Summary

The company's main submission (CS) claims cerliponase alfa will permanently stabilise, or even improve all characteristic aspects of CLN2 disease, preventing the deterioration of motor, language, and visual function, and the frequency of seizures. Thus, treatment will eliminate disease-related mortality in patients treated in the early stages of the disease and allow treated patients to live long, fulfilling lives, achieving development milestones in line with unaffected children. The ERG considers the company's interpretation unreasonably optimistic, which was often contradicted by available evidence and clinical opinion. The company assumed substantial changes to current service provision for the success of this treatment, including implementation of a [redacted]. These limitations are discussed below.

Critique of the company's description of the underlying health problem and the technology

The ERG noted two main concerns about the company's description of CLN2 and the biological plausibility of assumptions made about the likely benefits of cerliponase alfa.

Firstly, the CS fails to acknowledge the extra-neuronal components of CLN2, both in the contextual discussion of the disease mechanism and the anticipated impact of long-term treatment with cerliponase alfa. The ERG considers this evidence important to the appraisal. The ERG noted that expression of TPP1 is not limited to the CNS; the pathological accumulation of lipofuscin in other organs is well documented in CLN2 disease, and the consequences are seen in other forms of Batten disease. Pre-clinical studies indicated there may be serious implications for patient morbidity and mortality associated with cardiac, pancreatic, and hepatic impairment unless ERT is administered systemically.

The ERG has particular concerns regarding cardiac involvement, with severe cardiac and hepatic impairment seen in canine models of CLN2 treated with TPP1. Cardiac hypertrophy and conduction disorders are common in longer-lived CLN3 patients and were observed in [redacted] patients in the presented trial evidence; [redacted] of patients at baseline had ECG abnormalities [redacted] at last observation, many of these abnormities were prognostic of cardiac hypertrophy and conduction disorders. The ERG therefore reiterates the concerns of the European Medicines Agency (EMA), the US Food and Drug Administration (FDA), and clinicians regarding the failure of this treatment to address the likely consequences of extra-neuronal disease pathology, and highlights this as an important limitation of the technology.

Secondly, the ERG noted that cerliponase alfa administered via intracerebroventricular (ICV) infusion is unlikely to reach therapeutic concentrations due to the blood-retinal barrier.

cerliponase alfa arm and the standard care arm). Utility values based on the vignettes were elicited using eight clinical experts who were asked to complete an online version of the EQ-5D-5L as a proxy for patients who would be experiencing the description given in the vignettes. To account for the impact of CLN2 on disease on the family, the company applied a disutility for both caregivers (parents) and siblings. Disutility due to an adverse event was also included in the model. The company model included the following costs: drug acquisition and cost of administration for cerliponase alfa; health state costs, associated with monitoring and providing supportive care for patients and their families; and treatment costs relating to progressive symptoms associated with CLN2 disease.

The company found cerliponase alfa to be more costly (cost difference of [redacted]), but also more effective (gains of 30.42 QALYs) than standard care. The estimated deterministic ICER for cerliponase alfa compared with standard care was [redacted] per QALY. The results of the DSA indicate that the parameters with the largest influence on the ICER were the drug cost and the health state utility values for cerliponase alfa. The probabilistic ICER estimated by the company was [redacted] per QALY. The company undertook a range of scenario analyses. Two scenarios were considered by the company to present the likely range within which the ICER lies, as they combine the optimistic and pessimistic elements of the scenario analyses. These scenarios had an associated ICER of [redacted] and [redacted], respectively.

1.6 Summary of the ERG's critique of cost effectiveness evidence submitted

The ERG raised a number of concerns in its critique of the company's model, these issues concerned the long-term effectiveness of cerliponase alfa, the population modelled, assumptions made regarding the long-term mortality of patients receiving cerliponase alfa; and, problems with the way in which the HRQoL values used in the model were derived. Each of these issues is summarised in brief below.

Long-term effectiveness of Cerliponase alfa

A central assumption to the company base-case is that all patients receiving cerliponase alfa stabilise after 96 weeks and experience no further disease progression. The ERG considers this assumption to be subject to very considerable uncertainty, and has substantive concerns regarding the company's interpretation of the clinical evidence cited in justification of this assumption. Specifically, the ERG note that there is only limited evidence from the 201/202 cohort that all patients stabilise, and that a number of patients ([redacted]) continue to experience further disease progression in the later part of the 190-201/202 study (post 48 weeks). The ERG, also highlights evidence from animal models which suggests patients receiving cerliponase alfa will continue to experience disease progression.

worsen [13]. The ERG noted that cardiac hypertrophy and conduction disorders have been identified in older CLN2 patients [14, 15] and are common in CLN3 patients [16]. Furthermore, canine models of CLN2 disease exhibited severe progressive cardiac and hepatic impairment when treatment with exogenous TPP1 enzyme[1] was administered through the ICV route alone, indicating a potential need for systemic administration of TPP1. The European public assessment report (EPAR) for cerliponase alfa emphasised the importance of close monitoring of cardiac events, recommending ECG monitoring every 6 months, and during each ICV infusion in patients with present or past bradycardia, conduction disorders, or with structural heart disease – which included [redacted] of trial patients [17].

