the analysis.

10.1.13 If appropriate, what was the baseline quality of life assumed in the analysis if different from health states? Were quality-of-life events taken from this baseline?

The utility study described above was specific for the health states in the cost-effectiveness analysis, as such no adjustments were made for baseline utility.

10.1.14 Please clarify whether HRQL is assumed to be constant over time. If not, provide details of how HRQL changes with time.

HRQL is assumed to be constant over time for each health state. A discount rate of 1.5% was applied in the base case of the cost-effectiveness analysis (please see section 12.1), to account for discounting of QALYs over time.

10.1.15 Have the values been amended? If so, please describe how and why they have been altered and the methodology.

HRQL values obtained from the utility study were not amended.

Treatment continuation rules

10.1.16 Please note that the following question refers to clinical continuation rules and not patient access schemes. Has a treatment continuation rule been assumed? If the rule is not stated in the (draft) SPC/IFU, this should be presented as a separate scenario by considering it as an additional treatment strategy

alongside the base-case interventions and comparators.

Consideration should be given to the following.

- The costs and health consequences of factors as a result of implementing the continuation rule (for example, any additional monitoring required).
- The robustness and plausibility of the endpoint on which the rule is based.
- Whether the 'response' criteria defined in the rule can be reasonably achieved.
- The appropriateness and robustness of the time at which response is measured.
- Whether the rule can be incorporated into routine clinical practice.
- Whether the rule is likely to predict those patients for whom the technology constitutes particular value for money.
- Issues with respect to withdrawal of treatment from non-responders and other equity considerations.

Treatment with cerliponase alfa was assumed to stop in the cost-effectiveness model when a score of 0 is reached on the CLN2 clinical rating scale (equivalent to health state 7). This stopping rule was validated by clinical experts, as described in section 12.2.5. At this point, patients were assumed to use the same transition probabilities and utility values as the patients in the standard care arm, as described in more detail in section 12.2.1.

Section D – Value for Money and cost to the NHS and personal social services

Section D requires sponsors to present economic evidence for their technology. All statements should be evidence-based and directly relevant to the decision problem.

11 Existing economic studies

11.1 Identification of studies

11.1.1 Describe the strategies used to retrieve relevant health economics studies from the published literature and to identify all unpublished data. The search strategy used should be provided as in section 17.3.

Health economic data were identified using the broad search strategy outlined in the HRQL studies section 10.1.5 and Appendix 8, section 17.8.

11.1.2 Describe the inclusion and exclusion criteria used to select studies from the published and unpublished literature. Suggested headings are listed in table D1 below. Other headings should be used if necessary.

Articles were included in the SLR if they met the eligibility criteria presented in Table D1.

Table D1. Selection criteria used for health economic studies

Domain	Economic evaluations	Utility Studies	Cost and resource use studies	Justification
Inclusion criteria				

Domain	Economic evaluations	Utility Studies	Cost and resource use studies	Justification
Population	Patients with any variant of CLN2 disease or TPP1 deficiency	Patients with any variant of CLN2 disease or TPP1 deficiency, their family or their carers	Patients with any variant of CLN2 disease or TPP1 deficiency	Patients with CLN2 disease are specified in the decision problem. The impact of the disease on HRQL of family or carers, as well as on patients, was also specified in the decision problem.
Interventions	Any intervention			Due to the lack of existing treatments, a broad approach with regards to both intervention and comparator was adopted.
Comparators	Any or no comparator			
Outcomes	Outcomes of relevant study designs, including: ICERs Cost per clinical outcome Total QALYs Total (progression-free) life years gained Total costs Incremental costs and QALYs	Original health state utility data, for example those measured using: EQ-5D SF-6D HUI3 Time trade-off Standard gamble CHU9D Any other relevant HRQL data	Original costs and resource use data	These outcomes encompass the economic outcomes specified as relevant in the NICE decision problem for this submission.
Study design	Any of the following analysis types: Cost-effectiveness Cost-utility	Primary research publications (e.g. discrete choice experiments, observational studies, cross-sectional studies, randomised controlled trials [RCTs] and non-RCTs)	Primary research publications (e.g. observational studies, cross-sectional studies, RCTs and non-RCTs)	The study designs specified as eligible for inclusion were those considered most likely to report relevant data for this SLR.

Domain	Economic evaluations	Utility Studies	Cost and resource use studies	Justification
	Cost-benefit Cost-minimisation Cost-consequence			
	SLRs, meta-analyses and HTAs (to be included at the title/abstract review stage, then excluded following supplementary searching of their reference lists at the full-text review stage) unless presenting original data			
Other considerations	English language full-texts Studies on human subjects			The review team did not have the linguistic capability to review non-English language articles; however, studies were not limited to those conducted in specific geographical locations. Additionally, studies on non-human subjects were not considered relevant to the decision problem.
Exclusion criteria				
Population	Individuals without any variant of CLN2 disease or TPP1 deficiency, their family or their carers			Patients without CLN2 disease were not relevant to the decision problem.
Interventions	No limits regarding interventions			Due to the lack of existing treatments, a broad approach with regards to both intervention and comparator was adopted.
Comparators	No limits regarding comparators			
Outcomes	Studies not presenting relevant outcomes	Studies not reporting original HRQL data	Studies not reporting original, relevant cost or resource use data	Outcomes which were not specified as relevant in the NICE decision problem for this submission were excluded.
Study design	Publications without original data Comments Letters Editorials			Study designs not specified as eligible for inclusion were those considered least likely to report relevant data for this SLR.

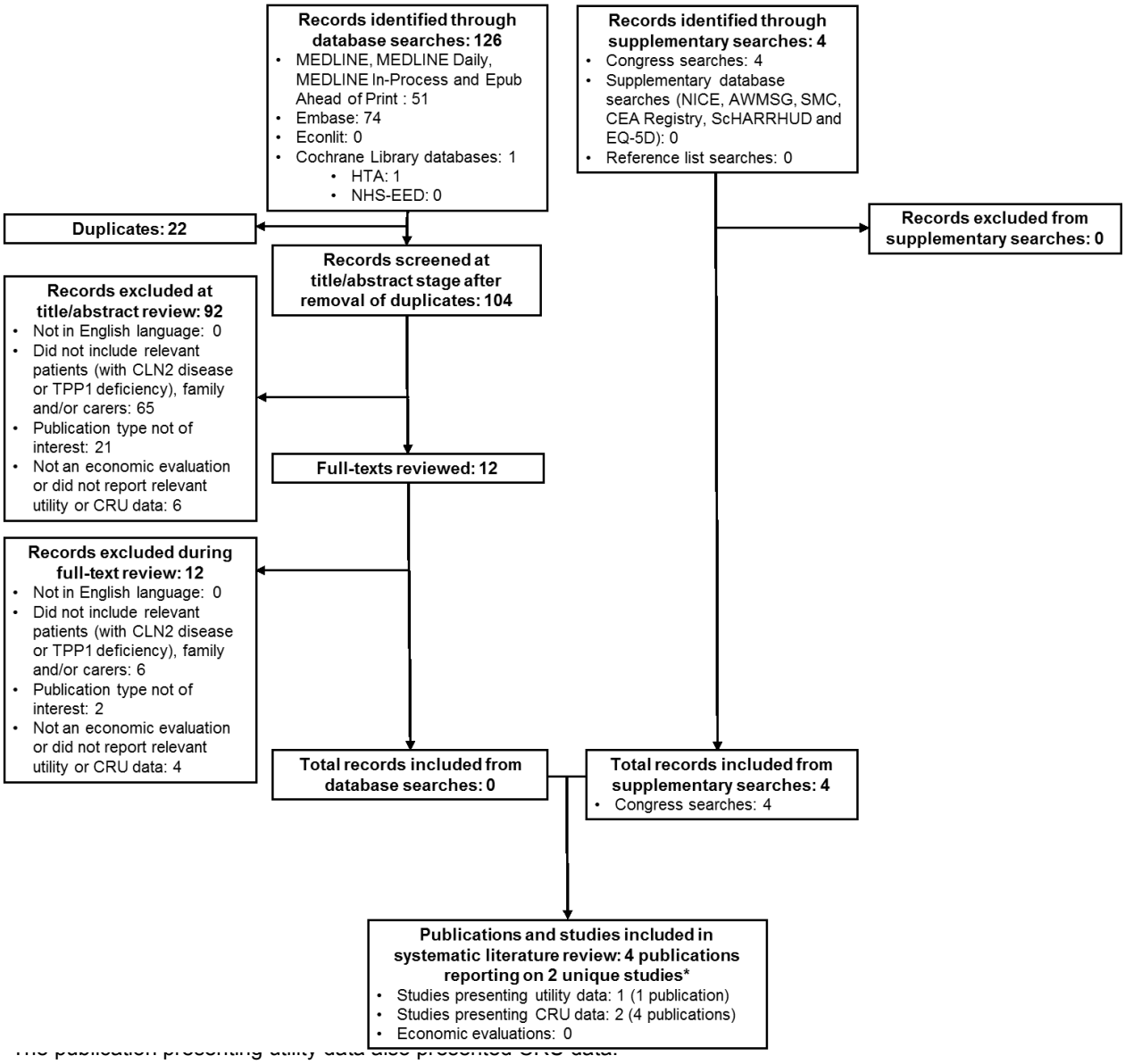
Domain	Economic evaluations	Utility Studies	Cost and resource use studies	Justification
	Non-systematic/ narrative reviews			
Other considerations	Non-English language full-texts Studies on non-human subjects			The review team did not have the linguistic capability to review non-English language articles; however, studies were not limited to those conducted in specific geographical locations. Additionally, studies on non-human subjects were not considered relevant to the decision problem.

ABBREVIATIONS: CHU9D: Child Health Utility 9 Dimensions; CLN2: genetically/enzymatically confirmed neuronal ceroid lipofuscinosis type 2; EQ-5D: EuroQol 5 Dimensions; HRQL: health-related quality of life; HUI3: Health Utilities Index Mark 3; ICER: incremental cost-effectiveness ratio; TPP1: tripeptidyl-peptidase 1; QALY: quality-adjusted life year; RCT: randomised controlled trial; SF-6D: Short-Form 6 Dimensions.

11.1.3 Report the numbers of published studies included and excluded at each stage in an appropriate format.

The electronic database searches identified a total of 126 records. After screening of titles and abstracts, 12 relevant citations were selected. Following a detailed evaluation of the full texts of these articles, all of the records were excluded as none of them met the review inclusion criteria. Additionally, 4 records were identified through supplementary searches, all of which met the inclusion criteria. In total 4 publications reporting on 2 unique studies were included in the review[23, 77, 80, 81]. This included 1 study presenting utility data (1 publication) and 2 studies presenting CRU data (4 publications).

Figure D19. PRISMA flow diagram of economic SLR



*The publication presenting utility data also presented CRU data.

ABBREVIATIONS: AWMSG: All Wales Medicines Strategy Group; CEA: cost-effectiveness analysis; CLN2: neuronal ceroid lipofuscinosis type 2; CRU: cost and resource use; EQ-5D: EuroQol 5

Dimensions questionnaire; HTA: health technology assessment; NHS-EED: NHS Economic Evaluation Database; ScHARRHUD: School of Health and Related Research Health Utilities Database; SMC: Scottish Medicines Consortium; TPP1: tripeptidyl-peptidase 1; NICE: National Institute for Health and Care Excellence.

11.2 Description of identified studies

11.2.1 Provide a brief review of each study, stating the methods, results and relevance to the scope. A suggested format is provided in table D2.

No relevant studies were identified.

11.2.2 Provide a complete quality assessment for each health economic study identified. A suggested format is shown in table D3.

This section is not applicable as no relevant studies were identified.

12 Economic Analysis

Section 12 requires the sponsor to provide information on the de novo cost-effectiveness analysis.

The de novo cost-effectiveness analysis developed should be relevant to the scope.

All costs resulting from or associated with the use of the technology should be estimated using processes relevant to the NHS and personal social services.

- A de novo cost-effectiveness analysis of treatment with cerliponase alfa, in comparison to standard of care, was conducted for patients with a confirmed diagnosis of CLN2 disease, in line with the NICE scope.
- A multi-state Markov model was developed to track the progression of patients through 10 health states based on the CLN2 clinical rating scale and other key clinical characteristics, based on clinical expert opinion.
- Progressive symptoms, adverse event disutility, caregiver disutility, mortality, and sibling disutility were also included.
- A number of key assumptions were made, related to the patient population, transitions between health states, and administration of cerliponase alfa. However, these assumptions were validated by expert clinical opinion or sourced from a Delphi panel. The impact of these assumptions were also explored in several sensitivity analyses.
- Transition probabilities for the standard care arm were based on patient level data from study 190-901 (natural history study) and expert clinical opinion, and transition probabilities for the cerliponase alfa arm were based on study 190-201/202 (pivotal clinical trial) and expert clinical opinion.
- Utilities were derived from a utility study in which vignettes describing the health states were developed, validated by a clinical expert, and sent to 8 clinical experts who completed the EQ-5D-5L questionnaire as a proxy for patients experiencing the health states.
- Costs and resource use data were identified through an SLR, and were implemented from an NHS and Personal Social Services perspective. Wherever cost information was not available, expert clinical opinion informed the assumptions used for these inputs.

- Base case cost-effectiveness results found that cerliponase alfa provided an incremental gain of 30.42 QALYs and 40.04 life years versus standard of care.
- Base case cost-effectiveness results found that cerliponase alfa provided an ICER of [redacted] per QALY versus standard of care. An alternative base case, where a discount rate of 1.5% was applied for benefits, and 3.5% was applied for costs, provided an ICER of [redacted] per QALY versus standard of care.
- Scenario analyses tested a wide range of assumptions employed in the base case analysis, including progression rates, starting populations, and utility values; the majority of scenario analyses demonstrated similar conclusions as the base case analyses. Scenario analyses provided ICERs in the range of [redacted] per QALY versus standard of care.
- Deterministic sensitivity analyses, in which each variable was varied by ±15%, found the major driver of change to the base case ICER to be drug cost, followed by base health state utilities.
- Probabilistic sensitivity analysis found the analyses performed to be robust, with values found through this analysis aligning closely with the deterministic base case values.
- In summary, the cost-effectiveness analysis presents a robust evaluation, finding cerliponase alfa to offer significant benefits to patients.

12.1 Description of the de novo cost-effectiveness analysis

Patients

12.1.1 What patient group(s) is (are) included in the cost-effectiveness analysis?

The cost-effectiveness analysis of cerliponase alfa is conducted within its licensed indication for the treatment of patients with CLN2 disease.[82] In line with the scope defined by NICE, the cost-effectiveness analysis considers patients with a confirmed diagnosis of CLN2 disease.

Technology and comparator

12.1.2 Provide a justification if the comparator used in the cost-effectiveness analysis is different from the scope.

Cerliponase alfa is compared with established clinical management without cerliponase alfa (“the standard of care strategy”), in line with the scope.

Model structure

12.1.3 Provide a diagram of the model structure you have chosen.

A Markov model structure with a cycle length of 2 weeks was used to track the progression of patients through a series of health states.

An overview of the properties of the model is provided in Table D2.

Table D2. Model properties

Aspect	Details	Justification
Analytical method	Multi-state Markov model	A multi-state Markov model is the most appropriate way of modelling a long-term chronic disease with dynamic disease progression.
Software used	Microsoft Excel 2016	Microsoft Excel includes a transparent programming language, which is widely used.
Model perspectives	Base case: Healthcare system (NHS and Personal Social Services [PSS]) Additional scenario: Societal	All relevant perspectives
Cycle length	2 weeks	This cycle length is in line with the fortnightly treatment administration of cerliponase alfa, and the frequency of concomitant patient examinations.
Discounting	1.5% costs and benefits Additional scenarios: 3.5% costs and benefits, 1.5% for benefits, 3.5% for costs	Given the beneficial impact of the treatment is expected to be substantial and sustained over a very long period, a discount rate of 1.5% has been used as this is considered reasonable within the context of the NICE Guide to the methods of technology appraisal 2013.
Time horizon	Lifetime (95 years from the start of the model)	The model intends to capture the full costs and benefits over patients' lifetimes. Patients start at an age of 4.8, based on the trial population, and the ONS life tables provide mortality data up to the age of 100.
Patient population	Patients with a confirmed diagnosis of CLN2 disease	In line with the licensed indication and the scope.
Health states	10 health states based on the CLN2 clinical rating score and other clinical key characteristics (described in more detail in Table D3)	The health states and their defining characteristics were validated by clinical experts.
Comparator	Standard of care	No treatment is currently available for CLN2 disease, and this is in line with the scope.

In order to accurately model the clinical reality of disease progression, ten mutually exclusive health states were identified based on natural history data

and following advice from clinical experts. Health states 1–7 were defined by a score on the CLN2 clinical rating scale (consisting of two domains, motor and language, and ranging from a score of 6 [least severe] to a score of 0 [most severe]). Health state 8 was defined as a score of 0 on the CLN2 clinical rating scale plus a complete vision loss (i.e. complete blindness), beyond which point clinical experts felt no further loss of vision would be expected to impact the patient's quality of life. Health state 9 was the same as health state 8 plus the additional requirement for palliative care, health state 10 was death. A brief description of each health state is presented in Table D3. For details of the CLN2 clinical rating scale and further information about the health states, please see section 6.1 and section 12.1.4, respectively.

Table D3. Health states

Health state	Score on the CLN2 clinical rating scale*	Additional characteristics†
1	6	NA
2	5	NA
3	4	NA
4	3	NA
5	2	NA
6	1	NA
7	0	NA
8	0	Complete vision loss (VL)
9	0	Vision loss and requiring palliative care (VL/PC)
10	NA	Death

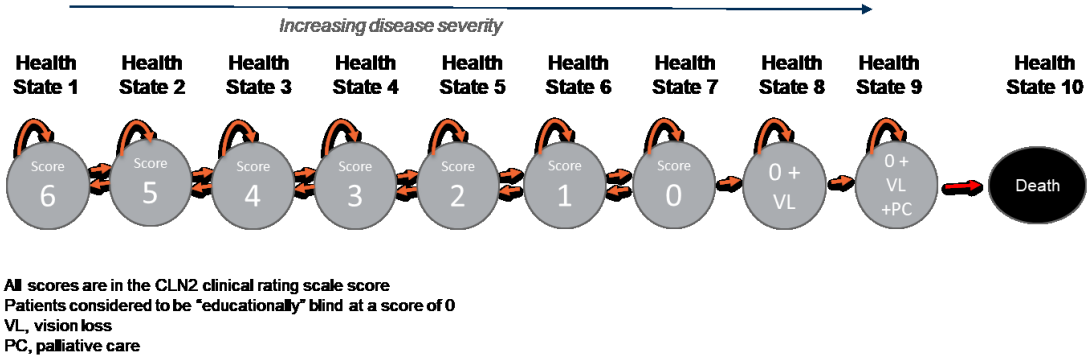
Abbreviations: CLN2: neuronal ceroid lipofuscinosis type 2; NA, not applicable; PC, palliative care; VL, vision loss.

*Wherever appropriate, the different combinations of scores that could lead to a particular score on the CLN2 clinical rating scale were considered. The most prevalent combination, based on trial and natural history data, was chosen whenever the specific combination was required.

† In addition, progressive symptoms were associated with each health state, as described in section 12.1.7.

The hypothetical cohort in the model transitions between these health states over the course of the model time horizon, following the structure described in Figure D20. Costs and benefits are accrued according to the time spent in the different health states.

Figure D20. Model structure diagram



All scores are in the CLN2 clinical rating scale score
Patients considered to be "educationally" blind at a score of 0
VL, vision loss
PC, palliative care

All scores are in the CLN2 clinical rating score.

Abbreviations: CLN2: neuronal ceroid lipofuscinosis type 2; PC: palliative care; VL: vision loss

At model entry, the cohort is distributed across the health states according to the expected population that will receive treatment for CLN2 disease. This expected population was validated by clinical experts,[83] and is detailed in Table D15. As disease progression occurs, patients develop more severe symptoms and transition from health state 1 to 9, and ultimately health state 10 (death). As noted above, the cycle length applied in the model is 2 weeks. At each cycle patients can either remain in the same health state, progress to a more severe health state or improve and move to a less severe health state, with the exception that once patients reach health state 8, they can no longer return to a previous health state.

The benefit of cerliponase alfa is in delaying disease progression, i.e. the transition to more severe health states, with evidence from the pivotal trial suggesting that patients can stabilise (remain at the same health state) or improve (transition to a less severe health state). For further information on the clinical efficacy of cerliponase alfa, please see section 9.6.

12.1.4 Justify the chosen structure in line with the clinical pathway of care.

CLN2 disease is a rare rapidly progressive genetic disorder caused by a loss-of-function mutation in the gene encoding the lysosomal enzyme TPP1. Children affected by CLN2 disease appear to develop normally for the first few years of life before the onset of rapid disease progression, accompanied by a steady decline of mental and other capacities. Clinical features include epileptic seizures, and a deterioration of language, general motor skills, increasing visual impairment and swallowing. This eventually results in the loss of mobility and the necessity for feeding and ventilation support in later disease stages. Death is inevitable and usually occurs between the ages of 6 and 12 years, with current standard of care.[3, 24] For more information on the natural history of CLN2 disease, please see section 6.

A multi-state Markov model was chosen, due to it being the most appropriate approach to modelling long-term chronic conditions with progressive and dynamic deterioration in health status, and due to the predictable decline of the disease, across patients.

Health states were based primarily on the CLN2 clinical rating scale, which is a subset of an adapted version of the established four domain Hamburg scale measure.[8] The CLN2 clinical rating scale consists of two domains, motor function and language function (i.e. does not include the vision and seizure domains that are present in the adapted-Hamburg scale). Clinical experts agreed that changes to the motor and language domains most accurately captured disease progression, and that their combined score (the CLN2 clinical rating scale) was an appropriate tool for defining the health states of the model (as opposed to the full four domain adapted-Hamburg scale). The seizure and vision domains were limited in their ability to measure symptoms, and did not provide meaningful measures of disease progression.

Patients were scored on the CLN2 clinical rating scale in both the cerliponase alfa trial (Study 190-201/202) and the natural history study of comparable untreated patients (Study 190-901. In addition, as explained in section 12.2.1, changes in the CLN2 clinical rating scale were used as the basis for the transition probabilities between health states. As well as these two domains, clinical experts were also asked about other elements of patient experience, such as chronic seizures, disease-related distress, dystonia, myoclonus, vision and the use of a feeding tube, to further define the health states and capture the clinical reality of disease progression, during the course of the Delphi panel described in section 12.2.5.

A maximum score of 6 can be obtained by achieving a score of 3 in both domains, with 0 being obtained by a score of 0 on both domains. However, experts advised that even after a score of 0 is obtained by patients, further disease progression and deterioration of quality of life can occur, hence further health states after health state 7 were built into the model. For health state 8, patients have suffered complete vision loss as well as obtaining a score of 0 on the CLN2 clinical rating scale, and in the final non-death health state, health state 9, palliative care is also required due to the disease progression.

The use of these health states, and their definition, was validated by clinical experts with experience of CLN2 disease and cerliponase alfa – further details can be found in section 12.2.5.

12.1.5 Provide a list of all assumptions in the model and a justification for each assumption.

Table D4. Model assumptions

Aspect	Model assumption	Justification
Patient population	The population was assumed to be 50% male and 50% female.	Clinical experts believed that no difference in prevalence with regard to sex is expected, when asked in workshop 3, as described in section 12.2.5.
	The distribution of patients across the health states reflects the expected population of treatment given future improvements in diagnosis. For further details of the starting population of patients in the model please see Table D15.	The model assumes that were cerliponase alfa to be introduced it would be given to children as soon as they have been diagnosed and that future improvements in diagnosis will lead to patients being diagnosed when at an earlier stage of the disease. This assumption was validated by clinical experts, as described in section 12.2.5.
	The starting age of patients in the model, which affects age-related mortality and dosing of cerliponase alfa, was assumed to be the mean starting age across study 190-201 and the natural history study.	As it is currently not known at what age patients in the future will be diagnosed with CLN2 disease (as noted above, it is anticipated that patients will be diagnosed at a younger age) the age at which patients in the trial were started on treatment was used.
Transitions between health states	Patients receiving cerliponase alfa treatment for more than 16 weeks are assumed to either be early stabilisers or late stabilisers. Early stabilisers remain in the health state that they are in at 16 weeks for the rest of the model time horizon, whilst late stabilisers continue to progress at a rate of 1 point on the CLN2 clinical rating scale (i.e. 1 health state) per 80 weeks until 96 weeks, after which point they remain in the health state that they are in for the rest of the model time horizon. These assumptions about transitions are only observed for patients whilst they are receiving treatment – if treatment has been discontinued	This is in line with what is seen in the trial, where 6 patients were seen to progress 1 more point on the CLN2 clinical rating scale between 16 weeks and 96 weeks, and 17 continued to stay at the score that they are at. In addition, this was validated by clinical experts, as described in section 12.2.5. The benefits of cerliponase alfa are expected to be maintained for as long as patients receive the treatment.

	then they will transition in accordance with the transition probabilities applied to the standard care arm.	
	Time to complete vision loss (52 weeks) from reaching a score of 0 on the CLN2 clinical rating scale, i.e. transition between health state 7 and health state 8, is the same for both cerliponase alfa and standard of care arms in the model.	Data were not available on these transitions, as no patients progressed beyond a score of 0 on the CLN2 clinical rating scale in the trial, and no information was available in the natural history data on the time to vision loss or time to requirement of palliative care, thus information was sourced from the Delphi panel[84] detailed in section 12.2.5. The experts provided estimates of the time taken for a patient to make these transitions when receiving standard of care. In the absence of equivalent information for patients receiving cerliponase alfa, as such transitions have not yet been observed in the trial setting, assumptions were made that the time to make these transitions is the same for patients treated with cerliponase alfa as compared to standard of care. As cerliponase alfa has been shown to slow disease progression, it is expected that patients receiving cerliponase alfa would take longer to make these transitions, and thus spend more time in the less severe health states. As such, these assumptions are conservative.
	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.	
	When calculating transition probabilities, health states 1 and 2 were grouped together, health states 3, 4, and 5 were grouped together, and health states 6 and 7 were grouped together, for both treatment arms of the model.	Transition probabilities was grouped in order to increase the number of transitions observed in the trial, increasing the sample size and preventing clinically implausible transition probabilities from being applied. This approach was validated by clinical experts, as described in section 12.2.5. For further details of how transition probabilities were calculated please see section 12.2.1.

Treatment of seizures	All patients receive anti-epileptic drugs (AEDs).	Patient narratives from studies 190-201 and 190-202 showed that all patients in the trial received some form of AEDs. The breakdown between these medications was used to inform the average annual costs of AEDs.[85]
	It was assumed that all patients requiring medications for treating myoclonus are already taking AEDs, so only the costs for phenobarbital are applied, as this is the only myoclonus medication not also prescribed for epilepsy. It is also assumed that the proportions of patients using each of the myoclonus medications is the same across all medications.	There are no data available on which medications are most commonly used when treating myoclonus in CLN2 patients. All patients are modelled as receiving AEDs, so it could be assumed that all patients with myoclonus would therefore be receiving AEDs. As phenobarbital is the only myoclonus medication not also prescribed for epilepsy, this additional cost was added for a proportion of patients based on equal distribution across all available myoclonus medications.
	Hospitalisation cost for chronic seizures is applied only to the proportion of rescue medication delivered intravenously.	Data were not available on which seizures required hospital admission for patients, 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 in each health state experiencing progressive symptoms (epilepsy, reported distress, dystonia, myoclonus, and the requirement of a feeding tube) are the same in the cerliponase alfa arm as the standard of care arm.	Data were not available on the proportion of patients experiencing progressive symptoms when receiving cerliponase alfa or standard of care. Thus in the absence of data, a conservative assumption was made that these proportions would be the same.
	For the health state costs for health state 9, it was assumed that the number of each type of appointment would be the same as health state 8, with the exception of appointments associated with palliative care (the number of specialist nurse visits, palliative care visits, and educational support appointments), which were informed by separate expert opinion. The full list can be found in	Data on the different types of appointment received by patients in health state 8 were obtained from the Delphi panel described in section 12.2.5. However, equivalent data were not collected for health state 9. Due to the similarities between the health states, it was assumed that the numbers of appointments would be the same across both health state 8 and 9 with the exception of the

	section 12.3.7.	appointments associated with palliative care. Separate expert opinion was collected to inform the estimates regarding the palliative care appointments.
	It was assumed that all patients with a score of 2 or lower on the language domain of the CLN2 clinical rating scale required a feeding tube.	This assumption was based on clinical expert opinion collected during the Delphi panel[84] described in section 12.2.5.
	Feeding tubes were assumed to require replacement every two years.	This is in line with usual practice at Great Ormond Street Hospital.[86]
	It was assumed that the proportions of patients using the different reported distress medications recommended in the literature[24] 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 (99.74%), which was taken to be the same as the rate observed in the trial, was assumed to be constant throughout the model time horizon.	The number of infusions that this adherence rate was based on, was based on a large sample of infusions (776), so it was assumed that this adherence rate would be maintained over time.[22]
	Drug dosing for cerliponase alfa was assumed to be the regular dose (300mg) every 2 weeks, after patients reach an age of 2 years. If patients in the model are older than 2 years old, they receive the regular dose, but if patients start at an age lower than this, a lower dose was provided – more details are provided in section 12.3.6.	This is in line with drug dosing information provided by the EMA[1]. Further details of the drug dosing can be found in section 12.3.6.

	Patients stop receiving cerliponase alfa treatment when they reach health state 7 (CLN2 clinical rating scale score of 0). Upon discontinuing cerliponase alfa, patients switch to transition probabilities and utility values observed in the standard of care arm.	This stopping rule was proposed by clinical experts[83] who felt this was the expected point at which cerliponase alfa treatment would typically no longer be recommended based on ongoing discussions for the managed access agreement.
	The rate of cerliponase alfa related adverse events was assumed to be constant through the model time horizon.	There are no data available on how the rate of cerliponase alfa related adverse events for cerliponase alfa treatment changes over time beyond the trial, so the rates of adverse events that were observed during 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 190-201/190-202, so this was thought to be an acceptable assumption to make in the absence of further information.
	Replacements of the ICV delivery device were assumed to only be required if an infection occurred.	No data were available on the regularity of replacement of the ICV delivery device in CLN2 patients, but the literature on ICV delivery devices across treatments suggested that in most cases, removal of an ICV device was necessary to treat infections, and the average rate of infections was taken from the same literature.[87]
Other adverse events	Hypersensitivity, headaches, and vomiting were assumed to last for one day, when calculating the disutility due to adverse events.	No data were available for how long patients experienced these adverse events 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 adverse events.
	No treatment related adverse events were applied to the standard care arm of the model.	In the standard of care arm of the model, patients do not receive the treatment (cerliponase alfa) and thus no treatment related adverse events are applied to these patients.

	Additional mortality from adverse events was not considered	No deaths due to adverse events occurred in study 190-201/190-202, so this was thought 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, for example 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.	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.[83]
	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. As such, costs were applied to the proportion of care provided by non-family caregivers only.
	Number and proportion of family versus non-family caregivers is same for both cerliponase alfa and standard of care arms in the model.	Data were not available on the numbers and proportion of family versus non-family caregivers for patients treated with cerliponase alfa so a conservative assumption was made that the same data as the standard of care arm would also apply to the cerliponase alfa arm. This information was collected in the Delphi panel[84], and it is expected that patients receiving cerliponase alfa would require less care than patients receiving standard care, this assumption can be considered conservative.
	Number of caregivers and proportion of care that is provided by family is the same for health state 9 as it is for health state 8	Data on the number of caregivers and proportion of care that is provided by family in health state 8 were obtained from the Delphi panel described in section 12.2.5. However, equivalent data were not collected for health state 9. Due to the similarities between the health states, it was assumed that the numbers of appointments would be

		the same across both health state 8 and 9.
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, as detailed in section 12.1.7.	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.[83] 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 were available on how child sibling disutility changes over time – due to the relatively low impact of sibling disutility on overall results this was considered to be a reasonable assumption.

ABBREVIATIONS: CLN2: neuronal ceroid lipofuscinosis type 2; ICV: intracerebroventricular.

12.1.6 Define what the model's health states are intended to capture.

The health states in the model are intended to capture the disease progression of a patient from the onset of CLN2 disease through to death. The various health states include all the points at which the disease has a substantial impact on cost and quality of life, based on expert opinion and a systematic review of the literature. Further details on the health states can be found in section 12.1.4.

12.1.7 Describe any key features of the model not previously reported. A suggested format is presented below in table D4.

In this section, features of the model that have not previously been reported, such as progressive symptoms, adverse event disutility, caregivers, mortality, and sibling disutility will be detailed.

Progressive symptoms

A number of additional symptoms not captured by the CLN2 clinical rating scale, and their associated costs and disutilities, were modelled alongside the health states of the model. These additional symptoms are hereafter referred to as progressive symptoms and were the following: epilepsy, reported distress, dystonia, myoclonus, and the requirement of a feeding tube. As well as the progressive loss of motor and language skills, as measured by the CLN2 clinical rating scale, clinical experts advised that these progressive symptoms vary in severity across the different stages of disease progression and typically only affect a proportion of patients. These symptoms were selected based on Williams et al. 2017[24], and were validated in the Delphi panel[84] described in section 12.2.5. To gauge the impact of these symptoms on quality of life, they were included in the vignettes used for the utility study (see section 12.2.1), for each health state where >50% of the population in the health state were said to be experiencing that symptom, and the costs associated with these symptoms were applied to the proportions of patients expected to experience these symptoms. Further details on the costs applied for these symptoms are provided in section 12.3.9.

The patient narratives[85] from studies 190-201 and 190-202 suggested that all patients used AEDs, even those in the early stages of disease progression, so epilepsy was modelled as being experienced and managed for all patients.

For the other progressive symptoms, the Delphi panel described in section 12.2.5 was used to determine the proportions of patients experiencing these symptoms. Data were not available on the proportion of patients experiencing progressive symptoms when receiving cerliponase alfa or standard of care.

Thus in the absence of data, a conservative assumption was made that these proportions would be the same.

For proportions of patients experiencing reported distress, dystonia, and myoclonus, the mean values after three rounds of answers in the Delphi panel were used across both arms in the model.

Table D5. Percentage of patients experiencing reported distress, dystonia, and myoclonus

Health state	Percentage of patients experiencing reported distress	Percentage of patients experiencing dystonia	Percentage of patients experiencing myoclonus	Source
Health state 1	3%	0%	3%	UK Delphi panel, mean values after three rounds of questions, December 2016
Health state 2	9%	15%	25%	
Health state 3	30%	15%	50%	
Health state 4	39%	30%	98%	
Health state 5	48%	60%	100%	
Health state 6	51%	73%	100%	
Health state 7	54%	63%	100%	
Health state 8	56%	63%	100%	
Health state 9	56%	63%	100%	

For the requirement of a feeding tube, clinical experts advised that patients with a score of 2 or lower on the language domain of the CLN2 clinical rating scale would experience this, according to UK practice. All of the trial data and natural history data were collated, and the proportions of patients with a score of 2 or lower on the language domain of the CLN2 clinical rating scale were calculated for each health state. These proportions were taken to be the values for proportions of patients requiring a feeding tube for the different health states of the model.

Table D6. Percentage of patients requiring a feeding tube

Health state	Percentage of patients requiring a feeding tube	Source
Health state 1	0%	Trial data and natural history data – the proportion of patients with the overall CLN2 clinical rating scale scores determining the health states with a score of 2 or lower on the language domain
Health state 2	89%	
Health state 3	100%	
Health state 4	100%	
Health state 5	100%	
Health state 6	100%	
Health state 7	100%	
Health state 8	100%	
Health state 9	100%	

Adverse event disutilities

Adverse event disutilities were sourced from the literature for the cerliponase alfa related adverse events reported during study 190-201/202 and applied to the cerliponase alfa arm of the model (see section 12.2.1). The annual disutility due to an adverse event was calculated, and the rate of occurrence of adverse events (shown in section 12.2.4) was assumed to be constant through the model time horizon, in line with the dosing schedule of cerliponase alfa being unchanged throughout the model time horizon. Total annual disutility due to adverse events is detailed in Table D7.

Table D7. Adverse event disutility calculation

Adverse event	Disutility	Source	Time adverse event experienced for (days)	Source	Annual occurrences of adverse events	Source	Total annual disutility from adverse event
Pyrexia	-0.11	Beusterien et al. (2010)[88]	[redacted]	Study 190-202 patient narratives[85]	[redacted]	Study 201/202, Patient Narratives[85]	[redacted]
Hypersensitivity	-0.03	Kauf et al. (2010)[89]	1	Assumption	[redacted]		[redacted]
Headache	-0.12	Maniadakis et al. (2013)[90]	1		[redacted]		[redacted]
Vomiting	-0.05	Beusterien et al. (2010)[88]	1		[redacted]		[redacted]
Infection	-0.2	Song et al. (2012)[91]	N/A	N/A	N/A	N/A	N/A

Abbreviations: NA: not applicable

Caregivers

Due to the severity of CLN2 disease, and the fact that it affects children, caregivers are required to support these children, with increasing levels of support required as the disease progresses. This care is typically provided by a combination of both family and non-family caregivers. The Delphi panel described in section 12.2.5 was used to determine the number of caregivers required for each of the different health states in the model, and the proportion of that care that would be provided by family caregivers, and non-family caregivers. The number and breakdown of caregivers can be seen in Table D8.

Caregiver costs were applied only to the proportion of the care provided by non-family caregivers. The annual cost of caregivers was taken from NHS pay rates – NHS-funded school nurses, which came in Band 6, were deemed the relevant caregiver, and the middle point of this band (point 25) was taken as the reference salary – this salary was £30,661.00.[92] This was applied to the proportion of caregivers that were non-family caregivers, across all health states.

Table D8. Number of caregivers applied in model

Health state	Average number of caregivers required	Percentage of care provided by family caregivers	Percentage of care provided by non-family caregivers	Number of family caregivers applied in model	Number of non-family caregivers applied in model	Source
Health state 1	0.06	100%	0%	0.06	0	UK Delphi panel, mean values after three rounds of questions, December 2016
Health state 2	0.67	100%	0%	0.67	0	
Health state 3	0.75	100%	0%	0.75	0	
Health state 4	1	83%	17%	0.83	0.17	
Health state 5	1	78%	22%	0.78	0.22	
Health state 6	1	79%	21%	0.79	0.21	
Health state 7	1.25	75%	25%	0.9375	0.3125	
Health state 8	1.14	73%	27%	0.8322	0.3078	
Health state 9	1.14	73%	27%	0.8322	0.3078	

The value for caregiver disutility was obtained from a report on the challenges of living with and caring for a child affected by CLN2 disease.[13] The EQ-5D-5L crosswalk score (UK) was compared to 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. Data was not available on the patients' stage of disease when this disutility value was measured, so the disutility for the first two health states was provided by clinical experts (as described in section 12.2.5), and for the remaining seven health states, disutility was assumed to increase in a linear way from 0, as shown in Table D9, with -0.108 being applied to the midpoint of these remaining seven health states, to the proportion of caregivers that are family caregivers, as noted above.

Table D9. Caregiver disutility

Health state	Caregiver disutility	Source
Health state 1	-0.02	Clinical expert opinion[83]
Health state 2	-0.025	
Health state 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
Health state 4	-0.054	
Health state 5	-0.081	
Health state 6	-0.108	'Challenges of living with and caring for a child affected by CLN2 disease, a type of Batten disease' (p.132)[13]
Health state 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
Health state 8	-0.162	
Health state 9	-0.189	

ABBREVIATIONS: CLN2: neuronal ceroid lipofuscinosis type 2

Sibling disutility

Due to the severity of CLN2 disease, the negative impact on the family unit is considerable.[13] As well as the burden felt by family caregivers, additional

disutility was added to the model to represent the impact on quality of life felt by siblings unaffected directly by CLN2 disease.

Sibling disutility was applied across all but the first two health states, in line with guidance from clinical experts.[83] 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.[13] Child sibling utility values were found to be 0.91 on the CHU-9D, and if children might be expected to be 1 under normal circumstances, a -0.09 decrement is applied. Data was not available on the patients' stage of disease when this disutility value was measured, so it was assumed that no disutility would be applied to the first two health states, and for the remaining seven health states, disutility was assumed to increase in a linear way, as shown in, with -0.090 being applied to the midpoint of these remaining seven health states to the average number of unaffected (unaffected directly by CLN2 disease) siblings in a family with CLN2 disease. The number of siblings this is applied to is 0.94, based on a BDFA survey showing there to be 32 siblings (without CLN2 disease) across an analysis of 34 CLN2 patients.

Table D10. Sibling disutility

Health state	Caregiver disutility	Source
Health state 1	0.000	'Challenges of living with and caring for a child affected by CLN2 disease, a type of Batten disease' (p.141)[13], 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
Health state 2	0.000	
Health state 3	-0.023	
Health state 4	-0.045	
Health state 5	-0.068	
Health state 6	-0.090	
Health state 7	-0.113	
Health state 8	-0.135	
Health state 9	-0.158	

Mortality

Three types of mortality were modelled – disease related mortality, infection related mortality, and age related mortality.

Disease related mortality is applied as described in section 12.2.1, with the transition probability from the final health state (death) depending on the

average time spent receiving palliative care. The value for mean time spent receiving palliative care was 52 weeks, which is in line with the time spent in the other health states where CLN2 clinical rating scale score has reached 0. An assumption was made 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 the transition probability of health state 9 to death. Clinical experts believed that applying disease related mortality only to the final health state would be a suitable way to model this, as patients in the earlier health states do not die from CLN2.

Infection related mortality was assumed to be zero, in the model, as none of the infections in the trials had thus far led to a patient death.

12.2 Clinical parameters and variables

12.2.1 Describe how the data from the clinical evidence were used in the cost-effectiveness analysis.

Data collected on transition probabilities, the starting population, adverse event occurrences, and utility values, were used to inform model inputs. Further details are provided below.

Transition probabilities

Patients can transition between health states after each 2-week cycle, as illustrated by the arrows in Figure D20. Probabilities for the transitions between the first seven health states (health state 1 [CLN2 clinical rating scale score of 6] to health state 7 [CLN2 clinical rating scale score of 0) were based on patient-level data from Study 190-201/202 for the cerliponase alfa arm, and the one-to-one matched patients from the natural history control Study 190-901 for the standard of care arm.

Patient-specific disease progression during the Study 190-201/202 was examined in approximate 8-week intervals and assessed by investigators via scores on the CLN2 clinical rating scale. In the beginning of Study 190-201, patients were examined more frequently than every 8 weeks, so the initial time points for these patients were therefore grouped accordingly and treated as one 8-week interval, with the first and last observed score determining the overall change in scoring for this interval, potentially negating increases followed by decreases, or vice versa, during this time. Examinations in study 190-901 were performed in less frequent intervals. Periods in between examination dates were consequently split into 8-week intervals to match the intervals from study 190-201/202. Observed changes in the CLN2 clinical rating score were fitted to the whole time period between observations; it was

assumed that an observed score change would occur at the midpoint of the 8-week time periods, or if multiple changes, these changes would be evenly spread across the 8-week time periods, with the remaining 8-week intervals before and after these changes being counted as instances of maintaining the respective score.

The scores from consecutive examinations were compared and the changes classified as either an increase by one point, a decrease by one point, or the observed score remaining the same. If, for example, a decrease across two points was observed for one 8-week interval, this was counted as two separate one-step decreases for each of the affected scores (e.g. a decrease from a score of 6 to a score of 4 was counted as one instance of decreasing from 6 to 5 and one separate instance of decreasing from 5 to 4 for this interval). The same approach was taken for increases across two points.

The occurrences of possible changes for each score (increase, decrease, or remain the same) and for each 8-week interval were summed across the whole study period and all patients, and divided by the sum of all changes for this specific score to determine the probability for each health state-specific change (Table D11).

Due to the small number of patients with each CLN2 clinical rating scale score (equivalent health states 1–6), this approach to determining transition probabilities resulted in clinically implausible results in some instances (e.g. a probability of 100% for improving from a health state with a score of 0, based on the single observation from one patient). In order to account for this problem and the overall low sample size, probabilities were determined for combined groups of scores (scores of 6 and 5 [health states 1 and 2], scores of 4 to 2 [health states 3–5], and scores of 1 and 0 [health states 6–7] on the CLN2 clinical rating score), with this approach validated by clinical experts.[83] As a result, for example, transition probabilities for health state 1 (CLN2 clinical rating scale score of 6) and health state 2 (CLN2 clinical rating scale score of 5) were the same, even though different costs and utilities were applied to each of these health states. Clinical experts deemed the similarity in the health states to be sufficient for this, and it prevented clinically implausible results from arising. As the disease progression varies dependent on the stage of disease, it was deemed inappropriate to group all the health states together when calculating transition probabilities. The grouping of the health states was done with similar health states, at similar stages of disease progression.

2-week transition probabilities, matching the cycle length implemented in the Markov model, were calculated by converting the 8-week transition probabilities, assuming a constant rate of transition.

The data from study 190-201/202 suggested that scores fluctuated more in the initial stages of treatment, before stabilising, which is why the transition probabilities were split up across the time periods, in order to better reflect clinical reality. It was deemed most appropriate that the calculation of the long term probabilities (for the later time periods in the model) did not include the initial fluctuations in the early stages of treatment; as a result, the probabilities were grouped into the separate time periods, with the transition probabilities to be used in the early stages of the model being based on observations in the early stages of the trial. This was not applied to the standard care arm, as there was no suggestion that there were any initial fluctuations before stabilisation, so it was assumed that all the timepoints could be grouped together to calculate the transition probabilities.

In the base case of the model, data from the first 24 weeks of Study 190-201/202 were used to calculate the transition probabilities in the first 24 weeks of the time horizon, for the cerliponase alfa arm.

For patients receiving cerliponase alfa, patients transition through the model using the transition probabilities calculated from the trial data until 16 weeks. 16 weeks was chosen as it is at this point that response levels were measured in the trial. [redacted] of the patients in the trial [redacted] experienced no further disease progression (in terms of CLN2 clinical rating scale score) after 16 weeks, and [redacted] of the patients in the trial experienced a decline of 1 point on the CLN2 clinical rating scale between 16 weeks and 96 weeks of the trial.[68] Further information on trial outcomes can be found in section 6. The model assumes that after 16 weeks, [redacted] of patients in the cerliponase alfa arm will continue to remain in the health state that they are in, and [redacted] of patients will decline at a rate of 1 point (1 health state) per 80 weeks (the rate was assumed constant and an exponential function was used to calculate the transition probability), up to the point of 96 weeks. After 96 weeks, this cohort will be assumed to have stabilised, and will remain in the health state that they are in for the remainder of the time horizon. The model does this by splitting up the cohort into cohorts called ‘early stabilisers’ and ‘late stabilisers’ – in the early stabiliser cohort, the probability of remaining in a health state is 1, and in the late stabiliser cohort, the probability of remaining in a health state is 1 after 96 weeks. Further information on stabilisation is provided in section 9. This approach was validated by clinical experts, as described in section 12.2.5.

Patients are modelled to stop receiving treatment when a CLN2 clinical rating scale score of 0 is reached. This is health state 7 in the model, and at this point, patients in the cerliponase alfa arm switches to use the same transition probabilities and utility values as the standard of care arm.

The assumptions around the transition probabilities used in the model were tested using scenario analyses, see section 12.4.1 for more details.

In the absence of data for patients who have progressed beyond health state 7 in Study 190-201/202, transition probabilities for health states 7–9 were based on expert opinion and the consensus results of a Delphi panel performed in 2016. The mean time taken for transition from health state 7 to health state 8 (52 weeks) was obtained from the Delphi panel in workshop 2 with clinical experts (see section 12.2.5), and the mean time taken for transition from health state 8 to health state 9 (52 weeks) was obtained from a palliative care expert (see section 12.2.5). The mean time taken for transition from health state 9 to death (52 weeks) was based on the assumption that this time would match the values for the health states prior to this. Once the values for these mean times were obtained, exponential functions that would result in the same mean times provided by the clinical experts were used to calculate the relevant transition probabilities, assuming the transition probabilities are constant over time.

Table D11. Transition probabilities for health states (health states 1 to 7)

		Cerliponase alfa				Standard care			
		0–24 weeks	24-48 weeks	48-96 weeks	96 weeks onwards	0–24 weeks	24-48 weeks	48-96 weeks	96 weeks onwards
Health states 1 and 2	Improve	[redacted]	N/A	N/A	N/A	0.00	0.00	0.00	0.00
	Maintain	[redacted]	N/A	N/A	N/A	0.92	0.92	0.92	0.92
	Decline	[redacted]	N/A	N/A	N/A	0.09	0.09	0.09	0.09
Health states 3, 4, and 5	Improve	[redacted]	N/A	N/A	N/A	0.00	0.00	0.00	0.00
	Maintain	[redacted]	N/A	N/A	N/A	0.88	0.88	0.88	0.88
	Decline	[redacted]	N/A	N/A	N/A	0.12	0.12	0.12	0.12
Health state 6 and 7	Improve	[redacted]	N/A	N/A	N/A	0.00	0.00	0.00	0.00
	Maintain	[redacted]	N/A	N/A	N/A	0.97	0.97	0.97	0.97
	Decline	[redacted]	N/A	N/A	N/A	0.04	0.04	0.04	0.04

***For health state 7, the probability of losing vision, based on a mean of 52 weeks, is also applied, to obtain the probability of declining**
Abbreviations: N/A: not applicable

Table D12 shows the transition probabilities for the proportion of patients defined as ‘early stabilisers’, when being treated with cerliponase alfa. If patients reach health state 7 then they will switch to using the transition probabilities for standard care, and even when classified as an ‘early stabiliser’ or ‘late stabiliser’, patients in health state 7 will be able to transition to health states 8, 9 and death.

Table D12. Transition probabilities after 16 weeks for ‘early stabilisers’

Transition	Probability
Improve	0.00
Maintain	1.00
Decline	0.00

Table D13. Transition probabilities for ‘late stabilisers’

Transition	0–24 weeks	24-48 weeks	48-96 weeks	96 weeks onwards
Improve	0.00	0.00	0.00	0.00
Maintain	0.98	0.98	0.98	1.00
Decline	0.03	0.03	0.03	0.00

Table D14 shows the transition probabilities that are applied to patients once they reach health states 8 and 9, and can no longer improve their health, as they have reached 0 on the CLN2 clinical rating scale. These probabilities are based on the average time taken to lose vision, require palliative care, and die, once palliative care is required.

Table D14. Transition probabilities for health states (health states 8 to 9)

		Cerliponase alfa				Standard care			
		0–24 weeks	**24-48 weeks**	**48-96 weeks**	**96 weeks onwards**	**0–24 weeks**	**24-48 weeks**	**48 weeks onwards**	**96 weeks onwards**
Health state 8	Improve	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
	Maintain	0.96	0.96	0.96	0.96	0.96	0.96	0.96	0.96
	Decline	0.04	0.04	0.04	0.04	0.04	0.04	0.04	0.04
Health state 9	Improve	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
	Maintain	0.96	0.96	0.96	0.96	0.96	0.96	0.96	0.96
	Decline (Death)	0.04	0.04	0.04	0.04	0.04	0.04	0.04	0.04

Starting population

The distribution of the two patient cohorts across the different health states at model entry is based on the population that is expected to receive treatment for CLN2 disease in the UK. This is shown in Table D15, and these proportions were validated with a clinical expert, as described in section 12.2.5. it incorporates the assumption that patients will be diagnosed in an earlier health state than they currently are, in the future. The starting age of all patients in the model of 4.8 years and is derived from Study 190-201 patient baseline characteristics.

Table D15. Distribution of the starting population at model entry (based on expected distribution of patients that will receive treatment for CLN2 disease)

Health state	Cerliponase alfa	Standard care
Health state 1	40%	40%
Health state 2	40%	40%
Health state 3	10%	10%
Health state 4	5%	5%
Health state 5	5%	5%
Health state 6	0%	0%
Health state 7	0%	0%
Health state 8	0%	0%
Health state 9	0%	0%

The effect of the starting population on the results is explored through using different distributions across health states in different scenarios.

Adverse event proportions

The proportion of patients suffering from treatment related adverse events (pyrexia, hypersensitivity, headache, and vomiting) at any time in the model was based on the most common study drug-related adverse events reported by patients in Study 190-202 (Table D16). In addition, an infection rate of 0.45% for each performed ICV infusion was based on published clinical trial data.

No treatment-related adverse events were applied to the standard care cohort.

Table D16. Adverse event proportions

Pyrexia	Hypersensitivity	Headache	Vomiting	Source
[redacted]	[redacted]	[redacted]	[redacted]	Study 190-201/202[64]

Utility Values

Utility values obtained through a utility study conducted in July 2017 were used in the model.[75] Brief descriptions of the health states (vignettes) were produced, based on the most prevalent combinations of the motor and language domain scores on the CLN2 clinical rating scale, and details of the other progressive symptoms typically experienced by patients in each health state. A vignette was produced for each health state, and separate vignettes were produced to describe patient experience in the two treatment arms of the model (treated with cerliponase alfa and treated with standard care). The vignettes were validated by a clinical expert with experience of CLN2 disease and cerliponase alfa (see section 12.2.5 for further details), to ensure that they were realistic and representative of the reality of the patient experience at different stages of disease progression. The vignettes can be found in full in the appendices of this document, in Appendix 10, section 17.10.[75]

The vignettes were sent to 8 clinical experts, who were asked to complete the EQ-5D-5L questionnaire as a proxy for patients that would be experiencing the description given in the vignettes. No disagreement was raised by the clinical experts regarding the content in the vignettes. The clinical experts completed the questionnaires online, and the mean values obtained from their completed questionnaires, as shown in Table D17, were used in the economic model. The EQ-5D-5L values were mapped to EQ-5D-3L values[78] to obtain the utility values, in line with NICE preferences.[79]

Table D17. Mean base health state utility values from utility study, after mapping from EQ-5D-5L to EQ-5D-3L

Health state	Cerliponase alfa	Standard care
Health state 1	[redacted]	[redacted]
Health state 2	[redacted]	[redacted]
Health state 3	[redacted]	[redacted]
Health state 4	[redacted]	[redacted]
Health state 5	[redacted]	[redacted]
Health state 6	[redacted]	[redacted]
Health state 7	[redacted]	[redacted]
Health state 8	[redacted]	[redacted]
Health state 9	[redacted]	[redacted]
Health state 10 (death)	[redacted]	[redacted]

Utility values from the data collected in studies 190-201/202 (limited amounts of EQ-5D-5L and pedsQL data) were not used in the model, due to the small sample size of values and the fact that utility values could not be obtained for all of the health states in the model. Further assumptions would have been required if this option were chosen, as there were no utility data available for the standard care arm.

The choice of utility values for the model, and the effect on the results, was explored further through scenario analyses in section 12.4.1.

12.2.2 Are costs and clinical outcomes extrapolated beyond the study follow-up period(s)? If so, what are the assumptions that underpin this extrapolation and how are they justified?

Costs and clinical outcomes are extrapolated beyond the study follow-up periods, as the model time horizon is 95 years in the base case. The same costs are applied to patients at all points in the model time horizon, with a discount rate of 1.5% applied, and utilities are accrued according to the health state that patients are in, with a discount rate of 1.5% applied.

The transition probabilities used in the model for the standard care arm, based on the patient data from Study 190-901, are assumed to remain the same

throughout the time horizon of the model. For the cerliponase alfa arm, it is assumed that early stabilisers remain in the health state that they are in after 16 weeks, and late stabilisers remain in the health state that they are in after 96 weeks. This was validated with clinical experts, but these assumptions were tested using scenario analysis, as outlined in section 12.4.1.

12.2.3 Were intermediate outcome measures linked to final outcomes (for example, was a change in a surrogate outcome linked to a final clinical outcome)? If so, how was this relationship estimated, what sources of evidence were used and what other evidence is there to support it?

As part of the implemented modelling approach, no intermediate measures were linked to the final outcomes.

12.2.4 Were adverse events included in the cost- effectiveness analysis? If appropriate, provide a rationale for the calculation of the risk of each adverse event.

Treatment related adverse events were included in the model and the proportion of patients suffering from them, the type of adverse event, and frequency, were based on reported safety data from Study 190-202, as described in section 12.2.1.

12.2.5 Provide details of the process used when the sponsor's clinical advisers assessed the applicability of available or estimated clinical model parameter and inputs used in the analysis.

A series of workshops were carried out in order to gather feedback from a total of 13 expert clinical advisors, and information on clinical inputs. Each of the workshops is described below.

Workshop 1

The aim of this workshop was to check the proposed model structure with clinical experts, and to confirm the understanding of the disease and the appropriate modelling method. This meeting was held in person.

The clinical experts at this workshop were all either primary investigators or sub-primary investigators on the recent 190-201 and 190-202 trials, and hence had experience with CLN2 disease and the effects of cerliponase alfa on disease progression. They agreed that the motor and language domains of

the Hamburg scale can be used to represent disease progression, but said that there are other elements that need to be considered, including progressive symptoms and seizures, for the health states to be fully representative of clinical reality. It was hence determined that the motor and language domains would be used to determine disease progression (the transition probabilities), but the costs associated with the other symptoms would be captured in the model, by working out the proportion of patients suffering from these symptoms during different health states. In addition, the clinical experts believed that patients' health deteriorates further even after a score of zero has been reached on both the motor and language domain. When discussing mortality, the clinical experts expected patients to die only after completing disease progression.

This meeting confirmed that the CLN2 clinical rating scale (consisting of the motor and language domains of the Hamburg scale) can be used to model disease progression for CLN2 patients, as long as other factors are also considered.

Workshop 2

The aim of this workshop was to determine clinical inputs for the model that could not be sourced from the trial data or literature.[84] The format of this workshop was a Delphi panel, with four clinical experts. This Delphi panel was conducted in person. The clinical experts at this workshop all had experience of treating patients with CLN2 disease in the UK, and the Delphi panel aimed to obtain information on standard practice for management of CLN2 disease in the UK, and regular progression of CLN2 disease in the UK, so their expertise was deemed appropriate.

Questions were provided to the clinical experts before the meeting, for them to answer, and these answers were discussed in the meeting. The same questions were then asked again, following the discussion, with the summary of answers across the clinical experts, from the previous iteration, available to see. After discussion of this second round of answers, the questions were asked for a third time. If a consensus was achieved in the answers (≥75% of the responses were the same) then the question was not asked in the next round. The answers following the three rounds of questions were used to inform the economic model.

The questions and answers from the Delphi panel provided information on the use of a feeding tube, the levels of vision loss during the later stages of CLN2 disease, and when this vision loss occurs. In addition, information on the number of appointments required by patients, proportions of patients suffering from progressive symptoms, and numbers of caregivers required, at different stages of the disease, were collected. As not all the clinical experts in this

meeting had experience of patients treated with cerliponase alfa, the answers were only used to inform values for the standard care arm of the model. Further details of the inputs provided can be found in sections 12.1.7, 12.2.1, 12.2.6, and 12.3.7.

Workshop 3

The aim of this workshop was to finalise the model – this involved checking the key assumptions that had been made in the model, and providing any UK clinical inputs that had not been found from trial data or literature searches. This meeting was held in person.

The clinical experts at this workshop had experience of treating patients with CLN2 disease in the UK, so their expertise was deemed appropriate.

The assumption about the patients' long-term stabilisation, the expected starting population distribution across health states, and the expected treatment stopping rule (at health state 7, when the CLN2 clinical rating scale score reaches 0) were all presented to the experts on Microsoft PowerPoint slides, and the experts validated the assumptions as clinically appropriate.

Caregiver disutility for health states 1 and 2 were provided by the experts in this workshop. They were shown the disutility levels being applied for the other health states in the model, and asked to base the carer disutility levels for the first two health states on this. The values provided can be seen in Table D9.

The other model inputs that were obtained in this workshop were the educational support requirements across the different health states, the average number of siblings a patient with CLN2 disease would be expected to have, the level of expected uptake of cerliponase alfa across patients over five years, if it were approved, and the incident population of CLN2 disease patients over five years.

Other

In addition to the workshops detailed above, a call was held with a palliative care specialist, to obtain more information about the final health states in the model. There was little information available in the literature about this later stage of the disease. This information related to the appointments required for patients in health states 8 and 9. Microsoft PowerPoint slides, detailing the background of the disease and the economic model structure, were presented and the inputs suggested were used in the model. Further details can be found in sections 12.2.1 and 12.2.6.

12.2.6 Summarise all the variables included in the cost-effectiveness analysis. Provide cross-references to other parts of the submission. A suggested format is provided in table D5 below.

Table D18. Summary of variables applied in the cost-effectiveness model

Variable	Value	Source
Starting population in model	See section 12.2.1	Assumption, with clinical validation
Number of caregivers	See section 12.1.7	Delphi panel, 2016, see section 12.2.5
Adverse event frequencies	See section 12.2.1	Study 190-201
Progressive symptom proportions	See section 12.1.7	Delphi panel, 2016, see section 12.2.5
Transition probabilities	See section 12.2.1	Study 190-201, 190-202, 190-901, and assumptions
Mortality	See section 12.2.1 for disease related mortality and section 12.1.7 for infection related and age related mortality	ONS life tables,[93] Study 190-201, 190-202, 190-901, and assumptions
Utility values		
Health state utility	See section 12.2.1	Utility study, 2017[75]
Caregiver disutility	See section 12.1.7	'Challenges of living with and caring for a child affected by CLN2 disease , a type of Batten disease – Focus Groups and Home Surveys[13]
Sibling disutility	See section 12.1.7	'Challenges of living with and caring for a child affected by CLN2 disease, a type of Batten disease: Results Summary', p.141
Adverse event disutility	See section 12.1.7	Literature, further details provided in section 12.1.7
Cost values		

Health state costs	See section 12.3.7	Delphi panel, 2016, see section 12.2.5, NHS reference costs 2015-16[94], PSSRU 2016[95]
Adverse event costs	See section 12.3.8	N/A
Progressive symptom costs	See section 12.3.9	BNF 2017[96], eMit 2017[97], NHS reference costs 2015-16[94]
Treatment costs	See section 12.3.6	BioMarin, NHS reference costs 2015-16[94]
Seizure costs	See section 12.3.9	BNF 2017[96], eMit 2017[97], NHS reference costs 2015-16[94]

Abbreviations: N/A: not applicable

12.3 Resource identification, measurement and valuation

NHS costs

12.3.1 Describe how the clinical management of the condition is currently costed in the NHS in terms of reference costs and the payment by results (PbR) tariff.

NHS reference costs were used whenever possible for the unit costs of managing patients while on treatment. This was done to provide a high level of detail and granularity, and allowed the implementation of a detailed micro-costing approach. Furthermore, use of NHS reference costs allows the analysis to reflect the costs to the healthcare provider. The HRG codes used are listed below, with details of how they are used provided in sections 12.3.6, 12.3.7, 12.3.8 and 12.3.9.

Table D19. HRG codes used

HRG code used in model	Item
AA50F	Very Complex Intracranial Procedures, 18 years and under, with CC Score 0-5
AA57B	Minimal Intracranial Procedures, 18 years and under
WF01B, 291	Non-Admitted Face to Face Attendance, First, Paediatric Neuro-Disability, consultant led
WF01C, 291	Non-Admitted Face to Face Attendance, Follow-Up, Paediatric Neuro-Disability, consultant led
N29CF	Other Specialist Nursing, Child, Face to face
WF01B, 290	Non-Admitted Face to Face Attendance, First, Community Paediatrics consultant led
WF01C, 290	Non-Admitted Face to Face Attendance, Follow-Up, Community Paediatrics, consultant led
A13C1	Speech and Language Therapist, Child, One to One
A08C1	Physiotherapist, Child, One to One
WF01B, 216	Non-Admitted Face to Face Attendance, First, Paediatric Opthalmology, consultant led
WF01A, 216	Non-Admitted Face to Face Attendance, Follow-Up, Paediatric Opthalmology, non-consultant led
N03F	Health Visitor, Other Clinical Intervention), A06C1 (Occupational Therapist, Child, One to One
XB01Z	Paediatric Critical Care, Advanced Critical Care 4, Critical Care Sheet
XB02Z	Paediatric Critical Care, Advanced Critical Care 4, Critical Care Sheet
N21CF	Specialist Nursing, Palliative/Respite Care, Child, Face to face
FZ93B	Day cases, endoscopic insertion of gastrostomy tube, 18 years and under
FZ62A	Endoscopic or Intermediate, Upper Gastrointestinal Tract Procedures, between 2 and 18 years
PR02A	Paediatric Epilepsy Syndrome with CC Score 6+ (non-elective short stay)
AA25G	Cerebral Degenerations or Miscellaneous Disorders of Nervous System, with CC Score 0-4

Resource identification, measurement and valuation studies

12.3.2 Provide a systematic search of relevant resource data for the NHS in England. Include a search strategy and inclusion criteria, and consider published and unpublished studies.

Resource use data were identified using the search strategy outlined in the HRQL studies section 10.1.5 and Appendix 3, section 17.8. Eligibility criteria for these studies are specified in section 11.1.2.

Two published studies presenting CRU data were identified by the SLR, and are described below. Study details and extracted data are presented in Table D20.

Ballinger 2016

The Ballinger et al. (2016) study aimed to evaluate the burden of CLN2 disease on families. Caregivers and adult siblings of CLN2 patients in the UK and Germany (as well as countries bordering Germany) completed a home-based assessment. This included questions regarding family background, a qualitative and quantitative survey of disease burden and qualitative questionnaires. The reported results included: disease severity, physical health impacts on caregivers, amount of caring time per week, average length of caregiver's sleep as well as the consequences of disrupted sleep, health related quality of life data, financial burden and financial impacts of CLN2 disease on the families of patients.[77]

Williams 2016a

The Williams et al. (2016) study presents data on current management strategies specific to CLN2 disease. The authors conducted an online survey which was completed by 23 international disease experts (healthcare professionals and patient advocates). The topics discussed in the survey included: seizure management, physical, occupational, speech and holistic therapies, pain management and palliative care as well as end-of-life care considerations.[23]

Table D20. Study characteristics and data extracted from included cost and resource use studies

Study	Objective and population	Country [Cost year]	Valuation methods	Technology and other costs	Resource use	Applicability to UK clinical practice
Ballinger 2016[77] (ICON Study)	To determine the burden of CLN2 disease on families. Caregivers and adult siblings (aged ≥18 years) or child siblings (aged 6–17) of patients with CLN2 disease (self-reported) who were residents in the UK, Germany or countries bordering Germany (specific countries not specified) who were sufficiently fluent in English or German and able to provide written informed consent (aged ≥16 in UK or ≥18 in Germany) or informed assent with caregiver written consent (child siblings aged	UK, Germany or countries bordering Germany (specific countries not specified) [NR]	Qualitative surveys were conducted face-to-face at family homes or quiet rooms in hospital. Audio recordings were transcribed verbatim and thematic analysis was conducted to identify emerging themes.	NR	Mean number of medications per child was 6.25 (range:4–8) Of 26 parents of a child with CLN2 disease the average hours spent caring per week was 76.27. For primary caregivers this increased to 96 hours per week. The time spent caring for age/gender matched UK children was 2.82 hours.	Applicable. Respondents from the UK, Germany and countries bordering Germany contributed to this survey however the results were not presented separately for each country.

<table>
<tr><td></td><td>6–15) were included. Any caregivers or siblings who were participating or who had participated in any clinical trial for CLN2 disease were excluded.
These individuals were enrolled in a mixed-methods survey.</td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Williams 2016a[23]
Specchio 2016[80]
Williams 2016b[81]</td><td>To gain insight into current management strategies specific to CLN2 disease.
CLN2 disease experts from 8 countries including the following specialties: neurology/paediatric neurology (11 experts), paediatric palliative care (3), genetics (3), physiotherapy (2), patient advocacy (2), paediatric intensive</td><td>USA, Germany, UK, Italy, Australia, Argentina, Russia, and Turkey

[NR]</td><td>A total of 23 CLN2 disease experts completed an online survey on the management of CLN2 disease in June 2015.</td><td>NR</td><td><u>Common medications used by experts to treat CLN2-related symptoms:</u>
<table><tr><th>Seizures</th><th>Myoclonus</th><th>Spasticity</th></tr><tr><td>Valproic acid, clobazam,
levetiracetam, lamotrigine,
zonisamide and phenobarbital. The
most commonly used was
valproate in various add-on
combinations</td><td>Lamotrigine, zonisamide,
phenobarbital, levetiracetam,
valproate</td><td>Baclofen, tizanidine, THC,
diazepam, phenobarbital</td></tr><tr><th>Dystonia</th><th>Secretions</th><th>Pain</th></tr></table></td><td>Applicable. Respondents from the UK among other countries contributed to this survey however the results were not presented separately for each country.</td></tr>
</table>

	care/paediatric cardiologist (1), paediatric dietitian (1), neurodisability (1), paediatric pain management (1), paediatrics (1), ophthalmology (1), neuropsychology (1), sleep medicine (1).				Tizanidine, baclofen, benzodiazepines, trihexyphenidyl	Inhaled ipratropium bromide, atropine, glycopyrolate scopolamine (hyoscine)	Simple analgesia (acetaminophen, NSAIDs); stronger analgesics (methadone, morphine, hydromorphone); other (gabapentin, clonidine, pregabalin, amitriptyline)	

<u>Adjuvant therapies:</u>

Physical therapy and other interventions including: ankle foot orthosis, adaptive equipment (gait-trainers, therapy chair, lateral pillow, neck support and vests, etc.) were commonly reported adjuvant strategies used to treat myoclonus, dystonia and spasticity.

Physical, occupational and speech therapies were recommended to be initiated early and performed frequently by carers under supervision from professional therapists: experts recommended a minimum of 2–3 times a week for therapists to teach caregivers to do exercises at home.

Tube feeding (nasogastric or gastric tube) was

					recommended when aspiration risk is high, when the child could no longer swallow or struggled to eat (dysphagia), when weight loss/nutritional deficiencies were observed, or when the family struggled to feed their child. Non-pharmacologic interventions recommended to manage secretions included: suctioning, oral care, speech/feeding/physical therapies and corn whiskers tea. Non-pharmacologic interventions recommended to manage pain included: holistic therapies, positioning aids, physiotherapy and heat. <u>Ophthalmological considerations:</u> It was reported that no therapies existed to treat ophthalmological manifestations. OCT was considered useful and was recommended as an assessment to establish the extent of retinal degeneration. <u>Sleep disturbance:</u> Behavioural strategies (e.g. establishing bedtime and routine) and medications (e.g. melatonin, chloral hydrate) were recommended to manage the impact on quality of life of sleep disturbance on patients and their carers. <u>Speech and language impairment:</u>	

					Use of alternative and augmentative communication methods such as symbols, gestures and aids were recommended. <u>Palliative care and end-of-life considerations:</u> Experts recommended that palliative and hospice care services be offered to all patients with CLN2 disease. It was recommended that contact was initiated with a palliative care team early in the disease course and that psychological support was essential for the family throughout the course of the disease.	

ABBREVIATIONS: CLN2: genetically/enzymatically confirmed neuronal ceroid lipofuscinosis type 2; NR: not reported; NSAIDs: non-steroidal anti-inflammatory drugs; OCT: optical coherence tomography; THC: tetrahydrocannabinol.

12.3.3 Provide details of the process used when clinical advisers assessed the applicability of the resources used in the model[2].

Details of these processes can be found in section 12.2.5.

Technology and comparators' costs

12.3.4 Provide the list price for the technology.

The list price of Brineura in England is £20,107 per 300mg pack, consisting of 2 150mg vials.

12.3.5 If the list price is not used in the de novo cost- effectiveness model, provide the alternative price and a justification.

The list price is used in the de novo cost-effectiveness model.

12.3.6 Summarise the annual costs associated with the technology and the comparator technology (if applicable) applied in the cost effectiveness model. A suggested format is provided in tables D6 and D7. Table D7 should only be completed when the most relevant UK comparator for the cost analysis refers to another technology. Please consider all significant costs associated with treatment that may be of interest to commissioners.

Acquisition Costs

Acquisition costs were applied in the model in the cerliponase alfa arm only. The drug dose and vials required, in line with EMA summary of product characteristics[1] are shown in Table D21[1] are shown in Table D21.

Table D21. Dosing information

Age	Dose (mg)	Vials required
0-6 months	100	0.666666667
6 months to 1 year	150	1
1 year to 2 years	284.61538	1.897435897
>2 years	300	2

[2] Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee.

The dose required was combined with the adherence rate from the trial and the drug cost per vial to obtain an overall cost per dose, as shown in Table D22.

Table D22. Treatment cost items

Treatment cost item	Value	Source
Cost per 150mg vial	£10,053.50	BioMarin Europe Ltd (equivalent to £20,107 per 300mg pack)
Number of vials required per dose	2	Dosing guidelines[1]
Adherence rate	99.74%	Study 190-201/202[64]
Cost per dose	£20,055.18	N/A

Abbreviations: N/A: not applicable

Administration Costs

The costs associated with inserting the intracerebroventricular delivery tube, and the replacement costs, were included as administration costs for the cerliponase alfa arm only. Treatment was administered once every two weeks, in line with the practice followed in the trial, and there was a one-off cost associated with insertion, and an annual replacement cost. The costs were sourced from NHS reference costs, and Cohen-Pfeffer et al. (2017) was used to calculate the proportion of infusions that would require a replacement, and hence the annual replacement cost.[87, 94]

Table D23. Administration costs

Cost element	Value	Source
One-off insertion cost	£9,518.70	NHS reference costs, 2015-16, AA50F, Very Complex Intracranial Procedures, 18 years and under, with CC Score 0-5
Replacement cost	£4,387.99	NHS reference costs, 2015-16, AA57B, Minimal Intracranial Procedures, 18 years and under
Proportion of infusions that lead to an infection	0.45%	Cohen-Pfeffer et al. (2017)[87]
Proportion of infections that require a replacement	62%	Cohen-Pfeffer et al. (2017)[87]
Number of replacements per year	0.07254	Combination of proportion of infusions that lead to an infection and require a replacement
Annual replacement cost applied in model	**£318.30**	

Infusion costs

Treatment with cerliponase alfa is associated with an infusion cost due to the treatment being delivered in a hospital. This cost was taken from the NHS reference costs, a day case value was used and applied to the proportion of patients being treated with cerliponase alfa.

Table D24. Infusion cost

Item	Value	Source
Infusion cost (per infusion)	£466.00	NHS reference costs, 2015-16, AA25G, Cerebral Degenerations or Miscellaneous Disorders of Nervous System, with CC Score 0-4

Health-state costs

12.3.7 If the cost- effectiveness model presents health states, the costs related to each health state should be presented in table D8. The health states should refer to the states in section 12.1.6. Provide a rationale for the choice of values used in the cost- effectiveness model.

Table D25. List of health states and associated costs in the cost-effectiveness model, base case

Health states	Items	Units per year	Costs per year (1st year)	Costs per year (after 1st year)
Health state 1	Specialist clinician	1.63	£555.94	£224.94
	Specialist nurse	25.33	£3,470.21	£3,470.21
	General practitioner	2.75	£99.00	£99.00
	Community paediatrician	1.67	£371.49	£245.49
	Speech/language therapist	2.25	£211.50	£211.50
	Physiotherapist	2	£174.00	£174.00
	Family support worker	1.75	£56.00	£56.00
	Ophthalmologist	1.33	£150.02	£125.02
	Health visitor	0.67	£35.51	£35.51
	Occupational therapist	1.75	£229.25	£229.25
	Caregiver costs	0	£0.00	£0.00
	Critical care bed days	0	£0.00	£0.00
	Hospitalisation costs	0	£0.00	£0.00
	Palliative care	0	£0.00	£0.00
	Educational support	2	£2,796.00	£2,796.00
	Family caregiver productivity losses	0.06	£1,581.84	£1,581.84
	Total		**£8,148.92**	**£7,666.92**
Health state 2	Specialist clinician	1.63	£555.94	£224.94
	Specialist nurse	25.33	£3,470.21	£3,470.21
	General practitioner	2.75	£99.00	£99.00
	Community paediatrician	1.67	£371.49	£245.49
	Speech/language therapist	2.25	£211.50	£211.50
	Physiotherapist	2	£174.00	£174.00
	Family support worker	1.75	£56.00	£56.00
	Ophthalmologist	1.33	£150.02	£125.02
	Health visitor	0.67	£35.51	£35.51
	Occupational therapist	1.75	£229.25	£229.25
	Caregiver costs	0	£0.00	£0.00
	Critical care bed days	0	£0.00	£0.00
	Hospitalisation costs	0	£0.00	£0.00
	Palliative care	0	£0.00	£0.00

	Educational support	2	£2,796.00	£2,796.00
	Family caregiver productivity losses	0.67	£17,663.88	£17,663.88
	Total		**£8,148.92**	**£7,666.92**
Health state 3	Specialist clinician	2.67	£699.46	£368.46
	Specialist nurse	23.75	£3,253.75	£3,253.75
	General practitioner	5	£180.00	£180.00
	Community paediatrician	2.33	£468.51	£342.51
	Speech/language therapist	2.33	£219.02	£219.02
	Physiotherapist	3.33	£289.71	£289.71
	Family support worker	1.67	£53.44	£53.44
	Ophthalmologist	1.33	£150.02	£125.02
	Health visitor	0	£0.00	£0.00
	Occupational therapist	2.25	£294.75	£294.75
	Caregiver costs	0	£0.00	£0.00
	Critical care bed days	0	£0.00	£0.00
	Hospitalisation costs	0	£0.00	£0.00
	Palliative care	0	£0.00	£0.00
	Educational support	3	£4,194.00	£4,194.00
	Family caregiver productivity losses	0.75	£19,773.00	£19,773.00
	Total		**£9,802.66**	**£9,320.66**
Health state 4	Specialist clinician	2.67	£699.46	£368.46
	Specialist nurse	23.75	£3,253.75	£3,253.75
	General practitioner	5	£180.00	£180.00
	Community paediatrician	2.33	£468.51	£342.51
	Speech/language therapist	2.33	£219.02	£219.02
	Physiotherapist	3.33	£289.71	£289.71
	Family support worker	1.67	£53.44	£53.44
	Ophthalmologist	1.33	£150.02	£125.02
	Health visitor	0	£0.00	£0.00
	Occupational therapist	2.25	£294.75	£294.75
	Caregiver costs	0.17	£5,212.37	£5,212.37
	Critical care bed days	0	£0.00	£0.00
	Hospitalisation costs	2	£7,495.04	£7,495.04
	Palliative care	0	£0.00	£0.00
	Educational support	3.5	£4,893.00	£4,893.00
	Family caregiver productivity losses	0.83	£21,882.12	£21,882.12
	Total		**£23,209.07**	**£22,727.07**
Health state 5	Specialist clinician	2.67	£699.46	£368.46
	Specialist nurse	23.75	£3,253.75	£3,253.75
	General practitioner	5	£180.00	£180.00

	Community paediatrician	2.33	£468.51	£342.51
	Speech/language therapist	2.33	£219.02	£219.02
	Physiotherapist	3.33	£289.71	£289.71
	Family support worker	1.67	£53.44	£53.44
	Ophthalmologist	1.33	£150.02	£125.02
	Health visitor	0	£0.00	£0.00
	Occupational therapist	2.25	£294.75	£294.75
	Caregiver costs	0.22	£6,745.42	£6,745.42
	Critical care bed days	0	£0.00	£0.00
	Hospitalisation costs	2	£7,495.04	£7,495.04
	Palliative care	0	£0.00	£0.00
	Educational support	3.5	£4,893.00	£4,893.00
	Family caregiver productivity losses	0.78	£20,563.92	£20,563.92
	Total		**£24,742.12**	**£24,260.12**
Health state 6	Specialist clinician	3.17	£768.46	£437.46
	Specialist nurse	37.67	£5,160.79	£5,160.79
	General practitioner	17.33	£623.88	£623.88
	Community paediatrician	2.33	£468.51	£342.51
	Speech/language therapist	1.67	£156.98	£156.98
	Physiotherapist	4	£348.00	£348.00
	Family support worker	1.67	£53.44	£53.44
	Ophthalmologist	1	£119.00	£94.00
	Health visitor	0	£0.00	£0.00
	Occupational therapist	2.25	£294.75	£294.75
	Caregiver costs	0.21	£6,438.81	£6,438.81
	Critical care bed days	1	£5,462.00	£5,462.00
	Hospitalisation costs	2	£7,495.04	£7,495.04
	Palliative care	0	£0.00	£0.00
	Educational support	3.5	£4,893.00	£4,893.00
	Family caregiver productivity losses	0.79	£20,827.56	£20,827.56
	Total		**£32,282.66**	**£31,800.66**
Health state 7	Specialist clinician	3.17	£768.46	£437.46
	Specialist nurse	37.67	£5,160.79	£5,160.79
	General practitioner	17.33	£623.88	£623.88
	Community paediatrician	2.33	£468.51	£342.51
	Speech/language therapist	1.67	£156.98	£156.98
	Physiotherapist	4	£348.00	£348.00
	Family support worker	1.67	£53.44	£53.44
	Ophthalmologist	1	£119.00	£94.00
	Health visitor	0	£0.00	£0.00
	Occupational therapist	2.25	£294.75	£294.75

	Caregiver costs	0.3125	£9,581.56	£9,581.56
	Critical care bed days	1	£5,462.00	£5,462.00
	Hospitalisation costs	0	£0.00	£0.00
	Palliative care	24	£3,622.18	£3,622.18
	Educational support	3.5	£4,893.00	£4,893.00
	Family caregiver productivity losses	0.9375	£24,716.25	£24,716.25
	Total		**£31,552.55**	**£31,070.55**
Health state 8	Specialist clinician	3.17	£768.46	£437.46
	Specialist nurse	37.67	£5,160.79	£5,160.79
	General practitioner	17.33	£623.88	£623.88
	Community paediatrician	2.33	£468.51	£342.51
	Speech/language therapist	1.67	£156.98	£156.98
	Physiotherapist	4	£348.00	£348.00
	Family support worker	1.67	£53.44	£53.44
	Ophthalmologist	1	£119.00	£94.00
	Health visitor	0	£0.00	£0.00
	Occupational therapist	2.25	£294.75	£294.75
	Caregiver costs	0.3078	£9,437.46	£9,437.46
	Critical care bed days	1	£5,462.00	£5,462.00
	Hospitalisation costs	0	£0.00	£0.00
	Palliative care	36	£5,433.27	£5,433.27
	Educational support	2.5	£3,495.00	£3,495.00
	Family caregiver productivity losses	0.8322	£21,940.12	£21,940.12
	Total		**£31,821.54**	**£31,339.54**
Health state 9	Specialist clinician	3.17	£768.46	£437.46
	Specialist nurse	52	£7,124.00	£7,124.00
	General practitioner	17.33	£623.88	£623.88
	Community paediatrician	2.33	£468.51	£342.51
	Speech/language therapist	1.67	£156.98	£156.98
	Physiotherapist	4	£348.00	£348.00
	Family support worker	1.67	£53.44	£53.44
	Ophthalmologist	1	£119.00	£94.00
	Health visitor	0	£0.00	£0.00
	Occupational therapist	2.25	£294.75	£294.75
	Caregiver costs	0.3078	£9,437.46	£9,437.46
	Critical care bed days	1	£5,462.00	£5,462.00
	Hospitalisation costs	0	£0.00	£0.00
	Palliative care	36	£5,433.27	£5,433.27
	Educational support	2.5	£3,495.00	£3,495.00
	Family caregiver productivity losses	0.8322	£21,940.12	£21,940.12

	Total	**£33,784.75**	**£33,302.75**

For health state costs, whenever subsequent appointments were found to have a different cost to the first appointments, the cost of the first appointment was only applied in the first year of the model, with later years of the model being characterised by the unit costs of subsequent appointments.

The values used for appointments per year in each health state were obtained from the Delphi panel in workshop 2 (see section 12.2.5). The mean values after three rounds of questions were used to inform the values for each health state. For the final two health states (apart from death), any changes from the health state 'CLN2 score 0' were made due to advice from a palliative care specialist (further details in section 12.2.5). It was assumed that the number of appointments in the health states would be the same for both the cerliponase alfa and the standard care arm.

Table D26. List of health state-associated costs (per unit)

Items	Cost per unit (e.g. appointment, bed day, caregiver) – 1st occurrence	Cost per unit (e.g. appointment, bed day, caregiver) – subsequent occurrences	Reference
Specialist clinician	£469.00	£138.00	NHS Ref Costs 2015-16 [Non-Admitted Face to Face Attendance, First, Paediatric Neuro-Disability, consultant led (WF01B, 291)] and [Non-Admitted Face to Face Attendance, Follow-Up, Paediatric Neuro-Disability, consultant led (WF01C, 291)]
Specialist nurse	£137.00	£137.00	NHS Ref Costs 2015-16 [Other Specialist Nursing, Child, Face to face (N29CF)]
General practitioner	£36.00	£36.00	PSSRU 2016 [Per patient contact lasting 9.22 minutes (including carbon emissions (5 KgCO2e)2(carbon costs less than £1), with qualification costs]
Community paediatrician	£273.00	£147.00	NHS Ref Costs 2015-16 [Non-Admitted Face to Face Attendance, First, Community Paediatrics,

			consultant led (WF01B, 290)] and [Non-Admitted Face to Face Attendance, Follow-Up, Community Paediatrics, consultant led (WF01C, 290)]
Speech/language therapist	£94.00	£94.00	NHS Ref Costs 2015-16 [Speech and Language Therapist, Child, One to One (A13C1)]
Physiotherapist	£87.00	£87.00	NHS Ref Costs 2015-16 [Physiotherapist, Child, One to One (A08C1)]
Family support worker	£32.00	£32.00	PSSRU 2016 [Family support worker, unit cost per hour]
Ophthalmologist	£119.00	£94.00	NHS Ref Costs 2015-16 [Non-Admitted Face to Face Attendance, First, Paediatric Opthalmology, consultant led (WF01B, 216)] and [Non-Admitted Face to Face Attendance, Follow-Up, Paediatric Opthalmology, non-consultant led (WF01A, 216)]
Health visitor	£53.00	£53.00	NHS Ref Costs 2015-16 [Health Visitor, Other Clinical Intervention (N03F)]
Occupational therapist	£131.00	£131.00	NHS Ref Costs 2015-16 [Occupational Therapist, Child, One to One (A06C1)]
Caregiver costs	£30,661.00	£30,661.00	https://www.healthcareers.nhs.uk/about/careers-nhs/nhs-pay-and-benefits/agenda-change-pay-rates - NHS-funded school nurse, Band 6, Point 25
Critical care bed days	£5,462.00	£5,462.00	NHS Ref Costs 2015-16 [XB01Z, Paediatric Critical Care, Advanced Critical Care 5, Critical Care Sheet]
Hospitalisation days	£3,747.52	£3,747.52	NHS Ref Costs 2015-16 [XB02Z, Paediatric Critical Care, Advanced Critical Care 4, Critical Care Sheet]
Palliative care	£150.92	£150.92	NHS Ref Costs 2015-16 [Specialist Nursing, Palliative/Respite Care, Child, Face to face (N21CF)]
Educational	£1,398.00	£1,398.00	PSSRU 2016 [Education support, children aged 4-

support			11 with low functioning autism living in private households with family]
Family caregiver productivity losses	£26,364.00	£26,364.00	Average total pay (including bonuses) for employees in Great Britain, ONS, March 2017

Adverse-event costs

12.3.8 Complete table D9 with details of the costs associated with each adverse event included in the cost- effectiveness model. Include all adverse events and complication costs, both during and after longer-term use of the technology.

As adverse events reported are infusion related, the costs of treating adverse events will be covered by the infusion costs for treatment, and hence were not additionally included in the model.

Miscellaneous costs

12.3.9 Describe any additional costs and cost savings that have not been covered anywhere else (for example, PSS costs, and patient and carer costs). If none, please state.

Progressive Symptom Costs

Progressive costs were applied to the proportion of patients in each health state suffering from those progressive symptoms, as outlined in section 12.1.7.

Epilepsy

The cost of the required AEDs was used to determine the annual cost of epilepsy for the patients. The different AEDs used, and the breakdown between these medications, were taken from the patient narratives in studies 190-201 and 190-202. This annual cost was then applied to the average weight of the patients at that point in the model. Clonazepam was the only medication that was not dependent on the weight of patients, so was applied separately in the model.

Table D27. Cost of AEDs per year

		Cost per year (per kg)	Cost per year (not weight related)	Source	Proportion of AEDs usage	Source
Monotherapies	Sodium valproate (Vl)	£1.73	N/A	BNF 2017[96] eMit 2017[97]	[redacted]	Studies 190-201/190-202, Patient Narratives[85]
	Lamotrigine (Lm)	£16.27	N/A			
	Levetiracetam (Lv)	£18.43	N/A			
	Topiramate (Tp)	£2.88	N/A			
	Clobazam (Cb)	£76.17	N/A			
	Zonisamide (Zn)	£43.72	N/A			
	Clonazepam (Cn)	£1,379.70	N/A			
Combination therapies	Vl + Lv	£20.16	N/A			
	Vl + Lv + Zn	£63.88	N/A			
	Vl + Lv + Cn	£20.16	£1,379.70			
	Vl + Lv + Lm	£36.43	N/A			
	Vl + Lm + Zn	£61.72	N/A			
	Vl + Lm + Cb	£94.17	N/A			
	Vl + Lm + Tp	£20.88	N/A			
	Vl + Zn + Cb	£121.62	N/A			
	Vl + Cn + Tp	£4.61	£1,379.70			
	Lv + Zn + Cb	£138.32	N/A			
	Lv + Lm + Tp	£37.58	N/A			
AEDs cost per year (per kg)	**£46.21**					
AEDs cost per year (not weight related)	**£179.96**					

Abbreviations: AEDs : anti-epileptic drugs; N/A: not applicable

Reported Distress

The list of medications recommended for the treatment of reported distress in Williams et al 2017 was used to calculate annual medication costs for reported distress.[24] As the patient narratives did not provide the information on the breakdown of the usage of these medications, an even split across the medications was assumed, and costs were sourced from the BNF.

Table D28. Cost of reported distress medications per year

Medication	Cost per year	Source	Proportion of pain medication usage	Source
Acetaminophen	£92.47	BNF 2017[96] eMit 2017[97]	14%	Assumption that the proportions of patients using the different reported distress medications recommended in the treatment guidelines is equal across all medications
Methadone	£36.80		14%	
Morphine	£5.48		14%	
Hydromorphone	£344.93		14%	
Amitriptyline	£38.79		14%	
Gabapentin	£85.00		14%	
Pregabalin	£1,367.44		14%	
Reported distress medications cost per year	£281.56			

Dystonia

The list of medications for the treatment of dystonia was taken from Williams et al (2017),[24] and the assumption was made that all of the medications would be used in equal proportions. It was also assumed that patients with dystonia are already receiving AEDs, to avoid double-counting the clonazepam and clobazam costs. Tizanidine was the only medication that was not dependent on the weight of patients, so was applied separately in the model.

Table D29. Cost of dystonia medications per year

Medication	Cost per year (per kg for all except Tizanidine)	Source	Proportion of dystonia medication usage	Source
Baclofen	£4.02	BNF 2017[96] eMit 2017[97]	17%	Assumption that the proportion of patients using the different dystonia medications is the same across all recommended medications, and that all patients with dystonia are already receiving AEDs (to avoid double-counting clonazepam and clobazam costs)
Conidine	£15.22		17%	
Clonazepam	£1,379.70		17%	
Trihexyphenidyl	£80.30		17%	
Clobazam	£76.17		17%	
Tizanidine	£50.55		17%	
Dystonia medications cost per year (per kg) – excluding Tizanidine	£16.59			
Tizanidine cost per year	£8.43			

Myoclonus

The list of medications required for the treatment of myoclonus was taken from Williams et al (2017),[24] and the assumption was made that all of the medications would be used in equal proportions. It was also assumed that patients with dystonia are already receiving AEDs, to avoid double-counting medication costs. This meant that only the cost of Phenobarbital was applied in the model as an additional cost due to myoclonus. This annual cost was then applied to the average weight of the patients at that point in the model.

Table D30. Cost of myoclonus medications per year

Medication	Cost per year (per kg)	Source	Proportion of myoclonus medication usage	Source
Phenobarbital	£106.03	BNF 2017[96] eMit 2017[97]	14%	Assumption that all patients requiring medications for treating myoclonus are already taking AEDs, so to avoid double counting only the costs for phenobarbital are applied. It is also assumed that the proportions of patients using each of the myoclonus medications is the same across all medications.
Clobazam	£76.17		14%	
Clonazepam	£1,379.70		14%	
Lamotrigine	£16.27		14%	
Levetiracetam	£18.43		14%	
Valproate	£1.73		14%	
Zonisamide	£43.72		14%	
Myoclonus medications cost per year (per kg)	£15.15			

Feeding Tube

The costs of requiring a feeding tube were split into the insertion cost (which was a one-off cost) and the replacement costs. NHS reference costs were used to source these costs (Table D31).[94] Usual practice at Great Ormond Street Hospital is to change the feeding tube once every two years, so the annual replacement cost in the model was considered to be half the cost of a day case.[86] The feeding tube insertion cost was only applied to patients in the model when they initially require a feeding tube.

