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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
Authors	Matthew Walton, Research Fellow, CRD Joanne O'Connor, Research Fellow, CRD Nick Meader, Research Fellow, CRD Lindsay Claxton, Research Fellow, CRD Melissa Harden, Information Specialist, CRD Nerys Woolacott, Reader in Health Technology Assessment, CRD Robert Hodgson, Research Fellow, CRD
Correspondence to	Robert Hodgson, Research Fellow, CRD, University of York, York YO10 5DD
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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]	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.

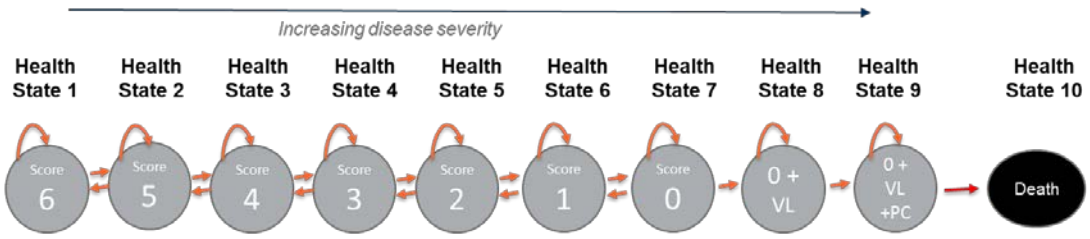
[41]

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)

Figure redacted commercial-in-confidence

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 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 predicts that even with zero drug acquisition costs, cerliponase alfa remains cost-ineffective 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 attributable to significant differences in predicted incremental QALYs (1.98 vs 29.24). The impact of the ERG base-case assumptions on QALYs accrued can be clearly observed in a 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.

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