This concern regarding non-neuronal pathologies was also echoed by the ERG's clinical advisor, who believed it biologically plausible and likely that patients would experience extra-neurological morbidity and mortality, as untreated accumulation of ceroid lipofuscin may well lead to pancreatic, intestinal, cardiac, and hepatic pathologies and impairment. Furthermore, the EMA suggests that close monitoring should be performed at a minimum until there is sufficient clinical evidence on long-term extra-neuronal involvement [11]. These concerns were raised with the company at the points for clarification stage (PfCs) by the ERG, but in their clarification response the company indicated that these were unlikely to happen based on clinical opinion they received. The ERG, however, considers that in in the absence of clinical evidence, it is prudent to defer to pre-clinical evidence and clinical opinion when making predictions regarding long-term treatment efficacy and safety.

2.1.3 Prevalence of CLN2 disease

There is a distinct lack of data on the prevalence of CLN2 disease in the UK, but the CS referenced a number of sources of incidence and prevalence data, with global prevalence averaging ~0.75 per million population, and an incidence of 0.5 per 100,000 live births. The CS identified a UK study which reported a prevalence of >0.31 per million population, with an incidence of 0.78 per 100,000 births – higher than the estimated global average. However, the company chose to use the global values to estimate an incident population of four to five children per year, and 30 – 40 children currently living with the disease in England and Wales. The ERG recognises that use of UK-specific rates would not significantly change the anticipated rate of cerliponase alfa uptake.

2.1.4 Quality of Life

The company conducted a systematic literature review and review of patient organisation websites to identify information on patient, caregiver, and family quality of life in CLN2 disease. These searches did not identify any relevant studies, so an elicitation exercise was performed with 'eleven key opinion leaders', who provided information on management of CLN2 patients. The company also investigated the correlation of disease severity in terms of the Weil Cornell rating scale with HRQoL,

seizures). The HRQoL of patients and their families was assessed using the PedsQL Generic Core Scale and Family Impact Modules, and the 190-202 trial also recorded EQ-5D-5L. The primary measure of patient HRQoL was the 'CLN2 Disease-based QoL instrument', which was designed by the company based on focus group feedback. The company also presented MRI outcome data, which was further to that specified in the final scope. However, the company did not report appropriate measurements of several outcomes included in the final scope, and omitted relevant data collected in the clinical trials. Despite the importance of vision loss in CLN2 disease, and to the company's expected impact of the drug, there was no specific examination (e.g. optical coherence tomography (OCT), electroretinogram, visual evoked responses) of ophthalmological function. The company presented disaggregated Hamburg vision domain scores upon request, however, this was considered an inadequate assessment of visual function by clinicians [11], who suggested ophthalmological functional endpoints would have been a more plausible representation of vision loss, and recommend OCT as an assessment of retinal degeneration in CLN disease. [23] The CS also omitted trial data and discussion of immunogenicity, electroencephalographic (EEG) epileptiform outcomes, and electrocardiographic (ECG) outcomes, which the ERG considered inappropriate given the potential significance of these outcomes to considerations of long-term clinical effectiveness and safety.

3.5 Other relevant factors

The CS includes a section on considerations of equality, and states that the company has not identified any relevant issues regarding equity or equality to this submission.

Table 1 Inclusion criteria for systematic review included in the CS (adapted from Table C1 in CS)

Domain	**Inclusion/Exclusion criteria**
Population	Patients with any variant of CLN2 disease or TPP1 deficiency
Interventions	Any intervention
Comparator	Any or none
Outcomes	Any efficacy or safety outcomes Studies where outcomes were not reported separately for population of interest were excluded
Study design	RCTs, or Interventional non-RCTs (such as single-arm clinical trials, non-randomised comparative studies, observational studies, retrospective studies, case reports, case series, registries) Exclusion criteria were: economic evaluations; editorials, notes, commentaries or letters; narrative or non-systematic literature reviews

The inclusion criteria for the systematic review were broad, comprehensive and reflective of the decision problem.

4.1.3 Critique of data extraction

Study selection and data extraction methods were conducted and reported in an acceptable manner (see Appendix 3, section 17.2.7). Full text articles were independently assessed for eligibility by two reviewers with any disagreement resolved by a third reviewer. Data extraction was conducted by a single reviewer and checked by another reviewer.