Table D31. Costs of requiring a feeding tube

Item	Value	Source
Feeding tube insertion cost	£1,074.44	NHS reference costs 2015-16, Day cases, endoscopic insertion of gastrostomy tube, 18 years and under (FZ93B)
Feeding tube replacement cost (annual)	£434.50	NHS reference costs, 2015-16, Endoscopic or Intermediate, Upper Gastrointestinal Tract Procedures, between 2 and 18 years, (FZ62A)

Chronic Seizures Costs

Despite taking AEDs, clinical experts were of the opinion that CLN2 disease patients would still suffer from chronic seizures. The cost of these seizures was modelled as being dependent on the number of seizures experience annually. For each of these seizure costs, rescue medications and a hospitalisation cost was applied. The breakdown of medications used for rescue medication incidents per year was provided in the patient narratives for studies 190-201 and 190-202, and this breakdown provided information on what proportion of rescue medication incidents required hospitalisation costs too. Hospitalisation costs were applied only for the proportion of incidents where intravenous medication was required, as shown in Table D32.

Table D32. Weighted cost per chronic seizure

Medication	Proportion of patients	Source	Cost per seizure	Source
Rectal diazepam	[redacted]	Patient narratives from studies 190-201 and 190-202	£0.61	eMit 2017[97]
Intravenous lorazepam	[redacted]		£0.35	BNF 2017[96]
Buccal midazolam	[redacted]		£22.25	BNF 2017[96], NICE CG137[98]
Intravenous phenobarbital	[redacted]		£5.77	eMit 2017[97]
Hospitalisation cost	[redacted]		£943.00	PR02A, NHS Reference Costs 2015-16, Paediatric Epilepsy Syndrome with CC Score 6+ (non-elective short stay) + assumption that hospitalisation costs are applied only for the seizures where intravenous medication is required
Weighted cost per chronic seizure	£428.75			

The weighted cost per chronic seizure was then combined with the expected annual number of chronic seizures to produce the annual cost of seizures. The expected annual numbers of chronic seizures were obtained when a clinical expert validated the vignettes described in section 12.2.1. The number of expected annual chronic seizures varied depending on the health state and the treatment arm, and after a score of 0 was reached on the CLN2 clinical rating scale, it was assumed that no seizures were experienced by patients, as they lacked the brain volume to experience a chronic seizure.

Table D33. Annual cost of seizures

Health State	Number of seizures (annually)			Annual cost of seizures	
	Cerliponase Alfa	Standard Care	Source	Cerliponase Alfa	Standard Care
Health state 1	1.00	1.00	Utility Study Report[75]	£428.75	£428.75
Health state 2	1.00	3.00		£428.75	£1,286.26
Health state 3	1.00	6.00		£428.75	£2,572.51
Health state 4	1.00	6.00		£428.75	£2,572.51
Health state 5	1.00	6.00		£428.75	£2,572.51
Health state 6	1.00	6.00		£428.75	£2,572.51
Health state 7	0.00	0.00		£0.00	£0.00
Health state 8	0.00	0.00		£0.00	£0.00
Health state 9	0.00	0.00		£0.00	£0.00

12.3.10 Are there any other opportunities for resource savings or redirection of resources that it has not been possible to quantify?

The benefit of cerliponase alfa is in delaying disease progression, and evidence from the Phase I/II trial, as well as expert clinical opinion,[83] suggests that patients stabilise on treatment, some stabilise earlier and others later.

Compared to standard care, it is likely that this would reduce home adaptation costs that would be associated with the later stages of CLN2 disease, which patients would experience with standard care. These costs can include adaptive beds, chest cough assist vests, and saliva suction machines. Costs such as adapting vehicles, or using vehicles like Motability vehicles, which are associated with the later stages of CLN2 disease, would also be reduced. Due to limited data on the specific costs associated with home adaptation and the requirements for patients with CLN2 disease at specific points of the disease, this has not been taken into account in the cost-effectiveness model. However, clinical experts stated that adapted vehicles could cost around £10,000, and housing adaptations can cost more than £50,000. The funding available for these adaptations is rarely sufficient to cover the full costs to the family, so this can place a further burden on the families. By delaying the progression to the later health states, cerliponase alfa can delay the point at which a wheelchair is required for patients, which is associated with expensive replacement costs.

If children stabilise on treatment, cerliponase alfa would be increasing the probability of patients reaching a working age and obtained a job. This employment would increase the mental wellbeing of patients with CLN2 disease, and would contribute to society through taxation, but this was not modelled due to limited data.

The impact of epilepsy gene panels on misdiagnosis has also not been quantified in the model, due to limited data.

12.4 Approach to sensitivity analysis

Section 12.4 requires the sponsor to carry out sensitivity analyses to explore uncertainty around the structural assumptions and parameters used in the analysis. All inputs used in the analysis will be estimated with a degree of imprecision. For technologies whose final price/acquisition cost has not been confirmed, sensitivity analysis should be conducted over a plausible range of prices.

Analysis of a representative range of plausible scenarios should be presented and each alternative analysis should present separate results.

12.4.1 Has the uncertainty around structural assumptions been investigated? State the types of sensitivity analysis that have been carried out in the cost- effectiveness analysis.

The uncertainty around the values of inputs has been investigated in deterministic and probabilistic sensitivity analyses, further details of which can be found in section 12.4.2.

In order to test the uncertainty around structural assumptions, scenario analyses were conducted, with particular inputs or assumptions being varied according to the scenario. A summary of these scenarios is provided in Table D34, with further details provided below.

Table D34. List of scenario analyses

Scenario	Change(s) made to model
Scenario 1	Starting population of patients evenly split across health states 1-2.
Scenario 2	All starting population starts in health state 1
Scenario 3	Utility values obtained using the PedsQL values from the trial, mapped to EQ-5D, with the assumption of the same utility values across both arms of the treatment
Scenario 4	Utility values for cerliponase alfa arm assumed to be the same as the standard care arm, from the utility study
Scenario 5	Patients stop receiving cerliponase alfa treatment at health state 6
Scenario 6	Patients do not stop receiving cerliponase alfa treatment until death

Scenario 7	No caregiver or sibling disutility is applied in the model, for the cerliponase alfa arm
Scenario 8	Discount rate of 3.5% for costs and benefits
Scenario 9	Discount rate of 3.5% for costs, 1.5% for benefits
Scenario 10	Reduced price, due to price evolution and PPRS rebate
Scenario 11	Time horizon of 75 years
Scenario 12	Societal perspective used
Scenario 13	Optimistic scenario - All starting population starts in health states 1-2, no caregiver or sibling disutility applied to the cerliponase alfa arm, 50% reduction in progressive symptoms, differential discount rate
Scenario 14	Pessimistic scenario - Utility values for cerliponase alfa arm assumed to be the same as the standard care arm, from the utility study, discount rate of 3.5% for costs and benefits

Scenarios 1 and 2 – alternative starting populations

In the base case analysis, the distribution of the starting population across health states used in the model, for both arms, was based on the expected started population, given treatment in the future. This approach was validated by clinical experts, as described in section 12.2.5.

In addition to this base case, alternative distributions of the starting population were explored in scenario analyses. Scenario 1 presented a starting population where all patients were evenly split across the first two health states, and scenario 2 presented a starting population where all patients start in the first health state. These represent optimistic scenarios where early diagnosis and treatment occurs. All other parameters remained the same across the scenarios.

Scenarios 3 and 4 – alternative utility values

In the base case analysis, the utility values used for the health states in the model were based on the utility study described in section 12.2.1.

In addition to this base case, a scenario was explored where the PedsQL values collected in the trial were mapped to utility values, using the algorithm presented in Khan et al (2014).[76] No quality of life data were available from the natural history study, so in this scenario, it was assumed that utility values would be the same across both arms. For the health states beyond health state 6, there were no data in study 190-201, so it was assumed that there would be a linear decrease from this last point to the final health state, down to a utility value of zero. All other parameters remained the same across the scenarios. The utility values used in this scenario are presented in Table D35.

Table D35. Utility values used in scenario 7

Health state	Cerliponase alfa	Standard care
Health state 1	0.916	0.916
Health state 2	0.820	0.820
Health state 3	0.719	0.719
Health state 4	0.722	0.722
Health state 5	0.645	0.645
Health state 6	0.529	0.529
Health state 7	0.353	0.353
Health state 8	0.118	0.118
Health state 9	0.000	0.000
Health state 10 (death)	0.000	0.000

Scenario 4 also explored the possibility of there being no difference in utility value in the same health state due to treatment with cerliponase alfa. The utility values used for both arms in the model were the utility values obtained from the utility study, for the standard care arm.

Scenario 5 and 6 – alternative treatment stopping rules

In the base case analysis, patients stopped receiving cerliponase alfa treatment at health state 7, when their CLN2 clinical rating scale score reached 0. At this point in the model, transition probabilities and utility values corresponding to the standard care arm were applied. This approach was validated by clinical experts, as described in section 12.2.5.

In addition to this base case, alternative scenarios of the stopping rule were explored in scenario analysis. Scenario 5 assumed that patients stopped receiving cerliponase alfa treatment at health state 6. Scenario 6 assumed that patients do not stop receiving cerliponase alfa treatment until death. All other parameters remained the same across the scenarios.

Scenario 7 – no caregiver or sibling disutility to cerliponase alfa arm

In the base case analysis, caregiver disutility was applied to the proportion of care provided by family caregivers for both cerliponase alfa and standard care treatment arms. This approach was validated by clinical experts, as described in section 12.2.5. Sibling disutility is applied as described in section 12.1.7.

In addition to this base case, scenario 7 assumed that no caregiver disutility or sibling disutility is applied to the cerliponase alfa arm, as it is likely that with disease stabilisation, caregiver burden will be significantly reduced or eliminated, enabling caregivers and their siblings to live as close to normal lives as possible.

Scenarios 8 and 9 – altered discount rate

In the base case analysis, a 1.5% discount rate was used for costs and benefits. As the beneficial impact of the treatment is expected to be sustained over a very long period, in order to fully reflect the costs and benefits, a lower discount rate than the NICE reference case was used in the base case.

In addition to this base case, scenario 8 used a discount rate of 3.5% for costs and benefits.

Scenario 9 uses a discount rate of 3.5% for costs, and 1.5% for benefits, in line with literature that argues that discounting health benefits at a lower rate than costs takes into account any potential increase in the future value of health effects.[99, 100] The authors in this literature argue that the discount rate on health effects should be 1% to 3.5% lower than the discount rate on costs, so a 2% difference was selected, with the NICE reference case value for discount rate on costs used (3.5%).

Scenario 10 – reduced price, due to price evolution and PPRS rebate

In the base case analysis, the list price of cerliponase alfa is used. In scenario 10, a 7.8% pharmaceutical price regulation scheme (PPRS) rebate is applied to the list price of cerliponase alfa. Over the time horizon of the drug, it would be expected that the price of the drug will fall. Analysis of IMS data on enzyme replacement therapy drug prices in Europe, where more than 10 years of price information were available, showed that prices generally fall. Scenario 10 also incorporates a price reduction of 9% after 10 years of the treatment being available, in line with the analysis of IMS data.

Scenario 11 – altered time horizon

In the base case analysis, a time horizon of 95 years was used, to reflect a lifetime time horizon. ONS life tables provide information up to 100 years, and with the starting age of the population assumed to be 4.78, based on the age of patients at the start of the trial, a time horizon of 95 years was deemed to be appropriate to go up to 100 years.

In addition to this base case, scenario 11 uses a reduced time horizon of 75 years.

Scenario 12 – altered perspective

In the base case analysis, a healthcare system perspective was used. Only costs that are directly relevant to the healthcare system are considered in this perspective. Family caregiver costs were not included in this base case analysis.

In addition to this base case, scenario 12 applies a societal perspective, and included the costs of productivity losses for the family caregivers in the health state costs.

Scenario 13 – optimistic scenario

In this scenario, all patients start in the first two health statesstate, andand cerliponase alfa treatment is assumed to reduce the progressive costs by half, as well as total removal of caregiver or sibling disutility. Given the gene-testing campaign proposed by the manufacturer it is highly probable that future patients initiated on treatment will in the early stages of disease. This scenario also applies a discount rate of 3.5% for costs, and 1.5% for benefits.

Scenario 14 – pessimistic scenario

In this scenario, utility values used for both arms in the model were the utility values obtained from the utility study, for the standard care arm. A discount rate of 3.5% was used for both costs and benefits.

12.4.2 Was a deterministic and/or probabilistic sensitivity analysis undertaken? If not, why not? How were variables varied and what was the rationale for this? If relevant, the distributions and their sources should be clearly stated.

A deterministic sensitivity analysis, where each variable was increased and decreased by 15%, whilst all other variables were held constant, was conducted in order to identify the key drivers of the model. The results are displayed in section 12.5.11 in the form of a tornado diagram, where the ten variables leading to the greatest variation in results are displayed.

A probabilistic sensitivity analysis, where each variable was stochastically chosen from a distribution for a particular simulation, was conducted in order to test the robustness of the model. Where confidence intervals were provided, they formed the basis of the distributions, but for the majority of variables, no confidence intervals were available. In these instances, a 15% variation was used, with the distribution selected depending on the variable. 1000 iterations were run, and a scatter plot of results was created, as shown in section 12.5.13.

12.4.3 Complete table D10.1, D10.2 and/or D10.3 as appropriate to summarise the variables used in the sensitivity analysis.

One-way scenario-based deterministic sensitivity analysis

As described in section 12.4.2, the deterministic sensitivity analysis was conducted by varying each variable by ±15% of their mean value in order to identify key model drivers. The exception to this method was wherever probabilities would be greater than one when increased by 15%. In these instances, an upper value of 1 was used in the deterministic sensitivity analysis.

Multi-way scenario-based sensitivity analysis

As described in section 12.4.1, various scenario analyses were conducted to explore the impact of assumptions that were included in the base case.

Probabilistic sensitivity analysis

The distributions used to perform the probabilistic sensitivity analysis are presented in the Appendix 6, in section 17.6.

12.4.4 If any parameters or variables listed above were omitted from the sensitivity analysis, provide the rationale.

Certain variables in the model were omitted from the various sensitivity analyses conducted. The discount rate was only altered in the scenario analyses, as this can be considered constant for all other scenarios. The transition probabilities used were only altered in the scenario analyses, as these were the result of structural assumptions. The drug dose, and the number of vials required, were not included in the sensitivity analyses as these can be considered constant. The drug cost was included in the one-way deterministic sensitivity analysis, to show whether it is a driver of the model results, but not included in the probabilistic sensitivity analysis, as there was no uncertainty or distribution around this value.

12.5 Results of economic analysis

Section 12.5 requires the sponsor to report the economic analysis results. These should include the following:

- costs, quality-adjusted life years (QALYs) and incremental cost per QALY
- the link between clinical- and cost-effectiveness results
- disaggregated results such as life years gained (LYG), costs associated with treatment, costs associated with adverse events, and costs associated with follow-up/subsequent treatment
- results of the sensitivity analysis.

Base-case analysis

12.5.1 When presenting the results of the base case incremental cost effectiveness analysis in the table below, list the interventions and comparator(s) from least to most expensive. Present incremental cost-effectiveness ratios (ICERs) compared with baseline (usually standard care) and then incremental analysis ranking technologies in terms of dominance and extended dominance. If the company has formally agreed a patient access scheme with the Department of Health, present the results of the base-case incremental cost-effectiveness analysis with the patient access scheme. A suggested format is available in table D11.

Table D36. Base case results

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental (QALYs)
Cerliponase alfa	[redacted]	45.01	29.45	[redacted]	40.04	30.42	[redacted]
Standard care	£149,829	4.97	-0.97	N/A	N/A	N/A	N/A
ICER, incremental cost-effectiveness ratio; LYG, life years gained; N/A, not applicable; QALYs, quality-adjusted life years							

In addition to these base case results, results from an alternative base case, where differential discount rates (1.5% for benefits and 3.5% for costs) are used, are presented below. Justification for this alternative is provided in section 12.4.1.

Table D37. Alternative base case results

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental (QALYs)
Cerliponase alfa	[redacted]	45.01	29.45	[redacted]	40.04	30.42	[redacted]
Standard care	£149,829	4.97	-0.97	N/A	N/A	N/A	N/A
ICER, incremental cost-effectiveness ratio; LYG, life years gained; N/A, not applicable; QALYs, quality-adjusted life years							

12.5.2 For the outcomes highlighted in the decision problem, please provide the corresponding outcomes from the model and compare them with clinically important outcomes such as those reported in clinical trials. Discuss reasons for any differences between modelled and observed results (for example, adjustment for cross-over). Please use the following table format for each comparator with relevant outcomes included.

As the starting population used in the model is different to the population seen in studies 190-201/202, and 190-901, there was no directly comparable outcome.

12.5.3 Please provide (if appropriate) the proportion of the cohort in the health state over time (Markov trace) for each state, supplying one for each comparator.

Figure D21. Proportion of the patient cohort across all health states over time, cerliponase alfa arm

Figure redacted: commercial in confidence

Table D38. Proportion of the patient cohort across all health states over time, cerliponase alfa arm

	Proportion in health state									
Time in model (years)	**Health State 1**	**Health State 2**	**Health State 3**	**Health State 4**	**Health State 5**	**Health State 6**	**Health State 7**	**Health State 8**	**Health State 9**	**Death**
10	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
20	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
30	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
40	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
50	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
60	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
70	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
80	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
90	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Figure D22. Proportion of the patient cohort across all health states over time, standard care arm

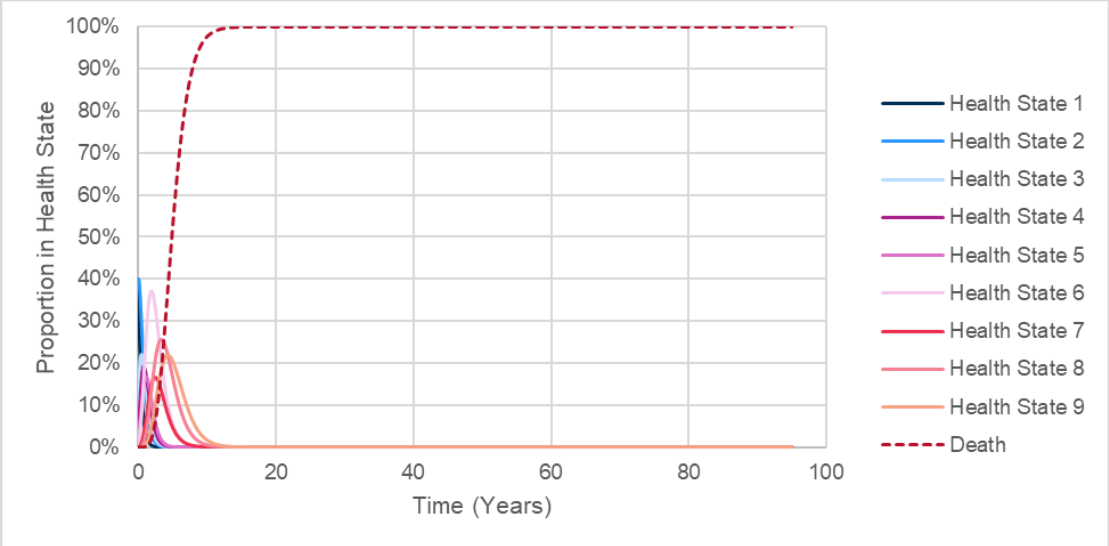
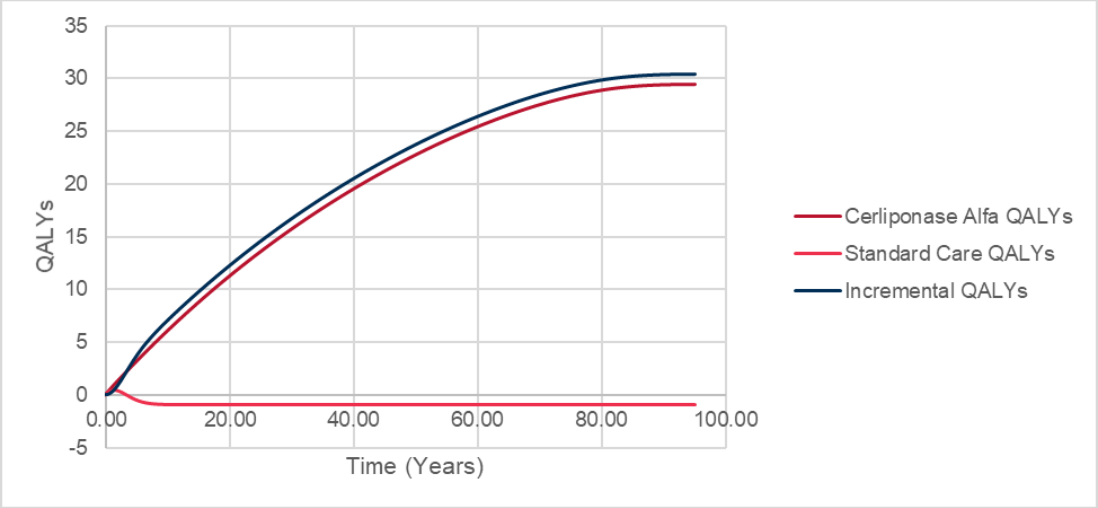


Table D39. Proportion of the patient cohort across all health states over time, standard care arm

	Proportion in health state									
Time in model (years)	**Health State 1**	**Health State 2**	**Health State 3**	**Health State 4**	**Health State 5**	**Health State 6**	**Health State 7**	**Health State 8**	**Health State 9**	**Death**
10	0%	0%	0%	0%	0%	0%	0%	1%	2%	98%
20	0%	0%	0%	0%	0%	0%	0%	0%	0%	100%
30	0%	0%	0%	0%	0%	0%	0%	0%	0%	100%
40	0%	0%	0%	0%	0%	0%	0%	0%	0%	100%
50	0%	0%	0%	0%	0%	0%	0%	0%	0%	100%
60	0%	0%	0%	0%	0%	0%	0%	0%	0%	100%
70	0%	0%	0%	0%	0%	0%	0%	0%	0%	100%
80	0%	0%	0%	0%	0%	0%	0%	0%	0%	100%
90	0%	0%	0%	0%	0%	0%	0%	0%	0%	100%

12.5.4 Please provide details of how the model assumes QALYs accrued over time. For example, Markov traces can be used to demonstrate QALYs accrued in each health state over time.

Figure D23. QALYs accrued over time



Abbreviations: QALYs: quality-adjusted life years

Table D40. QALYs accrued over time

	QALYs Accrued		
Time in model (years)	**Cerliponase Alfa**	**Standard Care**	**Incremental**
10	6.094231	-0.95246	7.046687
20	11.28295	-0.96934	12.25229
30	15.73647	-0.96934	16.70581
40	19.54484	-0.96934	20.51418
50	22.77104	-0.96934	23.74038
60	25.44203	-0.96934	26.41137
70	27.52664	-0.96934	28.49598
80	28.89437	-0.96934	29.86371
90	29.40538	-0.96934	30.37472

12.5.5 Please indicate the life years (LY) and QALYs accrued for each clinical outcome listed for each comparator. For outcomes that are a combination of other states, please present disaggregated results. For example:

The life years (LYs) accrued across health states are shown in Table D41 and Table D42. The quality-adjusted life years (QALYs) accrued across health states are shown in section 12.5.6.

Table D41. Summary of discounted life year gain by health state

Health State	Life years cerliponase alfa	Life years standard care	Increment	Absolute increment	% Absolute increment
Health State 1	9.273	0.172	9.101	9.101	20.30%
Health State 2	15.619	0.367	15.251	15.251	34.02%
Health State 3	9.942	0.305	9.637	9.637	21.49%
Health State 4	5.438	0.321	5.117	5.117	11.41%
Health State 5	3.502	0.324	3.178	3.178	7.09%
Health State 6	1.203	1.051	0.152	0.152	0.34%
Health State 7	0.007	0.515	-0.507	0.507	1.13%
Health State 8	0.014	0.966	-0.952	0.952	2.12%
Health State 9	0.013	0.951	-0.938	0.938	2.09%
Total	*45.011*	*4.971*	*40.039*	*44.834*	*100%*

Table D42. Summary of undiscounted life year gain by health state

Health State	Life years cerliponase alfa	Life years standard care	Increment	Absolute increment	% Absolute increment
Health State 1	15.544	0.173	15.372	15.372	20.35%
Health State 2	26.217	0.369	25.848	25.848	34.22%
Health State 3	16.724	0.307	16.417	16.417	21.74%
Health State 4	9.162	0.324	8.838	8.838	11.70%
Health State 5	5.900	0.329	5.571	5.571	7.38%
Health State 6	2.032	1.083	0.949	0.949	1.26%
Health State 7	0.007	0.535	-0.527	0.527	0.70%
Health State 8	0.014	1.019	-1.005	1.005	1.33%
Health State 9	0.014	1.019	-1.005	1.005	1.33%
Total	*75.615*	*5.157*	*70.457*	*75.532*	*100%*

12.5.6 Please provide details of the disaggregated incremental QALYs by health state. Suggested formats are presented below.

Table D43.Summary of quality-adjusted life year gain by health state

	QALY Cerliponase alfa	QALY Standard care	Increment	Absolute increment	% absolute increment
Health states					
Health State 1	9.122	0.172	8.950	8.950	29.27%
Health State 2	11.639	0.262	11.377	11.377	37.21%
Health State 3	5.844	0.156	5.688	5.688	18.60%
Health State 4	2.048	0.081	1.966	1.966	6.43%
Health State 5	0.836	0.001	0.835	0.835	2.73%
Health State 6	0.058	-0.111	0.169	0.169	0.55%
Health State 7	-0.004	-0.304	0.300	0.300	0.98%
Health State 8	-0.008	-0.568	0.560	0.560	1.83%
Health State 9	-0.009	-0.661	0.651	0.651	2.13%
Disutilities					
Pyrexia	-0.034	0.000	-0.034	0.034	0.11%
Hypersensitivity	-0.001	0.000	-0.001	0.001	0.00%
Headache	-0.002	0.000	-0.002	0.002	0.01%
Vomiting	-0.001	0.000	-0.001	0.001	0.00%
Infections	-0.040	0.000	-0.040	0.040	0.13%
Total	*29.446*	*-0.969*	*30.416*	*30.573*	*100%*

Abbreviations: QALY, quality-adjusted life year

Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee

The costs accrued over the health states, and across the different categories, are shown in sections 12.5.8, 1.1.1, and 1.1.1.

12.5.7 Please provide undiscounted incremental QALYs for the intervention compared with each comparator

Table D44. Summary of undiscounted quality-adjusted life year gain by health state

	QALY Cerliponase alfa	QALY Standard care	Increment	Absolute increment	% absolute increment
Health states					
Health State 1	15.290	0.172	15.118	15.118	29.77%
Health State 2	19.538	0.264	19.275	19.275	37.95%
Health State 3	9.831	0.157	9.674	9.674	19.05%
Health State 4	3.450	0.082	3.368	3.368	6.63%
Health State 5	1.409	0.001	1.407	1.407	2.77%
Health State 6	0.098	-0.114	0.212	0.212	0.42%
Health State 7	-0.004	-0.316	0.312	0.312	0.61%
Health State 8	-0.008	-0.599	0.591	0.591	1.16%
Health State 9	-0.010	-0.708	0.698	0.698	1.37%
Disutilities					
Pyrexia	-0.057	0.000	-0.057	0.057	0.11%
Hypersensitivity	-0.002	0.000	-0.002	0.002	0.00%
Headache	-0.003	0.000	-0.003	0.003	0.01%
Vomiting	-0.002	0.000	-0.002	0.002	0.00%
Infections	-0.068	0.000	-0.068	0.068	0.13%
Total	*49.461*	*-1.059*	*50.521*	*50.786*	*100%*

Abbreviations: QALY, quality-adjusted life year

Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee

12.5.8 Provide details of the costs for the technology and its comparator by category of cost.

Table D45. Summary of costs by category of cost per patient

Item	Cost cerliponase alfa	Cost Standard care	Increment	Absolute increment	% absolute increment
Treatment cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Health state costs	£531,894.45	£133,960.61	£397,933.84	£397,933.84	[redacted]
Progressive symptom costs	£99,413.01	£15,868.36	£83,544.65	£83,544.65	[redacted]
Infusion costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee

12.5.9 If appropriate, provide details of the costs for the technology and its comparator by health state.

Table D46. Summary of costs by health state per patient

Health state	Cost Cerliponase alfa	Cost Standard care	Increment	Absolute increment	% absolute increment
Health State 1	£71,222.28	£1,396.52	£69,825.76	£69,825.76	12.66%
Health State 2	£119,928.69	£2,952.33	£116,976.36	£116,976.36	21.21%
Health State 3	£92,755.69	£2,931.57	£89,824.13	£89,824.13	16.28%
Health State 4	£123,632.35	£7,363.49	£116,268.85	£116,268.85	21.08%
Health State 5	£84,993.04	£7,903.91	£77,089.13	£77,089.13	13.97%
Health State 6	£38,256.09	£33,456.27	£4,799.82	£4,799.82	0.87%
Health State 7	£227.71	£15,999.51	-£15,771.80	£15,771.80	2.86%
Health State 8	£429.57	£30,273.51	-£29,843.94	£29,843.94	5.41%
Health State 9	£449.02	£31,683.51	-£31,234.48	£31,234.48	5.66%
Total	*£531,894.45*	*£133,960.61*	*£397,933.84*	*£551,634.28*	*100%*

Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee

12.5.10 If appropriate, provide details of the costs for the technology and its comparator by adverse event.

No costs were applied to adverse events, as detailed in section 12.3.8.

Sensitivity analysis results

12.5.11 Present results of deterministic one-way sensitivity analysis of the variables described in table D10.1.

Figure D24. Results of the deterministic sensitivity analysis

Figure redacted: commercial in confidence

Abbreviations: ICER, incremental cost-effectiveness ratio

12.5.12 Present results of deterministic multi-way scenario sensitivity analysis described in table D10.2.

Table D47. Results from scenarios 1-2

Treatment	Total costs (£)	Total LYs	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£ per QALYs)
Base Case							
Cerliponase alfa	[redacted]	45.01	29.45	[redacted]	40.04	30.42	[redacted]
Standard care	£149,829	4.97	-0.97	N/A	N/A	N/A	N/A
Scenario 1 - Starting population of patients evenly split across health states 1-2							
Cerliponase alfa	[redacted]	45.49	32.93	[redacted]	40.34	33.77	[redacted]
Standard care	£151,685	5.15	-0.84	N/A	N/A	N/A	N/A
Scenario 2 - All starting population starts in health state 1							
Cerliponase alfa	[redacted]	45.56	37.55	[redacted]	40.20	38.16	[redacted]
Standard care	£152,985	5.36	-0.61	N/A	N/A	N/A	N/A

Abbreviations: ICER: incremental cost-effectiveness ratio; LY: life-years LYG: life-years gained; N/A: not applicable; QALYs: quality-adjusted life years

Table D48. Results from scenarios 3-4

Treatment	Total costs (£)	Total LYs	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£ per QALYs)
Base Case							
Cerliponase alfa	[redacted]	45.01	29.45	[redacted]	40.04	30.42	[redacted]
Standard care	£149,829	4.97	-0.97	N/A	N/A	N/A	N/A
Scenario 3 - Utility values obtained using the PedsQL values from the trial, mapped to EQ-5D, with the assumption of the same utility values across both arms of the treatment							
Cerliponase alfa	[redacted]	45.01	33.39	[redacted]	40.04	32.35	[redacted]
Standard care	£149,829	4.97	1.04	N/A	N/A	N/A	N/A
Scenario 4 - Utility values for cerliponase alfa arm assumed to be the same as the standard care arm, from the utility study							
Cerliponase alfa	[redacted]	45.01	26.68	[redacted]	40.04	27.65	[redacted]
Standard care	£149,829	4.97	-0.97	N/A	N/A	N/A	N/A

Abbreviations: ICER: incremental cost-effectiveness ratio; LY: life-years LYG: life-years gained; N/A: not applicable; QALYs: quality-adjusted life years

Table D49. Results from scenarios 5-6

Treatment	Total costs (£)	Total LYs	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£ per QALYs)
Base Case							
Cerliponase alfa	[redacted]	45.01	29.45	[redacted]	40.04	30.42	[redacted]
Standard care	£149,829	4.97	-0.97	N/A	N/A	N/A	N/A
Scenario 5 - Patients stop receiving cerliponase alfa treatment at health state 6							
Cerliponase alfa	[redacted]	43.62	29.25	[redacted]	38.65	30.22	[redacted]
Standard care	£149,829	4.97	-0.97	N/A	N/A	N/A	N/A
Scenario 6 - Patients do not stop receiving cerliponase alfa treatment until death							
Cerliponase alfa	[redacted]	45.05	29.45	[redacted]	40.08	30.42	[redacted]
Standard care	£149,829	4.97	-0.97	N/A	N/A	N/A	N/A

Abbreviations: ICER: incremental cost-effectiveness ratio; LY: life-years LYG: life-years gained; N/A: not applicable; QALYs: quality-adjusted life years

Table D50. Results from scenario 7

Treatment	Total costs (£)	Total LYs	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£ per QALYs)
Base Case							
Cerliponase alfa	[redacted]	45.01	29.45	[redacted]	40.04	30.42	[redacted]
Standard care	£149,829	4.97	-0.97	N/A	N/A	N/A	N/A
Scenario 7 - No caregiver or sibling disutility is applied in the model, for the cerliponase alfa arm							
Cerliponase alfa	[redacted]	45.01	31.25	[redacted]	40.04	32.22	[redacted]
Standard care	£149,829	4.97	-0.97	N/A	N/A	N/A	N/A

Abbreviations: ICER: incremental cost-effectiveness ratio; LY: life-years LYG: life-years gained; N/A: not applicable; QALYs: quality-adjusted life years

Table D51. Results from scenarios 8-9

Treatment	Total costs (£)	Total LYs	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£ per QALYs)
Base Case							
Cerliponase alfa	[redacted]	45.01	29.45	[redacted]	40.04	30.42	[redacted]
Standard care	£149,829	4.97	-0.97	N/A	N/A	N/A	N/A
Scenario 8 - Discount rate of 3.5% for costs and benefits							
Cerliponase alfa	[redacted]	26.83	17.56	[redacted]	22.09	18.42	[redacted]
Standard care	£142,105	4.75	-0.86	N/A	N/A	N/A	N/A
Scenario 9 - Discount rate of 3.5% for costs, 1.5% for benefits							
Cerliponase alfa	[redacted]	45.01	29.45	[redacted]	40.04	30.42	[redacted]
Standard care	£149,829	4.97	-0.97	N/A	N/A	N/A	N/A

Abbreviations: ICER: incremental cost-effectiveness ratio; LY: life-years LYG: life-years gained; N/A: not applicable; QALYs: quality-adjusted life years

Table D52. Results from scenario 10

Treatment	Total costs (£)	Total LYs	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£ per QALYs)
Base Case							
Cerliponase alfa	[redacted]	45.01	29.45	[redacted]	40.04	30.42	[redacted]
Standard care	£149,829	4.97	-0.97	N/A	N/A	N/A	N/A
Scenario 10 - Reduced price, due to price evolution and PPRS rebate							
Cerliponase alfa	[redacted]	45.01	29.45	[redacted]	40.04	30.42	[redacted]
Standard care	£149,829	4.97	-0.97	N/A	N/A	N/A	N/A

Abbreviations: ICER: incremental cost-effectiveness ratio; LY: life-years LYG: life-years gained; N/A: not applicable; QALYs: quality-adjusted life years

Table D53. Results from scenario 11

Treatment	Total costs (£)	Total LYs	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£ per QALYs)
Base Case							
Cerliponase alfa	[redacted]	45.01	29.45	[redacted]	40.04	30.42	[redacted]
Standard care	£149,829	4.97	-0.97	N/A	N/A	N/A	N/A
Scenario 11 - Time horizon of 75 years							
Cerliponase alfa	[redacted]	43.27	28.31	[redacted]	38.30	29.28	[redacted]
Standard care	£149,829	4.97	-0.97	N/A	N/A	N/A	N/A

Abbreviations: ICER: incremental cost-effectiveness ratio; LY: life-years LYG: life-years gained; N/A: not applicable; QALYs: quality-adjusted life years

Table D54. Results from scenario 12

Treatment	Total costs (£)	Total LYs	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£ per QALYs)
Base Case							
Cerliponase alfa	[redacted]	45.01	29.45	[redacted]	40.04	30.42	[redacted]
Standard care	£149,829	4.97	-0.97	N/A	N/A	N/A	N/A
Scenario 12 – Societal perspective used							
Cerliponase alfa	[redacted]	45.01	29.45	[redacted]	40.04	30.42	[redacted]
Standard care	£252,960	4.97	-0.97	N/A	N/A	N/A	N/A

Abbreviations: ICER: incremental cost-effectiveness ratio; LY: life-years LYG: life-years gained; N/A: not applicable; QALYs: quality-adjusted life years

Table D55. Results from scenario 13

Treatment	Total costs (£)	Total LYs	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£ per QALYs)
Base Case							
Cerliponase alfa	[redacted]	45.01	29.45	[redacted]	40.04	30.42	[redacted]
Standard care	£149,829	4.97	-0.97	N/A	N/A	N/A	N/A
Scenario 13 – Optimistic scenario							
Cerliponase alfa	[redacted]	45.49	34.18	[redacted]	40.34	35.01	[redacted]
Standard care	£151,685	5.15	-0.84	N/A	N/A	N/A	N/A

Table D56. Results from scenario 14

Treatment	Total costs (£)	Total LYs	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£ per QALYs)
Base Case							
Cerliponase alfa	[redacted]	45.01	29.45	[redacted]	40.04	30.42	[redacted]
Standard care	£149,829	4.97	-0.97	N/A	N/A	N/A	N/A
Scenario 14 – Pessimistic scenario							
Cerliponase alfa	[redacted]	26.83	15.92	[redacted]	22.09	16.78	[redacted]
Standard care	£142,105	4.75	-0.86	N/A	N/A	N/A	N/A

12.5.13 Present results of the probabilistic sensitivity analysis described in table D10.3.

Figure D25. Results of the probabilistic sensitivity analysis

Figure redacted: commercial in confidence

Abbreviations: QALYs: quality-adjusted life years

Table D57. Comparison of deterministic base case and probabilistic sensitivity analysis results

	Cerliponase Alfa		Standard Care		Increment		ICER
	Discounted cost	Discounted QALYs	Discounted cost	Discounted QALYs	Discounted cost	Discounted QALYs	
Probabilistic Results	[redacted]	29.45	£149,944	-0.97	[redacted]	30.42	[redacted]
Deterministic Results	[redacted]	29.45	£149,829	-0.97	[redacted]	30.42	[redacted]

ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years

12.5.14 What were the main findings of each of the sensitivity analyses?

Deterministic one-way sensitivity analysis

Figure D24 is a tornado diagram showing the top ten drivers of cost-effectiveness in the comparison of cerliponase alfa to standard care. It can be seen that the drug cost is the key driver of the model, followed by the utility values for the health states, which were collected using a utility study.[75] In interpreting model drivers from this tornado diagram it should be noted that transition probabilities and assumptions around disease progression were also key model drivers, but their impact was not captured by the deterministic one-way sensitivity analysis, and was instead explored in scenario analysis.

Deterministic multi-way scenario analysis

The results of the scenario analyses are presented in section 12.5.12.

In scenarios 1-2, it can be seen that the starting population has a significant effect on the incremental QALYs, and hence the ICER, with a starting population that has a higher proportion of patients in the early health states resulting in lower ICERs.

Scenario 3 shows that using the utility values obtained from using the PedsQL values in the trial results in an improvement to the ICER, but the utility study was deemed to be a more suitable source of utility values, due to the assumptions that would be required if the mapping from PedsQL values was selected. Scenario 4 shows that by assuming the same utility values for the cerliponase alfa arm compared to the standard care arm, the incremental QALYs gained decreases, but still remain substantial.

Scenarios 5-6 give results in line with what would be expected – if the treatment is stopped earlier, then the incremental QALYs obtained are lower, but the overall costs are also lower. The stopping rule appears to have a greater effect on the overall costs than the QALYs obtained by treatment.

Scenario 7 shows that caregiver disutility and sibling disutility only has a minimal impact on the model,

Scenarios 8 and 9 show that when the discount rate is the same for both costs and benefits, there is no substantial change to the ICER – a discount rate of 3.5% for both costs and benefits gives a lower ICER. However, if there are different discount rates for costs and benefits, as scenario 9 shows, then the ICER decreases.

Scenario 10 shows that effective price reductions in the future, which may arise through renegotiations, price evolution, and PPRS rebates, can have a significant effect on the ICER.

Scenario 11 shows that the time horizon does not have a significant effect on the ICER.

Scenario 12 shows that the choice of perspective is not a key driver of cost-effectiveness.

Scenarios 13-14 show the likely range within which the ICER lies, as they combine the optimistic and pessimistic elements of the scenario analyses.

Probabilistic sensitivity analysis

The results of the probabilistic sensitivity analysis, shown in Figure D25 and Table D57 show that the probabilistic results (that take into account the combined uncertainty across model parameters) are similar to those estimated in the deterministic base case analysis.

12.5.15 What are the key drivers of the cost results?

The key driver of the cost results is the cost of cerliponase alfa. Of the incremental costs, over [redacted] of the absolute increment is made up of the treatment cost, which is largely driven by the vial cost of cerliponase alfa, as seen in the deterministic one-way sensitivity analysis.

Miscellaneous results

12.5.16 Describe any additional results that have not been specifically requested in this template. If none, please state.

All relevant results have been presented in the previous sections, as part of the template.

12.6 Subgroup analysis

For many technologies, the capacity to benefit from treatment will differ for patients with differing characteristics. Sponsors are required to complete section 12.6 in accordance with the subgroups identified in the scope and for any additional subgroups considered relevant.

Types of subgroups that are not considered relevant are those based solely on the following factors.

- Individual utilities for health states and patient preference.
- Subgroups based solely on differential treatment costs for individuals according to their social characteristics.
- Subgroups specified in relation to the costs of providing treatment in different geographical locations within the UK (for example, if the costs of facilities available for providing the technology vary according to location).

12.6.1 Specify whether analysis of subgroups was undertaken and how these subgroups were identified. Cross-reference the response to the decision problem in table A1.

In line with the scope, analysis of a subgroup of asymptomatic and pre-symptomatic siblings with confirmed CLN2 disease was undertaken.

12.6.2 Define the characteristics of patients in the subgroup(s).

Patients in this subgroup had CLN2 disease, but were asymptomatic and pre-symptomatic.

12.6.3 Describe how the subgroups were included in the cost-effective ness analysis.

The assumption was made that if patients are asymptomatic and pre-symptomatic, then all patients will start in health state 1. All other assumptions and modelling methods were kept the same as the base case.

12.6.4 What were the results of the subgroup analysis/analyses, if conducted? The results should be presented in a table similar to that in section 12.5.6 (base-case analysis). Please also present the undiscounted incremental QALYs consistent with section 12.5.7

Table D58. Results for subgroup

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental (QALYs)
Cerliponase alfa	[redacted]	45.56	37.55	[redacted]	40.20	38.16	[redacted]
Standard care	£152,985	5.36	-0.61	N/A	N/A	N/A	N/A

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; N/A, not applicable; QALYs, quality-adjusted life years

Table D59. Summary of undiscounted quality-adjusted life year gain by health state for subgroup

	QALY Cerliponase alfa	QALY Standard care	Increment	Absolute increment	% absolute increment
Health states					
Health State 1	38.226	0.431	37.795	37.795	59.02%
Health State 2	18.390	0.335	18.056	18.056	28.19%
Health State 3	5.239	0.175	5.064	5.064	7.91%
Health State 4	1.117	0.087	1.030	1.030	1.61%
Health State 5	0.216	0.001	0.214	0.214	0.33%
Health State 6	0.012	-0.114	0.126	0.126	0.20%
Health State 7	0.000	-0.316	0.316	0.316	0.49%
Health State 8	-0.001	-0.599	0.598	0.598	0.93%
Health State 9	-0.001	-0.708	0.707	0.707	1.10%
Disutilities					
Pyrexia	-0.058	0.000	-0.058	0.058	0.09%
Hypersensitivity	-0.002	0.000	-0.002	0.002	0.00%
Headache	-0.003	0.000	-0.003	0.003	0.01%
Vomiting	-0.002	0.000	-0.002	0.002	0.00%
Infections	-0.069	0.000	-0.069	0.069	0.11%
Total	*63.065*	*-0.707*	*63.772*	*64.040*	*100%*

Abbreviations: QALY, quality-adjusted life year

Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee

12.6.5 Were any subgroups not included in the submission? If so, which ones, and why were they not considered?

All relevant subgroups were included in the submission.

12.7 Validation

12.7.1 Describe the methods used to validate and cross-validate (for example with external evidence sources) and quality-assure the model. Provide references to the results produced and cross-reference to evidence identified in the clinical and resources sections.

The model was validated by clinical experts, in order to confirm that the model aligns with clinical reality. Full details of this validation process are provided in section 12.2.5.

12.8 Interpretation of economic evidence

12.8.1 Are the results from this cost-effectiveness analysis consistent with the published economic literature? If not, why do the results from this evaluation differ, and why should the results in the submission be given more credence than those in the published literature?

Due to the rarity of CLN2 disease and the lack of current treatment options, there is no economic literature available for comparison.

12.8.2 Is the cost- effectiveness analysis relevant to all groups of patients and specialised services in England that could potentially use the technology as identified in the scope?

Based on the applied settings and input data, the performed cost-effectiveness analysis is relevant to all groups of patients in England indicated for the treatment with cerliponase alfa, as identified in the scope.

12.8.3 What are the main strengths and weaknesses of the analysis? How might these affect the interpretation of the results?

Strengths

- Whenever appropriate, trial data or natural history data were used to inform the model.
- Where inputs could not be sourced from the literature or trial data, multiple clinical experts were consulted to source these inputs.
- The results and the assumptions were validated by clinical experts with expertise in CLN2 disease and cerliponase alfa, in order to reliably reflect clinical reality.

Weaknesses

- Long term data were not available for patients treated with cerliponase alfa, so assumptions were required to inform the model, both for the starting population and the disease progression, but these assumptions were validated by clinical experts.
- Whilst a one-to-one matching was available, there was no trial data directly comparing outcomes for patients treated with cerliponase alfa against patients treated with standard care.

12.8.4 What further analyses could be undertaken to enhance the robustness/completeness of the results?

The ongoing clinical trials, studies 190-201/202 will provide additional efficacy results that will validate the assumptions made about the disease progression for patients treated with cerliponase alfa.

The robustness of the assumptions made about the long term disease progression, when treated with cerliponase alfa, could be tested when more data are available. Further information on the point of diagnosis of CLN2 disease, and the time at which treatment will begin, will be available in the future.

13 Cost to the NHS and Personal Social Services

The purpose of Section 13 is to allow the evaluation of the affordability of the technology.

13.1 How many patients are eligible for treatment in England? Present results for the full marketing authorisation and for any subgroups considered. Also present results for the subsequent 5 years.

As discussed in section 6.2, published literature suggests an estimated prevalence of 0.1-0.75 per million and an estimated incidence of 0.15-0.78 per 100,000 live births. The numbers of patients diagnosed per year and numbers of patients living in England have been provided by clinical and patient experts.

The estimated population of CLN2 patients that are eligible for treatment in England, in line with the marketing authorisation for cerliponase alfa, is presented in Table D60 below. It has been assumed that of the prevalent population in year 1 of the model, [redacted] patients will receive cerliponase alfa treatment if it were approved. For new patients, both in year 1 and subsequently, [redacted] are assumed to receive cerliponase alfa. In the budget impact model, costs are applied according to the years spent receiving treatment, and no discounting is applied. Hence, patients that enter in year 2 will receive costs associated with the first year of treatment, in year 2, whereas patients that have been in the model since year 1 will be modelled to receive costs associated with the second year of treatment, in year 2. The costs calculated in the cost-effectiveness model, described in section 12, were used in the budget impact model.

Table D60. Eligible patients for cerliponase alfa over 5 years in England

	Year				
	1	**2**	**3**	**4**	**5**
Starting prevalent population	34	N/A			
Expected uptake of cerliponase alfa (patients)	[redacted]				
Incident population	5	5	5	5	5
Expected uptake of cerliponase alfa (patients)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total incident population	39	5	5	5	5
Patients treated with Cerliponase alfa	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: SoC: standard of care; N/A: not applicable

13.2 Describe the expected uptake of the technology and the changes in its demand over the next five years.

There are currently no treatments specifically indicated for CLN2 disease; management is limited to symptomatic treatment and supportive care. Due to the progressive nature of the disease, a broad group of medications are required for symptom management, including myoclonus, spasticity, and pain. In addition, virtually all patients receive antiepileptic therapy; however, even with polytherapy seizures often become refractory. Physical, occupational and speech therapies are important early in the disease, in order to prolong functioning and keep patients in mainstream activities as long as possible.[24] Please see section 8 for more details.

Currently there are 6 patients receiving cerliponase alfa through ongoing participation in the clinical trial programme and 1 patient receiving treatment through an expanded access scheme. The expected uptake of cerliponase alfa is based on patients moving from the clinical trial programme and expanded access scheme onto commercial supplies and data from a survey conducted by the BDFA and clinical experts regarding the expected uptake of cerliponase alfa amongst current and newly diagnosed patients.[83] Figures for the expected uptake can be found in Table D60.

It should be noted that in the future it is expected that the diagnosis of CLN2 disease will occur earlier in the disease course. This is in part due to the adoption of the disease awareness and early diagnosis campaign that is proposed by BioMarin. It was assumed that patients starting treatment with cerliponase alfa will be distributed across CLN2 clinical rating scale scores as

per the base case starting population of the cost-effectiveness model. For further details, please see section 12.

13.3 In addition to technology costs, please describe other significant costs associated with treatment that may be of interest to NHS England (for example, additional procedures etc).

Diagnosis of CLN2 Disease

As described in section 8.2, 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. Currently, however, diagnosis takes an average of 2 years from onset of symptoms, leading to patients being diagnosed once disease has progressed. In order to improve diagnosis times, BioMarin are investigating a disease awareness and early diagnosis campaign using an epileptic gene panels. It is hoped that this approach will avoid the costs associated with misdiagnosis of epilepsy, and ensure that CLN2 disease patients are treated at an earlier stage of disease.

Cost of ICV Implantation and Replacement

As cerliponase alfa is administered intracerebroventricularly, additional costs are incurred due to the ICV access device (reservoir and catheter), implantation procedure, and specialist care required. A one-off cost of £9,518.70, taken from NHS reference costs,[94] for implantation of the device, is included for all patients receiving cerliponase alfa. Furthermore, it is assumed that the device will be replaced in response to infections, based on a reported infection rate of 0.45%.[87] Based on literature, 62% of infections were modelled to require a replacement.[87]

Additional Treatment and Monitoring Costs

Cerliponase alfa is administered via ICV infusion every two weeks in a hospital setting and currently involves an overnight stay in an ICU for both child and parent. It is anticipated that were cerliponase alfa be adopted in the clinical practice, the infusion procedure would be carried out in day care units, thus lowering the costs associated with administration and monitoring. More information regarding the administration of cerliponase alfa can be found in section 2. Furthermore, as cerliponase alfa is a frozen product there will be additional costs associated with transportation and storage.

The long-term use of cerliponase alfa is likely to be associated with additional monitoring costs. For example, patients with other lysosomal storage disorders are known to experience cardiac abnormalities, as such it was advised by clinical expert opinion that annual echocardiograms may be recommended for CLN2 patients receiving long-term treatment with cerliponase alfa.[83]

13.4 Describe any estimates of resource savings associated with the use of the technology.

By delaying disease progression, cerliponase alfa maintains patients in earlier health states for longer than the standard of care – see section 12 for more details. Later health states in the cost-effectiveness model are associated with greater resource use, such as greater numbers of appointments with specialist clinicians, nurses and therapists. Other costs, such as annual seizure costs, additionally increase as patients progress through health states. As such, resource savings can be expected due to the greater number of patients remaining in less severe health states compared to if patients were receiving standard of care.

As noted above, it is also anticipated that the use of epileptic gene panels to improve diagnosis time will reduce costs associated with the inappropriate treatment of misdiagnosed epilepsy. In addition, the earlier diagnosis of patients in the disease pathway will increase the cost savings associated with delayed disease progression by enabling patients to remain in less severe health states.

13.5 Are there any other opportunities for resource savings or redirection of resources that it has not been possible to quantify?

It is not anticipated that any additional resource savings or redirection of resources would occur.

13.6 Describe any costs or savings associated with the technology that are incurred outside of the NHS and PSS.

In terms of additional savings, the earlier health states of the disease are associated with a lower requirement of care. By delaying progression into the later health states, and increasing the time spent in the earlier health states, the level of care required for patients is lower, and lower productivity losses can be expected as a result.

Due to the rarity of the disease, there are currently few specialist centres able to administer treatment, or provide ongoing care. As a result, there can be substantial journey times and transportation costs for the family of the patient.

13.7 What is the estimated budget impact for the NHS and PSS over the first year of uptake of the technology, and over the next 5 years?

The budget impact of cerliponase alfa for the NHS and PSS in England is estimated to be [redacted] in year 1, rising to a total of [redacted] in year 5. Full budget impact results are presented in Table D61.

Table D61. Budget impact of cerliponase alfa in England over 5 years

Costs	Year				
	1	2	3	4	5
Treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Health state	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Progressive symptoms & chronic seizures	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total Population Budget Impact	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

The NHS has a single budget for specialised services of approximately £16.6 billion,[101] which includes medicines. The budget impact of cerliponase alfa in year 1 represents approximately [redacted] of this.

13.8 Describe the main limitations within the budget impact analysis (for example quality of data inputs and sources and analysis etc).

As the budget impact model is based on the progression of patients through the cost-effectiveness model, it is therefore subject to the same limitations as the cost-effectiveness model, as described in section 12.8.3.

Section E – Impact of the technology beyond direct health benefits

The purpose of Section 14 is to establish the impact of the technology beyond direct health benefits, that is, on costs and benefits outside of the NHS and PSS, and on the potential for research. Sponsors should refer to section 5.5.11 – 5.5.13 of the Guide to Methods for Technology Appraisal 2013 for more information.

It is also aimed at describing factors that are relevant to the provision of the (highly) specialised service by NHS England. Such factors might include issues relating to specialised service organisation and provision, resource allocation and equity, societal or ethical issues, plus any impact on patients or carers.

14 Impact of the technology beyond direct health benefits

14.1 Describe whether a substantial proportion of the costs (savings) or benefits are incurred outside of the NHS and personal social services, or are associated with significant benefits other than health.

The majority of costs (savings) and benefits from the use of cerliponase alfa treatment are expected to be incurred within the NHS and/or PSS. Once cerliponase alfa is made available, however, additional savings are expected to accrue to other government departments (see section 14.2) and to the families of CLN2 patients (see section 14.3).

Treatment with cerliponase alfa is expected to halt the decline of CLN2 disease. In so far as this might reduce the burden on caregivers and their families, the introduction of this technology could have a positive beneficial impact on the following non-health domains:

- The emotional and psychological impact of caring for an affected child caregivers;

- Family and social relationships, including the impact on non-affected siblings;
- The education and social interaction of the affected child; and
- Family finances.

14.2 List the costs (or cost savings) to government bodies other than the NHS.

The financial burden of caregiving for a child or children with CLN2 disease is significant – caregivers (typically the parents of an affected child) have to work reduced hours, or give up work completely in order to care for their child(ren).

Some parents need to give up work, or reduce their hours, in order to care for an affected child. In a study and survey commissioned by the manufacturer,[13] families described the financial impact of caring for a child with CLN2 disease, which included giving up work to care or being unable to return to work, having time off from work, additional expenses, benefits and waiting for funding. During focus group 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 for a few years.[13]

Families with one or more children affected by CLN2 disease receive financial assistance and support from other government departments; this can relate to the care for their affected child, other children or for themselves.[13]

Child tax benefit is the most frequently reported form of financial assistance received by primary caregivers, however disability living allowance for children, carers' allowance and income support were also common and is received by all families in England. Similarly, most primary caregivers reported receiving a reduction on council tax. Primary caregivers also reported receiving additional school support, paid for by the education authorities, and a blue disability badge.[13] The physical and emotional burden for families for applying and navigating the benefits systems is also high and they rely on support from organisations such as the BDFA to help and advocate on their behalf.

It is expected that the introduction of cerliponase alfa would reduce the expenditure currently incurred by the Department of Work and Pensions, the Department of Communities and Local Government and local County Councils in providing support for families affected by CLN2 disease.

14.3 List the costs borne by patients that are not reimbursed by the NHS.

Families caring for a child affected by CLN2 disease have to cope with many difficult emotional, physical, professional, organisational and financial challenges. [13] Some families have more than one affected child, leading to even greater burden. These challenges typically endure from before diagnosis and continue to the point and after the child's death, leaving a long-term legacy of ill-healthm emotional distress and poor health. The financial costs typically borne by patients, their caregivers and families that are not reimbursed by the NHS include:

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

  Because of the rarity and severity of CLN2 disease, there are very few centres and healthcare professionals in the UK with the specialist expertise needed to be able to care for a child with CLN2 disease. The lack of access to a specialist centre creates anxiety for families when diagnosed with a rare disease as they want to see someone with expertise in their child's condition and care. For families living some distance these specialist centres, every hospital appointment typically involves substantial journey times and transportation costs for the family, often involving overnight stays. Once cerliponase alfa is available, it is anticipated that access to specialist centres will improve (due to the integration within the more prevalent existing LSD centres), resulting in reduced travel time. Reduced travel would not just have financial benefits but also impact on family quality of life, continuity of education and siblings.

- **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 e.g., home adaptations could cost up to £30,000; specially designed wheelchairs could cost up to £3,000 and adapted cars could cost up to £10,000 (personal communication, BDFA).

  Although grants and funding are rarely available to meet the costs of these adaptations/equipment, a number of caregivers reported long-waits for funding which was extremely stressful and increased their care burden.

Families described the stress and frustration at having to wait for very long periods of time (many months) while funding decisions were made and requests for equipment or adaptations were processed.[13]

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

A survey and focus group programme commissioned by the manufacturer reported that some parents need to give up work, or reduce their hours of employment, in order to care for a child affected by CLN2. Families described the financial impact of caring for a child with CLN2 disease, which included giving up work to care or being unable to return to work, and having time off from work. During focus group 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 for a few years. .[13]

A study by the US Batten Disease Support and Research Association (BDSRA) included a 120-question needs assessment survey with 93 parents and caregivers (aged 25-71 with 70% (n=65) of them aged between 35 and 55 years, 86% (n=80) were women, and 95% (n=84) Caucasian) of children with Batten disease (33% of those with CLN2 disease) along with 6 in-depth interviews in the US.[21] 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 Batten 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.[21]

14.4 Provide estimates of time spent by family members of providing care. Describe and justify the valuation methods used.

Despite the terminal nature of this progressive and rare disease, there is little published research about the impact of CLN2 disease on the child's family. Assessments of the impact of CLN2 disease have, however, been carried out by the UK Batten Disease Family Association (BFDA),[102] the US BDSRA[21] and the manufacturer.[13]

In a study commissioned by the manufacturer, caregivers in the UK and Germany reported significantly lower life satisfaction, lower happiness with their partner, on average 73.45 more caring hours per week and on average

1.32 fewer hours sleeping per night, compared with parents of a non-sick or disabled child of the same age.[13]

These differences were all in the same direction when compared with parents who care for a sick or disabled child, although only statistically significant for hours sleep per night ($p<0.01$).[13]

Disease stage (early/decline, severe and deceased) had an impact on caregiver burden: caregivers of children in the severe stage of CLN2 reported a greater number of hours caring and less sleep than both caregivers of children in the early/decline stage and of children who have deceased. Overall happiness reduced with disease stage, but life satisfaction was broadly similar across stages.[13]

14.5 Describe the impact of the technology on strengthening the evidence base on the clinical effectiveness of the treatment or disease area. If any research initiatives relating to the treatment or disease area are planned or ongoing, please provide details.

UK centres are participating in the ongoing clinical trials for cerliponase alfa (190-202, 190-203), continuing to develop and expand UK specialist knowledge of this very rare, life-limiting condition.

BioMarin is committed to investing in further research in this area. As part of its commitment to US and European regulators, the manufacturer is planning an observational study that will collect safety data on patients treated with cerliponase alfa over a 10-year period. In addition, BioMarin is in the process of investigating a disease awareness and early diagnosis campaign, designed to promote early genetic diagnostics in the management of children with seizures and shorten the time to diagnosis of patients with late-infantile CLN2 disease.

14.6 Describe the anticipated impact of the technology on innovation in the UK.

As described in section 6.1 above, CLN2 disease is a rapidly-progressing, life-limiting disorder causing extensive morbidity and a rapid loss of function, reduced quality of life and early mortality. There are currently no available treatment options specifically to treat CLN2 and none that correct the underlying biological cause of the condition. As noted in section 8.1 above, current care is symptomatic only. The available management options consist of supportive or palliative care, which includes both medication and other

interventions to relieve symptoms, maintain function and health-related quality of life. CLN2 disease therefore represents a significant unmet medical need.

Cerliponase alfa is an innovative, breakthrough technology that, once it becomes routinely available, will represent a step-change in the management of CLN2 disease because:

- It is the first pharmacological treatment approved for the treatment of CLN2 disease;
- It is approved for use in CLN2 in patients of all ages;
- It is the first treatment option (pharmacological or otherwise) that addresses the underlying biological cause of this severe, rapidly-progressing and life-limiting disease. As noted in section 8.2, cerliponase alfa is the first ERT administered directly into the CNS via ICV administration. As such, it is expected to restore TPP1 enzyme activity in the brain, addressing the underlying cause of the disease and reducing the progressive, pathologic accumulation of lysosomal storage materialin the brain and body so as to stabilise or slow the rapid and predictable decline in motor and language function described in section 6.1 and improve signs and symptoms of the disease otherwise allowing children to maintain motor and language function.
- It is the first treatment option to have a positive impact on motor and language function in CLN2 in clinical trials, slowing or stabilising the rate of decline as measured by the CLN2 clinical rating scale in 87% of patients (20 out of 23) in Study 190-201/190-202. Great Ormond Street Hospital in London is one of the trial centres for Study 190-201/190-202.

As demonstrated by the clinical trial data presented in section 9.6, stabilising the decline of the CLN2 clinical rating scale score is associated with improvement in the quality of life of patients, parents and families and can allow children with the disease to maintain function and thus has a significant positive impact on the lives of patients, parents, caregivers and families in the UK.

14.7 Describe any plans for the creation of a patient registry (if one does not currently exist) or the collection of clinical effectiveness data to evaluate the benefits of the technology over the next 5 years.

UK centres are participating in the ongoing clinical trials for cerliponase alfa (190-202, 190-203 and 190-502), continuing to develop and expand UK specialist knowledge of this very rare, life-limiting condition.

BioMarin is committed to investing in further research in this area. As part of its commitment to US and European regulators, the manufacturer is planning an observational study that will collect safety data on patients treated with cerliponase alfa over a 10-year period. In addition, BioMarin is in the process of investigating a disease awareness and early diagnosis campaign, designed to promote early genetic diagnostics in the management of children with seizures and shorten the time to diagnosis of patients with late-infantile CLN2 disease.

14.8 Describe any plans on how the clinical effectiveness of the technology will be reviewed.

14.9 Study 202 is still ongoing and so will provide longer term data on clinical effectiveness and 203 data will provide additional insights on effectiveness in patients under the age of 3 and potential impact of early intervention. In addition, results captured from the proposed registry will help substantiate the long term clinical effectiveness. What level of expertise in the relevant disease area is required to ensure safe and effective use of the technology?

Because CLN2 disease is exceptionally rare, only a small number of specialist centres and healthcare professionals in England and Wales are able to initiate treatment and/or provide ongoing care. Care is currently offered at the Evelina Children’s Hospital and Great Ormond Street Hospital, both in London.

Cerliponase alfa can only be administered by the ICV route and by a healthcare knowledgeable in ICV administration. Once the infusion has been initiated, however, a specialist nurse can - with training - supervise the ongoing infusion.

14.10 Would any additional infrastructure be required to ensure the safe and effective use of the technology and equitable access for all eligible patients?

Cerliponase alfa can only be administered by the ICV route and by a healthcare knowledgeable in ICV administration and experienced in delivery of enzyme replacement therapies[1]; In addition creating the port/ICV access will constitute a surgical procedure in its own right – this must be done prior to the first infusionand will thus require the services of a paediatric neuro-surgeon

Section F - Managed Access Arrangements (please see sections 55-59 of the HST methods guide on MAAs)

15 Managed Access Arrangement

15.1 Describe the gaps identified in the evidence base, and the level of engagement with clinical and patient groups to develop the MAA

The long-term efficacy, safety and tolerability of cerliponase alfa continues to be investigated in the ongoing 190-201/202 study. Data is available on some patients up to 136 weeks of treatment and the total study duration is 240 weeks.

The MAA is still in development and the proposed criteria still need to be ratified with NHS England. However, there have been several discussions between the manufacturer, UK clinicians treating patients with CLN2 and the UK patient group, the Batten Disease Family Association to develop the MAA.

15.2 Describe the specifics of the MAA proposal

The MAA is still in development and the proposed criteria still need to be ratified and further developed with NHS England. The precise contents of the MAA could, therefore, evolve following discussions with NHS England.

[redacted]

Duration

- [redacted]
- [redacted]

Patient Eligibility

[redacted]

- [redacted]
- [redacted]
- [redacted]

Criteria for starting treatment

[redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

Criteria for stopping treatment

[redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]

[redacted]:-

- [redacted]
- [redacted]
- [redacted]

[redacted]

Stopping criteria for patients who are currently on treatment

[redacted].

[redacted]:-

- [redacted]
- [redacted].
- [redacted]
- [redacted]
- [redacted].

Data collection and monitoring

Data will be collected from all patients who start during the term of the MAA.

Patients will be asked for permission for their data to be collected via a patient registry and/or database. The purposes of the registry and database are to: (i) characterise and describe the CLN2 population as a whole, including the heterogeneity, progression and natural history of CLN2; (ii) to evaluate the

long-term effectiveness and safety of Brineura (cerliponase alfa): (iii) to help the CLN2 medical community with the development of recommendations for monitoring subjects and reports on subject outcomes to optimise subject care; (iv) to collect data on other treatment paradigms, evaluate the prevalence of their use and their effectiveness; (v) to characterise the effects of long term treatment of cerliponase alfa treatment in subjects; and (vi) to collect additional data to: (a) help broaden knowledge of identified and potential risks of cerliponase alfa, as well as increase the size of the safety database and possibly provide new information on use in identified subgroups (pregnancy, hepatic and renal impairment, cardiac impairment); and (b) to help evaluate long-term effectiveness of cerliponase alfa.

Data collected will be shared with NHS England, NICE and the Marketing Authorisation Holder and may be stored both inside and outside of the EU on static databases and portable devices (including being stored in the United States of America).

The MAA will provide access for NHS England to this data to assist it in assessing the clinical impact of cerliponase alfa on CLN2 disease.

Funding

The treatment will be funded by NHS England from publication of the NICE guidance and the start of the MAA.

Biomarin is open to the idea of entering into a funding arrangement as part of the MAA. Commercial negotiations have not yet started but, based on discussions with NICE/NHS England, it is anticipated that negotiations will commence after the Evaluation Consultation Document has been published

In addition to the MAA, BioMarin is intending to launch a gene panel testing campaign – Uncover the Seizure, Discover the Gene - which will lead to earlier diagnosis of CLN2 disease and other paediatric onset epilepsies. This campaign is designed to identify cases of CLN2 disease early, avoiding misdiagnosis of unprovoked seizures, thus resulting in better health outcomes as well as cost savings by avoiding other diagnosis tests and misdiagnosis.

15.3 Describe the effect the MAA proposal will have on value for money; if possible, include the results of economic analyses based on the MAA

BioMarin anticipates the MAA will significantly increase the value for money of cerliponase alfa for all of the reasons identified in section 15.2, including:

- [redacted]
- [redacted]
- [redacted]

[redacted]

Given that the commercial negotiations have not yet started, it is not possible to provide results of economic analysis at this time.

16 Bibliography

1. European Medicines Agency. Brineura - Summary of Product Characteristics, 2017.
2. Schulz A KA, Mink J, Simonati A, Williams R. NCL diseases - clinical perspectives. Biochim Biophys Acta 2013:1832(11):1801-1806.
3. Chang M CJ, Davidson B, et al. CLN2. In: Mole S, Williams R, Goebel H, eds. The Neuronal Ceroid Lipofuscinoses (Batten Disease): Oxford University Press, 2011:80-109.
4. Worgall S, Kekatpure MV, Heier L, et al. Neurological deterioration in late infantile neuronal ceroid lipofuscinosis. Neurology 2007;69:521-35.
5. Schulz A, Kohlschutter A. NCL Disorders: Frequent Causes of Childhood Dementia. Iran J Child Neurol 2013;7:1-8.
6. Nickel M JD, Lezius S, et al. Natural history of CLN2 disease: Quantitative assessment of disease characteristics and rate of progression. 12th Annual WORLD Symposium. San Diego, CA, USA, 2016.
7. Nickel M SA, Jacoby D, et al. Natural history of CLN2 disease: Quantitative assessment of disease characteristics and rate of progression in an international cohort of 137 patients. Manuscript on File. 2016.
8. Steinfeld R HP, von Gregory H, et al. Late infantile neuronal ceroid lipofuscinosis: quantitative description of the clinical course in patients with CLN2 mutations. Am J Med Genet. 2002:112(4):347-354.
9. DEM-CHILD. Epidemiology/natural history project. Available from http://www.dem-child.eu/index.php/wp03-epidemiology-natural-history.html. Last accessed 20th September 2017.
10. Sleat DE GR, Sohar I, et al. Mutational analysis of the defective protease in classic late-infantile neuronal ceroid lipofuscinosis, a neurodegenerative lysosomal storage disorder. Am J Hum Genet. 1999;64(6):1511-1523.
11. Williams RE, Aberg L AT, Goebel HH, Kohlschutter A, Lonnqvist T. Diagnosis of the neuronal ceroid lipofuscinoses: an update. Biochim Biophys Acta. 2006;1762(10):865-872.
12. Perez-Poyato MS MM, Abizanda IF, et al. Late infantile neuronal ceroid lipofuscinosis: mutations in the CLN2 gene and clinical course in Spanish patients. J Child Neurol 2013:470-478.
13. 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.
14. Moore SJ BD, MacMillan A, et al. . The clinical and genetic epidemiology of neuronal ceroid lipofuscinosis in Newfoundland. Clin Genet. 2008;74(3):213-222.
15. Raat H, Landgraf JM, Oostenbrink R, et al. Reliability and validity of the Infant and Toddler Quality of Life Questionnaire (ITQOL) in a general population and respiratory disease sample. Qual Life Res 2007;16:445-60.
16. BioMarin. Relationship of CLN2 rating measures with QoL measures. Data on File. 2016.

17. Varni JW, Burwinkle TM, Seid M. The PedsQL as a pediatric patient-reported outcome: reliability and validity of the PedsQL Measurement Model in 25,000 children. Expert Rev Pharmacoecon Outcomes Res 2005;5:705-19.
18. Williams RE. The Neuronal Ceroid Lipofuscinoses (Batten Disease): NCL Incidence and Prevalence Data: Oxford University Press, 2011.
19. Poupetova H, Ledvinova J, Berna L, et al. The birth prevalence of lysosomal storage disorders in the Czech Republic: comparison with data in different populations. J Inherit Metab Dis 2010;33:387-96.
20. Al-Maawali AA, Joshi SN, Koul RL, et al. Spectrum of paediatric lysosomal storage disorders in oman. Sultan Qaboos Univ Med J 2012;12:295-9.
21. Frazier M. Batten Family Voices: 2014 BDSRA Needs Assessment. Columbus, OH: Batten Disease Support and Research Association, 2014.
22. BioMarin. Study 201/202 Interim Clinical Study Report. Data on File, 2017.
23. Williams RE, Adams HR, Blohm M. Expert opinion on the management of CLN2 disease. 12th Annual WORLD Symposium. San Diego, CA, USA, 2016.
24. Williams RE, Adams HR, Blohm M, et al. Management Strategies for CLN2 Disease. Pediatr Neurol 2017;69:102-112.
25. Fietz M, AlSayed M, Burke D, et al. Diagnosis of neuronal ceroid lipofuscinosis type 2 (CLN2 disease): Expert recommendations for early detection and laboratory diagnosis. Mol Genet Metab 2016;119:160-7.
26. BioMarin. Cerliponase alfa Study 190-201: Clinical Study Report. 2016.
27. Lukacs Z, Santavuori P, Keil A, et al. Rapid and simple assay for the determination of tripeptidyl peptidase and palmitoyl protein thioesterase activities in dried blood spots. Clin Chem 2003;49:509-11.
28. Sleat DE, Donnelly RJ, Lackland H, et al. Association of mutations in a lysosomal protein with classical late-infantile neuronal ceroid lipofuscinosis. Science 1997;277:1802-1805.
29. Sharp JD, Wheeler RB, Lake B, et al. Loci for classical and a variant late infantile neuronal ceroid lipofuscinosis map to chromosomes 11p15 and 15q21–23. Human molecular genetics 1997;6:591-595.
30. Barisic N, Logan P, Pikija S, et al. R208X mutation in CLN2 gene associated with reduced cerebrospinal fluid pterins in a girl with classic late infantile neuronal ceroid lipofuscinosis. Croat Med J 2003;44:489-93.
31. Le NM, Parikh S. Late infantile neuronal ceroid lipofuscinosis and dopamine deficiency. J Child Neurol 2012;27:234-7.
32. Lorenz R. A casuistic rationale for the treatment of spastic and myocloni in a childhood neurodegenerative disease: neuronal ceroid lipofuscinosis of the type Jansky-Bielschowsky. Neuro Endocrinol Lett 2002;23:387-90.
33. Lorenz R. On the application of cannabis in paediatrics and epileptology. Neuro Endocrinol Lett 2004;25:40-4.

34. Mohamed S, El Melegy EM, Talaat I, et al. Neurometabolic disorders associated with early childhood epilepsy: A single center experience in Saudi Arabia. Journal of Inherited Metabolic Disease 2015;1:S336.
35. Mohamed S, El Melegy EM, Talaat I, et al. Neurometabolic Disorders-Related Early Childhood Epilepsy: A Single-Center Experience in Saudi Arabia. Pediatr Neonatol 2015;56:393-401.
36. Rubenstein JE, Kossoff EH, Pyzik PL, et al. Experience in the use of the ketogenic diet as early therapy. J Child Neurol 2005;20:31-4.
37. Johannsen J, Nickel M, Schulz A, et al. Considering Valproate as a Risk Factor for Rapid Exacerbation of Complex Movement Disorder in Progressed Stages of Late-Infantile CLN2. NCL 2016. Boston, 2016.
38. Yamada Y, Doi K, Sakura S, et al. Anesthetic management for a patient with Jansky-Bielschowsky disease. Can J Anaesth 2002;49:81-3.
39. Veneselli E, Biancheri R, Buoni S, et al. Clinical and EEG findings in 18 cases of late infantile neuronal ceroid lipofuscinosis. Brain and Development 2001;23:306-311.
40. Yuza Y, Yokoi K, Sakurai K, et al. Allogenic bone marrow transplantation for late-infantile neuronal ceroid lipofuscinosis. Pediatrics international 2005;47:681-683.
41. Lehwald LM, Pappa R, Steward S, et al. Neuronal Ceroid Lipofuscinosis and Associated Sleep Abnormalities. Pediatric neurology 2016;59:30-35.
42. Selden NR, Al-Uzri A, Huhn SL, et al. Central nervous system stem cell transplantation for children with neuronal ceroid lipofuscinosis. J Neurosurg Pediatr 2013;11:643-52.
43. Worgall S, Sondhi D, Hackett NR, et al. Treatment of late infantile neuronal ceroid lipofuscinosis by CNS administration of a serotype 2 adeno-associated virus expressing CLN2 cDNA. Hum Gene Ther 2008;19:463-74.
44. Crystal RG. Administration of a Replication-Deficient Adeno-Associated Virus Gene Transfer Vector Expressing the Human CLN2 cDNA to the Brain of Children with Late Infantile Neuronal Ceroid Lipofuscinosis. Human Gene Therapy 2004;15:1131-1154.
45. Souweidane MM, Fraser JF, Arkin LM, et al. Gene therapy for late infantile neuronal ceroid lipofuscinosis: neurosurgical considerations: Clinical article. Journal of Neurosurgery: Pediatrics 2010;6:115-122.
46. de los Reyes E, Schulz A, Specchio N, et al. Intracerebroventricular Cerliponase Alfa (BMN 190) in Children with CLN2 Disease: Results from a Phase 1/2, Open-Label, Dose-Escalation Study. Ann Neurol 2016;80:S413.
47. Schulz A, Specchio N, Gissen P, et al. Intracerebroventricular Cerliponase Alfa (BMN 190) in Children with CLN2 Disease: Results from a Phase 1/2, Open-Label, Dose-Escalation Study. Epilepsia 2016;57:6-255.
48. Schulz A, Specchio N, Gissen P, et al. Intracerebroventricular cerliponase alfa (BMN 190) in children with CLN2 disease: results from a phase 1/2, open-label, dose-escalation study. J Inherit Metab Dis 2016;39:S51.

49. Eto K, Takamura A, Osaka H, et al. Case Presentation of Neuronal Ceroid Lipofuscinosis 1 and 2. NCL 2016. Boston, 2016.
50. Ravi K, Williams R, Allen N, et al. Use of Ketogenic diet for epilepsy in Batten Disease. ICNC 2016. Amsterdam, 2016.
51. Schulz A, Specchio N, Gissen P, et al. Intracerebroventricular cerliponase alfa (BMN 190) in children with CLN2 disease: Results from a Phase 1/2, open-label, dose-escalation study. NCL 2016. Boston, 2016.
52. Schulz A, Specchio N, Gissen P, et al. Intracerebroventricular cerliponase alfa (BMN 190) in children with CLN2 disease: Results from a Phase 1/2, open-label, dose-escalation study. 12th Annual WORLD Symposium, 2016.
53. EU Clinical Trials Register. A Multicenter, Multinational, Extension Study to Evaluate the Long-Term Efficacy and Safety of BMN 190 in Patients with CLN2 Disease. (2015). Retrieved from https://www.clinicaltrialsregister.eu/ (Identification No. 2014-003480-37).
54. ClinicalTrials.gov. A Multicenter, Multinational, Extension Study to Evaluate the Long-Term Efficacy and Safety of BMN 190 in Patients With CLN2 Disease. (2015). Retrieved from http://clinicaltrials.gov/ (Identification No. NCT02485899).
55. ClinicalTrials.gov. Neuronal Ceroid Lipofuscinosis and Associated Sleep Abnormalities. (2013). Retrieved from http://clinicaltrials.gov/ (Identification No. NCT01966757).
56. ClinicalTrials.gov. Study of HuCNS-SC Cells in Patients With Infantile or Late Infantile Neuronal Ceroid Lipofuscinosis (NCL). (2006). Retrieved from http://clinicaltrials.gov/ (Identification No. NCT00337636).
57. ClinicalTrials.gov. Safety Study of a Gene Transfer Vector for Children With Late Infantile Neuronal Ceroid Lipofuscinosis. (2005). Retrieved from http://clinicaltrials.gov/ (Identification No. NCT00151216).
58. ClinicalTrials.gov. Safety Study of a Gene Transfer Vector (Rh.10) for Children With Late Infantile Neuronal Ceroid Lipofuscinosis. (2010). Retrieved from http://clinicaltrials.gov/ (Identification No. NCT01161576).
59. ClinicalTrials.gov. A Multicenter, Multi-national Open-label Program to Provide BMN 190 to Patients Diagnosed With CLN2 Disease. (2016). Retrieved from http://clinicaltrials.gov/ (Identification No. NCT02963350).
60. ClinicalTrials.gov. AAVRh.10 Administered to Children With Late Infantile Neuronal Ceroid Lipofuscinosis (2010). Retrieved from http://clinicaltrials.gov/ (Identification No. NCT01414985).
61. ClinicalTrials.gov. Safety and Efficacy Study of HuCNS-SC in Subjects With Neuronal Ceroid Lipofuscinosis. (2010). Retrieved from http://clinicaltrials.gov/ (Identification No. NCT01238315).
62. ClinicalTrials.gov. A Safety, Tolerability, and Efficacy Study of Intracerebroventricular BMN 190 in Patients With CLN2 Disease. (2016). Retrieved from http://clinicaltrials.gov/ (Identification No. NCT02678689).

63. EU Clinical Trials Register. A Phase 2, Open-Label, Multicenter Study to Evaluate Safety, Tolerability, and Efficacy of Intracerebroventricular BMN 190 in Pediatric Patients < 18 years of age with CLN2 Disease. (2016). Retrieved from https://www.clinicaltrialsregister.eu/ (Identification No. 2015-000891-85).
64. ClinicalTrials.gov. A Phase 1/2 Open-Label Dose-Escalation Study to Evaluate Safety, Tolerability, Pharmacokinetics, and Efficacy of Intracerebroventricular BMN 190 in Patients With Late-Infantile Neuronal Ceroid Lipofuscinosis (CLN2) Disease. (2013). Retrieved from http://clinicaltrials.gov/ (Identification No. NCT01907087).
65. EU Clinical Trials Register. A Phase 1/2 Open-Label Dose-Escalation Study to Evaluate Safety, Tolerability, Pharmacokinetics, and Efficacy of Intracerebroventricular BMN 190 in Patients With Late-Infantile Neuronal Ceroid Lipofuscinosis (CLN2) Disease. (2013). Retrieved from https://www.clinicaltrialsregister.eu/ (Identification No. 2012-005430-11).
66. Cherukuri A, Cahan H, van Tuyl A, et al. Immunogenicity to Cerliponase Alfa, an Enzyme Replacement Therapy for Patients with CLN2 Disease: Results from a Phase 1/2 Study 13th Annual WORLD Symposium. San Diego, CA, USA, 2017.
67. Specchio N, Bellusci M, Pietrafusa N, et al. Photosensitivity is an early marker of neuronal ceroid lipofuscinosis type 2 disease. Epilepsia 2017;58:1380-1388.
68. European Medicines Agency. Brineura - European Public Assessment Report, 2017.
69. BioMarin. Study 901 Clinical Study Report - Supplemental Report. Data on File, 2016.
70. Msall ME. Measuring functional skills in preschool children at risk for neurodevelopmental disabilities. Ment Retard Dev Disabil Res Rev 2005;11:263-73.
71. Schulz A. Intracerebroventricular cerliponase alfa (BMN 190) in children with CLN2 disease: Results for a Phase 1/2, open-label, dose-escalation study and extension. 14th International Child Neurology Conference. Amsterdam, NL, 2016.
72. Lobel U. Volumetric Description of Brain Atrophy in Neuronal Ceroid Lipofuscinosis 2: Supratentorial Gray Matter Shows Uniform Disease Progression. Am J Neuroradiol 2016;37:1938-1943.
73. Biomarin. Response to request for information by the FDA. Data on File. 2016.
74. Schulz A, Ajayi T, Specchio N, et al. Intraventricular Cerliponase alfa Attenuates Neurologic Decline in CLN2 Disease . Manuscript on File. 2017.
75. BioMarin. CLN2 Disease Utility Study Report. Data on File, 2017.
76. Khan KA, Petrou S, Rivero-Arias O, et al. Mapping EQ-5D utility scores from the PedsQL generic core scales. Pharmacoeconomics 2014;32:693-706.
77. Ballinger R, Eliasson L, West A, et al. The burden of CLN2 disease on families. NCL 2016. Boston, 2016.

78. van Hout B, Janssen MF, Feng YS, et al. Interim scoring for the EQ-5D-5L: mapping the EQ-5D-5L to EQ-5D-3L value sets. Value Health 2012;15:708-15.
79. NICE. Position statement on use of the EQ-5D-5L valuation set. 2017.
80. Specchio N, Williams R, Adams HR, et al. Expert Opinion on the Management of CLN2 disease. SSIEM 2016. Rome, 2016.
81. Williams RE, Adams HR, Blohm M. Expert opinion on the management of CLN2 disease. ICNC 2016. Amsterdam, 2016.
82. European Medicines Agency. Brineura (cerliponase alfa). Available from http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/004065/human_med_002111.jsp. Last accessed 24th September 2017.
83. BioMarin. Expert Clinical Opinion, 2017.
84. BioMarin. Delphi Workshop Report - UK Treatment Practices for the Management of CLN2 Disease. Data on File. 2017.
85. BioMarin. Study 201/202 Integrated Subject Narratives. Data on File, 2017.
86. Great Ormond Street Hospital for Children. Gastrostomy management. Available from http://www.gosh.nhs.uk/health-professionals/clinical-guidelines/gastrostomy-management. Last accessed 28th September 2017.
87. Cohen-Pfeffer JL, Gururangan S, Lester T, et al. Intracerebroventricular Delivery as a Safe, Long-Term Route of Drug Administration. Pediatr Neurol 2017;67:23-35.
88. Beusterien KM, Davies J, Leach M, et al. Population preference values for treatment outcomes in chronic lymphocytic leukaemia: a cross-sectional utility study. Health Qual Life Outcomes 2010;8:50.
89. Kauf TL, Farkouh RA, Earnshaw SR, et al. Economic efficiency of genetic screening to inform the use of abacavir sulfate in the treatment of HIV. Pharmacoeconomics 2010;28:1025-39.
90. Maniadakis N, Kourlaba G, Mougiakos T, et al. Economic evaluation of agomelatine relative to other antidepressants for treatment of major depressive disorders in Greece. BMC Health Serv Res 2013;13:173.
91. Song Y, Tai JH, Bartsch SM, et al. The potential economic value of a Staphylococcus aureus vaccine among hemodialysis patients. Vaccine 2012;30:3675-82.
92. NHS Health Careers. Agenda for change - pay rates. Available from https://www.healthcareers.nhs.uk/about/careers-nhs/nhs-pay-and-benefits/agenda-change-pay-rates. Last accessed 27th September 2017.
93. Office for National Statistics. National Life Tables: United Kingdom. Available from https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/lifeexpectancies/datasets/nationallifetablesunitedkingdomreferencetables. Last accessed 27th September 2017.
94. Department of Health. NHS Reference Costs 2015-16. Available from https://www.gov.uk/government/publications/nhs-reference-costs-2015-to-2016. Last accessed 27th September 2017.

95. Personal Social Services Research Unit (PSSRU). Unit Costs of Health and Social Care 2016. Available from http://www.pssru.ac.uk/project-pages/unit-costs/2016/index.php. Last accessed 27th September 2017.
96. MedicinesComplete. British National Formulary. Available from https://www.medicinescomplete.com/mc/bnf/64/. Last accessed 27th September 2017.
97. Department of Health. Drugs and pharmaceutical electronic market information (eMit). Available from https://www.gov.uk/government/publications/drugs-and-pharmaceutical-electronic-market-information-emit. Last accessed 27th September 2017.
98. National Institute for Health and Care Excellence (NICE). Epilepsies: diagnosis and management (CG 137) - 1.14 Prolonged or repeated seizures and convulsive status epilepticus. Available from https://www.nice.org.uk/guidance/cg137/chapter/1-Guidance#prolonged-or-repeated-seizures-and-convulsive-status-epilepticus-2. Last accessed 27th September 2017.
99. Gravelle H, Smith D. Discounting for health effects in cost–benefit and cost-effectiveness analysis. Health Economics 2001;10:587-599.
100. Severens JL, Milne RJ. Discounting Health Outcomes in Economic Evaluation: The Ongoing Debate. Value in Health 2004;7:397-401.
101. NHS England. Specialised Services Budget.
102. Scrambler S, Williams RE. The Support Needs of Families of Children with Batten Disease: An Audit of the Efficacy of Existing Services and an In-Depth Study of Families' Needs. Farnborough, UK: Batten Disease Family Association, 2008.

17 Appendices

17.1 **Appendix 1: Management of CLN2 disease**

17.2 **Appendix 2: Search strategy for clinical evidence**

17.3 **Appendix 3: Methodology, quality assessments and results of studies identified by the SLR but not considered relevant to the submission**

17.4 **Appendix 4: Additional information about the clinical rating scales**

17.5 **Appendix 5: Study 190-201/202 additional efficacy outcomes after 96 weeks of treatment (ITT population)**

17.6 **Appendix 6: Study 190-201/202 Sensitivity Analyses on the Primary Endpoint**

17.7 **Appendix 7: Search strategy for adverse events**

17.8 **Appendix 8: Search strategy for economic evidence**

17.9 **Appendix 9: Resource identification, measurement and valuation**

17.10 **Appendix 10: Utility study**

17.11 **Appendix 11: List of inputs included in the cost-effectiveness analysis**

17.12 **Appendix 12: Videos for the CLN2 clinical rating scale**

18 Related procedures for evidence submission

18.1 Cost- effectiveness models

An electronic executable version of the cost-effectiveness model should be submitted to NICE with the full submission.

NICE accepts executable models using standard software – that is, Excel, TreeAge Pro, R or WinBUGs. If you plan to submit a model in a non-standard package, NICE should be informed in advance. NICE, in association with the Evidence Review Group, will investigate whether the requested software is acceptable, and establish if you need to provide NICE and the Evidence Review Group with temporary licences for the non-standard software for the duration of the assessment. NICE reserves the right to reject cost models in non-standard software. A fully executable electronic copy of the model must be submitted to NICE with full access to the programming code. Care should be taken to ensure that the submitted versions of the model programme and the written content of the evidence submission match.

NICE may distribute the executable version of the cost model to a consultee if they request it. If a request is received, NICE will release the model as long as it does not contain information that was designated confidential by the model owner, or the confidential material can be redacted by the model owner without producing severe limitations on the functionality of the model. The consultee will be advised that the model is protected by intellectual property rights, and can be used only for the purposes of commenting on the model's reliability and informing comments on the medical technology consultation document.

Sponsors must ensure that all relevant material pertinent to the decision problem has been disclosed to NICE at the time of submission. NICE may request additional information not submitted in the original submission of evidence. Any other information will be accepted at NICE's discretion.

When making a full submission, sponsors should check that:

- an electronic copy of the submission has been given to NICE with all confidential information highlighted and underlined
- a copy of the instructions for use, regulatory documentation and quality systems certificate have been submitted
- an executable electronic copy of the cost model has been submitted
- the checklist of confidential information provided by NICE has been completed and submitted.

- A PDF version of all studies (or other appropriate format for unpublished data, for example, a structured abstract) included in the submission have been submitted

18.2 Disclosure of information

To ensure that the assessment process is as transparent as possible, NICE considers it highly desirable that evidence pivotal to the Highly Specialised Technology Evaluation Committee's decisions should be publicly available at the point of issuing the consultation document and final guidance.

Under exceptional circumstances, unpublished evidence is accepted under agreement of confidentiality. Such evidence includes 'commercial in confidence' information and data that are awaiting publication ('academic in confidence').

When data are 'commercial in confidence' or 'academic in confidence', it is the sponsor's responsibility to highlight such data clearly, and to provide reasons why they are confidential and the timescale within which they will remain confidential. The checklist of confidential information should be completed: if it is not provided, NICE will assume that there is no confidential information in the submission. It is the responsibility of the manufacturer or sponsor to ensure that the confidential information checklist is kept up to date.

It is the responsibility of the sponsor to ensure that any confidential information in their evidence submission is clearly underlined and highlighted correctly. NICE is assured that information marked 'academic in confidence' can be presented and discussed during the public part of the Highly Specialised Technology Evaluation Committee meeting. NICE is confident that such public presentation does not affect the subsequent publication of the information, which is the prerequisite allowing for the marking of information as 'academic in confidence'.

Please therefore underline all confidential information, and highlight information that is submitted under 'commercial in confidence' in blue and information submitted under 'academic in confidence' in yellow.

NICE will ask sponsors to reconsider restrictions on the release of data if there appears to be no obvious reason for the restrictions, or if such restrictions would make it difficult or impossible for NICE to show the evidential basis for its guidance. Information that has been put into the public domain, anywhere in the world, cannot be marked as confidential.

Confidential information submitted will be made available for review by the Evidence Review Group and the Highly Specialised Technology Evaluation

Committee. NICE will at all times seek to protect the confidentiality of the information submitted, but nothing will restrict the disclosure of information by NICE that is required by law (including in particular, but without limitation, the Freedom of Information Act 2000).

The Freedom of Information Act 2000, which came into force on 1 January 2005, enables any person to obtain information from public authorities such as NICE. The Act obliges NICE to respond to requests about the recorded information it holds, and it gives people a right of access to that information. This obligation extends to submissions made to NICE. Information that is designated as 'commercial in confidence' may be exempt under the Act. On receipt of a request for information, the NICE secretariat will make every effort to contact the designated company representative to confirm the status of any information previously deemed 'commercial in confidence' before making any decision on disclosure.

18.3 Equality

NICE is committed to promoting equality and eliminating unlawful discrimination, including paying particular attention to groups protected by equalities legislation. The scoping process is designed to identify groups who are relevant to the evaluation of the technology, and to reflect the diversity of the population. NICE consults on whether there are any issues relevant to equalities within the scope of the evaluation, or if there is information that could be included in the evidence presented to the Highly Specialised Technology Evaluation Committee to enable them to take account of equalities issues when developing guidance.

Evidence submitters are asked to consider whether the chosen decision problem could be impacted by NICE's responsibility in this respect, including when considering subgroups and access to recommendations that use a clinical or biological criterion.

For further information, please see the NICE website (www.nice.org.uk/aboutnice/howwework/NICEEqualityScheme.jsp).

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Highly Specialised Technologies (HST)

Cerliponase alfa for the treatment of neuronal ceroid lipofuscinosis type 2 (CLN2) [ID943]

Dear Andrew,

The Evidence Review Group, NHS Centre for Reviews and Dissemination and Centre for Health Economics-York, and the technical team at NICE have looked at the submission received on 3 October by BioMarin. In general terms they felt that it is well presented and clear. However, the ERG and the NICE technical team would like further clarification relating to some of the data (see questions listed at the end of the letter).

The ERG and the technical team at NICE will be addressing these issues in their reports.

Please provide a written response to the clarification questions by **5pm** on **10 November 2017**. Two versions of this written response should be submitted; one with academic/commercial in confidence information clearly marked and one from which this information is removed.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, and all information submitted under 'academic in confidence' in yellow.

If you present data that is not already referenced in the main body of your submission and that data is seen to be academic/commercial in confidence information, please complete the attached checklist for in confidence information.

Please do not 'embed' documents (i.e. PDFs, spreadsheets) in your response as this may result in your information being displaced or unreadable.

If you have any further queries on the technical issues raised in this letter then please contact Thomas Paling, Technical Lead (Thomas.Paling@nice.org.uk). Any procedural questions should be addressed to Joanne Ekeledo, Project Manager (Joanne.Ekeledo@nice.org.uk).

Yours sincerely

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Section A: Clarification on effectiveness data

A1. **Priority Question:** Please clarify how many patients were screened for inclusion in the study 190-201 and how many were excluded.

A2. Tables C11 and C12 mention that intervention and control were matched by key prognostic variables: 'i.e. age, genotype, CLN2 clinical rating score'. Elsewhere in the company submission it was stated that patients were matched only by age and gender. Please clarify if they were also matched by genotype. If not, please could you provide this information for both groups so that it is possible to assess if they are sufficiently similar.

A3. **Priority Question:** Please provide baseline characteristics and results for each patient separately. In addition, age at diagnosis and first clinical signs are provided for the control group but the ERG were unable to find this data for the cerliponase group (only onset of disease and age of enrolment in study 190-201 was identified for cerliponase). Please provide this data or a reference for where this is listed in the submission or Clinical Study Report (CSR).

A4. Distance to travel for treatment was mentioned in some of the family case studies provided by the Batten's Disease Family Association as an important disadvantage of the treatment. Please provide the distance travelled for treatment for each patient included in the trial.

A5. **Priority Question:** It would be helpful to have further information about the psychometric properties and any validation of the CLN2 clinical rating scale – as data from this scale is the primary efficacy outcome.

A6. The ERG were unable to find citation 16 on the relationship between CLN2 and QoL measures in the company submission. In addition, it would be helpful to present data on the inter-rater reliability of the CLN2 clinical rating scale and also evidence for the equivalence of the Weill Cornell and Hamburg clinical rating scales on the language motor/gait domains if such data are available.

A7. Further to the previous question, appendix 4 states that the majority of patients were assessed by a single rater for the duration of the trial. Please provide details on the number of patients who were assessed by a single rater and those who were not. For patients with more than one rater, please state how many raters in total were used over the period of the trial.

A8. Has any further data been collected in study 190-202 after November 2016, if so please provide the most recent data. In addition, the company submission states that three patients in the sibling study (study 190-203) have been recruited approximately a year ago – please provide any data available for these patients.

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A9. Please provide further information about the slope analysis. A reference [22] is given in the company submission to the methods in the clinical study report (CSR), but when reading the CSR details detail on the methods are also not provided there but reference is made to an appendix 16.1.9 that we could not find (see p70 of CSR).

The title of reference 22 in the company submission bibliography is inconsistent with the title of reference 22 in the reference pack. Please submit the correct CSR(s) or clarify this inconsistency.

A10. **Priority Question:** The company submission states several times (e.g. p21) that vision loss will be stabilised by cerliponase alfa treatment, and this is reflected in the economic model. However, it is the ERG's understanding that progressive vision loss in CLN2 is caused by deterioration of the retinal cells. The 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, therefore the drug will have no significant effect upon vision loss in CLN2. This is supported by animal studies of TPP1 ERT [1, 2]. Does the company agree with the ERG's interpretation that this drug cannot prevent vision loss?

A11. **Priority Question:** The company submission provides total scores on the CLN2 rating scale (motor and language domains combined) and also total scores on the Hamburg rating scale (motor, language, vision and seizures). Please provide scores for each domain separately i.e. motor, language, vision and seizures.

A12. **Priority Question:** Management strategies of CLN2 recommend cardiology assessment, due to evidence of cardiac abnormalities in progressed disease [3, 4], and severe cardiac functional impairment in non-human studies and other forms of human NCL. Please provide any non-neurological (cardio/respiratory, blood cTn1 levels, CK activity, ALT activity) outcomes recorded in the pivotal trials. If these have not been recorded, please clarify why this was the case.

A13. **Priority Question:** Non-human trials of targeted delivery of TPP1 to the CNS have shown that elongation of life through inhibiting the progression of neurological pathology allows progressive and severe functional impairment of non-neuronal organs to become evident (such as, the heart, lungs, and liver). Studies cited in the company submission suggest that delaying neurological progression of the disease without addressing extra-neuronal pathology will soon lead to death due to the failure of other vital organs [5]. What do the company believe would be the implications of this evidence on long-term outcomes, and the assumption of normal life-expectancy of treated patients in the model?

A14. Please clarify whether the current market authorisation for cerliponase alfa has any age restrictions.

Section B: Clarification on cost-effectiveness data

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Model Structure

B1. A significant number of assumptions made regarding the model structure are based on clinical expert opinion, referencing a BioMarin Expert Opinion Report (citation 83). This citation is missing from our file. Please provide this report.

B2. The model structure was informed by a series of three workshops. Only one reference is provided, which relates to the Delphi panel undertaken for workshop 2. Please provide details of the other workshops.

B3. **Priority Question:** One of the consequences of the short cycle length and memoryless Markov approach is that a non-negligible proportion of patients can experience successive falls in CLN2 score over a very short period i.e. some patients experience a drop of 6 points in only 12 weeks. These issues mean that a non-negligible proportion of patients experience a drop 3 or more points in the first 48 weeks of the model. Please comment on the plausibility of patients experiencing such a rapid decline.

Further to the above, one way in which the impact of this issue can be ameliorated is to increase the cycle length. Can the company present additional scenario analysis where the cycle length is increased so that it aligns with the minimum expected time over which a fall in CLN2 score would be observed?

Population

B4. **Priority Question:** The distribution of patients across the health states is very different in the model than suggested by the baseline CLN2 scores in the 190-201 trial. The justification for this difference in the company submission is an expectation of increased clinical awareness of CLN2, also noting a campaign by the company to increase awareness. Please provide any evidence to support the expectation of an increase in awareness of CLN2 and any evidence that an awareness programme would lead to earlier diagnosis (e.g. success in other countries).

B5. It has been suggested by the clinical advisor to the ERG that the only way to increase early diagnosis significantly, so that the majority of children are diagnosed before significant loss of function, is to institute a wide scale genetic screening programme. Please comment on this.

B6. **Priority Question:** Please provide summary data from the historical cohort giving the distribution of patients across the health states at diagnosis/onset.

B7. **Priority Question:** Please provide two additional scenario analyses to the economic model:

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a) The distribution of patients is the same as the trial population at base-line assessment

b) If data is available, the distribution of patients is the same as the trial population at diagnosis/onset of disease

Quality of life

B8. **Priority Question:** Please justify the difference in utility values between treatment arms. Please comment on the differences in the vignettes, the implied seizure control and improved control of dystonia and myoclonus. Please provide evidence to show that cerliponase alfa provides these clinical benefits.

B9. **Priority Question:** When standard care patients move between health states 7 and 8, this results in an increase in HRQoL. Please justify this and comment why the same is not true for patients receiving cerliponase alfa.

B10. **Priority Question:** When in health state 1, patients are assumed to have near perfect health. How plausible do the company consider this assumption? Please make specific reference to the following in your response:

a) Patients do not have full seizure control;

b) Language deterioration was measured relative to best achieved rather than typical development for the age of child and therefore a number of the children with a score of 3 on the language domain are likely to have experienced some developmental delay; and

c) Currently, diagnosis of children usually requires them to be symptomatic of the disease.

B11. The clinical advisor to the ERG suggested that children with CLN2 may have other behavioural and/or developmental disorders such as autism spectrum disorder or attention deficit hyperactivity disorder. Presently, due to the progressive nature of the disease, these developmental disorders go undiagnosed but this may not be the case if cerliponase alpha is able to alter the course of the disease. Please comment on this.

B12. **Priority Question:** There are negative health states for both the cerliponase alpha and standard care in health states 7, 8 and 9. These imply quality of life that is worse than death and are rarely used in health economic evaluations. The ERG acknowledges that clinical experts verified that states worse than death are possible in this disease area. However, the values used in the model are quite low, particularly when compared with the values collected in the clinical trial and the actual (EQ-5D-5L) values collected from the clinicians in the vignette study.

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a) Please justify the use of these negative health states in health states 7, 8 and 9. In your response please make reference to other degenerative diseases.

b) Please include an additional scenario analysis usingEQ-5D-5L utility values.

B13. Were EQ VAS data collected as part of the vignette study? If so, please provide this data.

Treatment effectiveness and transitions

B14. **Priority Question:** The explanations of how and what transition probabilities are used in the model are not clear and are lacking in transparency. Can the company please address the following concerns:

a) Please confirm that the transition probabilities defined in table D11 are only used for standard care patients in the base-case model?

b) On page 200 of the company submission it was noted that: “The data from study 190-201/202 suggested that scores fluctuated more in the initial stages of treatment, before stabilising, which is why the transition probabilities were split up across the time periods, in order to better reflect clinical reality.” In the base-case analysis, however, the same transition probabilities are used for all of the trial period 0 to 96 weeks. Please explain this inconsistency.

c) It is not clear where the transition probabilities presented in Table D13 come from or how they were derived. This is crucial as these are the transition probabilities used in the base-case analysis. Please provide details on what the transition probabilities are and how they were derived.

d) Minimal details are provided on how transition probabilities for patients in the standard care arm were derived other than they were based on data from the matched natural history cohort. Please provide further details of the company’s approach to deriving these transition probabilities.

e) The efficacy data in Figure C8 suggests that 35% of patients experience a drop of 1 or more points on the CLN2 scale in the first 48 weeks. The base-case analysis, however, assumes that only 26% of patients can experience any kind of drop in their score in the first 48 weeks. Please comment on this inconsistency.

f) Similarly, Table C22 suggests that 48% of patients experience a drop of 1 or more points on the CLN2 scale in the first 96 weeks. The base-case analysis, however, assumes that only 26% of patients can experience any kind of drop in their score in the first 96 weeks. Please comment on this inconsistency.

B15. **Priority Question:** There was little explanation of the methods applied to calculate the transitional probabilities used in the economic model. Please provide full details of the data used to calculate the transition probabilities used in the model and a detailed description of the approach taken to calculate them.

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B16. **Priority Question:** The company's base-case makes assumes that after 96 weeks all patients have stabilised disease. This assumption has significant impact on the total QALYs accrued. Please justify this assumption and where appropriate make reference to experience on other lipid storage diseases with ERTs.

B17. **Priority Question:** Given the points raised in questions A10, A13, and B16 please present additional scenario analyses in which more conservative assumptions regarding the long-term effectiveness are assumed.

B18. **Priority Question:** Please provide full details of how the proportion of early stabilisers at 16 weeks (74%) was calculated. The EPAR reference provided by the company does not contain any information regarding response levels in patients. The values of 73.9% or 74% do not correspond to the clinical sections of the company's submission. Within the results of the relevant studies for Study 190-201 (p 105 of CS), the results state that the "CLN2 clinical rating scale score was stabilised in 65% (15 of 23) of patients, who had no change or an improvement in score from baseline". Please explain this inconsistency and confirm the correct figure.

B19. **Priority Question:** Please comment on Question 12 in the Delphi study report, where the clinical experts agreed that they would need patients to have the same CLN2 clinical rating scale score for 26 weeks to consider progression to have stabilised. This is inconsistent with the economic model where early stabilisers are identified at week 16.

Resource Use

B20. **Priority Question:** The ERG notes that the dose of cerliponase alfa required does not increase after the age of two. Please provide some insight in how the dose of cerliponase alfa was determined and comment on whether the dose would be the same in adolescents/adults as in children.

B21. **Priority Question:** The health state costs used in the model assume that the patients are children. For example, costs are assigned for community paediatrician, speech and language therapy, non-family caregivers and education support. For the majority of the model, patients receiving cerliponase alfa are not children and will have different support needs. Please comment on how support needs and resource use change as patients enter adolescence and adulthood. If appropriate, please present any scenario analyses around this.

B22. Please confirm that in the 190-201/202 study patients received therapy in ICU which required an overnight stay.

B23. **Priority Question:** The states that patients spend on average one year in a palliation health before they die (page 201). This appears to contradict the costs for this health state, where it was assumed that patients received 36 visits per year for palliative care. Based on the health state vignettes, this implies that it is expected that children would require a ventilator to aid with respiration for one year.

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a) Please provide further justification on this assumption and comment on whether patients would be ventilated for this duration of time in practice.
b) Please describe the costs and resource use associated with providing this service (respiration support and end of life care). For example, could the breathing apparatus be provided at home, or would patients receive care in a hospice? Please quantify (i.e. suggest the proportion of patients, units received) the type of care received in each setting, if possible.
c) It was noted that the amount of palliative care was same in Health State 8 and Health State 9 (Table D25), where patients were assumed to receive 36 units (visits) per year. It is understood that HS9 specifically captures patients receiving palliative care (page 198). Please provide justification why levels of palliative care did not differ between these two health states, and why patients did not receive 52 units of palliative care in HS9?

B24. **Priority Question:** Caregivers are required to support CLN2 patients, and care was assumed to be provided by a combination of both family and non-family caregivers (page 194). For each stage of the disease, please comment on how care is provided by non-family caregivers, i.e. the healthcare professional involved, the frequency of visits to the home, duration of visit, and the activities undertaken.

B25. **Priority Question:** Please comment on some additional resources that were not included in the model.

a) The resource use study identified by the company stated that psychological support for the family is essential (page 219). What consideration was given to these costs for use in the model? Please provide any information on whether any support was provided to families who participated in the trials, and what kind of support is available in the UK. Please provide details on the potential providers of this support, the proportion of families who accessed this support, and when was this support accessed (e.g. during more severe health states, at diagnosis etc.).

b) Cerliponase alfa is required to be administered using a strict aseptic technique (page 294), and the SPC states that this should be by a trained healthcare professional (HCP). Please describe the costs associated with this training. Please consider, the frequency of training, whether retraining is required, and who provides this training.

c) Are there any additional monitoring requirements for cerliponase alfa patients e.g. ECG and routine testing of cerebrospinal fluid (CSF) samples (as suggested in the SPC), liver function tests etc.

B26. It was assumed in the model that the ICV delivery device may only be replaced if an infection occurs (page 187). The infection rate in the model is low, and it may be that patients have the same delivery device for many years before it needs replacing. It seems reasonable to assume that it would need replacing as patients get older, and that the device and insertion area may need maintaining (such as, cleaning). The company submission

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states that there is no data available relating to the regularity of replacement of the ICV delivery device in CLN2 patients: are there any other treatments administered in a similar fashion with data that could be used to comment on how this may occur for cerliponase alfa patients.

B27. **Priority Question:** The ERG has some concerns regarding the components of care included in the health state costs. Specifically, the ERG notes the following:

- Patients are assumed to continue to receive speech and language therapy and physiotherapy in Health States 7, 8 and 9. This is despite the fact the patient now has no speech or language function.
- In Health State 8 and 9, costs relating to visits to an ophthalmologist are included even though it is assumed that the patient has complete loss of vision at this stage of the disease.
- In Health State 7 and 8, it is assumed patients receive palliative care. This seems inconsistent with health state 9 which is defined specifically with respect to the fact that patients are receiving end of life care.
- Children with no motor or language function and receiving of end life care (Health State 9) continue to receive educational support. The ERG does not consider this to be plausible.

Please comment on the above concerns and provide justification for the inclusion of these costs.

Section C: Textual clarifications and additional points

C1. The numbers reported in the records identified through database searches box of the PRISMA flow diagram (Figure C6, page 72) do not match the search results reported in the search strategies contained in Appendix 2 (Table 1 MEDLINE, Table 2 EMBASE, and Table 3 Cochrane). For example, in the PRISMA diagram 1686 records are reported as being retrieved from MEDLINE, however in Table 1 at line 91, 1597 records are reported as retrieved from MEDLINE. Please clarify this discrepancy for MEDLINE, EMBASE and the Cochrane Library.

C2. Please could the source of the search filters used to limit retrieval to RCTs and non-RCTs for the clinical evidence searches of MEDLINE and EMBASE be provided? (Appendix 2, Tables 1 & 2)

C3. Please could the source of the search filters used to limit retrieval to economic studies and quality of life studies for the economic evidence searches of MEDLINE and EMBASE be provided? (Appendix 8, Tables 24 & 25)

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References

1. Whiting, R.E.H., et al., Enzyme replacement therapy delays pupillary light reflex deficits in a canine model of late infantile neuronal ceroid lipofuscinosis. Experimental Eye Research, 2014. 125: p. 164-172.

2. Katz, M.L., et al., Enzyme replacement therapy attenuates disease progression in a canine model of late-infantile neuronal ceroid lipofuscinosis (CLN2 disease). Journal of Neuroscience Research, 2014. 92(11): p. 1591-1598.

3. Williams, R.E., et al., Management Strategies for CLN2 Disease. Pediatric Neurology, 2017. 69: p. 102-112.

4. Fukumura, S., et al., Progressive conduction defects and cardiac death in late infantile neuronal ceroid lipofuscinosis. Developmental Medicine and Child Neurology, 2011. 54(7): p. 663-666.

5. Katz, M.L., et al., Extraneuronal pathology in a canine model of CLN2 neuronal ceroid lipofuscinosis after intracerebroventricular gene therapy that delays neurological disease progression. Gene Therapy, 2017. 24(4): p. 215-223.

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Highly Specialised Technologies (HST)

Cerliponase alfa for the treatment of neuronal ceroid lipofuscinosis type 2 (CLN2) [ID943]

Dear Sheela Upadhyaya,

Thank you for the opportunity to respond to the clarification questions from the Evidence Review Group, NHS Centre for Reviews and Dissemination and Centre for Health Economics-York, and the technical team at NICE. We thank the teams for their general comments on the submission and hope that our responses to the individual questions below provide the additional information and clarity that was requested.

As requested, we have uploaded to NICE Docs, all of the accompanying references to these responses, as well as a confidentiality checklist.

Please do not hesitate to get in touch should you have any questions regarding our response.

Kind regards,

Andrew Olaye

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Section A: Clarification on effectiveness data

A1. **Priority Question:** Please clarify how many patients were screened for inclusion in the study 190-201 and how many were excluded.

24 patients were screened for inclusion in study 190-201 and all of them met the inclusion criteria and were subsequently included in the study. As such, no patients were excluded. One subject withdrew consent from the study after ICV access device placement and a single infusion during the dose escalation phase because of inability to continue with study procedures.

A2. Tables C11 and C12 mention that intervention and control were matched by key prognostic variables: 'i.e. age, genotype, CLN2 clinical rating score'. Elsewhere in the company submission it was stated that patients were matched only by age and gender. Please clarify if they were also matched by genotype. If not, please could you provide this information for both groups so that it is possible to assess if they are sufficiently similar.

Tables C11 and C12 provides a summary of the critical appraisal of study 201 and 202 respectively. We would like to clarify that no matching was done based on "age and gender" for the efficacy analysis, as gender is not a known prognostic variable. The 1:1 matching was based on an exact match of baseline CLN2 clinical rating score (i.e. Motor and Language domain) and age (matching for age based on a ≤ 12 month difference). In the November 2016 data cut (which is the latest data cut and included in our submission), 21/23 subjects in the 190-201/202 ITT population were matched to naturally history subjects from the 190-901 study; two subjects could not be matched because the subject's closest match had an age difference of greater than 12 months. These subjects have been omitted from these analyses; thus, the ITT population for these 1:1 matching analyses has an n=21. As a sensitivity analysis, a many-to-one matching was done based on exact CLN2 score; exact CLN2 score + age (≤ 12 months); and exact CLN2 score and genotype. The results of these sensitivity analysis were similar to the results of the 1:1 matching, and are provided in the responses to question A11. Further details on how the matching has been done is available in Appendix 1 of the Integrated Summary of Effectiveness[32].

The only age and gender matching that was done was matching of the respondents in the CLN2 family burden of disease to the general population in order to accurately estimate the burden of CLN2 disease on family members.

A3. **Priority Question:** Please provide baseline characteristics and results for each patient separately. In addition, age at diagnosis and first clinical signs are provided for the control group but the ERG were unable to find this data for the cerliponase group (only onset of disease and age of enrolment in study 190-201 was identified for cerliponase). Please provide this data or a reference for where this is listed in the submission or Clinical Study Report (CSR).

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The baseline characteristics and results for each patient in the 201 study are included in the reference pack[33]. The Baseline characteristics of the subjects treated with cerliponase alfa in the 201 study are summarized in the table below. It can be found in Table 11.2.2 of the 190-201 CSR. The age at diagnosis and the first clinical signs were not collected in the 201 study and as such are not available.

Table 1: Baseline characteristics of patients in study 190-201 study

	C1 (n = 3)	C2 (n = 3)	C3 (n = 4)	SDO (n = 14)	Overall (n = 24)
Age at Disease Onset (yr)					
< 3	0	1 (33%)	0	6 (43%)	7 (29%)
3- < 5	1 (33%)	1 (33%)	2 (50%)	8 (57%)	12 (50%)
≥ 5	1 (33%)	1 (33%)	2 (50%)	0	4 (17%)
Pre-symptomatic	1 (33%)	0	0	0	1 (4%)
N	2	3	4	14	23
Mean (SD)	4.0 (1.36)	3.6 (1.42)	4.7 (1.59)	3.0 (0.29)	3.4 (1.07)
Median	4.0	3.0	4.7	3.0	3.0
Min , Max	3.1 , 5.0	2.5 , 5.2	3.2 , 6.3	2.6 , 3.6	2.5 , 6.3
Genotype					
c.622C>T	0	1 (33%)	1 (25%)	3 (21%)	5 (21%)
c.509-1G>C	0	1 (33%)	0	1 (7%)	2 (8%)
c.622C>T and c.509-1G>C	0	0	0	2 (14%)	2 (8%)
c.622C>T and Other	1 (33%)	0	2 (50%)	1 (7%)	4 (17%)
c.509-1G>C and Other	2 (67%)	0	1 (25%)	1 (7%)	4 (17%)
Other	0	1 (33%)	0	6 (43%)	7 (29%)
Screening ML Scale Score					
6	1 (33%)	0	1 (25%)	0	2 (8%)
5	0	0	0	2 (14%)	2 (8%)
4	0	0	1 (25%)	6 (43%)	7 (29%)
3	2 (67%)	3 (100%)	2 (50%)	6 (43%)	13 (54%)
n	3	3	4	14	24

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	C1 (n = 3)	C2 (n = 3)	C3 (n = 4)	SDO (n = 14)	Overall (n = 24)
Mean (SD)	4.0 (1.73)	3.0 (0.00)	4.0 (1.41)	3.7 (0.73)	3.7 (0.95)
Median	3.0	3.0	3.5	4.0	3.0
Min , Max	3 , 6	3 , 3	3 , 6	3 , 5	3 , 6
Baseline ML Scale Score					
6	1 (33%)	0	1 (25%)	0	2 (8%)
5	0	0	0	2 (14%)	2 (8%)
4	0	0	1 (25%)	5 (36%)	6 (25%)
3	2 (67%)	3 (100%)	1 (25%)	6 (43%)	12 (50%)
2	0	0	1 (25%)	1 (7%)	2 (8%)
n	3	3	4	14	24
Mean (SD)	4.0 (1.73)	3.0 (0.00)	3.8 (1.71)	3.6 (0.85)	3.6 (1.06)
Median	3.0	3.0	3.5	3.5	3.0
Min , Max	3, 6	3, 3	2, 6	2, 5	2, 6
300 mg Baseline ML Scale Score					
6	1 (33%)	0	1 (33%)	0	2 (9%)
5	0	0	0	2 (14%)	2 (9%)
4	0	0	0	5 (36%)	5 (22%)
3	2 (67%)	2 (67%)	1 (33%)	6 (43%)	11 (48%)
2	0	0	1 (33%)	1 (7%)	2 (9%)
1	0	1 (33%)	0	0	1 (4%)
0	0	0	0	0	0
n	3	3	3	14	23
Mean (SD)	4.0 (1.73)	2.3 (1.15)	3.7 (2.08)	3.6 (0.85)	3.5 (1.20)
Median	3.0	3.0	3.0	3.5	3.0
Min , Max	3, 6	1, 3	2, 6	2, 5	1, 6

C1 –cohort 1 of dose escalation phase (dosed at 30mg every 2 weeks)
C2 - cohort 2 of dose escalation phase (dosed at 100mg every 2 weeks)
C3 – cohort 3 of dose escalation phase (dosed at 300mg every 2 weeks)
SDO – Stable dose of 300mg every 2 weeks

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A4. Distance to travel for treatment was mentioned in some of the family case studies provided by the Batten's Disease Family Association as an important disadvantage of the treatment. Please provide the distance travelled for treatment for each patient included in the trial.

The distance travelled for treatment for each patient in the clinical trial is not a proxy of the distance that patients in England will travel to receive treatment. This is because the clinical trial was conducted in a limited number of centres. In clinical practice, patients will be infused in the two reference centres (London and Manchester) and once stabilised could then be infused in paediatric neurology departments which has an emergency response unit. .

The 201 and 202 studies were both conducted in only four centres, with one centre each in UK, Germany, Italy and the USA. Given the limited number of centres and the ultra-rare nature of the disease, a number of the patients relocated in order to participate in the trials. In fact of the 24 patients enrolled in the study, [redacted] The exact distance patients travelled for each patient was not collected and as such is not available. Our understanding from the discussions with BDFA, is that although in some cases families had to travel from far during the study, they did not view this as a significant disadvantage. This was because, firstly they understood, that they were participating in a clinical trial and as such access will be limited in that period pending treatment approval and funding. Secondly, any inconvenience experience was minimal in context of the significant benefits experienced in quality of life and clinical outcomes.

Since the approval of cerliponase alfa by the EMA, BioMarin has opened several centres in which the drug will be administered. At present cerliponase alfa is available at one expert centre in UK (Great Ormond Street Hospital, London). However, at the time of NICE guidance, it is anticipated that cerliponase alfa will also be available at the lysosomal storage disorder expert centre at the Royal Manchester Childrens Hospital in Manchester. BioMarin is committed to work with the clinical and patient community to ensure that patients are able to access treatment. Hence if need be, cerliponase alfa can be made available at other LSD centres in England.

Table 2. XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX

Table redacted – commercial in confidence

A5. **Priority Question:** It would be helpful to have further information about the psychometric properties and any validation of the CLN2 clinical rating scale – as data from this scale is the primary efficacy outcome.

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Psychometric properties of the CLN2 clinical rating scale including the 0-6 total score and the separate motor and language scores, were examined using Study 190-201 clinical trial data. The CLN2 rating scale showed good reliability (internal consistency and inter-rater reliability), construct validity and responsiveness. [redacted] [34].

A6. The ERG were unable to find citation 16 on the relationship between CLN2 and QoL measures in the company submission. In addition, it would be helpful to present data on the inter-rater reliability of the CLN2 clinical rating scale and also evidence for the equivalence of the Weill Cornell and Hamburg clinical rating scales on the language motor/gait domains if such data are available.

Citation 16 is included in the reference pack accompanying these responses.

In 2016, [redacted] conducted a formal inter-rater study to assess the inter-rater reliability of the CLN2 clinical rating scale. [redacted]

[redacted] Further details of the inter-rater reliability analyses and results are also detailed in the CLN2 rating scale clinician-Reported Outcome Evidence Dossier supplied [34]

A7. Further to the previous question, appendix 4 states that the majority of patients were assessed by a single rater for the duration of the trial. Please provide details on the number of patients who were assessed by a single rater and those who were not. For patients with

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more than one rater, please state how many raters in total were used over the period of the trial.

The majority of assessments for all participants were performed by a single rater. However there were a limited number of time-points that were assessed by alternative trained raters. [redacted] It should be noted that all raters at all sites were required to participate in a training session [redacted] The training was designed to standardize definitions, criteria and scale anchor points across the study, before study ratings took place in order to reduce variability of assessment.

In addition, every 24 weeks, CLN2 scale assessments were videotaped for all patients across all study sites. These video recordings were reviewed and scored by an independent adjudicator (who was not an investigator on the study). The scores of the independent adjudicator and that of the assessor was compared and any observed discrepancies was documented. The assessor was the final arbiter of all ratings following discussions with the independent adjudicator. Also for any patient that had a 1 or more point change in either the Motor or Language subscales in the ratings interval; the reason for the change was verified in the source documentation of that ratings visit. [redacted]

A8. Has any further data been collected in study 190-202 after November 2016, if so please provide the most recent data. In addition, the company submission states that three patients in the sibling study (study 190-203) have been recruited approximately a year ago – please provide any data available for these patients.

Study 190-202 is still ongoing and will continue until 2020. However the last data cut was in November 2016.

[redacted]

[redacted]

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[redacted]

[redacted][37].

A9. Please provide further information about the slope analysis. A reference [22] is given in the company submission to the methods in the clinical study report (CSR), but when reading the CSR details detail on the methods are also not provided there but reference is made to an appendix 16.1.9 that we could not find (see p70 of CSR).

The slopes analysis of the CLN2 clinical rating score is the rate of decline in the CLN2 (ML) scale score, scaled to a 48-week time period. Since the analysis measures rate of decline, as opposed to a rate of change, it is generally expected to be a positive number, with larger values representing a steeper deterioration of clinical status over time.

The slope analysis was calculated as follows:
Step 1: The slope of the line between the starting (CLN2 score at baseline) and ending CLN2 scores (at latest time point available):

$$\text{Slope} = \frac{\text{(Ending CLN2 score)} - \text{(Starting CLN2 score)}}{\text{(Ending date)} - \text{(Starting date)}}$$

Step 2: The rate of decline was then scaled to a 48-week time period using the equation below:

$$\text{Rate of decline} = (-1) \times (48 \times 7) \times \text{Slope (from step 1)}$$

Further details on how the slope analysis has been estimated is available in Appendix 1 of the Integrated Summary of Effectiveness Statistical Analytical Plan[32].

The title of reference 22 in the company submission bibliography is inconsistent with the title of reference 22 in the reference pack. Please submit the correct CSR(s) or clarify this inconsistency.

We can confirm that reference 22 included in the reference pack is the same as what's referenced in the company submission bibliography. We have updated the title accordingly and re-submitting in the accompanying reference pack [38].

A10. **Priority Question:** The company submission states several times (e.g. p21) that vision loss will be stabilised by cerliponase alfa treatment, and this is reflected in the economic model. However, it is the ERG's understanding that progressive vision loss in CLN2 is caused by deterioration of the retinal cells. The 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

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infusion, therefore the drug will have no significant effect upon vision loss in CLN2. This is supported by animal studies of TPP1 ERT [1, 2]. Does the company agree with the ERG's interpretation that this drug cannot prevent vision loss?

Progressive vision loss in CLN2 patients has been shown to be due to both retinal changes and central changes in the brain [39, 40]. As such cerliponase alfa's distribution to the optical centres of the brain could have an effect on the rate of progression of vision impairment.

[redacted]

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Table 3. XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX

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A11. **Priority Question:** The company submission provides total scores on the CLN2 rating scale (motor and language domains combined) and also total scores on the Hamburg rating scale (motor, language, vision and seizures). Please provide scores for each domain separately i.e. motor, language, vision and seizures.

As requested, please find below scores for each of the separate domains of the full Hamburg scale (i.e. motor, language, vision and seizures). Results are presented for both the cerliponase treated patients in the 201/202 study and the 901 natural history study. The number of patients of the natural history study arm was lower due to the lack of follow-up data at this time for some of the matched patients. The 1:1 matching analysis showed that cerliponase alfa had a clinically significant treatment effect across all four domains, with majority of patients either stabilising or improving after treatment compared to a considerable loss of function across all domains in the majority of the matched natural history patients.

These data are supported by the 1: many matching analysis, in which a 201/202 patient has been matched to more than 1 natural history patient. In fact, the results from this analysis show similar finding to the 1:1 matching and indicates that the lower number of patients in the natural history study (901) arm of the 1:1 matching does not affect the results.

Table 4. XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX

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Table 5. XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX

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Table 6. XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX

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Table 7. [redacted]

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A12. **Priority Question:** Management strategies of CLN2 recommend cardiology assessment, due to evidence of cardiac abnormalities in progressed disease [3, 4], and severe cardiac functional impairment in non-human studies and other forms of human NCL. Please provide any non-neurological (cardio/respiratory, blood cTn1 levels, CK activity, ALT activity) outcomes recorded in the pivotal trials. If these have not been recorded, please clarify why this was the case.

Although cardiac abnormalities have been recognized in other forms of NCL, such as CLN3, to date the cardiac abnormalities have only been reported in one case of late infantile CLN2 disease [4]. In case studies of atypical CLN2 disease progression, patients have been reported to have slower neurological decline living to over the age of 20 years [43], ultimately dying due to pneumonia secondary to neurological manifestations of the disease, and not peripheral disease. As such, it is possible that the sole reported case of cardiac involvement in late stage CLN2 disease could have been as a result of other unrelated comorbidities that the patient suffered from. It is also worth clarifying that the CLN2 management strategies recommended cardiology assessments as a precaution, as opposed to direct evidence of cardiac abnormalities.

The main drivers of morbidity and mortality in CLN2 patients particularly in the early and rapid decline phase of the classic CLN2 phenotype is due to neurological decline. The 201/202 study was designed to investigate the effect of cerliponase alfa treatment on the neurological decline in CLN2 disease. The study was not designed to investigate effects on possible extra-neuronal signs as they were not expected. Nevertheless non-neurological assessments were done for safety. Specifically CK activity and ALT activity were both monitored as part of Clinical laboratory assessments done every 12 weeks, ECGs were done every 24 weeks, and vital signs (Blood pressure [SBP and DBP], heart rate, respiration rate, and temperature) were measured every two weeks. Any abnormality from these assessments were listed as adverse events. As at the last data cut (96 weeks of treatment for all patients), no clinically meaningful abnormalities have been reported. Individual subject laboratory measurements, vital signs and ECGs can be found in the patient listings safety results included in the reference pack[44]. Long-term safety studies and monitoring trends in safety reports for CLN2 patients may provide additional insight into the nature and prevalence of extra-neuronal disease progression in future years.

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A13. **Priority Question:** Non-human trials of targeted delivery of TPP1 to the CNS have shown that elongation of life through inhibiting the progression of neurological pathology allows progressive and severe functional impairment of non-neuronal organs to become evident (such as, the heart, lungs, and liver). Studies cited in the company submission suggest that delaying neurological progression of the disease without addressing extra-neuronal pathology will soon lead to death due to the failure of other vital organs [5].
What do the company believe would be the implications of this evidence on long-term outcomes, and the assumption of normal life-expectancy of treated patients in the model?

The company believes that it is not possible to assess the implications of extra-neurological pathology seen in animal CLN2 models (administered with human recombinant cerliponase alfa), on long term outcomes of CLN2 patients treated with recombinant cerliponase alfa. To date, despite treatment with cerliponase alfa for up to 4 years, extra-neuronal pathology has not been observed in patients. Indeed, there is no evidence from other variants of TPP1 deficiency such as SCAR7 (where patients can live into their 60s) or atypical CLN2 patients that death has resulted from extra-neurological pathologies. Long-term safety studies and monitoring trends in safety reports for CLN2 patients may provide additional insight into the nature and prevalence of extra-neuronal disease progression in future years and can form the basis of future reassessments.

A14. Please clarify whether the current market authorisation for cerliponase alfa has any age restrictions.

As per the summary of product characteristics (section 4.1 and 4.2), cerliponase alfa is approved and indicated for CLN2 patients of all ages. Hence, there are no age restrictions in the market authorisation.

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Section B: Clarification on cost-effectiveness data

Model Structure

B1. A significant number of assumptions made regarding the model structure are based on clinical expert opinion, referencing a BioMarin Expert Opinion Report (citation 83). This citation is missing from our file. Please provide this report.

The expert opinion relating to citation 83 (BioMarin. Expert Clinical Opinion, 2017) was obtained during two meetings and an additional personal communication with the relevant experts. A summary of the relevant meetings and communications are provided in Table 1. The report for the cerliponase alfa economic model workshop (workshop 1) and the minutes of the CLN2 disease model finalisation meeting (workshop 3) are also provided in response to these clarification questions.[6, 7]

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Table 1. Details of meetings and communications relating to expert clinical opinion

Page Number of Submission	Statement	Details of meeting/communication
181	At model entry, the cohort is distributed across the health states according to the expected population that will receive treatment for CLN2 disease. This expected population was validated by clinical experts.	CLN2 disease model finalisation meeting[7]
187	Patients stop receiving cerliponase alfa treatment when they reach health state 7 (CLN2 clinical rating scale score of 0). This stopping rule was proposed by clinical experts.	Cerliponase alfa economic model workshop[6]
188	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.	CLN2 disease model finalisation meeting[7]
189	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.	Supplementary information report[8]
196	Caregiver disutilities health states 1 and 2.	CLN2 disease model finalisation meeting[7]
197	Sibling disutility was applied across all but the first two health states, in line with guidance from clinical experts.	Supplementary information report[8]
199	In order to account for this problem and the overall low sample size, probabilities were determined for combined groups of scores (scores of 6 and 5 [health states 1 and 2], scores of 4 to 2 [health states 3–5], and scores of 1 and 0 [health states 6–7] on the CLN2 clinical rating score), with this approach validated by clinical experts.	Supplementary information report[8]

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239	The benefit of cerliponase alfa is in delaying disease progression, and evidence from the Phase I/II trial, as well as expert clinical opinion, suggests that patients stabilise on treatment, some stabilise earlier and others later.	CLN2 disease model finalisation meeting[7]
282	The expected uptake of cerliponase alfa is based on patients moving from the clinical trial programme and expanded access scheme onto commercial supplies and data from a survey conducted by the BDFA and clinical experts regarding the expected uptake of cerliponase alfa amongst current and newly diagnosed patients.	CLN2 disease model finalisation meeting[7] and supplementary information report[8]
284	For example, patients with other lysosomal storage disorders are known to experience cardiac abnormalities, as such it was advised by clinical expert opinion that annual echocardiograms may be recommended for CLN2 patients receiving long-term treatment with cerliponase alfa.	CLN2 disease model finalisation meeting[7]

ABBREVIATIONS: BDFA, Batten Disease Family Association; CLN2: neuronal ceroid lipofuscinosis type 2.

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B2. The model structure was informed by a series of three workshops. Only one reference is provided, which relates to the Delphi panel undertaken for workshop 2. Please provide details of the other workshops.

A description of the three workshops was provided in section 12.2.5 of the submission. Clarification regarding the naming of the workshops is provided in Table 2 below. As noted above, the report for the cerliponase alfa economic model workshop (workshop 1) and the minutes of the CLN2 disease model finalisation meeting (workshop 3) are additionally provided in response to these clarification questions. The report for the Delphi panel (workshop 2) was included in the original reference pack.

Table 2. Clarification regarding naming of the workshops

Workshop Number	Title	Date	Supporting Reference
1	Cerliponase alfa economic model workshop	September 2016	Report[6]
2	Delphi workshop	December 2016	Report[9]
3	CLN2 disease model finalisation meeting	August 2017	Minutes[7]

ABBREVIATIONS: CLN2: neuronal ceroid lipofuscinosis type 2.

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B3. **Priority Question:** One of the consequences of the short cycle length and memoryless Markov approach is that a non-negligible proportion of patients can experience successive falls in CLN2 score over a very short period i.e. some patients experience a drop of 6 points in only 12 weeks. These issues mean that a non-negligible proportion of patients experience a drop 3 or more points in the first 48 weeks of the model. Please comment on the plausibility of patients experiencing such a rapid decline.

Further to the above, one way in which the impact of this issue can be ameliorated is to increase the cycle length. Can the company present additional scenario analysis where the cycle length is increased so that it aligns with the minimum expected time over which a fall in CLN2 score would be observed?

It is acknowledged that the consequences of the Markov approach and short cycle length is that a small number of patients can rapidly transition between the health states. In terms of plausible rates of decline, as noted in the submission, results from the natural history control group (Study 190-901) gave an estimated mean rate of decline in the CLN2 clinical rating scale score of 2 points per 48 weeks.[10] It is true, however, that it would not be plausible for patients in the cerliponase alfa arm to have declined by more than 2 points in the first 48 weeks of the model, based on what was seen in the clinical trial.

Using the data from the natural history control group (Study 190-901), and the two-week cycle length, gave results in the model showing 90% of patients in the standard care to have died within 7.8 years of starting treatment, which is equivalent to patients of the age 12.6. As this modelled result is reasonably close to the results seen in natural history, the modelling method was deemed to be suitable and plausible.

The 2-week cycle length was considered the optimum cycle length because of the fortnightly treatment administration of cerliponase alfa, and the frequency of concomitant patient examinations. In order to account for this cycle length, 2-week transition probabilities were calculated from the available data by converting the 8-week transition probabilities from the available data and assuming a constant rate of transition (as described in section 12.2.1. of the submission). All relevant probabilities were adjusted according to the 2-week cycle length in order to most accurately capture the transitions that could occur. The rate of decline itself was not adjusted, and hence it was expected that no changes to plausibility were made by making these adjustments to probabilities. A longer cycle length was not deemed suitable as it may have reduced the accuracy of the model.

Results from a scenario where an 8 week cycle-length is used are presented in Table 3. 8 weeks was deemed suitable as this was the interval between measurements in the clinical trial. As can be seen, this change in cycle length only resulted in a minimal difference to the overall results.

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Table 3. Additional cycle length scenario results

Treatment	Total costs (£)	Total LYs	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£ per QALYs)
Base Case							
Cerliponase alfa	[redacted]	45.01	29.45	[redacted]	40.04	30.42	[redacted]
Standard care	£149,829	4.97	-0.97	N/A	N/A	N/A	N/A
Additional Scenario – 8 week cycle length							
Cerliponase alfa	[redacted]	45.13	29.80	[redacted]	39.74	30.80	[redacted]
Standard care	£163,263	5.40	-1.00	N/A	N/A	N/A	N/A

Abbreviations: ICER: incremental cost-effectiveness ratio; LY: life-years LYG: life-years gained; N/A: not applicable; QALYs: quality-adjusted life years

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Population

B4. **Priority Question:** The distribution of patients across the health states is very different in the model than suggested by the baseline CLN2 scores in the 190-201 trial. The justification for this difference in the company submission is an expectation of increased clinical awareness of CLN2, also noting a campaign by the company to increase awareness. Please provide any evidence to support the expectation of an increase in awareness of CLN2 and any evidence that an awareness programme would lead to earlier diagnosis (e.g. success in other countries).

The starting population used in the base case of the model was validated by clinical experts during the CLN2 disease model finalisation meeting, and is therefore deemed to be a reasonable prediction of the expected distribution of patients receiving cerliponase alfa in the future.[7]

A lack of awareness amongst health care professionals (HCPs) regarding rare conditions is frequently highlighted by patients and their families as a factor related to delayed or incorrect diagnoses.[11, 12] CLN2 disease patients can typically experience a delay of 2–3 years between symptom onset and diagnosis of symptoms.[13] As a result, most patients are currently diagnosed around the age of 5 years old, by which point substantial loss of function has already occurred.[14] Lack of awareness is acknowledged as a primary reason for delays in diagnosis,[3] and therefore it is anticipated that an awareness campaign would lead to earlier diagnosis and as a result improved care for patients and their families.

[redacted]Early use of epileptic gene panels has been shown to reduce the cost of diagnosis in paediatric epilepsy,[15] and high diagnostic yield has been seen in cases of early onset seizures.[16, 17]

[redacted]

B5. It has been suggested by the clinical advisor to the ERG that the only way to increase early diagnosis significantly, so that the majority of children are diagnosed before significant loss of function, is to institute a wide scale genetic screening programme. Please comment on this.

The currently recommended method of diagnosing CLN2 disease is testing of TPP1 enzyme activity using a dried blood spot, and/or a genetic test for each allele of the *TPP1* gene.[3] As described above, the planned "[redacted]

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[redacted] In the long-term it is hoped that new born genetic screening will become established as standard clinical practice.

B6. **Priority Question:** Please provide summary data from the historical cohort giving the distribution of patients across the health states at diagnosis/onset.

The mean age at diagnosis of the historical cohort (Study 190-901) was 58.9 months.[18] The distribution of patients in Study 190-901 across Hamburg CLN2 disease rating scale score at (or prior) to diagnosis is presented in Table 4. Please note the updated supplemental report for Study 190-901 is provided in response to these clarification questions.[18]

Table 4. Distribution of patients from the historical cohort (evaluable population) across health states at (or prior) to diagnosis

Score at (or prior to) diagnosis*	Health state	Proportion of patients in Study 190-901 (N=49)
5	Health state 2	5 (10%)
4	Health state 3	12 (24%)
3	Health state 4	7 (14%)
2	Health state 5	8 (16%)
1	Health state 6	1 (2%)
0	Health state 7	4 (8%)
Missing	NA	12 (24%)

*Scores measured on the Hamburg CLN2 disease rating scale (HML) scale, which is the combined Motor and Language domain scores of the Hamburg scale
ABBREVIATIONS: NA, not applicable. Source: 190-901 Supplemental Report 21st July[18]

It should be noted that the historical cohort includes patients born between 1965–2011. As improvements in diagnosis have been made during this time, the distribution of patients across health states is likely to differ significantly from what would be observed in the present day, with the expectation that there has been a trend towards earlier diagnosis. There is no evidence from Study 190-901 to suggest, however, despite the improvements in diagnosis, the rates of decline have not changed significantly over time, suggesting comparability of patients; rates of decline in Motor Language score are similar between patient groups that were defined by date of birth (5Table 5).

Table 5. [redacted]

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B7. **Priority Question:** Please provide two additional scenario analyses to the economic model:

a) The distribution of patients is the same as the trial population at base-line assessment
b) If data is available, the distribution of patients is the same as the trial population at diagnosis/onset of disease

The distribution of the Study 190-201 population at baseline is presented in Table .

Table 6. Distribution of Study 190-201 population at baseline*

Health state	Proportion of patients in Study 190-201 (N=23)
Health state 1	2 (9%)
Health state 2	2 (9%)
Health state 3	5 (22%)
Health state 4	11 (48%)
Health state 5	2 (9%)
Health state 6	1 (4%)
Health state 7	0
Health state 8	0
Health state 9	0

*Baseline defined as the last observation preceding the first 300 mg infusion

A diagnosis of CLN2 disease by TPP1 enzyme activity was determined at the point of study entry during an initial screening step. The distribution of the Study 190-201 population at screening is presented in Table .

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Table 7. Distribution of Study 190-201 population at screening

Health state	Proportion of patients in Study 190-201 (N=24)
Health state 1	2 (8%)
Health state 2	2 (8%)
Health state 3	7 (29%)
Health state 4	13 (54%)
Health state 5	0
Health state 6	0
Health state 7	0
Health state 8	0
Health state 9	0

The results of the scenario analyses in which the starting population was altered as requested are presented in Table .

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Table 8. Additional starting population scenario results

Treatment	Total costs (£)	Total LYs	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£ per QALYs)
Base case							
Cerliponase alfa	[redacted]	45.01	29.45	[redacted]	40.04	30.42	[redacted]
Standard care	£149,829	4.97	-0.97	N/A	N/A	N/A	N/A
Additional scenario a) – Starting population matches population in Study 190-201/202 at baseline							
Cerliponase alfa	[redacted]	43.14	17.32	[redacted]	38.77	18.74	[redacted]
Standard care	£143,430	4.37	-1.42	N/A	N/A	N/A	N/A
Additional scenario b) – Starting population matches population of Study 190-201/202 at screening							
Cerliponase alfa	[redacted]	44.17	18.62	[redacted]	39.72	20.01	[redacted]
Standard care	£145,201	4.44	-1.40	N/A	N/A	N/A	N/A

Abbreviations: ICER: incremental cost-effectiveness ratio; LY: life-years LYG: life-years gained; N/A: not applicable; QALYs: quality-adjusted life years

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Quality of life

B8. **Priority Question:** Please justify the difference in utility values between treatment arms. Please comment on the differences in the vignettes, the implied seizure control and improved control of dystonia and myoclonus. Please provide evidence to show that cerliponase alfa provides these clinical benefits.

In the absence of published literature, a utility study in which expert clinicians completed the EQ-5D-5L questionnaire was deemed the most reliable way to collect robust utility data for both the standard care and cerliponase alfa arms of the cost-effectiveness model.[19] The participants in the study were all experts from different countries in the treatment of patients with CLN2 disease and have experience with cerliponase alfa, and therefore their opinion is considered reliable and representative of current clinical opinion. It should also be noted that the vignettes were validated by an expert clinician and utility collection expert prior to completion of the questionnaire by participants, ensuring that the vignettes were representative of clinical reality and the study was conducted in a robust manner. The vignettes are further supported by the videos that were provided in Appendix 12 of the submission.

In support of the improvements in seizures and myoclonus suggested in the vignettes, please find below results of additional exploratory analyses. The first analysis investigated the change in the CLN2QL domain scores between baseline and Week 97 of Study 190-201/202. The results are presented in **Error! Reference source not found.** and [redacted], which is suggestive of a significant improvement in seizures.

Table 9. [redacted]

Table redacted – academic in confidence

*p-values <0.05 are considered significant and are highlighted in bold
CLN2QL Feeding G-Tube score not shown as there were insufficient data to conduct the rates of change analysis
ABBREVIATIONS: CI, Confidence Interval

Analysis of the cross-sectional Weill Cornell data collected in the Weill Cornell natural history study suggests a relationship between age and Weill Cornell total and myoclonus domain score, as seen in Table 10 and Figure 1.

Table 10. [redacted]

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Figure 1. [redacted]

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An analysis investigated the change in the myoclonus domain scores of the Weill Cornell scale between baseline and Week 97 of Study 190-201/202. The results are presented in Table 11 and show a small decrease in score of [redacted] This decline is significantly less than what is predicted from cross-sectional analysis of natural history data, which indicates a decline of [redacted]

Table 11. [redacted]

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Myocolonus domain is scored from 0 – 3; 3 – represents None of myoclonus, chorea/tremor/athetosis, and upgoing toes; 2 - One of myoclonus, chorea/tremor/athetosis, and upgoing toes; 1 - Three of myoclonus, chorea/tremor/athetosis, and upgoing toes; 0 - Myoclonus and chorea/tremor/athetosis, and upgoing toes

B9. **Priority Question:** When standard care patients move between health states 7 and 8, this results in an increase in HRQoL. Please justify this and comment why the same is not true for patients receiving cerliponase alfa.

These results were based on the values collected in the utility study. Expert opinion stated that they would expect health-related quality of life (HRQoL) to decrease from health state 7 to 8. The results for health state 8 (-0.326 ± 0.044) do fall within the error bars for health state 7 (-0.358 ± 0.038), as such we cannot definitively say HRQoL increases when moving from health state 7 to 8. In addition, given these values are within the lowest values possible on the EQ-5D-5L, it is possible the EQ-5D floor effects prevents the detection of differences between health states 7 and 8. Nevertheless the increase seen is not a large increase, and would not be expected to have a substantial impact on the results.

Patients in the cerliponase alfa arm will not be receiving cerliponase alfa treatment by the time they reach health states 7 and 8 in the base case, due to treatment discontinuation. When patients are not receiving cerliponase alfa treatment in the model, the utility values applied are from the standard care arm, so this difference is not relevant in the base case of the model

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B10. **Priority Question:** When in health state 1, patients are assumed to have near perfect health. How plausible do the company consider this assumption? Please make specific reference to the following in your response:

a) Patients do not have full seizure control;
b) Language deterioration was measured relative to best achieved rather than typical development for the age of child and therefore a number of the children with a score of 3 on the language domain are likely to have experienced some developmental delay; and
c) Currently, diagnosis of children usually requires them to be symptomatic of the disease.

Descriptive vignettes of the individual health states (including health state 1) were developed in cooperation with, and further validated by, clinical experts, before being subsequently used in the determination of health state-specific utility values via clinical expert opinion as part of the utility study detailed in Section 12.2.1 of the submission.[19]

As per the vignette for health state 1, patients in this state have their epilepsy well-managed through anti-epileptic treatment and experience on average one single generalised tonic-clonic seizure per year. This very low seizure frequency was judged not to have a noticeable effect on HRQoL. Furthermore, there is also no evidence pointing to an association between a delay in language development and a reduction in HRQoL for patients under 4 years of age.

It should be noted that the diagnosis of CLN2 disease does not require the patients to be symptomatic. Nonetheless, the poor clinical awareness of the disease in combination with first non-specific symptoms leads to a delay in diagnosis in current clinical practice with the majority of patients being diagnosed later in the disease course at which point they already will be in a health state lower than health state 1.

As described above, the utility values for health state 1 were obtained from an expert opinion-based utility study. These utility values were included in both the probabilistic and deterministic sensitivity analyses, and details of their results were provided in section 12.5 of the submission. An additional scenario analysis has been conducted where the utility value for health state 1 in both arms has been reduced by 10%. The results of this scenario analysis are provided in Table 5

Results from another scenario analysis, where a reduction in quality of life was incorporated to factor for patients' quality of life deteriorating over time, are shown in Table 5 too. The Kind et al (1999) paper was used to determine how utility values change over time.[20] The value for health state utility for the population under 25 was taken as the baseline value, and then proportional reductions in quality of life for the subsequent age groups were made in line with what was seen in the literature, and applied to health state utility in the model, according to the age of patients at that point in the model.

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Table 5. Additional health state 1 utility value scenario results

Treatment	Total costs (£)	Total LYs	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£ per QALYs)
Base Case							
Cerliponase alfa	[redacted]	45.01	29.45	[redacted]	40.04	30.42	[redacted]
Standard care	£149,829	4.97	-0.97	N/A	N/A	N/A	N/A
Additional Scenario – utility values for health state 1 reduced by 10%							
Cerliponase alfa	[redacted]	45.01	28.53	[redacted]	40.04	29.52	[redacted]
Standard care	£149,829	4.97	-0.99	N/A	N/A	N/A	N/A
Additional Scenario – utility values decrease over time in line with literature							
Cerliponase alfa	[redacted]	45.01	27.80	[redacted]	40.04	28.76	[redacted]
Standard care	£149,829	4.97	-0.97	N/A	N/A	N/A	N/A

Abbreviations: ICER: incremental cost-effectiveness ratio; LY: life-years LYG: life-years gained; N/A: not applicable; QALYs: quality-adjusted life years

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B11. The clinical advisor to the ERG suggested that children with CLN2 may have other behavioural and/or developmental disorders such as autism spectrum disorder or attention deficit hyperactivity disorder. Presently, due to the progressive nature of the disease, these developmental disorders go undiagnosed but this may not be the case if cerliponase alpha is able to alter the course of the disease. Please comment on this.

Clinical experts, opinion is that autism spectrum disorders would be diagnosed in CLN2 patients and indeed captured in the patients' medical history.
Autism spectrum is a term that has been inaccurately used to describe communication (language delay and difficulties), learning difficulties and behavioural problems that patients experience in the early and late stages of the disease. They account for some of the initial presenting symptoms reported by parents. In the latter stages of the disease, patients lose their ability to communicate effectively, and the disease manifestations also significantly limits patients' functionality. There is no evidence of patients presenting with attention deficit hyperactivity disorder, and given the impact of cerliponase alfa on language and motor abilities, it is likely that symptoms similar to those mentioned may reduce over time as the brain develops.

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B12. **Priority Question:** There are negative health states for both the cerliponase alpha and standard care in health states 7, 8 and 9. These imply quality of life that is worse than death and are rarely used in health economic evaluations. The ERG acknowledges that clinical experts verified that states worse than death are possible in this disease area. However, the values used in the model are quite low, particularly when compared with the values collected in the clinical trial and the actual (EQ-5D-5L) values collected from the clinicians in the vignette study.

a) Please justify the use of these negative health states in health states 7, 8 and 9. In your response please make reference to other degenerative diseases.

The utility study conducted provided negative values for these health states. These values were provided by clinical experts, and were also validated by experts following the study, who confirmed the results are realistic. In addition, negative utility values have been seen and used in the latter stages of diseases such as Dementia with Lewis Bodies (24% reported negative values), Stroke, multiple sclerosis and myasthenia gravis.[20-22, 46]

b) Please include an additional scenario analysis using EQ-5D-5L utility values.

In accordance with the NICE position statement, the EQ-5D-5L results were mapped to EQ-5D-3L for use in the base case of the cost-effectiveness model.[23] The unmapped EQ-5D-5L results are presented in the Utility study report, and also provided in Table 6 and

Table 7 below. The results of a scenario analysis using the unmapped utility values are shown in Table 8.

Table 6. Summary of results (no mapping to EQ-5D-3L) for vignettes of patients treated with cerliponase alfa

		Cerliponase alfa				
	CLN2 Motor Language Scale Score	Mean Value	Standard Error	Median Value	Minimum Value	Maximum Value
Health State 1	6	**0.990**	0.010	1.000	0.924	1.000
Health State 2	5	**0.850**	0.008	0.846	0.825	0.901
Health State 3	4	**0.745**	0.019	0.761	0.642	0.801
Health State 4	3	**0.502**	0.061	0.539	0.302	0.666
Health State 5	2	**0.425**	0.073	0.373	0.186	0.658
Health State 6	1	**0.338**	0.053	0.317	0.167	0.652
Health State 7	0	**0.129**	0.057	0.179	-0.213	0.282
Health State 8	0	**0.119**	0.065	0.186	-0.281	0.282
Health State 9	0	**0.104**	0.065	0.174	-0.281	0.268

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Table 7. Summary of results (no mapping to EQ-5D-3L) for vignettes of patients treated with standard care

		Cerliponase alfa				
	CLN2 Motor Language Scale Score	Mean Value	Standard Error	Median Value	Minimum Value	Maximum Value
Health State 1	6	**1.000**	0.000	1.000	1.000	1.000
Health State 2	5	**0.814**	0.032	0.846	0.608	0.901
Health State 3	4	**0.660**	0.036	0.665	0.447	0.801
Health State 4	3	**0.327**	0.069	0.367	-0.102	0.522
Health State 5	2	**0.174**	0.065	0.261	-0.137	0.329
Health State 6	1	**0.158**	0.053	0.228	-0.137	0.329
Health State 7	0	**-0.140**	0.049	-0.206	-0.276	0.073
Health State 8	0	**-0.082**	0.061	-0.120	-0.276	0.206
Health State 9	0	**-0.124**	0.066	-0.213	-0.281	0.191

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Table 8. Additional utility value scenario results

Treatment	Total costs (£)	Total LYs	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£ per QALYs)
Base Case							
Cerliponase alfa	[redacted]	45.01	29.45	[redacted]	40.04	30.42	[redacted]
Standard care	£149,829	4.97	-0.97	N/A	N/A	N/A	N/A
Additional Scenario – EQ-5D-5L values from utility study used in model							
Cerliponase alfa	[redacted]	45.01	32.59	[redacted]	40.04	32.79	[redacted]
Standard care	£149,829	4.97	-0.20	N/A	N/A	N/A	N/A

Abbreviations: ICER: incremental cost-effectiveness ratio; LY: life-years LYG: life-years gained; N/A: not applicable; QALYs: quality-adjusted life years

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B13. Were EQ VAS data collected as part of the vignette study? If so, please provide this data.

These data were not collected as part of the vignette study.

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Treatment effectiveness and transitions

B14. **Priority Question:** The explanations of how and what transition probabilities are used in the model are not clear and are lacking in transparency. Can the company please address the following concerns:

a) Please confirm that the transition probabilities defined in table D11 are only used for standard care patients in the base-case model?

Table D11 in the submission contains transition probabilities both for the standard care arm and for the cerliponase alfa arm, with the headings indicating which probabilities were used in which arm. The probabilities in table D11 are used throughout the model duration for the standard care arm and the 1st 16 weeks for the cerliponase alfa arm. For the cerliponase alfa arm, after 16 weeks in the model, a different set of transition probabilities is used (Tables D12 and D13), as further detailed in section 12.2.1. Table D11 is reproduced in Table 10.

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Table 9. Transition probabilities for health states (health states 1 to 7)

		Cerliponase alfa				Standard care			
		0–24 weeks	24-48 weeks	48-96 weeks	96 weeks onwards	0–24 weeks	24-48 weeks	48-96 weeks	96 weeks onwards
Health states 1 and 2	Improve	[redacted]	N/A	N/A	N/A	0.00	0.00	0.00	0.00
	Maintain	[redacted]	N/A	N/A	N/A	0.92	0.92	0.92	0.92
	Decline	[redacted]	N/A	N/A	N/A	0.09	0.09	0.09	0.09
Health states 3, 4, and 5	Improve	[redacted]	N/A	N/A	N/A	0.00	0.00	0.00	0.00
	Maintain	[redacted]	N/A	N/A	N/A	0.88	0.88	0.88	0.88
	Decline	[redacted]	N/A	N/A	N/A	0.12	0.12	0.12	0.12
Health state 6 and 7	Improve	[redacted]	N/A	N/A	N/A	0.00	0.00	0.00	0.00
	Maintain	[redacted]	N/A	N/A	N/A	0.97	0.97	0.97	0.97
	Decline	[redacted]	N/A	N/A	N/A	0.04	0.04	0.04	0.04

***For health state 7, the probability of losing vision, based on a mean of 52 weeks, is also applied, to obtain the probability of declining**

Abbreviations: N/A: not applicable

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b) On page 200 of the company submission it was noted that: "The data from study 190-201/202 suggested that scores fluctuated more in the initial stages of treatment, before stabilising, which is why the transition probabilities were split up across the time periods, in order to better reflect clinical reality." In the base-case analysis, however, the same transition probabilities are used for all of the trial period 0 to 96 weeks. Please explain this inconsistency.

As detailed in section 12.2.1, for the cerliponase alfa arm different transition probabilities are used for the first 16 weeks (Table D11) and the remaining trial period (Tables D12 and D13), in order to account for initial fluctuations in scores observed in study 190-201/202. In the case of the standard care arm, the same transition probabilities are used for all of the trial period (Table D11), since there was no evidence to suggest these initial fluctuations for the untreated patients.

c) It is not clear where the transition probabilities presented in Table D13 come from or how they were derived. This is crucial as these are the transition probabilities used in the base-case analysis. Please provide details on what the transition probabilities are and how they were derived.

As detailed in section 12.2.1, after 16 weeks in the model [redacted] of patients in the cerliponase alfa arm were classified as 'late stabilisers' and it was assumed, based on data from Study 190-201/202, that these patients would decline at a constant rate of 1 point per 80 weeks up to 96 weeks, after which they would remain in their current health state for the remainder of the time horizon. This figure of [redacted] is based on [redacted]. An exponential function was used to calculate the transition probabilities (Table D13) from this assumed rate of decline for this group of patients.

d) Minimal details are provided on how transition probabilities for patients in the standard care arm were derived other than they were based on data from the matched natural history cohort. Please provide further details of the company's approach to deriving these transition probabilities.

Please see the response to Question B15.

e) The efficacy data in Figure C8 suggests that 35% of patients experience a drop of 1 or more points on the CLN2 scale in the first 48 weeks. The base-case analysis, however, assumes that only [redacted] of patients can experience any kind of drop in their score in the first 48 weeks. Please comment on this inconsistency.

As detailed in section 12.2.1, all patients in the cerliponase alfa arm can experience one or multiple drops in their score prior to 16 weeks, based on the transition probabilities detailed in Table D11. Between 16 weeks and 96 weeks, [redacted] of patients (classified as 'early stabilisers') remain in their health state (Table D12), whereas [redacted] of patients (classified as 'late stabilisers') were able to experience further drops in their score, based on the transition probabilities in Table D13.
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f) Similarly, Table C22 suggests that 48% of patients experience a drop of 1 or more points on the CLN2 scale in the first 96 weeks. The base-case analysis, however, assumes that only [redacted] of patients can experience any kind of drop in their score in the first 96 weeks. Please comment on this inconsistency.

All patients in the cerliponase alfa arm can experience one or multiple drops in their score prior to 16 weeks, based on the transition probabilities detailed in Table D11. Between 16 weeks and 96 weeks, XXXXXXXXX of patients (classified as 'early stabilisers') remain in their health state (Table D12), whereas XXXXXXXXX of patients (classified as 'late stabilisers') were able to experience further drops in their score, based on the transition probabilities in Table D13. After 96 weeks, and for the remainder of the time horizon, all patients in the cerliponase alfa arm remain in their respective health states.

B15. **Priority Question:** There was little explanation of the methods applied to calculate the transitional probabilities used in the economic model. Please provide full details of the data used to calculate the transition probabilities used in the model and a detailed description of the approach taken to calculate them.

Transition probabilities for the first 16 weeks of the cerliponase alfa arm as well as the entire duration of the standard care arm were calculated from individual patient data (IPD) derived from Studies 190-201/202 and 190-901. For this, the following steps were undertaken:

- Observed values for the CLN2 clinical rating score for individual patients were aligned in 8-week intervals (including an extrapolation step for the patient-matched natural history data, which were collected in less regular intervals)
- For each 8-week interval, changes in the score were classified as either 'improve', 'maintain' or 'decline'
- All changes were summed up across all patients of the respective study and for the appropriate time period (the first 24 weeks for Study 190-201/202 and the entire trial period for Study 190-901)
- The number of instance for each type of change ('improve', 'maintain' or 'decline') for each health state was divided by the total number of observed changes for this health state to obtain a ratio, which equates to the 8-week transition probability for this specific change in this health state
- Instantaneous event rates were calculated from the 8-week transition probabilities (see attached spreadsheet for detailed formulae)
- Final 2-week transition probabilities were calculated from the instantaneous event rates (see attached spreadsheet for detailed formulae)
- The results for several health states were grouped in order to account for the scarcity of data in some instances: health states 1/2, health states 3/4/5, health states 6/7. Clinical experts validated this as acceptable, considering the scarcity of data

Please note, an Excel file detailing the initially collected IPD and calculated transition probabilities are provided in response to these clarification questions.[25]

B16. **Priority Question:** The company's base-case assumes that after 96 weeks all patients have stabilised disease. This assumption has significant impact on the total QALYs accrued. Please justify this assumption and where appropriate make reference to experience on other lipid storage diseases with ERTs.

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This assumption was validated with clinical experts, and was used as no decline was seen after 96 weeks in the trial. Additional scenario analyses are presented in response to B17.

Enzyme replacement therapy has previously shown long term benefits for Gaucher disease with the majority of patients experiencing stabilisation of disease, and the patients that didn't see stabilisation being the ones that had significant disease burden at the time of treatment initiation.

Figure 2.

[redacted]

Figure redacted. Academic in confidence

The rate of events has been shown to decrease over time in CLN2 patients treated with cerliponase alfa.

[redacted]

[redacted]

Ongoing monitoring of the cerliponase alfa treated patients will provide further insights into future changes in grey matter loss (as observed through MRIs).

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B17. **Priority Question:** Given the points raised in questions A10, A13, and B16 please present additional scenario analyses in which more conservative assumptions regarding the long-term effectiveness are assumed.

Results from a scenario with more conservative assumptions about long-term effectiveness are presented in Table 10. In this scenario, at 16 weeks, the point at which patients split into 'late stabilisers' and 'early stabilisers' in the base case, 5% of patients split into 'non-stabilisers'. These patients then progress at the same rate as the patients in the standard care arm. The proportion of patients splitting into 'late stabilisers' and 'early stabilisers' is adjusted accordingly. There are no data from the clinical trial to support the presence of these 'non-responders' so an assumption of 5% was made.

As a conservative estimate, the probability of mortality, based on ONS life tables, was doubled for the scenario in Table 10, at age 20 (the only reported case of cardiac abnormalities, was in a patient aged 23), and gradually increased to four times at age 40 and beyond.

In addition, a disutility factor due to deterioration in vision was included, from the age of 6 onwards. This factor increased up to 13% (health state utility values were thus multiplied by a factor of 0.87) by age 20 and remained at this level for the rest of the time horizon of the model. This value of 13% was based on literature on the quality of life associated with neovascular macular degeneration in the UK.[27]

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Table 10. Additional long-term effectiveness scenario results

Treatment	Total costs (£)	Total LYs	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£ per QALYs)
Base Case							
Cerliponase alfa	[redacted]	45.01	29.45	[redacted]	40.04	30.42	[redacted]
Standard care	£149,829	4.97	-0.97	N/A	N/A	N/A	N/A
Additional Scenario – 5% of patients in the cerliponase alfa arm do not stabilise, life table mortality doubled, quality of life decreases due to loss of vision over time							
Cerliponase alfa	[redacted]	38.44	22.43	[redacted]	33.47	23.40	[redacted]
Standard care	£149,829	4.97	-0.97	N/A	N/A	N/A	N/A

Abbreviations: ICER: incremental cost-effectiveness ratio; LY: life-years LYG: life-years gained; N/A: not applicable; QALYs: quality-adjusted life years

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B18. **Priority Question:** Please provide full details of how the proportion of early stabilisers at 16 weeks ([redacted]) was calculated. The EPAR reference provided by the company does not contain any information regarding response levels in patients. The values of [redacted] do not correspond to the clinical sections of the company's submission. Within the results of the relevant studies for Study 190-201 (p 105 of CS), the results state that the "CLN2 clinical rating scale score was stabilised in 65% (15 of 23) of patients, who had no change or an improvement in score from baseline". Please explain this inconsistency and confirm the correct figure.

The value of [redacted] for the proportion of stabilisers described in Section 9.6.1.3 of the submission refers to patients who experienced no change in the CLN2 clinical rating score over the first 48 weeks of treatment (i.e. the duration of Study 190-201). In contrast, the proportion of early stabilisers used in the economic model [redacted]) is based on an observation period spanning from week 16 to week 96, corresponding to the time frame this value is applied for in the model. The details of how this value was obtained can be found on page 45 of the Brineura European Public Assessment Report.[24] [redacted]

[redacted]

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B19. **Priority Question:** Please comment on Question 12 in the Delphi study report, where the clinical experts agreed that they would need patients to have the same CLN2 clinical rating scale score for 26 weeks to consider progression to have stabilised. This is inconsistent with the economic model where early stabilisers are identified at week 16.

Question 12 in the Delphi panel report was considered to be no longer applicable following changes to the model after the panel. The 16 weeks that was chosen in the model is due to patients achieving stabilisation as was observed in the clinical trial. This approach is therefore consistent with the observed data.

The results of an additional scenario, where this point of stabilisation identification is 26 weeks, are presented in Table 11.

Table 11. Additional scenario, stabilisation identified at 26 weeks

Treatment	Total costs (£)	Total LYs	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£ per QALYs)
Base Case							
Cerliponase alfa	[redacted]	45.01	29.45	[redacted]	40.04	30.42	[redacted]
Standard care	£149,829	4.97	-0.97	N/A	N/A	N/A	N/A
Additional Scenario – Patients split into 'early' and 'late' stabilisers at 26 weeks							
Cerliponase alfa	[redacted]	44.82	27.79	[redacted]	39.85	28.76	[redacted]
Standard care	£149,829	4.97	-0.97	N/A	N/A	N/A	N/A

Abbreviations: ICER: incremental cost-effectiveness ratio; LY: life-years LYG: life-years gained; N/A: not applicable; QALYs: quality-adjusted life years

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Resource Use

B20. **Priority Question:** The ERG notes that the dose of cerliponase alfa required does not increase after the age of two. Please provide some insight in how the dose of cerliponase alfa was determined and comment on whether the dose would be the same in adolescents/adults as in children.

The dose was determined based on the guidelines in the Summary of Product Characteristics.[26] Expert clinical opinion validated the use of this, as well as the use of the same dose for patients across the whole time horizon. The drug dose and vials required are shown in Table 12.

Table 12. Dosing information

Age	Dose (mg)	Vials required
0-6 months	100	0.666666667
6 months to 1 year	150	1
1 year to 2 years	284.61538	1.897435897
>2 years	300	2

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B21. **Priority Question:** The health state costs used in the model assume that the patients are children. For example, costs are assigned for community paediatrician, speech and language therapy, non-family caregivers and education support. For the majority of the model, patients receiving cerliponase alfa are not children and will have different support needs. Please comment on how support needs and resource use change as patients enter adolescence and adulthood. If appropriate, please present any scenario analyses around this.

Details of the adult equivalent health-state associated costs are provided in Table 13 and results of a scenario analysis in which these adult health-state costs were used are presented in Table 14. Clinical expert opinion advised that the intensity and frequency of resource use will likely be reduced as patients transition to adult care. The extent of change will be variable depending on their state of health at treatment initiation. Patients will also be transitioned to an adult metabolic physician and likely adult social care. However the adult service is not as well set up as the child service in most areas. Ongoing support they are likely to receive is for vision impairment.

Given the difficulties in predicting resource use as patients grow older, a conservative approach has been taken where the healthcare resource use costs have been assumed to be stable. In reality, these costs would most likely reduce particularly for health states 1,2 and 3 whereas in health states 4,5 and 6 resource use costs may be closer to those of paediatric patients.

Table 13. List of adult health state-associated costs (per unit)

Items	Cost per unit (e.g. appointment, bed day, caregiver) – 1st occurrence	Cost per unit (e.g. appointment, bed day, caregiver) – subsequent occurrences	Reference
Specialist clinician	£217.00	£161.00	NHS Ref Costs 2015-16 [Non-Admitted Face to Face Attendance, First, Neurology, consultant led (WF01B, 400)] and [Non-Admitted Face to Face Attendance, Follow-Up, Neurology, consultant led (WF01A, 400)]
Specialist nurse	£77.00	£77.00	NHS Ref Costs 2015-16 [Other Specialist Nursing, Adult, Face to face (N29AF)]
General practitioner	£36.00	£36.00	PSSRU 2016 [Per patient contact lasting 9.22 minutes (including carbon emissions (5

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			KgCO2e)2(carbon costs less than £1), with qualification costs]
Community paediatrician	NA	NA	NA
Speech/language therapist	£88.00	£88.00	NHS Ref Costs 2015-16 [Speech and Language Therapist, Adult, One to One (A13A1)]
Physiotherapist	£49.00	£49.00	NHS Ref Costs 2015-16 [Physiotherapist, Adult, One to One (A08A1)]
Family support worker	£32.00	£32.00	PSSRU 2016 [Family support worker, unit cost per hour]
Ophthalmologist	£110.00	£63.00	NHS Ref Costs 2015-16 [Non-Admitted Face to Face Attendance, First, Ophthalmology, consultant led (WF01B, 130)] and [Non-Admitted Face to Face Attendance, Follow-Up, Ophthalmology, non-consultant led (WF01A, 130)]
Health visitor	£53.00	£53.00	NHS Ref Costs 2015-16 [Health Visitor, Other Clinical Intervention (N03F)]
Occupational therapist	£79.00	£79.00	NHS Ref Costs 2015-16 [Occupational Therapist, Adult, One to One (A06A1)]
Caregiver costs	£25,551.00	£25,551.00	https://www.healthcareers.nhs.uk/about/careers-nhs/nhs-pay-and-benefits/agenda-change-pay-rates - adult nurse, Band 5, Point 20
Critical care bed days	£2,588.00	£2,588.00	NHS Ref Costs 2015-16 [XC01Z, Critical Care, Medical adult patients (unspecified specialty), Adult Critical Care, 6 or more Organs Supported]
Hospitalisation days	£1,682.00	£1,682.00	NHS Ref Costs 2015-16 [XC02Z, Critical Care, Medical adult patients (unspecified specialty), Adult Critical Care, 5 Organs Supported]

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Palliative care	£92.00	£92.00	NHS Ref Costs 2015-16 [Specialist Nursing, Palliative/Respite Care, Adult, Face to face (N21AF)]
Educational support	NA	NA	NA
Family caregiver productivity losses	£26,364.00	£26,364.00	Average total pay (including bonuses) for employees in Great Britain, ONS, March 2017

Abbreviations: NA, not applicable; NHS, National Health Service; ONS, Office of National Statistics; PSSRU, Personal Social Services Research Unit.

Table 14. Additional scenario, adult-equivalent health state costs used

Treatment	Total costs (£)	Total LYs	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£ per QALYs)
Base Case							
Cerliponase alfa	[redacted]	45.01	29.45	[redacted]	40.04	30.42	[redacted]
Standard care	£149,829	4.97	-0.97	N/A	N/A	N/A	N/A
Additional Scenario – Adult-equivalent health state costs used							
Cerliponase alfa	[redacted]	45.01	29.45	[redacted]	40.04	30.42	[redacted]
Standard care	£88,072	4.97	-0.97	N/A	N/A	N/A	N/A

Abbreviations: ICER: incremental cost-effectiveness ratio; LY: life-years LYG: life-years gained; N/A: not applicable; QALYs: quality-adjusted life years

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B22. Please confirm that in the 190-201/202 study patients received therapy in ICU which required an overnight stay.

In accordance with the 190-201/202 trial protocols, patients in the 190-201/202 study received therapy as an in-patient stay and were monitored over 24 hours. However, commercial patients and those on expanded access have been subsequently receiving cerliponase alfa as a day case. It is anticipated that this will be administered as a daycase moving forwards. As such, the model has assumed this when determining treatment costs in order to better reflect what will actually occur if cerliponase alfa were implemented as a treatment in the future.

B23. **Priority Question:** The states that patients spend on average one year in a palliation health before they die (page 201). This appears to contradict the costs for this health state, where it was assumed that patients received 36 visits per year for palliative care. Based on the health state vignettes, this implies that it is expected that children would require a ventilator to aid with respiration for one year.

a) Please provide further justification on this assumption and comment on whether patients would be ventilated for this duration of time in practice.
b) Please describe the costs and resource use associated with providing this service (respiration support and end of life care). For example, could the breathing apparatus be provided at home, or would patients receive care in a hospice? Please quantify (i.e. suggest the proportion of patients, units received) the type of care received in each setting, if possible.
c) It was noted that the amount of palliative care was same in Health State 8 and Health State 9 (Table D25), where patients were assumed to receive 36 units (visits) per year. It is understood that HS9 specifically captures patients receiving palliative care (page 198). Please provide justification why levels of palliative care did not differ between these two health states, and why patients did not receive 52 units of palliative care in HS9?

Clinical expert opinion stated that patients will be ventilated throughout this period using a combination of continuous positive airways pressure and/or bilevel positive airway pressure (BiPAP) at night. Clinical experts also believe that patients would have an aspirator with suction tubes to suck out the excess saliva given the difficulties in swallowing.

There are interventions to manage saliva secretions such as Scopoderm transdermal therapeutic system patches which all patients receive and a proportion of patients also have botulinum toxin injections. Clinical experts believed that all patients would receive care at home, with occasional respite stay in a hospice.

The resource use levels between health state 8 and 9 were assumed to be the same, unless informed otherwise by the palliative care expert. This is because no information on health state 9 was collected in the Delphi panel, which informed the resource use levels in the model.

B24. **Priority Question:** Caregivers are required to support CLN2 patients, and care was assumed to be provided by a combination of both family and non-family caregivers (page

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194). For each stage of the disease, please comment on how care is provided by non-family caregivers, i.e. the healthcare professional involved, the frequency of visits to the home, duration of visit, and the activities undertaken.

Non-family caregiver costs were based on the salary of NHS-funded community nurses and added to the individual health states as detailed in Table D8 of the submission. The number of non-family caregivers applied in the model was based on the Delphi panel conducted to inform model inputs. The type of care provided by caregivers depends on the area that patients live in, and the availability of formal care in the area are variable across UK. Nevertheless information on the type of care for each stage of the disease is provided in Table 22. This was obtained from the BDFA based on their experience supporting families and does not capture the variations in provision across the country which is difficult to capture. .

Table 22: Details of care received by patients per health state.

Health State	Description	Type of formal caregiver	Frequency of visit	Duration of visit	Activities undertaken
1	ML Score 6	None Formal Parent only	N/A	N/A	N/A
2	ML Score 5	None Formal Parent only	N/A	N/A	N/A
3	ML Score 4	Direct Payment Worker or Agency Staff	3 per week	1 hour	Depends on discussion with family as to what family would like support with e.g. support whilst getting siblings ready for school.
4	ML Score 3	Direct Payment Worker or Agency Staff	5 per week	1 hour or combine visits	Depends on discussion with family as to what family would like support with e.g. support

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					whilst getting siblings ready for school.
5	ML Score 2	Direct Payment Worker or Agency Staff	10 per week	1 hour visits of combine for an overnight	Support before or after school or 1 overnight per week
6	ML Score 1	Direct Payment Worker or Agency Staff & Nurses or HCA's	Daily during week possibly once at weekend	A few hours visits or combine hours for overnights – 56 hours a week – 3 overnights and 20 hours of day support	Support before & after school or at weekends or for overnights
7	ML Score 0	Direct Payment Worker or Agency Staff & Nurses or HCA's	Daily during week possibly once over weekend	A few hours visits or combine hours for overnights – 80 hours a week – 5 overnights and 20 hours of day support	Support before & after school or at weekends or for overnights
8	Ml Score 0 + Vision Impairment (i.e. legally blind)	Direct Payment Worker or Agency Staff and Nurses or HCA's	Daily during week possibly once over weekend	A few hours visits or combine hours for overnights – 97 hours a week – 6 overnights and 25 hours of day support	Support before & after school or at weekends or for overnights

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9	MI Score 0 + Vision Impairment + Palliative Care	Direct Payment Worker or Agency Staff & Nurses or HCA's	Daily	A few hours visits or combine hours for overnights – 109 hours a week – 5 overnights and 30 hours of day support	Support before & after school or at weekends or for overnights

These are highly dependent on geographical location and what is provided by each local authority. Ideally, children from an ML score of 3 should receive 7 overnight care per week but that rarely happens. Children will also potentially access respite from local childrens' hospice provision from ML 4 onwards.

Care might include:

- Getting ready for school in the mornings for affected child or support with siblings
- One-to-one support at school
- Shopping trips, social or cultural events, leisure and sport
- Help with personal care, meals and feeding
- Attending medical appointments
- Doing activities at home
- Getting ready for bed and perhaps a bedtime story
- Supporting the family to establish daily routines

B25. **Priority Question:** Please comment on some additional resources that were not included in the model.

a) The resource use study identified by the company stated that psychological support for the family is essential (page 219). What consideration was given to these costs for use in the model? Please provide any information on whether any support was provided to families who participated in the trials, and what kind of support is available in the UK. Please provide details on the potential providers of this support, the proportion of families who accessed this support, and when was this support accessed (e.g. during more severe health states, at diagnosis etc.).
b) Cerliponase alfa is required to be administered using a strict aseptic technique (page 294), and the SPC states that this should be by a trained healthcare professional

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(HCP). Please describe the costs associated with this training. Please consider, the frequency of training, whether retraining is required, and who provides this training.

c) Are there any additional monitoring requirements for cerliponase alfa patients e.g. ECG and routine testing of cerebrospinal fluid (CSF) samples (as suggested in the SPC), liver function tests etc.

Psychological support was not included as a cost in the model – clinical experts confirmed that patients and families would usually receive this support through their lysosomal storage disease centre. In the clinical trial, support was provided for patients by the Batten Disease Family Association.

A clinical expert confirmed that no additional training will be required for health professionals, as these health professionals involved in the treatment of CLN2 disease with cerliponase alfa will already be experience in the delivery of other treatments requiring aseptic techniques.

Section 4.4. of the summary of product characteristics provides information on additional monitoring requirements.[26] Specifically, the recommendations are that:

- Vital signs should be monitored before infusion starts, periodically during infusion, and post-infusion in a healthcare setting. Upon completion of the infusion, the patient status should be clinically assessed and observation may be necessary for longer periods if clinically indicated, particularly in patients less than 3 years.
- Electrocardiogram (ECG) monitoring during infusion should be performed in patients with a history of bradycardia, conduction disorder, or with structural heart disease, as some patients with CLN2 disease may develop conduction disorders or heart disease. In cardiac normal patients, regular 12-lead ECG evaluations should be performed every 6 months.
- CSF samples should routinely be sent for testing to detect subclinical device infections.

The costs associated with these requirements are relatively minor

B26. It was assumed in the model that the ICV delivery device may only be replaced if an infection occurs (page 187). The infection rate in the model is low, and it may be that patients have the same delivery device for many years before it needs replacing. It seems reasonable to assume that it would need replacing as patients get older, and that the device and insertion area may need maintaining (such as, cleaning). The company submission states that there is no data available relating to the regularity of replacement of the ICV delivery device in CLN2 patients: are there any other treatments administered in a similar fashion with data that could be used to comment on how this may occur for cerliponase alfa patients.

A recent review by Cohen-Pfeffer et al. analysed the long-term application of ICV delivery across a variety of indications in a total of 5,815 patients (aged one day to 84 years).[27] As a result of this review, it was concluded that the included studies support the long-term use of ICV devices and the possibility of these devices remaining in place indefinitely, with one

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study (in patients aged three months to 21 years) reporting a median duration per device of 1,336 days, with maximum duration of continuous device placement of approximately 19 years.[28] Consequently, the possibility of the same ICV device staying in place for many years was deemed feasible, validating the assumptions made in the model regarding the complication-based replacement rate.

In addition, it is anticipated that the earliest patients will require catheter replacement due to brain growth in children is a period of 4-5 years.

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B27. **Priority Question:** The ERG has some concerns regarding the components of care included in the health state costs. Specifically, the ERG notes the following:

a) Patients are assumed to continue to receive speech and language therapy and physiotherapy in Health States 7, 8 and 9. This is despite the fact the patient now has no speech or language function.
b) In Health State 8 and 9, costs relating to visits to an ophthalmologist are included even though it is assumed that the patient has complete loss of vision at this stage of the disease.
c) In Health State 7 and 8, it is assumed patients receive palliative care. This seems inconsistent with health state 9 which is defined specifically with respect to the fact that patients are receiving end of life care.
d) Children with no motor or language function and receiving of end life care (Health State 9) continue to receive educational support. The ERG does not consider this to be plausible.

Please comment on the above concerns and provide justification for the inclusion of these costs.

There is an ongoing need for speech therapy support for patients in health states 7, 8 and 9 in particular to assist with swallowing. In addition, these support services provide valuable patient assessments, education and motivation for the families to deal with ongoing requirements.

The resource use inputs were provided and validated by clinical experts. Due to questions about health state 9 not being asked in the Delphi panel, an assumption was made that resource use levels for health state 9 would match health state 8, except for where further information was available. It is possible that by applying this assumption, some of the inputs for resource use were inconsistent with the definitions of the health states.

We were informed by the palliative care expert that patients would still receive some palliative care before reaching the final stages of the disease, which is what is represented by health state 9. An additional scenario was programmed in the model where the health state costs over which concern was raised above have been removed from the model. Results from this additional scenario are provided in Table 15. As can be seen, this change does not lead to a substantial difference to the results.

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Table 15. Additional scenario, inconsistencies noted by ERG in health state costs adjusted

Treatment	Total costs (£)	Total LYs	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£ per QALYs)
Base Case							
Cerliponase alfa	[redacted]	45.01	29.45	[redacted]	40.04	30.42	[redacted]
Standard care	£149,829	4.97	-0.97	N/A	N/A	N/A	N/A
Additional Scenario – Inconsistencies noted by ERG in health state costs adjusted							
Cerliponase alfa	[redacted]	45.01	29.45	[redacted]	40.04	30.42	[redacted]
Standard care	£145,942	4.97	-0.97	N/A	N/A	N/A	N/A

Abbreviations: ICER: incremental cost-effectiveness ratio; LY: life-years LYG: life-years gained; N/A: not applicable; QALYs: quality-adjusted life years

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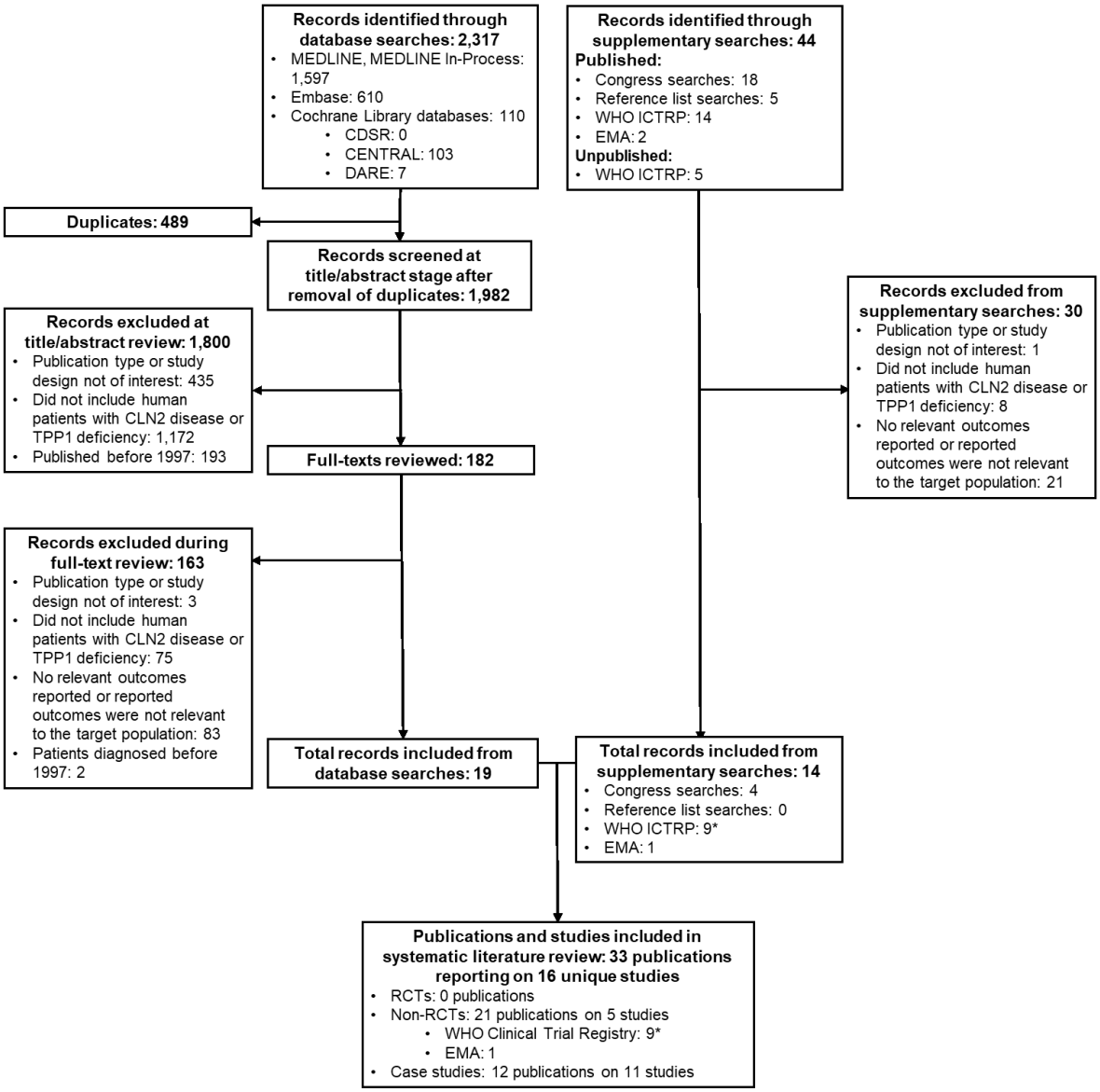
Section C: Textual clarifications and additional points

C1. The numbers reported in the records identified through database searches box of the PRISMA flow diagram (Figure C6, page 72) do not match the search results reported in the search strategies contained in Appendix 2 (Table 1 MEDLINE, Table 2 EMBASE, and Table 3 Cochrane). For example, in the PRISMA diagram 1686 records are reported as being retrieved from MEDLINE, however in Table 1 at line 91, 1597 records are reported as retrieved from MEDLINE. Please clarify this discrepancy for MEDLINE, EMBASE and the Cochrane Library.