4.1.4 Quality assessment

Quality assessments were conducted for all included studies using appropriate criteria (see CS Appendix 3, section 17.3). The critical appraisal questions were based on an adaptation of the CASP tool for cohort studies. The criteria were appropriate and included items on recruitment, measurement of exposure, measurement of outcome, identification and adjustment for important confounding factors, completeness of follow up and precision of results. However, the company should also have reflected on whether the length of follow up was appropriate, which is a key issue in the context of this submission and was also included as a question in the original CASP checklist.

It was not reported whether these were conducted by a single reviewer or checked by another reviewer.

4.1.5 Evidence synthesis

No formal evidence synthesis was conducted of included studies other than those conducted by BioMarin.

Tables C2-C4 of the CS reported the population, intervention, comparator and outcomes of included studies in the systematic review. Table C2 reported data for included studies identified in the original search, Table C3 reported similar data for unpublished trials identified in trial registries and Table C4 reported data for two further trials identified after the original search was conducted. A very limited narrative summary was also provided of the two trials summarised in Table C4. More detailed data abstraction from included studies was provided in Appendix 3, section 17.3 of the CS.

The justification for no formal evidence synthesis of non-BioMarin trials was that none of these included studies were relevant to the submission. It is unclear why the eligibility criteria of the company systematic review included studies not relevant to the submission. But the ERG considered this unlikely to impact on the validity of the conclusions of the systematic review.

The primary study included in the CS was of 23 patients who received cerliponase alfa over 48 weeks (study 190-201) and then followed up to approximately 96 weeks in an extension study (study 190-202). In addition, there was a study of natural history controls (study 190-901) used to compare the efficacy of cerliponase alfa against conventionally-treated patients.

4.2 Studies on the clinical efficacy and safety of cerliponase alfa

The primary study 190-201 evaluating the clinical efficacy and safety of cerliponase alfa was on 23 patients with CLN2 disease followed up over 48 weeks. Ten patients were enrolled during the dose escalation period (one patient dropped out after the first dose) and fourteen patients started during the stable dose period.

After 48 weeks, those who had completed study 190-201 were then enrolled in extension study 190-202, which is intended to follow patients for up to 240 weeks. Most data in the trial is reported for up to 96/97 weeks of follow up, although some slightly longer-term data is also available for some outcomes.

Two further studies 190-502 (an expanded access scheme for patients who couldn’t participate in the trial) and 190-203 (where siblings of participants in 190-201 have an opportunity to enrol) were also

5.1.3 Studies included and excluded in the cost-effectiveness review

The electronic database searches identified 126 records. Of these, 104 records were excluded at the initial screening stage (22 records were duplicates). The remaining 12 records were assessed based on their full text. None of the 12 records met the inclusion criteria and they were not included in the systematic literature review. Supplementary searches of congress proceedings identified four publications, which related to three separate studies. One study presented utility data and the other two presented cost and resource use data. No relevant economic evaluations were identified.

5.1.4 Conclusions of the cost-effectiveness review

The company's search did not identify any relevant economic evaluation studies. A number of studies were identified, which related to utility data and cost and resource use data. These studies were discussed in their respective sections of the CS. It may have been useful, given the acknowledged small body of evidence surrounding this disease, to include other CLN disease populations, to help inform the model structure and model inputs.

5.2 ERG's summary and critique of company's submitted economic evaluation

An overall summary of the company's approach, and signposts to the relevant sections in the company's submission, are reported in Table 11.

Table 2: Summary of the company's economic evaluation (and signposts to the CS)

	Approach	Source / Justification	Signpost (location in the CS)
Model	A multi-state Markov model was developed. Cycle length was two weeks and a lifetime (95 years from the start of the model) was used.	The submission states that a multi-state Markov model is the most appropriate way of modelling a long-term chronic disease with dynamic disease progression The cycle length is in line with the fortnightly treatment administration of cerliponase alfa, and the frequency of concomitant patient examinations. In the model, patients start at an age of 4.8 and the ONS life tables provide mortality data up to the age of 100.	Section 12.1 Pages 178-190
States and events	The model consisted of 10 health states based on the CLN2 clinical rating scale. Health states 1-7 were defined by a score on the CLN2 clinical rating scale, ranging from a score of 6 (least severe) to a score of 0 (most severe). Health state 8 was defined as a score of 0 on the CLN2 clinical rating scale plus complete vision loss. Health state 9 was the same as health state 8 plus the additional requirement for palliative care. Health state 10 was death.	These health states were selected to capture the clinical reality of disease progression. The health states and their defining characteristics were validated by clinical experts.	Section 12.1 Pages 180-182
Comparators	The comparator used in the company's model was standard care which was described as established clinical management without cerliponase alfa.	No treatment is currently available for CLN2 disease, and this is in line with the NICE scope.	Section 12.1.3 Pages 179