The numbers of identified records in Figure C6 were mistakenly based on preliminary searches. The correct information from the final searches is given in Appendix 2 and a revised version of Figure C6 provided below.

Figure C6. PRISMA flow diagram of clinical SLR [Corrected]



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*The nine studies included from WHO ICTRP provided supplementary data to three non-RCT publications.

ABBREVIATIONS: CLN2: neuronal ceroid lipofuscinosis type 2; RCT: randomised controlled trial; TPP1: tripeptidyl-peptidase 1; WHO ICTRP: World Health Organization International Clinical Trials Registry Platform.

C2. Please could the source of the search filters used to limit retrieval to RCTs and non-RCTs for the clinical evidence searches of MEDLINE and EMBASE be provided? (Appendix 2, Tables 1 & 2)

The search strategies for RCTs and non-RCTs were based on filters developed by the Scottish Intercollegiate Guidelines Network (SIGN), the “randomised controlled trials” and “observational studies” filters respectively, including minor in-house additions to improve sensitivity.[29]

C3. Please could the source of the search filters used to limit retrieval to economic studies and quality of life studies for the economic evidence searches of MEDLINE and EMBASE be provided? (Appendix 8, Tables 24 & 25)

Search terms for the retrieval of economic evidence were based on the “economic studies” filter provided by SIGN and the additional terms for quality of life studies were aligned with recommendations developed by the School of Health and Related Research (ScHARR) at the University of Sheffield and the York Health Economics Consortium (YHEC).[29-31]

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References

1. Whiting REH, *et al.* Enzyme replacement therapy delays pupillary light reflex deficits in a canine model of late infantile neuronal ceroid lipofuscinosis. Experimental Eye Research 2014;125:164-172.

2. Katz ML, *et al.* Enzyme replacement therapy attenuates disease progression in a canine model of late-infantile neuronal ceroid lipofuscinosis (CLN2 disease). Journal of Neuroscience Research 2014;92:1591-1598.

3. Williams RE, *et al.* Management Strategies for CLN2 Disease. Pediatric Neurology 2017;69:102-112.

4. Fukumura S, *et al.* Progressive conduction defects and cardiac death in late infantile neuronal ceroid lipofuscinosis. Developmental Medicine and Child Neurology 2011;54:663-666.

5. Katz ML, *et al.* Extraneuronal pathology in a canine model of CLN2 neuronal ceroid lipofuscinosis after intracerebroventricular gene therapy that delays neurological disease progression. Gene Therapy 2017;24:215-223.

6. BioMarin. Cerliponase Alfa Economic Model Workshop Report. Data on File. 2016.

7. BioMarin. CLN2 Disease Model Finalisation Meeting - Minutes. Data on File. 2017.

8. BioMarin. Supplementary Information Report. 2017.

9. BioMarin. Delphi Workshop Report - UK Treatment Practices for the Management of CLN2 Disease. Data on File. 2017.

10. Biomarin. Response to request for information by the FDA. Data on File. 2016.

11. Rare Disease UK. 2010. Experience of Rare Diseases: An Insight from Patients and Families Last accessed 02.11.17. Available at http://www.rarediseasе.org.uk/media/1594/rduk-family-report.pdf.

12. Eurodis. 2009. The Voice of 12,000 Patients. Last accessed 02.11.17. Available at https://www.eurordis.org/IMG/pdf/voice_12000_patients/EURORDISCARE_FULLBOOKr.pdf.

13. Schulz A, *et al.* Neuronal ceroid lipofuscinosis-2 (CLN2) natural history and path to diagnosis: International experts' current experience and recommendations on CLN2 disease, a type of Batten disease, resulting from TPP1 enzyme deficiency. European Journal of Paediatric Neurology;19:S119.

14. Nickel M JD, Lezius S, et al. Natural history of CLN2 disease: Quantitative assessment of disease characteristics and rate of progression. 12th Annual WORLD Symposium. San Diego, CA, USA, 2016.

15. D. Kumar Pal ea. Poster presentation 32nd IEC, 2-6 Sept 2017.

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16. Trump N, *et al.* Improving diagnosis and broadening the phenotypes in early-onset seizure and severe developmental delay disorders through gene panel analysis. J Med Genet 2016;53:310-7.

17. Moller RS, *et al.* Gene Panel Testing in Epileptic Encephalopathies and Familial Epilepsies. Mol Syndromol 2016;7:210-219.

18. BioMarin. Study 190-901 - Supplemental Report. Data on File, 2017.

19. BioMarin. CLN2 Disease Utility Study Report. Data on File, 2017.

20. Bostrom, Fredrik and Jonsson, Linus and Minthon, Lennart and Londos, Elisabet. "Patients with dementia with lewy bodies have more impaired quality of life than patients with Alzheimer disease" Alzheimer Dis Assoc Disord, 2007, Vol: 21, Issue: 2, pp. 150-154.

21. Orme M, *et al.* The effect of disease, functional status, and relapses on the utility of people with multiple sclerosis in the UK. Value Health 2007;10:54-60.

22. Peres J, *et al.* Rituximab in generalized myasthenia gravis: Clinical, quality of life and cost–utility analysis. Porto Biomedical Journal 2017;2:81-85.

23. NICE. 2017. NICE position statement on the EQ-5D-5L. Last accessed 03.11.17. Available at https://euroqol.org/nice-position-statement-on-the-eq-5d-5l/.

24. European Medicines Agency. Brineura - European Public Assessment Report, 2017.

25. BioMarin. IPD and Transition Probabilities Calculations. Data on File.

26. European Medicines Agency. Brineura - Summary of Product Characteristics, 2017.

27. Cohen-Pfeffer JL, *et al.* Intracerebroventricular Delivery as a Safe, Long-Term Route of Drug Administration. Pediatr Neurol 2017;67:23-35.

28. Peyrl A, *et al.* Safety of Ommaya reservoirs in children with brain tumors: a 20-year experience with 5472 intraventricular drug administrations in 98 patients. J Neurooncol 2014;120:139-45.

29. Scottish Intercollegiate Guidelines Network. Search Filters. Last accessed 30th Oct 2017. Available at http://www.sign.ac.uk/search-filters.html.

30. Arber M, *et al.* PERFORMANCE OF OVID MEDLINE SEARCH FILTERS TO IDENTIFY HEALTH STATE UTILITY STUDIES. Int J Technol Assess Health Care 2017:1-9.

31. Papaioannou D, *et al.* Systematic searching and selection of health state utility values from the literature. Value Health 2013;16:686-95.

32. BioMarin Integrated Summary of Effectiveness Statistical Analytical Plan

33 BioMarin Study 190-201 Patient Listings - Individual Demographics and baseline characteristics

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34 A Clinician-Reported Outcome Evidence Dossier - The 0-6 Hamburg Scale (HML and ML) in Patients with Neuronal Ceroid Lipofuscinosis Type 2 (CLN2)

35. Study 190-201 CLN2 Assessors (by Site, Subject and Timepoint)

36. Study 190-202 CLN2 Assessors (by Site, Subject and Timepoint)

37. Study 190-203 Interim Clinical Study Report

38. Study 190-202 Interim Clinical Study Report

39. Orlin A, Sondhi D, Witmer MT, et al. Spectrum of Ocular Manifestations in CLN2-Associated Batten (Jansky-Bielschowsky) Disease Correlate with Advancing Age and Deteriorating Neurological Function. Claudepierre T, ed. PLoS ONE. 2013;8(8):e73128. doi:10.1371/journal.pone.0073128.

40. R. Steinfeld, P. Heim, H. von Gregory, et al. Late infantile neuronal ceroid lipofuscinosis: quantitative description of the clinical course in patients with CLN2 mutations. Am J Med Genet, 112 (2002), pp. 347-354

41. BioMarin Integrated Summary of Effectiveness , 1:1 Matching Outputs - Tables

42. BioMarin Integrated Summary of Effectiveness , 1:Many Matching Outputs - Tables

43. Di Giacopo, R et al. Protracted late infantile ceroid lipofuscinosis due to TPP1 mutations: Clinical, molecular and biochemical characterization in three sibs. Journal of the Neurological Sciences. Volume 356, Issues 1–2, 15 September 2015, Pages 65-71

44. BioMarin Study 190-202 Patient Listings - Individual Safety Reults

45. BioMarin Integrated Summary of Effectiveness ,Kaplan-Meier Analysis (week 96 results) 46. Ward Fuller G, Hernandez M, Pallot D, Lecky F, Stevenson M, Gabbe B. Health State Preference Weights for the Glasgow Outcome Scale Following Traumatic Brain Injury: A Systematic Review and Mapping Study. Value in Health. 2017;20(1):141-151. doi:10.1016/j.jval.2016.09.2398.

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B6. **Priority Question:** Please provide summary data from the historical cohort giving the distribution of patients across the health states at diagnosis/onset.

Additional clarification request: In question B6 the ERG requested a number of additional analyses considering alternative starting population including one using data form the historical control population at diagnosis. In the your response to the clarification letter you note that this was unrepresentative of the current incident population due to the age of the cohort – some patients were recruited as far back as the 60's. To provide a more realistic portrait of the incident population the ERG request the company provide information on the starting population from the historical control data as per question B6, but restricted to patients born after the year 2000 – the first genetic test for CLN2 was developed in 1999.

The requested data are available for the 69 CLN2 patients in the DEM-CHILD database as of August 2016 (of which 49 patients were ultimately included in the evaluable population for Study 190-901). [redacted] patients were born in or after the year 2000 and the mean age at diagnosis of these patients was [redacted] months. The distribution of these patients across the Hamburg CLN2 disease rating scale score at (or prior) to diagnosis is presented in Table 1.

Table 1. Distribution of patients (born in 2000 or later) from the DEM-CHILD database across health states at (or prior) to diagnosis

Score at (or prior to) diagnosis*	Health state	Proportion of patients (n=38)
6	Health state 1	[redacted]
5	Health state 2	[redacted]
4	Health state 3	[redacted]
3	Health state 4	[redacted]
2	Health state 5	[redacted]
1	Health state 6	[redacted]
0	Health state 7	[redacted]
Missing	NA	[redacted]

*Scores measured on the Hamburg CLN2 disease rating scale (HML) scale, which is the combined Motor and Language domain scores of the Hamburg scale
ABBREVIATIONS: NA, not applicable. Source: 190-901 Supplemental Report 21st July

As noted in the original response to Question B6, it is anticipated that there has been a trend towards earlier diagnosis over time, and as such the distribution of patients across health states is likely to be different in the present day.

Appendix D – Patient statement template

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Cerliponase alfa for treating neuronal ceroid lipofuscinosis type 2 [ID943]

Patient statement contents

1. BDFA Statement
2. BDFA Annual Report 2015-2016
3. BDFA CLN2 (Late Infantile Batten disease) leaflet
4. CLN2 Family Case Study 1 of a child not on treatment
5. CLN2 Family Case Study 2 of a child on treatment
6. CLN2 Family Case Study 3 of a family with two children affected children
7. CLN2 Family Case Study 4 of compassionate use
8. BDFA Leaflets
    a. Education Issues specific to NCL
    b. Education, Health and Care Assessments
    c. Equipment
    d. on the Ketogenic Diet
    e. Behaviour Frustration and Anxiety
    f. Education
    g. NCL Disease and visual impairment
    h. Personal Budgets
    i. Physiotherapy and Hydrotherapy
    j. School placements
    k. Siblings
    l. Social Services
    m. Speech and Language Therapy
    n. Support from School
    o. Constipation
    p. Drooling or Hypersalivation
    q. Epilepsy
    r. Movements disorders in Batten disease
    s. Nutrition and gastrointestinal symptoms
    t. PEG Feeding
    u. Sleep for those with Batten disease

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About you

Your name: [redacted]

Name of your organisation: Batten Disease Family Association (BDFA)

Brief description of the organisation:
(*For example: who funds the organisation? How many members does the organisation have? What proportion of the total English patient population does this represent?)*

The Batten Disease Family Association (BDFA) is a UK charity which aims to support families, raise awareness and directly fund research into the group of devastating neurodegenerative diseases commonly known as Batten disease. We are based in Hampshire but work with children, young people, families and professionals across the UK. There are currently 14 different forms of Batten disease and the BDFA represents patients and families with all forms in the UK.

Formed in 1998 with the help of SeeAbility and Contact-a-Family, by a small group of parents of children with Batten disease . We were granted Registered Charity status in 2001 and the work of the charity has continued to go from strength to strength.

The charity is funded predominantly by supporter fundraising, a small proportion from grants and foundations, and specific project grants from pharmaceutical companies. Details of funding, structures and work can be found in the attached latest BDFA Annual Report 2015-2016. This annual report is also available on the Charity Commission Website. More details of the organisation and our work can also be found at www.bdfa-uk.org.uk.

The BDFA response to this consultation is based on almost 20 years experience of working with and supporting families living with a diagnosis of CLN2 (Late Infantile Batten disease)

We currently work with 32 CLN2 families in England (with living children) which we believe to represent approximately 90% of the English CLN2 population.

Are you (tick all that apply):

- a patient with the condition for which NICE is considering this technology?
- a carer of a patient with the condition for which NICE is considering this technology?
- **an employee of a patient organisation that represents patients with the condition for which NICE is considering the technology? If so, give your position in the organisation where appropriate (e.g. policy officer, trustee, member, etc)**
- other? (please specify)

Appendix D – Patient statement template

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Links with, or funding from the tobacco industry - please declare any direct or indirect links to, and receipt of funding from the tobacco industry: ***None***

How does the condition impact on patients, their families or carers?

1(i). Please describe whether patients experience difficulties or delays in receiving:
- a diagnosis
- appropriate treatment
- helpful information about the condition

and the impact these difficulties have on patients and their families or carers.

- **Diagnosis**

Based on feedback and our experience of working with families, diagnosis for children with CLN2 (Late Infantile Batten disease) can take, because of the rarity of the condition and lack of specialised service, 2 years from first onset of symptoms. In real terms for families this means that children can already have experienced significant deterioration before a diagnosis is received.

The age at which the disease is currently diagnosed in England may mean that some families have younger siblings who are also affected but not showing symptoms. They may also have children who are unaffected carriers or children who are unaffected by any aspect of the disease. There are a number of families in England with more than one affected child.

Prior to diagnosis children will have usually been seen by a paediatrician initially and then a paediatric neurologist because of seizures. Diagnosis is done by enzyme tests and follow up genetic testing.

Receiving a diagnosis is not simply about providing a label for a condition. It allows families to access appropriate ongoing information and care, plan for their child or children's needs and to make informed reproductive choices about future pregnancies.

Critically, in the case of Cerliponase Alpha, early diagnosis enables an early treatment intervention to maintain skills and quality of life for longer. It is critical to develop a mechanism within the NHS to deliver an earlier diagnosis for these families, specifically around the early manifestation of symptoms such as language/motor delay and seizures.

A delayed and protracted diagnostic process means families face what they have described as a "traumatic diagnostic odyssey" of uncertainty, anxiety and an inability to make these choices.

- **Appropriate Treatment**

Currently there is no cure for CLN2 disease. Cerliponase Alpha is the first available treatment. Current standard of care centres on appropriate and effective symptom management to maintain a good quality of life for children and their families. Holistic support for parents, siblings and wider family members is also vital to build resilient family networks to enable them to better manage the devastating impact of this disease.

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Families tell us that the lack of access to specialist care resulting from the failure to include Batten disease in the specification for the LSD centres, has resulted in inequitable access to treatment and timely information. In a rare condition it is vital that families have confidence and trust in clinicians who they believe to be knowledgeable about the condition and the care of their children.

- **Appropriate information**

A lack of timely diagnosis prevents families from accessing appropriate support and information from a range of sources and risks further isolating families. It also impacts negatively on their ongoing ability to manage the progression of the disease and quality of life for their families.

Children with CLN2 disease are not routinely seen at LSD centres and do not always receive information about the BDFA and the support they can receive from other organisations and agencies. Families tell us that they are still receiving information by trawling the internet where information is often inappropriate and incorrect.

Relationship with current and future LSD centres for treatment

Currently Batten disease is excluded under the NHS specification for the LSD centres. Families tell us that this has a detrimental effect on their ability to access specific expertise which they value and trust. When they receive the devastating diagnosis of CLN2 disease they want to know that their referral is to a professional who is knowledgeable and experienced in care of the disease. This is the case not just for clinicians but also associated health, social care and education professionals.

Until the development of Cerliponase Alpha most children were cared for by their local teams who would then consult with a Batten specialist at the Evelina Childrens' Hospital London or Great Ormond Street Children's Hospital. Because of Cerliponase Alpha this landscape is now changing and is welcomed by families and the BDFA. It is critical that children are seen at LSD Centres to meet their needs and those of their families and to further develop the pool of professional and research expertise in this disease.

Families tell us that they want to be seen by a specialist centre, where they have expertise in the management of care and also where the need for long journeys with vulnerable and medically fragile children are reduced.

The BDFA is a member of the LSD Patient Collaborative which meets with all of the LSD centres on a yearly basis to review the services provided and to promote an ongoing dialogue.

(ii) Please describe how patients and their families or carers have to adapt their lives as a result of the condition, and the impact the condition has on the following aspects:
- physical health
- emotional wellbeing

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- everyday life (including if applicable: ability to work, schooling, relationships, social functioning)
- other impacts not listed above (any impact the condition has had on carers and family members, specifically the ability to work and requirements to update the family home)

- **Physical Health (Please see attached BDFA CLN2 Leaflet)**

Children with CLN2 disease are born seemingly healthy and develop normally for the first few years of life.

Towards the end of the second year, developmental progress may start to slow down and some children are slow to talk. The first definite sign of the disease is usually epilepsy. Seizures may be drops, vacant spells or motor seizures with violent jerking of the limbs and loss of consciousness. Seizures may be controlled by medicines for several months but always recur, becoming difficult to control. Children tend to become unsteady on their feet with frequent falls and skills such as walking, playing and speech are lost. Children become less able, and increasingly dependent. The disease then shows a rapid progression of physical and mental decline.

By 4-5 years the children usually have myoclonic jerks of their limbs and head nods. They may have difficulties sleeping and become distressed around this time, often for no obvious reason. Vision is gradually lost.

The rapid progression of the disease means that by the age of 6 years, most will be completely dependent on families and carers for all of their daily needs. They will lose their ability to swallow and need a feeding tube and their arms and legs may become stiff. Some children get frequent chest infections. They will also experience progressive dementia. Death usually occurs between the ages of 6 and 12 years dependent on the levels and standard of care received.

1. Complete control of seizures is not always possible with anticonvulsants being necessary from early in the disease process.
2. Myclonic jerks are common interfering with sleep and adding distress to both children and families.
3. Multiple medications are required to manage this symptoms placing significant stress on families to monitor and administer these medications.
4. Support is needed for progressive difficulties with swallowing, constipation, hydration, respiratory function, oral secretions, sleep disturbance and visual impairment. Also posture, seating, skin and mouth care.
5. Children will be required to be fitted with a gastrostomy.
6. A multi-disciplinary professional team are involved in the care of these children and this also places significant burden on the family to manage.
7. Families tell us frequently that whilst they accept that their childrens' needs are very complex there are times when they just want to be their "mum" or a "dad" and not their doctor or nurse.

The physical health of parents and carers is also impacted by this disease. For example, as children become more immobile during the course of the disease parents need to move and

carry increasingly heavier children resulting in back problems. The vast majority of parents report sleep deprivation even when respite and overnight care is provided.

- **Emotional Well-Being**

Parents start grieving when they are given the life-limiting diagnosis for their child. They grieve for the life they had hoped for and will never see long before their child passes away and in the case of families with a CLN2 diagnosis, until now there has been no hope. The introduction of a treatment which will stabilise the condition and slow down the rate of progression will have a positive impact on the emotional well-being of parents. Enabling them to have time to make choices about their family life, to manage the impact on siblings, to reduce strain on family relationships, and to build strong resilient coping strategies. All of these things are challenging currently because of the rapidity of the progression of this disease and the lack of responsiveness of service provision which can leave parents and carers reeling and unable to cope emotionally.

- **Everyday Life**
-

In a report published commissioned by the BDFA (2008) CLN2 disease was found to have a major impact on all aspects of family life.

1. The impact of the challenges of care and life on daily routine. A daily routine which involves administering medication, feeding, positioning , changing, suctioning and maintaining airways, hydration and stimulation creates pressures on families.
2. Families face daily challenges of navigating systems to access equipment, housing adaptions, school placement, care and services for their affected child. They attend multiple meetings and fill out numerous forms placing additional time and emotional burdens. E.g filling out Disability Living Allowance Forms for 1 and sometimes 2 children emphasises for parents and carers the skills that their children have lost and will continue to lose.
3. Living with the impact of this disease creates difficulties and challenges with scheduling for families leisure activities and holidays, depriving them of down time and the ability to make precious memories.
4. Sleep deprivation is reported by the vast majority of parents and carers, even when support and respite is provided by other care providers.
5. This disease places significant pressure on relationships between parents and many families experience relationship breakdown adding additional emotional and financial pressures.
6. Parents and carers report having to give up work to care for their children and suffering financial hardship as a result. Having to give up work can also have a negative impact on emotional well-being as parents also report work as a respite from the pressures of caring.
7. As a rare disease, accessing peer support is challenging for parents and carers. A key role of the BDFA is to connect families with each other to reduce isolation and enable them to provide support to each other.

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What do patients, their families or carers consider to be the advantages and disadvantages of the technology for the condition?

2. Advantages
(i) Please list the specific aspect(s) of the condition that you expect the technology to help with. For each aspect you list please describe, if possible, what difference you expect the technology to make for patients, their families or carers.

Feedback from families on treatment has told us that by decreasing the rapidity of decline and stabilisation in children, the treatment will:

1. Enable children to maintain mobility for longer. This will enable them to remain part of their family, school community and reduce the frustration which a lack of mobility causes.
2. Parents also tell us that the treatment is enabling their children to retain critical life skills that keep them happy and satisfied as human beings.
3. It enables them to continue to speak, eat, sing, play, interact and stay happy and content.
4. It enables them to engage in school and with their peer group.
5. In terms of education, parents and professionals have reported that children are learning and acquiring new skills at an age when we know that their untreated cohort would be regressing.

One parent has said:

"My child has their own hobbies and interests, favourite songs, sneaky sense of humour and quick wit - all of which would be long gone if it weren't for the treatment"

(ii) Please list any short-term and long-term benefits that patients, their families or carers expect to gain from using the technology. These might include the effect of the technology on:
- the course and outcome of the condition

The treatment has been shown to significantly slow down the progression of the disease and stabilise the condition for some children. Reducing and delaying the progression of symptoms (as identified in previous sections) for these children will have a significant impact on their level of disability for longer, the quality of life for themselves and their parents and wider family.

Some parents with children on treatment report that their children have regained a degree of skills, specifically speech and walking which they had previously lost.

Whilst we understand that the availability of long-term data is limited, the safety and efficacy data that is available shows great promise for these children.

3. Disadvantages
Please list any problems with or concerns you have about the technology.
Disadvantages might include:

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- aspects of the condition that the technology cannot help with or might make worse

We are aware that the treatment does not help with vision loss in CLN2 disease and that the children on treatment will continue to lose their sight.

- difficulties in taking or using the technology

Currently the infusion is delivered every two weeks at Great Ormond Street Children's Hospital. For almost all of the children this involves no sedation and they can return home the same day. All families have said that whilst the travel from their home to hospital can be challenging and being tied to an appointment every two weeks has an impact on work and family life this is completely acceptable to enable their children to access this treatment.

- side effects (please describe which side effects patients might be willing to accept or tolerate and which would be difficult to accept or tolerate)

Families do not report any side effects of the treatment.

- impact on others (for example family, friends, employers)

Families do report the challenges of travelling to London for treatment. This impacts on their family life, school attendance, interaction with siblings and work. Whilst this has been reduced as all children return home on the same day as treatment this situation would be greatly eased if treatment was to be continued more locally in LSD Centres. Despite these challenges, all families state that the benefits of the treatment to their children far outweigh any impacts that travel and logistics have on their daily lives.

- **financial impact on the patient or their family (for example cost of travel needed to access the technology, or the cost of paying a carer)**

One of the challenges that families report for travel for treatment is the financial impact on the family. Many fundraise in their communities to finance the fortnightly trips to London. However, despite this, they categorically state that the treatment is critical and far outweighs any financial impact.

4. Are there differences in opinion between patients about the usefulness or otherwise of this technology? If so, please describe them.

All families who are on treatment are unanimous as to the invaluable benefits for their children and families in terms of their physical and emotional health and their quality of life.

5. (i) Are there any groups of patients who might benefit **more** from the technology than others? Are there any groups of patients who might benefit **less** from the technology than others?

1. We believe that if children are diagnosed and treated earlier that they will benefit more from the technology.

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(ii) The scope states that if the evidence allows, the following subgroups should be considered:

- based on disease progression
- pre-symptomatic siblings with confirmed CLN2
- asymptomatic siblings with confirmed CLN2

Are there agreed definitions for classifying people into these subgroups? If a clinical rating scale is used, please describe how you would apply the scale to define these subgroups

Classification of children is done using the Hamburg Scale. These scales and ratings are clinician aministered and would not be applied by the BDFA but by experienced clinicians.

6. Comparing the technology with alternative available treatments or technologies

NICE is interested in your views on how the technology compares with existing treatments for this condition in the UK.

(i) Please list current standard practice (alternatives if any) used in the UK.

As there are no curative treatments for CLN2 disease standard practice centres on appropriate and effective symptom management and holistic care to maintain quality of life for the child and family .e.g

- Anticonvulsant medication to manage seizures.
- Medication to manage spasticity
- Dietary management
- Physiotherapy
- Speech and language therapy
- Hydration management
- Gastrostomy fitting
- Management of oral secretions including suctioning
- Skin and mouth care
- Posture and seating management
- MDT involvement and care
- Hospice and palliative care team involvement
- Patient organisation support and advocacy team
- Specialist education support including visual impairment professional

(ii) If you think that the new technology has any **advantages** for patients over other current standard practice, please describe them. Advantages might include:

- improvement of the condition overall
- improvement in certain aspects of the condition
- ease of use (for example tablets rather than injection)
- where the technology has to be used (for example at home rather than in hospital)
- side effects (please describe nature and number of problems, frequency, duration, severity etc)

There is an huge unmet need for treatment for CLN2 disease as no other treatment for the disease exists. The treatment has been shown to be safe and demonstrates a significant

effect in slowing down the progression of the disease and even stabilising symptoms in certain children.

(iii) If you think that the new technology has any **disadvantages** for patients compared with current standard practice, please describe them. Disadvantages might include:
- worsening of the condition overall
- worsening of specific aspects of the condition
- difficulty in use (for example injection rather than tablets)
- where the technology has to be used (for example in hospital rather than at home)
- side effects (for example nature or number of problems, how often, for how long, how severe).

The treatment has not been shown to worsen the condition overall or any aspects of the condition. Whilst it involves an intrathecal injection, currently in a hospital setting, every two weeks, the safety and efficacy profile show a significant benefit to children with CLN2 disease and to the quality of life of their families.

7. Research evidence on patient, family or carer views of the technology

(i) If you are familiar with the evidence base for the technology, please comment on whether patients' experience of using the technology as part of their care reflects that observed under clinical trial conditions. Were there any unexpected outcomes for patients?

Family reports of their experience of being on treatment reflects that observed under the clinical trial conditions.

This is also the case for those families who children are receiving treatment as part of the compassionate use programme.

(ii) Are there any adverse effects that were not apparent in the clinical trials but have come to light since the treatment has become available?

The treatment is currently available on the clinical trials and as part of a compassionate use programme. There have been no adverse effects reported in our follow-up with families on treatment.

(iii) Are you aware of any research carried out on patient, family or carer views of the condition or existing treatments that is relevant to an evaluation of this technology? If yes, please provide references to the relevant studies.

1. Frazier M. Batten Family Voices: 2014 BDSRA Needs Assessment. Columbus, OH: Batten Disease Support and Research Association, 2014
2. Scambler, S, Dr and Williams,R, Dr *The Support Needs of Children with Batten Disease, An Audit of the Efficacy of Existing Services and an In-Depth Study of Family needs.* Final Report April 2008

3. 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

8. Availability of this technology to patients

(i) What key differences, if any, would it make to patients, their families or carers if this technology was made available?

There is no other treatment for CLN2 disease therefore this treatment makes a fundamental difference to the care for children with this disease.

We anticipate that the availability of a treatment will also drive forward awareness and earlier diagnosis.

Earlier diagnosis will enable families to make informed choices about future children and pregnancies.

(ii) What implications would it have for patients, their families or carers if the technology was **not** made available?

If the treatment were not made available it would have a devastating impact on those currently on treatment, those to be diagnosed and also those families for who a treatment has come too late. As a small, close-knit community, the investment in hope for treatments is high. The implications for the whole community if the technology were not made available will be significant. Those families on treatment feel privileged to have been able to contribute to a significant piece of work that will benefit many more than their own child. One parent stated:

"We feel proud on our child's behalf that they are participating in a trial that may ultimately save other children's lives"

To have participated in such ground-breaking work, to have been given hope and then for that hope to be take away would have catastrophic implications for families.

(iii) Are there groups of patients that have difficulties using the technology?

We know of no groups of patients that have difficulties using the treatment.

(iv) Are there any situations where patients may choose not to use this technology?

A very small number of families chose not to participate in the clinical trial despite the fact that their children met the inclusion criteria. The reasons for this were unique to each family and came at the end of long and very challenging discussions. The broad areas of discussion were:

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1. It was an experimental treatment
2. Families had multiple affected children at different stages
3. The trial involved relocation to the trial site for up to a year which was felt to be too detrimental on their family's quality of life.
4. Complying with the protocol was felt to be too onerous for their children.

The BDFA has sought the thoughts of the whole CLN2 community concerning the treatment from those children who are newly diagnosed to bereaved families. They are a well informed community who make informed decisions about their childrens' care. Each family will make the decision about treatment based on their own personal circumstances and advice from their clinicians. The BDFA will support families to make the decisions that are right for them.

9. Please provide any information you may have on the number of patients in England with the condition. How many of them would be expected to receive treatment with the technology?

- The BDFA supports families with 28 affected children. For all of these children the disease is far progressed and they would be unlikely to be expected to receive treatment.
- The children currently on treatment via clinical trials or the compassionate use programmes would be expected to continue to receive treatment.
- To the date of this submission 2 children have been newly diagnosed in England. These children are currently not on treatment.
- It is anticipated up to a decision from NICE that up to a further 4 new children may be diagnosed.

Equality

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that this evaluation:

- could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which cerliponase will be licensed; - could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;
- could lead to recommendations that have any adverse impact on people with a particular disability or disabilities.

Please tell us what evidence should be obtained to enable the Evaluation Committee to identify and consider such impacts.

None

Other Issues

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Please consider here any other issues you would like the Evaluation Committee to consider when evaluating this technology.

NICE National Institute for Health and Care Excellence

Clinical expert statement

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- Your response should not be longer than 13 pages.

About you	
1. Your name	[redacted]
2. Name of organisation	[redacted]
3. Job title or position	[redacted]

4. Are you (please tick all that apply):	☐ an employee or representative of a healthcare professional organisation that represents clinicians? **x** a specialist in the treatment of people with this condition? ☐ a specialist in the clinical evidence base for this condition or technology? ☐ 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)	**x** yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ other (they didn't submit one, I don't know if they submitted one etc.)
6. 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	

7. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	To prevent disease progression, to stabilise disease process. CLN2 disease is a neurodegenerative condition usually leading to death in childhood.
8. What do you consider a clinically significant treatment response?	Maintained developmental skills, including motor, language and cognitive skills for at least six months from the initiation of treatment at an age/stage of CLN2 disease when deteriorating function would have been expected with no disease modifying therapy.
9. In your view, is there an unmet need for patients and healthcare professionals in this condition?	yes
What is the expected place of the technology in current practice?	
10. How is the condition currently treated in the NHS?	The goals of treatment currently are of symptom control (epilepsy, movement disorder, oral secretions and chest health etc), maintenance of function as long as possible and optimising quality of life for child and family.
• Are any clinical guidelines used in the	No clinical guidelines exist. See

treatment of the condition, and if so, which?	
• Is the pathway of care well defined? Does current care vary due to differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	There is no clearly defined clinical pathway for CLN2 disease. Most children will have been referred from primary care to general paediatric services for the evaluation of developmental/language delay or onset of seizures. The diagnosis is made some time later following further investigation by tertiary paediatric neurology services when seizures are uncontrolled following initial treatment (NICE CG137) or developmental progress plateaus or regresses. Children will then be supported by local multidisciplinary paediatric health teams and other agencies sometimes with support form tertiary neurology services and paediatric palliative care services. The Evelina Batten Disease Clinic takes referrals from primary and secondary care and has been involved in the care of over 20 children affected by this disease (and over 100 children and families affected by any of the NCLs) since 2003 when I was appointed.
• What impact would the technology have on the current pathway of care?	Significant changes would be necessary. A standardised pathway providing regular expert paediatric neurology/metabolic follow up would be necessary for treated and untreated children in order to deliver treatment, manage emerging symptoms optimally for all and ensure monitoring/data collection to inform future practise.
11. How will the technology be used in NHS clinical practice?	
• How does healthcare resource use differ between the technology and current care?	The setting in which care is delivered (tertiary centres vs community care); The frequency of health service contacts (every 2 weeks); the expertise and training of staff required to deliver technology and care; the financial implications of the drug costs and other resources required to deliver the treatment; the need for emotional and practical support for families travelling to centres for care etc
• In what clinical setting should the technology be used? (For example,	Specialist paediatric neurology/metabolic service with on-call or on-site access to paediatric Neurosurgery, Paediatric Intensive Care and Paediatric Emergency services. Staff delivering this treatment will require

primary or secondary care, specialist clinics.)	training from a neurosurgical team in cannulation of the reservoir and delivery of the infusion drug, the investigation and treatment of adverse events (for example CNS infection and catheter blockage).
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	Development of diagnostic pathway and access to diagnostic investigations early in course of disease, for example in all young children presenting with seizures and/or language delay, so that maximum benefit can be achieved from the technology. In practice, this is likely to mean either a national neonatal screening program or access to very much cheaper biochemical/genetic investigations for huge numbers of children presenting to paediatric services with language delay or first seizure between 2 and 4 years of age. Specialist multidisciplinary teams with expertise in delivery of cerebro-ventricular infusions of enzyme replacement therapy and the management of symptoms of CLN2 disease. Psychological and emotional support for families attempting to make decisions regarding initiation of therapy, often soon after receiving the potentially devastating diagnosis and with potential for far-reaching consequences on future family life. Ethical framework necessary for individualised care decisions. Care pathway and agreed protocol/guideline for long term monitoring of patients for response to therapy, adverse events, and emerging extra-CNS disease (cardiac, gut, pancreatic and potentially other). Resources to collect and analyse this long term data.
12. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes, if provided within an appropriate clinical decision making framework and resources clinical service, I would expect children to survive with halted or slowed disease progression, reduced health needs at least in the short term and improved quality of life in the short term at least. The effect on medium and long term quality of life and survival is I think unknown.
• Do you expect the technology to increase length of life more than current care?	Yes, although there is no detailed information available about life expectancy in treated compared with untreated patients to date as far as I am aware. I understand that amongst the children receiving treatment so far, the rate of expected disease progression based on motor and language skills has slowed significantly. Children continue to have epileptic seizures and may still have shortened lives, but if progressive neurodisability can be prevented, delayed or slowed down, the consequent problems (for

	example swallowing difficulties and necessity for tube feeding, aspiration pneumonia and spinal scoliosis) may be mitigated, and life-expectancy could be increased.
• Do you expect the technology to increase health-related quality of life more than current care?	The aim of current care is to control symptoms as much as possible and optimise health-related quality of life. I would expect the technology to increase HR-QoL at least in the short term if provided at an early stage of the disease.
13. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	More effective: Young children before the onset of symptoms (for example younger siblings diagnosed following diagnosis based on symptoms in an older child), and children at a very early stage of the disease when developmental skills are still being gained but at a rate slower than typically developing children at the same age. Less effective: For those children who have already lost developmental skills significantly.
The use of the technology	
14. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional	For children and families – regular travel to specialist centre for treatment every 2 weeks which is potentially for life. A clear and transparent ethically based framework for making decisions regarding eligibility for treatmen Long term monitoring of cardiac, pancreatic and gut function should be put in place.

clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	Development of specialist multidisciplinary teams expert in management of NCL diseases with additional resources for an independent clinical registry or database collating clinical information for treated and untreated children (for example enhanced funding for the existing DEM-CHILD international Registry).
15. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	
16. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	
17. Do you consider the technology to be innovative in its potential to make a	Yes

significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	
• Is the technology a 'step-change' in the management of the condition?	Yes – no doubt!
• Does the use of the technology address any particular unmet need of the patient population?	This disease is currently untreatable and there are no other disease modifying therapies available. There is an active research community and it is likely that other novel therapies are in development. Any processes put in place to deliver this technology will need to be able to adapt to a changing therapeutic landscape.
18. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Catheter blockage and infection are the main predictable adverse events with potentially increased risks of both if the treatment is delivered outside major centres of expertise. These may require removal and replacement of the reservoir and ventricular catheter and antibiotic treatment, prolonging inpatient stay and interrupting or possibly preventing further treatment. Burden of travel and disruption to family life, impact on parents' employment and siblings.

Sources of evidence	
19. Do the clinical trials on the technology reflect current UK clinical practice?	No, trials involved selected children and families who were supported by expert clinical teams and had increased access to BDFA support and resources and were supported by eachother in a single UK centre.
• If not, how could the results be extrapolated to the UK setting?	
• What, in your view, are the most important outcomes, and were they measured in the trials?	The trial attempted to capture cognitive (developmental) and quality of life outcomes which I believe are the most important. However measurement of these outcomes are challenging in the setting of a neurodegenerative disorder and where visual impairment is an important clinical feature. Parents of children with CLN3 disease where Visual impairment is the leading symptoms and significant cognitive decline occurs several years later have told me that vision is hugely important to quality of life and that their children's lives would be very different if vision could be maintained for longer. If this treatment modifies neurological disease progression especially with regards to motor and verbal skills but does not have the same effect on vision, we may see a cohort of visually impaired children who are physically able. These children may also have disorders of social communication which become more apparent over time especially if physical skills are maintained. Some children are referred for evaluation of social communication at around the time a positive diagnosis of NCL is made and any autistic spectrum disorder diagnosis at this stage becomes relatively unimportant to parents and professionals.

• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	
20. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	
21. How do data on real-world experience compare with the trial data?	n/a – no real world experience outside clinical trial or treatment given on compassionate basis in the same tertiary centre.
Equality	
22a. Are there any potential equality issues that should be taken into account when considering this treatment?	Equity of access based on geography (distance from a treating centre)

22b. Consider whether these issues are different from issues with current care and why.	
Topic-specific questions	
23a. Can treatment with cerliponase alfa stabilise disease progression? Or will treatment slow progression without completely stabilising the disease?	Unknown in the long term
23b. How long would patients have to remain in a constant health state to consider disease progression to have stabilised?	6-24 months probably
Key messages	

24. In up to 5 bullet points, please summarise the key messages of your statement.

- Concerns about medium and long-term quality of life for children and families
- Need for service reconfiguration and development to deliver this treatment
- Need for long term monitoring of potential emerging extra-CNS disease
- Need for an ethical framework for decision making regarding eligibility criteria for treatment
- Cost of implementation of all the above for the NHS

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.

NICE National Institute for Health and Care Excellence

Clinical expert statement

Cerliponase alfa for treating neuronal ceroid lipofuscinosis type 2 [ID943]

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About you	
1. Your name	[redacted]
2. Name of organisation	[redacted]

3. Job title or position	[redacted]
4. Are you (please tick all that apply):	☐ an employee or representative of a healthcare professional organisation that represents clinicians? X☐ a specialist in the treatment of people with this condition? ☐ a specialist in the clinical evidence base for this condition or technology? ☐ 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)	X☐ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ other (they didn't submit one, I don't know if they submitted one etc.)
6. 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	
7. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	The main aim of cerliponase alfa is to stop neurodegeneration and allow developmental progress in children with CLN2 type Batten disease (NCL)
8. What do you consider a clinically significant treatment response?	CLN2 patients treated with cerliponase alfa deteriorated less than matched controls in the first year of treatment and none of the patients lost any skills after the first year of treatment.
9. In your view, is there an unmet need for patients and healthcare professionals in this condition?	There are no currently approved disease specific therapies that reduce the speed of progression of neurodegeneration for patients with CLN2. The current symptomatic treatments fail to control seizures, myoclonus and progressive spasticity in CLN2. Therefore, there is a huge unmet need in CLN2 where relentless neurodegeneration leads to fatal and extremely distressing outcome.
What is the expected place of the technology in current practice?	
10. How is the condition currently treated in the NHS?	CLN2 cardinal features include epilepsy, progressive loss of speech and mobility, progressive spasticity, increasing myoclonus and vision impairment. Current treatment consists of anti-epileptic medications and

	largely supportive measures for the other symptoms and signs. The epilepsy is usually difficult to control and no measures can stop the progress of the disease.
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	There are published guidelines for the use of antiepileptic medication in CLN2 (see below). Standard local protocols are used for management of myoclonus and spasticity. **Williams RE, Adams HR, Blohm M, Cohen-Pfeffer JL, de Los Reyes E, Denecke J, Drago K, Fairhurst C, Frazier M, Guelbert N, Kiss S, Kofler A, Lawson JA, Lehwald L, Leung MA, Mikhaylova S, Mink JW, Nickel M, Shediac R, Sims K, Specchio N, Topcu M, von Löbbecke I, West A, Zernikow B, Schulz A. Management Strategies for CLN2 Disease. Pediatr Neurol. 2017 Apr;69:102-112.**
• Is the pathway of care well defined? Does current care vary due to differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	CLN2 disease is a lysosomal storage disorder due to a deficiency of a lysosomal enzyme TPP1 and the patients may be referred to the lysosomal storage disease treatment centres. However, not all patients are currently referred as it is felt that very little additional help can be offered to the patients in such centres.
• What impact would the technology have on the current pathway of care?	cerliponase alfa is the enzyme replacement therapy containing human recombinant TPP1 enzyme which needs to be delivered two-weekly via intra-cerebro-ventricular port. The patients will need to attend the centres initially for the insertion of the port and then two-weekly attendance of the hospital for infusions until such infusions can be performed locally. All patients will need to be referred to the centres for treatment which will have an impact upon the overall workload of the lysosomal storage disease treatment centres.
11. How will the technology be used in NHS clinical practice?	Upon diagnosis, all patients will be referred for treatment to the lysosomal storage disease (LSD) treatment centres where they will have intra-cerebro-ventricular port inserted and then will attend every two weeks for cerliponase alfa infusions. The patients will be monitored by the centres. It is possible that local arrangements can be made where the infusions are performed in the local centres. For example, Manchester LSD centre provides clinical cover for Liverpool, Leeds and Newcastle. It is possible that local

	patients for example from Liverpool will be attending Alder Hey Hospital for infusions but the doctors from Manchester LSD centre will continue monitoring the patient at regular intervals.
• How does healthcare resource use differ between the technology and current care?	As mentioned above due to the lack of disease specific therapy until now not all CLN2 patients are referred to the LSD centres and are sometimes managed locally. With the introduction of cerliponase alfa all patients will have to be referred for treatment.
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Cerliponase alfa is a drug that is delivered via intra-cerebro-ventricular infusions (into the brain ventricles) that last for 4 hours. Up until now it has been given as part of a clinical trial or expanded access programme at Great Ormond Street Hospital. Patients are currently infused on day ward. I anticipate that once approved cerliponase alfa will be delivered in specialist hospitals under the care of specialists in inherited metabolic disorders supported by a neurosurgical team. In the future, it is possible that the drug may be delivered in local hospital (with appropriate support) or potentially home setting by qualified staff as for other enzyme replacement therapies.
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	The patients will require two-weekly attendance and therefore this will create additional pressure on staff of the LSD centres. The facilities and the equipment are standard and used by the neurosurgical teams already. In order to perform the infusions the nurses and doctors will need training on how to use the intra-cerebro-ventricular ports, however, this is a standard equipment used in the hospital.
12. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Based on the experience of the clinical trial Cerliponase alfa will provide significant and clinically meaningful benefits to patients as compared with the current care.
• Do you expect the technology to increase	On the basis of the clinical trial results I expect that cerliponase alfa will substantially increase length of life compared with the current care.

length of life more than current care?	
• Do you expect the technology to increase health-related quality of life more than current care?	On the basis of the clinical trial results I expect that cerliponase alfa will substantially and significantly increase health-related quality of life a lot more than the current care.
13. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Based on the results of the clinical trial all patients started on cerliponase alfa benefited. In the first year the neurological deterioration was less in most of the patients compared with matched natural history controls. After the first year of treatment none of the patients on cerliponase alfa suffered further clinical deterioration whilst the disease progressed relentlessly in all natural history controls.
The use of the technology	
14. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant	Cerliponase alfa is the first and only disease specific therapy in CLN2 and therefore it is difficult to compare with the current care which is only supportive in this condition. As mentioned above administration of cerliponase alfa requires insertion of the intra-cerebro-ventricular ports and two-weekly hospital attendance.

treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	Some patients will require sedation during the infusion. As per standard protocols for administration of enzyme replacement therapy the patients will require antihistamine administration. Careful monitoring of the port and CSF will be required in order to prevent or provide early treatment for possible infections.
15. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Yes, the plan is to introduce “a managed access agreement” which will state clear and simple “starting and stopping” rules. They will be based on assessment by the clinical team which is currently in use already but will be formalised.
16. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	Yes I do consider that many of the benefits are difficult to measure using current tools for QALY calculation. These include the retained ability to communicate and enjoy their environment in patients with limited mobility and speech.

17. 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 is the first effective therapy for CLN2 that has shown in clinical trials that it reduced progression of the disease in the first year of treatment and then stopped progression of the disease after the first year of treatment. It satisfies the unmet need for treatment for this patient group.
• Is the technology a 'step-change' in the management of the condition?	Yes this is a dramatic step change in treatment of CLN2.
• Does the use of the technology address any particular unmet need of the patient population?	There are no available effective treatments for CLN2.
18. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	The side effect and adverse event profile of cerliponase alfa is minimal as shown by the clinical trials. The fact that Brineura has to be delivered via infusions two-weekly in the hospital will have an effect on patients quality of life.

Sources of evidence	
19. Do the clinical trials on the technology reflect current UK clinical practice?	Yes the clinical trials compared treated patients with the matched natural history controls that reflected the current UK practice.
• If not, how could the results be extrapolated to the UK setting?	
• What, in your view, are the most important outcomes, and were they measured in the trials?	The most important outcomes were measured in the clinical trials which showed very significant reduction in neurological deterioration in the first year of treatment and no further deterioration after the first year of treatment. It showed preservation of language development and mobility. Patients in the trials continued to gain new skills unlike the controls who continued to deteriorate relentlessly.
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	No.
20. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No.

21. How do data on real-world experience compare with the trial data?	Natural history controls reflect will the real world experience.
Equality	
22a. Are there any potential equality issues that should be taken into account when considering this treatment?	No.
22b. Consider whether these issues are different from issues with current care and why.	
Topic-specific questions	
23a. Can treatment with cerliponase alfa stabilise disease progression? Or will treatment slow progression	Yes cerliponase alfa stabilises disease progression in the first year. No further progression of the disease is seen after the first year of treatment.

without completely stabilising the disease?	
23b. How long would patients have to remain in a constant health state to consider disease progression to have stabilised?	After 6 months in a constant health state the disease progression can be considered to have stabilised.

Key messages

24. In up to 5 bullet points, please summarise the key messages of your statement.

- Cerliponase alfa is effective at stabilising neurological deterioration in patients with CLN2 disease.
- After 1st year of treatment with cerliponase alfa there has been no further loss of skills in any of the patients.
- Cerliponase alfa is delivered by two-weekly infusions via intra-cerebro-ventricular ports. These infusions are well tolerated with minimal adverse effects.
- Cerliponase alfa is an innovative therapy that satisfies the unmet need for treatmet in CLN2 disease.
- Cerliponase alfa makes a significant difference to the patients and families 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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Cerliponase alfa for treating neuronal ceroid lipofuscinosis type 2 [ID943]

Thank you for agreeing to give us your views on the technology and the way it should be used in the NHS.

Patients, carers and patient organisations can provide a unique perspective on the technology, which is not typically available from the published literature.

To help you give your views, we have provided a template. The questions are there as prompts to guide you. You do not have to answer every question. Please do not exceed 12 pages.

About you

Your name: [redacted]

Name of your organisation: I am a parent expert and have been nominated by the BDFA

Brief description of the organisation:
N/A

Are you (tick all that apply):

X I am a parent of a patient with the condition for which NICE is considering this technology.

How does the condition impact on patients, their families or carers?

How would we describe our lives and the impact Batten Disease has had on us? It is such a hard question to answer concisely because there are so many strands and layers to how this condition tears you apart and drags you to the darkest of places.

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We know you will have lots of details about our two beautiful daughters, [redacted] and [redacted] and their journey up to this point with Batten Disease. You have facts and statistics about the condition and we know you will have scrutinised the results of the clinical trial and you cannot fail to see the proof that this treatment works.
We would like to give you the chance to briefly see the world through the eyes of us as parents to three children, two of which have this most brutal condition. We hope it will allow you to gain a true understanding of how our lives have changed since 16th September 2016 when we were given [redacted]'s diagnosis and what the future holds for our family and the other families who are living with CLN2 Batten Disease.

Our Story
We were blessed with our three children and as any parents among you reading this will understand the immediate feeling of overwhelming love and insurmountable desire to keep them safe from harm, forever. We have painfully had to come to terms with the fact we cannot do this.

[redacted] language delay was highlighted in her two year check with our health visitor. Speech and Language therapy was introduced but due to [redacted]'s severe lack of attention and concentration, it was a challenging period of time. We pursued with speech and language, Makaton etc but nothing was sticking. It was only when she started in the school nursery that it was a bigger concern, although because [redacted] was a clever, astute little girl who understood everything, everyone was confident that she would soon 'pick up' the language when we was surrounded by other children every day.

When school and language therapists expressed their concern that they could not see any improvement, we decided to take [redacted] to our local hospital to get her assessed by a paediatrician to rule out a physical problem with her vocal chords which could be preventing her from speaking. After a series of tests, we were advised that there was a much bigger issue, [redacted] was displaying behaviours of an 18mnth old baby (she was 3yrs at this time) and was diagnosed with Global Developmental Delay.
Then a matter of days after this meeting, [redacted] had her first seizure and we were rushed to hospital. After EEG and ECG, she was diagnosed with Epilepsy shortly after at our hospital The Royal Victoria Infirmary, Newcastle Upon Tyne.

The doctors always thought there was an underlying problem which was linking all of the health issues [redacted] was experiencing - no speech, GDD and Epilepsy, aswell as short statue ([redacted] is tiny – she was 4lb 8 when she was born) but they said we may never find out what it is.

It was during Spring of 2016, [redacted] was 4 years old, when we noticed she was looking unsteady on her feet. This quickly progressed to wobbling and stumbling, until she could not be left on her own because she was constantly falling and banging her head. We kept saying to the doctors, there is something not right, we even thought it could be the epilepsy medication being too much for her. It was when

things got so bad that when she was falling and couldn't get herself back up. She was literally on all fours shaking, unable to push herself up to sitting. This is when we went back to our doctors and insisted something was definitely not right. There must be an underlying issue. It was only due to our persistence that the test for Batten Disease was done and our world came crashing down. She was diagnosed with Batten Disease on 16th September 2016 age 4.5yrs old. [redacted] lost her ability to walk and stand and is now fully dependent on us when she walks.
[redacted] moved to a specialist school in November 2016 which has been the best thing we could have done for her. She is a beautiful bright happy girl & we are so fortunate that [redacted] has her needs met in this amazing provision of Hadrian school.

We strongly feel that parents and professional should be educated on looking out for the early signs of this condition to intervene as early as possible.

Impact on patients and their families or carers.
Please describe how patients and their families or carers have to adapt their lives as a result of the condition, and the impact the condition has on the following aspects:

Physical health

[redacted] has lost her ability to walk, as we have described earlier, however she has been doing amazingly well with the limited independence she now has and is always keen to keep moving.
It is not only [redacted]'s general character & responses that have improved, but [redacted]'s physiotherapist at school feels that it is a very positive sign that [redacted] has maintained her level of mobility over the last year since commencing school. One of the most significant points they mentioned was that fact that [redacted] has needed a very limited amount of intervention, which is something they have not experienced with children with Batten Disease in the past.
She continues to be very motivated to use her Cavalier walker at home and school for independent mobility and to walk with the facilitation of one adult. She has maintained good head control and postural control in her trunk only requiring a basic seat set up with feet supported and a lap belt for safety. [redacted] also continues to have full range of movement in her upper and lower limbs. All the team have also commented on her being more content and happy to be handled and touched when previously she was unhappy with this. She gives lovely eye contact now and is very responsive to familiar adults and children in her class group.

Us as Parents
The impact on physical health on our lives is hugely important. We have both always kept ourselves fit and healthy, being part of various clubs and gyms, however it is now not only an enjoyable pastime, but an essential part of our lives. It is paramount that we look after ourselves physically. We both need to make sure we are physically strong to lift [redacted] so we both need to keep ourselves healthy and fit. It takes a huge toll on your body to be lifting and carrying a child who weighs 14kgs up and

down stairs, out to the car everyday. Healthy body, healthy mind is how we view fitness, but it is now something that is a necessity, because as [redacted] is getting older and heavier we need to be able to manage this.

Emotional wellbeing

[redacted] and [redacted]'s big brother [redacted]

[redacted] is the best big brother in the world. [redacted] and [redacted] adore him. We know [redacted] misses the sister he once had.
We have recently had to seek intervention and support from a Play Specialist to give [redacted] an outlet to share his feelings etc. We have also had to seek support from the school welfare officer aswell as the play specialist surrounding his behaviour recently, so we know it is affecting him. We know he misses the sister he once had and he is going through so many emotions and is perhaps struggling to process them. There is bound to be anger, he maybe grieving for the life he has lost and what his life is like now, compared to the carefree exciting life he had before Batten Disease came in and turned our worlds upside down.
We have to be extra conscious of the fact [redacted] will need reassurance and more importantly, our time. We have to leave him every two weeks to travel to hospital, but we have taken [redacted] with us to both London and Hamburg to try and include him and show him where we are going every two weeks and why we have to leave him.

Us as Parents.

It is very difficult to express the strain this diagnosis puts on your emotional wellbeing. Aswell as having no family close by to help us, [redacted] also works full time in between hospital visits so the time when he is home, he is working. It is an incredible amount of stress and we both regularly feel emotionally drained to put it mildly. As we only have each other, the stress and strains are often directed at the person you need the most, it is inevitable that this happens but the main thing is we always know we are strong team and we will always be there to support each other. We have coped with this journey so far by taking each day as it comes and always focussing on the positives, because each day is a blessing. We cannot allow ourselves to think or visualise what our future could be. We have hope in our hearts and this is what keeps us going, that and the fact that we have such wonderful support around us in our friends and family and community.

Everyday life (including if applicable: ability to work, schooling, relationships, social functioning)
We would give anything to be able to just grab our coats on a whim and go out to the park or walk our dog somewhere adventurous, nothing spectacular, just simple pleasures, are things that are sadly now out of our reach due to this condition.
Our days are very different, no longer are they carefree and full of excitement, our days and weeks are now planned around hospital appointments, meetings with various healthcare professionals, everything has to be tightly orchestrated with lots of

preparation and forward planning to ensure we have everything covered for the care of [redacted] as she is fully reliant on us for every aspect of her daily routine.
Having three small children is a challenge in itself, juggling school runs, meals, after school clubs, play dates, school activities, general doctors / dentist appointments, food shopping, housework….
Now try to imagine all of the normal stresses and strains on top of having to care for a child with additional complex needs who is fully reliant on you, cannot speak or walk, needs medication twice a day to control her seizures. Plus having a 2 year old who can be quite demanding and also needs your attention. To have to listen and hold yourself together when your 7 year old son asks if he sister is going to die, or if she will ever be able to walk or talk again. Then playing with his littlest sister, [redacted] who is currently perfect and saying "I don't want [redacted] to ever loose her abilities because I want to be able to play with her".
Before Batten Disease started to take away our beautiful girl's abilities, [redacted] was always running around the garden and acting silly with her big brother. She was a daredevil and loved to climb. We were never to know that she would lose her mobility and would never be able to do this with her little sister when she came along. It is truly heart-breaking for us to watch and acknowledge.
We know we are running on empty a lot of the time, when [redacted] is not in hospital with the girls, he is at work.

Other impacts not listed above

The impact on the wider family network (and friends to a degree)

We live in [redacted] and have no family close by us to help us to help us with the children so it is a lot to manage. [redacted]s family are in [redacted] and mine is [redacted] (which is my sister and brother in law who are the closest to us at 40mins away & have two small children of their own), [redacted]

We have had to call upon our families to come and help us with hospital trips to look after [redacted] and take him to his clubs. A diagnosis of Batten Disease changes so many people's lives and it adds an additional pressure knowing that we have to ask our families to put themselves out and arrange time off from their own employment in order for us to take our children to hospital. After 25years, [redacted] mam made the decision to leave work which was a huge decision but something she wanted to do to allow her to be able to support us and not be restricted to when she could come up around work. It was that and also the desire to actually spend more time with the girls, as we all are painfully aware, time is precious with Batten Disease. No family should have to do this and make these considerations.

The grief they must feel but will never express fully to us is very hard to acknowledge. Our families will have cried many tears and feel helpless, guilty, that it could have been them. Our families adore our girls and [redacted] and it will undoubtedly put strains on them and they maybe feel they don't know how to cope…but of course they would never tell us. This condition is so cruel and the

reaches of it's affect are infinite. It's not always the obvious signs, but the hidden emotions that bury themselves deep inside.

What do patients, their families or carers consider to be the advantages and disadvantages of the technology for the condition?

Advantages

Since [redacted] has been having the infusions everyone has noticed an improvement, friends & family regularly comment on how much better [redacted] is now, compared to this time last year, before treatment had begun.

We have seen with our own eyes that this treatment has not only stabilised [redacted]'s condition, but it has actually improved her. [redacted] is proof that Brinuera works.

Before [redacted] started her enzyme replacement therapy in January 2017, she used to get agitated, very easily. So much so that we stopped going out as a family for fear that she would have a meltdown and be uncontrollable, crying and screaming. It was a very stressful experience.

She is so much calmer, much more receptive to new experiences. Since treatment, we have started to go out again as a family, because she is far more tolerant of new environments that she ever has been. Ourselves, family and friends have all commented on the huge improvement they see in [redacted], she is brighter, happier and much more alert.

We have got a part of our life back thanks to Brinuera.

Disadvantages

The biggest disadvantage for us is the travel as our two girls are being treated in different countries. [redacted] in London and [redacted] in Hamburg, Germany,

[redacted] is part of a Sibling Trial in Hamburg and she is now on infusion number 13th. The reason we travel is that the Sibling Trial is specifically looking at the impact of the treatment on younger siblings who are showing little or no symptoms as is the case with [redacted]. She is the youngest child in the world to have this treatment which is just incredible because she could change the course of this disease for the future.

She is a ray of hope in the Batten Community.

The reason she cannot be treated in London is that there is no Sibling Trial up and running in GOSH yet but this is in the process of being initiated.

The cost of the travel to London every fortnight is obviously a disadvantage - our long term aim would be to have access to the treatment in our local hospital in Newcastle.

Another disadvantage is being away from our little boy every two weeks and separating our family.

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However we must stress that no matter what disruption or disadvantages we face, nothing could ever override the blessing we have been given in this treatment for our daughters.

So, we would like to emphasise that although we have noted the disadvantages, they would never stop us from travelling with our girls to get this treatment.

- difficulties in taking or using the technology
- side effects (please describe which side effects patients might be willing to accept or tolerate and which would be difficult to accept or tolerate)
- impact on others (for example family, friends, employers)
- financial impact on the patient and/or their family (for example cost of travel needed to access the technology, or the cost of paying a carer).

Are there differences in opinion between patients about the usefulness or otherwise of this technology? If so, please describe them.

Are there any groups of patients who might benefit more from the technology than others? Are there any groups of patients who might benefit less from the technology than others?

Comparing the technology with alternative available treatments or technologies

There are no current treatments. This is the only treatment for CLN2 Batten Disease. Before this, parents and carers were told there was nothing that could be done, and managing the symptoms was the only thing that could be done.

If you think that the new technology has any advantages for patients over other current standard practice, please describe them.

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Since [redacted] has been having the infusions everyone has noticed an improvement, friends & family regularly comment on how much better [redacted] is now, compared to this time last year, before treatment had begun.
We have seen with our own eyes that this treatment has not only stabilised [redacted]'s condition, but it has actually improved her. [redacted] is proof that Brinuera works.
Before [redacted] started her enzyme replacement therapy in January 2017, she used to get agitated, very easily. So much so that we stopped going out as a family for fear that she would have a meltdown and be uncontrollable, crying and screaming. It was a very stressful experience.
She is so much calmer, much more receptive to new experiences. Since treatment, we have started to go out again as a family, because she is far more tolerant of new environments that she ever has been. Ourselves, family and friends have all commented on the huge improvement they see in [redacted], she is brighter, happier and much more alert.
We have got a part of our life back thanks to Brinuera.
~
It has had a measurable impact on [redacted]'s enjoyment and engagement at school and she is now far more interactive and responsive in her lessons. When [redacted]'s first joined Hadrian School in November 2016 on a part time basis and is now attending full time only being away from school when she attends GOSH for her treatment.
[redacted]'s class teacher described how when [redacted] first joined her class, she appeared quite agitated, making lots of guttural vocal sounds and frequent repetitive hand movements. [redacted] is now much more settled and the class rarely hear the vocal sounds related to her agitation and the hand movements are only observed occasionally.
[redacted] has made really good progress with her acceptance of touch – initially she found it difficult to tolerate any touch based activities but again, they have seen a significant change in this and she is now much more tolerant of Story Massage sessions, TacpPac and physio stretches.
[redacted] is also beginning to demonstrate a greater awareness of what is going on around her in regular and familiar small group activities. [redacted] loves seeing her photograph in circle time, looking towards an adult when they call her name and taking part in her favourite songs and rhymes with support, she always shows us that she is enjoying something by smiling or giggling or even an excited scream.
When [redacted] first started at Hadrian School staff also noted that her emotional responses eg, smiling were very fleeting and [redacted] would not tend to repeat the smile during the activity, however we are now observing that [redacted] is sustaining her happy reactions for longer periods of time.
The teachers final comment was "[redacted] is a lovely happy little girl who really enjoys coming to school, being with her friends and taking part in a variety of activities in her therapeutic curriculum. She lights up our day with her smile".
It is not only [redacted]'s general character & responses that have improved, but [redacted]'s physiotherapist at school feels that it is a very positive sign that [redacted] has maintained her level of mobility over the last year since commencing school. One

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of the most significant points they mentioned was that fact that [redacted] has needed a very limited amount of intervention, which is something they have not experienced with children with Batten Disease in the past.
She continues to be very motivated to use her Cavalier walker at home and school for independent mobility and to walk with the facilitation of one adult. She has maintained good head control and postural control in her trunk only requiring a basic seat set up with feet supported and a lap belt for safety. [redacted] also continues to have full range of movement in her upper and lower limbs. All the team have also commented on her being more content and happy to be handled and touched when previously she was unhappy with this. She gives lovely eye contact now and is very responsive to familiar adults and children in her class group.

If you think that the new technology has any disadvantages for patients compared with current standard practice, please describe them. Disadvantages might include:

- worsening of the condition overall
- worsening of specific aspects of the condition
- difficulty in use (for example injection rather than tablets)
- where the technology has to be used (for example in hospital rather than at home)
- side effects (for example nature or number of problems, how often, for how long, how severe).

We have no disadvantages to note from our family and experience.

Research evidence on patient or carer views of the technology

If you are familiar with the evidence base for the technology, please comment on whether patients' experience of using the technology as part of their routine care reflects that observed under clinical trial conditions.

Are there any adverse effects that were not apparent in the clinical trials but have come to light since the treatment has become available?

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Are you aware of any research carried out on patient, family or carer views of the condition or existing treatments that is relevant to an evaluation of this technology? If yes, please provide references to the relevant studies.

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Availability of this technology to patients in the NHS

What key differences, if any, would it make to patients, their families and/or carers if this technology was made available?

The availability of this treatment would be the difference between a life filled with love and hope than that of a life filled with dread and devastation.

[redacted] is not showing any symptoms at yet and we hope with all of our hearts that she never does. It is very difficult to see the difference in our daughters. [redacted] is chatting away and beginning to count, she is such an independent little lady who can already newly 2yrs old, can put her own coat, shoes and socks on. She is developing amazing well and in a lot of areas, she is exceeding. We cannot express the hope that this treatment has given to us.
[redacted] has paved the way becoming the youngest child in the world to be given this treatment, so she is the hope for the future.
[redacted] is developing in line with her big brother, we are regularly being told that she is advanced for her age, she is a clever capable little girl.
[redacted], was not speaking at this age, she never participated in roll play the way [redacted] does. [redacted] is never without her dolly or her pushchair, she regular feeds the baby and rocks in to sleep! It is beautiful to see, because we never saw this with [redacted]. [redacted] was never engaged enough to play 'princess castle' for example, she would look for two mins the off she went onto something else, whereas [redacted] loves to sit and play.

So we are in the position where we can clearly compare our three children and their development. It is obviously extremely painful to see the stark contrast between them, however this serves a concrete evidence that this treatment is having a positive affect on [redacted] as she is exceeded her development milestones unlike [redacted]. The fact that [redacted] is doing fantastic at school and far more engaged than she has ever been, is another example of the results of this treatment.

We are all full of hope and optimism that she could potentially beat Batten Disease, because she is having the treatment so early, before symptoms have begun, we are all hoping and praying that she may never develop the symptoms like her big sister….because of this treatment being given to her so early in her precious life.

We are standing here today, not just for our families, but for families around the United Kingdom who deserve a chance of life, to be given a feeling of hope to replace despair and dread at what is coming for their children if they are denied access to this treatment.
For a few days following [redacted]'s diagnosis, we thought our lives had ended, we didn't know how we would ever carry on. But this treatment changed that.

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Anything is possible if you have hope in your heart….and you have the chance to give us all that hope by recognising and offering this treatment as a viable therapy to stabilise this brutal condition.

So please, we ask….no, we are begging you, do not throw our hope and lives away, give the children of this country the right to something that would change theirs and their families lives immeasurably.
Every child is born with the right to have the best shot at life, and this is now in your hands.

What implications would it have for patients, their families and/or carers if the technology was not made available?

Quite simply, it would be a death sentence for our children.

Are there groups of patients that have difficulties using the technology?

Equality and Diversity

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that this evaluation:

- Could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which the treatment is licensed;
- Could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;
- Could lead to recommendations that have any adverse impact on people with a particular disability or disabilities

Please tell us what evidence should be obtained to enable the Evaluation Committee to identify and consider such impacts.

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Other Issues

Please include here any other issues you would like the Evaluation Committee to consider when evaluating this technology. Some brave and beautiful children, of a similar age to [redacted], are sadly longer with us because there has been no treatment before this. You could not have a more harsh awakening to what would lie ahead for our children if the NHS deny this remarkable treatment for CNL2 type Battens.
We are living in a country whose brave children and families have given themselves up to be part of the trials to assess if the drug works….yet, having contributed to the successful results culminating in the drug being licensed, they may be excluded from feeling the benefits of this treatment.

The facts are:

We know there is a drug in existence which has been proven to work.
We know this drug is available to children in other parts of the world right now.
Yet, even though our families have contributed to trials, we may be denied access to the thing we were helping to assess.
Batten Disease is a rare condition so monetary concerns should be quashed because it is only going to be prescribed to a minority, thus not being a financial burden to the NHS.

Having listened to the facts, we hope and pray NICE and NHS England make the right decision.

NICE National Institute for Health and Care Excellence

Patient expert statement

Cerliponase alfa for treating neuronal ceroid lipofuscinosis type 2 [ID943]

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	
1.Your name	[redacted]
2. Are you (please tick all that apply):	☐ a patient with the condition? X a carer of a patient with the condition? ☐ a patient organisation employee or volunteer?

	☐ other (please specify):
3. Name of your nominating organisation	Batten Disease Family Association
4. Did your nominating organisation submit a submission?	☒ yes, they did ☐ no, they didn't ☐ I don't know
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 ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ other (they didn't submit one, I don't know if they submitted one etc.)

6. 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
7. How did you gather the information included in your statement? (please tick all that apply)	☒ I have personal experience of the condition ☐ I have personal experience of the technology being appraised ☐ I have other relevant personal experience. Please specify what other experience: ☐ I am drawing on others' experiences. Please specify how this information was gathered:
Living with the condition	
8. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	As a parent of a child with CLN2 Disease it is extremely physically and emotionally demanding due to the regressive nature of the disease. Once given a terminal diagnosis, we are grieving for our child. Children with Batten Disease need to have 1:1 care 24 hours a day. As parents we cannot work to provide financially for our children. CLN2 Disease causes seizures, children have to be monitored during the night and administered medication. As a parent/carer I have to make critical decisions regarding my children's health and well-being. Since my children were diagnosed with Batten Disease, I have had to learn to support and care for my children. In addition to [redacted] and [redacted], I have had to continue to care for my two older healthy children ensuring they still have a 'normal' childhood. Due to having two terminally ill children, as a family we cannot plan ahead. Every decision is based around the children's care. I have experienced negative and difficult circumstances where I have felt unsupported. It is a battle to find the

	right medical care for a child with batten disease. Without treatment a child's body quickly regresses. Rapid medial intervention is needed to prolong the skills the child has. [redacted] was diagnosed in February 2015 and by December 2015 he had lost his ability to walk. In February 2015, he was talking in full sentences and running around playing football. As parents, we had no indication that he was a terminally ill child. Had [redacted] had access to the treatment at the time, his motor skills and other aspects of his development may have been maintained. [redacted] is showing incredibly positive signs that she has not regressed since starting treatment. She is in fact progressing and learning new skills. For example, she has recently learnt new vocabulary and is forming longer sentences such as 'I want that', 'where they go' and using descriptive words like 'excited' in context. [redacted] will also follow demands and retains information. She develops new schemas and applies new skills with confidence. She has recently started mainstream school and enjoys learning new routines, particularly finding her name on her peg and joining in with whole class inputs. As a parent with two children with CLN2 Disease, I have had two different experiences. [redacted]'s learning and development regressed quickly while he was not on treatment and [redacted] has continued to develop due to having early access to treatment. For a parent, this provides comfort and hope that the treatment may offer a prolonged and more comfortable life for a child with CLN2 Disease. Due to the treatment taking place every two weeks, it also provides a positive and pro-active routine for families. Without treatment, CLN2 Disease has a devastating impact on the child and families.
Current treatment of the condition in the NHS	
9. What do patients or carers think of current treatments and care available on the NHS?	There is no treatment available on the NHS for anyone diagnosed with CLN2 Disease in the UK. However, treatment is funded in other European countries and the US. There is a need for the UK to follow suit and provide the treatment for children with CLN2 Disease. Every child should be provided the same opportunities.
10. Is there an unmet need for patients with this condition?	There is definitely an unmet need for the treatment to be available on the NHS in the UK. Children are being diagnosed with CLN2 Disease and given no treatment. When [redacted] was diagnosed with Batten Disease and treatment was not available, we were simply handed a leaflet with information about Batten Disease and told there was nothing that could help our child. Children are currently being let down, they

	are the ones that suffer with the condition. If there is treatment that is positively helping children with CLN2 Disease, it should be available for every child diagnosed with CLN2 Disease.
Advantages of the technology	
11. What do patients or carers think are the advantages of the technology?	The treatment is showing positive signs of slowing down the progression of CNL2 Batten Disease. Having two children receiving treatment at different stages of the disease we have the rare opportunity to compare. Since starting the treatment, [redacted]'s seizures have become very well controlled, meaning less hospital admissions. [redacted] has only ever had one seizure, since starting treatment she has been seizure free. The treatment has enabled both children to be able to attend main stream school. It has given them the opportunity to continue to be able to interact, socialise and learn alongside their peers. At the age of Six years and eleven months our little boy is still able to eat orally and his swallow is still safe. This is very unusual for a child of this age with CLN2 Disease. Health professionals believe this is due to the treatment slowing down the process of the disease. [redacted] is still able to walk, run, climb, she is able to speak in clear sentences and is still learning new words. We have been given hope by medical professionals that she has the ability to learn. She is currently taking part in phonic sessions at school, recognising letters and sounds and giving meaning to mark making. Both our children remain happy and are able to communicate their needs to others. The enzyme treatment is not invasive, both children recovered from the operation to place the shunt into the brain with no complications. Each infusion is done without sedation, [redacted] and [redacted] are able to

	sit throughout the infusion. Neither show any signs of pain or discomfort throughout the infusions. They are discharged from hospital the same day and are able to return home. As the infusions are every fortnight the children are seen regularly by professionals, this helps to prevent other problems arising as the children are being constantly monitored. This treatment is keeping our family of six together. It is giving our children a better quality of life. This treatment is keeping our children alive and stable. Knowing that we are helping children that will be diagnosed with CLN2 Disease in the future is an additional emotional benefit. Comparing how [redacted] is now compared to [redacted] at the same age there is a huge difference. [redacted] is continuing to learn, she is not losing skills and her balance and mobility is as it should be for a child of her age. She interacts well and has had no hospital admissions for health reasons in the past year. [redacted] at this age was losing skill very fast. He was struggling to walk, and losing words and sounds. He experienced seizures daily and spent his time in and out of hospital Slowing down the disease, provides families with comfort and provides more time to make choices and provide more stability to the whole family.
Disadvantages of the technology	
12. What do patients or carers think are the disadvantages of the technology?	Every two weeks we travel by train for two hours to hospital. This can be tiring and can also put emotional and financial strain onto the family. However, this is a very small disadvantage compared to the positive impact that the treatment has. This issue can easily be resolved by transferring the care over to our local hospital which has the facilities to administer the treatment.

Patient population	
13. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	Since Batten Disease is a regressive disease, as children get older they lose more of their skills, it is more beneficial that children are diagnosed early. When [redacted] showed signs of developmental delay during early childhood (before they age of four) his symptoms were passed off as immature development and common childhood speech delay. It would have been extremely beneficial for these early symptoms such as speech delay, clumsiness, behaviour changes to have been explored further and identified as possible signs of Batten Disease. [redacted] was given a diagnosis at the age of four while he was still in the early stages of the disease. When [redacted] started receiving treatment in November 2016 at the age of five years and ten months, he had regressed without treatment previously and could no longer walk. However, since receiving treatment [redacted] has maintained skills. For example, [redacted] can still swallow allowing him to process food orally. Most children with CLN2 Disease would have lost the ability to swallow at [redacted]'s age without treatment. [redacted] also attends mainstream school and is able to access opportunities alongside his peers. We believe that [redacted] represents the importance of receiving the treatment early in childhood in order to benefit from the treatment. [redacted] was diagnosed with Batten Disease when she was two years old and started receiving treatment when she was three years and eleven months. As previously stated, [redacted] has continued to develop and is much more capable at her age now at 4 years 9 months than [redacted] was at her age due to her receiving the treatment. [redacted] attends mainstream school, enjoys activities such as dancing and gymnastics, demonstrating she is physically capable to keep up with her peers. The treatment will benefit those diagnosed as early as possible and then a rapid response is needed to provide treatment before the disease develops.
Equality	
14. Are there any potential equality issues that should be taken into account when	Providing treatment on the NHS will provide greater equality for all groups. The treatment will become more available across the country resulting in more opportunities for children to be treated nearer to home resulting in less travel, time and expense for families. Due to the treatment possibly being available across the UK, more professionals will be informed about Batten Disease, perhaps resulting

considering this condition and the technology?	in more early diagnosis for patients. Batten Disease is a rare disease meaning the number of patients we are highlighting is limited.
Other issues	
15. Are there any other issues that you would like the committee to consider?	Once the treatment becomes available on the NHS, consideration of where the treatment will be available needs to be addressed. Since both children have started treatment they have had less hospital admissions. This results in less resources being used. [redacted] does not receive physiotherapy or occupational therapy because of her good health.
Key messages	

17. In up to 5 bullet points, please summarise the key messages of your statement:

- Children need access to the treatment as early as possible to delay progression of the disease.
- There is a huge difference between [redacted] and [redacted], due to [redacted] receiving treatment earlier than [redacted].
- The treatment is having a positive impact on both children and delaying the progress of the disease.
- The treatment needs to be available on the NHS so children diagnosed with CLN2 Disease have a prolonged quality of life.
- Although attending hospital for treatment, overall children will be in hospital less. It may reduce the number of unplanned hospital visits. [redacted] has not been admitted to hospital for any other health reasons for thirteen months due to her good health.

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.

NICE National Institute for Health and Care Excellence

NHS commissioning expert statement

Cerliponase alfa for treating neuronal ceroid lipofuscinosis type 2 [ID943]

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. Your response should not be longer than 10 pages.

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- Your response should not be longer than 10 pages.

About you	
1. Your name	**Edmund Jessop**
2. Name of organisation	**NHS England**

3. Job title or position	**Public health adviser, Highly Specialised services**
4. Are you (please tick all that apply):	**x**☐ commissioning services for a CCG or NHS England in general? ☐ commissioning services for a CCG or NHS England for the condition for which NICE is considering txhis technology? ☐ responsible for quality of service delivery in a CCG (for example, medical director, public health director, director of nursing)? ☐ an expert in treating the condition for which NICE is considering this technology? ☐ an expert in the clinical evidence base supporting the technology (for example, an investigator in clinical trials for the technology)? ☐ other (please specify):
Current treatment of the condition in the NHS	
5. Are any clinical guidelines used in the treatment of the condition, and if so, which?	No
6. Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your	The pathways to Lysosomal Storage Disease (LSD) expert centres are well defined for most LSD, especially those which are treatable with disease modifying drugs or which are predominantly metabolic. CLN is somewhat different as a primarily neurological disorder with an unremitting degenerative course.

experience is from outside England.)	
7. What impact would the technology have on the current pathway of care?	Patients with CLN2 would be directed to the LSD expert centres to access the technology.
The use of the technology	
8. To what extent and in which population(s) is the technology being used in your local health economy?	Not at all except for patients on the compassionate use or expanded access programmes.
9. How will the technology be used in NHS clinical practice?	At LSD expert centres in accordance with NICE guidance.
• How does healthcare resource use differ between the technology and current care?	The key extra is insertion of the intra cerebral conduit for drug delivery, and of course the drug delivery itself.
• In what clinical setting should the technology be used? (For example,	Only under the care of an LSD expert centre.

primary or secondary care, specialist clinics.)	
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	Neurosurgery as indicated above. It is also increasingly clear that there are service costs associated with the monitoring of any managed access agreement (MAA).
• If there are any rules (informal or formal) for starting and stopping treatment with the technology, does this include any additional testing?	None yet but see previous comment about MAA.
10. What is the outcome of any evaluations or audits of the use of the technology?	
Equality	
11a. Are there any potential equality issues that should be	

taken into account when considering this treatment?	
Topic-specific questions	
12. How many CLN2 patients do you believe are eligible for treatment with cerliponase alfa?	Probably 10 at present.
13. Please include here any other issues you would like the evaluation committee to consider when evaluating this highly specialised technology.	

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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Evidence Review Group's Report
Cerliponase alfa for the treatment of neuronal ceroid lipofuscinosis type 2 (CLN2)

Produced by	CRD and CHE Technology Assessment Group, University of York, Heslington, York YO10 5DD
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Date completed	Date completed (11/12/2017)

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Declared competing interests of the authors
None

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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 HTA Programme. Any errors are the responsibility of the authors.

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Contributions of authors

Nick Meader, Matthew Walton and Nerys Woolacott undertook the critique of the clinical effectiveness submission: Nick Meader took overall responsibility. Melissa Harden critiqued the literature searches in the submission. Robert Hodgson, Joanne O'Connor and Lindsay Claxton undertook the critique of the cost-effectiveness submission and conducted the ERG exploratory analyses. Robert Hodgson took overall responsibility the critique of cost-effectiveness section and the project as a whole.

Note on the text

All commercial-in-confidence (CIC) data have been highlighted in blue and underlined, all academic-in-confidence (AIC) data are highlighted in yellow and underlined

Copyright statement

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List of abbreviations

AE	Adverse event
AED	Anti-epileptic drug
BDFA	Battens Disease Family Association
BNF	British National Formulary
CASP	Critical Appraisal Skills Programme
CI	Confidence interval
CrI	Credible interval
CLN2	Classic late-infantile neuronal ceroid lipofuscinosis
CLN3	Juvenile neuronal ceroid lipofuscinosis (JNCL/Batten disease)
CNS	Central nervous system
CS	Company submission
CSF	Cerebrospinal fluid
CSR	Clinical study report
DEM-CHILD	A Treatment-Oriented Research Project of NCL Disorders as a Major Cause of Dementia in Childhood
DSA	Deterministic sensitivity analysis
ECG	Electrocardiogram
EEG	Electroencephalogram
EMA	European Medicine Agency
eMit	Electronic market information tool
EPAR	CHMP European Public Assessment Report
EQ-5D	EuroQol 5-Dimensions
ERG	Evidence review group
ERT	Enzyme replacement therapy
FDA	US Food and Drug Administration
HR	Hazard ratio
HRQoL	Health-related quality of life
ICER	Incremental cost-effectiveness ratio
ICV	Intracerebroventricular
ITQoL	Infant Toddler Quality of Life questionnaire
ITT	Intention to treat

IV	Intravenous
LOCF	last observation carried forward
LSD	Lysosomal storage disorder
MAA	Managed access agreement
ML	Motor and language
MRI	Magnetic resonance imaging
NCL	Neuronal ceroid lipofuscinosis
NH	Natural history
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
OR	Odds ratio
PfCs	Points for clarification stage
PSA	Probabilistic sensitivity analysis
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
QALY	Quality-adjusted life year
QoL	Quality of life
RCT	Randomised controlled trial
SAE	Serious adverse event
SD	Standard deviation
SE	Standard error
SF-36	Short Form 36 Health Survey
SIGN	Scottish Intercollegiate Guidelines Network
TPP1	Tripeptidyl-peptidase 1

1 Summary

The company's main submission (CS) claims cerliponase alfa will permanently stabilise, or even improve all characteristic aspects of CLN2 disease, preventing the deterioration of motor, language, and visual function, and the frequency of seizures. Thus, treatment will eliminate disease-related mortality and allow treated patients to live long, fulfilling lives, achieving development milestones in line with unaffected children. The ERG considers the company's interpretation unreasonably optimistic, which was often contradicted by available evidence and clinical opinion. The company assumed substantial changes to current service provision for the success of this treatment, including implementation of a large-scale neonatal genetic screening programme. These limitations are discussed below.

1.1 Critique of the company's description of the underlying health problem and the technology

The ERG noted two main concerns about the company's description of CLN2 and the biological plausibility of assumptions made about the likely benefits of cerliponase alfa.

Firstly, the CS fails to acknowledge the extra-neuronal components of CLN2, both in the contextual discussion of the disease mechanism and the anticipated impact of long-term treatment with cerliponase alfa. The ERG considers this evidence important to the appraisal. The ERG noted that expression of TPP1 is not limited to the CNS; the pathological accumulation of lipofuscin in other organs is well documented in CLN2 disease, and the consequences are seen in other forms of Batten disease. Pre-clinical studies indicated there may be serious implications for patient morbidity and mortality associated with cardiac, pancreatic, and hepatic impairment unless ERT is administered systemically.

The ERG has particular concerns regarding cardiac involvement, with severe cardiac and hepatic impairment seen in canine models of CLN2 treated with TPP1. Cardiac hypertrophy and conduction disorders are common in longer-lived CLN3 patients and were observed in [redacted] patients in the presented trial evidence; [redacted] of patients at baseline had ECG abnormalities [redacted] at last observation, many of these abnormities were prognostic of cardiac hypertrophy and conduction disorders. The ERG therefore reiterates the concerns of the European Medicines Agency (EMA), the US Food and Drug Administration (FDA), and clinicians regarding the failure of this treatment to address the likely consequences of extra-neuronal disease pathology, and highlights this as an important limitation of the technology.

Secondly, the ERG noted that cerliponase alfa administered via intracerebroventricular (ICV) infusion cannot reach the affected retinal cells, therefore without an adjunct intravitreal injection of the drug the prevention of vision loss as claimed in the CS lacks biological plausibility. These conclusions are

reflected in clinical opinion, pharmacokinetic analysis, several pre-clinical studies, and the drug's EU and US marketing authorisation.

1.2 Critique of the decision problem in the company's submission

The decision problem addressed by the company broadly reflected the population specified in the NICE scope, i.e. people with a confirmed diagnosis of CLN2 disease. However, the clinical evidence presented in the company's submission (CS) was derived from a narrower population of children aged >3 with mild-to-moderate disease and 'stable' seizures, who therefore may not represent the total NHS patient population.

The intervention in the submission is cerliponase alfa (Brineura™), with evidence presented on the currently licensed dose of 300mg every other week. This matches the intervention described in the final NICE scope.

The company identified the comparator as established clinical management of CLN2 disease following the principles of paediatric palliative care, using a multidisciplinary approach which aims to manage symptoms and maintain function and quality of life for as long as possible. Comparator group evidence in the CS was derived from an independent natural history cohort treated optimally according to local clinical opinion.

The decision problem in the CS included most of the outcomes described in the NICE scope, including aggregated Hamburg scores, mortality, and adverse events. The health related quality of life (HRQoL) of patients and their families was also assessed. The company did not record or present adequate measures of visual function, considering the magnitude of their claims. The CS also omitted trial data and discussion of assessed immunogenicity, electroencephalographic (EEG) outcomes, and electrocardiographic (ECG) outcomes, which the ERG considered relevant to this appraisal.

1.3 Summary of clinical effectiveness evidence submitted by the company

The primary study 190-201/202 evaluating the clinical efficacy and safety of cerliponase alfa included 23 patients with CLN2 disease (one further patient dropped out early in the study) followed up over approximately 96 weeks.

Primary efficacy analyses

At the 48 week follow up, the mean rate of decline in the CLN2 rating scale was 0.4 points per 48 weeks in the cerliponase alfa group, which reduced to [redacted] points per 48 weeks after 96 weeks. Estimates from the natural history controls varied depending on the method used, more sophisticated analyses resulted in lower rates of mean decline (1.29 to 1.46 points) compared with methods used in the primary analyses (mean = 2.09). However, there appeared to be a clinically significant reduction

in mean rate of decline in CLN2 score regardless of method used. Time-to-event and responder analyses both showed that cerliponase alfa patients were substantially less likely to experience a 2-point decline in the CLN2 score compared with natural history controls.

Adverse events

All 24 patients treated with cerliponase alfa experienced at least one adverse event and [redacted] patients experienced at least one serious adverse event. However, no patients withdrew due to adverse events and no deaths have yet been reported during the follow up period.

All patients experienced infections ([redacted] experienced a Grade III event) and nervous system related disorders ([redacted] experienced a Grade III event). Seizures and epilepsy were among the most common adverse events: seizure ([redacted]), generalised tonic-clonic seizure ([redacted]), epilepsy ([redacted]). [redacted] of patients developed new EEG epileptiform activity during the trial. Hypersensitivity was also a common event with [redacted] ([redacted]) experiencing [redacted] hypersensitivity events [redacted]).

[redacted] patients experienced [redacted] cardiovascular adverse events (all Grade I/II). At baseline [redacted] had normal ECG readings; however, during the course of the trial [redacted] of patients experienced ECG abnormalities. However, no clear patterns of myocardial damage have yet been identified except two patients with suspected left ventricular hypertrophy.

1.4 Summary of the ERG's critique of clinical effectiveness evidence submitted

The ERG considers the evidence presented in the CS suggests that cerliponase alfa slows the decline of motor and language function relative to conventional management for up to 96 weeks. Although there was important uncertainty regarding the magnitude of mean decline in the natural history controls, it still appears that cerliponase alfa was more effective.

However, whether cerliponase alfa leads to a long term stabilisation or halting of disease progression is highly uncertain based on the data provided in the CS. The follow up period (approximately 96 weeks) was judged by the ERG to be insufficient to support the company's conclusions of life-long symptom stability and normal life expectancy.

Although there were some patients who experienced no unreversed declines between baseline and 96 weeks, it is highly uncertain whether this reflects a long term halting of disease progression or extension of life of several decades. Assumptions of long term stability were particularly problematic for the group of patients classified as late stabilisers by the company (who experienced unreversed declines in CLN2 score after 16 weeks but were assumed to have no further declines after 96 weeks). A number of patients also experienced declines either at last or penultimate follow up after 96 weeks,

with a mean trend indicating further decline. EEG and MRI outcomes also provided evidence against the conclusion that progression had not been halted therefore assumptions of long term or indefinite stability are directly contradicted by the clinical effectiveness data. Furthermore, cerliponase alfa doesn't address the non-neuronal aspects of CLN2 which has implications for life expectancy. Non-human studies have showed the treatment only slowed progression of symptoms, with modest reductions in short-term mortality. The company also failed to account for potential loss of response due to immunogenicity, despite generation of anti-drug antibodies in [redacted] of trial patients. The high risk of infection and replacement of the ICV delivery device also raises questions regarding the longevity of safe and successful treatment.

1.5 Summary of cost effectiveness submitted evidence by the company

The company submission included a broad systematic literature review to identify economic evaluations in CLN2 disease, as well as quality of life data and resource use data. The company submission was based on a multi-state Markov model comparing cerliponase alfa with established clinical management without cerliponase alfa (standard care). The model uses a cycle length of 2 weeks and time horizon of 95 years. The nine alive health states included in the model were primarily defined by the CLN2 clinical rating scale, which is a subset of an adapted version of the four domain Hamburg scale measure. Severity of disease at initiation of treatment was based on expert clinical opinion. The distribution of patients across health states upon entry in the economic model incorporated the assumption that the incident patients will be diagnosed in an earlier health state in the future.

The primary sources of data used to inform the cost-effectiveness model were the 190-201, 190-202 and selected patients from the DEM-CHILD cohort study. The economic model adopted a National Health Service and personal social services (NHS and PSS) perspective and a discount rate of 1.5% per annum was applied to both costs and outcomes in the company's base-case. Within the model, patients receiving cerliponase alfa were assumed to be either early stabilisers or late stabilisers. Early stabilisers were defined as patients who do not experience any further decline in CLN2 rating scale after 16 weeks. Late stabilisers are defined as patients who continued to progress at a rate of 1 point on the CLN2 clinical rating scale per 80 weeks, until week 96. After 96 weeks, all patients receiving cerliponase alfa were assumed to be stabilised and experience no further disease progression. Patients receiving cerliponase alfa were presumed to continue therapy until death or until progression to health state 7 (CLN2 clinical rating scale score of 0). The company's base-case model includes disease related mortality and other cause mortality. Disease related mortality is only applied in health state 9 to reflective the progressive nature of CLN2 disease.

Health state utilities were derived from a utility study undertaken by the company. The utility study used vignettes (brief descriptions of each of the nine health states in the economic model, for both the

cerliponase alfa arm and the standard care arm). Utility values based on the vignettes were elicited using eight clinical experts who were asked to complete an online version of the EQ-5D-5L as a proxy for patients who would be experiencing the description given in the vignettes. To account for the impact of CLN2 on disease on the family, the company applied a disutility for both caregivers (parents) and siblings. Disutility due to an adverse event was also included in the model. The company model included the following costs: drug acquisition and cost of administration for cerliponase alfa; health state costs, associated with monitoring and providing supportive care for patients and their families; and treatment costs relating to progressive symptoms associated with CLN2 disease.

The company found cerliponase alfa to be more costly (cost difference of [redacted]), but also more effective (gains of 30.42 QALYs) than standard care. The estimated deterministic ICER for cerliponase alfa compared with standard care was [redacted] per QALY. The results of the DSA indicate that the parameters with the largest influence on the ICER were the drug cost and the health state utility values for cerliponase alfa. The probabilistic ICER estimated by the company was [redacted] per QALY. The company undertook a range of scenario analyses. Two scenarios were considered by the company to present the likely range within which the ICER lies, as they combine the optimistic and pessimistic elements of the scenario analyses. These scenarios had an associated ICER of [redacted] and [redacted], respectively.

1.6 Summary of the ERG's critique of cost effectiveness evidence submitted

The ERG raised a number of concerns in its critique of the company's model, these issues concerned the long-term effectiveness of cerliponase alfa, the population modelled, assumptions made regarding the long-term mortality of patients receiving cerliponase alfa; and, problems with the way in which the HRQoL values used in the model were derived. Each of these issues is summarised in brief below.

Long-term effectiveness of Cerliponase alfa

A central assumption to the company base-case is that all patients receiving cerliponase alfa stabilise after 96 weeks and experience no further disease progression. The ERG considers this assumption to be subject to very considerable uncertainty, and has substantive concerns regarding the company's interpretation of the clinical evidence cited in justification of this assumption. Specifically, the ERG note that there is only limited evidence from the 201/202 cohort that all patients stabilise, and that a substantial number of patients continue to experience further disease progression in the later part of the 190-201/202 study (post 48 weeks). The ERG, also highlights evidence from animal models which suggests patients receiving cerliponase alfa will continue to experience disease progression.

Population modelled

The ERG had a number of concerns about the assumed distribution of patients at initiation of treatment. The distribution of patients across health states was based on clinical expert opinion and incorporated the assumption that there would be significant improvements in diagnosis in the future. To justify this assumption the company stated that they would be implementing a campaign to improve awareness amongst clinicians of CLN2 and also state that [redacted]. The ERG, however, notes that no such programme exists in the UK presently and the company's commitment to such a programme remains unclear. Further, the benefits of any such programme are highly uncertain.

Life expectancy of patients treated with cerliponase alfa

The ERG considers it unrealistic to assume that patients who receive cerliponase alfa will experience general population levels of mortality. The ERG believes there are a number of reasons why they may experience shorter life expectancy than that predicted in the model. Firstly, there is significant uncertainty regarding the assumption that patients experience no further disease progression after 96 weeks. Any relaxation of this assumption will lead to reduced life expectancy for cerliponase patients. Secondly, the ERG considers there to be significant risk that patients receiving cerliponase alfa will experience significant morbidity and mortality risks due to extra-neuronal lipofuscin storage. Thirdly, there may be other disease related mortality not directly attributable to progression of the disease, but associated with the significant neuro-disability experienced by CLN2 patients.

Health related quality of life

The ERG's primary concern within HRQoL is the difference in the vignette descriptions used in the utility study as the vignettes imply significant additional benefits of treatment with cerliponase alfa over and above the effects on disease progression. Specifically, the vignettes implied that cerliponase alfa improves seizure control, improves control of dystonia and myoclonus, and delays the need for a feeding tube. The ERG is also concerned that the utility values applied in the less severe health states (health state 1 and 2) are very high, and while potentially a reasonable representation of the HRQoL of children, would imply utility values that exceed adult general population. This is of particular concern in scenarios where disease stability is assumed.

In addition to the above, the ERG identified a number of further issues. These included: a failure to properly account for the effects of vision loss in cerliponase alfa patients; assumptions made with regards to health state costs including a failure to appropriately model a number of important costs of care, and to account for the fact adult patients will have different needs to paediatric patients;

application of carer and sibling disutilities beyond a reasonable time period; and, inappropriate application of 1.5% discount rate.

1.7 ERG commentary on the robustness of evidence submitted by the company

1.7.1 Strengths

With the exception of the discount rate used, the company economic submission met the requirements of the NICE reference case and utilised appropriate available evidence. The economic model accommodated a number of key clinical elements of the treatment and management of CLN2 disease and included a range of sensitivity and scenario analyses to address uncertainties.

1.7.2 Weaknesses and areas of uncertainty

The principle weakness of the economic evidence submitted by the company relates to health state utilities and implied benefits of cerliponase alfa treatment which were not substantiated by provided clinical evidence. The ERG also had substantive concerns relating to the health state resource use, in particular, a failure to appropriately model a number of important costs of care, and to account for the fact adult patients will have different needs to paediatric patients.

In addition, to the above weaknesses in the company's approach, there are three significant areas of uncertainty in the cost-effectiveness analysis. The first relates to the long-term effectiveness of cerliponase alfa, as it is unclear of whether patients will continue to progress or will stabilise. The second relates to uncertainty regarding the impact of extra-neuronal disease pathology; it is currently unclear how this will impact on long-term morbidity and mortality. The third concerns the diagnosis of patients and whether greater awareness CLN2 disease will shorten time to diagnosis. The ERG also notes that the company model is very heavily reliant on expert opinion to inform the parameters, which introduces additional uncertainty into the model.

All three of these uncertainties are potentially very important to determining the cost-effectiveness of cerliponase alfa, and the ERG judged the company's position on all three of these issues to be overly optimistic, in each case assuming the most positive outcome despite weak or contradictory evidence.

1.8 Summary of exploratory and sensitivity analyses undertaken by the ERG

The ERG corrections of calculation errors suggest that the ICER for cerliponase alfa compared with standard care is £[redacted] per QALY gained. The ERG's additional exploratory analyses, using a range of alternative assumptions, indicate that the company's base-case is likely to be overly optimistic and to significantly overestimate the benefits of cerliponase alfa.

The ERG conducted a series of exploratory analyses exploring the robustness of the cost-effectiveness results to specific assumptions and additional uncertainties identified by the ERG. The most important of these scenarios relate to changes made by the ERG to the distribution of ML scores at the start of

treatment, and the impact of cerliponase alfa on disease stabilisation. The ERG also presents an alternative base-case based on a combination of a number of these scenario analyses.

The ERG explored the following amendments to the company's revised base-case:

- Revised starting population (the distribution of patient CLN2 rating scores at baseline);
- Revised cerliponase alfa transition probabilities from 190-201 and 190-202 trial data;
- Assuming *(i)* partial disease stabilisation or *(ii)* no disease stabilisation of cerliponase alfa patients by week 96;
- Long-term mortality for disease stabilisers (inclusion of extra-neurological mortality and neuro-disability-related mortality);
- The development of blindness in cerliponase alfa patients, who incur additional related support costs and disutility;
- Quality of life (alternative data to inform utility value, removal of HRQL benefit for cerliponase alfa patients, age-adjusted utilities, removal of carer and sibling disutility after 30 years);
- Additional resource use (ECG monitoring, behavioural support and residential care);
- A discount rate of 3.5%.for costs and benefits

The results of these scenario analyses including the ERG's preferred range of scenarios are summarised in Table 1.

The ERG's preferred base-case predicts a substantially lower number of QALYs and lower treatment costs for cerliponase alfa patients, attributable to the increased mortality of these patients and a starting population with a more severe stage of CLN2 disease. The ERG's base-case ICER was [redacted] for cerliponase alfa compared to standard care. This is substantially higher than the company predicted ICER of [redacted] – in the company model, the benefits of cerliponase alfa are realised over an extended period with patients being maintained in the less serve health states for a protracted period of time. This contrasts with the ERG's base-case where progressive decline is observed together with a growing mortality risk. The ERG base-case predicts that even with zero drug acquisition costs, cerliponase alfa remains cost-ineffective at threshold of [redacted] per QALY.

The ERG also conducted alternative scenarios within the ERG base-case analysis, to further explore the impact of a number of assumptions; acknowledging that some of the assumptions made in the ERG base-case are somewhat speculative and potentially represent a conservative interpretation of the available evidence. A scenario, considered an "optimistic" base-case scenario (early stabilisers are able to achieve long-term stabilisation, no extra-neurological mortality is assumed, and cerliponase

alfa is assumed be associated with HRQoL benefits over and above delayed progression) results in an ICER of [redacted] per QALY.

Table 1

#	Scenarios	Treatments	Costs	QALYs	Inc. cost	Inc. QALY	ICER	Threshold	Change in ICER
-	***CS base-case[$] (corrected)***	Cerliponase alfa	[redacted]	29.24	[redacted]	30.20	[redacted]	[redacted]	-
		Standard care	£151,608	-0.96	N/A	N/A	N/A	N/A	N/A
1	**Patient distribution in 190-901 trial**	Cerliponase alfa	[redacted]	17.38	[redacted]	18.79	[redacted]	[redacted]	[redacted]
		Standard care	£143,004	-1.41	N/A	N/A	N/A	N/A	-
2	**Patient distribution in 190-901 trial, restricted to CLN2 score of 2+**	Cerliponase alfa	[redacted]	18.11	[redacted]	19.51	[redacted]	[redacted]	[redacted]
		Standard care	£145,156	-1.40	N/A	N/A	N/A	N/A	-
3	**ERG re-estimated transition probabilities for cerliponase alfa**	Cerliponase alfa	[redacted]	29.28	[redacted]	30.24	[redacted]	[redacted]	[redacted]
		Standard care	£151,608	-0.96	N/A	N/A	N/A	N/A	-
4	**Disease stabilisation for early stabilisers on cerliponase alfa**	Cerliponase alfa	[redacted]	23.55	[redacted]	24.51	[redacted]	[redacted]	[redacted]
		Standard care	£151,608	-0.96	N/A	N/A	N/A	N/A	-
5	**No disease stabilisation for cerliponase alfa patients**	Cerliponase alfa	[redacted]	10.85	[redacted]	11.81	[redacted]	[redacted]	[redacted]
		Standard care	£151,608	-0.96	N/A	N/A	N/A	N/A	-
6	**Extra-neurological mortality**	Cerliponase alfa	[redacted]	12.18	[redacted]	13.14	[redacted]	[redacted]	[redacted]
		Standard care	£151,608	-0.96	N/A	N/A	N/A	N/A	-
7	**Neurodisability-related mortality**	Cerliponase alfa	[redacted]	28.23	[redacted]	29.19	[redacted]	[redacted]	[redacted]
		Standard care	£151,475	-0.96	N/A	N/A	N/A	N/A	-
8	**Development of blindness in cerliponase alfa patients**	Cerliponase alfa	[redacted]	25.64	[redacted]	26.61	[redacted]	[redacted]	[redacted]
		Standard care	£151,608	-0.96	N/A	N/A	N/A	N/A	-
9	**EQ-5D-5L data to model HRQL**	Cerliponase alfa	[redacted]	32.36	[redacted]	32.55	[redacted]	[redacted]	[redacted]
		Standard care	£151,608	-0.20	N/A	N/A	N/A	N/A	-
10	**PedsQL data to model HRQL**	Cerliponase alfa	[redacted]	33.15	[redacted]	32.12	[redacted]	[redacted]	[redacted]
		Standard care	£151,608	1.03	N/A	N/A	N/A	N/A	-

11	**Age-adjusted utilities**	Cerliponase alfa	[redacted]	27.50	[redacted]	28.46	[redacted]	[redacted]	[redacted]
		Standard care	£151,608	-0.96	N/A	N/A	N/A	N/A	-
12	**Removed carer and sibling disutility after 30 years**	Cerliponase alfa	[redacted]	30.20	[redacted]	31.17	[redacted]	[redacted]	[redacted]
		Standard care	£151,608	-0.96	N/A	N/A	N/A	N/A	-
13	**Same utility values in each arm**	Cerliponase alfa	[redacted]	26.49	[redacted]	27.45	[redacted]	[redacted]	[redacted]
		Standard care	£151,608	-0.96	N/A	N/A	N/A	N/A	-
14	**Additional ECG cost**	Cerliponase alfa	[redacted]	29.24	[redacted]	30.20	[redacted]	[redacted]	[redacted]
		Standard care	£151,608	-0.96	N/A	N/A	N/A	N/A	-
15	**Psychiatric support**	Cerliponase alfa	[redacted]	29.24	[redacted]	30.20	[redacted]	[redacted]	[redacted]
		Standard care	£151,608	-0.96	N/A	N/A	N/A	N/A	-
16	**Residential care**	Cerliponase alfa	[redacted]	29.90	[redacted]	30.86	[redacted]	[redacted]	[redacted]
		Standard care	£151,608	-0.96	N/A	N/A	N/A	N/A	-
17	**Discounted cost and QALYs at 3.5%**	Cerliponase alfa	[redacted]	17.27	[redacted]	18.12	[redacted]	[redacted]	[redacted]
		Standard care	£142,486	-0.84	N/A	N/A	N/A	N/A	-
18	**ERG preferred scenario (#1 +#5 + #6 + #7 + #8 + #11 + #12 + #13 + #14 + #15 + #16 + #17**	**Cerliponase alfa**	[redacted]	**2.02**	[redacted]	**3.32**	[redacted]	[redacted]	[redacted]
		Standard care	**£135,549**	**-1.30**	**N/A**	**N/A**	**N/A**	**N/A**	-

$, all ERG corrections and adjustments implemented to the company's base-case model; CS, company submission; PAS, patient access scheme; ICER, incremental cost-effectiveness ratio; Inc, incremental; n/a, not applicable; QALY, quality adjusted life year; ERG, evidence review group

2 Background

2.1 Critique of company's description of underlying health problem.

2.1.1 Overview of the condition

This section presents an overview of the underlying health problem described in the company's submission. The company provided an overview of the key issues relating to CLN2 disease; including details of the underlying disease mechanisms, a description of the typical course of the disease, and its epidemiology. The company also explored the impact of the condition upon the quality of life of patients and carers.

The Company Submission (CS) describes classic late-infantile neuronal ceroid lipofuscinosis (CLN2 disease) as a hereditary, autosomal recessive, neurodegenerative disorder; one of a family of around 14 lysosomal storage disorders collectively referred to as the neuronal ceroid lipofuscinoses (NCLs). CLN2 disease is caused by a mutation in the *CLN2* (*TPP1*) gene, encoding the lysosomal enzyme tripeptidyl-peptidase 1 (TPP1). This enzyme is expressed in the lysosomes of all cells, and is involved in the breakdown and recycling of ceroid lipofuscin, a type of lysosomal storage material. However, in the absence of sufficient enzymatic activity, this material accumulates to a lethal level in the cell. The CS states this accumulation occurs in the neuronal, glial, and retinal cells, leading to progressive degeneration of the brain and retina. However, the ERG noted that pathological lipopigment storage is detectable in many tissues outside the nervous system [1-7], as with the other neuronal ceroid lipofuscinoses [8]. Therefore, the disease cannot be considered to be limited to the central nervous system (CNS), despite the early manifestation of these aspects. This incomplete characterisation of the disease mechanism is an important omission, as the company did not go on to address the potential effects of long-term partial treatment of the disease pathology.

The CS stated correctly that symptoms typically become apparent in late infancy, initially marked by unprovoked seizures and ataxia between the ages of two and four years old, although this is often preceded by a history of delayed speech development. Progression of the disease is rapid and predictable; over the course of 2.5 years, independent mobility and motor control is lost, with most patients non-communicative and unable to sit unsupported by age six. Patients lose the ability to swallow, necessitating artificial feeding via a nasogastric or gastrostomy tube. Visual acuity declines from around the age of four, leading to blindness within three years. Beyond the age of six, patients are bedridden, suffering myoclonus, epilepsy, dystonia, and ultimately blindness. Based on the literature cited in the CS, death occurs between the age of 8 and 12 years [9, 10]; the DEM-CHILD natural history cohort (the largest of its kind for CLN2) found a median time from first symptom to death of [redacted].

CLN2 disease is described as an 'ultra-rare' condition, with an incidence of 0.5 cases per 100,000 live births, equating to four to six new diagnoses every year in England and Wales, and a total of 25-30 children currently affected.

The CS correctly describes the management of CLN2 as complex, with extensive multidisciplinary care and a wide range of drugs required for palliation and symptomatic relief. However, no currently available treatments are capable of modifying the disease course, or addressing the underlying cause of the disease. The CS highlights the unmet need for a technology that targets and arrests the disease mechanism, stating that such a treatment would have significant benefits upon the quality of life of patients, families, and to society as a whole.

2.1.2 Disease morbidity and clinical evaluation

This section of the CS briefly describes the disease and its typical course, with a particular focus on the evaluation of disease progression in CLN2.

The CS presents a description of the Hamburg Scale and the Weill Cornell scale - two commonly used disease-specific instruments for evaluating the severity and progression of CLN2 disease. The Hamburg Scale assigns a value of 3 to 0 for each of the following symptoms: motor (walking ability), language, visual, and seizures, with 3 representing normality (relative to the patient's best), and 0 representing a complete loss of function. The Weill Cornell scale similarly assesses gait and language, with the addition of myoclonus and feeding (swallowing dysfunction), each scored from 3 to 0. The CS describes and compares the constituent domains used to evaluate clinical progression, stating that as deterioration of motor function and language ability best reflect early progression of CLN2 disease, these aspects of the above scales should be combined to quantify clinical progression. The visual, myoclonus, seizures, and feeding domains were discarded, retaining only the motor and language domains as the 'CLN2 clinical rating scale', which is scored from 0 to 6, and is used in the clinical trials conducted by the company. The ERG noted that many of the clinical advisors to the EMA were concerned that this scale did not cover cognitive and developmental aspects of the disease, and that it was unable to capture developmental improvements [11]. Other clinicians criticised the omission of vision and seizure criteria, which prevented a more comprehensive description of the patients' clinical situation [11].

The ERG deemed the company's description of the disease largely appropriate, given current clinical evidence, however, only the neurological aspects of this condition were included. While death usually occurs due to complications arising from neurological degeneration, the expression of TPP1 is not limited to the CNS; the disease-related accumulation of ceroid lipofuscin in other organs is well established[1, 2, 4-8]. Cardiac involvement in CLN2 is widely regarded as a concern [1, 11, 12], particularly if treatment prolongs lifespan and allows underlying cardiac conduction and structural abnormalities to

worsen [13]. The ERG noted that cardiac hypertrophy and conduction disorders have been identified in older CLN2 patients [14, 15] and are common in CLN3 patients [16]. Furthermore, canine models of CLN2 disease exhibited severe progressive cardiac and hepatic impairment when treatment with exogenous TPP1 enzyme[1] was administered through the ICV route alone, indicating a potential need for systemic administration of TPP1. The European public assessment report (EPAR) for cerliponase alfa emphasised the importance of close monitoring of cardiac events, recommending ECG monitoring every 6 months, and during each ICV infusion in patients with present or past bradycardia, conduction disorders, or with structural heart disease – which included [redacted] of trial patients [17].

This concern regarding non-neuronal pathologies was also echoed by the ERG's clinical advisor, who believed it biologically plausible and likely that patients would experience extra-neurological morbidity and mortality, as untreated accumulation of ceroid lipofuscin may well lead to pancreatic, intestinal, cardiac, and hepatic pathologies and impairment. Furthermore, the EMA suggests that close monitoring should be performed at a minimum until there is sufficient clinical evidence on long-term extra-neuronal involvement [11]. These concerns were raised with the company at the points for clarification stage (PfCs) by the ERG, but were dismissed by the company in their clarification response. The ERG, however, considers that in in the absence of clinical evidence, it is prudent to defer to pre-clinical evidence and clinical opinion when making predictions regarding long-term treatment efficacy and safety.

2.1.3 Prevalence of CLN2 disease

There is a distinct lack of data on the prevalence of CLN2 disease in the UK, but the CS referenced a number of sources of incidence and prevalence data, with global prevalence averaging ~0.75 per million population, and an incidence of 0.5 per 100,000 live births. The CS identified a UK study which reported a prevalence of >0.31 per million population, with an incidence of 0.78 per 100,000 births – higher than the estimated global average. However, the company chose to use the global values to estimate an incident population of four to five children per year, and 30 – 40 children currently living with the disease in England and Wales. The ERG recognises that use of UK-specific rates would not significantly change the anticipated rate of cerliponase alfa uptake.

2.1.4 Quality of Life

The company conducted a systematic literature review and review of patient organisation websites to identify information on patient, caregiver, and family quality of life in CLN2 disease. These searches did not identify any relevant studies, so an elicitation exercise was performed with 'eleven key opinion leaders', who provided information on management of CLN2 patients. The company also investigated the correlation of disease severity in terms of the Weil Cornell rating scale with HRQoL,

and performed a survey to evaluate the impact of the disease on caregivers and families in the UK and Germany.

[redacted]

The company's survey of 19 families in the UK and Germany highlighted the severe impact of CLN2 disease on caregivers, siblings, and families as a whole. This study described substantial disruption and changes to daily life and a significant emotional burden for families, with detrimental effects on family relationships and the wellbeing of unaffected siblings. Families described a significant financial burden, driven by sacrificing employment to provide care, and funding specialist equipment and adaptations to the home and car. Family HRQoL was assessed using EQ-5D-5L, PedsQL Parent Report for Toddlers, and PedsQL family impact module (PedsQL-FIM). This study suggested that disease stage and severity had an impact on caregiver burden, with families of severe-stage CLN2 disease patients having a significantly lower HRQoL than those of children in early/decline phase and of deceased children. Caregivers reported lower life satisfaction, lower happiness with their partner, and 73.45 more caring hours per week compared with parents of healthy children of the same age. Notably, family quality of life was found to be higher in the bereaved stage than at any point throughout their child's disease.

2.2 Critique of company's overview of current service provision

The CS provides a description of the current state of diagnostics and treatment options for CLN2 disease, and explains how the company envisages cerliponase alfa would fit into the clinical pathway of care in the UK.

The CS describes a protracted diagnostic process typically taking between two and three years from symptom onset to diagnosis. A lack of disease awareness due to the condition's rarity means non-specific symptoms such as language delay will usually be overlooked, and control of seizures generally takes precedence over determining their cause. Children are often referred to speech therapists and provided treatment for epilepsy before referral to an appropriate specialist, with studies suggesting an average delay of between 20 months[18] and 2.3 years [19] from symptom onset to final diagnosis. The CS states that most patients are diagnosed at approximately five years of age, by which

point the disease has progressed substantially, emphasising the importance of early diagnosis. The gold standard diagnostic process is based on demonstration of TPP1 enzymatic deficiency in leukocytes, fibroblasts, or a dried blood spot test, with confirmation by mutation analysis of the *TPP1* gene.

Elicitation exercises performed by the company found global consistency in clinical management of CLN2 disease. Management strategies are guided by the principles of paediatric palliative care, aiming to maintain function and quality of life as long as possible. There are no currently available treatments which address the underlying cause of the disease, so a multidisciplinary approach is taken to manage the many medical, practical, and psychosocial needs of patients and families. Patients are typically given multiple anti-epileptic drugs and muscle relaxants to control seizures and movement disorders, while analgesics and anti-muscarinic drugs are used to manage pain and secretions. A survey cited by the CS reported that mood changes, sleeping, vision, and communication difficulties were also managed pharmacologically [20]. While general patient care in early disease is typically provided by parents, who must often provide full-time commitment as a caregiver, the CS refers to 20 other professionals involved in the care of CLN2 patients and their families. Further to this, the ERG's clinical advisor noted that many patients require 24-hour at-home nursing and special adaptations in the home once they become bed-ridden, with parents unable to provide the necessary level of care alone.

The CS refers to the two expert reference centres for treatment of CLN2; Great Ormond Street Hospital, and the Royal Manchester Children's Hospital, and expects these hospitals to be the only sites in the UK with the expertise to administer cerliponase alfa upon its introduction. However, the company clarified that once stabilised, patients could potentially be infused in any paediatric neurology department with an emergency response unit. The plausibility of such a change to service provision is uncertain, and may be associated with an increased risk of infection.

2.2.1 Description of the technology under assessment

The CS provides a brief overview of cerliponase alfa (Brineura™), describing the drug as a recombinant form of the TPP1 enzyme administered to the cerebrospinal fluid (CSF) by infusion via a surgically implanted intracerebroventricular (ICV) access device. The blood-brain barrier prevents large molecules such as this from passing into the brain, and therefore necessitates administration of the drug directly to the affected tissues. Cerliponase alfa is an enzyme replacement therapy (ERT), delivered to the target cells as an inactive proenzyme which is then activated following translocation to the lysosomes within brain and central nervous system (CNS) cells. Cerliponase alfa received marketing authorisation from the European Medicines Agency (EMA) on the 30th May 2017, the drug has an 'orphan designation' and as it was approved under exceptional circumstances, the decision is subject to review whenever new information arises.

The ICV access device is surgically implanted prior to the first infusion, this device comprises an injection port and reservoir under the scalp of the patient, attached to a catheter leading directly to the cerebral ventricles. Cerliponase alfa is supplied as a sterile solution in single use 5ml vials (30mg/ml), with a recommended dose of 300mg to be infused over approximately 4.5 hours, administered every other week. The drug is to be administered by a healthcare professional trained in ICV administration, observing strict aseptic technique to reduce the risk of infection. Anti-histamines and antipyretics are recommended 30-60 minutes prior to the start of infusion. The company anticipate that this drug would be used for the duration of the patient's life, subject to clinical judgement. The ERG noted that the EMA pharmacokinetic profile of cerliponase alfa states that the drug remains localised within the CNS when administered via ICV infusion, and due to the presence of the blood-retinal barrier, is unlikely to reach therapeutic concentrations in the affected cells of the retina [11]. While the ERG recognises there is a potential central component implicated in vision loss, which may be slowed by treatment, degeneration of the retina still appears to occur at the same rate [21]. Therefore, cerliponase alfa will not prevent vision loss without separate intravitreal injection of the drug.

The CS states that no additional tests or investigations would be required for monitoring patients. However, as stated in Section 2.1.2, the EMA approval document recommends close observation of cardiac health through frequent electrocardiogram (ECG) monitoring in patients with and without cardiac abnormalities [11]. The ERG notes this is also mandated in the United States by the Food and Drug Administration (FDA) [22].

2.2.2 Anticipated impact of the technology

Across the company's main submission and particularly in the economic modelling, the CS presents a narrative of treatment with cerliponase alfa being essentially curative with regards to symptomatic progression. The CS anticipates that treatment will permanently stabilise or improve all characteristic aspects of CLN2 disease, thereby eliminating disease-related mortality, and expects patients to achieve a life expectancy in line with the general population.

The ERG has particular concerns with the company's presentation and unduly optimistic interpretation of the pre/clinical evidence, and considers it important to note the discrepancies between the company's claims regarding the impact of this technology, and what can be reasonably supported by the available biological and clinical evidence. This is discussed in Sections 4 and 5.

3 Critique of company's definition of decision problem

3.1 Population

In the statement of the decision problem, the company identified the population as 'people with a confirmed diagnosis of CLN2 disease'. While this is in line with the population specified in the NICE

scope, the ERG considers the population within clinical evidence presented by the company to be far narrower, and as such it may not reflect the characteristics of the wider patient population in England and Wales. The patient populations in the trial evidence submitted by the company had mild to moderate disease (a two-domain Hamburg score of 3 to 6), requiring seizures to be 'stable' in the opinion of the investigator, and patients to be over the age of 3. It is unclear what population the trial population represents, as it was clearly neither the incident nor prevalent population. The ERG believes the imposition of strict selection criteria may have systematically excluded a significant proportion of patients covered in the NICE scope, however, all patients officially screened for the 190-201 trial were included, which suggests there may have been a pre-screening process.

3.2 Intervention

The intervention described in the CS is cerliponase alfa (Brineura™), which matches the intervention described in the final NICE scope. Cerliponase alfa is an enzyme replacement therapy, comprising a recombinant form of tripeptidyl-peptidase 1 (rhTTP1) – the enzyme implicated in the pathogenesis of CLN2 disease. A 300mg dose is infused directly into the brain every two weeks via an implanted intracerebroventricular (ICV) delivery system.

European marketing authorisation was granted for the treatment of patients with CLN2 disease on 30th May 2017. Cerliponase alfa was authorised under 'exceptional circumstances', as the company were unable to provide sufficiently comprehensive data on the efficacy and safety of the drug. The currently licensed dose is 300mg of cerliponase alfa in patients 2 years and older, there is no data in patients younger than two years of age, so posology in these patients is based on estimated brain mass. Patients aged 0 - 6 months are to receive a dose of 100mg, those aged 6 – 12 months receive 150mg, and between 1 and 2 years patients are given 200mg for their first four doses, and 300mg for subsequent doses.

3.3 Comparators

The comparator specified in the NICE scope is established clinical management of CLN2 disease, including the multidisciplinary and multiagency approach used to manage symptoms and complications. The decision problem addressed in the company submission reflects the NICE scope, as does the submitted evidence. Patients in the comparator groups described in the CS belong to an independent natural history cohort, whom it is assumed were treated optimally according to expert clinical opinion.

3.4 Outcomes

The decision problem addressed in the CS included most of the outcomes described in the NICE scope, providing trial data on disease progression in terms of the company's CLN2 rating scale, aggregated Hamburg scores, mortality, and adverse events (including myoclonus, dystonia, and

seizures). The HRQoL of patients and their families was assessed using the PedsQL Generic Core Scale and Family Impact Modules, and the 190-202 trial also recorded EQ-5D-5L. The primary measure of patient HRQoL was the 'CLN2 Disease-based QoL instrument', which was designed by the company based on focus group feedback. The company also presented MRI outcome data, which was further to that specified in the final scope. However, the company did not report appropriate measurements of several outcomes included in the final scope, and omitted relevant data collected in the clinical trials. Despite the importance of vision loss in CLN2 disease, and to the company's expected impact of the drug, there was no specific examination (e.g. optical coherence tomography (OCT), electroretinogram, visual evoked responses) of ophthalmological function. The company presented disaggregated Hamburg/Weill Cornell vision domain data upon request, however, this was considered an inadequate assessment of visual function by clinicians [11], who suggested ophthalmological functional endpoints would have been a more plausible representation of vision loss, and recommend OCT as an assessment of retinal degeneration in CLN disease [23]. The CS also omitted trial data and discussion of immunogenicity, electroencephalographic (EEG) epileptiform outcomes, and electrocardiographic (ECG) outcomes, which the ERG considered inappropriate given the potential significance of these outcomes to considerations of long-term clinical effectiveness and safety.

3.5 Other relevant factors

The CS includes a section on considerations of equality, and states that the company has not identified any relevant issues regarding equity or equality to this submission.

4 Clinical Effectiveness

This section contains a critique of the methods of the review(s) of clinical effectiveness data, followed by a description and critique of the trials included in the review, including a summary of their quality and results and the results of any synthesis of studies.

4.1 Critique of the methods of review(s)

4.1.1 Searches

The CS contained the search strategies used to identify studies of interventions for CLN2 disease or TPP1 deficiency. The search strategies were briefly described in the main submission in Section 9.1.1 (published studies) and Section 9.1.2 (unpublished studies). Full search strategies were provided in Appendix 2, Section 17.2.

The following databases were searched on 23rd January 2017: MEDLINE (including MEDLINE daily, MEDLINE In-Process and Epub), Embase, Cochrane Database of Systematic Reveiws (CDSR), Cochrane Central Register of Controlled Trials (CENTRAL) and Database of Abstracts of Reviews of Effects (DARE). Retrieval was limited in MEDLINE and Embase to the following study designs: RCTs or non-RCTs, observational studies, registries and case studies. The search was not limited by language or date.

The database searches were supplemented by searches of the following conference proceedings: International Conference on Neuronal Ceroid Lipofuscinosis (2016), WORLD Symposium (2015, 2016), International Child Neurology Congress (2016) and the Society for the Study of inborn Errors of Metabolism Meeting (2016). In addition, reference checking of relevant systematic reviews and meta-analyses identified by the database searches was undertaken. The company also searched the European Medicines Agency website for any European Public Assessment Reports of relevant treatments. In August 2017, the company searched their own internal database to identify any further relevant published studies.

Clinical data from unpublished studies was sought via a search of the World Health Organization International Clinical Trials Registry Platform (WHO ICTRP) on 13th February 2017.

Overall the searches were appropriate, and well performed and reported. A wide range of synonyms and appropriate subject headings were included in the strategies for CLN2 disease and TPP1 deficiency. All search lines were combined correctly, search syntax across all databases was used correctly and no typographical errors were found. The reporting of the searches was clear with sufficient detail to allow the searches to be reproduced in all sources. A slight discrepancy between the total number of search results per database reported in the PRISMA diagram and the totals

reported in the search strategies was found. The manufacturer sent a corrected version of the PRISMA diagram in their responses to the points for clarification.

The search strategies for MEDLINE and Embase were structured around terms for CLN2 disease or TPP1 deficiency, limited to specific study designs. Search filters developed by the Scottish Intercollegiate Guidelines Network (SIGN) were used to restrict retrieval to RCTs or non-RCTs, observational studies, registries and case studies. This approach has the benefit of potentially retrieving studies on cerliponase alfa as well as studies on any other comparator interventions for this condition. However, studies could have been missed in MEDLINE and Embase, due to limiting to specific study designs. Although previous research has shown that validated RCT filters are generally reliable and the risk of missing studies is minimal, this is not the case for non-RCT search filters. The company stated in their responses to the points for clarification that attempts were made to increase the sensitivity of the SIGN search filters through in-house additions. These additions may have gone some way towards minimising the risk of missing studies.

Restricting the search in MEDLINE and Embase to RCTs and non-RCTs may have resulted in relevant systematic reviews on interventions for CLN2 disease or TPP1 deficiency to be missed. Although DARE was searched to identify systematic reviews, this database closed in March 2015 so any relevant systematic reviews published from 2015 onwards may not have been identified by the searches presented.

4.1.2 Inclusion criteria

The systematic review in the CS reported the following inclusion criteria for both published and unpublished studies (see Table 2).

Table 2 Inclusion criteria for systematic review included in the CS (adapted from Table C1 in CS)

Domain	Inclusion/Exclusion criteria
Population	Patients with any variant of CLN2 disease or TPP1 deficiency
Interventions	Any intervention
Comparator	Any or none
Outcomes	Any efficacy or safety outcomes Studies where outcomes were not reported separately for population of interest were excluded
Study design	RCTs, or Interventional non-RCTs (such as single-arm clinical trials, non-randomised comparative studies, observational studies, retrospective studies, case reports, case series, registries) Exclusion criteria were: economic evaluations; editorials, notes, commentaries or letters; narrative or non-systematic literature reviews

The inclusion criteria for the systematic review were broad, comprehensive and reflective of the decision problem.

4.1.3 Critique of data extraction

Study selection and data extraction methods were conducted and reported in an acceptable manner (see Appendix 3, section 17.2.7). Full text articles were independently assessed for eligibility by two reviewers with any disagreement resolved by a third reviewer. Data extraction was conducted by a single reviewer and checked by another reviewer.

4.1.4 Quality assessment

Quality assessments were conducted for all included studies using appropriate criteria (see CS Appendix 3, section 17.3). The critical appraisal questions were based on an adaptation of the CASP tool for cohort studies. The criteria were appropriate and included items on recruitment, measurement of exposure, measurement of outcome, identification and adjustment for important confounding factors, completeness of follow up and precision of results. However, the company eliminated a question on whether the length of follow up was appropriate, which is a key issue in the context of this submission.

It was not reported whether these were conducted by a single reviewer or checked by another reviewer.

4.1.5 Evidence synthesis

No formal evidence synthesis was conducted of included studies other than those conducted by BioMarin.

Tables C2-C4 of the CS reported the population, intervention, comparator and outcomes of included studies in the systematic review. Table C2 reported data for included studies identified in the original search, Table C3 reported similar data for unpublished trials identified in trial registries and Table C4 reported data for two further trials identified after the original search was conducted. A very limited narrative summary was also provided of the two trials summarised in Table C4. More detailed data abstraction from included studies was provided in Appendix 3, section 17.3 of the CS.

The justification for no formal evidence synthesis of non-BioMarin trials was that none of these included studies were relevant to the submission. It is unclear why the eligibility criteria of the company systematic review included studies not relevant to the submission. But the ERG considered this unlikely to impact on the validity of the conclusions of the systematic review. Critique of trials of the technology of interest, their analysis and interpretation (and any standard meta-analyses of these)

The primary study included in the CS was of 23 patients who received cerliponase alfa over 48 weeks (study 190-201) and then followed up to approximately 96 weeks in an extension study (study 190-202). In addition, there was a study of natural history controls (study 190-901) used to compare the efficacy of cerliponase alfa against conventionally-treated patients.

4.2 Studies on the clinical efficacy and safety of cerliponase alfa

The primary study 190-201 evaluating the clinical efficacy and safety of cerliponase alfa was on 23 patients with CLN2 disease followed up over 48 weeks. Ten patients were enrolled during the dose escalation period (one patient dropped out after the first dose) and fourteen patients started during the stable dose period.

After 48 weeks, those who had completed study 190-201 were then enrolled in extension study 190-202, which is intended to follow patients for up to 240 weeks. Most data in the trial is reported for up to 96/97 weeks of follow up, although some slightly longer-term data is also available for some outcomes.

Two further studies 190-502 (an expanded access scheme for patients who couldn't participate in the trial) and 190-203 (where siblings of participants in 190-201 have an opportunity to enrol) were also

described in the CS, but no further data was reported there. In response to an ERG request for clarification preliminary data from 190-203 was reported.

The primary analyses were on the 23 patients who continued to receive cerliponase alfa for the duration of the trial. Sensitivity analyses were conducted on: a) the efficacy population which excluded two further patients (n=21) who began treatment with a maximum CLN2 rating score of 6 but experienced no decline during 190-201 or the 190-202 extension study b) the full population of 24 patients with an imputed 4-point loss for the patient who withdrew from the trial c) full population with the two patients with no decline over follow up excluded (n=22).

4.2.1 Patient characteristics: inclusion criteria and baseline characteristics

Summary inclusion criteria

Detailed inclusion criteria for study 190-201 and the extension study 190-202 are provided in Tables C5 and C6 in the CS.

For study 190-201, patients were required to have mild-to-moderate (defined as between 3-6 on the CLN2 rating scale with at least one point in both motor and language domains) CLN2 disease. Diagnosis was required to be determined by TPP1 enzyme activity (dried blood spot test). If no genotype information available then blood was collected for CLN2 gene analysis at baseline. Seizures also had to be judged stable by the investigator. Patients under 3 years and over 16 years were not eligible for inclusion in the trial.

For entry into study 190-202, patients had to complete 48 weeks in study 190-201. Patients who had lost 3 or more points or had a score of 0 in the combined motor and language domains of the CLN2 rating scale were not eligible for inclusion.

Baseline characteristics and generalisability

Table 3 Baseline characteristics of cerliponase alfa patients (adapted from Table 11.2.2.1 in CSR)

Study	Age		Gender: number of patients (%)	Ethnicity: number of patients (%)	Genotype: number of patients (%)	Baseline CLN2 score (ML): number of patients (%)		
	Disease onset (years)	At enrolment (years)				Screening	Start of study	Start 300mg
Study 190-201/202	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Mean age ([redacted] years) and time from mean disease onset and enrolment ([redacted] years) appear to reflect approximately the literature cited in the background section of the CS (see Table 3). Although there were a substantially larger proportion of males included in the trial; this was unlikely to impact on findings as gender is not known to be a prognostic factor in CLN2 disease. The majority of patients ([redacted]) were observed to have one or both of the most common mutations (c.622C>T or c.509-1G>C).

Baseline CLN2 scores reflect the trial inclusion criteria of mild-to-moderate disease. However, since the decision problem includes all CLN2 patients, the trial population is unlikely to be representative of all patients in England and Wales. Furthermore, the company expects to diagnose and treat patients much earlier (80% of participants with CLN2 score 5 or 6) than that reflected in the trial (16% of participants with CLN2 score 5 or 6).

A further factor impacting on generalisability is that patients were required to have stable seizures and therefore these findings may not be applicable to those without stabilisation of seizures.

4.2.2 Outcome measures in studies of cerliponase alfa

Primary efficacy analyses concerned scores on the combined motor and language domains of the CLN2 clinical rating scale developed for the purposes of the study (Table 4).

A European Medicines Agency (EMA) [11]ad-hoc experts meeting confirmed that the CLN2 clinical rating scale was acceptable as a primary outcome at least in the short term context of study 190-201/202. However, reservations were noted that focusing on motor and language domains prevented a more comprehensive evaluation of patients' clinical situation. The omission of vision and seizures from the original Hamburg/Weill Cornell scales (from which the CLN2 scales was adapted) and not assessing cognitive and developmental aspects was raised by experts as a limitation of the primary efficacy analyses. In addition, the need for appropriate measures to assess long term efficacy and safety was also raised.

Secondary outcomes included MRI measures of brain atrophy and CSF volume. Quality of life was examined using PedsQL a standard measure of quality of life in paediatric patients, Denver II Developmental Screening Test (a measure to monitor whether development deviates from the general population) and the CLN2 quality of life scale. The data presented for the CLN2 quality of life scale had several limitations; there was very little information provided about the items or domains of the scale, how the company developed the scale, and its psychometric properties.

Table 4 Outcome measures used in study 190-201/202 (adapted from tables C5 and C6 in the CS)

Study	CLN2 score	MRI outcomes	Quality of life
190-201/202	**Primary outcome: combined motor and language domains** Responder (% less than 2-point drop) Slope analyses (mean decline per 48 weeks) Time-to-2-point decline **Secondary outcome: full Hamburg scale:** motor, language, vision, seizures	**Secondary outcomes:** Whole brain volume Cortical grey matter White matter Cerebrospinal fluid Whole brain ADC	**Secondary outcomes:** Denver II Developmental Screening Test PedsQL CLN2 Disease Based Quality of Life Instrument

4.2.3 Quality assessment of studies of cerliponase alfa patients

The ERG identified greater uncertainty in their quality assessment ratings compared with ratings conducted by the company (see Table 5). For example, the ERG noted substantial differences between baseline CLN2 scores in the trial and the starting population in England and Wales assumed by the company to receive the treatment if cerliponase alfa is recommended (see Section 4.2.2 for further details). Similarly, to be eligible for the trial, patients required a CLN2 score of between 3 and 6 points, a narrower population than that specified in the decision problem.

It was also noted that the primary efficacy analyses were subjective outcomes which were open to interpretation. The ERG agreed that assessment of CLN2 disease requires clinical judgement and that it was appropriate for data from the CLN2 clinical rating scale to be the primary outcome. However, it is important to note that the use of subjective outcomes in the context of a single arm trial is associated with a high risk of bias. The largest systematic review of meta-epidemiological studies found that a lack of blinding of outcome assessors was associated with on average a 36% over-estimation of treatment effects.[24]

A further point of disagreement between the ERG and company quality assessments was on the precision of findings. Whilst the ERG agreed that the company provided confidence intervals and p-values for most data, the ERG considered that the data did not constitute a precise estimate of the treatment effect of cerliponase alfa. A lack of statistical power inherent in a trial of 23 patients negatively impacts on the likelihood that a nominally statistically significant result in comparison with natural history controls reflects a true effect. When an underpowered study discovers a true effect it is likely the estimate of the magnitude is exaggerated (sometimes referred to as the 'winners curse'). [25] The ERG accepts that within the context of a rare disease, such as CLN2, a trial sufficiently powered for comparisons between treatment and natural history controls is unlikely to be feasible and therefore this potential bias is difficult to mitigate.

The ERG also noted that an important question in the CASP tool was not included in the company assessment: 'Was the follow up of subjects long enough?' The ERG considered the follow up period was not of sufficient length to support the conclusions drawn by the company.

Table 5 Quality assessments conducted by the ERG and the company on study 190-201/202 (partly adapted from table C11 in company submission)

Question	Company assessment	ERG assessment
Was the cohort recruited in an acceptable way?	Yes	No – The inclusion criteria are narrower than that reflected in the decision problem. This sample is not generalizable to the population assumed to receive the treatment in practice as the company assumes patients will be diagnosed and treated much earlier.
Was the exposure accurately measured to minimise bias?	Yes	Yes – this is largely judged to be clinically acceptable. However, clinical experts consulted by the EMA and our clinical advisor noted that this provides only a limited measure of CLN2 disease progression but the best currently available.
Was the outcome accurately measured to minimise bias?	Yes	**Primary efficacy analyses and quality of life measures** No - The CLN2 scale is a subjective measure therefore there is a high risk of bias associated with these data in the context of an open-label trial. **MRI outcomes** Yes
Have the authors identified all important confounding factors?	Not clear	No – vision and genotype were not identified as factors to match on.
Have the authors taken account of the confounding factors in the design and/or analysis?	Not clear	No – vision loss was higher in natural history controls compared with cerliponase alfa patients.
Was the follow-up of patients complete?	Yes	Yes However, assessment misses out the second part of this question in the CASP tool: was the follow up of subjects long enough? ERG assessment was no. Given the extrapolations of the company's findings to several decades in the future the follow up period was not judged to be sufficient.
How precise (for example, in terms of confidence interval and p values) are the results	Yes	No

4.2.4 Natural history controls

The natural history (NH) population from which matched controls and estimates of the natural rate of untreated disease progression were derived was the DEM-CHILD database, a European extension of

the international 190-901 study. The DEM-CHILD database included 74 patients, spread across two clinical sites, Hamburg and Verona. The company required patients to have at least two Hamburg ML scale scores between 1 and 5 (inclusive), with one score ≥3, and at least one score ≥6 after baseline assessment. Thirty-three (44.6%) patients did not fulfil these eligibility criteria, leaving 33 at the Hamburg site, and 8 from Verona (total n = 41). There was limited demographic information available for this population, however, 59% of patients were male, and 32% were female. Eighty-five percent of the included patients were born after 1989, but some assessments were dated from the 1960s. The mean age of patients at diagnosis of CLN2 disease was 4.98 (SD 1.41) years, only 10% of patients had an ML score of 5 at diagnosis, with 51% of scores falling between 2 and 4.

Disease progression was calculated using three methods: a 'first point/last point algorithm', wherein the time between the first point – the first ML assessment of <6, and the last point – the last ML assessment >0 was calculated. A line was fitted between these two points and formed the slope which was said to represent clinical decline. This method estimated the rate of ML score decline to be 2.09 (SD 0.966) points per 48 weeks for the Hamburg and Verona populations. The second method comprised a simple linear regression analysis on all data points between the previously defined first and last points, this method also estimated a 2.09 (SD 0.988) point decline per 48 weeks. The third method used a mixed-effects model repeated measures (MMRM) approach, which modelled HML scores at 6-monthly intervals from diagnosis and from 3 years of age until the first ML score of 0. The rate of decline was between 1.29 (95% CI 1.03 to 1.54; autoregressive variance) and 1.46 (95% CI 1.12 to 1.79; unstructured variance) points from diagnosis to the first ML score of 0, substantially lower than the estimates derived using the first point/last point methods. The ERG considered the estimates of decline using MMRM methods more likely to be valid because it made better use of the data reported over time. In addition, these estimates were similar to analyses of a matched (CLN2 score, age and genotype) sample of the natural history controls that found a decline of 1.9 points at 48 weeks and 2.8 points at 96 weeks (a decline of approximately 1.4 points/48 weeks). [26]

Matching with cerliponase alfa patients

Patients in the 190-201/202 studies were matched to the 190-901 NH population using a 1:1 matching algorithm. This matched trial patients based on their CLN2 clinical rating scale score and age within 12 months. All but one of the patients in the 190-201 study were matched in this way, yielding a total of 22 matched comparisons. While the company stated each trial patient was matched to one NH patient, the ERG noted significant differences between the baseline CLN2 rating scores between the matched NH population and the source population. Firstly, Table C30 of the CS indicates two trial patients with an ML score of 6 were matched to 2 NH patients with a score of 6, however, Table 8.4 of the Study 190-901 Supplement Report [27] shows there were no patients with a score of 6 at or prior to diagnosis. The CS also shows 10 trial patients with an ML score of 3 were matched with 10 NH

patients with an ML score of 3 however, there were only 4 patients in this cohort with a score of 3 at diagnosis. We could not identify any clarification provided in the CS for these discrepancies. Potential explanations may include: trial patients were matched with imputed NH data at suitable time points; or the NH patients were not assessed using the Hamburg CLN2 scale at the times stated in the CSR, with scores assigned retrospectively (rather than being generated through imputation). This may mean trial patients' CLN2 rating scale scores were not being compared against the same outcome in the natural history population, but against estimated or imputed outcome data.

The matched populations were similar in age at baseline (190-901 4.7 ± 0.77, 190-201/202 4.7 ± 0.93). Gender composition differed substantially, with 190-901 comprising only 23% females compared to 59% in the trial population; however, there is no evidence of a difference in disease presentation or course between sexes. The Hamburg vision domain scores differed between the matched groups; NH patients had a lower vision score on average (median [redacted] vs [redacted]) which implies a systematic difference between the two groups. Deteriorating vision is a sign of more advanced disease [2] and a [redacted] difference between the cerliponase alfa and NH matched groups suggests the latter group may be more progressed overall, which could inflate the apparent efficacy of cerliponase alfa.

These results and the outcomes of matched comparisons with trial participants are subject to uncertainty for several reasons. Firstly, the ERG was unable to replicate any of the analyses produced by the company, as the origin of the data provided in the 190-901 study documents was unclear and appeared inconsistent with the company's analyses. Many assessment dates and Hamburg rating scores appeared to be imputed or estimated, as numerous patients had been assessed with this instrument many times over several years before diagnosis was confirmed. The ERG was also unable to confirm whether eligibility criteria had been appropriately applied due to this addition of imputed entries to the dataset. Furthermore, estimates of CLN2 rating score decline appeared to be sensitive to the stage of the disease and the duration of observation, as estimates varied widely. This casts uncertainty upon the company's comparison of treatment effectiveness against a 2-point annual drop, particularly given the subjectivity of the CLN2 rating scale as being representative of the natural history of the disease.

4.2.5 Summary of clinical efficacy results

Main findings were based on a study of 23 patients (study 190-201/202) compared with natural history controls (study 190-901) receiving treatment as usual. Primary efficacy analyses were based on the motor and language domains of the CLN2 clinical rating scale adapted by the company for use in their trial.

Secondary analyses included scores on vision and seizure domains, parent reported quality of life for patients, and MRI outcomes.

4.2.5.1 Disease stabilisation (CLN2 scale)

Summary of CLN2 data for cerliponase alfa patients

Mean CLN2 scale scores reported in Table 6 are based on estimates extracted independently by two ERG authors from Fig 11.4.1.2.3.1 in the interim CSR for study 190-202. Due to challenges reading off graphs these are approximate values, as means and standard deviations at these key time points were not reported in the CS.

Table 6 Summary of CLN2 scale data in study 190-201/202 (based on Table C21 in the CS, Figure 11.4.1.2.3.1)

Follow up time (weeks)	CLN2 score (ML): Mean (SD)	Absence of unreversed reduction in scores from baseline: number (%)	Absence of unreversed 2-point reduction from baseline: number (%)	Decline in CLN2 points per 48 weeks: mean (SD)
Baseline	3.48 (1.20)	N/A	N/A	N/A
16	3.04 (1.33)	14 (57)	22 (96)	NR
48	3.13 (1.36)	15 (65)	20 (87)	0.40 (0.81)
96	[redacted]	[redacted]	[redacted]	[redacted]
Last follow up	[redacted]	[redacted]	[redacted]	[redacted]

Decline in CLN2 scores for cerliponase alfa patients slows over time as shown both in the mean rate of decline and mean CLN2 score (see Table 6). However, the number of patients who experienced no decline continued to fall in later follow up periods, which suggests the need for caution when interpreting the long-term benefits of cerliponase alfa.

At 16 weeks there was a drop in mean CLN2 score of 0.44 points followed by a small increase of 0.09 points at 48 weeks. Mean CLN2 score then declined again at week 96. There was further decline up to [redacted] however, this is difficult to interpret in terms of trend in decline as assessment timing varies across patients.

The number of patients with no unreversed point reductions in CLN2 score (i.e. those thought not to be experiencing disease progression) originally improved from 14 patients in week 16 to 15 patients in week 48. However, this dropped at week 96 and at [redacted]. The data on the number of patients not experiencing reductions in CLN2 score at 96 weeks was reported inconsistently between different sections of the company

submission. For example, Table C23 reports that [redacted] patients experienced no unreversed declines at 96 weeks, but Table C21 reported that [redacted] patients experienced no unreversed declines at 96 weeks. Our reading of Figure 11.4.1.2.3.1 suggested that [redacted] patients appeared to experience no unreversed declines during that period.

'Early' and 'Late' stabilisers

Although the mean CLN2 score values are helpful for identifying average trends across the study participants, on the basis of the data on 23 patients presented in the company submission there are potentially different patterns of response to treatment.

For the cerliponase alfa group, eight patients experienced an unreversed decline of one point in the first 16 weeks. Those who experienced no further unreversed declines after 16 weeks were classified by the company as 'early stabilisers'. [redacted] patients experienced any unreversed point decline after 16 weeks (three had previously experienced an unreversed point decline before 16 weeks and the other three experienced an unreversed point decline for the first time after 16 weeks) these were classified as 'late stabilisers' by the company. Early stabilisers were assumed by the company to experience no further decline in CLN2 score after 16 weeks. Late stabilisers were assumed by the company to experience no further decline after 96 weeks.

However, there are a number of limitations to these assumptions based on the data in the trial. Firstly, no *a priori* definition of stabilisation was developed or tested; therefore, there is no way of substantiating whether these post-hoc determined categories of early and late stabilisation are due to sampling error or a genuine reflection of different response patterns to cerliponase alfa treatment.

Secondly, follow up is currently of insufficient length (most data is reported at 96 weeks) to make long term judgements about stabilisation of disease over many decades. Therefore assumptions about stabilisation of CLN2 score beyond week 96 for both early and late stabilisers aren't testable. Although there is evidence of a slowing in progression of disease, and potential stabilisation of symptoms in some patients, it is highly uncertain whether this stabilisation will be maintained long term.

While we identified [redacted] patients classified as early stabilisers who did not experience any declines in CLN2 score after week 16, in Figure 14.2.3.2.1 of the CSR (which plots CLN2 scores for each patient over the 96 week study) a substantial number of patients continued to experience declines (as well as improvements) in CLN2 score throughout the period of 16 weeks to last follow up. For example, one 'early stabiliser' ([redacted]) who appeared to be classified as stable throughout the treatment period (due to 0 point change at last follow up compared with baseline) experienced a total of four one-point declines, one two-point decline, two one-point improvements, and one two-point

improvement. Classifying patients like this as an early stabiliser calls into question the validity of this category and it is unclear whether such fluctuations reflect measurement error (and therefore the validity of the CLN2 scale to monitor treatment effectiveness in a trial) or genuine instability of symptoms (and therefore whether disease progression has been halted).

There is also substantial evidence that challenges the assumption of long term stability of CLN2 scores in 'late stabilisers' after 96 weeks. Plotting mean CLN2 score over the course of the study suggests this assumption is unlikely to be valid (see Figure 1). Reported declines in CLN2 were observed [redacted] Since declines in CLN2 score have been observed [redacted] this assumption is directly contradicted by the data.

Figure 1 Mean CLN2 score at 16, 48 and 96 weeks for patients classified as early and late stabilisers (based on data reported in Figure 14.2.3.2.1)

Figure redacted – academic-in-confidence

Primary efficacy analyses

Primary efficacy outcomes concerned analyses of change in CLN2 scale scores (a clinical rating scale of progression in motor and language aspects of CLN2 disease). All comparisons were based on a 2 point decline in the natural history controls per 48 weeks. As discussed in section 4.2.5, estimates of mean decline in the natural history controls varied depending on the statistical method used. The more sophisticated mixed effects models of repeated measures data resulted in a substantially lower estimate of mean decline (autoregressive variance: 1.29 points, 95% CI 1.03 to 1.54, unstructured variance: 1.46 points, 95% CI 1.12, 1.79) than those used in the main analyses using a line connecting

the first and last points on the CLN2 scale (2.09 points, 95% CI 1.79 to 2.40). The ERG judged that the estimates from the mixed effects model were likely to have greater validity.

Slope analysis

The mean and median rate of decline over time was estimated by calculating the decline from baseline and scaling this over a 48 week period. At the 48 week follow up the mean rate of decline in CLN2 scale was 0.4 points in the cerliponase alfa group. At 96 week follow up, the mean rate of decline had reduced to [redacted] points per 48 weeks.

Sensitivity analyses at the 96 week follow up show that the mean rate of decline increases to [redacted] per 48 weeks when the two cerliponase alfa patients with a stable CLN2 score of 6 are excluded and the patient who received a single dose before dropping out was imputed as a [redacted]-point loss. These analyses still suggest a substantial difference in mean rate of decline between groups in the natural history cohort (estimates varied from 1.29 to 2.09 points decline).

Responder analysis (% patients with less than 2 point decline per 48 weeks)

Response was defined as an absence of a two point decline in the CLN2 score based on the analyses of the mean rate of decline in natural history controls (n=41) summarised above and in Section 4.2.5. A total of [redacted] of patients at weeks 48 and 96 were responders according to this definition ([redacted]) compared with 50% of historical controls which was statistically significant.

The CS reports that 65% (15/23) of cerliponase alfa patients experienced no change or an improvement in score at week 48 but this reduced at week 96. As discussed above, the number of patients at week 96 with no decline was either [redacted] (Table C21), [redacted] (Figure 11.4.1.2.3.1) or [redacted] (Table C23).

Time-to-event data (time to a 1 or 2 unreversed points decline)

Again, an assumption of 2 points decline in natural history controls was the basis for the time-to-event analyses. Natural history patients were much more likely to experience an unreversed 2-point decline in CLN2 score compared with cerliponase alfa patients ([redacted]), similar results were found for the motor ([redacted]) and language ([redacted]) domains separately. Figure C12 in the CS suggests this analysis was based on a comparison with the full natural history cohort rather than the matched sample used in other analyses, but analyses were adjusted for baseline CLN2 score, age, genotype, and sex.

Cox regression analyses, or any other comparative data analyses, assessing the difference between cerliponase alfa and natural history groups were not reported for time to one-point decline.

Secondary efficacy analyses

Scores for Motor, Language, Vision and Seizure Domains of the Hamburg Scale

Primary analyses in the CS include data on changes in CLN2 scale which includes only motor and language domains. Table 7 CLN2 Domain Scores at weeks 48 and 97 (adapted from company response to request for clarification point A10 and A11) summarises change in vision and seizure domains along with motor and language provided in response to an ERG request for clarification. Scores on the seizure domain improved for cerliponase alfa patients by [redacted] points at week 97 relative to baseline and declined by [redacted] point in the natural history group. Although there were improvements in the seizure domain for cerliponase alfa patients this doesn't necessarily reflect a halt in the deterioration of seizures, as the seizure domain of the Hamburg reflects only the frequency of tonic-clonic seizures, and does not take into account the activity of other movement disorders. Although medical history of seizures or epilepsy was common ([redacted]), relative to baseline, [redacted] patients showed new focal epileptiform activity, [redacted] new generalised epileptiform activity, and [redacted] showed both new focal and generalised activity.

Decline in the vision domain was slower than that observed in the natural history group. However, vision scores were substantially higher ([redacted] points) in the cerliponase alfa group at baseline which potentially limits comparisons with the natural history group. Including vision along with motor and language in the Hamburg rating scale total score leads to an increase in estimated declined based on total scores on the clinical rating scale (change from baseline [redacted] points compared with [redacted] points at week 97).

The vision domain of the Hamburg rating scale may not have been sufficient to monitor progression of vision loss over time in these groups. For example, assessment of vision on the Hamburg scale requires a certain level of motor function (e.g. grabbing objects) therefore declines in the motor domain inevitably impact on assessment of the visual domain. Vision could have been better assessed using more specialised ophthalmological functional endpoints and for example Optical Coherence Tomography (OCT) as an assessment of retinal degeneration. In addition, company conclusions regarding long term declines in progression of vision loss in association with cerliponase alfa treatment were judged by the ERG to lack biological plausibility (see section 2.2.1 for further details).

Table 7 CLN2 Domain Scores at weeks 48 and 97 (adapted from company response to request for clarification point A10 and A11)

	Seizures				Vision				Motor				Language			
	Natural history		Cerliponase alfa		Natural history		Cerliponase alfa		Natural history		Cerliponase alfa		Natural history		Cerliponase alfa	
	Mean (SD)	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)	N
Baseline	[redacted]															
Week 49	[redacted]															
Change from baseline at week 49	[redacted]															
Week 97	[redacted]															
Change from baseline at week 97	[redacted]															

4.2.5.2 MRI outcomes

No comparative data from the natural history cohort was available on MRI outcomes. From baseline to week 96 cerliponase alfa patients experienced a mean loss of [redacted] total cortical grey matter volume. The annualised rate of change at week 97 (change from baseline [redacted] incremental rate of change: [redacted]) reduced from that observed at week 48 (change from baseline: [redacted], incremental rate of change: [redacted]). Change from baseline to last observation remained at a mean loss of [redacted] suggesting no further decline after week 97. However, it is unclear how long after 97 weeks the last observation was, and whether this halt in decline of grey matter loss will be maintained in later follow up periods. The ERG requested in the points for clarification document if more recent data was available beyond November 2016 but the company declined to provide these for study 190-201/202.
Quality of life

Quality of life data from the PedsQL and the CLN2QL scales show an initial improvement in quality of life reported by parents. However, between weeks 49 to 97 these scales indicate a [redacted] decline in patient quality of life during this period.

Denver II developmental screening test
Very limited information is provided about scores on the Denver II developmental screening test in both the company submission and interim CSR. All 22 patients evaluated were classified as 'suspect' at baseline, no change in classification was observed throughout the follow up period week 97 (in 21 patients).

PedsQL Parent report for toddlers
From baseline to week 49 there was a mean improvement of 2.4 points on the PedsQL parent report for toddlers. However, from week 49 to 97 there was a mean decline of [redacted] points ([redacted] points decline from baseline at week 97). Assuming a minimal clinically important difference of [redacted] points as commonly reported for PedsQL in the literature (e.g. Varni et al, 2003) there is a [redacted] reduction in quality of life from baseline and also from week 49 to 97.

Similarly, for the family impact module total score there was an initial increase of 3.7 points from baseline at week 49. However, from week 49 to week 97 there was a decline [redacted] in the parent report of quality of life ([redacted] decline from baseline at week 97).

CLN2QL
Similarly, scores for the CLN2 disease-based instrument improved by 8.1 points from baseline to week 49 but from week 49 to 97 scores declined by [redacted] points ([redacted] point improvement from baseline at week 97). It is unclear what a minimal clinically important difference is for this scale developed by the company; however, the pattern of an improvement followed by a decline reflects the pattern identified by the PedsQL seems also to be observed for this instrument.

EQ-5D-5L

Data from the EQ-5D-5L found no change or favourable scores for most subjects when comparing baseline to week 97. However, the company did not report data at week 49 therefore it is unclear whether a similar decline from week 49 to 97 is also observed when using this scale.

The EQ Visual Analogue Scale (VAS) showed a mean decline [redacted] from baseline at week 97. As above, as data at week 49 was not reported it is unclear whether there was a similarly [redacted] decline in quality of life from weeks 49 to 97.

4.2.6 Summary of critique

Data on the effectiveness of cerliponase alfa are based on a single arm trial (190-201) of 23 patients and its extension (190-202) with most outcomes collected and reported for up to 96 weeks. Given that the company expects cerliponase alfa to extend life by several decades, the follow up time used in the submission is of limited use for making such judgements. In addition, small open label single arm trials are inherently at high risk of bias and lack precision. This is particularly the case for this study as the primary outcomes (CLN2 clinical rating scale) require a subjective judgement of symptoms and therefore is at substantial risk of bias. In addition, there was great uncertainty regarding the mean rate of decline in the natural history controls which varied widely depending on which method was used to estimate these outcomes. The primary analyses used estimates that were less conservative and based on less sophisticated analytic methods which may have over-estimated decline in the control group.

Long term benefits on motor and language domains

Responder, time-to-event, and slope analyses all suggest a reduction in the rate of disease progression for cerliponase alfa patients compared with natural history controls over an approximately 96 week period (follow up time varies a little between outcomes). MRI outcomes showed loss of grey matter slowed over time and data at last observation showed no further loss compared with that found at week 96 but it is unclear how long this period of time reflects as there was variability of follow up time across patients. Even so, based on the data presented in the company submission it appears unlikely that no further disease progression will occur beyond 96 weeks.

Firstly, although the mean rate of decline in CLN2 scores in cerliponase alfa patients appears to be reducing when comparing data at week 48 and week 96, the slope analyses suggest on average patients receiving cerliponase alfa continue to experience further declines after week 96.

Secondly, although some patients experience stabilisation of symptoms during the course of the trial this was not the case for all patients. There was evidence of decline in CLN2 score in some cerliponase alfa patients up to and beyond the end of the 96 week period, again suggesting the assumption that no further declines will occur in any patients after 96 weeks is directly contradicted by the data and therefore implausible.

Thirdly, although PedsQL and CLN2QL scales initially indicate an improvement in quality of life to week 48, a [redacted] decline to week 97 is reported by parents. This suggests that although the clinician rated data indicates slowing of disease progression these clinical benefits may not translate into improvements or slowing of decline in quality of life as observed by parents in the long term. In addition, such a reduction in quality of life observed during this period provides evidence against the assumption that disease progression has been halted in patients receiving cerliponase alfa.

Long term benefits on seizures

Although there were improvements in the seizure domain of the clinical rating scale for cerliponase alfa patients, this doesn't necessarily reflect a halt in the deterioration of seizures, as the seizure domain of the Hamburg scale reflects only the frequency of tonic-clonic seizures, and does not take into account the activity of other movement disorders. Seizures and epilepsy were among the most common adverse events reported. In addition, relative to baseline, [redacted] patients appeared to experience new epileptiform activity. This provides important evidence that progression of disease has not yet been halted in this population.

Long term benefits on vision

Although decline in the vision domain was slightly slower in cerliponase alfa patients compared with natural history controls, conclusions on the long term benefits for vision associated with this treatment are limited by a number of factors. Firstly, there are baseline imbalances, with lower vision scores reported for the natural history controls at baseline, which may have impacted on comparisons over time. Secondly, despite the importance of vision deterioration in this disease, the trials included no specific examination of ophthalmological function beyond the Hamburg scale. In the company's application for European marketing authorisation this was justified by reasoning that ICV administration does not allow sufficient access of the drug to the affected retinal tissues, therefore vision loss was thought by the company to be unlikely to be prevented [11], which is supported by all animal studies of cerliponase alfa.

4.3 Adverse events

[redacted] patients treated with cerliponase alfa experienced at least one adverse event and [redacted] patients experienced at least one serious adverse event (see Table 9). However, [redacted] patients withdrew due to adverse events and [redacted].

Table 8 Summary of adverse events (adapted from Table C35)

Safety category	**n (%)**
Total included patients	[redacted]
Any AE	[redacted]
Any Serious AE	[redacted]
Grade III AEs	[redacted]
Grade IV AEs	[redacted]
Device related AE	[redacted]
Grade III AE	[redacted]
Discontinuations due to AE	[redacted]
Deaths	[redacted]

Grade III adverse events were relatively common with more than half of trial participants experiencing at least one event (54%) and one patient experienced a Grade IV adverse event (status epilepticus). Device related adverse events were also common with 50% of patients experiencing at least one, and four patients (17%) experienced a total of five Grade III device related events.

Table 9 Grade III and Grade IVAEs occurring in ≥ 20% of participants by system organ class and preferred term (adapted from Clinical Study Report, Table 12.2.3.1.1)

Safety category	**n (%)**
Grade IV adverse event	
Status epilepticus	[redacted]
Grade III adverse events	
Infection Upper respiratory tract infection	[redacted]
Nervous system disorder	[redacted]
Hypersensitivity	[redacted]
Respiratory, thoracic, mediastinal	[redacted]
Immune system	[redacted]
Gastro-intestinal	[redacted]
Seizure	[redacted]
Product issue	[redacted]

All patients experienced infections ([redacted] experienced a Grade III event) and nervous system related disorders ([redacted] experienced a Grade III event) (see Table 9).

Seizures and epilepsy were among the most common adverse events: seizure ([redacted]), generalised tonic-clonic seizure ([redacted]), epilepsy ([redacted]). It is not clear if these are treatment related or an indication of worsening or uncontrolled symptoms of the underlying disease.

Hypersensitivity was also a common event with [redacted] experiencing [redacted] hypersensitivity events (three experienced at least one Grade III event). The EMA [11] judged this to be the most relevant safety concern related to cerliponase alfa. Although most hypersensitivity reactions appeared manageable (e.g. through antihistamines, antipyretics, steroids) life threatening anaphylactic reactions as a result of cerliponase alfa cannot yet be excluded.

[redacted] patients experienced [redacted] cardiovascular adverse events (all Grade I/II). At baseline [redacted] had normal ECG readings; however, [redacted] of patients experienced ECG abnormalities post-baseline. Although not reported as adverse events, [redacted] patients shifted from a normal ECG reading at baseline to one or more abnormal readings at post-baseline. Three patients with abnormal baseline ECGs also had one or more abnormal ECGs post-baseline, whereas one patient with an abnormal baseline ECG shifted to normal ECGs post-baseline. All but one of the patients with abnormal ECGs had repolarisation abnormalities, while other abnormalities (such as right bundle branch blocks, t-wave inversion, rhythm abnormalities, p-sinistrocardiale) suggestive of potential conduction disorders were identified. However, no clear patterns of myocardial damage have yet been identified except two patients with suspected left ventricular hypertrophy. For at least one of these patients Grade II hypotension was reported eight hours after receiving cerliponase alfa infusion which suggests this may have been related to receiving the treatment.

4.4 Critique of the indirect comparison and/or multiple treatment comparison

N/A

4.5 Additional work on clinical effectiveness undertaken by the ERG

N/A

4.6 Conclusions of the clinical effectiveness section

Long term stability of CLN2 ratings

The evidence presented in the CS suggests that cerliponase alfa slows decline in disease progression for CLN2 patients compared with conventional management for up to 96 weeks. Although there was important uncertainty regarding the magnitude of mean decline in the natural history controls, it still appears that cerliponase alfa was more effective in the short term.

However, whether cerliponase alfa leads to a long-term stabilisation or halting of disease progression is highly uncertain based on the data provided in the CS. The follow up period (approximately 96 weeks) was judged by the ERG to be of insufficient length to draw conclusions about disease progression in the long term (the company assumes these benefits will be maintained for several decades). Although there are some patients who experienced no unreversed declines from baseline to 96 weeks, it is highly uncertain whether this reflects a long-term halting of disease progression or a

substantial extension of life. Assumptions of long term stability were particularly problematic for the group of patients classified as late stabilisers by the company (who experienced unreversed declines in CLN2 score after 16 weeks but were assumed to have no further declines after 96 weeks). [redacted] experienced declines [redacted] and therefore directly contradicted these assumptions.

The impact of cerliponase alfa on more objective markers of disease is also unclear; while patients' motor, language, and seizures stabilised or improved according to the Hamburg scale, EEG examinations during study 201/202 found new (focal and/or generalised) epileptiform activity in [redacted] of patients, which the ERG's clinical advisor suggested may be an indicator that disease progression had not been halted, though further study is required to confirm this. Moreover, MRI measurements showed substantial reductions in whole brain volume, cortical grey matter, and white matter.

A further uncertainty regarding the long-term stabilisation of disease progression not addressed by the company was the potential for loss of response due to immunogenicity, despite generation of anti-drug antibodies in [redacted] of trial patients. The risk of loss of response requires longer term observation to assess.

Non-neuronal aspects of CLN2 disease

Cerliponase alfa doesn't address the extra-neuronal aspects of CLN2 disease which has important potential implications for life expectancy. Non-human studies have shown the treatment only slowed progression of symptoms, with only modest reductions in short-term mortality. Furthermore, ECG abnormalities developed in [redacted] of patients, and two cases of suspected left ventricular hypertrophy were observed in study 190-201/202, which is consistent with the potential for the cardiac problems identified in non-human studies.

5 Cost Effectiveness

This section focuses on the economic evidence submitted by the company and the additional information provided to the ERG following points for clarification. The submission was subject to a critical review on the basis of the company's report and direct examination of the electronic version of the economic model. The critical appraisal was conducted with the aid of a checklist to assess the quality of economic evaluations and a narrative review to highlight key assumptions and possible limitations. Section 6 presents additional work undertaken by the ERG to address some remaining uncertainties.

The company's initial economic submission included:

- A description of the search strategy and databases used in the literature review of cost-effectiveness studies and quality-of-life studies (CS, Section 10.1.5 pp 157-160 and Appendix 8); and cost and resource use studies (Appendix 9).
- A report on the *de novo* economic evaluation, conducted by the company. The report outlined the intervention; comparators and patient population; modelling methods; resource components and unit costs; data input sources and assumptions; base-case results; and sensitivity analysis (CS, Section 12, pp 176-280).
- The company's electronic Excel-based *de novo* model.

Following the points of clarification raised by the ERG, a number of addenda were submitted by the company. These included:

- A descriptive reply to the ERG's points for clarification, as well as appendices with additional data requested by the ERG.
- An updated Excel-based model, which included additional scenario analyses requested by the ERG.

5.1 ERG comment on the company's review of cost-effectiveness evidence

The company conducted a broad systematic literature review to identify economic evaluations of treatments for patients with CLN2 disease and TPP1 deficiency. The ERG's critique of the systematic review, presented by the company, is given below.

5.1.1 Searches

The CS contained the search strategies to identify studies on health-related quality of life (HRQoL), economic evaluations and studies presenting cost and resource use relating to CLN2 disease or TPP1 deficiency. The search strategies were briefly described in the main submission in Section 10.1.5

(HRQoL), Section 11.1 (economic studies) and Section 12.3.2 (cost and resource use). Full search strategies were provided in Appendix 8, Section 17.8.

The following databases were searched on 23rd January 2017: MEDLINE (including MEDLINE Daily, MEDLINE In-Process and Epub), Embase, the Health Technology Assessment database and the NHS Economic Evaluations Database. The search was not limited by language or date.

The database searches were supplemented by searches of the following conference proceedings in February 2017: International Conference on Neuronal Ceroid Lipofuscinosis (2016), WORLD Symposium (2015, 2016), International Child Neurology Congress (2016), the Society for the Study of Inborn Errors of Metabolism Meeting (2016) and the International Society for Pharmacoeconomics and Outcomes Research (European meetings in 2015, 2016). Reference checking of relevant systematic reviews and meta-analyses was also undertaken.

Previous relevant health technology assessment (HTA) submissions were sought through searches of the following websites on 13th February 2017: National Institute of Health and Care Excellence (NICE), All Wales Medical Strategy Group (AWMSG), and Scottish Medical Consortium (SMC). Searches for unpublished studies were undertaken on 13th February 2017 via the World Health Organization International Clinical Trials Registry Platform (WHO ICTRP).

Three further databases were searched for HRQoL data on 13th February 2017: the Cost-Effectiveness Analysis (CEA) Registry, the University of Sheffield Health Utilities Database (ScHARRHUD) and the EQ-5D Publications Database. In August 2017, the company searched their own internal database to identify any further relevant published studies.

Overall the searches were appropriate, and well carried out and reported. A wide range of synonyms and appropriate subject headings was included for CLN2 disease and TPP1 deficiency. All search lines were combined correctly, the search syntax across all databases was used correctly and no typographical errors were found. The reporting of the searches was clear with sufficient detail to allow the searches to be reproduced in all sources.

Appropriate, sensitive search strategies to restrict the retrieval to HRQoL studies, economic evaluations and cost and resource use studies were employed in MEDLINE and Embase. The company clarified that the terms used were developed from the SIGN economic studies search filter and the terms for quality of life were based on recommendations from the School of Health and Related Research (ScHARR) at the University of Sheffield and the York Health Economics Consortium (YHEC).

The databases and sources searched by the company were appropriate to capture HRQoL, economic and cost and resource use studies. Efforts were made to identify studies from sources of both published and unpublished literature.

5.1.2 Inclusion/exclusion criteria used for study selection

The inclusion/exclusion criteria used in study selection are listed in Table 10.

Table 10: Inclusion/exclusion criteria for study selection (adapted from the CS, Table D1)

	Inclusion criteria	Exclusion criteria
Population	Patients with any variant of CLN2 disease or TPP1 deficiency	Individuals without any variant of CLN2 disease or TPP1 deficiency, their family or carers
Interventions	Any intervention	No limits
Comparators	Any or no comparator	No limits
Outcomes	Outcomes of relevant study designs, including: ICERs, Cost per clinical outcome, Total QALYs, Total (progression-free) life-years gained, Total costs, Incremental costs and QALYs	Studies not presenting relevant outcomes
Study design	Any of the following analysis types: Cost-effectiveness, Cost-utility, Cost-benefit, Cost-minimisation, Cost-consequence. SLRs, meta-analyses and HTAs (to be included at the title/abstract review stage, then excluded following supplementary searching of their reference lists at the full-text review stage, unless presenting original data)	Publications without original data Comments Letters Editorials
Publication type	Studies on human subjects	Non-human studies
Language	English-language full-texts	Non-English
Time restrictions		Congress searches were limited to those held a maximum of two years ago as it was assumed that high-quality studies reported in abstract form before this time have since been published in a peer-reviewed journal.
CLN2, neuronal ceroid lipofuscinosis type 2; TPP1, tripeptidyl peptidase 1; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year; SLR, systematic literature review; HTA, health technology assessment		

The ERG considers the inclusion and exclusion criteria to be reasonable. The exclusion of non-English studies may have led to some studies being missed, although the ERG does not consider this very likely. In order to inform the model being developed for this submission, it may also have been useful to broaden the inclusion criteria to allow economic evaluations for other variants of CLN disease to be identified. Although these studies would not have been directly applicable, the assumptions used and the data included could have provided a useful reference point for the submission.

5.1.3 Studies included and excluded in the cost-effectiveness review

The electronic database searches identified 126 records. Of these, 104 records were excluded at the initial screening stage (22 records were duplicates). The remaining 12 records were assessed based on their full text. None of the 12 records met the inclusion criteria and they were not included in the systematic literature review. Supplementary searches of congress proceedings identified four publications, which related to three separate studies. One study presented utility data and the other two presented cost and resource use data. No relevant economic evaluations were identified.

5.1.4 Conclusions of the cost-effectiveness review

The company's search did not identify any relevant economic evaluation studies. A number of studies were identified, which related to utility data and cost and resource use data. These studies were discussed in their respective sections of the CS. It may have been useful, given the acknowledged small body of evidence surrounding this disease, to include other CLN disease populations, to help inform the model structure and model inputs.

5.2 ERG's summary and critique of company's submitted economic evaluation

An overall summary of the company's approach, and signposts to the relevant sections in the company's submission, are reported in Table 11.

Table 11: Summary of the company's economic evaluation (and signposts to the CS)

	Approach	Source / Justification	Signpost (location in the CS)
Model	A multi-state Markov model was developed. Cycle length was two weeks and a lifetime (95 years from the start of the model) was used.	The submission states that a multi-state Markov model is the most appropriate way of modelling a long-term chronic disease with dynamic disease progression The cycle length is in line with the fortnightly treatment administration of cerliponase alfa, and the frequency of concomitant patient examinations. In the model, patients start at an age of 4.8 and the ONS life tables provide mortality data up to the age of 100.	Section 12.1 Pages 178-190
States and events	The model consisted of 10 health states based on the CLN2 clinical rating scale. Health states 1-7 were defined by a score on the CLN2 clinical rating scale, ranging from a score of 6 (least severe) to a score of 0 (most severe). Health state 8 was defined as a score of 0 on the CLN2 clinical rating scale plus complete vision loss. Health state 9 was the same as health state 8 plus the additional requirement for palliative care. Health state 10 was death.	These health states were selected to capture the clinical reality of disease progression. The health states and their defining characteristics were validated by clinical experts.	Section 12.1 Pages 180-182
Comparators	The comparator used in the company's model was standard care which was described as established clinical management without cerliponase alfa.	No treatment is currently available for CLN2 disease, and this is in line with the NICE scope.	Section 12.1.3 Pages 179

	Approach	Source / Justification	Signpost (location in the CS)
Subgroups	An analysis of a subgroup of asymptomatic and pre-symptomatic siblings with confirmed CLN2 disease was undertaken.	In line with the scope	Section 12.6 Pages 276-278
Treatment effectiveness	Treatment effectiveness was estimated using the CLN2 clinical rating scale scores, a subset of an adapted version of the established four-domain Hamburg scale measure.[28] A number of additional symptoms, not captured by the CLN2 clinical rating scale, were also included in the company's model (vision loss and requirement for palliative care). At 16 weeks (cycle 8) patients receiving cerliponase alfa were classified as early or late stabilisers dependent on response to treatment between week 16 and week 96. Early stabilisers were assumed to experience no further progression of disease. Late stabilisers were assumed to experience further progression of disease up to 96 weeks (cycle 48). After 96 weeks it was assumed all patients receiving cerliponase alfa were stable and experienced no further disease progression.	Transition probabilities for patients receiving cerliponase alfa were based on the 190-201/202 study (pivotal clinical trial)[29] and expert clinical opinion. Transitions probabilities for patients receiving standard care were based on patient level data from the 190-901 study (natural history study)[30] and expert opinion.	Section 12.2 Pages 179-205
Mortality	Mortality of patients in health states 1 to 8 was based general population mortality adjusted for sex and age. Patients in these health states were assumed to have mean life-expectancy of 52 weeks with transitions to the death state estimated using an exponential function.	ONS mortality statistics and expert opinion.	Section 12.1.3.1 page 179 Section 12.1.7 page 197
Adverse events	Treatment-related adverse events were included in the company's model. These included pyrexia, hypersensitivity, headache and vomiting. An infection rate of 0.45% for each performed ICV infusion was also included. No treatment-related adverse events were applied to the standard care cohort.	Adverse event rates were taken from Study 190-201/202[29] for cerliponase alfa.	Section 12.2 Page 206
Health-related quality of life	Utility values were derived from a utility study in which vignettes describing the health states for both cerliponase alfa and standard care were developed. The vignettes were validated by a clinical expert, and sent to 8 clinical experts who completed the EQ-5D-5L questionnaire as a proxy for patients experiencing the health states. These were mapped to the EQ-5D-3L before being applied in the model. Adverse event disutility, caregiver disutility and sibling disutility were also incorporated into the company's model.	The utility data collected in the clinical studies (190-201/202)[29] were not used due to the fact that utility values were not available for all health states and no utility values were available for standard care. Adverse event disutility estimates were derived from published studies.[31-34] The midpoint values for caregiver and sibling disutility were derived from a published study.[20] The company assumed a linear progression of this value across the health states.	Section 12.2 Pages 206-210 Section 12.1.7 Pages 192-197

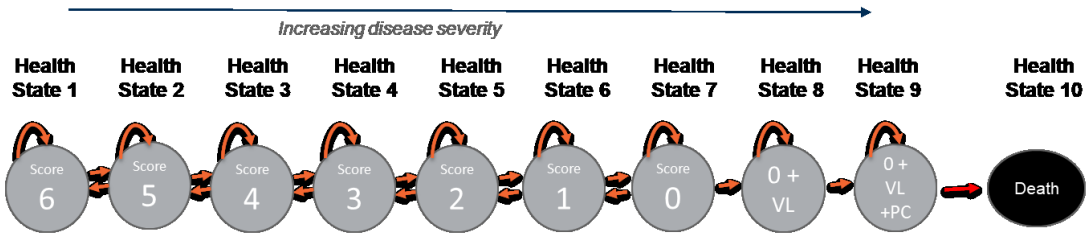
	Approach	Source / Justification	Signpost (location in the CS)
Resource utilisation and costs	Resource use and costs included: cerliponase alfa drug acquisition and administration costs; ICV implantation and replacement costs; health-state costs (routine care costs); drug acquisition and procedure costs associated with the relief of progressive symptoms; and, seizure costs. A NHS and Personal Social Services perspective was taken when identifying the relevant costs.	Drug acquisition costs were based upon the list price of cerliponase alfa, source BioMarin Europe Ltd. Administration and ICV implantation and replacement costs were based on NHS Reference costs 2015-2016.[35] Health state costs were estimated using the company's Delphi panel[36], NHS reference costs 2015-2016[35] and PSSRU 2016[37]. Progressive symptom costs and seizure costs were estimated using the BNF 2017[38], eMIT 2017[39] and NHS reference costs 2015-2016[35]. Costs and resource use data were identified through a SLR. Expert clinical opinion informed the assumptions used for inputs where cost information was unavailable.	Section 12.3 Pages 212-239
Discount rates	The costs and benefits were discounted at 1.5% per annum.	The submission states that the beneficial impact of the treatment was expected to be substantial and sustained over a very long period. Therefore, a discount rate of 1.5% was considered reasonable within the context of the NICE Guide to the methods of technology appraisal 2013.[40] [41]	Section 12.1.3 Page 179
Sensitivity analysis	Probabilistic sensitivity analysis was performed. Deterministic analysis was performed on a series of model parameters. A series of scenario analyses was also performed.	In accordance with the NICE reference case.	Section 12.4 Pages 239-275
ONS, Office for National Statistics; CLN2, Neuronal Ceroid Lipofuscinosis Type 2; ICV, intracerebroventicular infusion; EQ-5D-5L, European Quality of life, 5 domain instrument of health outcomes, 5 level; PSSRU, Personal Social Services Research Unit; BNF, British National Formulary; eMIT, electrical market information tool; SPC, Summary of Product Characteristics; SLR, systematic literature review.			

5.2.1 Model structure

The company submission is based on a multi-state Markov model comparing cerliponase alfa with standard care. The model used a cycle length of 2 weeks and a time horizon of 95 years. The company chose the cycle length as it was in line with the fortnightly treatment administration of cerliponase alfa, and the frequency of concomitant patient examinations. The time horizon was justified on the basis that general population mortality data are only available up to the age of 100. The model structure adopted consists of ten mutually exclusive health states, which characterise the progression of CLN2 patients over the course of the model's time horizon. The ten health states included in the model were defined by the CLN2 clinical rating scale, which is a subset of an adapted version of the four-domain Hamburg scale measure.[28] The adapted version consists of the motor and language domains of the scale only, and does not include the vision and seizure domains. Within the CLN2 clinical rating scale framework, a maximum score of 6 can be obtained by achieving a score of 3 in

both domains; this is the least severe health state, and defined health state 1 in the model. Patients with scores from 5 to 0, defined health states 2 to 7, respectively. A score of 0, which is the most severe score, defined health state 7. Health state 8 was defined as a score of 0 on the CLN2 clinical rating scale plus complete vision loss (i.e. complete blindness). Health state 9 was the same as health state 8 plus the additional requirement for palliative care. Health state 10 was death. A graphical presentation of the Markov model is presented in Figure 2.**Error! Reference source not found.**

Figure 2: Model Structure (CS, Figure D20, p.181)



All scores are in the CLN2 clinical rating scale score
Patients considered to be "educationally" blind at a score of 0
VL, vision loss
PC, palliative care

To account for the symptom load not captured by the CLN2 clinical rating scale, it was assumed that each health state was associated with additional symptoms including epilepsy, disease-related distress, dystonia, myoclonus, vision loss and the requirement of a feeding tube. These were selected based on Williams et al. 2017[12] and validated in the Delphi panel study.[36] These additional elements were labelled as progressive symptoms in the CS and were associated with additional drug and therapy costs. The HRQoL impact of these symptoms was also captured in the health-state utilities, see Section 5.2.8 for details. Movement through the model was determined by transition probabilities. Probabilities for the transitions between the first seven health states (health state 1 [CLN2 clinical rating scale score of 6] to health state 7 [CLN2 clinical rating scale score of 0]) were based on patient-level data from Study 190-201/202 for the cerliponase alfa arm, and the one-to-one matched patients from the natural history control Study 190-901 for the standard care arm. Data were not available on the transition probabilities in the final health states (7, 8 and 9) as no progressed beyond health state 7 in Study 190-201/202. The transition probabilities for health states 7 to 9 were, therefore, based on expert opinion. See section 5.2.7 for further details.

Within the model, patients receiving cerliponase alfa were assumed either to be early stabilisers or late stabilisers. These groups were based on patients receiving cerliponase alfa treatment for more than 16 weeks in the trial. Early stabilisers were defined as patients who did not experience any further decline in CLN2 clinical rating scale score after 16 weeks. Late stabilisers were defined as patients who continued to progress at a rate of 1 point on the CLN2 clinical rating scale per 80 weeks, until week 96. After 96 weeks, all patients receiving cerliponase alfa were assumed to be stabilised

and experienced no further disease progression. The company's justified using 16 weeks as the time point at which to determine stabilisation was that it was at this point that the response levels were measured in the trial, and in order to account for the initial fluctuations in scores observed in the trial. At this time point, [redacted] of the patients in the trial [redacted] experienced no further disease progression (in terms of CLN2 clinical rating scale score), and [redacted] of the patients in the trial experienced a decline of 1 or more point on the CLN2 clinical rating scale between 16 weeks and 96 weeks of the trial.[29]

ERG comment

The ERG considers the use of a multi-state Markov model to be broadly appropriate and that the model structure captures a number of important elements of CLN2 disease. The ERG, however, has a number of substantive concerns regarding the model structure. Particularly, the ERG is concerned that while the company model is able to accurately represent disease progression in the standard care arm, it fails to adequately account for a number of elements of disease progression in patients treated with cerliponase alfa. Details of the ERG's concerns are considered in detail below:

Markov structure: Markov models are described as "memoryless" because previous transitions have no impact on future transitions. In the context of the current model, this feature of Markov models combined with the short cycle length, means that some patients progress through the model very quickly. For example, it is possible for patients to transition from health state 1 [CLN2 rating scale 6] to heath state 7 [CLN2 rating scale 0] in just 6 cycles (12 weeks). The impact of this is that a non-negligible proportion of patients experience disease progression inconsistent with the clinical data. This is potentially important in the company's base-case model, because patients receiving cerliponase alfa are assumed to stabilise after 96 weeks. Any inaccuracy in the distribution of patients at 96 weeks is, therefore, extrapolated over the remaining time horizon of the model. At the Points for Clarification stage (PfC's), the ERG requested that the company comment on this issue. The company's response acknowledged that the rate of decline that is seen in the model for some patients is not plausible and is inconsistent with the decline observed in the 190-201/202 study and natural history cohort. During PfCs, the ERG also asked the company to undertake a scenario analysis increasing the cycle length; this would mitigate the impact of this issue and prevent patients declining very quickly. In response, the company provided a model with an eight-week cycle length. In this scenario, the ICER decreased by a small amount (6%; note the model provided by the company included an error, this figure therefore does not align with the results presented in the PfCs response). Therefore, the ERG notes the limitation of the model structure element, but no further analyses were undertaken.

Vision loss: Within the model, the impact of progressive vision loss is accounted for in the health state utilities, with complete vision loss defining health state 8. This is reasonable in the context of the standard care arm, as vision loss is linked to disease progression, but it is more problematic for

patients receiving cerliponase alfa. As described in Section 2, progressive vision loss in CLN2 patients is due to both retinal changes and central changes in the brain. This means that while cerliponase alfa may impact on the rate of vision loss it cannot prevent complete vision loss. The implications of this are that for patients receiving cerliponase alfa, vision loss will not correlate with deterioration in motor and language scores. The model structure, therefore, does not account for the progressive vision loss that will be experienced by patients receiving cerliponase alfa.

At the PfCs the ERG requested that the company develop a scenario analysis to account for the progressive loss of vision that would occur in cerliponase alfa patients. In response, the company presented a scenario analysis in which it was assumed that vision loss occurred from the age 6 and impacted on HRQoL. The disutility associated with vision loss was applied in the form of a progressively decreasing multiplier which was applied to the health state utility values. The multiplier was assumed to decrease by 0.01 points per year up to a value of 0.87 at the age of 20 years. The value of 0.87 was based on the quality of life associated with neovascular macular degeneration in the UK.[42] While the ERG considers that this scenario analysis is a more realistic reflection of the impact of vision loss on cerliponase alfa patients, the rate of decline was modelled to be too slow. As described in Section 2, degeneration of the retina in patients receiving cerliponase alfa will continue at the same rate [21] as untreated patients. Complete vision loss in patients receiving cerliponase alfa will therefore occur at approximately the same time as in patients on standard care; this is normally before the age of eight and not the age of 20 as implied by the company's scenario. The ERG, therefore, presents an alternative scenario, incorporating the effects of vision loss in patients receiving cerliponase alfa, in Section 6.

Extra-neurological progression: As described in Section 2, the ERG is concerned that there is a significant risk that patients receiving cerliponase alfa will continue to experience extra-neurological symptoms of CLN2. The most significant impact of these extra-neurological symptoms is likely to be on the mortality of patients receiving cerliponase alfa. However, these symptoms would also impact on quality of life (QoL). For example, it has been shown that extra-neurological lipofuscin storage occurs rapidly in the smooth muscle that makes up the gullet, bladder and bowels.[1-7] Symptoms of extra-neurological pathology would be, therefore, likely to include difficulty swallowing, and loss of bladder and bowel control, all of which would have a significant impact on QoL. The model structure is, however, not able to accommodate these additional symptoms and no account for them is made in either the company's base-case analysis, or in any scenario analyses presented by the company. Including the impact of these symptoms is, however, very difficult due to the lack of long-term data on the effects of cerliponase alfa and the uncertainty around the symptoms that patients would experience. The ERG, therefore, does not explore the impact of extra-neurological pathology on HRQoL in their additional analysis, but does consider it an important omission from the model.

However, the ERG does consider the implications of extra-neurological pathology on mortality; see Section 5.2.7 for further discussion.