	Approach	Source / Justification	Signpost (location in the CS)
Subgroups	An analysis of a subgroup of asymptomatic and pre-symptomatic siblings with confirmed CLN2 disease was undertaken.	In line with the scope	Section 12.6 Pages 276-278
Treatment effectiveness	Treatment effectiveness was estimated using the CLN2 clinical rating scale scores, a subset of an adapted version of the established four-domain Hamburg scale measure.[28] A number of additional symptoms, not captured by the CLN2 clinical rating scale, were also included in the company's model (vision loss and requirement for palliative care). At 16 weeks (cycle 8) patients receiving cerliponase alfa were classified as early or late stabilisers dependent on response to treatment between week 16 and week 96. Early stabilisers were assumed to experience no further progression of disease. Late stabilisers were assumed to experience further progression of disease up to 96 weeks (cycle 48). After 96 weeks it was assumed all patients receiving cerliponase alfa were stable and experienced no further disease progression.	Transition probabilities for patients receiving cerliponase alfa were based on the 190-201/202 study (pivotal clinical trial)[29] and expert clinical opinion. Transitions probabilities for patients receiving standard care were based on patient level data from the 190-901 study (natural history study)[30] and expert opinion.	Section 12.2 Pages 179-205
Mortality	Mortality of patients in health states 1 to 8 was based general population mortality adjusted for sex and age. Patients in health state 9 were expected to transition from health state 9 to the death state based on an exponential function with a mean of 52 weeks.	ONS mortality statistics and expert opinion.	Section 12.1.3.1 page 179 Section 12.1.7 page 197
Adverse events	Treatment-related adverse events were included in the company's model. These included pyrexia, hypersensitivity, headache and vomiting. An infection rate of 0.45% for each performed ICV infusion was also included. No treatment-related adverse events were applied to the standard care cohort.	Adverse event rates were taken from Study 190-201/202[29] for cerliponase alfa.	Section 12.2 Page 206
Health-related quality of life	Utility values were derived from a utility study in which vignettes describing the health states for both cerliponase alfa and standard care were developed. The vignettes were validated by a clinical expert, and sent to 8 clinical experts who completed the EQ-5D-5L questionnaire as a proxy for patients experiencing the health states. These were mapped to the EQ-5D-3L before being applied in the model. Adverse event disutility, caregiver disutility and sibling disutility were also incorporated into the company's model.	The utility data collected in the clinical studies (190-201/202)[29] were not used due to the fact that utility values were not available for all health states and no utility values were available for standard care. Adverse event disutility estimates were derived from published studies.[31-34] The midpoint values for caregiver and sibling disutility were derived from a published study.[20] The company assumed a linear progression of this value across the health states.	Section 12.2 Pages 206-210 Section 12.1.7 Pages 192-197

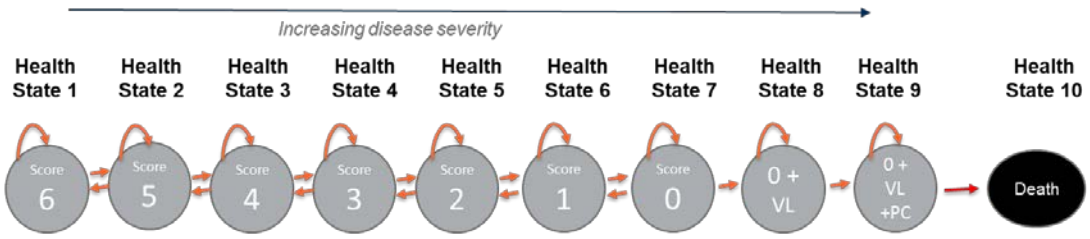
	Approach	Source / Justification	Signpost (location in the CS)
Resource utilisation and costs	Resource use and costs included: cerliponase alfa drug acquisition and administration costs; ICV implantation and replacement costs; health-state costs (routine care costs); drug acquisition and procedure costs associated with the relief of progressive symptoms; and, seizure costs. A NHS and Personal Social Services perspective was taken when identifying the relevant costs.	Drug acquisition costs were based upon the list price of cerliponase alfa, source BioMarin Europe Ltd. Administration and ICV implantation and replacement costs were based on NHS Reference costs 2015-2016.[35] Health state costs were estimated using the company's Delphi panel[36], NHS reference costs 2015-2016[35] and PSSRU 2016[37]. Progressive symptom costs and seizure costs were estimated using the BNF 2017[38], eMIT 2017[39] and NHS reference costs 2015-2016[35]. Costs and resource use data were identified through a SLR. Expert clinical opinion informed the assumptions used for inputs where cost information was unavailable.	Section 12.3 Pages 212-239
Discount rates	The costs and benefits were discounted at 1.5% per annum.	The submission states that the beneficial impact of the treatment was expected to be substantial and sustained over a very long period. Therefore, a discount rate of 1.5% was considered reasonable within the context of the NICE Guide to the methods of technology appraisal 2013.[40] [41]	Section 12.1.3 Page 179
Sensitivity analysis	Probabilistic sensitivity analysis was performed. Deterministic analysis was performed on a series of model parameters. A series of scenario analyses was also performed.	In accordance with the NICE reference case.	Section 12.4 Pages 239-275
ONS, Office for National Statistics; CLN2, Neuronal Ceroid Lipofuscinosis Type 2; ICV, intracerebroventicular infusion; EQ-5D-5L, European Quality of life, 5 domain instrument of health outcomes, 5 level; PSSRU, Personal Social Services Research Unit; BNF, British National Formulary; eMIT, electrical market information tool; SPC, Summary of Product Characteristics; SLR, systematic literature review.			