Distinction between early and late responders: The distinction between early and late stabilisers is a central component of the way in which patients receiving cerliponase alfa are modelled in the first 48 cycles of the model. In the context of the model, this distinction is, however, purely descriptive and does not impact on the predictions of the model. Indeed, the distinction between these two groups is unnecessary from a modelling perspective and is, in fact, nothing more than a convenient way in which to model the transition of patients in the period from week 16 to week 96. The ERG is, however, concerned about how biologically plausible these assumptions are when extrapolated beyond the trial setting. The distinction between early and late stabilisers was not established a priori and, therefore, there is no way of substantiating whether these post-hoc determined categories are an artefact of the study or a genuine reflection of different response patterns to cerliponase alfa treatment. Further, the ERG highlights that the proportion of early stabilisers is highly dependent upon the time period considered. For example, defining the response with respect to the period from week 16 to the last observation, results in a different proportion of patients being defined as early responders. In addition, the assumption of stabilisation does not allow HRQoL and resource use to progress for patients on cerliponase alfa. By assuming stabilisation, the model implicitly assumes that these values for utilities and costs, which are relevant for ~4- to 5-year-olds, will still be appropriate for patients when they are in early, mid and late adulthood.

5.2.2 The company's economic evaluation compared with the NICE reference case checklist

Table 12 compares the company's model with the NICE reference case.

Table 12: Comparison of the company's economic evaluation against the NICE reference case checklist

Attribute	Reference Case	Included in CS	Comment on whether *de novo* evaluation meets the requirements of the NICE reference case
Comparator(s)	The NICE scope defined the comparators as follows: Established clinical management without cerliponase alfa	Yes	Yes
Type of economic evaluation	Cost-effectiveness analysis	Yes	Yes
Perspective - costs	NHS and PSS	Yes	Yes
Perspective - benefits	All health effects on individuals	Yes	
Time horizon	Sufficient to reflect any differences in costs or outcomes between the technologies being compared	Yes	The economic model had a lifetime horizon of 95 years. No patients were expected to be alive beyond this period.
Synthesis of evidence on outcomes	Systematic review	Yes	
Outcome measure	QALYs	Yes	
Health states for QALY measurement	Described using a standardised and validated instrument	Yes	The utility study elicited utilities for all health states from clinicians using the EQ-5D-5L questionnaire. The trial elicited utility values using several instruments; however, these values were not used in the company's base case model.
Benefit valuation	Time Trade-Off or Standard Gamble	Partial	The utility value set used as part of the vignette utility study was based on both time trade-off data and discrete choice experiment data.
Source of preference data	Representative sample of the public	Partial	Utilities were elicited directly from clinicians who were familiar with both the patient population and with cerliponase alfa.
Discount rate	3.5% on costs and health benefits	No	Costs and benefits were discounted at 1.5% per annum in the base case analysis. A 3.5% discount rate was explored in the scenario analyses.
Equity weighting	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Yes	
Sensitivity analysis	Probabilistic sensitivity analysis	Yes	Yes

NHS: National Health Service; NICE: National Institute for Health and Care Excellence; PSS; Personal Social Services; QALY: Quality-adjusted life-year

5.2.3 Population

The primary sources of data used to inform the cost-effectiveness model were the 190-201, 190-202 and selected patients from the DEM-CHILD cohort study.[17, 29, 30] As previously stated in Section 3.1, the populations in these studies can be considered to match the NICE scope, but some differences may

exist between patients in the 190-201/190-202 and those eligible to receive cerliponase alfa treatment in England.

The modelled population was a cohort aged 4.78 years of age at initiation of treatment; based on the mean age at enrolment in the 190/201 study. The sex mix was assumed to be 50% male and 50% female patients, which differed from the sex mix of the patients in the 190-201 study (190/201 study was 73% male and 23% female, 5% unknown), but was assumed because the incidence of CLN2 is roughly equal for boys and girls. The severity of disease at the initiation of treatment, described in

Table **13**, was based on clinical expert opinion. The company noted that the distribution of patients across health states incorporated the assumption that the incident patients would be diagnosed in an earlier health state in the future. The distribution of patients across the health states, therefore, assumes that there are more patients in the less severe health states (and conversely fewer in the more severe health states) than we would expect to see, based on current diagnostic practice. To justify this assumption the company stated that they would be implementing a campaign to improve awareness of CLN2 amongst clinicians. Details of the nature of this campaign or evidence relating to the likely effectiveness of this campaign were, however, not included in the submission. The company were asked in the PfCs to provide further details of this campaign, but they presented no further evidence to support the modelled assumptions. The company, however, did state [redacted]

Table 13: Severity of patients at initiation of treatment (CS, Table D15, p 205)

Health state	Distribution of patients used in base-case model
Health state 1	40%
Health state 2	40%
Health state 3	10%
Health state 4	5%
Health state 5	5%
Health state 6	0%
Health state 7	0%
Health state 8	0%
Health state 9	0%

In addition to the base-case analysis, two further scenario analyses exploring alternative distributions of patients across health states were considered. In the first (scenario 1), patients were assumed to be equally split between health states 1 and 2 at the initiation of treatment. In the second (scenario 2), all patients were assumed to be in health state 1 at the initiation of treatment. These scenarios were

presented to represent optimistic scenarios in which early diagnosis and treatment occurs. Scenario 2 was also presented as a subgroup analysis representing the treatment of asymptomatic and pre-symptomatic siblings with confirmed CLN2 disease. No other parameters were altered in these scenario analyses. No further subgroup analysis was considered.

ERG comment

As described in Section 3.1, the ERG has a number of concerns about how well the population recruited to the 190-201/202 study reflects the eligible population, given the restrictive inclusion criteria applied, and the ERG notes that the recruited population reflects neither an incident nor a prevalent population. This raises issues about the external validity of the results observed in the 190-201-202 trial. The notable differences between the model population and the population recruited in the 190-201/202 trial also raises further issues about the validity of extrapolating the observed results to the modelled population. These issues are likely to have a significant impact on estimated effectiveness, and, therefore, cost-effectiveness, particularly if treatment effectiveness is correlated with CLN2 clinical rating scale score at baseline.

A further important concern, with respect to the population modelled, is the starting population and the distribution of patients at the initiation of treatment. The distribution of patients at the initiation of treatment is one of the most important drivers of cost-effectiveness, because cerliponase alfa is not restorative and can only stabilise/slow progression. The degree of progression at initiation of treatment is, therefore, a significant factor in determining the health state in which a patient is stabilised, and, consequently, is a significant factor in determining overall costs and benefits. The impact of the starting population, is demonstrated in an additional analysis, requested at the PfCs, which shows that basing the distribution of patients on the baseline CLN2 clinical rating scale scores of the 190-201 population, results in a more than 50% increase in the ICER.

As described above, the distribution of patients across health states was based on clinical expert opinion and assumes that there will be improvements in diagnosis in the future. The ERG considers these assumptions to be profoundly problematic. While the ERG acknowledges that the implementation of an awareness campaign and/or diagnostic programme in the UK may improve time to diagnosis, such a programme does not exist in the UK presently and the company's commitment to such a programme remains unclear. Furthermore, the benefits of such a programme are highly uncertain and the logic behind the assumed distribution of patients in the company's base-analysis is unclear and does not appear to be linked either to the rate of progression in untreated disease, or to expected reductions in time to diagnosis. A comparison of the assumed distribution of patients, and the CLN2 clinical rating scale scores of patients in the 190-901 cohort at diagnosis (see Table 14), also shows that the impact of these assumptions is not trivial, and that the company is assuming

significant improvements in diagnosis, with significant consequences in terms of estimated cost-effectiveness.

Table 14: Distribution of patients (CS, Table D15, p. 205 and PfC Response, Table 1 (amended))

Health state	Distribution of patients used in the base-case model	Distribution of patients in the 901-201 natural history cohort at diagnosis (patients born after the year 2000)
Health state 1	40%	[redacted]
Health state 2	40%	[redacted]
Health state 3	10%	[redacted]
Health state 4	5%	[redacted]
Health state 5	5%	[redacted]
Health state 6	0%	[redacted]
Health state 7	0%	[redacted]
Health state 8	0%	[redacted]
Health state 9	0%	[redacted]

Given these uncertainties, the ERG does not consider it reasonable to assume that such improvements in diagnosis will occur, an issue which is explored further in Section 6, where alternative distributions are explored, including basing the distribution of patients at the initiation of treatment on recent diagnostic practice. The ERG notes that it does not consider the baseline scores of the 190-201 study population to be reflective of an incident population, as these patients were recruited from the prevalent population.

A further substantive issue raised by the assumed distribution of patients at initiation of treatment is that it is implicitly considering an incident population rather than a prevalent population. This is an important distinction because the cost-effectiveness of cerliponase alfa in these two groups is likely to be very different, with the cost-effectiveness of cerliponase in a prevalent population very much dependent upon the composition of the prevalent population and who is eligible to receive treatment. The ERG does not explore this issue further as it is unclear which patients from the eligible population would be eligible for treatment.

5.2.4 Interventions and comparators

The economic model, presented in the CS, compares cerliponase alfa with established clinical management without cerliponase alfa (standard care). As described in Section 3.3, there are no licenced treatments available to treat the underlying cause of CLN2 disease, the established clinical management without cerliponase alfa, therefore, aims to achieve symptomatic relief and provide supportive care for daily needs. No direct comparator treatment was, therefore, considered in the model. The drug acquisition costs for the treatment of the symptoms of CLN2 were, however, applied

to both patients receiving cerliponase alfa and standard care patients. Symptoms modelled included: epilepsy, distress, dystonia and myoclonus. Additionally, one-off costs for a feeding tube were also included. The frequency with which symptoms were experienced was assumed to vary by health state with increasing frequency of symptoms in more severe health states (See Tables D5 and D6, in the CS). The frequency with which symptoms were experienced in each health state did not vary depending upon whether a patient was receiving treatment with cerliponase alfa or not.

Dosing of cerliponase alfa was assumed to be 300mg every two weeks, in line with the licensed dose for children over the age of two years. Adherence to therapy was presumed to be 99.74%, based on the 190-201/202 trials. The dosing of other drug therapies, used for symptomatic relief, was primarily based on weight and calculated in line with the market authorisation for the respective drugs. The weights of the patients were sourced from the Royal College of Paediatrics and Child Health, School Age Chart. For drugs whose dosing was not based on weight, dosing was based on the recommended doses outlined in the BNF and eMit.[38, 39]

Patients receiving cerliponase alfa were presumed to continue their therapy until death or until progression to health state 7 (CLN2 clinical rating scale score of 0). Upon discontinuation of cerliponase alfa, patients were assumed to switch to natural history transition probabilities and utility values. No discontinuation of the therapies given to achieve symptomatic relief was permitted in the model.

ERG comment

The ERG considers that the interventions and comparators used in the model were in line with the NICE scope and that the comparator therapy reflected the current provision for patients with CLN2. The ERG, however, notes two issues, one relating to the stopping rule applied and a second relating to the dosing of therapies used to provide symptomatic relief.

Stopping rule: The ERG has some concerns regarding the stopping rule applied. While the ERG notes that the stopping rule was validated by clinical experts and that it is consistent with the draft managed access agreement, the ERG is concerned that a proportion of patients may continue to receive therapy after progressing to health state 7. Clinical advice, received by the ERG, suggests that some parents and carers value extension of life more than quality of life and are likely to request therapy to continue as long as possible, even in patients who have experienced significant progression. This assumption is not important in the company's base-case because a negligible proportion of patients who received cerliponase alfa reached health state 7. However, in scenarios where continued disease progression is assumed, this assumption is likely to be much more important. The ERG explores this issue further in a scenario analysis presented in Section 6.

Dosing of therapies used to provide symptomatic relief: As stated above, the dosing of the majority of the therapies used to provide symptomatic relief was based on bodyweight. The ERG, however, noted that the weight of patients was assumed to not change beyond the age of 18 years. This assumption lacks face validity and is unnecessary, given widely available NHS data on mean weight of adults in the UK. The impact of this issue on the estimated cost-effectiveness is, however, not substantial, due to the relatively small drug acquisition costs associated with these therapies. The ERG, therefore, does not explore this issue further in Section 6.

5.2.5 Perspective and time horizon

The economic model adopted a National Health Service (NHS) perspective in accordance with the NICE reference case.

The NICE reference case indicates that the time horizon used for estimating clinical and cost-effectiveness should be sufficiently long to reflect any differences in costs and benefits between the technologies being compared. The time horizon, used in the economic model, was 95 years; equivalent to a lifetime horizon. This was justified on the basis that cerliponase alfa stabilises patients and that patients would revert to the mortality of the general population. The ERG considers this more than adequate to capture any differences between cerliponase alfa and usual care.

5.2.6 Discounting

A discount rate of 1.5% per annum was applied to both costs and outcomes in the company's base-case. The company justified the use of a 1.5% discount rate on the basis that the benefits of treatment with cerliponase alfa are expected to be substantial and sustained over a very long period. The NICE Methods Guide states that a discount rate of 1.5% for costs and benefits may be considered in cases where the treatment restores individuals, who would otherwise die or have a very severely impaired life, to full or near full health, and when this is sustained over a very long period (normally at least 30 years).[41]

The ERG does not consider the 1.5% discount rate applied in the model to be reasonable, given these criteria. There is no clinical evidence to suggest that cerliponase alfa is restorative, with the primary effects of treatment being limited to preventing/slowing future decline. It is also unclear whether the benefits of treatment with cerliponase alfa are sustained over a sufficiently long period of time. The ERG therefore considers that the standard NICE reference case discount rate of 3.5% should be applied.

In addition to the 1.5% discount rate applied in the base-case analysis, the company explored the impact of using alternative discount rates. Two scenarios were presented. In the first, a discount rate of 3.5% was presented as per the NICE reference case. In the second scenario, discount rates of 3.5%

for costs, and 1.5% for benefits, were applied. The company's justification for this scenario cited literature[43, 44], in which theoretical and empirical evidence in support of differential discounting of costs and benefits was presented and discussed. Given the inconsistency of this scenario with the NICE reference case, the ERG does not present a detailed account of the arguments for and against differential discount rates, other than to note that there is no academic consensus regarding the appropriate way to discount costs and benefits, and that there are strong theoretical arguments supporting the use of uniform discounting.

5.2.7 Treatment effectiveness and extrapolation

5.2.7.1 Treatment effectiveness: cerliponase alfa

The transitions probabilities, used to describe the progression of patients receiving cerliponase alfa, were dependent upon the time point in the model, with the model's time horizon split into three distinct phases. The first period covered weeks 0 to 16; the second, weeks 17 to 96; and the third, weeks 97 onwards.

Weeks 0 to 16: During the first period of the model all patients receiving cerliponase alfa were assumed to experience different risks of progression, dependent upon the health state that they are in, with transition probabilities derived from the 190-201 study. Due to the small number of patients within each CLN2 clinical rating scale score, the transition probabilities for patients were calculated for three groups of scores (scores of 6 and 5 [health states 1 and 2], scores of 4 to 2 [health states 3 to5], and scores of 1 and 0 [health states 6 and 7] on the CLN2 clinical rating scale). Patients in health states 8 and 9 were assumed not to receive cerliponase alfa, and their transition probabilities were derived using a different approach, see section 5.2.7.2 below. It was not made clear, in the CS, why the transition probabilities were assumed to vary across health states in this period. The transition probabilities used in the model, for this period, are presented in Table 15 below.

Table 15: Transition probabilities for patients receiving cerliponase alfa- Weeks 0 to 16 (CS, Table D11, p 202)

		Transition probability
Health states 1 and 2	Improve	[redacted]
	Maintain	[redacted]
	Decline	[redacted]
Health states 3, 4, and 5	Improve	[redacted]
	Maintain	[redacted]
	Decline	[redacted]
Health state 6 and 7	Improve	[redacted]
	Maintain	[redacted]
	Decline	[redacted]

Weeks 17 to 96: Unlike the period of weeks 0 to 16, the transition probabilities in the period of weeks 17 to 96 were not assumed to vary according to the health state a patient is in. Instead, the transition probabilities were dependent upon whether a patient is an early responder or a late responder. As described in Section 5.2.1, response was defined retrospectively, rather than prospectively, and refers to patient's response during the period from 17 to 96 weeks. Early responders were defined as patients who experienced no reduction in motor or language function (CNL2 clinical rating scale) after the first 16 weeks of treatment, and late responders were patients who did experience a reduction in function. The proportion of early responders, assumed in the company's base-case analysis, was estimated to be [redacted] of patients, based on the results of the 190-201/202 study.[29]

As early responders were defined by their lack of a drop in CLN2 clinical rating scale score during the period of weeks 17 to 96, early responders were assumed to be stabilised and experience no further progression of disease. In contrast, late responders to treatment were assumed to experience some deterioration in function over the period of weeks 17 to 96. During this period, late responders were assumed to experience an average drop in CLN2 clinical rating scale score of 1 point, with transition probabilities generated by assuming a constant rate of transition during this period. This assumption was based on the observed progression of late stabilisers in the 190-201/202 trial. The transition probabilities for early and late responders for the period from 17 to 96 weeks are described in Table 16.

Table 16: Transition probabilities for patients receiving cerliponase alfa, weeks 0 to 16 (CS, Tables D12 and D13, p 203)

		Transition probability	
		Early responders	**Late responders**
Health states 1 and 2	Improve	0	0.00
	Maintain	1	0.975
	Decline	0	0.025

Week 97 onwards: After week 96, all patients receiving cerliponase alfa were assumed to be stabilised and experienced no further progression of disease.

ERG Comment

The ERG's concerns relating to the transition probabilities are two fold, and relate to technical issues; relating to how the transition probabilities are calculated and the assumption that all patients receiving cerliponase alfa are stabilised after 96 weeks.

Technical issues: The ERG noted a discrepancy in the calculation of the transition probabilities: the transition probabilities used for cerliponase alfa patients, in the first 16 weeks of the model, were based on the first 24 weeks of data. It is unclear why this approach was taken by the company, but there is a clear inconsistency with the clinical data. The impact of this inconsistency is difficult to assess, but is potentially significant, as while these transition probabilities are only applied for a short period of time, the assumption of stability after this period, for many patients, means that they are an important determinant of the total costs and QALYs.

Assumption of stability: The assumption that all patients stabilise after 96 weeks is the single most important assumption in the economic model and a significant driver of both incremental QALYs and the ICER. As described in Sections 4, there is no long-term evidence on the effectiveness of cerliponase alfa and, therefore, the company have drawn upon clinical expertise, evidence from other disease areas in which ERT is used (e.g., Gaucher's disease) and the short-term evidence provided by the 190-201/202 trial, to justify this assumption. As stated in Section 4, the ERG has substantive concerns regarding the company's interpretation of the clinical evidence. Specifically, the ERG notes that there is only limited evidence from the 190-201/202 cohort that all patients stabilise, [redacted]patients continue to experience further disease progression in the later part of the 190-201/202 study (post 48 weeks). Furthermore, while a proportion of patients do appear to achieve short-term stabilisation of disease, the ERG notes this number continues to fall as follow up lengthens. Furthermore, in direct contradiction to the modelled assumption of stability for of all patients post 96 weeks [redacted]

Examination of more objective markers of disease also cast doubt on this assumption; EEG examinations during study 201/202 found new (focal and/or generalised) epileptiform activity in [redacted] of patients, which the ERG's clinical advisor suggested may be an indicator that disease progression had not been halted. Moreover, MRI measurements showed substantial reductions in whole brain volume, cortical grey matter, and white matter. The ERG, also highlights evidence from non-human studies, which showed that treatment only slowed progression of symptoms, with only modest reductions in short-term mortality. The ERG, therefore, considers the assumption of long-term stabilisation to be highly uncertain and likely to be overly optimistic, given the current limited evidence.

These significant concerns regarding the assumption of long-term stability were raised with company at the PfC stage and as part of this, the ERG requested that the company present a scenario making more conservative assumptions with respect to the long-term effectiveness of cerliponase alfa. The company's response to this question provided a scenario in which it was assumed that 5% of patients

do not stabilise after 96 weeks and instead experience standard care progression. It also assumed elevated mortality for patients over the age of 20 years and applied a disutility to account for progressive vision loss. The ERG, does not consider this new scenario to be a useful exploration of the available clinical evidence; the assumption that 5% of patients do not stabilise is arbitrary and it is nonsensical to assume that they would experience standard care rates of progression, given the available evidence. Given the remaining uncertainty regarding the long-term effectiveness of cerliponase alfa, additional analyses, which consider more plausible extrapolations of the available effectiveness evidence, are presented in Section 6.

5.2.7.2 Treatment effectiveness: standard care

Patients not receiving cerliponase alfa were assumed to experience disease progression, based primarily on data from a natural history cohort matched to the 190-201/202 trial patients.[30] Transition probabilities, generated from the natural history data, were assumed to experience different risks of progression dependent upon the health state. Mirroring the transition probabilities applied to patients receiving cerliponase alfa, the transition probabilities for patients were calculated for three groups of CLN2 clinical rating scale scores; scores 6 and 5 [health states 1 and 2], scores of 4 to 2 [health states 3 to 5], and scores of 1 and 0 [health states 6 and 7]. As above, no justification was given for this assumption to vary transition probabilities by health state. Unlike patients receiving cerliponase alfa, the same transition probabilities were applied across all periods of the model. The transition probabilities, for patients not receiving cerliponase alfa, are presented in Table 17.

Table 17: Transition probabilities for patients receiving standard care (CS, Table D11, p202 and Table D14 p204)

		Transition probability
Health states 1 and 2	Improve	0.00
	Maintain	0.92
	Decline	0.09
Health states 3, 4, and 5	Improve	0.00
	Maintain	0.88
	Decline	0.12
Health states 6 and 7	Improve	0.00
	Maintain	0.97
	Decline	0.04
Health states 8 and 9	Improve	NA
	Maintain	0.96
	Decline	0.04

The transition probabilities for the standard care patients were also applied to patients initiating treatment with cerliponase alfa, but who had discontinued treatment; patients initiating on cerliponase alfa were assumed to discontinue treatment if they transitioned to health state 7.

ERG Comment

The ERG considers the company's approach, to the modelling of the transitions for patients receiving standard care, to be reasonable and the data source (DEM-CHILD) was appropriate given the limited data available. As stated in Section 4, the ERG does have concerns about the matching process that was undertaken to generate the 190-901 cohort, as well general concerns regarding the use of a non-randomised comparator. This may have implications in terms of the rate of decline predicted by the transition probabilities. Examination of the Markov traces for the standard care arm, however, shows that the predicted rate of decline aligns with the described disease progression. Further, exploratory analysis carried out by the ERG shows that varying the transition probabilities for the standard care arm did not have a significant impact on the ICER; halving/doubling the rate of decline resulted in a less than 2% change in the ICER. Therefore, despite the significant limitations of the data source, the ERG does not consider this uncertainty to be a significant factor in determining cost-effectiveness.

5.2.7.3 Mortality

The company's base-case model included disease-related mortality and other-cause mortality. The executable model also allowed for an additional mortality risk associated with ICV infection, in the base-case, this was, however, assumed to be a zero risk.

Disease-related mortality was only applied in health state 9 to reflect the progressive nature of CLN2 disease. Patients in other health states were, therefore, assumed to experience a zero risk of disease-related mortality. The disease-related mortality, applied in health state 9, assumed a mean time spent in health state 9 of 52 weeks (26 cycles). This mean time in state was based on clinical expert opinion and was used to calculate the appropriate transition probabilities, assuming a constant probability of dying each cycle.

In addition to disease-related mortality, all patients in the model were subject to other-cause mortality, based on national life tables[45], which were adjusted for the age and sex of the cohort. The ratio of male and female patients was assumed to be 50:50 with age at initiation of treatment based on the mean age at base-line in the 190-201 study.

The mean and median overall survival of patients in standard care in the model were 9.93 years and 9.62 years, respectively. This is consistent with evidence presented in the CS, relating to the life expectancy of patients in the [redacted]

The mean and median overall survival of patients receiving cerliponase alfa, in the model were 80.38 years and 83.89 years, respectively. This significant extension to life expectancy, predicted by the model, is a consequence of the assumption of disease stability after 96 weeks for all patients receiving

cerliponase alfa and the assumption that prior to health state 9, patients experienced general population mortality.

ERG Comment

The company's assumptions regarding the mortality of patients, together with the assumption that patients experience no further progression in disease, are some of the most important factors in determining both the total incremental QALYs and the ICER. The assumption that patients experience general population mortality is not unreasonable, 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, align with external data on the life expectancy of patients receiving standard care.

The ERG, however, has significant concerns about the assumption that patients who receive cerliponase alfa will experience general population levels of mortality. While there is no long-term evidence regarding the mortality of patients receiving cerliponase alfa, there are a number of reasons that we might expect patients receiving cerliponase alfa to experience substantially shorter life expectancy than is being predicted in the company's base-case analysis. These arguments relate to three potential causes of death: neurological progression, extra-neurological progression and other-disease-related mortality, not directly attributable to progression of the disease. Each of these is discussed, in turn, below.

Neurological progression: As discussed above, the ERG considers that the company's interpretation of the clinical data is potentially overly optimistic, and there is significant uncertainty regarding the assumption that patients experience no further disease progression after 96 weeks. Any relaxation of this assumption will lead to a reduced life expectancy for cerliponase alfa patients, because even slow progression in at least some patients will result in a substantially reduced life expectancy. As outlined above, the ERG explored alternative assumptions regarding stabilisation in Section 6. These scenarios will account for any disease-progression-related mortality, using assumptions already made in the company's base-case, i.e. that once patients decline to health state 9 they have a mean life expectancy of 52 weeks.

Extra-neurological progression: As discussed in Sections 2, the ERG considers there to be a significant risk that patients receiving cerliponase alfa will experience significant morbidity and mortality due to the extra-neuronal storage of ceroid lipofuscin. Specifically, the ERG notes that expression of TPP1 is not limited to the CNS; the pathological accumulation of lipofuscin in other organs is well documented in CLN2 disease, and the consequences are seen in other forms of Batten disease. Furthermore, pre-clinical studies indicated there may be serious implications for patient morbidity and mortality associated with cardiac, pancreatic, and hepatic impairment unless ERT is

administered systemically. The ERG has particular concerns regarding cardiac involvement, indeed, over the short duration of the presented trials, from [redacted] at baseline, [redacted] of patients had ECG abnormalities. Importantly the morbidity and mortality consequences of extra-neurological disease pathology will be unrelated to neurological progression and therefore, represent an additional mortality risk. This would affect all patients regardless of the ability of cerliponase alfa to slow/stabilise neurological progression. The lack of any long-term human data on the life expectancy of patients receiving cerliponase alfa makes these risks difficult to quantify and, as such, the impact of this additional mortality is subject to significant uncertainty. The clinical advisor to the ERG, however, concurred with an interpretation of the evidence that extra-neurological pathology is both biologically plausible and likely, given the available evidence.

The evidence described above relating to extra-neurological pathology was put to the company, at the PfCs, and the company was asked to present a scenario analysis that was more conservative in its assumptions regarding the prognosis of patients. The company's response, was, however, relatively dismissive of the potential for extra-neurological pathology, citing the lack of evidence in humans. The company, however, did provide an additional, more conservative, scenario analysis in which mortality risk was doubled at the age of 20 years and increased linearly to a four times risk at age 40 years and beyond. The mean and median overall survival of patients receiving cerliponase alfa, in this scenario analysis, were 67.7 years and 70.04 years, respectively. While the ERG acknowledges the lack of human evidence in CLN2 patients upon which to base these modifications, the ERG does not consider this scenario to adequately account for the impact of extra-neurological pathology on mortality. The mean and median life expectancy of patients in this new scenario is still very high and suggests life-year gains of more than 50 years. It is also inconsistent with the evidence from both the animal studies and the related Batten's disease sub-type CLN3. The animal studies showed evidence of significant cardiac functional impairment in dogs aged 12 to 17 months of age and life expectancy of no greater than 190% of untreated dogs,[3] while the evidence from the related Batten's disease sub-type CLN3 observed significant heart abnormalities in all patients over the age of 14 years and reported on two cases of heart failure in patients in their 20's.[16] This evidence would suggest that the effects of extra-neurological-related mortality would mean that it would be unlikely for patients to live much beyond their 20's and, potentially, that mean life expectancy may be even be as early as the late teens. To reflect the mortality risks associated with extra-neurological disease progression the ERG presents an additional scenario analysis, in Section 6.

Other-disease-related mortality: Evidence from the related Batten's disease sub-type CLN3 shows that the actual cause of death for a substantial proportion of CLN3 patients was either pneumonia or infection. Therefore, the actual cause of death was not directly related to either neurological failure or extra-neurological pathology. Advice received by the ERG from their clinical advisor -suggests that

the cause of death in these patients is likely to be related to symptom burden and, in particular, loss of ambulation and neurological disability. The clinical advisor speculated this may be a consequence of poor secretion management and difficulties with swallowing which increase infection risk or may be associated with an increased medication load used to control disease symptoms.

While there is a lack of evidence in patients with CLN2, on the long-term effects of neurodisability on mortality, evidence from other disease areas suggests that a loss of ambulation and/or neurological disability results in significant increases in mortality risk. For example, long-term follow-up studies of people who have suffered traumatic brain injuries (TBIs) show significant increases in long-term mortality compared with matched controls.[46, 47] These studies also show that the mortality risk increases substantially with the severity of injury, with patients who have suffered a severe TBI experiencing approximately a 10-fold increase in mortality risk, compared with matched controls. Similar results have also been seen in patients with loss of ambulation following spinal cord injuries{van den Berg, 2010 #64. Given this evidence, the ERG also performed a scenario analysis which considered increased mortality risks for patients stabilised in the neurologically impaired health states.

5.2.7.4 Adverse events

The adverse events (AEs) associated with cerliponase alfa were captured in the company's model, with event probabilities based on the safety profile in the 190-201/202 study. All-cause event rates were extracted from the safety population, with the selection of adverse events included in the model based on the most common study drug-related adverse events reported by patients in the 190-202 study. Adverse events included the model were: pyrexia, hypersensitivity, headache, and vomiting. In addition, ICV-infusion-related infections were also included as adverse events, with the infusion risk based on a systematic review investigating the long-term risk of ICV use.[48]

The adverse event probabilities incorporated into the model are presented in Table 18 and were assumed to be constant throughout the time horizon of the model. These were based on the number of patients experiencing each type of event during the on-treatment period in the respective clinical trials. Patients experiencing multiple instances of a particular adverse event were only counted once.

Table 18: Adverse events proportions in the model (CS, Table D16, p206)

Adverse events	**% of patients**
Pyrexia	[redacted]
Hypersensitivity	[redacted]
Headache	[redacted]
Vomiting	[redacted]
ICV infusion (risk per infusion)	0.45%

Adverse events related to therapy used to provide symptomatic relief were not included in the economic model.

Adverse events were modelled to impact on both quality of life and costs. The costs, and disutility, associated with adverse events in the model are discussed in Section 5.2.9.3 and Section 5.2.8, respectively.

ERG comment

The ERG considers that the company's approach to modelling AE's was generally appropriate, but is concerned about the company's approach to the selection of AE's to include in the model. Specifically, the ERG is concerned that the company's focus is on the most frequent events rather than the most severe. As can be seen from Table 19, which lists the frequency of grades III and IV adverse events, there a number of serious adverse events that were not included in the company's base-case analysis. The implications of these AE's are more serious and by extension more important in terms of quality of life, and their costs are not accounted for in the model. The impact of this omission is, however, likely to be small given the infrequency of grades III and IV events listed in Table 19, and therefore the ERG did not explore this further in its additional analysis.

Table 19: Grade 3 and grade 4 adverse events

Safety category	**n (%)**
Grade IV adverse event	
Status epilepticus	[redacted]
Grade III adverse events	
Infection Upper respiratory tract infection	[redacted]
Nervous system disorder	[redacted]
Hypersensitivity	[redacted]
Respiratory, thoracic, mediastinal	[redacted]
Immune system	[redacted]
Gastro-intestinal	[redacted]
Seizure	[redacted]

Product issue	[redacted]

5.2.8 Health-related quality of life

The company conducted a systematic literature review to identify the literature on health-related quality of life (HRQoL). The searches used were described in Section 5.1. The inclusion/exclusion criteria used in the study selection were presented in the CS, Table D1 (pp. 170-3). The company searched for studies that included patients with any variant of CLN2 disease or TPP1 deficiency, their family or their carers, and collected original health-state utility data. Apart from these additional inclusion/exclusion criteria, the criteria for the HRQoL review followed those presented in Table 10. The review identified one study.[20] This study collected HRQoL values, using the EQ-5D-5L, from caregivers and siblings of patients with CLN2, who were resident in the UK and Germany. The ERG considers the eligibility criteria to be reasonable and that the review is not likely to have missed any relevant studies. As the values identified in the literature search were not sufficient for the cost-effectiveness analysis, and not all of the required utilities for each health state were collected in the trials, the company undertook a utility study which used vignettes to obtain the utility values required for the cost-effectiveness model.

5.2.8.1 Vignettes

The company's utility study employed an indirect elicitation method using proxy reporting via clinicians. The utility study involved the use of vignettes, which were brief descriptions of each of the nine health states in the economic model, for both the cerliponase alfa arm and the standard care arm, (18 vignettes in total being used.). Only one vignette was used for each health state, with the most common combination of the motor and language domain scores on the CLN2 clinical rating scale being used. The vignettes also described additional symptoms/care requirements including vision loss and the requirement for palliative care, which is as per the health state definitions, see 5.2.1; as well as details of other progressive symptoms (epilepsy, reported distress, dystonia, myoclonus and the requirement for a feeding tube). The disutility associated with these symptoms was, therefore, incorporated into the health-state utilities. The CS states that the vignettes were validated by a clinical expert with experience of CLN2 disease and cerliponase alfa. The descriptions of each health state used in the utility study are presented in Table 20.

Table 20: Vignette health state descriptions (CS, Appendix 10, pp. 84-89)

	Standard care without cerliponase alfa	Cerliponase alfa
ML Score 6	The patient is a child that: -Has normal gait, no prominent ataxia, and doesn't suffer from pathologic falls. These features correspond to a Motor score of 3 on the CLN2 Clinical Rating Scale. -They have apparently normal language levels and are intelligible for their age. These features	The patient is a child that: -Has normal gait, no prominent ataxia, and doesn't suffer from pathologic falls. These features correspond to a Motor score of 3 on the CLN2 Clinical Rating Scale. -They have apparently normal language levels and are intelligible for their age. These features correspond to

	correspond to a Language score of 3 on the CLN2 Clinical Rating Scale. -Their vision is normal. -They have epilepsy, which is managed using anti-epileptic medications, but experience one generalised tonic-clonic seizure per year. -They don't experience disease-related pain/distress, dystonia, or myoclonus. -They are not using a feeding tube -They have normal social interactions.	a Language score of 3 on the CLN2 Clinical Rating Scale. -Their vision is normal. -They have epilepsy, which is managed using anti-epileptic medications, but experience one generalised tonic-clonic seizure per year. -They don't experience disease-related pain/distress, dystonia, or myoclonus. -They are not using a feeding tube -They have normal social interactions. -**They are currently being treated with cerliponase alfa, which is administered every other week by intracerebroventricular infusion for four hours.**
ML Score 5	The patient is a child that: -Has an independent gait, but obvious instability, and may have intermittent falls. These features correspond to a Motor score of 2 on the CLN2 Clinical Rating Scale. -They have apparently normal language levels and are intelligible for their age. These features correspond to a Language score of 3 on the CLN2 Clinical Rating Scale. -Their vision is normal. -They have epilepsy, which is managed using anti-epileptic medications, but experience **three** generalised tonic-clonic seizures per year. -They don't experience disease-related pain/distress, dystonia, or myoclonus. -**They are using a feeding tube.** -They have relatively normal social interactions.	The patient is a child that: -Has an independent gait, but obvious instability, and may have intermittent falls. These features correspond to a Motor score of 2 on the CLN2 Clinical Rating Scale. -They have apparently normal language levels and are intelligible for their age. These features correspond to a Language score of 3 on the CLN2 Clinical Rating Scale. -Their vision is normal. -They have epilepsy, which is managed using anti-epileptic medications, but experience **one** generalised tonic-clonic seizure per year. -They don't experience disease-related pain/distress, dystonia, or myoclonus. -**They are not using a feeding tube.** -They have relatively normal social interactions. **-They are currently being treated with cerliponase alfa, which is administered every other week by intracerebroventricular infusion for four hours.**
ML Score 4	The patient is a child that: -Has an independent gait, but obvious instability, and may have intermittent falls. These features correspond to a Motor score of 2 on the CLN2 Clinical Rating Scale. -Their language is limited for their age. This corresponds to a Language score of 2 on the CLN2 Clinical Rating Scale. -Their vision is normal. -They have epilepsy, which is managed using anti-epileptic medications, but experience **six** generalised tonic-clonic seizures per year. -They don't experience dystonia, **but do experience myoclonus and spasticity, which cause disease-related pain/distress.** -**They are using a feeding tube.** -They have relatively normal social interactions.	The patient is a child that: -Has an independent gait, but obvious instability, and may have intermittent falls. These features correspond to a Motor score of 2 on the CLN2 Clinical Rating Scale. -Their language is limited for their age. This corresponds to a Language score of 2 on the CLN2 Clinical Rating Scale. -Their vision is normal. -They have epilepsy, which is managed using anti-epileptic medications, but experience **one** generalised tonic-clonic seizure per year. -They don't experience dystonia, **but do experience minimal myoclonus and minimal spasticity, which cause minimal disease-related pain/distress**. -**They are not using a feeding tube**. -They have relatively normal social interactions. -**They are currently being treated with cerliponase alfa, which is administered every other week by intracerebroventricular infusion for four hours.**
ML score 3	The patient is a child that:	The patient is a child that:

	-Requires external assistance to walk. This corresponds to a Motor score of 1 on the CLN2 Clinical Rating Scale. -Their language is limited for their age. This corresponds to a Language score of 2 on the CLN2 Clinical Rating Scale. -They experience problems recognising objects at distance. -They have epilepsy, which is managed using anti-epileptic medications, but experience **six** generalised tonic-clonic seizures per year. -They don't experience dystonia, **but do experience myoclonus and spasticity, which cause disease-related pain/distress**. -They are using a feeding tube. -They have some difficulty with social interactions.	-Requires external assistance to walk. This corresponds to a Motor score of 1 on the CLN2 Clinical Rating Scale. -Their language is limited for their age. This corresponds to a Language score of 2 on the CLN2 Clinical Rating Scale. -They experience problems recognising objects at distance. -They have epilepsy, which is managed using anti-epileptic medications, but experience **one** generalised tonic-clonic seizure per year. -They don't experience dystonia, **but do experience minimal myoclonus and minimal spasticity, which cause minimal disease-related pain/distress**. -They are using a feeding tube. -They have some difficulty with social interactions. -**They are currently being treated with cerliponase alfa, which is administered every other week by intracerebroventricular infusion for four hours.**
ML Score 2	The patient is a child that: -Requires external assistance to walk. This corresponds to a Motor score of 1 on the CLN2 Clinical Rating Scale. -The patient is hardly understandable. This corresponds to a Language score of 1 on the CLN2 Clinical Rating Scale. -They have problems recognising objects at distance. -They have epilepsy, which is managed using anti-epileptic medications, but experience **six** generalised tonic-clonic seizures per year. -They experience dystonia, **myoclonus, and spasticity, which cause disease-related pain/distress**. -They are using a feeding tube. -They have **moderate difficulty** with social interactions.	The patient is a child that: -Requires external assistance to walk. This corresponds to a Motor score of 1 on the CLN2 Clinical Rating Scale. -The patient is hardly understandable. This corresponds to a Language score of 1 on the CLN2 Clinical Rating Scale. -They have problems recognising objects at distance. -They have epilepsy, which is managed using anti-epileptic medications, but experience **one** generalised tonic-clonic seizure per year. -They experience dystonia, **minimal myoclonus and minimal spasticity, which cause minimal disease-related pain/distress**. -They are using a feeding tube. -They have **some difficulty** with social interactions. -**They are currently being treated with cerliponase alfa, which is administered every other week by intracerebroventricular infusion for four hours**.
ML Score 1	The patient is a child that: -Requires external assistance to walk. This corresponds to a Motor score of 1 on the CLN2 Clinical Rating Scale. -The patient is not understandable, with no intelligible words. This corresponds to a Language score of 0 on the CLN2 Clinical Rating Scale. -They can only recognise objects right in front of them. -They have epilepsy, which is managed using anti-epileptic medications, but experience **six** generalised tonic-clonic seizures per year. -They experience dystonia, **myoclonus, and spasticity, which cause disease-related pain/distress.** -They are using a feeding tube. -They have **severe difficulty** with social interactions.	The patient is a child that: -Requires external assistance to walk. This corresponds to a Motor score of 1 on the CLN2 Clinical Rating Scale. -The patient is not understandable, with no intelligible words. This corresponds to a Language score of 0 on the CLN2 Clinical Rating Scale. -They can only recognise objects right in front of them. -They have epilepsy, which is managed using anti-epileptic medications, but experience **one** generalised tonic-clonic seizure per year. -They experience, dystonia, **minimal myoclonus, and minimal spasticity, which cause minimal disease-related pain/distress**. -They are using a feeding tube. -They have **moderate difficulty** with social interactions.

		-**They are currently being treated with cerliponase alfa, which is administered every other week by intracerebroventricular infusion for four hours**.
ML Score 0	The patient is a child that: -Cannot walk or crawl. This corresponds to a Motor score of 0 on the CLN2 Clinical Rating Scale. -The patient is not understandable, with no intelligible words. This corresponds to a Language score of 0 on the CLN2 Clinical Rating Scale. -They are functionally blind. -They have epilepsy, which is managed using anti-epileptic medications. They do not experience generalised tonic-clonic seizures. -They experience, dystonia, **myoclonus, and spasticity, which cause disease-related pain/distress.** -They are using a feeding tube. -They have **extreme difficulty** with social interactions.	The patient is a child that: -Cannot walk or crawl. This corresponds to a Motor score of 0 on the CLN2 Clinical Rating Scale. -The patient is not understandable, with no intelligible words. This corresponds to a Language score of 0 on the CLN2 Clinical Rating Scale. -They are functionally blind. -They have epilepsy, which is managed using anti-epileptic medications. They do not experience generalised tonic-clonic seizures. -They experience dystonia, **minimal myoclonus, and minimal spasticity, which cause minimal disease-related pain/distress.** -They are using a feeding tube. -They have **serious difficulty** with social interactions. **-They are currently being treated with cerliponase alfa, which is administered every other week by intracerebroventricular infusion for four hours.**
ML score 0, with vision loss	The patient is a child that: -Has lost their ability to walk or crawl. This corresponds to a Motor score of 0 on the CLN2 Clinical Rating Scale. -They have no intelligible words or vocalisations. This corresponds to a Language score of 0 on the CLN2 Clinical Rating Scale. -They have complete vision loss. -They have epilepsy, which is managed using anti-epileptic medications. They do not experience generalised tonic-clonic seizures. -They experience dystonia, **myoclonus, and spasticity, which cause disease-related pain/distress.** -They are using a feeding tube. -They are unable to interact socially.	The patient is a child that: -Has lost their ability to walk or crawl. This corresponds to a Motor score of 0 on the CLN2 Clinical Rating Scale. -They have no intelligible words or vocalisations. This corresponds to a Language score of 0 on the CLN2 Clinical Rating Scale. -They have complete vision loss. -They have epilepsy, which is managed using anti-epileptic medications. They do not experience generalised tonic-clonic seizures. -They experience dystonia, **minimal myoclonus, and minimal spasticity which cause minimal disease-related pain/distress**. -They are using a feeding tube **and require secretion management** -They are unable to interact socially. -**They are currently being treated with cerliponase alfa, which is administered every other week by intracerebroventricular infusion for four hours.**
ML Score 0, requiring palliative care	The patient is a child that: -Has lost their ability to walk or crawl. This corresponds to a Motor score of 0 on the CLN2 Clinical Rating Scale. -They have no intelligible words or vocalisations. This corresponds to a Language score of 0 on the CLN2 Clinical Rating Scale. -They have complete vision loss. -They have epilepsy, which is managed using anti-epileptic medications. They do not experience generalised tonic-clonic seizures. -They experience dystonia, **myoclonus, and spasticity, which cause disease-related pain/distress.** -They are using a feeding tube, require secretion management, and have significant respiratory	The patient is a child that: -Has lost their ability to walk or crawl. This corresponds to a Motor score of 0 on the CLN2 Clinical Rating Scale. -They have no intelligible words or vocalisations. This corresponds to a Language score of 0 on the CLN2 Clinical Rating Scale. -They have complete vision loss. -They have epilepsy, which is managed using anti-epileptic medications. They do not experience generalised tonic-clonic seizures. -They experience dystonia, **minimal myoclonus, and minimal spasticity, which cause disease-related pain/distress.**

	assistance requirements, requiring a ventilator day and night. -They are incontinent of bowel and bladder. -They are unable to interact socially.	-They are using a feeding tube, require secretion management, have significant respiratory assistance requirements, requiring a ventilator day and night. -They are incontinent of bowel and bladder. -They are unable to interact socially. **-They are currently being treated with cerliponase alfa, which is administered every other week by intracerebroventricular infusion for four hours.**

Utility values based on the vignettes were elicited using eight clinical experts with experience of cerliponase alfa and treatment of patients with CLN2 disease. The eight clinical experts were asked to complete an online version of the EQ-5D-5L, as a proxy for patients who would be experiencing the description given in the vignettes. Before they completed the EQ-5D-5L questionnaires, they were presented with brief background information about the economic model, and the use of the utility values within the model.

In line with NICE methods guidance[40, 49], the EQ-5D-5L values collected were then mapped to the EQ-5D-3L values to obtain the utility values used in the model. The EQ-5D-3L values used in the model, are presented in Table 21.

Table 21: Utility values for cost-effectiveness analysis [EQ-5D-5L values mapped to EQ-5D-3L] (CS, Table C38, p. 165)

Health state	Cerliponase alfa	Standard care
Health state 1	[redacted]	[redacted]
Health state 2	[redacted]	[redacted]
Health state 3	[redacted]	[redacted]
Health state 4	[redacted]	[redacted]
Health state 5	[redacted]	[redacted]
Health state 6	[redacted]	[redacted]
Health state 7	[redacted]	[redacted]
Health state 8	[redacted]	[redacted]
Health state 9	[redacted]	[redacted]
Health state 10 (death)	[redacted]	[redacted]

The ERG accepts that a utility study was required, given the lack of utility value estimates in both the literature and within the relevant trials, for all health states and for standard care. The ERG also considers that the methods used by the company to be broadly appropriate, including the decision to map the EQ-5D-5L values to EQ-5D-3L. The ERG, however, does have some concerns with respect to the methodology and face validity of the generated values. These concern the widespread use of negative utilities, the external validity of the elicited values, the content of the vignettes and the

assumption of differential utility, the impact of comorbidities on HRQoL and the face-validity of the values used, given the limitations of the CLN2 clinical rating scale.

Use of negative utilities

The ERG is not concerned with the use of negative utilities per se, given the severity of the disability experienced by patients, but does note that the unmapped EQ-5D-5L values, presented in Table 22, show much higher utility values across the health states and very few negative utility values, when compared with the EQ-5D-3L values (Table 21). The ERG therefore suggests the EQ-5D-5L may be a better reflection of QoL experienced by CLN2 patients.

Reflecting these concerns, the ERG requested in the PfCs that the company justify the use of negative health states in health states 7, 8, and 9, noting that the EQ-5D-5L differed substantively from the EQ-5D-3L values used in the model. The company's response stated that the values were validated by experts following the study and that negative utility values have been used in the latter stages of diseases, such as Dementia with Lewy Bodies (24% reported negative values), stroke, multiple sclerosis and myasthenia gravis.[50-52] The company's response, unfortunately, did not address the disparity between the elicited EQ-5D-5L and the mapped EQ-5D-3L. The ERG is also not clear whether it was the EQ-5D-5L values or the EQ-5D-3L values that were verified by the clinical experts. The ERG, while acknowledging the NICE methods guideline, is still concerned that the EQ-5D-5L may be more reflective of the experienced HRQoL. On this point, the ERG also notes that the EQ-5D-5L better reflects the QoL data collected in the 190-201/202 trials, see details below. The ERG presents a scenario analysis, in section 6, using the EQ-5D-5L utility values.

Table 22: EQ-5D-5L values (BioMarin utility report[53])

Health state	Cerliponase alfa	Standard care
Health state 1	[redacted]	[redacted]
Health state 2	[redacted]	[redacted]
Health state 3	[redacted]	[redacted]
Health state 4	[redacted]	[redacted]
Health state 5	[redacted]	[redacted]
Health state 6	[redacted]	[redacted]
Health state 7	[redacted]	[redacted]
Health state 8	[redacted]	[redacted]
Health state 9	[redacted]	[redacted]

External Validity: Trial utilities

In the 190-201 and 190-202 studies, HRQoL was assessed as an exploratory endpoint using two instruments: PedsQL a paediatric quality of life tool and CLNQoL a disease-specific QoL instrument. In addition, the 190-202 study (only) collected HRQoL data using the EQ-5D-5L instrument.

However, the HRQoL data collected from the 190-201/202 studies was not used in the company's base-case analysis, because utility values could not be obtained for all of the health states in the model and because the data were only available for patients receiving cerliponase alfa. Comparison of these trial-based utilities, however, provides a useful validation of the elicited values used in the base-case analysis. Table 23 presents the health-state values obtained from the 190-201/202 studies along with the elicited values used in the base-case- analysis.

Table 23: PedsQL utility values and corresponding vignette utility values (CS, Table D35, p242)

Health state	Cerliponase alfa utilities from PedsQL (mapped to EQ-5D-3L)	Vignettes	Difference
Health state 1	[redacted]	[redacted]	[redacted]
Health state 2	[redacted]	[redacted]	[redacted]
Health state 3	[redacted]	[redacted]	[redacted]
Health state 4	[redacted]	[redacted]	[redacted]
Health state 5	[redacted]	[redacted]	[redacted]
Health state 6	[redacted]	[redacted]	[redacted]
Health state 7*	NA	[redacted]	NA
Health state 8*	NA	[redacted]	NA
Health state 9*	NA	[redacted]	NA
*Utility values were not available in health states 7-9 as no patients in the trial were in these health states.			

As can be seen from Table 23, the vignettes appear to be underestimating the utilities, with the degree of underestimation increasing as the patient moves up the health states. The reason for this difference is not clear, but it may be because PedsQL is bound at zero. It is, however, notable that the PedsQL aligns much better with the unmapped EQ-5D-5L. This may suggest that the mapping of the elicited EQ-5D-5L to the EQ-5D-3L has led to an overestimation of the impact of CLN2 on HRQoL. The PedsQL is also, arguably, methodologically superior to the clinician-elicited values as they are elicited directly from patients (or directly through a caregiver). The ERG, therefore, considers that there are convincing arguments in favour of the use of the PedsQL mapped values (no established mapping algorithm is available for CLNQoL values). On balance, however, the ERG's preference is to use the clinician-elicited values. This is in part because they include the effects of progressive symptoms, but primarily due to the fact that PedsQL instrument is bound at zero. As noted above, the ERG considers that the use of the negative values is appropriate, in the present context, and highlights that the use of such values aligns with other serious degenerative disorders, such as multiple sclerosis and myasthenia gravis. Given the uncertainty, however, the ERG presents a scenario analysis, in Section 6, exploring the impact of alternative assumptions regarding health-state utilities.

Content of the Vignettes

The ERG has a number of concerns regarding the content of the vignettes. These primarily concern the differences between the descriptions provided for patients receiving cerliponase alfa and standard care. From a comparison of the vignettes for each health state (the ERG has highlighted (in bold) the differences in the vignette descriptions between the comparators for each health state in Table 20), it is clear that the vignettes imply significant additional benefits of treatment with cerliponase alfa over and above the effects on disease progression. Specifically, the vignettes imply that cerliponase alfa improves seizure control, control of dystonia and myoclonus, and delays the need for a feeding tube.

At the PfCs, the ERG asked the company to justify these differences in the vignettes and to provide evidence to show that cerliponase alfa provides the implied clinical benefits. The evidence provided by the company, to justify the implied seizure control and delay in needing a feeding tube, were changes in CLNQoL scores. The ERG, however, does not agree with the company's interpretation of this evidence; because CLNQoL scores are not clinical measures, but are patient-reported outcomes. Further, with respect to improved seizure control, the ERG's clinical advisor notes that tonic-clonic seizures are only one aspect of epilepsy and that similar improvements in epileptiform activity were not observed in the trial patients indicating that cerliponase alfa does not induce overall improved seizure control. No evidence was provided for the implied improvement in control of dystonia.

The evidence provided, with respect to myoclonus, was also problematic, as while it demonstrates that the severity of myoclonus increases at slower rate in patients receiving cerliponase alfa compared with standard care, it does not provide evidence by health state. It is expected that the severity of progressive symptoms in the cerliponase alfa and natural history groups will diverge as they are correlated with disease progression and cerliponase alfa slows the rate of progression. The observed differences are therefore entirely expected and do not support the differential control of symptoms implied in the vignettes.

Given the lack of clinical evidence to suggest these clinical benefits, the ERG believes that it would be more appropriate to assume that the utilities are the same for both treatment and comparator patients. This will be explored further in Section 6.

Face validity

The ERG is concerned about the utility values used in health state 1, which assume near perfect health. The ERG questions whether this is reasonable given that nearly all patients will have some symptom load, e.g., epilepsy, language delay, and cognitive impairment. The ERG, particularly, notes the language component of the CLN2 clinical rating scale compares to best achieved and, therefore, a score of 3 does not imply normal development. At the PfCs, the ERG requested that the company comment on the validity of the assumed values in health state 1, noting the issues stated above. In response, the company emphasised that not all patients are symptomatic at diagnosis and that, in health state 1, patients are assumed to have well-controlled epilepsy and very low seizure frequency. The company also emphasised that the individual health states were validated by clinical experts. To address the ERG's concerns, the company, however, also provided two scenario analyses. In the first, the utility value for health state 1 in both arms was reduced by 10%. In the second, a reduction in quality of life was incorporated, to factor for patients' quality of life deteriorating over time. This was applied for patients over 25 years and assumed, based on data from a published study.[50]

Impact of comorbidities

As noted above, the utility values applied in the less severe health states (health states 1 and 2) were very high and, while potentially a reasonable representation of the HRQoL of children, would imply utility values that exceed those of the adult general population. This is of particular concern in scenarios where disease stabilisation is assumed, as no account for age-related decline in utility due to disability and comorbidities is included in the model. The ERG, therefore, considers that utilities in the health states should be further adjusted for age (in line with the NICE Guide to the methods of technology appraisal 2013: CS, Table 83). This scenario is presented in Section 6.

5.2.8.2 Parent/Carer and sibling disutility

As described above, the utilities review carried out by the company identified one relevant study, which reported on the HRQoL of parents and siblings of children with CLN2 disease.[20] This study included families from the United Kingdom (as well as Germany). The study found that caregivers (parents) reported generally lower health-related quality of life, compared with matched controls in the general population, with the main negative influences being pain, depression and anxiety.[20] The study has also shown that CLN2 disease has a wide-ranging and severe impact on caregivers, siblings and families, with personal and financial adjustments needed, as one parent often needs to give full-time commitment to care-giving.

To account for the impact of CLN2 disease on the family, the company applied a disutility for both caregivers (parents) and siblings.

The caregiver disutility value applied was also obtained from the ICON study[20], which reported on the challenges of living with and caring for a child affected by CLN2 disease. This study compared the EQ-5D-5L crosswalk score to matched norms (based on age-group and gender) taken from Health Survey for England, and found that UK caregivers had a significantly lower EQ-5D-5L score (difference -0.108). As data were not available on the patients' stage of disease when this disutility value was measured, the company made a number of assumptions regarding the relationship between the CLN2 clinical rating scale score and carer disutility. Health states 1 and 2 were derived from expert opinion, and assumed a disutility of 0. The disutility for the remaining seven health states assumed a linear relationship between CLN2 clinical rating scale score and carer disutility, with the -0.108 value taken from the ICON study[20] being used for health state 6 (the mid-point of health states 3 to 9). The values used are presented in

Table 24. The model assumed a number of family caregivers in each of the health states, as presented in Table 25 below.

Table 24: Number of caregivers applied in the model (CS, Table D8, p195)

Health State	Average number of caregivers required	Percentage of care provided by family caregivers	Number of family caregivers applied in the model.	Caregiver disutility applied
Health state 1	0.06	100%	0.06	-0.02
Health state 2	0.67	100%	0.67	-0.025
Health state 3	0.75	100%	0.75	-0.027
Health state 4	1	83%	0.86	-0.054
Health state 5	1	78%	0.78	-0.081
Health state 6	1	79%	0.79	-0.108
Health state 7	1.25	75%	0.9375	-0.135
Health state 8	1.14	73%	0.8322	-0.162
Health state 9	1.14	73%	0.8322	-0.189

The number of caregivers required, see Table 24, was elicited from a Delphi panel of eight clinical experts.[36] The Delphi panel estimated the average number of caregivers required for each health state and the percentage of care provided by family caregivers, these estimates were multiplied together to give an estimate of the average number of family caregivers in each health state. To estimate the total caregiver disutility, the average number of caregivers was multiplied by the relevant disutility.

As well as the burden felt by caregivers, the company's model takes account of the disutility experienced by the siblings who are unaffected directly by CLN2 disease. The model applied a sibling disutility to health states 3 to 9 (guidance from clinical experts suggested no disutility in health states 1 and 2). The sibling disutility applied was also sourced from the ICON study.[20] This study estimated child sibling utility using the CHU-9D, and it was found to be 0.91, assuming that, under normal circumstances, the child's utility would be 1, this implies a -0.09 decrement. As with the caregiver's disutility, -0.09 was applied to the mid-point of the health states (i.e. health state 6) and disutility was assumed to increase in a linear way starting at health state 3, until health state 9. The estimated disutility values for siblings for each health state are presented in Table 25.

Table 25: Caregiver disutility (CS, Table D9, p.196) and Sibling disutility (CS, Table D10, p. 197)

Health State	Aver average number of siblings	Sibling disutility
Health state 1	0.94	0.000
Health state 2	0.94	0.000
Health state 3	0.94	-0.023
Health state 4	0.94	-0.045
Health state 5	0.94	-0.068
Health state 6	0.94	-0.090
Health state 7	0.94	-0.113
Health state 8	0.94	-0.135
Health state 9	0.94	-0.158

As with carer disutilities the total disutility applied was determined by multiplying the average number of siblings by the relevant health-state disutility. The number of siblings was based on a Batten Disease Family Association (BDFA) survey, which showed that there were 32 siblings (without CLN2 disease) across an analysis of 34 CLN2 patients. The company, therefore, applied a multiplier of 0.94 (32/34) to the estimated sibling disutilities.

ERG Comment

The ERG considers the inclusion of caregiver and siblings disutilities to be appropriate, given the evidence provided regarding the substantial impact of CLN2 on family life. The ERG also considers the broad approach taken by the company to be reasonable, given the limited data available; the ERG also notes that removing caregiver and sibling disutilities (scenario 7, Table D50, p267) had minimal impact on the ICER. The ERG is, however, concerned about the length of time over which these disutilities were applied, as both caregiver and sibling disutilities were applied for the whole 95-year time horizon. Given the assumptions about the life expectancy of patients treated with cerliponase alfa (general population mortality was assumed) this implies that these disutilities continue on average for more than 80 years. This is unrealistic given the life-expectancy of caregivers and the fact that healthy siblings will often leave home. In Section 6, a scenario analysis was undertaken by the ERG, in which caregiver and siblings disutilities are stopped after a reasonable period of time.

5.2.8.3 Adverse event disutility

Adverse event disutilities were sourced from the literature for the cerliponase alfa-related adverse events, reported during studies 190-201/202, and applied to the cerliponase alfa arm of the model. The annual disutility due to an adverse event was calculated, and the rate of occurrence of adverse events was assumed to be constant through the model time horizon, in line with the dosing schedule of

cerliponase alfa being unchanged throughout the model time horizon. The total annual disutility due to adverse events, included in the model, is presented in Table 26.

Table 26: Adverse event disutility calculation (CS, Table D7, p193)

Adverse event	Disutility	Source	Time adverse event experienced for (days)	Source	Annual occurrences of adverse events	Source	Total annual disutility from adverse event
Pyrexia	-0.11	Beusterien et al. (2010)[31]	[redacted]	Study 190-202 patient narratives[54]	[redacted]	Study 190-201/202, Patient Narratives[54]	[redacted]
Hypersensitivity	-0.03	Kauf et al. (2010)[32]	1	Assumption	[redacted]		[redacted]
Headache	-0.12	Maniadakis et al. (2013)[33]	1		[redacted]		[redacted]
Vomiting	-0.05	Beusterien et al. (2010)[31]	1		[redacted]		[redacted]
Infection	-0.2	Song et al. (2012)[34]	N/A	N/A	N/A	N/A	N/A

The proportion of patients suffering from treatment-related adverse events at any time in the model was based on the most common study drug-related adverse events reported by patients in Study 190-202. These events (and their associated proportions) were pyrexia ([redacted]); hypersensitivity ([redacted]); headache [redacted] and vomiting ([redacted]). In addition, the CS assumed an infection rate of 0.45% for each performed ICV infusion, based on published clinical trial data.[29] Within the model, no treatment-related adverse events were applied to the standard care arm.

ERG Comment

The adverse event disutility calculations appear to be appropriate. However, as noted in Section 5.2.7.4, the company included only the most common study drug-related AEs in the model, and did not include the grade 3/4 AEs, which is a common criterion for selection of AEs. The impact of AEs in this appraisal is, however, likely to be very small and, therefore, the disutilities associated with additional AEs are not explored further by the ERG.

5.2.9 Resources and costs

The company's submission provided details of the resource use and costs associated with each relevant strategy of care (Table D18, Section 12.3 of CS). The company described the following elements of care associated with the technology and management of CLN2:

- The cost and administration of cerliponase alfa;

- Health-state costs associated with monitoring and providing supportive care for patients and their families; and
- Treatment of progressive symptoms associated with CLN2 disease.

Given a lack of national, published guidelines for the treatment and management of CLN2 disease, resource utilisation was based upon advice from a number of clinicians with expertise in this disease area (described in Section 5.2.11). The unit costs were identified from national sources, where available, including NHS Reference Costs[35], PSSRU[37], the British National Formulary (BNF)[38] and the eMit national database[39].

The company also undertook a systematic search of resource use studies (Section 12.3.2 of the CS). Given the paucity of evidence in this disease area, the company stated that a broad scope was taken. The company searched for economic evaluations and studies presenting cost and resource use data. In the CS, two published studies were described[12, 20], and these reported data on the burden of disease on families, and management strategies, in a number of European countries. The resource use, described in these studies, broadly appears to be consistent with the assumptions used in the model. There were some additional resources described in the studies that were not captured by the model (described further in Section 5.2.9.2 and Section 5.2.9.4).

5.2.9.1 Treatment and administration costs

Drug cost of cerliponase alfa

The price of cerliponase alfa is £20,107 per 300mg pack, consisting of two 150mg vials. Drug cost calculations were based on the recommended dose for patients over the age of two years, which is 300mg every two weeks. The company has reportedly entered into discussion with NHS England regarding a Managed Access Agreement (MAA), which is still in development, and state in their submission that they are open to entering into a funding arrangement as part of the MAA.

The company reported an adherence rate to cerliponase alfa of 99.74%. The mean cost of a vial of cerliponase alfa was reduced by the corresponding amount to allow for a reduced mean number of doses being administered. This is equivalent to a per-dose price of £20,055 per patient. The adherence rate was estimated from the 190-201/202 trials, and based on 776 infusions, and was assumed to be constant throughout the model time horizon.

Administration costs of cerliponase alfa

Cerliponase alfa is administered directly into the brain via an intracerebroventricular (ICV) delivery tube. Administration costs consist of those for an initial procedure to insert the ICV tube; the cost associated with the infusion of cerliponase alfa; and, replacement of the ICV device in a proportion of cases of infection.

The implantation cost of £9,518.70 (NHS Reference Costs, AA50F very complex intracranial procedures) was applied to all cerliponase alfa patients at treatment initiation. Cerliponase alfa would then be subsequently administered in a specialised hospital setting. In the clinical trial, patients were monitored for 24 hours after cerliponase alfa was administered. However, it was assumed that treatment would, henceforth, be administered as a day case (as per those on expanded access). This had an associated cost of £466 per administration (NHS Reference Costs, AA25G cerebral degenerations or miscellaneous disorders of nervous system with CC score 0-4).

Replacement of the ICV was assumed to occur as result of infusion-related infections with 62% of infusion-related infections requiring replacement of the ICV. This was based on data from a published study[48] and is equivalent to 0.07254 replacements per child per year. The replacement of the ICV device was assumed to require an inpatient stay.

Comparator costs

There was no direct comparator treatment to cerliponase alfa for CLN2 patients, and so no specific treatment costs were associated with the comparator treatment. This was assumed to consist of management costs only (see Section 5.2.9.2 Health State Costs).

ERG comment

The ERG is broadly satisfied by the assumptions made to estimate the treatment costs of cerliponase alfa, but notes that dosing was based on the assumption that all children started treatment over the age of 3 years (reflecting the trial) and received two vials of cerliponase alfa. Children under the age of one would require a dose consisting of one vial. However, it does not seem likely that this dose will be applied until wide-scale genetic testing is in place and children are diagnosed significantly earlier.

With respect to the administration costs, the ERG considers the assumption that no additional training would be needed was reasonable, as the health professionals involved with administering cerliponase alfa will already be experienced in the delivery of other treatments requiring aseptic techniques (response to PFC B25). The unit costs also appear to be generally appropriate, although it is difficult to comment on the infusion cost for cerliponase alfa because the treatment is administered in specialist centres, which might have higher associated costs (different overheads, staff mix). The ERG notes that the hospital costs associated with the replacement of the ICV are for paediatric patients. While the cost of replacing the ICV device is higher in adults (£4,388 for patients under 18 and £6,986 for patients over 18), using the alternative unit cost as the patient ages makes little difference to the ICER and was not explored further.

Further to the above, the ERG also noted that there may be additional monitoring costs associated with treatment of cerliponase alfa not included in the company's model. The Summaries of Product Characteristics (SPC) report for cerliponase alfa states the following requirements:

- Cerebrospinal fluid (CSF) samples should routinely be sent for testing to detect subclinical device infections,
- Pre-treatment of patients with antihistamines with or without antipyretics is recommended 30 to 60 minutes prior to the start of infusion,
- Electrocardiogram (ECG) monitoring during infusion should be performed in patients with a history of bradycardia, conduction disorders, or with structural heart disease, as some patients with CLN2 disease may develop conduction disorders or heart disease.

Given the company's assumption of life-long treatment for treatment responders, these additional costs could have the potential to impact the cost-effectiveness results of the analysis. The ERG has explored the impact of including additional costs in the model, and present the results of this analysis in Section 6.

5.2.9.2 Health-state costs

To capture the costs of the ongoing management of CLN2 patients, the company consulted a panel of clinical experts to determine which healthcare professionals are involved in the care of these patients, and the frequency at which they would be accessed. The number of visits varied by health state, with the more severe health states generally associated with a higher number of resources, and some resources applied only in the more severe health states (critical care bed days, palliative care). The company assumed that patients receiving cerliponase alfa and patients receiving standard care would receive the same number of resources when in each health state. The number of units of each resource per health state is presented in Table 27.

Table 27 Health state resource use – number of units per year, per health state (CS, Table D25, pp.223-7)

Resource	HS 1	HS 2	HS 3	HS 4	HS 5	HS 6	HS 7	HS 8	HS 9
Specialist clinician	1.63	1.63	2.67	2.67	2.67	3.17	3.17	3.17	3.17
Specialist nurse	25.33	25.33	23.75	23.75	23.75	37.67	37.67	37.67	52
General practitioner	2.75	2.75	5	5	5	17.33	17.33	17.33	17.33
Community paediatrician	1.67	1.67	2.33	2.33	2.33	2.33	2.33	2.33	2.33
Speech/language therapist	2.25	2.25	2.33	2.33	2.33	1.67	1.67	1.67	1.67
Physiotherapist	2	2	3.33	3.33	3.33	4	4	4	4
Family support worker	1.75	1.75	1.67	1.67	1.67	1.67	1.67	1.67	1.67
Ophthalmologist	1.33	1.33	1.33	1.33	1.33	1	1	1	1
Health visitor	0.67	0.67	0	0	0	0	0	0	0
Occupational therapist	1.75	1.75	2.25	2.25	2.25	2.25	2.25	2.25	2.25
Caregiver costs	0	0	0	0.17	0.22	0.21	0.3125	0.3078	0.3078
Critical care bed days	0	0	0	0	0	1	1	1	1
Hospitalisation costs	0	0	0	2	2	2	0	0	0
Palliative care	0	0	0	0	0	0	24	36	36
Educational support	2	2	3	3.5	3.5	3.5	3.5	2.5	2.5

Costs in the first year of treatment, and costs in subsequent years, were estimated separately (where subsequent appointments have a different cost). Care was assumed to either be given by a family member or by an NHS worker. Caregiver costs were applied to the proportion of care was that provided by the NHS, and no associated cost for family-provided care was applied in the company base-case. Unit costs are presented in Table 28.

Table 28: Health-state associated unit costs (CS, Table D26, pp. 228-312)

Items	Cost per unit (e.g., appointment, bed day, caregiver) – 1st occurrence	Cost per unit (e.g., appointment, bed day, caregiver) – subsequent occurrences	Reference
Specialist clinician	£469.00	£138.00	NHS Ref Costs 2015-16 [Non-Admitted Face to Face Attendance, First, Paediatric Neuro-Disability, consultant led (WF01B, 291)] and [Non-Admitted Face to Face Attendance, Follow-Up, Paediatric Neuro-Disability, consultant led (WF01C, 291)]

Items	**Cost per unit (e.g., appointment, bed day, caregiver) – 1st occurrence**	**Cost per unit (e.g., appointment, bed day, caregiver) – subsequent occurrences**	**Reference**
Specialist nurse	£137.00	£137.00	NHS Ref Costs 2015-16 [Other Specialist Nursing, Child, Face to face (N29CF)]
General practitioner	£36.00	£36.00	PSSRU 2016 [Per patient contact lasting 9.22 minutes (including carbon emissions (5 KgCO2e)2(carbon costs less than £1), with qualification costs]
Community paediatrician	£273.00	£147.00	NHS Ref Costs 2015-16 [Non-Admitted Face to Face Attendance, First, Community Paediatrics, consultant led (WF01B, 290)] and [Non-Admitted Face to Face Attendance, Follow-Up, Community Paediatrics, consultant led (WF01C, 290)]
Speech/language therapist	£94.00	£94.00	NHS Ref Costs 2015-16 [Speech and Language Therapist, Child, One to One (A13C1)]
Physiotherapist	£87.00	£87.00	NHS Ref Costs 2015-16 [Physiotherapist, Child, One to One (A08C1)]
Family support worker	£32.00	£32.00	PSSRU 2016 [Family support worker, unit cost per hour]
Ophthalmologist	£119.00	£94.00	NHS Ref Costs 2015-16 [Non-Admitted Face to Face Attendance, First, Paediatric Opthalmology, consultant led (WF01B, 216)] and [Non-Admitted Face to Face Attendance, Follow-Up, Paediatric Opthalmology, non-consultant led (WF01A, 216)]
Health visitor	£53.00	£53.00	NHS Ref Costs 2015-16 [Health Visitor, Other Clinical Intervention (N03F)]
Occupational therapist	£131.00	£131.00	NHS Ref Costs 2015-16 [Occupational Therapist, Child, One to One (A06C1)]
Caregiver costs	£30,661.00	£30,661.00	https://www.healthcareers.nhs.uk/about/careers-nhs/nhs-pay-and-benefits/agenda-change-pay-rates - NHS-funded school nurse, Band 6, Point 25
Critical care bed days	£5,462.00	£5,462.00	NHS Ref Costs 2015-16 [XB01Z, Paediatric Critical Care, Advanced Critical Care 5, Critical Care Sheet]
Hospitalisation days	£3,747.52	£3,747.52	NHS Ref Costs 2015-16 [XB02Z, Paediatric Critical Care, Advanced Critical Care 4, Critical Care Sheet]

Items	Cost per unit (e.g., appointment, bed day, caregiver) – 1st occurrence	Cost per unit (e.g., appointment, bed day, caregiver) – subsequent occurrences	Reference
Palliative care	£150.92	£150.92	NHS Ref Costs 2015-16 [Specialist Nursing, Palliative/Respite Care, Child, Face to face (N21CF)]
Educational support	£1,398.00	£1,398.00	PSSRU 2016 [Education support, children aged 4-11 with low functioning autism living in private households with family]

Table 29 presents a summary of health-state costs. Costs increase as the patients' health status becomes more severe, with a large increase in costs observed between HS3 and HS4 as the motor score drops to 1 and patients were assumed to start experiencing vision loss, corresponding to the requirement of hospitalisation and NHS-provided carers.

Table 29 Health state costs (CS, Table D25, pp.223-7)

Health state	Cost – 1st occurrence	Cost – subsequent occurrences
Health state 1	£8,148.92	£7,666.92
Health state 2	£8,148.92	£7,666.92
Health state 3	£9,802.66	£9,320.66
Health state 4	£23,209.07	£22,727.07
Health state 5	£24,742.12	£24,260.12
Health state 6	£32,282.66	£31,800.66
Health state 7	£31,552.55	£31,070.55
Health state 8	£31,821.54	£31,339.54
Health state 9	£33,784.75	£33,302.75

ERG Comment

The company's model appears to be relatively insensitive to the assumptions made around resource use, with any variation resulting in a small percentage change to the ICER. However, the ERG is concerned that this is a consequence of the very high treatment costs and large number of incremental QALYs for cerliponase alfa patients, which result in the other cost items carrying less weight overall, particularly in relation to the estimated benefit. These arise due to the assumptions of continued survival and stability of disease of patients on cerliponase alfa. As discussed in Section 5.2.7, the ERG does not consider that these two assumptions around the patients' long-term prognosis are appropriate, given the available evidence. If these two assumptions were to be relaxed the treatment cost may become less of a factor in determining the likely cost-effectiveness, and greater

weight may be given to the other cost items. This will be further compounded if the company introduces a Patient Access Scheme (PAS) for cerliponase alfa at a later stage, reducing the total treatment costs. In this instance, some cost items will have a greater impact on the estimated cost-effectiveness, particularly if they are associated with the treatment of cerliponase alfa patients, or are accumulated over the patients remaining lifetime.

The ERG also identified a number of other concerns regarding resource utilisation, which were addressed only partially at the clarification stage. The health state costs used in the model assume that the patients are children. For example, costs were assigned for a community paediatrician, speech and language therapy, non-family caregivers and education support. For the majority of the model time horizon, patients receiving cerliponase alfa are not children and will have different support needs. The company's clinical expert advised that the intensity and frequency of resource use was likely to be reduced as patients transition to adult care. The company provided a number of alternative scenarios: one in which the unit costs were those for adult patients but the frequency of visits remained the same, and another in which the inappropriate resources were removed from the more severe health states (i.e. patients in HS7 to HS9 would no longer receive educational support or access an ophthalmologist).

The ERG also considers that the level of caregiver support would vary as patient's age, with adult patients transitioning to adult social care, especially with family members less likely to be able to provide care as they get older. The clinical advisor to the ERG suggested that adult patients may require a comprehensive social care package depending on the level of disability, where some patients may continue to receive care at home, and some would transition into residential care (especially with more advanced forms of the disease). Residential care incurs substantially higher costs than currently applied in the model: the PSSRU estimates that a local authority own-provision care home for adults requiring physical support is £989 per resident week. A further issue with the estimation of caregiver costs was the inappropriate use of a unit cost for a NHS caregiver. The annual cost was that of the wage of a Band 6 Nurse taken from the Agenda for Change pay scale: a unit cost from the PSSRU is generally considered to be more appropriate as it incorporates other cost elements, such as salary, travel and overheads. For a Band 6 community nurse, the annual nurse cost can be estimated as £69,212, which is more than double that applied by the company. The company's base-case model, however, is largely insensitive to this cost.

In addition, based on discussions with the clinical expert consulted by the ERG and review of the resource-use article identified by the company, the ERG considers that a number of important cost items were excluded from the company analysis. Some of these costs were also described by the company but not explicitly included in the analysis. The ERG did not consider including the majority of these costs in their analyses, as it was expected that they would be applied to both arms in broadly

similar quantities (e.g., with psychological support and home adaptations) and, therefore, would not impact on the overall incremental costs, or that they might be borne, at least in part, by other sectors (e.g., the local authority or the patient). However, a brief description is provided by the ERG, below.

Adapted vehicles and housing adaptations are also often required in the later stages of the disease. Costs can be substantial and funding for the family is not always available. The company stated that adapted vehicles could cost around £10,000 and housing adaptations could cost upwards of £50,000. Wheelchair provision is also a necessary part of care as patients lose motor function: the PSSRU[37] estimate that this cost is £95 per attendant-propelled chair, and over £400 per powered chair per year.

For patients in the palliative care health states, the company describes the use of continuous positive airway pressure and/or bilevel positive airway pressure (BiPAP) at night to aid with ventilation, and an aspirator with suction tubes to suck out the excess saliva, given the difficulties in swallowing.

Psychological support for the family, including bereavement support, is a necessary part of care for those affected by CLN2 disease. Clinical experts confirmed that patients and families would usually receive this support through their lysosomal storage disease centre. The company stated that in the clinical trial, support was provided for patients by the Batten Disease Family Association (BDFA).

5.2.9.3 Adverse event costs

The company modelled the occurrence of five adverse events relating to cerliponase alfa treatment: pyrexia, hypersensitivity, headache, vomiting and infection (see Section 5.2.8.3 for details). No treatment costs relating to these adverse events were, however, included in the model. The company justified this assumption on the basis that the treatment of these AEs is incorporated within the infusion unit cost.

ERG Comment

The ERG agrees that the treatment costs associated with the AEs included in the company model are likely to be relatively minor and to likely be reflected within the unit cost for treatment administration. Exploratory analyses conducted by the ERG indicate that including an arbitrary small cost of treating these AEs had a relatively negligible impact on the ICER.

As described in Section 5.2.8.3, the ERG was concerned about the selection of AE included in the model, but given their low incidence rate did not consider this a significant issue.

5.2.9.4 Progressive symptoms

In addition to health state costs, the model also captured the cost of managing progressive symptoms associated with CLN2. The symptoms captured in the analysis included:

- Epilepsy;

- Reported distress;
- Dystonia;
- Myoclonus;
- Requirement of a feeding tube;
- Chronic seizures.

A summary of costs and resource use associated with the treatment of progressive symptoms are described in Table 30. Further details on each aspect of care are provided below.

Table 30: Costs and resource use associated with the treatment of progressive symptoms (CS, Tables D27-32 pp. 232-7)

Treatment	Annual cost of medications	Resource use assumption and proportion of patients cost applied to
Anti-epilepsy drugs	Cost per kg: £46.21 Cost of clobazam: £179.96 Cost for an adult: £3,054 (62.2kg) Cost for 8 year old: £1,368 (25.7kg)	Usage based on AED usage in 190-201
Distress	£281.56 per year	Each medication equally likely to be used List of medications: Williams et al[12]
Dystonia	Cost per kg: £16.59 Cost of tizanidine: £8.43 Cost for an adult: £1,040 (62.2kg) Cost for 8 year old: £455 (25.7kg)	Each medication equally likely to be used List of medications: Williams et al[12]
Myoclonus	Cost per kg: £15.15 Cost for an adult: £389 (62.2kg) Cost for 8 year old: £942 (25.7kg)	Each medication equally likely to be used List of medications: Williams et al[12] Only phenobarbital applied as other medications also used to treat epilepsy
Feeding tube	Insertion cost £1,074 Replacement cost £869	Applied to all patients with ML score of 2 or less Replaced every two years
Chronic seizures	Medication cost per seizure: £1.99 Hospitalisation: £943 Overall weighed cost per seizure: £429	Medication usage from 190-201 Hospitalisation for cases where intravenous rescue medication required (45%)

The average annual cost of AEDs was informed by medication usage in the trial. It was assumed that all patients would receive treatment with anti-epileptic drugs (AED), based on the patient narratives from the 190-201 and 190-202 studies where all patients in the trial received some form of AED.

Medications required for the treatment of distress, dystonia and myoclonus was informed by data reported in the Williams et al study.[12] For the treatment of each of these progressive symptoms, it was assumed that all medications were be 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

Unit costs and dosing for all medications were obtained from eMit and the BNF.[38, 39] The dose for the AEDs (with the exception of clonazepam), dystonia medications (with the exception of tizanidine) and the myoclonus medication was based on patient weight, which was varied over the patient lifetime (Section 5.2.3).

The proportion of patients experiencing progressive symptoms in each health state is presented in Table 31. It was assumed that all patients regardless of treatment arm or health state would be receiving medication for epilepsy. For distress, dystonia, myoclonus and requirement of a feeding tube, it was assumed that the same proportions of patients would experience symptoms regardless of treatment arm. The rates of the distress, dystonia, and myoclonus symptoms were based on advice required at the Delphi panel conducted by the company.

Table 31 Patients experiencing progressive symptoms (CS, Tables D5 and D6, pp. 191-2 and Appendix 10)

Health state	Distress	Dystonia	Myoclonus	Feeding tube	Annual seizures (CA)	Annual seizures (SC)
1	3%	0%	3%	0%	1	1
2	9%	15%	25%	89%	1	3
3	30%	15%	50%	100%	1	6
4	39%	30%	98%	100%	1	6
5	48%	60%	100%	100%	1	6
6	51%	73%	100%	100%	1	6
7	54%	63%	100%	100%	0	0
8	56%	63%	100%	100%	0	0
9	56%	63%	100%	100%	0	0

Feeding tube

It was assumed that 89% of patients with a score of 1 and all patients with a score of 2 or lower on the language domain would require a feeding tube, based on advice from the clinical experts consulted by the company. Costs associated with feeding tubes were the insertion cost and the replacement cost. A one-off insertion cost was applied to all patients with a feeding tube at the beginning of the model, and to patients as they subsequently entered HS5 for the first time over the course of the model. The

cost associated with inserting a feeding tube was assumed to be £1,074 (NHS Reference Costs, endoscopic insertion of gastronomy tube). Feeding tubes were assumed to be replaced every two years, in line with practice at Great Ormond Street Hospital (a centre in the trial that administered cerliponase alfa in the UK). This had an associated cost of £869 (NHS Reference Costs, Endoscopic or Intermediate, Upper Gastrointestinal Tract Procedures), which was halved and applied each year to patients with feeding tubes to reflect the replacement every two years.

Seizures

Despite receiving AEDs, patients were assumed to suffer chronic seizures. Costs were applied to the annual number of seizures in each arm (Table 31). A weighted cost per chronic seizure was estimated as a combination of rescue medication and hospitalisation. The proportion of rescue medications required was based on the patient narratives from the 190-201 and 190-202 studies, and included rectal diazepam, intravenous lorazepam, buccal midazolam and intravenous phenobarbital. It was assumed that seizures treated with intravenous rescue medication would also be associated with a hospitalisation cost, in the absence of available data to inform this parameter. This resulted in 45% of seizures with an associated hospitalisation cost of £943 (NHS reference costs, Paediatric epilepsy syndrome with CC Score 6+).

ERG comment

Similar to the health state costs described in Section 5.2.9.2, the unit costs applied for the treatment of progressive symptoms corresponded to those for paediatric patients. While this is suitable for patients in the standard care arm, it results in costs in the cerliponase alfa arm being less accurately estimated as patient's age. In general, there was a lack of transparency in the CS with how unit costs for medications were extracted and estimated, which made it difficult to assess whether these costs had been appropriately estimated. The model, however, appears to be relatively insensitive to these costs, so this was not explored further.

The ERG also noted an inconsistency with the estimation of dystonia and feeding tube placement costs and the health state vignettes for quality of life (Section 5.2.8). Most patients in HS2 and all patients from HS3 onwards had feeding tube costs applied regardless of receiving cerliponase alfa treatment. This is in agreement with the description of the health state vignettes for patients on standard care, but it was assumed by the company that patients receiving cerliponase alfa would not require a feeding tube until they were in HS4, resulting in a discrepancy between cost and expected HRQoL in HS2 and HS3 in this arm. The vignettes were defined with respect to the emergence of dystonia at HS5; however, a proportion of patients incurred dystonia costs in HS2 to HS4. We would also expect differing rates of medications for distress, dystonia and myoclonus between the cerliponase alfa and standard care arms based on the vignettes, but this was not the case.

Given the nature of CLN2 disease and the lack of active treatment options, there are a large number of resources that are used to treat and manage CLN2 patients. However, from a review of the resource use article identified by the company, the ERG considers that a number of important cost items were excluded from the company analysis. The Williams article described a number of additional resources used to support CLN2 patients and their families throughout the different stages of the disease. For the patient, these included the management of sleep disturbance, breathing difficulties, behavioural symptoms and secretion management. The management of these symptoms constitutes additional medications and may involve psychiatry consultation for behavioural symptoms. Saliva secretions may be managed through interventions such as Scopoderm transdermal therapeutic system patches botulinum toxin injections in a proportion of patients. Other home adaptation costs associated with the later stages of CLN2 disease, including adaptive beds, chest cough assist vests and saliva suction machines were also not applied.

The ERG considers that the cumulative impact of these additional costs may be substantial given the company's assumption of life long treatment for responders to cerliponase alfa. As such, the ERG has explored the impact of including some of these costs (specifically, the psychiatric support for behavioural symptoms) in the analyses in Section 6.

5.2.10 Cost effectiveness results

5.2.10.1 Base-case results

Cost-effectiveness results

Table 32 presents the results of the company base-case analysis. Costs and QALYs, using a 1.5% discount rate, were estimated over a lifetime time horizon. The company found cerliponase alfa to be more costly (cost difference of [redacted]), but also more effective (gains of 30.42 QALYs). The estimated deterministic ICER for cerliponase alfa compared with standard care was [redacted] per QALY.

Table 32: Results of base-case analysis (CS, Table D36, p. 247)

Technologies	Total QALYs	Total costs (£)	Incremental QALYs	Incremental costs (£)	ICER (£ per incremental discounted QALY)	CE threshold*
Cerliponase alfa	29.45	[redacted]	30.42	[redacted]	[redacted]	[redacted]
Standard care	-0.97	£149,829	N/A	N/A	N/A	N/A
ICER, incremental cost-effectiveness ratio; LYG, life years gained; N/A, not applicable; QALYs, quality-adjusted life years						

* Cost-effectiveness threshold estimated based on number of incremental undiscounted lifetime QALYs

The HST interim methods process guide[55] indicates that the magnitude of therapeutic improvement, as indicated by the gain in QALYs, determines the acceptability of a technology as an effective use of NHS resources. The methods guide states that an increased weight can be applied to QALYs gained where there is compelling evidence that the improvement in health exceeds 10 QALYs. The ERG was informed by NICE that the magnitude of the QALY gain is likely to be influenced by the number of undiscounted QALYs. The company report that the undiscounted QALY gain for cerliponase alfa compared to standard care is 50.52 QALYs, which would imply a weight of 3, or alternatively an increase in the cost-effectiveness threshold from £100,000 to £300,000 per QALY gained.

The CS presented the disaggregated costs and QALYs in each arm, by health state and a breakdown of QALYs accrued in each health state is presented in Table 33. The greatest QALY gains were observed from patients spending time in the two least severe health states (over 60% of QALY gains). In the standard care arm, QALY gains from patients spending time in HS1 to HS5 were offset by the negative QALYs accumulated in HS6 to HS9, as a result of a negative utility value for these health states. Disutilities for cerliponase alfa patients due to adverse events were negligible ([redacted] of the absolute increment).

Table 33: QALYs by health state (CS, Table D43, p. 258)

	Cerliponase alfa	Standard care	Increment	Absolute increment	% absolute increment
Health states					
Health State 1	[redacted]	0.172	[redacted]	[redacted]	[redacted]
Health State 2	[redacted]	0.262	[redacted]	[redacted]	[redacted]
Health State 3	[redacted]	0.156	[redacted]	[redacted]	[redacted]
Health State 4	[redacted]	0.081	[redacted]	[redacted]	[redacted]
Health State 5	[redacted]	0.001	[redacted]	[redacted]	[redacted]
Health State 6	[redacted]	-0.111	[redacted]	[redacted]	[redacted]
Health State 7	[redacted]	-0.304	[redacted]	[redacted]	[redacted]
Health State 8	[redacted]	-0.568	[redacted]	[redacted]	[redacted]
Health State 9	[redacted]	-0.661	[redacted]	[redacted]	[redacted]
Disutilities					
Pyrexia	[redacted]	0.000	[redacted]	[redacted]	[redacted]
Hypersensitivity	[redacted]	0.000	[redacted]	[redacted]	[redacted]
Headache	[redacted]	0.000	[redacted]	[redacted]	[redacted]
Vomiting	[redacted]	0.000	[redacted]	[redacted]	[redacted]
Infections	[redacted]	0.000	[redacted]	[redacted]	[redacted]
Total	**29.446**	**-0.969**	**30.416**	**30.573**	**100%**

Disaggregated costs are presented in Table 34. The costs of cerliponase alfa are the major component of total costs of this arm, and constitute [redacted] of the absolute increment in total treatment cost. Health state costs and costs for treating progressive symptoms were also higher for cerliponase alfa patients, which can be mostly attributed to the assumed increase in life-expectancy for patients receiving cerliponase alfa.

Table 34: Total costs by health state (CS, Table D45 and D46, pp. 260-1)

Health state	Cerliponase alfa	Standard care	Increment	Absolute increment	% absolute increment*
Health State 1	£71,222.28	£1,396.52	£69,825.76	£69,825.76	12.66%
Health State 2	£119,928.69	£2,952.33	£116,976.36	£116,976.36	21.21%
Health State 3	£92,755.69	£2,931.57	£89,824.13	£89,824.13	16.28%
Health State 4	£123,632.35	£7,363.49	£116,268.85	£116,268.85	21.08%
Health State 5	£84,993.04	£7,903.91	£77,089.13	£77,089.13	13.97%
Health State 6	£38,256.09	£33,456.27	£4,799.82	£4,799.82	0.87%
Health State 7	£227.71	£15,999.51	-£15,771.80	£15,771.80	2.86%
Health State 8	£429.57	£30,273.51	-£29,843.94	£29,843.94	5.41%
Health State 9	£449.02	£31,683.51	-£31,234.48	£31,234.48	5.66%
Total health state costs	***£531,894***	***£133,961***	***£397,934***	***£551,634***	[redacted]
Treatment cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Progressive symptom costs	£99,413	£15,868	£83,545	£83,545	[redacted]
Infusion costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total costs	[redacted]	[redacted]	[redacted]	[redacted]	***100%***

**Absolute increment for individual health state costs are reported as percentages of the total health state costs, not as percentages of total costs*

Clinical outcomes

An illustration of the proportion of patients in each health state over time (the Markov trace) is provided in Figure 3 for patients on cerliponase alfa and Figure 4 for patients on standard care.

As presented in Figure 4, the majority of patients in the standard care arm die within the first ten years of treatment. In contrast, as presented in Figure 3, for cerliponase alfa patients, the company model predicts a small initial shift in the proportion of patients in each health state, reflecting response to treatment, with the proportion of patients in each health state in the remaining time period observing a general stabilisation adjusted by a gradual decline to account for patients leaving the model at a rate determined by general population mortality. This appears to be generally reflective of how the transition probabilities were described as being calculated by the company.

Figure 3: Markov trace for cerliponase alfa [base-case analysis] (CS, Figure D21, p.250)

Figure redacted commercial-in-confidence

Figure 4: Markov trace for standard care [base-case analysis] (CS, Figure D22, p. 252)

Figure redacted commercial-in-confidence

It was not possible to validate outcomes from the model for cerliponase alfa patients against those in the clinical trials on which the analysis was based (190-201/202) from the information provided in the CS. This was because the starting population used in the model was different to the population in these studies, and so they cannot be directly compared. A scenario analysis where the starting population used in the model matched the 190-201 trial was, however, requested by the ERG at the PfCs stage; cost-effectiveness results are presented below in Section 5.2.10.5.

Figure 5 and

Figure 6 present the Markov traces for cerliponase alfa and standard care patients, respectively, in this subgroup.

Figure 5: Markov trace for cerliponase alfa [scenario analysis with starting population in the model reflecting 190-201 trial] (Figure from CS model)

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Figure 6: Markov trace for standard [scenario analysis with starting population in the model reflecting 190-201 trial] (Figure from CS model)

Figure redacted commercial-in-confidence

There were some small discrepancies between the trial outcomes and the modelled outcomes. Results presented in Table 35 allow for a comparison between the distribution of cerliponase alfa patients across health states at 48 weeks and at 96 weeks between the 190-201 trial and the model. At 96 weeks, the largest discrepancy appears to be in health states 4 to 6 (corresponding to ML scores of 3 to 1), where the model overestimated the number of patients with a score of 3 and underestimated the number of patients with a score of 2 and 1. Given that patients are assumed to be stabilised by week 96, the underestimation of patients in the more severe health states is expected to result in an overestimation of QALYs in the model.