Model structure

The company submission is based on a multi-state Markov model comparing cerliponase alfa with standard care. The model used a cycle length of 2 weeks and a time horizon of 95 years. The company chose the cycle length as it was in line with the fortnightly treatment administration of cerliponase alfa, and the frequency of concomitant patient examinations. The time horizon was justified on the basis that general population mortality data are only available up to the age of 100. The model structure adopted consists of ten mutually exclusive health states, which characterise the progression of CLN2 patients over the course of the model's time horizon. The ten health states included in the model were defined by the CLN2 clinical rating scale, which is a subset of an adapted version of the four-domain Hamburg scale measure.[28] The adapted version consists of the motor and language

both domains; this is the least severe health state, and defined health state 1 in the model. Patients with scores from 5 to 0, defined health states 2 to 7, respectively. A score of 0, which is the most severe score, defined health state 7. Health state 8 was defined as a score of 0 on the CLN2 clinical rating scale plus complete vision loss (i.e. complete blindness). Health state 9 was the same as health state 8 plus the additional requirement for palliative care. Health state 10 was death. A graphical presentation of the Markov model is presented in Figure 2.

Figure 1: Model Structure (CS, Figure D20, p.181)



All scores are in the CLN2 clinical rating scale score
Patients considered to be "educationally" blind at a score of 0
VL, vision loss
PC, palliative care

To account for the symptom load not captured by the CLN2 clinical rating scale, it was assumed that each health state was associated with additional symptoms including epilepsy, disease-related distress, dystonia, myoclonus, vision loss and the requirement of a feeding tube. These were selected based on Williams et al. 2017[12] and validated in the Delphi panel study.[36] These additional elements were labelled as progressive symptoms in the CS and were associated with additional drug and therapy costs. The HRQoL impact of these symptoms was also captured in the health-state utilities, see Section 5.2.8 for details. Movement through the model was determined by transition probabilities. Probabilities for the transitions between the first seven health states (health state 1 [CLN2 clinical rating scale score of 6] to health state 7 [CLN2 clinical rating scale score of 0]) were based on patient-level data from Study 190-201/202 for the cerliponase alfa arm, and the one-to-one matched patients from the natural history control Study 190-901 for the standard care arm. Data were not available on the transition probabilities in the final health states (7, 8 and 9) as no patients progressed beyond health state 7 in Study 190-201/202. The transition probabilities for health states 7 to 9 were, therefore, based on expert opinion. See section 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

standard care arm, as vision loss is linked to disease progression, but it is more problematic for patients receiving cerliponase alfa. As described in Section 2, progressive vision loss in CLN2 patients is due to both retinal changes and central changes in the brain. This means that while cerliponase alfa may impact on the rate of vision loss it cannot prevent complete vision loss. The implications of this are that for patients receiving cerliponase alfa, vision loss will not correlate with deterioration in motor and language scores. The model structure, therefore, does not account for the progressive vision loss that will be experienced by patients receiving cerliponase alfa.

At the PfCs the ERG requested that the company develop a scenario analysis to account for the progressive loss of vision that would occur in cerliponase alfa patients. In response, the company presented a scenario analysis in which it was assumed that vision loss occurred from the age 6 and impacted on HRQoL. The disutility associated with vision loss was applied in the form of a progressively decreasing multiplier which was applied to the health state utility values. The multiplier was assumed to decrease by 0.01 points per year up to a value of 0.87 at the age of 20 years. The value of 0.87 was based on the quality of life associated with neovascular macular degeneration in the UK.[42] While the ERG considers that this scenario analysis is a more realistic reflection of the impact of vision loss on cerliponase alfa patients, the rate of decline was modelled to be too slow. As described in Section 2, degeneration of the retina in patients receiving cerliponase alfa will continue at the same rate [21] as untreated patients. Complete vision loss in patients receiving cerliponase alfa will therefore occur at approximately the same time as in patients on standard care; this is normally before the age of eight and not the age of 20 as implied by the company's scenario. The ERG, therefore, presents an alternative scenario, incorporating the effects of vision loss in patients receiving cerliponase alfa, in Section 6.

Extra-neurological progression: As described in Section 2, the ERG is concerned that there is a significant risk that patients receiving cerliponase alfa will continue to experience extra-neurological symptoms of CLN2. The most significant impact of these extra-neurological symptoms is likely to be on the mortality of patients receiving cerliponase alfa. However, these symptoms would also impact on quality of life (QoL). For example, it has been shown that extra-neurological lipofuscin storage occurs rapidly in the smooth muscle that makes up the gullet, bladder and bowels.[1-7] Symptoms of extra-neurological pathology may therefore include loss of smooth muscle control which would lead to difficulties with swallowing, and loss of bladder and bowel control, all of which would have a significant impact on QoL. The model structure is, however, not able to accommodate these additional symptoms and no account for them is made in either the company's base-case analysis, or in any scenario analyses presented by the company. Including the impact of these symptoms is, however, very difficult due to the lack of long-term data on the effects of cerliponase alfa and the uncertainty

around the symptoms that patients would experience. The ERG, therefore, does not explore the impact of extra-neurological pathology on

Weeks 17 to 96: Unlike the period of weeks 0 to 16, the transition probabilities in the period of weeks 17 to 96 were not assumed to vary according to the health state a patient is in. Instead, the transition probabilities were dependent upon whether a patient is an early responder or a late responder. As described in Section 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 3: Transition probabilities for patients receiving cerliponase alfa, weeks 0 to 16 (CS, Tables D12 and D13, p 203)

		Transition probability	
		Early responders	**Late responders**
Health states 1 and 2	Improve	0	0.00
	Maintain	1	0.975
	Decline	0	0.025

Week 97 onwards: After week 96, all patients receiving cerliponase alfa were assumed to be stabilised and experienced no further progression of disease.

ERG Comment

The ERG's concerns relating to the transition probabilities are two fold, and relate to technical issues; relating to how the transition probabilities are calculated and the assumption that all patients receiving cerliponase alfa are stabilised after 96 weeks.

Technical issue: The ERG noted a discrepancy in the calculation of the transition probabilities: the transition probabilities used for cerliponase alfa patients, in the first 16 weeks of the model, which appear based on the data provided to be based on the first 24 weeks of data. It is unclear why this

approach was taken by the company, but implies a clear inconsistency with the clinical data. The impact of this inconsistency is difficult to assess, but is potentially significant, as while these transition probabilities are only applied for a short period of time, the assumption of stability after this period, for many patients, means that they are an important determinant of the total costs and QALYs.

Assumption of stability: The assumption that all patients stabilise after 96 weeks is the single most important assumption in the economic model and a significant driver of both incremental QALYs and the ICER. As described in Sections 4, there is no long-term evidence on the effectiveness of cerliponase alfa and, therefore, the company have drawn upon clinical expertise, evidence from other disease areas in which ERT is used (e.g., Gaucher's disease) and the short-term evidence provided by the 190-201/202 trial, to justify this assumption. As stated in Section 4, the ERG has substantive concerns regarding the company's interpretation of the clinical evidence. Specifically, the ERG notes that there is only limited evidence from the 190-201/202 cohort that all patients stabilise, and that a [redacted]continue to experience further disease progression in the later part of the 190-201/202 study (post 48 weeks). Furthermore, while a proportion of patients do appear to achieve short-term stabilisation of disease, the ERG notes this number continues to fall as follow up lengthens. Furthermore, in direct contradiction to the modelled assumption of stability for of all patients post 96 weeks, examination of the IPD data reported in the 190-202 interim CSR shows [redacted].

Examination of more objective markers of disease also cast doubt on this assumption; EEG examinations during study 201/202 found new (focal and/or generalised) epileptiform activity in [redacted] of patients, which the ERG's clinical advisor suggested may be an indicator that disease progression had not been halted. Moreover, MRI measurements showed substantial reductions in whole brain volume, cortical grey matter, and white matter. The ERG, also highlights evidence from non-human studies, which showed that treatment only slowed progression of symptoms, with only modest reductions in short-term mortality. The ERG, therefore, considers the assumption of long-term stabilisation to be highly uncertain and likely to be overly optimistic, given the current limited evidence.