Table 35: Distribution of cerliponase alfa patients across health states: comparison between trial and model (CS, Table C21, p. 118 and CS model)

Health state	Proportion of patients at baseline*	Proportion of patients at 48 weeks		Proportion of patients at 96 weeks	
		Trial	Model	Trial	Model
1	2 (9%)	2 (9%)	5%	[redacted]	[redacted]
2	2 (9%)	1 (4%)	9%	[redacted]	[redacted]
3	5 (22%)	5 (22%)	17%	[redacted]	[redacted]
4	11 (48%)	7 (30%)	32%	[redacted]	[redacted]
5	2 (9%)	5 (22%)	26%	[redacted]	[redacted]
6	1 (4%)	3 (13%)	7%	[redacted]	[redacted]
7-9	0%	2 (9%)	3%	[redacted]	[redacted]
Death	-	0%	0%	[redacted]	[redacted]

Budget impact

There are currently an estimated 34 patients in England was CLN2 disease, and it was assumed that [redacted] of these patients ([redacted]) would be eligible for treatment, in line with the market authorisation.

Based on the advice provided by clinical and patient experts consulted by the company, there are five estimated patients diagnosed per year, of which [redacted] ([redacted]) would be eligible for treatment with cerliponase alfa. This uptake rate was assumed to be constant over the 5 years from cerliponase alfa becoming available, and was based on patients moving from the clinical trial programme and expanded access scheme onto commercial supplies and data from a survey conducted by the BDFA and clinical experts regarding the expected uptake of cerliponase alfa amongst current and newly diagnosed patients. A summary of expected patient numbers is presented in Table 36.

Table 36: Eligible patients for treatment with cerliponase alfa patients over 5 years in England (CS, Table D60, p. 282)

	Year 1	Year 2	Year 3	Year 4	Year 5
Starting prevalent population	34				

Expected uptake of cerliponase alfa (patients)	[redacted]				
Incident population	5	5	5	5	5
Expected uptake of cerliponase alfa (patients)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total incident population	39	5	5	5	5
Patients treated with Cerliponase alfa	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

The reported population budget impact associated with the introduction of cerliponase alfa as a treatment option for patients with CLN3 was estimated as [redacted] in Year 1, and a total of [redacted] over five years (Table 37). Cerliponase alfa is associated with substantially higher treatment costs, but a reduction in health state costs and progressive symptom costs associated with the disease control of the treatment, where cerliponase alfa patients were assumed to remain in the less costly health states. Savings associated with health state and progressive symptom costs were estimated based on CLN2 scores at baseline should diagnosis of CLN2 disease occur earlier in the disease course (the assumption and distribution applied in the cost-effectiveness analysis, see Section 5.2.3).

Table 37 Population budget impact of cerliponase alfa in England over 5 years (adapted from Table D61 in CS)

Cost	**Year 1**	**Year 2**	**Year 3**	**Year 4**	**Year 5**
Treatment cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Health state	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Progressive symptoms	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cumulative total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

5.2.10.2 Sensitivity analysis

Deterministic sensitivity analysis

The CS presented the results of a variety of one-way deterministic sensitivity analyses (DSA) to identify the key drivers of the analysis.

Parameters included in the DSA were: HS utility values, carer and sibling disutility values, disutility values associated with infections and progressive symptoms, drug cost and infection frequency of cerliponase alfa, unit costs, mean number of siblings, frequency of appointments, and frequency of progressive symptoms. The company varied each parameter value by ±15% and reported the subsequent impact on the ICER. Model parameters relating to uncertainty in the clinical effectiveness and disease progression were not varied in the DSA, but explored in a series of scenario analyses (Section 5.2.10.3).

The company presented a tornado diagram depicting the results of the DSA (Figure 7). Of the model parameters varied in the DSA, the parameters with the largest influence on the ICER were the drug cost and the health state utility values for cerliponase alfa. The ERG notes, however, that utility values for cerliponase alfa and for standard care were varied independently. It may have been more accurate to apply a single utility value for a health state in each arm, adjusted for disutility relating to seizures (the key aspect that differentiated health states between arms), and then vary the health state utility value so that it was changed in each arm simultaneously.

Figure 7: Results of the deterministic sensitivity analysis (CS, Figure D24, p.263)

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Probabilistic sensitivity analysis

The company undertook a probabilistic sensitivity analysis (PSA) to explore and quantify uncertainty in the outcomes of the analysis. Probabilistic results were estimated from 1,000 iterations of the model, with values for key parameters sampled stochastically from assigned distributions to each parameter. The probabilistic ICER estimated by the company was [redacted] per QALY. The probabilistic results were similar to those estimated in the deterministic base-case analysis, and are presented in Table 38.

The standard error around the point estimate for the majority of variables varied in the company PSA was assumed to be 15% of the mean parameter value. No justification was provided for the assigned distributions to the input parameters, although the ERG felt that those chosen were reasonable.

The company did not vary the efficacy data that was used populate the model, specifically the transition probabilities and proportion of early and late responders was static, in their PSA. The company justified the exclusion of these parameters by noting that they were structural assumptions and therefore they were only explored in deterministic sensitivity analysis. The proportion of patients

in each health state at the beginning of the model was also not varied in the PSA. The ERG disagrees that these parameters are structural assumptions as both parameter sets can be varied within the context of the current model structure. Give the significant impact of both these parameters sets on estimated cost-effectiveness, the ERG therefore considers that the PSA does not adequately captures the uncertainty in the model.

Table 38: Results of the probabilistic sensitivity analysis (CS, Table D57, p. 273)

	Cerliponase alfa (total, discounted)		**Standard care (total, discounted)**		**Increment**		**ICER (95% CI)**
	Costs	**QALYs**	**Costs**	**QALYs**	**Costs**	**QALYs**	
Probabilistic Results	[redacted]	29.45 (29.31, 29.58)	[redacted]	-0.97 (-0.98, -0.97)	[redacted]	30.42 (30.29, 30.55)	[redacted]
Deterministic Results	[redacted]	29.45	[redacted]	-0.97	[redacted]	30.42	[redacted]

CS, company submission; QALY, quality-adjusted life year; ICER, incremental cost-effectiveness ratio; CI, confidence interval

Note: confidence intervals estimated by the ERG from the company model

Figure 8 presents the incremental cost-effectiveness plane for cerliponase alfa compared with standard care, resulting from the probabilistic sensitivity analysis. It appears from the scatterplot that there was little variation in incremental costs (an artefact of the drug costs not being varied in the PSA). There was a greater variation observed for incremental QALYs, likely due to the large impact of utility values on the outcomes of the analysis (as can be observed in the tornado diagram presented in Figure 7).

Figure 8: Results of the probabilistic sensitivity analysis (CS, Figure D25, p.272)

Figure redacted commercial-in-confidence

The company did not present a cost-effectiveness acceptability curve (CEAC). The ERG's review of the the company model revealed a framework with which to estimate this. The ERG henceforth re-created this analysis, and the results are presented in

Figure 9. This analysis revealed that, at the current list price, cerliponase alfa has a zero percent probability of being cost-effective at thresholds up to approximately [redacted] per QALY. At £800,000 per QALY, cerliponase alfa has an approximate [redacted] probability of being cost-effective.

Figure 9: Cost-effectiveness acceptability curve (CS Model)

Figure redacted commercial-in-confidence

5.2.10.3 Scenario analysis

The company undertook a range of scenario analyses around key structural assumptions in their base case analysis (Table D34 in CS). A summary of the scenario analyses and their associated results are presented in Table 39. The company provides a breakdown of results in Table D47 to Table D56 in the CS.

Scenarios 13-14 were considered by the company to present the likely range within which the ICER lies, as they combine the optimistic and pessimistic elements of the scenario analyses. These scenarios had an associated ICER of [redacted] and [redacted], respectively.

Of the scenarios described below, the starting population had the greatest impact on the ICER. When all patients started in HS1, the ICER was 20% lower. The company did not present any scenarios exploring the impact of patients entering in more severe health states than the base-case analysis.

Discounting (Scenario 8 and 9), time horizon (Scenario 11) and perspective (Scenario 12) were shown to not have a large impact on the ICER in the company base-case.

Table 39 Results of scenario analyses in the CS base-case model (CS, Tables D47 to D56, pp. 264-71)

Scenario	Change(s) made to model	ICER	Change from base-case ICER
Base-case	Base-case analysis	[redacted]	-
Scenario 1	Starting population of patients evenly split across health states 1-2.	[redacted]	-9%
Scenario 2	All starting population starts in health state 1	[redacted]	-20%
Scenario 3	Utility values obtained using the PedsQL values from the trial, mapped to EQ-5D, with the assumption of the same utility values across both arms of the treatment	[redacted]	-6%
Scenario 4	Utility values for cerliponase alfa arm assumed to be the same as the standard care arm, from the utility study	[redacted]	+10%
Scenario 5	Patients stop receiving cerliponase alfa treatment at health state 6	[redacted]	-3%
Scenario 6	Patients do not stop receiving cerliponase alfa treatment until death	[redacted]	0%
Scenario 7	No caregiver or sibling disutility is applied in the model, for the cerliponase alfa arm	[redacted]	-6%
Scenario 8	Discount rate of 3.5% for costs and benefits	[redacted]	-2%
Scenario 9	Discount rate of 3.5% for costs, 1.5% for benefits	[redacted]	-41%
Scenario 10	Reduced price, due to price evolution and PPRS rebate	[redacted]	-14%
Scenario 11	Time horizon of 75 years	[redacted]	0%
Scenario 12	Societal perspective used	[redacted]	+2%
Scenario 13	Optimistic scenario - All starting population starts in health states 1-2, no caregiver or sibling disutility applied to the cerliponase alfa arm, 50% reduction in progressive symptoms, differential discount rate	[redacted]	-48%
Scenario 14	Pessimistic scenario - Utility values for cerliponase alfa arm assumed to be the same as the standard care arm, from the utility study, discount rate of 3.5% for costs and benefits	[redacted]	+8%

5.2.10.4 Subgroup analysis

The company also provided a subgroup analysis of asymptomatic and pre-symptomatic siblings with confirmed CLN2 disease. In this analysis, all patients were assumed to have a CLN score of 6 (health state 1) at diagnosis and start of treatment. The company assumed all other assumptions and methods were the same as in the base-case analysis. Results of this analysis are presented in Table 40. Costs associated with each treatment arm are similar to those in the base-case; however, more QALYs are accrued by cerliponase alfa patients due to patients entering the model in a less severe health state and therefore are stabilised in less severe health state at the end of the trial period. As a result, cerliponase alfa is substantially more cost-effective in this subgroup, though the ICER still remains significantly above the threshold.

Table 40: Results of subgroup analysis of asymptomatic/pre-symptomatic siblings (CS, Table D58, p. 277)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental (QALYs)
Cerliponase alfa	[redacted]	[redacted]	37.55	[redacted]	[redacted]	38.16	[redacted]
Standard care	£152,985	5.36	-0.61	N/A	N/A	N/A	N/A

5.2.10.5 Additional cost effectiveness results

After reviewing the original company model, the ERG requested that the company provide additional information around some of the assumptions made in their analysis, and include some additional analyses in their model.

The results of these additional scenarios that address the concerns of the ERG, along with the point for clarification (PFC) to which they relate, are presented in Table 41 below. As can be observed, the majority of the additional analyses had a relatively modest impact on the ICER (with increases and decreases to the ICER seen in roughly equal measure). Changing the starting population in the model, however, had the impact of increasing the ICER by over 50%. The ERG requested a scenario relaxing the assumptions that all cerliponase alfa patients stabilise at week 96 and experience no further impact to mortality or vision symptoms. The company addressed this by assuming that 5% of cerliponase alfa patients did not stabilise, by gradually increasing general population mortality after stabilisation at 96 weeks (double at the age of 20 and four-fold by the age of 40), and applying a vision loss-associated reduction in utility of 13% after the age of 20. This scenario resulted in a 10% increase to the ICER. However, the ERG considered that the company remained very optimistic in these assumptions, specifically with regard to stabilisation and long-term mortality.

Table 41: Additional results, based on PFC adjustments

PFC Number	Scenario	ICER for cerliponase alfa vs standard care (£/QALY)
-	Company base-case	[redacted]
B3	Cycle length of 8 weeks	[redacted]
B7	Starting population in model based on 190-201 population at baseline	[redacted]
B7	Starting population in model based on 190-201 population at screening	[redacted]
B10	Utility values for HS1 reduced by 10%	[redacted]
B10	Utility values decrease over time (age adjustment)	[redacted]
B12	EQ-5D-5L values from utility study used in model	[redacted]
B17	5% of patients in the cerliponase arm do not stabilise, life table mortality doubled, quality of life decreases due to loss of vision over time	[redacted]
B19	Patients split into early and late stabilisers at 26 weeks	[redacted]
B21	Adult-equivalent health state costs used in HS1	[redacted]
B27	Removal of educational support, speech and language therapy and ophthalmologist costs in HS7 to HS9	[redacted]
PFC, points for clarification; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year		

5.2.11 Model validation and face validity check

5.2.11.1 Validation taken by the company

The company validated their economic model in discussion with clinical experts, discussed in Section 12.2.5 of the CS. This comprised a series of three workshops with a total of 13 expert clinical advisors.

- Experts at Workshop 1 validated the model structure, confirmed the company's understanding of the disease. Experts invited to the workshop were either primary investigators or sub-primary investigators on the 190-201 and 190-202 trials.
- Workshop 2 took the format of a Delphi panel of four clinical experts, with the aim of estimating clinical inputs that were not available from the literature. The experts provided information on standard practice for the management of CLN2 disease in the UK, including the use of feeding tubes, number of appointments required by patients and numbers of caregivers required. Information was also collected on regular progression of CLN2 disease in the UK, including the rate of vision loss and incidence of progressive symptoms.
- The model was finalised at Workshop 3. Key assumptions were checked: patients' long-term stabilisation, the expected starting population distribution across health states, and the expected treatment stopping rule. Experts also provided estimates for caregiver disutilities, level of educational support, average number of siblings, and the level of expected uptake of cerliponase alfa across patients over five years.

- Additionally, a palliative care specialist was consulted to provide information on resource use in the two most severe health states.

The company did not provide details on whether a technical model validation was undertaken. It was not possible to validate the economic model against existing literature given the paucity of cost-effectiveness evidence, as a result of the ultra-rate nature of the disease.

5.2.11.2 Validation taken by the ERG

The ERG undertook a review of the company's base-case and sensitivity analyses. This included the use of a checklist to carry out a series of black-box tests to evaluate the internal validity of the model.

Further to this, the code of the model was examined for potential errors. This included tracking how parameters fed into the model and an examination of the main calculation sheets, with a view to understanding how the QALYs and costs accumulated in the model.

- Discounting was not applied on a continuous basis;
- For standard care, costs were discounted using the discount rate for benefits (note that this does not affect results in the company base-case, but affects any scenarios presented where a different discount rate is used for costs and QALYs),
- Utility values for cerliponase alfa patients in HS1 and HS2 were linked to the non-half cycle corrected number of late responders,
- In both arms, the proportion of patients with distress was based on the rate for those with epilepsy, and the proportion of patients with epilepsy was based on the rate for those with distress,
- ICV replacement costs were not discounted,
- Feeding tube insertion costs for patients in the standard care arm were based on data inputs for cerliponase alfa,
- In the additional analyses presented by the company, the vision adjustment disutility was not applied to HS6 in the standard care arm.

Section 6 provides base-case results, adjusted for all the calculation errors identified by the ERG.

Further to the above the ERG would note that the economic model submitted by the company lacked transparency with respect to a number of calculations, including those for deterministic sensitivity analysis, probabilistic sensitivity analysis, and for changing model settings (e.g. with regard to selection of setting, starting population). These functions were performed through the use of macros written in Visual Basic for Applications (VBA) within the Excel spreadsheet, which did not have any associated supporting documentation and had insufficient commentary within the code.

5.3 Conclusions of the cost effectiveness section

The cost-effectiveness review carried out by the company did not identify any published evidence on the cost-effectiveness of cerliponase alfa for CLN2 disease. Consequently, the company's model represents the most relevant source of existing evidence. The base-case ICER presented in the CS was [redacted] per QALY (threshold 300,000 per QALY) and did not include any PAS. A draft MAA was however included in the CS.

In addition to the base-case analysis, the company presented a series of one-way sensitivity analyses and scenario analyses, to assess the impact of uncertainty around the key input variables and assumptions, on the ICER estimates. The results of these indicated that the base-case cost-effectiveness estimates were most sensitive to: (i) the starting population, (ii) health state utilities, and (iii) caregiver and sibling disutilities.

The ERG considers that the company's economic submission meets most of the requirements of the NICE reference case (except discounting), but is subject to a number of issues, which limit the credibility of the company's results. The main concerns relate to six key areas, which are outlined in brief below.

1. *Population modelled*

   The ERG noted that the modelled population does not represent an incident population based on current diagnostic practice and instead assumes significant improvements in diagnosis. To justify this assumption the company stated that they would be implementing a campaign to improve awareness amongst clinicians of CLN2 and state that [redacted]. The ERG, however, notes that no such programme exists in the UK presently and the company's commitment to such a programme remains unclear. Further, the benefits of any such programme are highly uncertain. Give these uncertainties, the ERG does not consider the assumptions made concerning the starting population to be reasonable and consider it more appropriate to base the starting population on current diagnostic practice.

2. *Implied HRQoL benefits over and above the main treatment effect*

   The health state utilities used in the base-case analysis were derived from an elicitation study which presented vignettes for each health state to eight clinical experts with experience of cerliponase alfa and treatment of patients with CLN2 disease. The ERG is concerned that these vignettes imply significant additional benefits of treatment with cerliponase alfa over and above the effects on disease progression. Specifically, the vignettes imply that cerliponase alfa improves seizure control, improves control of dystonia and myoclonus and

delays the need for a feeding tube. However, minimal evidence was presented to support these implied benefits and when asked at the PfCs stage to provide further evidence, the company presented evidence that failed to address the issue raised.

3. *No account for vision loss in patients receiving cerliponase alfa*

   Cerliponase alfa cannot prevent the progressive loss of vision that occurs in CLN2 patients because cerliponase alfa cannot cross the blood-retina barrier. Within the model, the impact of progressive vision loss is accounted for within the health state utilities, with complete vision loss defining health state 8. Progressive vision loss in patients receiving cerliponase alfa however, will not be correlated with deterioration in motor and language scores. The model structure therefore does not account for the progressive vision loss that will be experienced by patients receiving cerliponase alfa.

4. *Long-term effectiveness of Cerliponase alfa*

   A central assumption to the company base-case is that all patients receiving cerliponase alfa stabilise after 96 weeks and experience no further disease progression. The ERG considers this assumption to be subject to very considerable uncertainty and has substantive concerns regarding the company's interpretation of the clinical evidence that the company cite in justification of this assumption. Specifically, the ERG note that there is only limited evidence from the 201/202 study cohort that all patients stabilise and note that a substantial number of patients continue to experience further disease progression in the later part of the 190-201/202 study (post 48 weeks). The ERG also highlights evidence from animal models which suggests patients receiving cerliponase alfa will continue to experience disease progression.

5. *Life expectancy of patients treated with cerliponase alfa:*

   The ERG consider it unrealistic to assume that patients who receive cerliponase alfa will experience general population levels of mortality. The ERG believe there are a number of reasons why they may experience shorter life expectancy than that predicted in the model. Firstly, there is significant uncertainty regarding the assumption that patients experience no further disease progression after 96 weeks. Any relaxation of this assumption will lead to reduced life expectancy for cerliponase patients. Secondly, the ERG considers there to be significant risk that patients receiving cerliponase alfa will experience significant morbidity and mortality risks due to extra-neurological lipofuscin storage. Thirdly, there may be other disease related mortality, not directly attributable to progression of the disease, but associated with the significant neuro-disability experienced by CLN2 patients.

Additional analyses based on scenarios undertaken by the company and independent analyses undertaken by the ERG are presented in Section 6 to address these uncertainties along with a number of other less substantive concerns raised by the ERG.

6 Impact on the ICER of additional clinical and economic analyses undertaken by the ERG

6.1 Overview

This section details the ERG's further exploration of the assumptions and uncertainties raised in the review and critique of the company's cost-effectiveness analysis, presented in Section 5. This section is organised in four parts. Section 6.2 details the impact of errors identified in ERG's validation of the executable model. Section 6.3 details a series of scenario analyses exploring the robustness of the cost-effectiveness results to specific assumptions and additional uncertainties identified by the ERG. These analyses were conducted within the company corrected base-case analysis. The scenario analyses presented in Section 6.3 focus on exploring the following issues and uncertainties:

- The starting population (the distribution of patient CLN2 rating scale scores at baseline);
- Calculation of cerliponase alfa transition probabilities from 190-201 and 190-202 individual patient data;
- Long-term effectiveness of cerliponase alfa;
- Long-term mortality for disease stabilisers;
- The development of blindness in patients receiving cerliponase alfa;
- Quality of life (the data used to inform utility values and how they were modelled over time);
- Costs and resource use;
- Discount rate.

In Section 0, the ERG base-case is presented based on a combination of the exploratory analyses presented in Section 6.3. Further exploratory analysis is also presented exploring the impact of alternative assumptions in the context of the ERG base-case. Section 6.5 presents a brief conclusion summarising the ERG's additional analyses.

6.2 ERG corrections and adjustments to the company's base case model

A small number of errors were identified by the ERG in the company model, previously detailed in Section 5.2.11. Table 42 presents the results of the ERG corrections to the company model: the ICER increase by about 0.3% from [redacted] to [redacted] per QALY.

Table 42: Results of the ERG-corrected company base-case model

	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER	Threshold*
CS base-case						
Cerliponase alfa	[redacted]	29.45	[redacted]	30.42	[redacted]	[redacted]
Standard care	£149,829	-0.97	N/A	N/A	N/A	N/A
ERG-corrected base-case						
Cerliponase alfa	[redacted]	29.24	[redacted]	30.20	[redacted]	[redacted]
Standard care	£151,608	-0.96	N/A	N/A	N/A	N/A

ERG, Evidence Review Group; QALYs, quality-adjusted life year; ICER, incremental cost-effectiveness ratio; CS, company submission

* Cost-effectiveness threshold estimated based on number of incremental undiscounted lifetime QALYs (see Section 5.2.10 for details)

6.3 Additional ERG analyses

6.3.1 Starting population

The company base-case analysis modelled a starting population considered to be reflective of a hypothesised scenario where there was greater awareness of CLN2 disease amongst clinicians and/or a genetic testing programme has been put into place. The ERG, however, do not consider this representative of the current population at diagnosis and that it is not possible to determine how effective an awareness campaign or a future genetic testing programme may be. The ERG therefore presents two alternative scenarios considering alternative starting populations. In both scenarios, the distribution was based on the CLN2 rating scale score at diagnosis of patients who formed the cohort from the 190-901 trial of historical control patients. To ensure the distribution reflects current practice, the selection of patients from the cohort was restricted to patients born after the year 2000 as genetic testing for CLN2 disease was developed in the late 1990's.[56] The first scenario consisted of all eligible patients in the trial cohort, and the second scenario restricted to a CLN2 score of 2+ [redacted].

Table 43 presents the distribution of CLN2 rating scale scores at diagnosis for each scenario. This suggests that fewer patients are identified with a score of 5 or 6 than the company assumed, with the majority of patients diagnosed with a CLN2 rating scale score between 2 and 4.

Table 43: Distribution of CLN2 rating scale scores at diagnosis

Scenario	HS 1	HS 2	HS 3	HS 4	HS 5	HS 6	HS 7	HS 8	HS 9
Company base-case	40%	40%	10%	5%	5%	0%	0%	0%	0%
Cohort from 190-901	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Cohort from 190-901 (ML>1)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ML, motor language score; HS, health state									

Results of these analyses are presented in Table 44. While changing the baseline distribution had little impact on incremental costs, it had a substantial effect on the number of QALYs generated. As a result, the ICER increased from [redacted] to [redacted] in both scenarios. The observed increase in the ICER is due to patients entering the model in a more severe health state, which means that patients receiving cerliponase alfa are stabilised in more severe health states. These more severe health states are associated with fewer QALYs and greater costs, hence the increase in the ICER.

Table 44: Results of ERG analysis: starting population

	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER	Threshold*
ERG-corrected base-case						
Cerliponase alfa	[redacted]	29.24	[redacted]	30.20	[redacted]	[redacted]
Standard care	£151,608	-0.96	N/A	N/A	N/A	N/A
Scenario 1: Patient distribution in 190-901 trial						
Cerliponase alfa	[redacted]	17.38	[redacted]	18.79	[redacted]	[redacted]
Standard care	£143,004	-1.41	N/A	N/A	N/A	N/A
Scenario 2: Patient distribution in 190-901 trial, restricted to CLN2 score of 2+						
Cerliponase alfa	[redacted]	18.11	[redacted]	19.51	[redacted]	[redacted]
Standard care	£145,156	-1.40	N/A	N/A	N/A	N/A
ERG, Evidence Review Group; QALYs, quality-adjusted life year; ICER, incremental cost-effectiveness ratio * Cost-effectiveness threshold estimated based on number of incremental undiscounted lifetime QALYs (see Section 5.2.10 for details)						

6.3.2 Transition probabilities

Given the lack of transparency and apparent discrepancies in how the company estimated the transition probabilities for cerliponase alfa patients from the 190-201 and the 190-202 trials, the ERG extracted individual patient data from graphs presented in the relevant CSRs and recreated the transition probabilities for early responders and late stabilisers.

Per-cycle probabilities are presented in Table 45. Differences between the ERG-estimated probabilities and those estimated by the company were relatively small. Compared with the transition probabilities estimated by the company, the ERG estimated that the rate of disease progression up to Week 16 when in HS1-2 would be higher (6.94% vs 6.09%), but in all other instances the ERG-estimated transition probabilities were more favourable than the company transition probabilities for

cerliponase alfa. In particular, the ERG estimated that some late stabilisers would actually improve between Week 17 and Week 96.

Table 45: ERG-estimated transition probabilities for cerliponase alfa (per cycle probability)

Health state	Baseline to Week 16		Week 17 to Week 96 (late stabilisers*)	
	Probability of decline	Probability of improvement	Probability of decline	Probability of improvement
Health state 1 and 2	[redacted]	[redacted]	[redacted]	[redacted]
Health state 3 to 5	[redacted]	[redacted]		
Health state 6	[redacted]	[redacted]		

ERG, Evidence Review Group
*Early stabilisers assumed to remain in their health state at Week 16 (or move to the death health state)

The results of this analysis are presented in Table 46. Cerliponase alfa was associated with a small increase in QALYs and costs as a result of the reduced rate of disease progression. This resulted in the ICER increasing from [redacted] to [redacted] per QALY.

Table 46: Results of the ERG exploratory analysis with alternative transition probabilities for CA

	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER	Threshold*
ERG-corrected base-case						
Cerliponase alfa	[redacted]	29.24	[redacted]	30.20	[redacted]	[redacted]
Standard care	£151,608	-0.96	N/A	N/A	N/A	N/A
Scenario: ERG-estimated transition probabilities for cerliponase alfa						
Cerliponase alfa	[redacted]	29.28	[redacted]	30.24	[redacted]	[redacted]
Standard care	£151,608	-0.96	N/A	N/A	N/A	N/A

ERG, Evidence Review Group; CA, cerliponase alfa; QALYs, quality-adjusted life year; ICER, incremental cost-effectiveness ratio
* Cost-effectiveness threshold estimated based on number of incremental undiscounted lifetime QALYs (see Section 5.2.10 for details)

6.3.3 Disease stabilisation

The company base-case analysis made the assumption that all cerliponase alfa patients achieved disease stabilisation by week 96. The ERG considers this assumption to be subject to very considerable uncertainty and has substantive concerns regarding the company's interpretation of the clinical evidence cited by the company to justify this. Two alternative scenarios were presented that relaxed this assumption. The first scenario assumed that cerliponase alfa patients achieving stabilisation ("early stabilisers") by Week 16 would remain stable for the entire time horizon of the model. In contrast to the company analysis, "late stabilisers" were assumed to continue experiencing disease progression after Week 96 in this scenario, with the rate of progression after this point defined by the transition probabilities used to model progression between 17 weeks and 96 weeks (transition probabilities presented in Table 45). The second scenario assumed that no patients would achieve

stabilisation and disease progression would continue indefinitely. In this case, transition probabilities for Week 16 to Week 96 were estimated based on the dataset of all patients, and were applied beyond Week 96 for all patients.

The results of these scenarios are based on ERG-calculated transition probabilities using the IPD extracted from the trials' CSRs (as for the analysis in Section 6.3.2). Per-cycle probabilities are presented in Table 47.

Table 47: ERG estimated transition probabilities (per-cycle)

Health state	Probability of decline	Probability of improvement	Implementation in the analysis
Baseline to Week 16			
Health state 1 and 2	[redacted]	[redacted]	Applied for all cerliponase alfa patients in all analyses between baseline and Week 16
Health state 3 to 5	[redacted]	[redacted]	
Health state 6	[redacted]	[redacted]	
Partial stabilisation scenario: After Week 17 (late stabilisers*)			
All health states	[redacted]	[redacted]	Applied to cerliponase alfa patients who were "late stabilisers", from Week 17 until the end of the model time horizon
No stabilisation scenario: After Week 17 (all patients)			
All health states	[redacted]	[redacted]	Applied to all cerliponase alfa patients from Week 17 until the end of the model time horizon

ERG, Evidence Review Group
*Early stabilisers assumed to remain in their health state at Week 16 (or move to the death health state)

As illustrated in Table 48, it is evident that this assumption has a considerable impact on estimated cost-effectiveness. In both scenarios, the number of QALYs and total costs for cerliponase alfa decreased. One of the effects of these scenarios is that patients experience significantly shorter life expectancy. This is because patients are able to enter the more severe health states over time, which have an associated CLN2-related mortality that does not get applied in the company base-case analysis. The impact was particularly great when it was assumed that there would be no stabilisation: the ICER increased from [redacted] to [redacted]. The number of QALYs in this scenario reduced from 29.24 to 10.85.

Table 48: Results of the ERG exploratory analyses around disease stabilisation

	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER	Threshold*
ERG-corrected base-case						
Cerliponase alfa	[redacted]	29.24	[redacted]	30.20	[redacted]	[redacted]
Standard care	£151,608	-0.96	N/A	N/A	N/A	N/A
Scenario 1: Disease stabilisation for early stabilisers on cerliponase alfa						
Cerliponase alfa	[redacted]	23.55	[redacted]	24.51	[redacted]	[redacted]
Standard care	£151,608	-0.96	N/A	N/A	N/A	N/A
Scenario 2: No disease stabilisation for cerliponase alfa patients						
Cerliponase alfa	[redacted]	10.85	[redacted]	11.81	[redacted]	[redacted]
Standard care	£151,608	-0.96	N/A	N/A	N/A	N/A

ERG, Evidence Review Group; QALYs, quality-adjusted life year; ICER, incremental cost-effectiveness ratio
* Cost-effectiveness threshold estimated based on number of incremental undiscounted lifetime QALYs (see Section 5.2.10 for details)

6.3.4 Mortality

The ERG is concerned that there is a significant risk that patients receiving cerliponase alfa will experience significantly shorter life expectancy than predicted by the company model. This is a result of both the impact of neurological disability and the effects of extra-neurological disease pathology. The ERG, therefore, undertook scenario analyses exploring the impact of incorporating the effect of both of these mortality risks.

Modelling: mortality impact of neurological disability: To model the impact of neurological disability on mortality, a multiplier was applied to the general population mortality already included in the model. This multiplier is assumed to vary depending upon the degree of neurological disability. The multiplier applied is based on data characterising the long-term mortality effects of traumatic brain injury.[46] Table 49 presents the mortality applied by health state.

Table 49: Neuro-disability-related mortality multiplier

Health state	Risk ratio
HS 1 - 2	1.44
HS 3 - 5	2
HS 6 - 9	9.92

Modelling: mortality impact of extra-neurological pathology: The impact of extra-neurological disease is subject to high degree of uncertainty as there is no long-term data available upon which to base assumptions and minimal evidence in untreated patients. The ERG's approach therefore focused on using evidence of extra-neurological pathology in the CLN3 subtype. The ERG acknowledges that

this is an imperfect analogy, but consider this the strongest source of relevant evidence. To incorporate the mortality effect of extra-neurological related mortality, an additional mortality risk was added for patients receiving cerliponase alfa. This additional mortality risk was estimated using a Weibull distribution. A Weibull distribution was used because it allows the risk of an event occurring to increase over time; we would expect to observe an increased risk overtime as the extra-neuronal storage of lipopigments continues to damage visceral organs increasing the probability of failure. To parameterise the Weibull distribution, the function was fitted to three points: minimum age at which risk is greater than zero, the mean of the distribution (average life expectancy), and age at which cumulative survival is equal to 0.1%. These points were estimated from the limited data available in extra-neurological mortality in CLN2 and the related subtype CLN3. Table 50 present the data used to populate the function and the data source they are based upon.

Table 50: Parametrisation of the Weibull distribution

	Value used	**Justification and data sources**
Age at which risk >0	14	Evidence in CLN3 patients from Østergaard et al.[16] observed evidence of heart abnormalities in all assessed patients over the age of 14. This was interpreted as the point at which there was non-zero risk of extra- neurological related mortality.
Mean life expectancy	27.07	This is an average age of death based on 5 cases of heart failure in CLN3 and one with CLN2. This evidence is sourced from three publications Fukumura et al,[14] Hofman et al[57] and Østergaard et al.[16]
Age at which cumulative survival is equal to 0.1%.	40	This was based on the longest-lived patient with CLN3 in a cohort of 319 patients.[58] This was assumed to represent the maximum life expectancy of patients.

The results of incorporating these two sources of mortality are presented in Table 51. As can be seen the impact of incorporating the potential mortality effects of extra-neurological pathology is significant, resulting in a substantial reduction in incremental QALYs (29.24 vs 12.18). This is also accompanied by significant reduction in incremental costs leading to a reduction in the ICER from [redacted] to [redacted] per QALY. The reduction in the ICER is because the substantial drug costs associated with cerliponase alfa outweigh the QALY benefits being generated. A similar picture is also seen in Scenario 2, although the magnitude of the effect is much reduced. In this scenario, the ICER is reduced from [redacted] to [redacted] per QALY.

Table 51: Result of ERG exploratory analyses around mortality

	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER	Threshold*
ERG-corrected base-case						
Cerliponase alfa	[redacted]	29.24	[redacted]	30.20	[redacted]	[redacted]
Standard care	£151,608	-0.96	N/A	N/A	N/A	N/A
Scenario 1 Extra-neurological related mortality						
Cerliponase alfa	[redacted]	12.18	[redacted]	13.14	[redacted]	[redacted]
Standard care	£151,608	-0.96	N/A	N/A	N/A	N/A
Scenario 2: Neurodisability-related mortality						
Cerliponase alfa	[redacted]	28.23	[redacted]	29.19	[redacted]	[redacted]
Standard care	£151,475	-0.96	N/A	N/A	N/A	N/A

ERG, Evidence Review Group; QALYs, quality-adjusted life year; ICER, incremental cost-effectiveness ratio
* Cost-effectiveness threshold estimated based on number of incremental undiscounted lifetime QALYs (see Section 5.2.10 for details)

6.3.5 Vision loss

An important omission from the company base-case was the progressive vision loss that will be experienced by patients receiving cerliponase alfa; cerliponase alfa cannot prevent the progressive loss of vision that occurs in CLN2 patients because the drug cannot cross the blood-retina barrier. The ERG therefore implemented a scenario within the company base-case analysis where it was assumed that cerliponase alfa would not slow the rate of vision loss in CLN2 patients. In this scenario, complete blindness is assumed to occur at the same time as patients in the standard care arm.

To account the effects of vision loss the ERG scenario incorporated a disutility and additional costs. These were applied to the proportion of cerliponase alfa patients in health states 1 to 6 who were estimated to have complete vision loss (the cost and utility of patients in health states 7 to 9 were assumed to reflect that of patients with vision loss). The relative decrement in utility was estimated as 13%[42], which was extracted from a burden of illness study of neovascular age-related macular degeneration; this was the same sourced in the company's vision loss scenario. The ERG considers that there may be additional disutility associated with the intermediate vision loss, but this was not accounted for given a lack of data to model it appropriately. The additional cost of complete vision loss was also estimated from the burden of illness study, and included low vision rehabilitation, rehabilitation, vision-enhancing equipment, and social benefits and transportation subsidies. The annual cost of blindness was estimated by the study as £4,077 (inflated from the cost reported in 2005 of £3,307 using the hospital and community services index[59]).

The impact of this analysis was an increase in the ICER of around 14% from [redacted] to [redacted], as shown in Table 52. The exploration of this assumption is particularly relevant within the context of

the company base-case analysis where it was assumed that cerliponase alfa patients stabilise by week 96 and do not experience any further disease progression over their lifetime.

Table 52: Results of ERG exploratory analysis on the development of blindness

	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER	Threshold*
ERG-corrected base-case						
Cerliponase alfa	[redacted]	29.24	[redacted]	30.20	[redacted]	[redacted]
Standard care	£151,608	-0.96	N/A	N/A	N/A	N/A
Scenario: Vision loss in cerliponase alfa patients						
Cerliponase alfa	[redacted]	25.64	[redacted]	26.61	[redacted]	[redacted]
Standard care	£151,608	-0.96	N/A	N/A	N/A	N/A

ERG, Evidence Review Group; CA, cerliponase alfa; QALYs, quality-adjusted life year; ICER, incremental cost-effectiveness ratio

* Cost-effectiveness threshold estimated based on number of incremental undiscounted lifetime QALYs (see Section 5.2.10 for details)

6.3.6 Health-related quality of life

The ERG explored a number of alternative scenarios relating to the modelling of HRQoL. The results of these analyses are presented in Table 53.

Firstly, as the ERG were unsure which values were validated by clinicians as appropriate, the ERG explored the scenario where the EQ-5D-5L data, directly collected from the clinicians in the utility study, was used. The impact of this analysis was a decrease in the ICER of around 7% from [redacted] to [redacted], as shown in Table 53. This is due to a reduction in the negative utility values and therefore, the accumulation of a larger number of QALYs in patients receiving cerliponase alfa.

Secondly, the ERG explored the scenario where the utility data collected directly from the trial; PEDs-QL data was used. The impact of this analysis was a decrease in the ICER of around 6% from [redacted] to [redacted], as shown in Table 54. Once again, this is due to a reduction in the negative utility values and therefore, the accumulation of a larger number of QALYs in patients receiving cerliponase alfa.

Thirdly, the ERG believes it is appropriate to apply age-adjusted utilities within the company base-case analysis, to account for that fact that the benefits of cerliponase alfa were assumed to continue over the patient lifetime. A disutility was estimated from data reported by Ara *et al.*, and applied after patients reached the age of 18.[60] The impact of this analysis was an increase in the ICER of around 3% from [redacted] to [redacted], as shown in Table 53. This small increase is due to the small reduction in QALYs being accumulated in patients receiving cerliponase alfa.

Fourthly, the ERG considered it appropriate to include carer and sibling disutility in the company's model; however, not in perpetuity. Therefore, the ERG explored the scenario where carer and sibling disutility was removed after 30 years. The impact of this analysis was a decrease in the ICER of around 3% from [redacted] to [redacted], as shown in Table 53.

The final ERG scenario analysis conducted by the ERG around the utility estimates, explores the scenario where both arms have the same utility estimates. A primary concern of the ERG was that the vignette descriptions used in the utility study, as they implied significant additional benefits of treatment with cerliponase alfa over and above the effects on disease progression. The evidence in support of these additional benefits was weak, however. The ERG therefore consider this a more appropriate way to model HRQoL given the available evidence. In this scenario, the standard care values for EQ-5D-3L (mapped from EQ-5D-5L values) were used for both arms in the model. The impact of this analysis was an increase in the ICER of around 10% from [redacted] to [redacted], as shown in Table 53.

Table 53: Results of ERG exploratory analysis on HRQoL

	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER	Threshold*
ERG-corrected base-case						
Cerliponase alfa	[redacted]	29.24	[redacted]	30.20	[redacted]	[redacted]
Standard care	£151,608	-0.96	N/A	N/A	N/A	N/A
Scenario 1: EQ-5D-5L						
Cerliponase alfa	[redacted]	32.36	[redacted]	32.55	[redacted]	[redacted]
Standard care	£151,608	-0.20	N/A	N/A	N/A	N/A
Scenario 2: Peds-QL						
Cerliponase alfa	[redacted]	33.15	[redacted]	32.12	[redacted]	[redacted]
Standard care	£151,608	1.03	N/A	N/A	N/A	N/A
Scenario 3: Age-adjusted utilities						
Cerliponase alfa	[redacted]	27.50	[redacted]	28.46	[redacted]	[redacted]
Standard care	£151,608	-0.96	N/A	N/A	N/A	N/A
Scenario 4: Removed carer and sibling disutility after 30 years						
Cerliponase alfa	[redacted]	30.20	[redacted]	31.17	[redacted]	[redacted]
Standard care	£151,608	-0.96	N/A	N/A	N/A	N/A
Scenario 5: Same utility values in each arm						
Cerliponase alfa	[redacted]	26.49	[redacted]	27.45	[redacted]	[redacted]
Standard care	£151,608	-0.96	N/A	N/A	N/A	N/A

ERG, Evidence Review Group; QALYs, quality-adjusted life year; ICER, incremental cost-effectiveness ratio

* Cost-effectiveness threshold estimated based on number of incremental undiscounted lifetime QALYs (see Section 5.2.10 for details)

6.3.7 Costs and resource use

The ERG considered that there were some important cost items that were not included in the company analysis that had the potential to impact on the cost-effectiveness of cerliponase alfa. These include additional monitoring costs (ECGs), provision of psychiatric and psychological support, and residential care costs.

Additional ECG for cerliponase alfa patients

The EMA recommends an ECG during infusion every six months. However, since some of these CLN2 patients may develop conduction disorders or heart disease, ECG monitoring during each infusion is recommended in patients with present or past bradycardia, conduction disorders, or with structural heart disease. As such, an additional cost of ECG (£494, NHS Reference Costs, Day case, electrocardiogram monitoring or stress testing) has been applied to patients on treatment every six months and to the proportion of patients with heart disorders requiring an ECG every infusion. The proportion of patients requiring an ECG with each infusion was estimated from the clinical trial data, where 10% of patients had abnormal heart activity at baseline, rising to 71% at two years.

The impact of including the ECG cost in the model results in [redacted] additional cost for cerliponase alfa, and the ICER increasing from [redacted] to [redacted].

Psychiatric support for patients

The clinical expert consulted by the ERG advised that, due to the behavioural symptoms inherent to the disease, patients on cerliponase alfa would require psychiatric and psychological support as they enter young adulthood. A cost for psychiatric support was applied to these patients over the age of 13 with a language score of over 1 (i.e. in health states 1 to 5). A cost of £242 (NHS Reference Costs, Child and Adolescent Mental Health Services - Community contacts) was applied every quarter: it was advised that patients in the more severe health states would require more frequent support, but without any further information the ERG took what was considered a conservative assumption.

The impact of including a cost of psychiatric support in the model results in [redacted] of additional cost for cerliponase alfa. This resulted in the ICER increasing from [redacted] to [redacted].

Residential care

The clinical expert consulted by the ERG also advised that CLN2 patients entering adulthood would receive a care package and may no longer receive care at home, which might include stay in a care home with nursing. PSSRU reported an annual cost of £43,810 for a young adult with a severe acquired brain injury[37], which was used as a proxy since it was assumed that the level of care for these patients would be similar. It was applied in the model to these patients and replaced the cost of specialist nursing and NHS caregivers. The ERG assumed that this would apply to 50% of patients

over the age of 18. The ERG also removed the carer and sibling disutility for the proportion of patients in residential care.

The impact of including a cost of residential care in the model results in [redacted] additional costs and 0.66 additional QALYs for cerliponase alfa. This resulted in the ICER increasing from [redacted] to [redacted].

Table 54: Results of ERG exploratory analyses around resource use

	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER	Threshold*
ERG-corrected base-case						
Cerliponase alfa	[redacted]	29.24	[redacted]	30.20	[redacted]	[redacted]
Standard care	£151,608	-0.96	N/A	N/A	N/A	N/A
Scenario 1: Additional ECG cost						
Cerliponase alfa	[redacted]	29.24	[redacted]	30.20	[redacted]	[redacted]
Standard care	£151,608	-0.96	N/A	N/A	N/A	N/A
Scenario 2: Psychiatric support						
Cerliponase alfa	[redacted]	29.24	[redacted]	30.20	[redacted]	[redacted]
Standard care	£151,608	-0.96	N/A	N/A	N/A	N/A
Scenario 3: Residential care						
Cerliponase alfa	[redacted]	29.90	[redacted]	30.86	[redacted]	[redacted]
Standard care	£151,608	-0.96	N/A	N/A	N/A	N/A

ERG, Evidence Review Group; QALYs, quality-adjusted life year; ICER, incremental cost-effectiveness ratio; ECG, electrocardiogram

* Cost-effectiveness threshold estimated based on number of incremental undiscounted lifetime QALYs (see Section 5.2.10 for details)

6.3.8 Discounting

A discount rate of 1.5% per annum was applied to both costs and outcomes in the company's base-case. The ERG does not consider the 1.5% discount rate applied in the model to be reasonable given these criteria laid out in the NICE reference case. Table 55presents the results of scenario analysis in which the discount rate for both benefits and costs is set to 3.5%. The impact of this scenario is to reduce the ICER from [redacted] to [redacted] per QALY.

Table 55: Results of ERG exploratory analysis for discount rate

	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER	Threshold*
ERG-corrected base-case						
Cerliponase alfa	[redacted]	29.24	[redacted]	30.20	[redacted]	[redacted]
Standard care	£151,608	-0.96	N/A	N/A	N/A	N/A
Scenario: Discounted cost and QALYs at 3.5%						
Cerliponase alfa	[redacted]	17.27	[redacted]	18.12	[redacted]	[redacted]
Standard care	£142,486	-0.84	N/A	N/A	N/A	N/A

ERG, Evidence Review Group; QALYs, quality-adjusted life year; ICER, incremental cost-effectiveness ratio

* Cost-effectiveness threshold estimated based on number of incremental undiscounted lifetime QALYs (see Section 5.2.10 for details)

6.4 ERG preferred analysis

6.4.1 ERG preferred base-case analysis

Table 56 presents the ERG's preferred base-case which combines a number of the changes to the company base-case explored in Section 6.3. This scenario is based on the following sets of assumptions:

- Starting population based on the 190-901 cohort;
- ERG-calculated transition probabilities for cerliponase alfa patients;
- No long-term disease stabilisation for cerliponase alfa patients;
- Includes extra-neurological and neuro-disability-related mortality;
- All patients go blind over time, and incur related support costs and disutility;
- Utilities are the same for both treatment arms using EQ-5D-3L data
- Age-adjusted utilities are applied;
- Carer and sibling disutility are removed after 30 years;
- Additional resource use items are included (ECG, psychiatric support, residential care);
- Discount rate of 3.5% for costs and benefits.

Table 56: Results of the ERG-preferred base-case analysis

	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER	Threshold*
ERG-corrected base-case						
Cerliponase alfa	[redacted]	29.24	[redacted]	30.20	[redacted]	[redacted]
Standard care	£151,608	-0.96	N/A	N/A	N/A	N/A
ERG-preferred base-case analysis						
Cerliponase alfa	[redacted]	2.02	[redacted]	3.32	[redacted]	[redacted]
Standard care	£135,549	-1.30	N/A	N/A	N/A	N/A

ERG, Evidence Review Group; CA, cerliponase alfa; QALYs, quality-adjusted life year; ICER, incremental cost-effectiveness ratio

* Cost-effectiveness threshold estimated based on number of incremental undiscounted lifetime QALYs (see Section 5.2.10 for details)

The impact of the ERG's assumptions on the ICER are considerable; the ERG preferred base-case predicts a significant increase in the ICER ([redacted] vs [redacted] per QALY). The ERG base-case also case also predicts that even with zero drug acquisition costs, cerliponase alfa remains cost-ineffective at a at a threshold of [redacted] per QALY (predicted ICER [redacted] per QALY). This is because the significant costs of care associated with CLN2 disease outweigh the value generated by the additional QALYs. The marked differences between the company-base analysis and the ERG base-case are largely largely attributable to significant differences in predicted incremental QALYs (1.98 vs 29.24). The impact impact of the ERG base-case assumptions on QALYs accrued can be clearly observed in a comparison of comparison of the Markov traces from the ERG corrected base-case and the ERG's preferred base- (

Figure 10 and Figure 11). In the ERG corrected base-case, the benefits of cerliponase alfa are realised over an extended period with patients being maintained in the less severe health states for a protracted period of time. This contrasts with the ERG's base-case where progressive decline is observed together with a growing mortality risk.

Figure 10: Markov trace for cerliponase alfa - ERG corrected base-case analysis

Figure redacted commercial-in-confidence

Figure 11: Markov trace for cerliponase alfa - ERG preferred base-case analysis

Figure redacted commercial-in-confidence

6.4.2 Scenario analyses on the ERG preferred base-case

While the ERG considers the assumptions made in its base-case analysis the most plausible given the limited clinical evidence available, the ERG acknowledges that some of these assumptions are somewhat speculative, and potentially represent a conservative interpretation of the available evidence. To further explore the impact of these assumptions the ERG therefore carried out further scenario analyses using the ERG base-case. These scenarios focus on exploring the impact of assumptions made with regards to long-term effectiveness, extra-neurological mortality and HRQoL, as well as exploring the impact of alternative assumptions regarding stopping rules and discounting. Specifically, the following scenarios are addressed in this analysis:

- Partial stabilisation: early stabilisers are assumed to achieve long-term disease stability;
- Extra-neurological related mortality removed;
- Health stated utility values as per the company base: different utilities per treatment arm based on EQ-5D-3L data;
- PedsQL trial data used to model HRQoL;
- No stopping rule applied: cerliponase alfa therapy continued until death;
- Costs and benefits discounted at 1.5% as per the company base-case;
- Optimistic scenario: Partial stabilisation, no extra-neurological related mortality and differential utility values in each treatment arm: this represents an optimistic ERG base-case analysis.

The results of this additional analysis demonstrate that the ICER is sensitive to a number of assumptions, with ICERs produced ranging from [redacted] to [redacted] per QALY. The ERG's alternative optimistic scenario which assumes partial stabilisation, no extra-neurological related mortality and differential utility values in each treatment arm estimates an ICER of [redacted]. Of particular note is that the ICER is very sensitive to the utility values with the ICER reduced by approximately 28% and 36% in the two scenarios in which alternative health state utility values were used. The significant impact of health state utilities on the ICER can be attributed to the fact that these determine the value of additional life years generated by cerliponase alfa. [redacted]

Table 57: Results of exploratory analysis on the ERG preferred base-case

	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER	Threshold*
ERG-preferred base-case						
Cerliponase alfa	[redacted]	2.02	[redacted]	3.32	[redacted]	[redacted]
Standard care	£135,549	-1.30	N/A	N/A	N/A	N/A
Scenario 1: Partial stabilisation on cerliponase alfa (early stabilisers only)						
Cerliponase alfa	[redacted]	3.04	[redacted]	4.34	[redacted]	[redacted]
Standard care	£135,549	-1.30	N/A	N/A	N/A	N/A
Scenario 2: No extra-neurological related mortality						
Cerliponase alfa	[redacted]	2.55	[redacted]	3.84	[redacted]	[redacted]
Standard care	£135,549	-1.30	N/A	N/A	N/A	N/A
Scenario 3: Different utility values in each arm (EQ-5D-3L)						
Cerliponase alfa	[redacted]	3.29	[redacted]	4.59	[redacted]	[redacted]
Standard care	£135,549	-1.30	N/A	N/A	N/A	N/A
Scenario 4: PedsQL for HRQoL						
Cerliponase alfa	[redacted]	5.76	[redacted]	5.22	[redacted]	[redacted]
Standard care	£135,549	0.54	N/A	N/A	N/A	N/A
Scenario 5: Stopping rule – no discontinuation of cerliponase alfa						
Cerliponase alfa	[redacted]	1.93	[redacted]	3.23	[redacted]	[redacted]
Standard care	£135,549	-1.30	N/A	N/A	N/A	N/A
Scenario 6: Discounting at 1.5%						
Cerliponase alfa	[redacted]	2.37	[redacted]	3.77	[redacted]	[redacted]
Standard care	£142,875	-1.40	N/A	N/A	N/A	N/A
Scenario 7: Optimistic base-case analysis - partial stabilisation, no cardiac mortality and HRQoL benefit for CA						
Cerliponase alfa	[redacted]	7.53	[redacted]	8.83	[redacted]	[redacted]
Standard care	£135,549	-1.30	N/A	N/A	N/A	N/A

ERG, Evidence Review Group; QALYs, quality-adjusted life year; ICER, incremental cost-effectiveness ratio; HRQoL, health-related quality of life; CA, cerliponase alfa

* Cost-effectiveness threshold estimated based on number of incremental undiscounted lifetime QALYs (see Section 5.2.10 for details)

6.4.3 Subgroup analysis

In line with the NICE scope, the CS presented subgroup analysis in patients with asymptomatic and pre-symptomatic CLN2 disease. This was implement in the company model by assuming that all patients started in health state 1 (CLN2 rating score of 6). Table 58 presents results for the ERG-base case and ERG optimistic base-case in this subgroup. The ICER in the ERG base-case increases from [redacted] in the ERG corrected base-case to [redacted] per QALY. In the ERG optimistic base-case the ICER is [redacted] per QALY.

Table 58: Subgroup analysis on the ERG's base-case

	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER	Threshold*
ERG corrected base-case: asymptomatic and pre-symptomatic subgroup						
Cerliponase alfa	[redacted]	37.29	[redacted]	37.89	[redacted]	£300,000
Standard care	£155,422	-0.60	N/A	N/A	N/A	N/A
ERG-preferred base-case: asymptomatic and pre-symptomatic subgroup						
Cerliponase alfa	[redacted]	7.52	[redacted]	8.00	[redacted]	£106,423
Standard care	£145,065	-0.48	N/A	N/A	N/A	N/A
Optimistic base-case analysis: asymptomatic and pre-symptomatic subgroup						
Cerliponase alfa	[redacted]	15.53	[redacted]	16.01	[redacted]	£300,000
Standard care	£145,065	-0.48	N/A	N/A	N/A	N/A

6.5 Conclusions from ERG analyses

The ERG has presented a number of additional analyses. These analyses were carried out in a number of stages. The first stage addressed a number of minor calculation errors in the company's revised model (Section 6.2). The impact of these changes was to increase the ICER by a small amount from [redacted] per QALY to [redacted] per QALY.

Using the corrected model, the ERG then presented a number of analyses considering a range of issues raised in Section 5 (Section 6.3). These scenario analyses addressed the following issues:

- The starting population (the distribution of patient CLN2 rating scale scores at baseline);
- Long-term effectiveness of cerliponase alfa;
- Long-term mortality for disease stabilisers;
- The development of blindness in patients receiving cerliponase alfa;
- Quality of life (the data used to inform utility values and how they were modelled over time);
- Costs and resource use;
- Discount rate.

The most of important these scenarios related to the starting population, the long-term-effectiveness of cerliponase alfa, the inclusion of extra-neurological related mortality and vision loss. All scenarios on HRQoL also had a sizable impact on the ICER. The changes made by the ERG produce ICERs for cerliponase alfa from [redacted] to [redacted] per QALY, all of which exceed a threshold of [redacted] per QALY gained. The ERG's base-case analysis estimates that the ICER for cerliponase alfa compared with standard care to be £[redacted] per QALY. In this scenario, cerliponase alfa is not cost-effective at zero price. A number of scenarios were conducted on the ERG's preferred base-case analysis. A scenario, considered an "optimistic" base-case scenario whereby early stabilisers are to achieve long-term stabilisation; no extra-neurological mortality is assumed; and cerliponase alfa is

assumed be associated with HRQoL benefits over above delayed progression results in an ICER of £[redacted] per QALY.

These scenarios are considered to be as plausible as the one presented by the company (corrected for calculation errors), but are still subject to considerable uncertainty given the lack of long-term evidence for CLN2 patients receiving cerliponase alfa. Based on the ERG's base-case analysis, there is considerable uncertainty around whether cerliponase alfa is likely to represent good value to the NHS considering willingness to pay thresholds for highly specialised technologies.

7 Submissions from practitioner and patient groups

7.1 Batten Disease Family Association HST submission summary

The Batten Disease Family Association (BDFA) submitted evidence to NICE in support of this appraisal, this has been summarised by the ERG in the following section.

The Batten Disease Family Association (BDFA) was established in 1998, with the aim of supporting families, funding research, and raising awareness of Batten disease across the UK. The charity works with 32 families of living CLN2 patients in England, which they believe represents ~90% of the English CLN2 population.

The patient statement received by the BDFA provided an overview of the family perspective of diagnosis and treatment, the quality of life of patients and families, and their perceptions of the treatment. The BDFA also provided several testimonies from families, and examples of the literature they provide.

7.1.1 BDFA statement

The diagnostic process was described by families as a 'traumatic diagnostic odyssey' of uncertainty, anxiety, and an inability to access relevant information and care. Receiving a diagnosis allows families to plan for their child's needs, and to make informed reproductive choices, but reaching this point was a long and distressing process. Families also reported that Batten disease is not covered in the remit of NHS lysosomal storage disorder (LSD) centres, therefore access to treatment, expertise, and timely information was limited relative to other similar conditions. This means that families do not always receive information about the BDFA and other support organisations and agencies, instead having to find this information independently. Until the development of cerliponase alfa, most children were cared for in local centres, who would consult with specialists at the Evelina Children's Hospital or Great Ormond Street Hospital, rather than receiving access to specific expertise directly.

The submission describes the standard course of the disease and the increasing burden placed on parents over the course of their child's illness. The emotional wellbeing of parents is severely affected by a diagnosis of CLN2, who described the grieving process as beginning long before their child dies, and the rapidity of disease progression leaves parents unable to cope emotionally with each new development. Even with additional support, many parents must provide full time care for their children. Parents' daily routine involves administering medication, feeding, positioning, changing, suctioning and maintaining airways, hydration, and stimulation. Families must navigate systems to access equipment, housing adaptions, school placement, and care and services for their child. Families are deprived of leisure time and holidays, suffer financial hardships, and many suffer breakdown of relationships – further adding to the emotional and financial burden.

Families felt that reducing the rapidity of symptom deterioration would enable children to remain part of their family and school community, and retain critical life skills for longer which would keep them happier and more satisfied. The ability to behave and live as normal children for longer would allow them to progress in education and engage with peers at school, maintaining hobbies and interests outside. Some parents also reported that their children had regained some of previously lost skills, such as speech and walking; however, parents and caregivers were aware that cerliponase alfa does not help with vision loss, and considered this a disadvantage of the technology. They also reported that the financial and logistical challenges of travelling for treatment every two weeks presented many difficulties, but stated the potential benefits of the treatment far outweighed the impact of travel on their lives. The BDFA believed that if children were diagnosed and treated earlier they would receive a greater benefit from the technology.

The submission compared cerliponase alfa with current standard practice, listing the following as necessary in typical patient management: anticonvulsant medication for seizures and spasticity, dietary management, physiotherapy, speech and language therapy, hydration management, gastrostomy fitting, management of oral secretions, skin and mouth care, posture and seating management, hospice and palliative care team involvement, patient organisation support, specialist education support including visual impairment professional. The submission described a huge unmet need for treatment, as there are currently no other options other than the needs listed above, requiring significant multidisciplinary management. The BDFA also anticipated that the availability of treatment would increase awareness and improve time to diagnosis. If the treatment were not made available, the BDFA believe there would be a negative impact on the CLN2 community, those on treatment, and those involved in the trials for cerliponase alfa. They anticipated that all 28 children currently supported by the BDFA would be too far progressed in their disease to receive treatment, but those currently receiving treatment through clinical trials or compassionate use programmes would be expected to continue treatment.

7.1.2 BDFA family testimonies

The BDFA asked three families who had children involved in the cerliponase alfa trial to list the advantages and disadvantages of treatment.

All families expressed gratitude for the opportunity to receive cerliponase alfa, and were hopeful that it would slow down the progression of CLN2 symptoms. In response to treatment, families noticed positive changes in their children's social skills, and increased confidence allowed them to attend and engage with mainstream schooling, and improve relationships with peers. The slowing of clinical progression was also important to families, some of whom also noticed improved mobility, a regained ability to learn new words, and improved seizure control. Families also felt reassured by fortnightly

contact with specialists, and had better emotional wellbeing as a family due to symptom control and maintained or improved communication and ambulation.

The primary disadvantage reported by all families involved was the burden of fortnightly travel, specifically, the emotional strain of separating the family and arranging childcare for other children who are not receiving treatment, the financial impact of travelling, and the stress of the whole ordeal on children. Though this was viewed as necessary and worthwhile for the wellbeing of their child, regular long-distance travel could not be a long-term solution, with families hoping this, or more advanced treatments would be made available at local hospitals. One family expressed concern that this treatment did not prevent vision loss or the systemic symptoms caused by the lack of enzyme in other organs.

7.1.3 BDFA family case studies

The BDFA submission contained four case studies detailing the experiences of families of CLN2 disease patients. These were written by families of children with and without cerliponase alfa treatment, a family with two affected children, and another whose child received the drug under the compassionate use programme. The ERG judged that summarising these accounts would detract from their rich content on the experience of these families please see the submission by the BDFA for further details on these case studies.

8 Overall conclusions

The ERG acknowledge that the clinical data presented by the company demonstrate that ICV cerliponase alfa therapy can slow the deterioration of motor and language function in children with progressive CLN2 disease for at least 96 weeks, relative to conventional management. However, the magnitude and potential duration of this treatment effect is subject to significant uncertainty, due to the weakness of the presented clinical data, disagreement between outcome measures, and inconsistencies and uncertainty in the analysis of natural history controls. The ERG identified a number of serious issues with the company's presentation and interpretation of the clinical evidence and wider literature, which led to very significant differences in opinion between the ERG and the company with regards to the clinical and cost effectiveness of cerliponase alfa.

The CS clearly and consistently presents a narrative that cerliponase alfa is essentially curative for as long as treatment is administered, and will permanently stabilise, or even improve all characteristic aspects of CLN2 disease, explicitly preventing deterioration of motor, language, and visual function, and the frequency of seizures, thereby eliminating disease-related mortality. The ERG did not consider the clinical data presented in the CS to represent life-long stabilisation of symptoms in all patients, noting that there is only limited evidence from the 190-201/202 cohort that all patients

stabilise, and that a substantial number of patients continue to experience further disease progression for the duration of the trials. Examination of more objective markers of disease also cast doubt on this assumption; MRI and EEG outcomes suggested continued disease progression throughout the trials. The company also failed to address the potential loss of response associated with biological therapies due to immunogenicity, and the potential for treatment discontinuation due to ICV-related infection.

Further to the above, the CS failed to acknowledge the extra-neuronal components of the disease and the inability of ICV-administered cerliponase alfa to treat these pathologies, a factor which pre-clinical studies, regulatory, and clinical opinion suggested may lead to significant morbidity and mortality.

The economic evidence presented in the CS contained a number of substantial weaknesses which impacted significantly upon the size of the ICER. The base-case rested on a number of unrealistic or implausible assumptions regarding the long-term effectiveness of cerliponase alfa, the population modelled, the long-term mortality of patients receiving the drug, and questionable generation and use HRQoL values.

A key driver of the company base-case ICER was the assumption that cerliponase alfa treatment stabilised disease progression in all patients indefinitely, which returned them to general population mortality rates. The ERG did not believe these assumptions were supported by the provided clinical evidence. Instead, the ERG considered there to be significant risk that patients would experience disease-related morbidity and mortality, as there was insufficient evidence of symptomatic stabilisation. Further mortality risk may be introduced by extra-neuronal involvement and the significant burden of neuro-disability experienced by patients.

The ERG noted that the modelled population did not represent a realistic incident population based on current diagnostic practice, and required dramatic improvements to current service provision to realise the expected benefits. The ERG was also concerned that HRQoL values used in the model implied a number of benefits associated with cerliponase alfa treatment that were not supported by clinical evidence, including prevention of blindness, control of seizures and movement disorders, and feeding ability. They also implied treatment provided adult patients with a quality of life exceeding that of the general population; which the ERG deemed unrealistic given the company's expectation that treatment extends life by several decades.

The ERG's analyses took a more conservative approach to modelling treatment cost and clinical effectiveness. While the company model expects patients to receive benefits of stable disease over an extended period of time, the ERG base-case predicts progressive decline and a growing mortality risk over time. The ERG predicted a substantially diminished QALY gain associated with cerliponase alfa

treatment, resulting in [redacted] to the company's base case ICER; in the ERG's base-case, cerliponase alfa was not cost-effectiveness even when drug acquisition costs were excluded. The ERG also considered a more optimistic base-case scenario which made more optimistic assumptions regarding the long-term effectiveness of cerliponase alfa; excluded the impact no extra-neurological mortality, and retained the implied HRQoL benefits assumed in the company base. However, even in this scenario the estimated ICER for cerliponase alfa far exceeded willingness to pay thresholds for highly specialised technologies.

8.1 Implications for research

A central issue in evaluating the effectiveness and cost-effectiveness is the lack of long-term follow up data in patients treated with cerliponase alfa. The ongoing 190-202 trial, however, is due to continue to follow patients up for 240 weeks, which may help resolve some of this uncertainty. Further, observational assessment of the long-term prognosis of patients receiving cerliponase alfa would also help to resolve uncertainty regarding the life-expectancy of patients receiving cerliponase alfa and characterise the risks of extra-neurological disease progression. Future research into the effectiveness of screening and diagnostic programmes may also be warranted given the substantial benefits of early diagnosis.

9 References

1. Katz ML, Johnson GC, Leach SB, Williamson BG, Coates JR, Whiting REH, et al. Extraneuronal pathology in a canine model of CLN2 neuronal ceroid lipofuscinosis after intracerebroventricular gene therapy that delays neurological disease progression. Gene Ther 2017;24:215-23.

2. Kohlschütter A, Schulz A. CLN2 Disease (Classic Late Infantile Neuronal Ceroid Lipofuscinosis). Pediatr Endocrinol Rev 2016;13:Suppl 1: 682-8.

3. Katz ML, Coates JR, Sibigtroth CM, Taylor JD, Capentier M, Young WM, et al. Enzyme replacement therapy attenuates disease progression in a canine model of late-infantile neuronal ceroid lipofuscinosis (CLN2 disease). J Neurosci Res 2014;92:1591-8.

4. Anderson GW, Goebel HH, Simonati A. Human Pathology in NCL. Biochim Biophys Acta 2013;1832:1807-26.

5. Haltia M. The neuronal ceroid-lipofuscinoses. J Neuropathol Exp Neurol 2003;62:1-13.

6. Kida E, Golabek AA, Wisniewski KE. Cellular pathology and pathogenic aspects of neuronal ceroid lipofuscinosis. Adv Genet 2001;45:35-68.

7. Goebel HH, Zeman W, Pilz H. Significance of muscle biopsies in neuronal ceroid-lipofuscinoses. J Neurol Neurosurg Psychiatry 1975;38:985-93.

8. Mole SE, Williams RE. The Neuronal Ceroid Lipofuscinoses (Batten Disease). 2nd ed. Oxford: Oxford University Press; 2011.

9. Nickel M, Simonati A, Jacoby D, Lezius S, Kilian D, Van de Graaf B, et al. Natural history of late infantile CLN2 disease: quantitative assessment of disease characteristics and rate of progression in an international cohort of 140 patients. Manuscript on File 2016.

10. Moore SJ, Buckley DJ, MacMillan A, Marshall HD, Steele L, Ray PN, et al. The clinical and genetic epidemiology of neuronal ceroid lipofuscinosis in Newfoundland. Clin Genet 2008;74:213-22.

11. European Medicines Agency. Brineura (Cerliponase alfa): assessment report. Procedure No. EMEA/H/C/004065/0000. London: EMA; 2017.

12. Williams RE, Adams HR, Blohm M, Cohen-Pfeffer JL, de los Reyes E, Denecke J, et al. Management Strategies for CLN2 Disease. Pediatr Neurol 2017;69:102-12.

13. United States Food and Drug Administration Center for Drug Evaluation and Research. Brineura (Cerliponase alfa) injection: medical review. Silver Spring MD: Food and Drug Administration; 2017.

14. Fukumura S, Saito Y, Saito T, Komaki H, Nakagawa E, Sugai K, et al. Progressive conduction defects and cardiac death in late infantile neuronal ceroid lipofuscinosis. Dev Med Child Neurol 2011;54:663-6.

15. Gilbert-Barness E. Metabolic cardiomyopathy and conduction system defects in children. Ann Clin Lab Sci 2004;34:15-34.

16. Ostergaard JR, Rasmussen TB, Molgaard H. Cardiac involvement in juvenile neuronal ceroid lipofuscinosis [Batten disease]. Neurology 2011;76:1245-51.

17. BioMarin Pharmaceutical Inc. A multicenter, multinational, extension study to evaluate the long-term efficacy and safety of BMN 190 in patients with CLN2 disease. Interim Clinical Study Report: 190-202. Novato, CA: BioMarin Pharmaceutical Inc.; 2017.

18. Fietz M, AlSayed M, Burke D, Cohen-Pfeffer J, Cooper JD, Dvorakova L, et al. Diagnosis of neuronal ceroid lipofuscinosis type 2 (CLN2 disease): expert recommendations for early detection and laboratory diagnosis. Mol Genet Metab 2016;119:160-7.

19. Perez-Poyato MS, Marfa MP, Abizanda IF, Rodriguez-Revenga L, Sanchez VC, Gonzalez MJ, et al. Late infantile neuronal ceroid lipofuscinosis: mutations in the CLN2 gene and clinical course in Spanish patients. J Child Neurol 2013;28:470-8.

20. Ballinger R, Macey J, Llewellyn S, Patel C, Eliasson L, Peasgood T, et al. 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. Abingdon: ICON Patient Reported Outcomes; 2016.

21. Whiting REH, Narfström K, Yao G, Pearce JW, Coates JR, Castaner LJ, et al. Enzyme replacement therapy delays pupillary light reflex deficits in a canine model of late infantile neuronal ceroid lipofuscinosis. Exp Eye Res 2014;125:164-72.

22. United States Food and Drug Administration Center for Drug Evaluation and Research. Brineura (Cerliponase alfa) injection: printed labeling. Silver Spring MD: Food and Drug Administration; 2017. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2017/761052Orig1s000Lbl.pdf

23. Schulz A, Adams HR, Blohm M, Cohen-Pfeffer JL, de Los Reyes E, Denecke J, et al. Expert opinion on the management of CLN2 disease. Mol Genet Metab 2016;117:S103-S4.

24. Page MJ, Higgins JP, Clayton G, Sterne JA, Hrobjartsson A, Savovic J. Empirical evidence of study design biases in randomized trials: Systematic review of meta-epidemiological studies. PLoS One 2016;11:e0159267.

25. Button KS, Ioannidis JP, Mokrysz C, Nosek BA, Flint J, Robinson ES, et al. Power failure: why small sample size undermines the reliability of neuroscience. Nat Rev Neurosci 2013;14:365-76.

26. Schulz A, Ajayi T, Specchio N, De Los Reyes E, Gissen P, Ballon D, et al. Intraventricular cerliponase alfa attenuates neurologic decline in CLN2 disease. Manuscript on File.

27. BioMarin. Study 901 Clinical Study Report - Supplemental Report. Data on File 2016.

28. Steinfeld R, Heim P, von Gregory H, Meyer K, Ullrich K, Goebel HH, et al. Late infantile neuronal ceroid lipofuscinosis: Quantitative description of the clinical course in patients with CLN2 mutations. Am J Med Genet 2002;112:347-54. Available from: http://dx.doi.org/10.1002/ajmg.10660

29. BioMarin Pharmaceutical. A phase 1/2 open-label dose-escalation study to evaluate safety, tolerability, pharmacokinetics, and efficacy of intracerebroventricular BMN 190 in patients with late-infantile neuronal ceroid lipofuscinosis (CLN2) disease. ClinicalTrials.gov. Bethesda (MD): National Library of Medicine (US); 2013. Available from: https://clinicaltrials.gov/ct2/show/NCT01907087 [accessed 27th September 2017].

30. BioMarin Pharmaceutical Inc. Updated analysis of the natural history of CLN2 disease: estimated rate of decline from the DEM-CHILD multi-center clinical NCL. 190-901 Supplemental report. Novato, CA: BioMarin Pharmaceutical Inc.; 2017.

31. Beusterien KM, Davies J, Leach M, Meiklejohn D, Grinspan JL, O'Toole A, et al. Population preference values for treatment outcomes in chronic lymphocytic leukaemia: a cross-sectional utility study. Health Qual Life Outcomes 2010;8:50.

32. Kauf TL, Farkouh RA, Earnshaw SR, Watson ME, Maroudas P, Chambers MG. Economic efficiency of genetic screening to inform the use of abacavir sulfate in the treatment of HIV. Pharmacoeconomics 2010;28:1025-39.

33. Maniadakis N, Kourlaba G, Mougiakos T, Chatzimanolis I, Jonsson L. Economic evaluation of agomelatine relative to other antidepressants for treatment of major depressive disorders in Greece. BMC Health Serv Res 2013;13:173.

34. 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;30:3675-82.

35. Reference Cost Collection: National Schedule of Reference Costs - Year 2015-16 - NHS trust and NHS foundation trusts: Department of Health; 2016.

36. Costello Medical Consulting. BioMarin Europe Ltd. Delphi workshop report. UK treatment preactices for the management of CLN2 disease. Cambridge: Costello Medical Consulting Ltd.; 2016.

37. Curtis L, Burns A. Unit costs of health & social care 2016. Canterbury: Personal Social Services Research Unit; 2016.

38. MedicinesComplete. British National Formulary. Pharmaceutical Press; 2017. Available from: https://www.medicinescomplete.com/mc/bnf/64/ [accessed 27th September 2017].

39. eMIT National Database: NHS England; 2017.

40. EuroQol Research Foundation. NICE position statement on the EQ-5D-5L. Rotterdam: EuroQol Research Foundation; 2017. Available from: https://euroqol.org/nice-position-statement-on-the-eq-5d-5l/

41. National Institute for Health and Care Excellence (NICE). Guide to the methods of technology appraisal 2013. London: NICE; 2013.

42. Lotery A, Xu X, Zlatava G, Loftus J. Burden of illness, visual impairment and health resource utilisation of patients with neovascular age-related macular degeneration: results from the UK cohort of a five-country cross-sectional study. Br J Ophthalmol 2007;91:1303-7.

43. Gravelle H, Smith D. Discounting for health effects in cost benefit and cost effectiveness analysis. CHE Technical Paper Series 20. York: Centre for Health Economics, University of York; 2001.

44. Severens JL, Milne RJ. Discounting health outcomes in economic evaluation: the ongoing debate. Value Health 2004;7:397-401.

45. National Life Tables, United Kingdon, 1980-82 to 2014-16: Office for National Statistics; 2017.

46. Cameron CM, Purdie DM, Kliewer EV, McClure RJ. Ten-year outcomes following traumatic brain injury: A population-based cohort. Brain Inj 2008;22:437-49. Available from: <Go to ISI>://WOS:000256973600001

47. Fuller GW, Ransom J, Mandrekar J, Brown AW. Long-Term Survival Following Traumatic Brain Injury: A Population-Based Parametric Survival Analysis. Neuroepidemiology 2016;47:1-10. Available from: https://www.ncbi.nlm.nih.gov/pubmed/27165161

48. Cohen-Pfeffer JL, Gururangan S, Lester T, Lim DA, Shaywitz AJ, Westphal M, et al. Intracerebroventricular delivery as a safe, long-term route of drug administration. Pediatr Neurol 2017;67:23-35.

49. van Hout B, Janssen MF, Feng YS, Kohlmann T, Busschbach J, Golicki D, et al. Interim scoring for the EQ-5D-5L: mapping the EQ-5D-5L to EQ-5D-3L value sets. Value Health 2012;15:708-15.

50. Boström F, Jönsson L, Minthon L, Londos E. Patients With Dementia With Lewy Bodies Have More Impaired Quality of Life Than Patients With Alzheimer Disease. Alzheimer Disease & Associated Disorders 2007;21:150-4. Available from: http://journals.lww.com/alzheimerjournal/Fulltext/2007/04000/Patients_With_Dementia_With_Lewy_Bodies_Have_More.14.aspx

51. Orme M, Kerrigan J, Tyas D, Russell N, Nixon R. The effect of disease, functional status, and relapses on the utility of people with multiple sclerosis in the UK. Value Health 2007;10:54-60.

52. Peres J, Martins R, Alves JD, Valverde A. Rituximab in generalized myasthenia gravis: Clinical, quality of life and cost–utility analysis. Porto Biomedical Journal 2017;2:81-5. Available from: http://www.sciencedirect.com/science/article/pii/S2444866416301507

53. Costello Medical Consulting. BioMarin Europe Ltd. CLN2 disease utility study report. Cambridge: Costello Medical Consulting Ltd.; 2017.

54. BioMarin. Study 201/202 Integrated Subject Narratives. Data on File; 2017.

55. National Institue for Health and Care Excellence (NICE). Interim process and methods of the Highly Specialised Technologies programme. Updated to reflect 2017 changes. London: NICE; 2017. Available from: https://www.nice.org.uk/Media/Default/About/what-we-do/NICE-guidance/NICE-highly-specialised-technologies-guidance/HST-interim-methods-process-guide-may-17.pdf

56. Sohar I, Sleat DE, Jadot M, Lobel P. Biochemical characterization of a lysosomal protease deficient in classical late infantile neuronal ceroid lipofuscinosis (LINCL) and development of an enzyme-based assay for diagnosis and exclusion of LINCL in human specimens and animal models. J Neurochem 1999;73:700-11. Available from: <Go to ISI>://WOS:000081535200030

57. Hofman IL, van der Wal AC, Dingemans KP, Becker AE. Cardiac pathology in neuronal ceroid lipofuscinoses--a clinicopathologic correlation in three patients. Eur J Paediatr Neurol 2001;5 Suppl A:213-7. Available from: https://www.ncbi.nlm.nih.gov/pubmed/11589001

58. Wisneiwski KE, Kida E, Patxot OF, Connell F. Variability in the clinical and pathological findings in the neuronal ceroid lipofuscinoses: review of data and observations. Am J Med Genet 1992;42:525-32. Available from: https://www.ncbi.nlm.nih.gov/pubmed/1319116

59. Curtis L, Netten A. Unit costs of health & social care 2005. [serial online] 2005. [cited

60. Ara R, Brazier JE. Populating an economic model with health state utility values: moving toward better practice. Value Health 2010;13:509-18.

ADDENDUM
Evidence Review Group's Report
Cerliponase alfa for the treatment of neuronal ceroid lipofuscinosis type 2 (CLN2)

Additional results for ERG scenario analyses

1 Impact of additional clinical and economic analyses undertaken by the ERG.

This appendix presents additional results of the exploratory analyses conducted by the ERG (Section 6 of the main ERG report), specifically the number of incremental undiscounted QALYs for cerliponase alfa compared with standard care.

The sections of this addendum are as follows:

- Section 1.1 ERG exploratory analyses on the company base-case model;
- Section 1.2 ERG exploratory analyses on the preferred base-case model;
- Section 1.3 Subgroup analyses (asymptomatic and pre-symptomatic patients).

1.1 ERG exploratory analyses on the company base-case model

Addendum Table 1 presents the incremental undiscounted QALYs for cerliponase alfa compared with standard care for a number of analyses, including:

- The corrected company base-case;
- ERG exploratory analyses;
- The ERG base-case model (preferred scenario).

This table provides additional information to that included in Table 1 of the main ERG report.

Table 1 Results of the ERG exploratory analyses

#	Scenarios	Inc. undiscounted QALYs
-	***CS base-case[$] (corrected)***	**50.52**
1	Patient distribution in 190-901 trial	30.97
2	Patient distribution in 190-901 trial, restricted to CLN2 score of 2+	32.16
3	ERG re-estimated transition probabilities for cerliponase alfa	50.59
4	Disease stabilisation for early stabilisers on cerliponase alfa	40.33
5	No disease stabilisation for cerliponase alfa patients	15.01
6	Extra-neurological mortality	15.43
7	Neurodisability-related mortality	47.61
8	Development of blindness in cerliponase alfa patients	44.3
9	EQ-5D-5L data to model HRQL	54.99
10	PedsQL data to model HRQL	55.06
11	Age-adjusted utilities	46.3
12	Removed carer and sibling disutility after 30 years	52.57
13	Same utility values in each arm	45.86
14	Additional ECG cost	50.52
15	Psychiatric support	50.52
16	Residential care	51.78
17	Discounted cost and QALYs at 3.5%	50.52
18	**ERG preferred scenario (#1 +#5 + #6 + #7 + #8 + #11 + #12 + #13 + #14 + #15 + #16 + #17**	**4.19**

1.2 ERG exploratory analyses on the preferred base-case model

Addendum Table 2 presents the incremental undiscounted QALYs for cerliponase alfa compared with standard care for the scenario analyses undertaken within the ERG base-case model.

This table provides additional information to that included in Table 57 of the main ERG report.

Table 2 Scenario analyses on the ERG-preferred base-case analysis

Scenarios	Inc. undiscounted QALYs
ERG-preferred base-case	**4.19**
Scenario 1: Partial stabilisation on cerliponase alfa (early stabilisers only)	5.89
Scenario 2: No extra-neurological related mortality	5.93
Scenario 3: Different utility values in each arm (EQ-5D-3L)	5.91
Scenario 4: PedsQL for HRQoL	7.27
Scenario 5: Stopping rule – no discontinuation of cerliponase alfa	4.06
Scenario 6: Discounting at 1.5%	4.19
Scenario 7: Optimistic base-case analysis - partial stabilisation, no extra-neurological related mortality and HRQoL benefit for CA	**21.15**

1.3 Subgroup analyses (asymptomatic and pre-symptomatic patients)

Addendum Table 3**Error! Reference source not found.Error! Reference source not found.** presents the incremental undiscounted QALYs for cerliponase alfa compared with standard care for the subgroup analyses (asymptomatic and pre-symptomatic patients).

This table provides additional information to that included in Table 58 of the main ERG report.

Table 3 Subgroup analysis on the ERG's base-case analysis

Scenarios	**Inc. undiscounted QALYs**
ERG-corrected base-case: asymptomatic and pre-symptomatic subgroup	63.77
ERG-preferred base-case: asymptomatic and pre-symptomatic subgroup	10.64
ERG optimistic base-case analysis: asymptomatic and pre-symptomatic subgroup	39.72

National Institute for Health and Care Excellence

Centre for Health Technology Evaluation

Pro-forma Response

ERG report

Cerliponase alfa for treating neuronal ceroid lipofuscinosis type 2 [ID943]

You are asked to check the ERG report from Centre for Reviews and Dissemination and Centre for Health Economics – York to ensure there are no factual inaccuracies contained within it.

If you do identify any factual inaccuracies you must inform NICE by **5pm** on **Wednesday 20 December 2017** using the below proforma 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 Evaluation report.

The proforma document should act as a method of detailing any inaccuracies found and how and why they should be corrected.

Issue 1 Summary of key issues Identified with the ERG report

The company wishes to bring to the Evaluation Committee's attention its concerns about the tone and substantive content of the ERG report, as well as the ERG's apparent approach to assessing the evidence base for cerliponase alfa and the inaccuracy of a large number of clinical conclusions. In particular:

- The conclusions that the ERG has drawn on a number of topics (specifically, Motor-Language scale progression and decline, EEG and cardiac abnormalities, the importance of extra-neuronal pathology, lipofuscin storage) are at best misleading and, at worst, false. The clinical expert opinion conveyed in the ERG report runs contrary to the views of all the leading clinicians in this field that we know of. These conclusions are a false representation of the clinical evidence submitted, and do not correlate with the body of opinion of several clinicians expert in the management of the disease consulted by the company, their understanding of CLN2 or their experiences in real-life clinical practice.

ERG response: we disagree with this summary of the ERG report and respond in detail below to these claims.

- The ERG has based its conclusions partly on effect of gene therapy on pre-clinical animal models and on CLN3 disease. It has largely ignored or misrepresented the natural history of CLN2 disease in its assessment. Animal models treated with gene therapy, not cerliponase alfa, are not appropriate predictors of future outcomes in CLN2 disease in humans. Similarly, CLN3 is an entirely different disease to CLN2 (in terms of causality, pathology, clinical manifestation and disease progression) and as such cannot be used as an analogue.

ERG response: In evaluating the company's account of the natural history of CLN2 disease we identified important omissions regarding evidence on the non-neuronal aspects of CLN2 disease. For example, the CS did not discuss the accumulation of lipofuscin in other organs, nor did it discuss evidence from pre-clinical studies on the potential morbidity and mortality associated with cardiac, pancreatic, and hepatic impairment. Although we acknowledge limitations in extrapolating from CLN3 disease, data from this population are consistent with these other sources of evidence in CLN2 and taken together challenge the biological plausibility of the company claims regarding the natural history of CLN2.

- The tone of the report overall is particularly aggressive. The company is repeatedly, unfairly and falsely accused of being misleading, uncooperative and of having withheld relevant evidence from NICE. In addition, statements made in the Company Submission have been completely misrepresented by the ERG. For example, the company is criticised for claiming that treatment with cerliponase alfa could 'prevent vision loss' and 'halt seizures'. The company made no such claims. The company's responses to clarification questions have been largely ignored or totally misrepresented.

ERG response: we disagree that the tone of the report was particularly aggressive. We undertook a careful and independent evaluation of the company submission and identified a number of inconsistencies in reporting of primary endpoint data, and conclusions drawn that we judged did not adequately reflect the data.

Full details of the specific factual inaccuracies and incorrect statements are provided below.

Issue 2 Vision loss and the vision domain

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
The ERG report states "The company's main submission (CS) claims cerliponase alfa will permanently stabilise, or even improve all characteristic aspects of CLN2 disease, preventing the deterioration of motor, language, and visual function, and the frequency of seizures. Thus, treatment will eliminate disease-related mortality and allow treated patients to live long, fulfilling lives, achieving development milestones in line with unaffected children." This statement is not true. **On Pg 11 section 1. Summary**	Suggest to reword to state "The company's main submission (CS) claims cerliponase alfa will stabilise the main characteristic aspects of CLN2 disease by preventing the deterioration of motor, language, and slowing down progression of visual impairment, as well as reducing the frequency of seizures. Thus, treatment will reduce disease-related mortality and allow treated patients to live long, fulfilling lives, achieving development milestones".	It is not true to say that the company claimed that the cerliponase alfa would stabilise visual function or prevent vision loss. In fact, the contrary is true. In the company response to the ERG clarification question A10, the company clarified that cerliponase alfa would delay the rate of progression of visual impairment (as opposed to stabilisation of visual function). This was based on clinical trial results which showed that the decline in visual domain scores of cerliponase treated patients in the 201/202 study was significantly less than that observed in the 1:1 matched natural history cohort. The company highlighted that it does not know the physiological mechanism underlying the treatment effect observed, and that this could be as a result of impact on central components of the brain In addition, the company also provided a modelled scenario exploring the impact on the ICER of applying a utility decrement due to vision loss, as part of the response to clarification question B17. The results indicated that this assumption had a minimal impact on	Not a factual inaccuracy. Stabilisation of vision is claimed in several parts of the CS. For example, p21: 'By stabilising disease measured by the domains of motor and language function, as well as number of grad-mal seizures and vision, it is anticipated that patients treated with cerliponase alfa could remain in education for longer and/or require less educational support.' p115:' The addition of vision and seizure domains illustrates that the stabilisation of the clinical decline in CLN2 is broad-based and not a function of domain-specific therapeutic effect.'

		the ICER.	
"The company did not record or present adequate measures of visual function, considering the magnitude of their claims. The ERG report inaccurately states the company submission did not include adequate measures of visual function. **On Pg 12 section 1.2. Critique of decision problem**	Suggest this statement is deleted or at the minimal changed to, "Although the company presented vision domain scores from the CLN2 rating scale, the ERG would have preferred to see additional measures of visual function"	This statement is not correct. The company did record visual function measures showing the impact of cerliponase alfa on the visual domain scores as part of the total CLN2 (MLVS) scale in the company submission (Table C24 of the company submission) and as a separate score (response to the clarification question A10 and A11). The vision domain score of the total CLN2 scale (Hamburg scale) is a validated measure for measuring visual function in CLN2 patients. We are investigating whether some patients have additional retinal examinations as part of their standard of care, to support a more understanding of progression of visual impairment in CLN2 patients. As stated above, the company did not make the claims that have been attributed to it.	Not a factual inaccuracy. Although the vision domain score from the Hamburg scale was used as noted in p182 of the CS this does not adequately measure disease progression in vision: 'The seizure and vision domains were limited in their ability to measure symptoms, and did not provide meaningful measures of disease progression.'
The ERG report inaccurately states that cerliponase alfa administered via ICV cannot reach affected retinal cells **On Pg 11 & 12 section 1.1 Critique of company's description of underlying health**	Suggest this is amended to "… it is unclear if cerliponase alfa administered via intracerebroventricular (ICV) infusion would reach the affected retinal cells in sufficient therapeutic concentration…"	The EMA and US marketing authorisation does not state that the drug cannot reach the retinal cells, but rather questions if it reaches therapeutic concentrations at the eye. Also there is evidence (Katz et al) that cerliponase alfa administered via ICV can be detected in the blood stream in low concentrations (add levels seen) We are not clear why the vision domains of the CLN2 rating scale showed a treatment effect and needs to be investigated.	We've amended in errata to state "…cerliponase alfa administered via intracerebroventricular (ICV) infusion is unlikely to reach therapeutic concentrations due to the blood-retinal barrier".
The ERG report inaccurately states the that the company	Suggest this statement is deleted.	This is untrue as company did provide additional scenario in response to clarification	Not a factual inaccuracy. This modification was only provided in

failed to properly account for effects of vision loss in CA patients **On Pg 17 section 1.6. Summary of ERG critique of CE evidence (health related quality of life)**		question B17, exploring the impact of vision loss deterioration in cerliponase alfa patients. In this scenario a disutility factor due to deterioration in vision was included, from the age of 6 onwards. This factor increased up to 13% (health state utility values were thus multiplied by a factor of 0.87) by age 20 and remained at this level for the rest of the time horizon of the model.	response to ERG questions and was not included in the company's base-case. Further, the additional analysis provided by the company is presented when this is discussed in full.
The statement "The company presented disaggregated Hamburg/Weill Cornell vision domain data upon request, however, this was considered an inadequate assessment of visual function by clinicians" is inaccurate **On Pg 29 section 3.4**	Suggest this is amended to "In addition to the total Hamburg scale (which included vision domain) provided in the company submission, the company presented disaggregated Hamburg vision domain scores upon request"	First of all the Weill Cornell scale does not include or have a vision domain. Secondly the disaggregated vision domain (from the Hamburg scale) scores at 48 week or 96 week presented to the ERG at the clarification question stage wasn't presented to the EMA as (i) they had not been analysed separately (only as part of the Total Hamburg scale) (ii) 96 week data wasn't presented to EMA as it hadn't been analysed at the time of market authorisation application. EMA decision was based on the 72 week results. Given the above, it is inaccurate to say that the clinicians of the EMA considered it inadequate, as this is not stated anywhere in the EMA report.	Firstly, thank you for spotting the typo: we have removed reference to the Weill Cornell scale in errata. Secondly, the EPAR for cerliponase alfa states: 'although vision deterioration is a relevant component of the disease no specific examination (OCT, electro retinogram, visual evoked responses) was conducted.'(p59) None of the measures suggested by the EMA were included in study 190-201. In addition, as cited above the CS itself acknowledges the vision domain of the Hamburg scale is an inadequate measure of vision symptoms and disease progression: 'The seizure and vision domains were limited in their ability to measure symptoms, and did not provide meaningful measures of disease progression.'p182

Issue 3 Extra-neuronal pathology

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The ERG report states that during the pFC, the company dismissed the concerns of the ERG regarding the potential development of extra-neuronal pathology in CLN2 patients. This is untrue. **On Pg 11 section 1. Summary**	Suggest this is amended to "These concerns were raised with the company at the points for clarification stage (PfCs) by the ERG, but in their clarification response the company indicated that these were unlikely to happen based on clinical opinion they received.	This is inaccurate and misleading statement for two main reasons. The company discussed the concerns raised by the ERG with several clinical experts experienced in the treatment of CLN2 patients with and without cerliponase alfa. All of them indicated that extra-neuronal pathology had not been identified in any of their patients and it's not something they would expect to see in the near future. This was detailed in the response to the clarification question A11. Nevertheless the company modelled a conservative scenario looking at increased mortality risk (to account for the extra-neuronal pathology) and morbidity (decreased utility associated with blindness) for CLN2 patients as they grow older. As such, it is incorrect to state that the company dismissed the ERG's concerns.	Not a factual inaccuracy. We have however added additional text to clarify that clinical opinion considered by the company considered extra-neurological pathology unlikely. Note this change has been made on page 24 not page 11 as no reference to the company response was made on page 11.
The ERG report states the company submission fails to acknowledge the extra-neuronal components of CLN2 in the contextual discussion of disease mechanism or long-term impact of cerliponase alfa treatment. This is untrue. **On Pg 11 section 1.1 and on Pg 15 section 1.6. Summary of ERG critique of CE**	Suggest this is amended to "the company submission, does not account for the possible development of extra-neuronal pathology in CLN2 patients within the contextual discussion of disease mechanism or long-term impact of cerliponase alfa treatment.	This is untrue; the company did acknowledge the extra-neuronal components of CLN2 disease in the CS. In the response to the clarification questions (A10), the company acknowledged the potential for retinal damage leading to vision loss as an extra-neuronal pathology, and provided clarification (see response A12 & A13) that to-date there is practically no other evidence of other forms of extra-neuronal pathology (including cardiac dysfunction) in any of the phenotypes of CLN2 patient (beyond the sole	Not a factual inaccuracy. The CS did not discuss the accumulation of lipofuscin in other organs, nor did it discuss evidence from pre-clinical studies on the potential morbidity and mortality associated with cardiac, pancreatic, and hepatic impairment.

evidence (long-term effectiveness of cerliponase alfa)		article identified by the ERG). One clinical expert [redacted] with the largest cohort of atypical CLN2 patients who are living well into their 30's, has so far not seen any evidence of extra-neuronal pathology (involving heart, kidney and lungs) beyond visual loss. CLN3 disease is not a suitable analogue for CLN2 disease, nor can it be used to predict long-term outcomes in CLN2 disease. CLN3 is a very different disease to CLN2 disease in terms of causality, pathology, clinical presentation and progression of disease. We however also provided in response to clarification question B17, a modelled scenario exploring the impact of assuming increase in all-cause mortality due to involvement of extra-neuronal pathology, and disutility associated with continued vision loss. The results of this scenario indicated that these assumptions had a small impact on the ICER.	
The ERG report states that lipofuscin storage in tissues and organs outside the neurological system is pathological. This is untrue. **On Pg 11, 22, 74**	Suggest this is amended by removing pathological in the following sentences In pg 11 and 74 "the accumulation of lipofuscin in other organs is well documented in CLN2 disease, the consequences of which are unknown" In pg 22 "However, the ERG noted that lipofuscin storage is detectable in	Although lipofuscin storage has been identified in tissues and organs outside the neurological system in CLN2 patients, there is no evidence that this is pathological. Evidence from other lysosomal storage disorders indicate that the presence of stored materials in the lysosomes (owing the enzyme deficiency) does not necessary translate to cellular dysfunction. Some organs are more susceptible to stored materials than others. For example, Metachromatic leukodystrophy, Adrenal leukodystrophy, Sandhoff disease, Krabbe Disease are all inherently neurological conditions with limited evidence of extra-neuronal pathology despite the evidence of storage materials in various organs outside the nervous system.	Not a factual inaccuracy. The ERG simply pointed out that accumulation of ceroid lipofuscin is not confined to the 'neuronal, glial, and retinal cells'.

	many tissues outside the nervous system"	In addition evidence from atypical patients who have lived into their 30's have indicated extra-neuronal pathology is absent in these patients.	
The statement in the ERG report that difficulty swallowing, loss of bladder and bowel control experienced in CLN2 patients is due to extra-neuronal pathology is inaccurate **On Pg 61 section 5.2.1.**	Suggest this statement is deleted given it is untrue	The swallowing difficulties, loss of bladder and bowel control in CLN2 patients at the latest stages of disease are as a result of neuro-muscular disability due to neurological decline in the disease (Worgall et al 2007), and not an indication of extra-neuronal pathology as stated by the ERG. This view is also backed up by clinical experts experienced in researching CLN2 disease and treating the CLN2 patients We have included feeding in the Weill-Cornell scale which is a well-established part of loss of neurological control.	We have altered the text to may it clear that the ERG is being speculative as to the symptoms of of extra-neurological pathology.