These significant concerns regarding the assumption of long-term stability were raised with company at the PfC stage and as part of this, the ERG requested that the company present a scenario making more conservative assumptions with respect to the long-term effectiveness of cerliponase alfa. The company's response to this question provided a scenario in which it was assumed that 5% of patients

do not stabilise after 96 weeks and instead experience standard care progression. It also assumed elevated mortality for patients over the age of 20 years and applied a disutility to account for progressive vision loss. The ERG, does not consider this new scenario to be a useful exploration of

the available clinical evidence; the assumption that 5% of patients do not stabilise is arbitrary and it is nonsensical to assume that they would experience standard care rates of progression, given the available evidence. Given the remaining uncertainty regarding the long-term effectiveness of cerliponase alfa, additional analyses, which consider more plausible extrapolations of the available effectiveness evidence, are presented in Section 6.

5.2.7.2 Treatment effectiveness: standard care

Patients not receiving cerliponase alfa were assumed to experience disease progression, based primarily on data from a natural history cohort matched to the 190-201/202 trial patients.[30] Transition probabilities, generated from the natural history data, were assumed to experience different risks of progression dependent upon the health state. Mirroring the transition probabilities applied to patients receiving cerliponase alfa, the transition probabilities for patients were calculated for three groups of CLN2 clinical rating scale scores; scores 6 and 5 [health states 1 and 2], scores of 4 to 2 [health states 3 to 5], and scores of 1 and 0 [health states 6 and 7]. As above, no justification was given for this assumption to vary transition probabilities by health state. Unlike patients receiving cerliponase alfa, the same transition probabilities were applied across all periods of the model. The transition probabilities, for patients not receiving cerliponase alfa, are presented in Table 17.

Table 4: Transition probabilities for patients receiving standard care (CS, Table D11, p202 and Table D14 p204)

		Transition probability
Health states 1 and 2	Improve	0.00
	Maintain	0.92
	Decline	0.09
Health states 3, 4, and 5	Improve	0.00
	Maintain	0.88
	Decline	0.12
Health states 6 and 7	Improve	0.00
	Maintain	0.97
	Decline	0.04
Health states 8 and 9	Improve	NA
	Maintain	0.96
	Decline	0.04

The transition probabilities for the standard care patients were also applied to patients initiating treatment with cerliponase alfa, but who had discontinued treatment; patients initiating on cerliponase alfa were assumed to discontinue treatment if they transitioned to health state 7.

administered systemically. The ERG has particular concerns regarding cardiac involvement, indeed, over the short duration of the presented trials, from [redacted] at baseline, [redacted] of patients had ECG abnormalities. Importantly the morbidity and mortality consequences of extra-neurological disease pathology will be unrelated to neurological progression and therefore, represent an additional mortality risk. This would affect all patients regardless of the ability of cerliponase alfa to slow/stabilise neurological progression. The lack of any long-term human data on the life expectancy of patients receiving cerliponase alfa makes these risks difficult to quantify and, as such, the impact of this additional mortality is subject to significant uncertainty. The clinical advisor to the ERG, however, concurred with an interpretation of the evidence that extra-neurological pathology is both biologically plausible and likely, given the available evidence.

The evidence described above relating to extra-neurological pathology was put to the company, at the PfCs, and the company was asked to present a scenario analysis that was more conservative in its assumptions regarding the prognosis of patients. The company's response, was, however, relatively dismissive of the potential for extra-neurological pathology, citing the lack of evidence in humans. The company, however, did provide an additional, more conservative, scenario analysis in which mortality risk was doubled at the age of 20 years and increased linearly to a four times risk at age 40 years and beyond. The mean and median overall survival of patients receiving cerliponase alfa, in this scenario analysis, were 67.7 years and 70.04 years, respectively. While the ERG acknowledges the lack of human evidence in CLN2 patients upon which to base these modifications, the ERG does not consider this scenario to adequately account for the impact of extra-neurological pathology on mortality. The mean and median life expectancy of patients in this new scenario is still very high and suggests life-year gains of more than 50 years. It is also inconsistent with the evidence from both the animal studies and the related Batten's disease sub-type CLN3. The animal studies showed evidence of significant cardiac functional impairment in dogs aged 12 to 17 months of age and life expectancy of no greater than 190% of untreated dogs (note dogs were euthanized due to treatment and disease related complications), [3] while the evidence from the related Batten's disease sub-type CLN3 observed significant heart abnormalities in all patients over the age of 14 years and reported on two cases of heart failure in patients in their 20's.[16] This evidence would suggest that the effects of extra-neurological-related mortality would mean that it would be unlikely for patients to live much beyond their 20's and, potentially, that mean life expectancy may be even be as early as the late teens. To reflect the mortality risks associated with extra-neurological disease progression the ERG presents an additional scenario analysis, in Section 6.