Issue 4 Disease progression and evidence of decline

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The ERG report states that EEG and MRI outcomes provided evidence against conclusion that progression has not been halted. This is untrue. **On Pg 14 section 1.4 Summary of clinical effectiveness**	This statement should be removed	The development of new epileptiform activity in the treated CLN2 patients is not indicative of neuronal progression or worsening of seizures as asserted by the ERG. As per discussions with several clinical experts ([redacted]) this could be for a number of reasons 1. EEG findings are in no way correlated with the clinical picture. Clinical experts have reported been able to eliminate seizures or	Not a factual inaccuracy. The ERG in discussion with their clinical advisor considered the data and judged that new epileptiform activity potentially challenged the statement that progression of disease had been halted as suggested in the CS.

		significantly reduce their frequency and severity without seeing a correlated change in EEGs (i.e. still observing the development of epileptiform activity). This could be as a result of very difficulties in distinguishing from EEG readings what is a seizure, versus movement disorder or dystonia. 2. Given that CLN2 patients have epilepsy (with a life-long risk of seizures), development of abnormal epileptiform activity is to be expected, even when their seizures are well-managed by anti-epileptic drugs. 3. The development of epileptiform activity could also be as a result of detection (unmasking) of previously existing seizure types that are not obvious to patients who regularly experience generalised tonic-clonic seizures. In addition, children with CLN2 may have 100s of seizures (of different types; focal, atonic, absent etc) a day, which in the past were difficult to differentiate even in EEG outputs due to the very rapid deterioration of natural history patients 4. The EEG readings might be influenced by the time of the assessment and also a change in medication. Finally, it is also worth pointing out that the company did not claim that patients treated with cerliponase alfa will no	

		longer have seizures, but rather that cerliponase alfa will reduce the frequency of tonic-clonic seizures and the overall burden of seizures (as reflected by CLN2-QoL scores) on patient's quality of life. The base case modelled by the company includes the lifetime use of anti-epileptic drugs as a resource to reflect the ongoing risk of seizures, with no impact on outcomes. MRI showed significant slowing of brain loss, which could be attributed to debulking of lysosomal storage disorders as opposed to disease progression Finally as per the ERG report, the MRI data was shown to stabilise at Last observation (9 patients with data beyond 96 weeks). We appreciate the ERG's perspective that this is indicative of long-term stabilisation.	
The ERG report inaccurately asserts that "a substantial proportion of patients continue to experience further disease progression." **On Pg 15 section 1.6. Summary of ERG critique of CE evidence (long-term effectiveness of cerliponase alfa)**	This should be amended to read [redacted] ."	As shown in Table C21 of the company submission at Week 96, [redacted] in their ML score compared to 65% of patients at week 48 (15/23), which indicates that [redacted] between 48 and 96 weeks, this is certainly not a substantial proportion. After 96 weeks, [redacted], at their penultimate visit.	Not a factual inaccuracy. We have, however, edited the text to remove the value statement and add the figure of [redacted] to the sentence.
Decline in ML scores: The ERG report inaccurately states a number of patients also experienced	This should be either removed or amended to [redacted]	Examination of the individual patient plots contained in the 202-CSR (made available as part of CS) indicates that only [redacted] (of the 20 patients with	Not a factual inaccuracy. As stated in the ERG report [redacted]

declines post 96 weeks, and that the mean trend indicated further decline **On Pg 13 & 14 section 1.3. Summary**	[redacted]	data post 96 weeks) [redacted]at last observed follow-up compared to the Week 96 score. Although there were some fluctuation in scores between Week 96 and last observation period in [redacted], their actual score was the same, hence it cannot be said that these patients had a decline. [redacted] Given that [redacted] patients with available ML scores post 96 weeks were stable it cannot be said that the mean trend indicated further decline. It was pointing out that the mean (SD) score [redacted], [redacted].	[redacted]
CLN2 score at Week 96: The estimated rate of decline for week 96 is incorrect and the table wrongly references the CS. **On Pg 41 Table 6**	Estimated decline at week 96 should read as [redacted] and the data cut corrected to 1st Nov 2016. In addition the 2nd column and 3rd column (for last observed follow-up) should indicate these are based on the ERG own estimates	(i) The rate of decline at week 96 stated in the 5th column should be [redacted] i.e. the same as what was at the last follow-up (ii) The data cut on 3rd June 2016 was week 72 and not week 96 as reported here. (iii) It appears the CLN2 score quoted in the 2nd column has been subjectively misinterpreted from the graph by the ERG. This did not come directly from the table or graph referenced (iv) The 96 week data was included in the company submission as	i) Not a factual inaccuracy. As with other data on primary endpoints, mean rate of decline was reported inconsistently throughout the submission. Table C34 of the CS states mean decline was [redacted] and was reported to be at time of last data cut-off at June 2016. Since the last data cut-off was not as far as we are aware 72 weeks this appears inconsistent with your response. We note that p11 and p152 of the CS reports that mean decline of [redacted]) points per 48 weeks at Nov 2016. Since June 2016 was reported as 96 weeks in Table C34 of the CS for this analysis then logically Nov 2016 would be appear

		well as in the responses to the clarification questions (v) Results from any further data-cut would be made available as and when it becomes available.	to be post-96 weeks. But given the nature of the reporting this is difficult to tell. To complicate matters further the CSR p101 reports mean rate of decline at 96 weeks as [redacted] Taken together, we think we have summarised the data contained in the company submission as accurate as possible given the important inconsistencies and lack of clarity in reporting in the CS. Any uncertainties are largely due to deficiencies in reporting of primary endpoints in the CS. ii) Table C34 appears inconsistent with the company's response it is unclear why this is the case. iii) Since mean CLN2 scores for the primary analyses were not reported in the CS we used data from figure 11.4.1.2.3.1 and were presented in column 2 of table 6. Reference to this figure is made clear at the top of the table. The company response does not state how these data were misinterpreted so we cannot comment on this. iv) As above 96 week data is reported inconsistently across the submission and lack clarity we have sought to summarise it as best we can given these reporting limitations.
The ERG report states that: "Reported declines in CLN2 were observed [redacted]	This should be amended to "Reported unreversed declines	Compared to their 96 week scores, the CLN2 scores of these patients [redacted]	Not a factual inaccuracy. [redacted]

[redacted] Both of these statements are incorrect. **On Pg 14 section 1.4 Summary of clinical effectiveness and page 49, section 4.6.**	[redacted]	[redacted] The claim in the company submission is that patients would not see an unreversed decline in CLN2 score, the fluctuations seen in scores does not contradict this claim The fluctuations (improvement followed by a decline) between week 96 and [redacted] may reflect the impact of temporary illness, which could have a temporal impact on their ability to walk or talk at that point.	[redacted] However, it is clear from fluctuations in their data post-96 weeks even at this advanced stage of disease progression classifying them as experiencing disease stabilisation is not well supported by the data. [redacted] [redacted]
Slope analysis: The ERG report states that the "…slope analyses suggest on average patients receiving cerliponase alfa continue to experience further declines after week 96." This is an incorrect statement. It is not true that suggest that "on average" patients experienced further decline; [redacted]	This should be amended to "…slope analyses suggest on average patients receiving cerliponase alfa stabilise after week 96."	This is inaccurate as the slope analysis show that the scores at week 97 was [redacted] at last observed follow-up (Table C24 of company submission). The slight change of [redacted]. is insignificant and cannot be characterised [redacted]. In addition of the 20 patients who had CLN2 scores after 96 weeks, [redacted]. Given the limited data after this time point, it is not certain that [redacted]	Not a factual inaccuracy. The slope analysis suggests a mean decline in CLN2 score [redacted] at 96 week follow up. Therefore, applying this trend to data after 96 weeks we would expect on average patients to experience further declines after 96 weeks. This directly contradicts the company economic model, which assumes that patients will not experience any further declines after 96 weeks.

On Pg 48 Section 4.2.6.		[redacted]	

Issue 5 Comparisons between CLN2 and CLN3 disease

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
In several sections within the ERG report, the ERG inaccurately asserts that the presence of extra-neuronal pathology in CLN3 patients provides proof that it would occur in CLN2 patients as they get older **On Pg 12 section 1.2. Critique of decision problem** CLN3 is not a suitable analogue for CLN2 disease, nor a predictor of long-term outcomes in CLN2 disease. CLN3 disease differs from CLN2 disease in terms of causality, clinical manifestation, and progression of disease.	All references to CLN3 as a suitable analogue for CLN2 disease should be removed from the ERG report.	CLN3 disease and CLN2 disease, are very different from one another in how they present, the underlying mechanisms and disease aetiology. CLN3 disease is caused by mutations in a gene that codes for a transmembrane protein of unknown function, whereas CLN2 disease is caused by mutations in a different gene that codes for a soluble lysosomal enzyme tripeptidyl peptidase 1 (TPP-1). While we know something of the function of Tpp-1 in cleaving amino acids from proteins, the CLN3 protein is much more poorly understood. It remains unclear how mutations in these very different proteins result in the devastating effects of either disease upon affected individuals or their families. However, it is becoming apparent that how these diseases affect the brain and other organs are fundamentally different at a cellular level, and although some of the elements of the neurological pathology may be similar, the order in which they occur is different. A similar story is evident for their clinical presentation. Although visual loss is the initial presenting symptom in CLN3 patients, and seizures do not occur till much later in the disease. In contrast, seizures are the typically the first presenting symptoms in CLN2 disease, and visual loss tends to occur much later in disease progression. Seizures in CLN2 are often refractory and difficult to treat, compared to	Not a factual inaccuracy. The ERG acknowledges that this is a limitation of our analysis, but considers our approach reasonable given that both diseases are ultimately caused by accumulation of ceroid lipofuscin. The lack of any other evidence also requires that some assumptions be made.

		seizures in CLN3 patients. Also CLN3 patients tend to have behavioural problems characterized as psychoses, angry outbursts, physical violence, and anxiety with features of depression, whereas CLN2 patients do not have these symptoms (Schulz et al 2013 – Clinical perspectives). CLN2 and CLN3 have different types of movement disorder (such as parkinsonism in CLN3 patients vs dystonia in CLN2 patients) that localize to different systems in the brain (Mink 2014, Molecular Genetics and Metabolism 2014; 111 (2): S77). In summary although CLN2 and CLN3 diseases might superficially be confused with one another, marked differences in their clinical presentation and their age of onset, and the nature of cellular pathology are apparent. Given the radically different nature of the deficient proteins, the therapeutic solutions that are theoretically will also be quite distinct, with enzyme replacement (as typified by cerliponase alfa) only being applicable to CLN2 disease, with alternative strategies still in development for CLN3 disease.	
The leverage of CLN3 disease as a predictive model of outcomes for CLN2 patients is inaccurate **On Pg 125 & 126 Section 5.2.8.**	All references to CLN3 as a suitable analogue for CLN2 disease should be removed from the ERG report.	It is inaccurate to use CLN3 disease as a predictive model for future outcomes for CLN2 patients The cause of disease is different (trans-membrane protein vs enzyme deficiency) CLN3 patients have a completely different pathology to CLN2, with vision the initial presenting symptoms and severe behavioural problems (aggression etc) in CLN3 patients. The timing and order of signs and symptoms during the disease progression is unlike anything seen in CLN2. In CLN3 there is high burden of extra-neuronal pathology with a clear path to cardiac function deterioration but not in CLN2.	Not a factual inaccuracy. This issue has been addressed in the previous point.

Issue 6 Cardiac involvement in CLN2 disease

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The statement that cardiac involvement in CLN2 is widely regarded as a concern is inaccurate and a gross exaggeration and misleading. **On Pg 23 Section 2.1.2.**	Either delete or reword to state "the potential for cardiac involvement in CLN2 has been identified as a concern"	To date cardiac dysfunction has not been identified in any patient with a confirmed diagnosis of CLN2 disease. As mentioned in the responses to the clarification questions, cardiac dysfunction has not been identified even in patients with atypical presentation of CLN2 disease. This has been confirmed with the [redacted] clinician – [redacted], who manages the largest cohort of atypical CLN2 patients in the world The ERG inaccurately provided two papers as supportive evidence of cardiac involvement in CLN2 patients. The 1st paper, (Fukumura et al) is a sole case report in whom CLN2 cannot be confirmed as present (and if present may not be the only disease, clinical experts perceive this could be a CLN3 case wrongly diagnosed as CLN2 disease), as diagnosis was not based on either enzyme activity or identification of two pathological mutations on both alleles (only one mutation was identified), neither does the disease course match the disease course associated with typical or atypical CLN2 patients. In the second paper (a review by Gilbert-Barness), cardiac disease was not directly associated with CLN2 disease. Although the review identified hypertrophy and valve thickening in late infantile Batten patient, it is not clear if this was a CLN2 patient as late-infantile batten disease can also be caused by CLN5 disease. This needs further clarification.	Not a factual inaccuracy. The ERG cites several sources throughout the report which corroborate their position. The two papers that the company states are cited inaccurately are considered sufficient cause for concern by an extensive list of clinical experts, who in several papers cited these papers as evidence of cardiac involvement. The FDA and EMA have both raised this issue in their respective marketing authorisation documents.
The statement that cardiac hypertrophy and conduction	Either delete or reword to state "that cardiac	The 1st paper referenced to support this statement, (Fukumura et al) is a sole case report	Not a factual inaccuracy. The Gilbert-Barness paper states:

disorders have been identified in older CLN2 patients is untrue. **On Pg 24 Section 2.1.2.**	hypertrophy and conduction disorders have been reported in a patient with an unconfirmed diagnosis of CLN2 disease"	in whom CLN2 cannot be confirmed as present (and if present may not be the only disease), as diagnosis was not based on either enzyme activity or identification of two pathological mutations on both alleles (only one mutation was identified), neither does the disease course match the disease course associated with typical or atypical CLN2 patients. No were in the second paper (a review by Gilbert-Barness), is cardiac disease associated with CLN2 disease. Although the review identified hypertrophy and valve thickening in late infantile Batten patient, it is not clear if this was a CLN2 patient as late-infantile batten disease can also be caused by CLN5 disease. This view is supported by [redacted] clinical expert) who manages the largest cohort of atypical CLN2 patients.	'In the late infantile and juvenile forms [of neuronal ceroid lipofuscinosis], the heart is large and hypertrophied, and the valvular tissue is thickened' (p20).
The statement that "…ECG abnormalities in [redacted] of patients, and two cases of suspected left ventricular hypertrophy were observed in study 190-201/202, which is consistent with the potential for the cardiac problems identified in non-human studies.", is factually inaccurate. **On Pg 52 Section 4.6.**	This should be amended to "…although ECG abnormalities were identified in [redacted] of patients, and two cases of suspected left ventricular hypertrophy were observed in study 190-201/202, these were reported to be not clinically significant by the clinical investigators. It is uncertain if this could be attributed to the anti-epileptic drugs used (given conduction abnormalities are a known side-effect) or the potential for the cardiac problems as identified in	As reported in the response to the clarification questions and the CSR, none of the ECG abnormalities were clinically significant. No other abnormalities were observed in the heart hence it is inaccurate to say that they are consistent to cardiac problems such as impaired cardiac function and development of histopathological myocardial lesions observed in the animal studies involving gene therapy. ECG abnormality is a well-documented side effect associated with anti-epileptic drugs in children. In fact several articles have associated development of cardiac abnormalities with the mechanism of anti-epileptic drugs (Feldman & Gidal, Epilepsy & Behavior 26 (2013) 421–426; Shmuely et al. Seizure 44 (2017) 176–183). Also the company would like to clarify that the ECG abnormalities were not clinician-identified abnormalities, but rather machine reported	Not a factual inaccuracy.

	non-human studies"	abnormalities which upon review by the clinicians were identified as not-clinical abnormalities. The ECG abnormalities were temporary events which resolved spontaneously and not predictive of future cardiac morbidity. The temporal ECG abnormalities were recorded during infusions and were due to somnolence caused by pre-treatment of children with antihistamine given their lunch after which they fall asleep. During this time the ECG almost always record hypotension. This changes and resolves when the children wake up. Patients would continue to be followed as per the clinical trial protocol and SmPC recommendations.	

Issue 7 Animal models

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The statement that "canine models of CLN2 disease exhibited severe progressive cardiac and hepatic impairment when treatment with exogenous TPP1 enzyme was administered through the ICV route alone…" is misleading and inaccurate representation of the article being quoted **On Pg 24 Section 2.1.2**	This should be removed as the canine models were not treated with enzyme replacement therapy	This is a very misleading and inaccurate statement for several reasons: (i) Paper referenced by ERG report includes animals treated by ICV gene therapy and does not include animals treated by ICV ERT. (ii) Circulating enzyme levels following ICV gene therapy were not reported. In prior publication (Katz et al 2014), TPP1 enzyme was detected in heart and liver by immunostaining in dogs treated by ICV gene therapy. (iii) Circulating enzyme levels following ICV ERT have been reported in animals at approximately 1 ug/mL in plasma	Not a factual inaccuracy/ The section cited in the ERG report concerns disease background in older animals and not specifically response to ERT. We also disagree that this was a misrepresentation of the articles cited. For example, Katz et al 2017 states: 'disease-related pathology outside of the CNS becomes widespread when inhibiting the progression of neurological signs prolongs life span. In every affected treated dog there was a consistent progressive increase in blood cTn1 concentration and ALT activity level with increasing age, reflecting

		(Vuillemenot 2014, which was included in the company submission). (iv) Similar levels have been found in plasma PK studies from 190-201 in children treated with ICV ERT. The mean peak plasma concentration for Brineura in clinical studies [redacted]. This value is approximately [redacted] than the Kuptake for rhTPP1 found to be 183 ng/mL or 0.183 ug/mL. This means the concentration in plasma at peak concentration is approximately [redacted] than the concentration to achieve uptake into cells via the mannose-6-phosphate receptor. (v) The mean peak plasma concentrations for Brineura are similar to other ERTs for other lysosomal storage disorders. ○ Vimzim – [redacted] ○ Naglazyme – [redacted] ○ Brineura – [redacted] (vi) It is biologically plausible that cerliponase alfa delivered ICV could have some treatment effect outside the CNS. However, that hypothesis has not been tested in animals or clinically in children with CLN2. The circulating concentration of rhTPP1 following ICV administration is sufficient to reach cells in pancreatic, intestinal, cardiac, and hepatic tissues and potentially reduce accumulation of ceroid lipofuscin in those tissues.	increasing heart and liver pathology.'p219 And also: "Therefore, it seems likely that current efforts to treat the disease by exclusively targeting delivery of TPP1 to the CNS will not only fail to prevent disease-related blindness, but will also likely result in the appearance of clinically evident functional impairment of non-neuronal organs, particularly the heart, when life span is prolonged due to the delay in neurological sign progression."p220
The ERG report inaccurately states that the maximum gains in life expectancy demonstrated in the canine	This should be amended to "The animal studies showed evidence of significant cardiac	The statement that the maximum life expectancy of the dogs were 190% increase is wrong as several of the dogs were euthanized as precautions because they had infections that could be treated if occurring	We have altered the text to state that dogs were euthanised.

models treated with rhTPP1 was 190% **On Pg 75 Section 5.2.7.**	functional impairment in dogs aged 12 to 17 months of age and life expectancy of 190% of untreated dogs, however these dogs were euthanized as a result of treatable infections"	in humans. It is worth also pointing out that the dogs were administered human (as opposed to dog) TPP1 enzyme to which some of them had immune reactions. Given this it is wrong to asert the 190% improvements in mortality at the maximum life expectancy	

Issue 8 Omission of trial data and/or refusal to provide data

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
The ERG report states that the company submission omitted trial data and discussion of assessed immunogenicity, EEG outcomes, ECG outcomes. This is untrue. **On Pg 12 section 1.2. Critique of decision problem**	This statement should be deleted as it is false.	Trial data and discussions about the immunogenicity, EEG outcomes and ECG outcomes were provided in the CSR to the ERG as part of the company submission Discussion of ECG outcomes was made in the response to the clarification question A12. Furthermore additional patient level data was included in the reference pack accompanying the response to the clarification questions	Not a factual inaccuracy. These were not provided in the main company submission and were relevant to the decision problem.
The ERG report inaccurately states (1) "the company did not report appropriate measurements of several outcomes included in the final scope, and omitted relevant data collected in the clinical trials". (2) "The CS also omitted trial data and discussion of immunogenicity, electroencephalographic (EEG) epileptiform outcomes, and electrocardiographic (ECG) outcomes, which the ERG	This should be deleted as it is false	This is misleading and not true. As the company provided results for all outcomes (efficacy and safety) that were collected in the clinical trial and mentioned in the scope. In addition the CSR with relevant information including immunogenicity, EEG, ECG was provided as part of the company submission. In addition, patient level data on efficacy and safety (ECG, EEG, and other vital signs) was shared with the ERG during the clarification question stage. The statement wrongly portrays the company as being selective in data provided and uncooperative.	Not a factual inaccuracy. These responses have been replied to above. With regards to EEG, ECG and immunogenicity data these were provided in the CSR but they were not reported in the main company submission.

considered inappropriate given the potential significance of these outcomes to considerations of long-term clinical effectiveness and safety." **On Pg 29 Section 3.4.**			
The ERG report states that the company declined to provide longer term data beyond the 1st November 2016, requested at the clarification question This statement is untrue. **On Pg 44 Section 4.5.2**	This sentence should be removed from the ERG report.	In the response to clarification question A10, asking if data was available beyond 1st Nov 2016 data-cut, the company clarified that although study 202 was still ongoing, longer term data beyond 1st November 2016 was not available at that time. We will provide data from the latest data-cut to NICE as they become available.	Not a factual inaccuracy.

Issue 9 Disease-related mortality

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The ERG report states the company submission claims cerliponase alfa will eliminate all disease-related mortality. This is untrue; the company submission makes no such claim. **On Pg 11 section 1 Summary**	Modify the sentence in the ERG report to say that: "Treatment would eliminate disease-related mortality in patients initiated on treatment early in the disease stage"	The company claim of elimination of disease related mortality pertains only to patients initiated on treatment in the early stages of disease progression. As reflected in the transitions probabilities from health states, a proportion of patients who start treatment in the more progressed health states (i.e. Health state 6 which has ML score of 1), would transition to health state 7 and subsequently 8. Once in health state 8, they would then progress to health state 9, and then subsequently die from CLN2 disease. [redacted]	While substantively true their negligible numbers of disease related deaths in the company base-case model in patients treated with cerliponase alfa, the ERG have changed the text for clarity

		[redacted] This approach is in line with the natural history of disease which shows that death from CLN2 disease only occurs at the advanced stage of disease.	

Issue 10 [redacted])

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Information on the [redacted] programme should be commercial in confidence. **On Pg 11 section 1. Summary**	All references to the proposed [redacted] programme should be marked as Commercial In Confidence (CiC).	The company has marked this as CiC.	This has now been marked as CiC.
The ERG report states that the company submission claims implementation of a [redacted] programme. This is untrue. **On Pg 11 section 1. Summary**	Amend sentence to make it clear that the programme is still under discussion and has not (yet) been introduced. Moreover, if implemented, it would be programme to screen infants presenting [redacted]	This is incorrect. The [redacted] programme proposed by the company is not for [redacted] but rather those [redacted]. Although the programme is already in operation in the [redacted] etc. [redacted] and no claims were made in the CS about the success or otherwise of such a programme.	The assumed population in the economic model is substantially different from the trial and current practice and therefore assumes radical changes to diagnostic practices in England that were not well substantiated in the submission. However, the term [redacted] has been deleted in errata.

Issue 11 Mild-moderate disease

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The ERG report inaccurately states the clinical evidence presented in the CS was	Suggest this sentence is amended to "The clinical evidence presented in the	By the very nature of the disease, all patients with late infantile CLN2 disease have very severe disease irrespective of the extent of	Not a factual inaccuracy. Inclusion criteria for study 190-201, p82 in

derived from a narrower population of children aged >3 with mild-to moderate disease **On Pg 12 section 1.2 and pg 28, section 3.1** This is inaccurate – there is no such thing as mild-moderate CLN2 disease and the CS did not use such nomenclature.	company's submission (CS) was derived from a population of children aged >3 across all stages of disease progression and 'stable' seizures."	disease progression. There is no such thing as mild or moderate CLN2 disease. The patients were recruited at the early stage of the rapid progression stages of the disease. The CSR states mild to moderate progression as opposed to mild-moderate disease. This is better characterised as early rapid decline stages of disease progression. Worth also pointing out that at treatment baseline we had patients across all stages of disease progression as reflected by distribution of scores (1 – 6) presented in Table C21 of the CS. So the evidence base provided in the submission was for all stages of disease progression and not just the early or rapidly progressed stages	the CS: 'Mild to moderate disease documented by a two-domain score of 3- 6 on motor and language domains of the Hamburg Scale, with a score of at least 1 in each of these two domains'

Issue 12 MMRM methods

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The ERG report states the MMRM used in estimating the analyses is more sophisticated than the regression analysis. This is incorrect. **On Pg 12 section 1.3. Summary of clinical effectiveness (primary efficacy analysis**	Change to "Estimates from the natural history controls varied depending on the method used, MMRM (1.29 to 1.46 points) compared with methods used in the primary analyses (mean = 2.09).	The ERG's comment is not correct as the MMRM is based on significant assumptions, whereas the regression analysis was based on the actual observed data. Some of the assumptions made for the MMRM include: • Significant data imputation methods were used for the MMRM analyses – carry forward post-baseline and carry backward to baseline; • Modeling was performed to the first ML scale score of 0; • For the analysis from age 36 months	Not a factual inaccuracy. The MMRM analyses were more sophisticated than the regression analyses used in the primary analyses.

		onwards, many subjects had ML scale scores of 6 at age 36 months; and • For the analysis from age of diagnosis, a relatively high proportion of the follow-up is for the ML scale score transition from 1 to 0 (which has a relatively slower rate of decline than the transitions from 5 to 1. Basing the responder analysis on 2 point change (as shown by 1st and last point and simple regression methods) was the defined approach in the SAP. The FDA and EMA both agreed with this approach to statistical analysis.	

Issue 13 Loss of response - immunogenicity

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The ERG report indicated that the company failed to account for potential loss of response due to immunogenicity, despite generation of anti-drug antibodies in [redacted] of trial patients. This is untrue. **On Pg 14 section 1.4 Summary of clinical effectiveness**	This should be removed	The [redacted] quoted here is misleading as that refers to the proportion of patients with anti-drug antibodies in the serum as opposed to in the CSF (which is [redacted]). Given the drug's effect is on the brain and antibodies would not cross blood-brain barrier, the serum levels of antibodies are less relevant. Also although [redacted] patients out of 24) of patients had antibody levels detected in their CSF, [redacted] patients had their levels reduced to undetectable levels. In addition, in 190-201/202, a comparison of CSF and serum ADA negative and positive subjects showed no association between Anti-drug antibodies (ADA) titre levels and treatment outcome as measured by the ML scale. Subjects with CSF ADA titers showed a similar change from 300 mg Baseline to Last Available CLN2 scale score as did subjects with no CSF ADA titers. No association	Not a factual inaccuracy.

		was noted between mean serum ADA titer and change from 300 mg Baseline to Last Available ML scale score In assessing potential impact on response, only drug specific neutralizing antibodies could be potentially relevant, due to the possibility of binding to biological active sites of the enzyme. As reported in Page 192 (section 12.6) of the 202 clinical trial study report (made available to the ERG as part of the company submission), drug specific neutralising antibodies were not detected in any of the subjects It should also be worth noting that the presence of drug specific neutralising antibodies does not necessary indicate loss of response. Experiences from other ERTs have shown that no correlation exists between level of drug-specific neutralising antibodies and clinical response.	

Issue 14 1.5% discount rate

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The ERG report inaccurately states that there is an inappropriate application of 1.5% discount rate **On Pg 18 section 1.6. Summary of ERG critique of CE evidence (health related quality of life)**	This should be removed	This is not correct as the modelled results shows that treatment impact for CA would lead to greater than 30 life years gained. The patient in the early stage of disease (who would be the majority of the treated patients) would likely be restored to full health. We presented a modelled scenario using 3.5% discount rates in the company submission.	Not a factual inaccuracy. In the ERG's opinion a discount rate of 3.5% should be used. The ERG primary reason for this is that cerliponase does not restore patients to full health. This is a requirement for the 1.5% discount rate to be applied.

Issue 15 Discarding relevant domains

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The ERG report inaccurately states that the visual, myoclonus, seizures, and feeding domains were discarded, in the clinical trials undertaken by the company and included in their submission **On Pg 23 Section 2.1.2.**	The visual, myoclonus, seizures, and feeding domains were not included in the primary endpoint – the "CLN2 rating scale", used in the clinical trials conducted by the , and retained only the motor and language domains and is scored from 0 to 6,. The ERG noted that many of the clinical advisors to the EMA were concerned that this scale did not cover cognitive and developmental aspects of the disease, and that it was unable to capture developmental improvements [11]. Other clinicians criticised the omission of vision and seizure criteria, which prevented a more comprehensive description of the patients' clinical situation. However the company did collect vision, myoclonus and seizures as additional endpoints in the clinical trial programme and included this in their company submission"	This is not true as the Hamburg (containing vision and seizure domains) and Weill-Cornell scale (also containing myocolonus and feeding domains) were collected in the clinical trials, 190-201/202 and the outcomes recorded in the Clinical Study Reports. The positive impact of cerliponase alfa on myoclonus, vision and seizure domains were all included in the company submission and in responses to the clarification questions.	The section cited was summarising the 'CLN2 rating scale' (i.e. the primary endpoint). It is not a factual inaccuracy to state that only the language and motor domains were used in what the company submission termed the 'CLN2 rating scale'.

Issue 16 Incidence and Prevalence

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The statement "The CS identified a UK study which reported a prevalence of >0.31 per million population, with an incidence of 0.78 per 100,000 births – higher than the estimated global average. However, the company chose to use the global values to estimate an incident population of four to five children per year, and 30 – 40 children currently living with the disease in England and Wales." is misleading and inaccurately portrays the company as trying to down-play the incidence**.** **On Pg 24 Section 2.1.3.**	This should be amended to "The CS identified a UK study which reported a prevalence of >0.31 per million population, with an incidence of 0.78 per 100,000 births. However, the company chose to use the global values (given it was from more robust studies) to estimate an incident population of four to five children per year, and 30 – 40 children currently living with the disease in England and Wales. The ERG recognises that use of UK-specific rates does not change the estimated incidence or anticipated rate of cerliponase alfa uptake	The statement falsely implies that the company deliberately used the global incidence estimates instead of those derived from the UK study because it was lower. In the same document referenced by the ERG, the incidence in the UK is reported as 4.8 life year births per year, which is within the four to five new diagnosis predicted in the company submission. The company submission is in line with estimates from the BDFA and clinical experts.	Not a factual inaccuracy and we note in the next sentence that: 'The ERG recognises that use of UK-specific rates would not significantly change the anticipated rate of cerliponase alfa uptake.' We have however, changed for clarity.

Issue 17 Treatment addressing underlying cause

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The statement that "There are no currently available treatments which address the	Change to "Cerliponase alfa is the only treatment available that addresses	Cerliponase alfa treats and addresses the underlying cause of disease	Not a factual inaccuracy. The text cited in section 2.2 concerns current service provision and therefore does not comment

underlying cause of the disease, so a multidisciplinary approach is taken to manage the many medical, practical, and psychosocial needs of patients and families" is incomplete and inaccurate **On Pg 26 Section 2.2**	the underlying cause of the disease. . A multidisciplinary approach is recommended to manage the many medical, practical, and psychosocial needs of patients and families"		on cerliponase alfa as it has not yet been recommended by NICE.

Issue 18 Additional monitoring tests

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The statement that "The CS states that no additional tests or investigations would be required for monitoring patients. However, as stated in Section 2.1.2, the EMA approval document recommends close observation of cardiac health through frequent electrocardiogram (ECG) monitoring in patients with and without cardiac abnormalities" inaccurately implies that ECG monitoring would be an additional monitoring requirements only for cerliponase alfa treated patients **On Pg 27 Section 2.2.1.**	This should be deleted	As per the management guidelines, ECG monitoring is recommended to be undertaken in all CLN2 patients irrespective of if they are treated with cerliponase alfa or not. Hence it is inaccurate to classify this as an additional monitoring requirements.	Not a factual inaccuracy. See Issue 26.

Issue 19 Representativeness of study population

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The following statements are both inaccurate and misleading: (1) "**Baseline CLN2 scores reflect the trial inclusion criteria of mild-to-moderate disease**. However, since the decision problem includes all CLN2 patients, the trial population is unlikely to be **representative of all patients in England and Wales**." **On Pg 35 Section 4.2.1** (2) "Similarly, to be eligible for the trial, patients required a CLN2 score of between 3 and 6 points, **a narrower population than that specified in the decision problem**." **On Pg 37 Section 4.2.3**	Suggest this is amended to "**Baseline CLN2 scores reflect the trial inclusion criteria of patients across all stages of disease progression**.." **On Pg 35 section 4.2.1** **And the second bullet point is removed as shown below** ~~(2) "Similarly, to be eligible for the trial, patients required a CLN2 score of between 3 and 6 points, **a narrower population than that specified in the decision problem**~~."	As mentioned above in issue 5, none of the CLN2 patients included in the trial had mild-moderate disease, as disease is severe in all late infantile CLN2 patients. As stated in the company submission, although the study had an inclusion criterion of ML score ≥, at 300mg baseline, patient scores ranged from 1 – 6, which represents all stages of the disease. This is because a few patients ML scores declined between screening and baseline. Given the above it is inaccurate to say the baseline CLN2 scores reflect trial inclusion criteria of mild to moderate disease and my not be reflective of all England patients. The rationale for finding patients in the decline phase of the disease, where a treatment benefit could be more easily detectable using the CLN2 ratings scale.	Not a factual inaccuracy. The inclusion criteria for study 190-201 states patients were required to have: 'Mild to moderate disease documented by a two-domain score of 3- 6 on motor and language domains of the Hamburg Scale, with a score of at least 1 in each of these two domains'p82 of CS.

Issue 20 Clinical Trial design

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
ERG report claims that the primary efficacy analyses were subjective outcomes which **were open to interpretation.** This is untrue.	Suggest this sentence is amended to "although the primary efficacy analyses were subjective outcomes, the company submission indicates that attempts	The claims by the ERG that the primary efficacy analyses or the CLN2 rating scale (it was based on) were open to interpretation is baseless and contradicts the extensive evidence that was provided to them as part of the company	Not a factual inaccuracy Subjective outcomes are by definition open to interpretation. While it is understood the company made efforts to ensure consistency it remains the case that subjective outcome measures in the

On Pg 37 Section 4.2.3.	were made to ensure consistency of rating and interpretation, through training of raters, the use of a rating guide, and assessment of video recordings adjudicated by an independent assessor"	submission. Rather evidence was provided to the ERG in the response to the clarification questions, demonstrating (i) attempts of the company to ensure consistency in which the ratings were undertaken – by ensuring all raters were trained, followed a rating guide, and video-recordings adjudicated by an independent assessor to ensure consistency; (ii) extensive sensitivity analysis of the primary efficacy results consistently demonstrated the treatment effect versus an independent natural history registry	context of an open label single arm trial are at a high risk of bias.
The statement that "A lack of statistical power inherent in a trial of 23 patients negatively impacts on the likelihood that a nominally statistically significant result in comparison with natural history controls reflects a true effect. When an underpowered study discovers a true effect it is likely the estimate of the magnitude is exaggerated (sometimes referred to as the 'winners curse')." inaccurately implies that the study had no statistical power to detect a treatment effect **On Pg 37 Section 4.2.3**	This should be removed	As stated in study 190-201 CSR (section 9.7.8) and the statistical analytical plan,which were both included in the company submission, the study was powered to detect a treatment effect. As stated in section 9.6.1.6. of the company submission "A sample size of 22 was estimated to have 90% power to detect a reduction to a decline of 0.5 points per 48 weeks compared with a natural history decline of 2.0 points per 48 weeks with α=0.05." Given the above, it is grossly inaccurate to imply the study lacked statistical power to detect treatment effect.	Not a factual inaccuracy. There are a number of potential limitations regarding the power calculation which impact on potential precision including: 1) It doesn't appear to take into account multiple testing or what Gelman terms 'researcher degrees of freedom'. The power analysis appears to be conducted only based on the slope analysis however a great deal many more analyses were conducted than this which doesn't appear to be reflected in the power calculation 2) It uses the least conservative estimates of natural history decline which again over-estimates statistical power

Issue 21 Matching to natural history cohort

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The statement that "However, it is important to note that the use of subjective outcomes in the context of a single arm trial is associated with a high risk of bias" is an inaccurate and irrelevant assertion in the context of the evidence submitted by the company **On Pg 37 Section 4.2.3 and Page 47, Section 4.2.6**	Update to include that "however to minimise these bias, the manufacturer did undertake extensive 1:1 matching and 1: many matching analyses as part of their primary efficacy analysis and as additional sensitive analysis. The results of these analysis all demonstrated a treatment effect for cerliponase alfa compared to the natural history patients"	Within the context of the cerliponase alfa trial and rapidly progressive ultra-rare diseases, the statement that the single arm trial could be associated with a high risk of bias, is inaccurate, highly misleading and undermines the strength of the study. The primary efficacy analysis was based on a comparison against a matched natural history cohort, with each cerliponase treated patient matched 1:1 on ML score and age (and genotype in the sensitivity analysis) to an individual natural history patient. The company is shocked that the ERG makes no mention of the 1:1 matching that was undertaken as part of the primary efficacy analysis specifically undertaken to minimise any perceived bias. In addition all sensitivity analysis of 1:1 and many to 1 matching showed consistent positive findings as shared with the ERG during the clarification questions stage.	Not a factual inaccuracy. There is strong meta-epidemiological evidence that subjective outcomes in the context of a single arm open-label trial are at high risk of bias. Matching reduces the risk of confounding but is irrelevant to reducing the risk of detection bias.
Table 5 of the ERG report inaccurately states that (i) genotype was not identified as a matching factor by the company (ii) precise estimates of the results in terms of p values and confidence intervals were not included **On Pg 38 Table 5**	This should be changed to yes	The assertion that genotype was not identified as a matching factor is not correct as the company carried out 1:1 and 1:many matching analysis based on age, genotype and gender which was provided to the ERG in as part of the responses to the clarification questions (Question A2). All results from sensitivity analysis showed a consistent treatment effect to the primary efficacy analysis results Also there is no evidence to indicate that vision domain scores predicts future disease progression, it also occurs later in disease	Not factual inaccuracies. i) Genotype matching was not used on the primary endpoint analyses (only age and CLN2 score) therefore we think this judgement is justified. ii) We think you are misinterpreting the critical appraisal question. The question is not whether p-values or CIs have been reported it's asking whether they reflect a precise estimate of the treatment effect which is a different matter.

		progression and as such is not a relevant matching factor. Patients were recruited in the early rapid decline phase when the loss of motor and language are predominant drivers of disease morbidity. Finally precise estimates of the primary efficacy analyses and other outcomes were included in the company submission. For example, Tables C15-C19, C21-C23 of the company submission all report p values, SD, and confidence intervals for the change in CLn2 rating scale scores. In addition the hazard ratio estimates (Page 135) from the time to event analysis included 95% CI as well as p values.	

Issue 22 Transition probabilities

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The ERG report incorrectly states the transition probabilities in the first 16 weeks of the model, were based on the first 24 weeks of data **On Pg 70 Section 5.2.7.**	This should be corrected to make clear that transition probabilities were based on the first 16 weeks of data.	The transition rates were based on the first 16 weeks of data	Not a factual inaccuracy. Our interpretation of the provided calculations is that they were based on 24 weeks of data. We have edited the text though make it clear that this is our interpretation of the evidence.
The statement on the variation of transition probabilities for patients treated with cerliponase alfa across health states in the 0 to 16-weeks period is incorrect. On page 69: "It was not made clear, in the	BioMarin request that the statement be removed.	As stated by BioMarin within the company submission, and detailed further within the response to the ERG clarification questions, transition probabilities for patients treated with cerliponase alfa during 0 to 16 weeks were calculated from individual patient data from Study 190-201/202. It is therefore incorrect to refer to the variation in transition probabilities across health states as being "assumed".	Not a factual inaccuracy. The company approach makes the implied assumption that transitions depend on the health state a patient is in. No justification for this assumption was given in either the company's response to PfC or the company submission.

CS, why the transition probabilities were assumed to vary across health states in this period."			
The statement on the variation of transition probabilities for patients on standard care across health states is incorrect. On page 72: "As above, no justification was given for this assumption to vary transition probabilities by health state."	BioMarin request that the statement be removed.	BioMarin consider it incorrect to refer to patient data-derived transition probabilities as "assumed".	Not a factual inaccuracy.

Issue 23 Non-stabiliser

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The ERG report inaccurately states that the assumption that 5% of patients do not stabilise (after 96 weeks) is arbitrary and it is nonsensical to assume that they would experience standard care rates of progression, given the available evidence. **On Pg 71 and 72 Section 5.2.7.**	This should be amended to state that "…the assumption that 5% of patients do not stabilise (after 96 weeks) was [redacted] conservatively assumed that they would have standard care rates of disease progression"	As mentioned in the justification for amendment in issue X, [redacted] hence the assumption that 5% of patients may not stabilise is arbitrary. Also the comments that the assumption of standard care rates for patients not stabilised is nonsensical lacks any empirical basis and is misleading.	Given the lack of evidence on patients after 96 weeks, we do not believe that 5% is conservative and that it cannot be assumed that no additional patients experience a decline. We have, however, amended the language used in this statement to reflect this position.

Issue 24 Dystonia

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The statement that no evidence was provided for the implied improvement in control of dystonia is incorrect. The statement on the lack of evidence for an improved control of dystonia in patients treated with cerliponase alfa, as described in the health state vignettes, is incomplete. **On Pg 85 Section 5.2.8.**	BioMarin request that the statement be changed as follows: "Additional evidence on the myoclonus score of the Weill-Cornell scale was provided as evidence for the implied improvement in control of dystonia, In addition it was confirmed that the content of vignettes was validated by clinical experts, to ensure that health state descriptions were representative of clinical reality."	This is incorrect as the company did provide evidence of reduction in dystonia. In the response to clarification question B17, the company provided myoclonus domain scores (which scores myoclonus, dystonia, chorea and tremors), within the Weill-Cornell scale in cerliponase alfa treated patients and showed the decline was less than that would be expected in natural history patients. BioMarin consider it important in this context to mention the validation of health state descriptions through clinical expert opinion.	We have amended this section to address this issue including removing the statement that "No evidence was provided for the implied improvement in control of dystonia."

Issue 25 Age-adjusted utility

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The statement that the utility values applied in the less severe health states (health states 1 and 2) were very high and would imply utility values that exceed those of the adult general population is an inaccurate characterisation of the evidence supplied by the	Either delete or reword to state "the utility values applied in the less severe health states (health states 1 and 2) were viewed as very high by the ERG, and for the base case would imply utility values that exceed those of the adult general	In the response to the clarification question B10, the manufacturer did provide a scenario exploring the impact of decreasing the utilities of health state 1 as they grow older (i.e. age-adjusted values). The results (Table 12) showed this change had a very minimal impact on ICER ([redacted]).	Not a factual inaccuracy We acknowledge the additional analyses undertaken by the company in the appropriate section of the main report.

manufacturer **On Pg 23 Section 2.1.2.**	population. However the company did provide an additional scenario exploring the impact of age-adjusted utility values. The results indicated this assumption had a minimal impact on the ICER ”		

Issue 26 Additional monitoring costs

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The statement that there may be additional monitoring costs associated with treatment and these costs could have a high impact on cost effectiveness is inaccurate **On Pg 92 Section 5.2.8.**	This should be removed	All the monitoring categories mentioned in the ERG report are either tests that would be done even in patients not treated with cerliponase alfa (e.g. ECG tests) or represents minimal costs (e.g. pre-treatment with antihistamines with or without antipyretics prior to infusion, and tests of CSF samples which would be covered by the infusion costs). It should be noted that anti-histamines anti-pyretics all have minimal costs and costs of ECG (£128.59 HRG code: EY51Z, NHS Reference cost 2015-16) and biochemical tests of CSF are quite low and modest. In the UK there are two reference centres, one of the centres – Evelina Hospital leave the management of advanced patients to community hospitals. While the 2nd centre monitors these patients much more closely	Not a factual inaccuracy. This is the ERG’s interpretation of the cost-effectiveness evidence. While these items are associated with relatively low unit costs, there is some uncertainty surrounding the duration of time they would be applied for (depending on the predicted life expectancy) - under the company assumption of halted disease progression, the cumulative impact may not be as minimal as expected. The ERG’s statement reflects this uncertainty by noting that these costs “could” have a high impact on cost-effectiveness and the reason for this uncertainty has been stated elsewhere in the ERG report (Section 5.2.9.2, page 96). To our knowledge, ECGs are not routinely provided for patients not treated with cerliponase alfa, and the ERG cannot find any reference to the provision of ECGs in any of the cited papers on the management strategies for CLN2. They are recommended by the EMA which

			states “Based on available ECG measurements from therapeutic use of BMN 190, the need for routine ECG monitoring will be further pursued clinically”, which the ERG interprets as pertaining specifically to patients treated with cerliponase alfa.

Issue 27 Incorrect estimation of thresholds

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
In several modelled scenarios, the ERG uses a the number of the discounted incremental qalys (instead of undiscounted QALYS) to calculate the thresholds of the ICER **On Pg 92 Section 5.2.8.**	The thresholds should be re-estimated based on undiscounted incremental QALYs	The ICER thresholds used for the decision making is based on the undiscounted incremental QALYs as opposed to the discounted QALYs. All are provided in the health-economic model included as part of the company submission	Not a factual inaccuracy. The ERG based the estimation of all thresholds on the number of undiscounted QALYs and was unable to locate any inappropriately estimated thresholds. No changes have been made.

Issue 28 Modelled Mortality

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The way the ERG has modelled mortality is based on several inaccuracies and false assumptions **On Pg 132 Section 6.4.1.**	The modelled mortality should be repeated using assumptions from CLN2 disease and not CLN3 patients. For e.g. no CLN2 patients has developed cardiac abnormalities – the sole case with unconfirmed diagnosis	The assumptions of the ERG in their modelled assumption, that there is an increased risk of disease related mortality due to cardiac related conditions is inaccurate for several reasons: Heart abnormalities have not been identified in any CLN2 patient aged 14 while heart abnormalities were identified in all CLN3 patients aged 14 and older, thus further illustrating the	Not a factual inaccuracy. Please see previous comment on the comparisons between CLN2 and CLN3 disease.

	was at 23 years”	differences between CLN3 and CLN2 disease. As previously mentioned, the diagnosis of the patient reported in Fukumura et al, was not done properly. In addition, cardiac abnormalities only occurred at age 23. The cardiac abnormalities in this patient could have been addressed by a pacemaker and anti-arrhythmia drugs but the family of the patient declined because the patient had severe neurological disability. Had this patient not had significant neurological decline, it is plausible that patient’s life expectancy would have been significantly longer if they had a pacemaker.	
The statement on how mortality rates were applied across the different health states in the model is incorrect. On page 57: “Mortality of patients in health states 1 to 8 was based general population mortality adjusted for sex and age. Patients in these health states were assumed to have mean life-expectancy of 52 weeks with transitions to the death state estimated using an exponential function.”	BioMarin request that the statement be changed as follows: “Mortality of patients in health states 1 to 8 was based general population mortality adjusted for sex and age. Patients in health state 9 were expected to transition from health state 9 to the death state based on an exponential function with a mean of 52 weeks.”	BioMarin consider the amended statement to be reflective of the actual way mortality was applied within the economic model.	Thank you, we have amended in errata.

Issue 29 Formatting errors

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The below sentence appears to be incomplete. On page 33: "Critique of trials of the technology of interest, their analysis and interpretation (and any standard meta-analyses of these)"	BioMarin suggest that the sentence is completed, or alternatively removed.	N/A	Thank you, we have amended in errata.
The below sentence contains a formatting error. On page 59: "A graphical presentation of the Markov model is presented in Figure 2.**Error! Reference source not found.**"	BioMarin suggest that the referencing is amended.	N/A	Thank you, we have amended in errata.
The below sentence appears to be missing a word. On page 59: "Data were not available on the transition probabilities in the final health states (7, 8 and 9) as no progressed beyond health state 7 in Study 190-201/202."	BioMarin suggest that the sentence be amended as follows: "Data were not available on the transition probabilities in the final health states (7, 8 and 9) as no **patients** progressed beyond health state 7 in Study 190-201/202."	N/A	Thank you, we have amended in errata.
The below sentence appears to be inaccurate.	BioMarin suggest that the sentence be changed as follows:	The ERG appears to outline only five distinct areas following this sentence.	Thank you, we have amended in errata.

On page 117: "The main concerns relate to six key areas, which are outlined in brief below."	"The main concerns relate to **five** key areas, which are outlined in brief below."		

Issue 30 Incorrect statement around the quality assessment of included studies

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The statement on supposedly removed questions from the quality assessment tables is incorrect. On page 32: "However, the company eliminated a question on whether the length of follow up was appropriate, which is a key issue in the context of this submission."	BioMarin request that the statement in question be removed.	The statement incorrectly suggests that BioMarin actively set the questions for the quality assessment of included studies. This is not the case, since the tables for the quality assessment (and the therein contained questions) were taken directly from the most recent NICE HST submission template, without the removal (or addition) of any questions by BioMarin.	Thank you, the text has been amended in errata to state: 'However, the company should also have reflected on whether the length of follow up was appropriate, which is a key issue in the context of this submission and was also included as a question in the original CASP checklist.'

Issue 31 Inaccurate wording on the evidence for improved seizure control with cerliponase alfa

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The statement on the evidence provided for an improved seizure control in patient treated with cerliponase alfa is not entirely correct. On page 85:	BioMarin request that the wording of the statement is changed as follows: "The evidence provided by the company, to justify the implied seizure control~~,~~ were **significant**	BioMarin consider the amended statement to be in line with the actual content and wording within the relevant response to the ERG clarification questions.	Not a factual inaccuracy.

“The evidence provided by the company, to justify the implied seizure control and delay in needing a feeding tube, were changes in CLNQoL scores.”	changes in CLNQoL **seizure domain** scores.”		

Summary

The company's main submission (CS) claims cerliponase alfa will permanently stabilise, or even improve all characteristic aspects of CLN2 disease, preventing the deterioration of motor, language, and visual function, and the frequency of seizures. Thus, treatment will eliminate disease-related mortality in patients treated in the early stages of the disease and allow treated patients to live long, fulfilling lives, achieving development milestones in line with unaffected children. The ERG considers the company's interpretation unreasonably optimistic, which was often contradicted by available evidence and clinical opinion. The company assumed substantial changes to current service provision for the success of this treatment, including implementation of a [redacted]. These limitations are discussed below.

Critique of the company's description of the underlying health problem and the technology

The ERG noted two main concerns about the company's description of CLN2 and the biological plausibility of assumptions made about the likely benefits of cerliponase alfa.

Firstly, the CS fails to acknowledge the extra-neuronal components of CLN2, both in the contextual discussion of the disease mechanism and the anticipated impact of long-term treatment with cerliponase alfa. The ERG considers this evidence important to the appraisal. The ERG noted that expression of TPP1 is not limited to the CNS; the pathological accumulation of lipofuscin in other organs is well documented in CLN2 disease, and the consequences are seen in other forms of Batten disease. Pre-clinical studies indicated there may be serious implications for patient morbidity and mortality associated with cardiac, pancreatic, and hepatic impairment unless ERT is administered systemically.

The ERG has particular concerns regarding cardiac involvement, with severe cardiac and hepatic impairment seen in canine models of CLN2 treated with TPP1. Cardiac hypertrophy and conduction disorders are common in longer-lived CLN3 patients and were observed in [redacted] patients in the presented trial evidence; [redacted] of patients at baseline had ECG abnormalities [redacted] at last observation, many of these abnormities were prognostic of cardiac hypertrophy and conduction disorders. The ERG therefore reiterates the concerns of the European Medicines Agency (EMA), the US Food and Drug Administration (FDA), and clinicians regarding the failure of this treatment to address the likely consequences of extra-neuronal disease pathology, and highlights this as an important limitation of the technology.

Secondly, the ERG noted that cerliponase alfa administered via intracerebroventricular (ICV) infusion is unlikely to reach therapeutic concentrations due to the blood-retinal barrier.

cerliponase alfa arm and the standard care arm). Utility values based on the vignettes were elicited using eight clinical experts who were asked to complete an online version of the EQ-5D-5L as a proxy for patients who would be experiencing the description given in the vignettes. To account for the impact of CLN2 on disease on the family, the company applied a disutility for both caregivers (parents) and siblings. Disutility due to an adverse event was also included in the model. The company model included the following costs: drug acquisition and cost of administration for cerliponase alfa; health state costs, associated with monitoring and providing supportive care for patients and their families; and treatment costs relating to progressive symptoms associated with CLN2 disease.

The company found cerliponase alfa to be more costly (cost difference of [redacted]), but also more effective (gains of 30.42 QALYs) than standard care. The estimated deterministic ICER for cerliponase alfa compared with standard care was [redacted] per QALY. The results of the DSA indicate that the parameters with the largest influence on the ICER were the drug cost and the health state utility values for cerliponase alfa. The probabilistic ICER estimated by the company was [redacted] per QALY. The company undertook a range of scenario analyses. Two scenarios were considered by the company to present the likely range within which the ICER lies, as they combine the optimistic and pessimistic elements of the scenario analyses. These scenarios had an associated ICER of [redacted] and [redacted], respectively.

1.6 Summary of the ERG's critique of cost effectiveness evidence submitted

The ERG raised a number of concerns in its critique of the company's model, these issues concerned the long-term effectiveness of cerliponase alfa, the population modelled, assumptions made regarding the long-term mortality of patients receiving cerliponase alfa; and, problems with the way in which the HRQoL values used in the model were derived. Each of these issues is summarised in brief below.

Long-term effectiveness of Cerliponase alfa

A central assumption to the company base-case is that all patients receiving cerliponase alfa stabilise after 96 weeks and experience no further disease progression. The ERG considers this assumption to be subject to very considerable uncertainty, and has substantive concerns regarding the company's interpretation of the clinical evidence cited in justification of this assumption. Specifically, the ERG note that there is only limited evidence from the 201/202 cohort that all patients stabilise, and that a number of patients ([redacted]) continue to experience further disease progression in the later part of the 190-201/202 study (post 48 weeks). The ERG, also highlights evidence from animal models which suggests patients receiving cerliponase alfa will continue to experience disease progression.

worsen [13]. The ERG noted that cardiac hypertrophy and conduction disorders have been identified in older CLN2 patients [14, 15] and are common in CLN3 patients [16]. Furthermore, canine models of CLN2 disease exhibited severe progressive cardiac and hepatic impairment when treatment with exogenous TPP1 enzyme[1] was administered through the ICV route alone, indicating a potential need for systemic administration of TPP1. The European public assessment report (EPAR) for cerliponase alfa emphasised the importance of close monitoring of cardiac events, recommending ECG monitoring every 6 months, and during each ICV infusion in patients with present or past bradycardia, conduction disorders, or with structural heart disease – which included [redacted] of trial patients [17].

This concern regarding non-neuronal pathologies was also echoed by the ERG's clinical advisor, who believed it biologically plausible and likely that patients would experience extra-neurological morbidity and mortality, as untreated accumulation of ceroid lipofuscin may well lead to pancreatic, intestinal, cardiac, and hepatic pathologies and impairment. Furthermore, the EMA suggests that close monitoring should be performed at a minimum until there is sufficient clinical evidence on long-term extra-neuronal involvement [11]. These concerns were raised with the company at the points for clarification stage (PfCs) by the ERG, but in their clarification response the company indicated that these were unlikely to happen based on clinical opinion they received. The ERG, however, considers that in in the absence of clinical evidence, it is prudent to defer to pre-clinical evidence and clinical opinion when making predictions regarding long-term treatment efficacy and safety.

2.1.3 Prevalence of CLN2 disease

There is a distinct lack of data on the prevalence of CLN2 disease in the UK, but the CS referenced a number of sources of incidence and prevalence data, with global prevalence averaging ~0.75 per million population, and an incidence of 0.5 per 100,000 live births. The CS identified a UK study which reported a prevalence of >0.31 per million population, with an incidence of 0.78 per 100,000 births – higher than the estimated global average. However, the company chose to use the global values to estimate an incident population of four to five children per year, and 30 – 40 children currently living with the disease in England and Wales. The ERG recognises that use of UK-specific rates would not significantly change the anticipated rate of cerliponase alfa uptake.

2.1.4 Quality of Life

The company conducted a systematic literature review and review of patient organisation websites to identify information on patient, caregiver, and family quality of life in CLN2 disease. These searches did not identify any relevant studies, so an elicitation exercise was performed with 'eleven key opinion leaders', who provided information on management of CLN2 patients. The company also investigated the correlation of disease severity in terms of the Weil Cornell rating scale with HRQoL,

seizures). The HRQoL of patients and their families was assessed using the PedsQL Generic Core Scale and Family Impact Modules, and the 190-202 trial also recorded EQ-5D-5L. The primary measure of patient HRQoL was the 'CLN2 Disease-based QoL instrument', which was designed by the company based on focus group feedback. The company also presented MRI outcome data, which was further to that specified in the final scope. However, the company did not report appropriate measurements of several outcomes included in the final scope, and omitted relevant data collected in the clinical trials. Despite the importance of vision loss in CLN2 disease, and to the company's expected impact of the drug, there was no specific examination (e.g. optical coherence tomography (OCT), electroretinogram, visual evoked responses) of ophthalmological function. The company presented disaggregated Hamburg vision domain scores upon request, however, this was considered an inadequate assessment of visual function by clinicians [11], who suggested ophthalmological functional endpoints would have been a more plausible representation of vision loss, and recommend OCT as an assessment of retinal degeneration in CLN disease. [23] The CS also omitted trial data and discussion of immunogenicity, electroencephalographic (EEG) epileptiform outcomes, and electrocardiographic (ECG) outcomes, which the ERG considered inappropriate given the potential significance of these outcomes to considerations of long-term clinical effectiveness and safety.

3.5 Other relevant factors

The CS includes a section on considerations of equality, and states that the company has not identified any relevant issues regarding equity or equality to this submission.

Table 1 Inclusion criteria for systematic review included in the CS (adapted from Table C1 in CS)

Domain	**Inclusion/Exclusion criteria**
Population	Patients with any variant of CLN2 disease or TPP1 deficiency
Interventions	Any intervention
Comparator	Any or none
Outcomes	Any efficacy or safety outcomes Studies where outcomes were not reported separately for population of interest were excluded
Study design	RCTs, or Interventional non-RCTs (such as single-arm clinical trials, non-randomised comparative studies, observational studies, retrospective studies, case reports, case series, registries) Exclusion criteria were: economic evaluations; editorials, notes, commentaries or letters; narrative or non-systematic literature reviews

The inclusion criteria for the systematic review were broad, comprehensive and reflective of the decision problem.

4.1.3 Critique of data extraction

Study selection and data extraction methods were conducted and reported in an acceptable manner (see Appendix 3, section 17.2.7). Full text articles were independently assessed for eligibility by two reviewers with any disagreement resolved by a third reviewer. Data extraction was conducted by a single reviewer and checked by another reviewer.

4.1.4 Quality assessment

Quality assessments were conducted for all included studies using appropriate criteria (see CS Appendix 3, section 17.3). The critical appraisal questions were based on an adaptation of the CASP tool for cohort studies. The criteria were appropriate and included items on recruitment, measurement of exposure, measurement of outcome, identification and adjustment for important confounding factors, completeness of follow up and precision of results. However, the company should also have reflected on whether the length of follow up was appropriate, which is a key issue in the context of this submission and was also included as a question in the original CASP checklist.

It was not reported whether these were conducted by a single reviewer or checked by another reviewer.

4.1.5 Evidence synthesis

No formal evidence synthesis was conducted of included studies other than those conducted by BioMarin.

Tables C2-C4 of the CS reported the population, intervention, comparator and outcomes of included studies in the systematic review. Table C2 reported data for included studies identified in the original search, Table C3 reported similar data for unpublished trials identified in trial registries and Table C4 reported data for two further trials identified after the original search was conducted. A very limited narrative summary was also provided of the two trials summarised in Table C4. More detailed data abstraction from included studies was provided in Appendix 3, section 17.3 of the CS.

The justification for no formal evidence synthesis of non-BioMarin trials was that none of these included studies were relevant to the submission. It is unclear why the eligibility criteria of the company systematic review included studies not relevant to the submission. But the ERG considered this unlikely to impact on the validity of the conclusions of the systematic review.

The primary study included in the CS was of 23 patients who received cerliponase alfa over 48 weeks (study 190-201) and then followed up to approximately 96 weeks in an extension study (study 190-202). In addition, there was a study of natural history controls (study 190-901) used to compare the efficacy of cerliponase alfa against conventionally-treated patients.

4.2 Studies on the clinical efficacy and safety of cerliponase alfa

The primary study 190-201 evaluating the clinical efficacy and safety of cerliponase alfa was on 23 patients with CLN2 disease followed up over 48 weeks. Ten patients were enrolled during the dose escalation period (one patient dropped out after the first dose) and fourteen patients started during the stable dose period.

After 48 weeks, those who had completed study 190-201 were then enrolled in extension study 190-202, which is intended to follow patients for up to 240 weeks. Most data in the trial is reported for up to 96/97 weeks of follow up, although some slightly longer-term data is also available for some outcomes.

Two further studies 190-502 (an expanded access scheme for patients who couldn't participate in the trial) and 190-203 (where siblings of participants in 190-201 have an opportunity to enrol) were also

5.1.3 Studies included and excluded in the cost-effectiveness review

The electronic database searches identified 126 records. Of these, 104 records were excluded at the initial screening stage (22 records were duplicates). The remaining 12 records were assessed based on their full text. None of the 12 records met the inclusion criteria and they were not included in the systematic literature review. Supplementary searches of congress proceedings identified four publications, which related to three separate studies. One study presented utility data and the other two presented cost and resource use data. No relevant economic evaluations were identified.

5.1.4 Conclusions of the cost-effectiveness review

The company's search did not identify any relevant economic evaluation studies. A number of studies were identified, which related to utility data and cost and resource use data. These studies were discussed in their respective sections of the CS. It may have been useful, given the acknowledged small body of evidence surrounding this disease, to include other CLN disease populations, to help inform the model structure and model inputs.

5.2 ERG's summary and critique of company's submitted economic evaluation

An overall summary of the company's approach, and signposts to the relevant sections in the company's submission, are reported in Table 2.

Table 2: Summary of the company's economic evaluation (and signposts to the CS)

	Approach	Source / Justification	Signpost (location in the CS)
Model	A multi-state Markov model was developed. Cycle length was two weeks and a lifetime (95 years from the start of the model) was used.	The submission states that a multi-state Markov model is the most appropriate way of modelling a long-term chronic disease with dynamic disease progression The cycle length is in line with the fortnightly treatment administration of cerliponase alfa, and the frequency of concomitant patient examinations. In the model, patients start at an age of 4.8 and the ONS life tables provide mortality data up to the age of 100.	Section 12.1 Pages 178-190
States and events	The model consisted of 10 health states based on the CLN2 clinical rating scale. Health states 1-7 were defined by a score on the CLN2 clinical rating scale, ranging from a score of 6 (least severe) to a score of 0 (most severe). Health state 8 was defined as a score of 0 on the CLN2 clinical rating scale plus complete vision loss. Health state 9 was the same as health state 8 plus the additional requirement for palliative care. Health state 10 was death.	These health states were selected to capture the clinical reality of disease progression. The health states and their defining characteristics were validated by clinical experts.	Section 12.1 Pages 180-182
Comparators	The comparator used in the company's model was standard care which was described as established clinical management without cerliponase alfa.	No treatment is currently available for CLN2 disease, and this is in line with the NICE scope.	Section 12.1.3 Pages 179

	Approach	Source / Justification	Signpost (location in the CS)
Subgroups	An analysis of a subgroup of asymptomatic and pre-symptomatic siblings with confirmed CLN2 disease was undertaken.	In line with the scope	Section 12.6 Pages 276-278
Treatment effectiveness	Treatment effectiveness was estimated using the CLN2 clinical rating scale scores, a subset of an adapted version of the established four-domain Hamburg scale measure.[28] A number of additional symptoms, not captured by the CLN2 clinical rating scale, were also included in the company's model (vision loss and requirement for palliative care). At 16 weeks (cycle 8) patients receiving cerliponase alfa were classified as early or late stabilisers dependent on response to treatment between week 16 and week 96. Early stabilisers were assumed to experience no further progression of disease. Late stabilisers were assumed to experience further progression of disease up to 96 weeks (cycle 48). After 96 weeks it was assumed all patients receiving cerliponase alfa were stable and experienced no further disease progression.	Transition probabilities for patients receiving cerliponase alfa were based on the 190-201/202 study (pivotal clinical trial)[29] and expert clinical opinion. Transitions probabilities for patients receiving standard care were based on patient level data from the 190-901 study (natural history study)[30] and expert opinion.	Section 12.2 Pages 179-205
Mortality	Mortality of patients in health states 1 to 8 was based general population mortality adjusted for sex and age. Patients in health state 9 were expected to transition from health state 9 to the death state based on an exponential function with a mean of 52 weeks.	ONS mortality statistics and expert opinion.	Section 12.1.3.1 page 179 Section 12.1.7 page 197
Adverse events	Treatment-related adverse events were included in the company's model. These included pyrexia, hypersensitivity, headache and vomiting. An infection rate of 0.45% for each performed ICV infusion was also included. No treatment-related adverse events were applied to the standard care cohort.	Adverse event rates were taken from Study 190-201/202[29] for cerliponase alfa.	Section 12.2 Page 206
Health-related quality of life	Utility values were derived from a utility study in which vignettes describing the health states for both cerliponase alfa and standard care were developed. The vignettes were validated by a clinical expert, and sent to 8 clinical experts who completed the EQ-5D-5L questionnaire as a proxy for patients experiencing the health states. These were mapped to the EQ-5D-3L before being applied in the model. Adverse event disutility, caregiver disutility and sibling disutility were also incorporated into the company's model.	The utility data collected in the clinical studies (190-201/202)[29] were not used due to the fact that utility values were not available for all health states and no utility values were available for standard care. Adverse event disutility estimates were derived from published studies.[31-34] The midpoint values for caregiver and sibling disutility were derived from a published study.[20] The company assumed a linear progression of this value across the health states.	Section 12.2 Pages 206-210 Section 12.1.7 Pages 192-197

	Approach	Source / Justification	Signpost (location in the CS)
Resource utilisation and costs	Resource use and costs included: cerliponase alfa drug acquisition and administration costs; ICV implantation and replacement costs; health-state costs (routine care costs); drug acquisition and procedure costs associated with the relief of progressive symptoms; and, seizure costs. A NHS and Personal Social Services perspective was taken when identifying the relevant costs.	Drug acquisition costs were based upon the list price of cerliponase alfa, source BioMarin Europe Ltd. Administration and ICV implantation and replacement costs were based on NHS Reference costs 2015-2016.[35] Health state costs were estimated using the company's Delphi panel[36], NHS reference costs 2015-2016[35] and PSSRU 2016[37]. Progressive symptom costs and seizure costs were estimated using the BNF 2017[38], eMIT 2017[39] and NHS reference costs 2015-2016[35]. Costs and resource use data were identified through a SLR. Expert clinical opinion informed the assumptions used for inputs where cost information was unavailable.	Section 12.3 Pages 212-239
Discount rates	The costs and benefits were discounted at 1.5% per annum.	The submission states that the beneficial impact of the treatment was expected to be substantial and sustained over a very long period. Therefore, a discount rate of 1.5% was considered reasonable within the context of the NICE Guide to the methods of technology appraisal 2013.[40] [41]	Section 12.1.3 Page 179
Sensitivity analysis	Probabilistic sensitivity analysis was performed. Deterministic analysis was performed on a series of model parameters. A series of scenario analyses was also performed.	In accordance with the NICE reference case.	Section 12.4 Pages 239-275

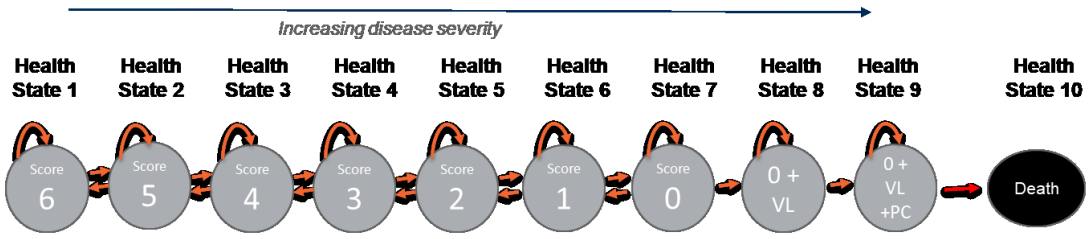
ONS, Office for National Statistics; CLN2, Neuronal Ceroid Lipofuscinosis Type 2; ICV, intracerebroventicular infusion; EQ-5D-5L, European Quality of life, 5 domain instrument of health outcomes, 5 level; PSSRU, Personal Social Services Research Unit; BNF, British National Formulary; eMIT, electrical market information tool; SPC, Summary of Product Characteristics; SLR, systematic literature review.

Model structure

The company submission is based on a multi-state Markov model comparing cerliponase alfa with standard care. The model used a cycle length of 2 weeks and a time horizon of 95 years. The company chose the cycle length as it was in line with the fortnightly treatment administration of cerliponase alfa, and the frequency of concomitant patient examinations. The time horizon was justified on the basis that general population mortality data are only available up to the age of 100. The model structure adopted consists of ten mutually exclusive health states, which characterise the progression of CLN2 patients over the course of the model's time horizon. The ten health states included in the model were defined by the CLN2 clinical rating scale, which is a subset of an adapted version of the four-domain Hamburg scale measure.[28] The adapted version consists of the motor and language

both domains; this is the least severe health state, and defined health state 1 in the model. Patients with scores from 5 to 0, defined health states 2 to 7, respectively. A score of 0, which is the most severe score, defined health state 7. Health state 8 was defined as a score of 0 on the CLN2 clinical rating scale plus complete vision loss (i.e. complete blindness). Health state 9 was the same as health state 8 plus the additional requirement for palliative care. Health state 10 was death. A graphical presentation of the Markov model is presented in **Figure 1**.

Figure 1: Model Structure (CS, Figure D20, p.181)



All scores are in the CLN2 clinical rating scale score
Patients considered to be "educationally" blind at a score of 0
VL, vision loss
PC, palliative care

To account for the symptom load not captured by the CLN2 clinical rating scale, it was assumed that each health state was associated with additional symptoms including epilepsy, disease-related distress, dystonia, myoclonus, vision loss and the requirement of a feeding tube. These were selected based on Williams et al. 2017[12] and validated in the Delphi panel study.[36] These additional elements were labelled as progressive symptoms in the CS and were associated with additional drug and therapy costs. The HRQoL impact of these symptoms was also captured in the health-state utilities, see Section 5.2.8 for details. Movement through the model was determined by transition probabilities. Probabilities for the transitions between the first seven health states (health state 1 [CLN2 clinical rating scale score of 6] to health state 7 [CLN2 clinical rating scale score of 0]) were based on patient-level data from Study 190-201/202 for the cerliponase alfa arm, and the one-to-one matched patients from the natural history control Study 190-901 for the standard care arm. Data were not available on the transition probabilities in the final health states (7, 8 and 9) as no patients progressed beyond health state 7 in Study 190-201/202. The transition probabilities for health states 7 to 9 were, therefore, based on expert opinion. See section **Error! Reference source not found.** for further details.

Within the model, patients receiving cerliponase alfa were assumed either to be early stabilisers or late stabilisers. These groups were based on patients receiving cerliponase alfa treatment for more than 16 weeks in the trial. Early stabilisers were defined as patients who did not experience any further decline in CLN2 clinical rating scale score after 16 weeks. Late stabilisers were defined as

patients who continued to progress at a rate of 1 point on the CLN2 clinical rating scale per 80 weeks, until week 96. After 96 weeks, all patients receiving cerliponase alfa were assumed to be stabilised

standard care arm, as vision loss is linked to disease progression, but it is more problematic for patients receiving cerliponase alfa. As described in Section 2, progressive vision loss in CLN2 patients is due to both retinal changes and central changes in the brain. This means that while cerliponase alfa may impact on the rate of vision loss it cannot prevent complete vision loss. The implications of this are that for patients receiving cerliponase alfa, vision loss will not correlate with deterioration in motor and language scores. The model structure, therefore, does not account for the progressive vision loss that will be experienced by patients receiving cerliponase alfa.

At the PfCs the ERG requested that the company develop a scenario analysis to account for the progressive loss of vision that would occur in cerliponase alfa patients. In response, the company presented a scenario analysis in which it was assumed that vision loss occurred from the age 6 and impacted on HRQoL. The disutility associated with vision loss was applied in the form of a progressively decreasing multiplier which was applied to the health state utility values. The multiplier was assumed to decrease by 0.01 points per year up to a value of 0.87 at the age of 20 years. The value of 0.87 was based on the quality of life associated with neovascular macular degeneration in the UK.[42] While the ERG considers that this scenario analysis is a more realistic reflection of the impact of vision loss on cerliponase alfa patients, the rate of decline was modelled to be too slow. As described in Section 2, degeneration of the retina in patients receiving cerliponase alfa will continue at the same rate [21] as untreated patients. Complete vision loss in patients receiving cerliponase alfa will therefore occur at approximately the same time as in patients on standard care; this is normally before the age of eight and not the age of 20 as implied by the company's scenario. The ERG, therefore, presents an alternative scenario, incorporating the effects of vision loss in patients receiving cerliponase alfa, in Section 6.

Extra-neurological progression: As described in Section 2, the ERG is concerned that there is a significant risk that patients receiving cerliponase alfa will continue to experience extra-neurological symptoms of CLN2. The most significant impact of these extra-neurological symptoms is likely to be on the mortality of patients receiving cerliponase alfa. However, these symptoms would also impact on quality of life (QoL). For example, it has been shown that extra-neurological lipofuscin storage occurs rapidly in the smooth muscle that makes up the gullet, bladder and bowels.[1-7] Symptoms of extra-neurological pathology may therefore include loss of smooth muscle control which would lead to difficulties with swallowing, and loss of bladder and bowel control, all of which would have a significant impact on QoL. The model structure is, however, not able to accommodate these additional symptoms and no account for them is made in either the company's base-case analysis, or in any scenario analyses presented by the company. Including the impact of these symptoms is, however, very difficult due to the lack of long-term data on the effects of cerliponase alfa and the uncertainty

around the symptoms that patients would experience. The ERG, therefore, does not explore the impact of extra-neurological pathology on

Weeks 17 to 96: Unlike the period of weeks 0 to 16, the transition probabilities in the period of weeks 17 to 96 were not assumed to vary according to the health state a patient is in. Instead, the transition probabilities were dependent upon whether a patient is an early responder or a late responder. As described in Section 0, response was defined retrospectively, rather than prospectively, and refers to patient's response during the period from 17 to 96 weeks. Early responders were defined as patients who experienced no reduction in motor or language function (CNL2 clinical rating scale) after the first 16 weeks of treatment, and late responders were patients who did experience a reduction in function. The proportion of early responders, assumed in the company's base-case analysis, was estimated to be [redacted] of patients, based on the results of the 190-201/202 study.[29]

As early responders were defined by their lack of a drop in CLN2 clinical rating scale score during the period of weeks 17 to 96, early responders were assumed to be stabilised and experience no further progression of disease. In contrast, late responders to treatment were assumed to experience some deterioration in function over the period of weeks 17 to 96. During this period, late responders were assumed to experience an average drop in CLN2 clinical rating scale score of 1 point, with transition probabilities generated by assuming a constant rate of transition during this period. This assumption was based on the observed progression of late stabilisers in the 190-201/202 trial. The transition probabilities for early and late responders for the period from 17 to 96 weeks are described in **Table 3**.

Table 3: Transition probabilities for patients receiving cerliponase alfa, weeks 0 to 16 (CS, Tables D12 and D13, p 203)

		Transition probability	
		Early responders	**Late responders**
Health states 1 and 2	Improve	0	0.00
	Maintain	1	0.975
	Decline	0	0.025

Week 97 onwards: After week 96, all patients receiving cerliponase alfa were assumed to be stabilised and experienced no further progression of disease.

ERG Comment

The ERG's concerns relating to the transition probabilities are two fold, and relate to technical issues; relating to how the transition probabilities are calculated and the assumption that all patients receiving cerliponase alfa are stabilised after 96 weeks.

Technical issue: The ERG noted a discrepancy in the calculation of the transition probabilities: the transition probabilities used for cerliponase alfa patients, in the first 16 weeks of the model, which appear based on the data provided to be based on the first 24 weeks of data. It is unclear why this approach was taken by the company, but implies a clear inconsistency with the clinical data. The

impact of this inconsistency is difficult to assess, but is potentially significant, as while these transition probabilities are only applied for a short period of time, the assumption of stability after this period, for many patients, means that they are an important determinant of the total costs and QALYs.

Assumption of stability: The assumption that all patients stabilise after 96 weeks is the single most important assumption in the economic model and a significant driver of both incremental QALYs and the ICER. As described in Sections 4, there is no long-term evidence on the effectiveness of cerliponase alfa and, therefore, the company have drawn upon clinical expertise, evidence from other disease areas in which ERT is used (e.g., Gaucher's disease) and the short-term evidence provided by the 190-201/202 trial, to justify this assumption. As stated in Section 4, the ERG has substantive concerns regarding the company's interpretation of the clinical evidence. Specifically, the ERG notes that there is only limited evidence from the 190-201/202 cohort that all patients stabilise, and that a [redacted]continue to experience further disease progression in the later part of the 190-201/202 study (post 48 weeks). Furthermore, while a proportion of patients do appear to achieve short-term stabilisation of disease, the ERG notes this number continues to fall as follow up lengthens. Furthermore, in direct contradiction to the modelled assumption of stability for of all patients post 96 weeks, examination of the IPD data reported in the 190-202 interim CSR shows [redacted].

Examination of more objective markers of disease also cast doubt on this assumption; EEG examinations during study 201/202 found new (focal and/or generalised) epileptiform activity in [redacted] of patients, which the ERG's clinical advisor suggested may be an indicator that disease progression had not been halted. Moreover, MRI measurements showed substantial reductions in whole brain volume, cortical grey matter, and white matter. The ERG, also highlights evidence from non-human studies, which showed that treatment only slowed progression of symptoms, with only modest reductions in short-term mortality. The ERG, therefore, considers the assumption of long-term stabilisation to be highly uncertain and likely to be overly optimistic, given the current limited evidence.

These significant concerns regarding the assumption of long-term stability were raised with company at the PfC stage and as part of this, the ERG requested that the company present a scenario making more conservative assumptions with respect to the long-term effectiveness of cerliponase alfa. The company's response to this question provided a scenario in which it was assumed that 5% of patients

do not stabilise after 96 weeks and instead experience standard care progression. It also assumed elevated mortality for patients over the age of 20 years and applied a disutility to account for progressive vision loss. The ERG, does not consider this new scenario to be a useful exploration of the available clinical evidence; the assumption that 5% of patients do not stabilise is arbitrary and it is

nonsensical to assume that they would experience standard care rates of progression, given the available evidence. Given the remaining uncertainty regarding the long-term effectiveness of cerliponase alfa, additional analyses, which consider more plausible extrapolations of the available effectiveness evidence, are presented in Section 6.

5.2.7.2 Treatment effectiveness: standard care

Patients not receiving cerliponase alfa were assumed to experience disease progression, based primarily on data from a natural history cohort matched to the 190-201/202 trial patients.[30] Transition probabilities, generated from the natural history data, were assumed to experience different risks of progression dependent upon the health state. Mirroring the transition probabilities applied to patients receiving cerliponase alfa, the transition probabilities for patients were calculated for three groups of CLN2 clinical rating scale scores; scores 6 and 5 [health states 1 and 2], scores of 4 to 2 [health states 3 to 5], and scores of 1 and 0 [health states 6 and 7]. As above, no justification was given for this assumption to vary transition probabilities by health state. Unlike patients receiving cerliponase alfa, the same transition probabilities were applied across all periods of the model. The transition probabilities, for patients not receiving cerliponase alfa, are presented in **Table 4**.

Table 4: Transition probabilities for patients receiving standard care (CS, Table D11, p202 and Table D14 p204)

		Transition probability
Health states 1 and 2	Improve	0.00
	Maintain	0.92
	Decline	0.09
Health states 3, 4, and 5	Improve	0.00
	Maintain	0.88
	Decline	0.12
Health states 6 and 7	Improve	0.00
	Maintain	0.97
	Decline	0.04
Health states 8 and 9	Improve	NA
	Maintain	0.96
	Decline	0.04

The transition probabilities for the standard care patients were also applied to patients initiating treatment with cerliponase alfa, but who had discontinued treatment; patients initiating on cerliponase alfa were assumed to discontinue treatment if they transitioned to health state 7.

administered systemically. The ERG has particular concerns regarding cardiac involvement, indeed, over the short duration of the presented trials, from [redacted] at baseline, [redacted] of patients had ECG abnormalities. Importantly the morbidity and mortality consequences of extra-neurological disease pathology will be unrelated to neurological progression and therefore, represent an additional mortality risk. This would affect all patients regardless of the ability of cerliponase alfa to slow/stabilise neurological progression. The lack of any long-term human data on the life expectancy of patients receiving cerliponase alfa makes these risks difficult to quantify and, as such, the impact of this additional mortality is subject to significant uncertainty. The clinical advisor to the ERG, however, concurred with an interpretation of the evidence that extra-neurological pathology is both biologically plausible and likely, given the available evidence.

The evidence described above relating to extra-neurological pathology was put to the company, at the PfCs, and the company was asked to present a scenario analysis that was more conservative in its assumptions regarding the prognosis of patients. The company's response, was, however, relatively dismissive of the potential for extra-neurological pathology, citing the lack of evidence in humans. The company, however, did provide an additional, more conservative, scenario analysis in which mortality risk was doubled at the age of 20 years and increased linearly to a four times risk at age 40 years and beyond. The mean and median overall survival of patients receiving cerliponase alfa, in this scenario analysis, were 67.7 years and 70.04 years, respectively. While the ERG acknowledges the lack of human evidence in CLN2 patients upon which to base these modifications, the ERG does not consider this scenario to adequately account for the impact of extra-neurological pathology on mortality. The mean and median life expectancy of patients in this new scenario is still very high and suggests life-year gains of more than 50 years. It is also inconsistent with the evidence from both the animal studies and the related Batten's disease sub-type CLN3. The animal studies showed evidence of significant cardiac functional impairment in dogs aged 12 to 17 months of age and life expectancy of no greater than 190% of untreated dogs (note dogs were euthanized due to treatment and disease related complications), [3] while the evidence from the related Batten's disease sub-type CLN3 observed significant heart abnormalities in all patients over the age of 14 years and reported on two cases of heart failure in patients in their 20's.[16] This evidence would suggest that the effects of extra-neurological-related mortality would mean that it would be unlikely for patients to live much beyond their 20's and, potentially, that mean life expectancy may be even be as early as the late teens. To reflect the mortality risks associated with extra-neurological disease progression the ERG presents an additional scenario analysis, in Section 6.

Other-disease-related mortality: Evidence from the related Batten's disease sub-type CLN3 shows that the actual cause of death for a substantial proportion of CLN3 patients was either pneumonia or

infection. Therefore, the actual cause of death was not directly related to either neurological failure or extra-neurological pathology. Advice received by the ERG from their clinical advisor -suggests that

At the PfCs, the ERG asked the company to justify these differences in the vignettes and to provide evidence to show that cerliponase alfa provides the implied clinical benefits. The evidence provided by the company, to justify the implied seizure control and delay in needing a feeding tube, were changes in CLNQoL scores. The ERG, however, does not agree with the company's interpretation of this evidence; because CLNQoL scores are not clinical measures, but are patient-reported outcomes. Further, with respect to improved seizure control, the ERG's clinical advisor notes that tonic-clonic seizures are only one aspect of epilepsy and that similar improvements in epileptiform activity were not observed in the trial patients indicating that cerliponase alfa does not induce overall improved seizure control. No evidence was provided for the implied improvement in control of dystonia.

Additional evidence on the myoclonus score of the Weill-Cornell scale was provided as evidence for the implied improvement in control of dystonia and myoclonus. The evidence provided, with respect to dystonia and myoclonus, was however, also problematic, as while it demonstrates that the severity of dystonia and myoclonus increases at aslower rate in patients receiving cerliponase alfa compared with standard care, it does not provide evidence by health state. It is expected that the severity of progressive symptoms in the cerliponase alfa and natural history groups will diverge as they are correlated with disease progression and cerliponase alfa slows the rate of progression. The observed differences are therefore entirely expected and do not support the differential control of symptoms implied in the vignettes.

Given the lack of clinical evidence to suggest these clinical benefits, the ERG believes that it would be more appropriate to assume that the utilities are the same for both treatment and comparator patients. This will be explored further in Section 6.

Face validity

The ERG is concerned about the utility values used in health state 1, which assume near perfect health. The ERG questions whether this is reasonable given that nearly all patients will have some symptom load, e.g., epilepsy, language delay, and cognitive impairment. The ERG, particularly, notes the language component of the CLN2 clinical rating scale compares to best achieved and, therefore, a score of 3 does not imply normal development. At the PfCs, the ERG requested that the company comment on the validity of the assumed values in health state 1, noting the issues stated above. In response, the company emphasised that not all patients are symptomatic at diagnosis and that, in health state 1, patients are assumed to have well-controlled epilepsy and very low seizure frequency. The company also emphasised that the individual health states were validated by clinical experts. To address the ERG's concerns, the company, however, also provided two scenario analyses. In the first, the utility value for health state 1 in both arms was reduced by 10%. In the second, a reduction in quality of life was incorporated, to factor for patients' quality of life deteriorating over time. This was applied for patients over 25 years and assumed, based on data from a published study.[50]

5.3 Conclusions of the cost effectiveness section

The cost-effectiveness review carried out by the company did not identify any published evidence on the cost-effectiveness of cerliponase alfa for CLN2 disease. Consequently, the company's model represents the most relevant source of existing evidence. The base-case ICER presented in the CS was [redacted] per QALY (threshold 300,000 per QALY) and did not include any PAS. A draft MAA was however included in the CS.

In addition to the base-case analysis, the company presented a series of one-way sensitivity analyses and scenario analyses, to assess the impact of uncertainty around the key input variables and assumptions, on the ICER estimates. The results of these indicated that the base-case cost-effectiveness estimates were most sensitive to: (i) the starting population, (ii) health state utilities, and (iii) caregiver and sibling disutilities.

The ERG considers that the company's economic submission meets most of the requirements of the NICE reference case (except discounting), but is subject to a number of issues, which limit the credibility of the company's results. The main concerns relate to five key areas, which are outlined in brief below.

1. *Population modelled*
   The ERG noted that the modelled population does not represent an incident population based on current diagnostic practice and instead assumes significant improvements in diagnosis. To justify this assumption the company stated that they would be implementing a campaign to improve awareness amongst clinicians of CLN2 and state that [redacted]. The ERG, however, notes that no such programme exists in the UK presently and the company's commitment to such a programme remains unclear. Further, the benefits of any such programme are highly uncertain. Give these uncertainties, the ERG does not consider the assumptions made concerning the starting population to be reasonable and consider it more appropriate to base the starting population on current diagnostic practice.

2. *Implied HRQoL benefits over and above the main treatment effect*
   The health state utilities used in the base-case analysis were derived from an elicitation study which presented vignettes for each health state to eight clinical experts with experience of cerliponase alfa and treatment of patients with CLN2 disease. The ERG is concerned that these vignettes imply significant additional benefits of treatment with cerliponase alfa over and above the effects on disease progression. Specifically, the vignettes imply that

cerliponase alfa improves seizure control, improves control of dystonia and myoclonus and delays the need for a feeding tube. However, minimal evidence was presented to support

Table 1 Results of ERG scenario analysis on disease-related mortality)

Scenario	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER	Threshold	Incremental undiscounted QALYs
No stabilisation (disease-related mortality)							
Cerliponase Alfa	[redacted]	10.85	[redacted]	11.81	[redacted]	£150,075	15.01
Standard Care	£151,608	-0.96	N/A	N/A	N/A	N/A	N/A
Extra neurological mortality							
Cerliponase Alfa	[redacted]	12.18	[redacted]	13.14	[redacted]	£154,282	15.43
Standard Care	£151,608	-0.96	N/A	N/A	N/A	N/A	N/A
Neurodisability-related mortality							
Cerliponase Alfa	[redacted]	28.23	[redacted]	29.19	[redacted]	£300,000	47.61
Standard Care	£151,475	-0.96	N/A	N/A	N/A	N/A	N/A
No stabilisation + Extra neurological mortality + Neurodisability-related mortality							
Cerliponase Alfa	[redacted]	8.19	[redacted]	9.14	[redacted]	£104,014	10.40
Standard Care	£151,475	-0.96	N/A	N/A	N/A	N/A	N/A