Other-disease-related mortality: Evidence from the related Batten's disease sub-type CLN3 shows that the actual cause of death for a substantial proportion of CLN3 patients was either pneumonia or

infection. Therefore, the actual cause of death was not directly related to either neurological failure or extra-neurological pathology. Advice received by the ERG from their clinical advisor -suggests that

At the PfCs, the ERG asked the company to justify these differences in the vignettes and to provide evidence to show that cerliponase alfa provides the implied clinical benefits. The evidence provided by the company, to justify the implied seizure control and delay in needing a feeding tube, were changes in CLNQoL scores. The ERG, however, does not agree with the company's interpretation of this evidence; because CLNQoL scores are not clinical measures, but are patient-reported outcomes. Further, with respect to improved seizure control, the ERG's clinical advisor notes that tonic-clonic seizures are only one aspect of epilepsy and that similar improvements in epileptiform activity were not observed in the trial patients indicating that cerliponase alfa does not induce overall improved seizure control. No evidence was provided for the implied improvement in control of dystonia.

Additional evidence on the myoclonus score of the Weill-Cornell scale was provided as evidence for the implied improvement in control of dystonia and myoclonus. The evidence provided, with respect to dystonia and myoclonus, was however, also problematic, as while it demonstrates that the severity of dystonia and myoclonus increases at aslower rate in patients receiving cerliponase alfa compared with standard care, it does not provide evidence by health state. It is expected that the severity of progressive symptoms in the cerliponase alfa and natural history groups will diverge as they are correlated with disease progression and cerliponase alfa slows the rate of progression. The observed differences are therefore entirely expected and do not support the differential control of symptoms implied in the vignettes.

Given the lack of clinical evidence to suggest these clinical benefits, the ERG believes that it would be more appropriate to assume that the utilities are the same for both treatment and comparator patients. This will be explored further in Section 6.

Face validity

The ERG is concerned about the utility values used in health state 1, which assume near perfect health. The ERG questions whether this is reasonable given that nearly all patients will have some symptom load, e.g., epilepsy, language delay, and cognitive impairment. The ERG, particularly, notes the language component of the CLN2 clinical rating scale compares to best achieved and, therefore, a score of 3 does not imply normal development. At the PfCs, the ERG requested that the company comment on the validity of the assumed values in health state 1, noting the issues stated above. In response, the company emphasised that not all patients are symptomatic at diagnosis and that, in health state 1, patients are assumed to have well-controlled epilepsy and very low seizure frequency. The company also emphasised that the individual health states were validated by clinical experts. To address the ERG's concerns, the company, however, also provided two scenario analyses. In the first, the utility value for health state 1 in both arms was reduced by 10%. In the second, a reduction in quality of life was incorporated, to factor for patients' quality of life deteriorating over time. This was applied for patients over 25 years and assumed, based on data from a published study.[50]

5.3 Conclusions of the cost effectiveness section

The cost-effectiveness review carried out by the company did not identify any published evidence on the cost-effectiveness of cerliponase alfa for CLN2 disease. Consequently, the company's model represents the most relevant source of existing evidence. The base-case ICER presented in the CS was [redacted] per QALY (threshold 300,000 per QALY) and did not include any PAS. A draft MAA was however included in the CS.

In addition to the base-case analysis, the company presented a series of one-way sensitivity analyses and scenario analyses, to assess the impact of uncertainty around the key input variables and assumptions, on the ICER estimates. The results of these indicated that the base-case cost-effectiveness estimates were most sensitive to: (i) the starting population, (ii) health state utilities, and (iii) caregiver and sibling disutilities.

The ERG considers that the company's economic submission meets most of the requirements of the NICE reference case (except discounting), but is subject to a number of issues, which limit the credibility of the company's results. The main concerns relate to five key areas, which are outlined in brief below.

1. *Population modelled*

   The ERG noted that the modelled population does not represent an incident population based on current diagnostic practice and instead assumes significant improvements in diagnosis. To justify this assumption the company stated that they would be implementing a campaign to improve awareness amongst clinicians of CLN2 and state that [redacted]. The ERG, however, notes that no such programme exists in the UK presently and the company's commitment to such a programme remains unclear. Further, the benefits of any such programme are highly uncertain. Give these uncertainties, the ERG does not consider the assumptions made concerning the starting population to be reasonable and consider it more appropriate to base the starting population on current diagnostic practice.

2. *Implied HRQoL benefits over and above the main treatment effect*

   The health state utilities used in the base-case analysis were derived from an elicitation study which presented vignettes for each health state to eight clinical experts with experience of cerliponase alfa and treatment of patients with CLN2 disease. The ERG is concerned that these vignettes imply significant additional benefits of treatment with cerliponase alfa over and above the effects on disease progression. Specifically, the vignettes imply that

cerliponase alfa improves seizure control, improves control of dystonia and myoclonus and delays the need for a feeding tube. However, minimal evidence was presented to support