NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

HIGHLY SPECIALISED TECHNOLOGY

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

The following documents are made available to the consultees and commentators:

1. **Response to consultee, commentator and public comments on the Evaluation Consultation Document (ECD)**

2. **Consultee and commentator comments on the Evaluation Consultation Document** from:
   - **BioMarin ECD response**
     - **Addendum: Response to ERG question on ECD response**
     - **Commercial offering**
   - **Battens Disease Family Association**

   The Department of Health and Social Care provided a "no comments" response.

3. **Comments on the Evaluation Consultation Document from experts:**
   - **Prof Paul Gissen – clinical expert**, nominated by BioMarin and Batten Disease Family Association
   - **Dr Ruth Williams – clinical expert**, nominated by Batten Disease Family Association
   - **Lucy Carroll – patient expert**, nominated by Batten Disease Family Association

4. **Comments on the Evaluation Consultation Document received through the NICE website**

5. **Company project initiation document**

6. **Company proposed Managed Access Agreement**

7. **Company response to NICE briefing document**
   - **Addendum**

8. **CLN2 Testing Metrics EUMEA program**

9. **Company additional evidence**
   - **Additional data on gene panel testing**

10. **Evidence Review Group critique of the company ECD response and additional evidence**
    - **Addendum**

11. Evidence Review Group report in response to NICE briefing document and critique of additional evidence

- **Addendum**

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

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Highly Specialised Technology Evaluation

Cerliponase alfa for treating neuronal ceroid lipofuscinosis type 2

Response to consultee, commentator and public comments on the Evaluation Consultation Document (ECD)

Definitions:

Consultees – Organisations that accept an invitation to participate in the appraisal including the manufacturer or sponsor of the technology, national professional organisations, national patient organisations, the Department of Health and relevant NHS organisations in England. Consultee organisations are invited to submit evidence and/or statements and respond to consultations. They are also have right to appeal against the Final Evaluation Determination (FED). Consultee organisations representing patients/carers and professionals can nominate clinical specialists and patient experts to present their personal views to the Evaluation Committee.

Clinical specialists and patient experts – Nominated specialists/experts have the opportunity to make comments on the ECD separately from the organisations that nominated them. They do not have the right of appeal against the FED other than through the nominating organisation.

Commentators – Organisations that engage in the evaluation process but that are not asked to prepare an evidence submission or statement. They are invited to respond to consultations but, unlike consultees, they do not have the right of appeal against the FED. These organisations include manufacturers of comparator technologies, Welsh Government, Healthcare Improvement Scotland, the relevant National Collaborating Centre (a group commissioned by the Institute to develop clinical guidelines), other related research groups where appropriate (for example, the Medical Research Council); other groups (for example, the NHS Confederation, and the *British National Formulary*).

Public – Members of the public have the opportunity to comment on the ECD when it is posted on the Institute's web site 5 days after it is sent to consultees and commentators. These comments are usually presented to the evaluation committee in full, but may be summarised by the Institute secretariat – for example when many letters, emails and web site comments are received and recurring themes can be identified.

Please note: Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

Comments received from consultees

Consultee	Comment	Response
BioMarin	1. Summary of company comments 1.1 The company is confused and perturbed by the NICE Evaluation Committee's ("the Committee") provisional recommendations and considers them to be flawed for a number of reasons: 1.1.1 The Committee concludes that all of the treatment benefits associated with cerliponase alfa are fully captured in the slowing of decline in motor and language scale (M/L) scores only. This conclusion is at odds with the evidence presented by the company, patient and clinical experts, which clearly identify additional treatment-related benefits over and above M/L scale scores including, but not limited to, improvements in the reduction of frequency and severity of seizures, reduction in myoclonus, improved wellbeing and reductions in vision loss, when compared to standard of care alone. 1.1.2 The Committee has clearly based its conclusions about the long-term benefits of cerliponase alfa treatment and several other topics (including the interpretation of M/L scale score progression and decline, EEG and cardiac abnormalities, the importance of extra-neuronal pathology) on, at best misleading or unreliable evidence put forward by the Evidence Review Group (ERG) and, at worst, incorrect or false evidence. In particular, the company is concerned that the ERG's perspective on the following topics has created a completely misleading or false	Comments noted. Please see response to the comments in the sections below.

Consultee	Comment	Response
	narrative about neuronal ceroid lipofuscinosis type 2 (CLN2) patients: 1.1.2.1 Utilisation of CLN3 disease as a proxy for predicting long-term outcomes and mortality risk for CLN2 patients, despite these being totally different diseases in terms of causation, pathology and course of disease; 1.1.2.2 Concluding that all CLN2 patients will die of extra-neuronal complications when the published evidence does not support this conclusion, with neurological complications being the main cause of death in all CLN2 patients and even CLN3 patients (of which only about 20% have been reported to die of extra-neuronal pathology); 1.1.2.3 It is wholly inappropriate and inaccurate to compare people experiencing traumatic brain injury and CLN2 patients to make assumptions about the mortality risk associated with neuro-disability; 1.1.2.4 Incorrectly assuming that all of the treatment benefits of cerliponase alfa are fully captured in the slowing of decline in M/L scale scores, thereby ignoring the benefits observed on the vision and seizure domains. 1.1.3 The ERG's narrative and conclusions on these topics form the main basis of the ERG's preferred modeling scenario, but do not accurately reflect the clinical evidence submitted. Nor does this correlate with the body of expert opinion in the UK and from other clinician experts in the management of CLN2 disease, and does not reflect their understanding of CLN2 and their experiences in real-life clinical practice. The company has to question, therefore, why and on what basis the Committee has chosen to give so much weight to the ERG's conclusions. 1.1.4 The company welcomes the Committee's acceptance that cerliponase alfa treatment leads to clinical benefit and improves patient quality of life in the short-term. It is, therefore, all the more inexplicable that the Committee has chosen to	

Consultee	Comment	Response
	completely disregard those same benefits when considering cost-effectiveness. Specifically: 1.1.4.1 In sections 1.2 and 4.13 of the Evaluation Consultation Document (ECD), the Committee acknowledges that cerliponase alfa treatment improves quality of life. This improvement is not, however, taken into account at all when calculating utility values for treated patients in the ERG's economic analyses. 1.1.4.2 The Committee accepted that, in the short-term, cerliponase alfa treatment is associated with improvements in M/L function and physical health, as well as reductions or slowing of progression on the seizure, pain, vision and myoclonus domains (see sections 1.2, 4.8, 4.9, 4.19 of the ECD). In spite of these findings, the Committee erroneously and perversely concludes that all of the treatment benefits associated with cerliponase alfa are fully captured in the slowing of decline in M/L scores only, and fails to take account of any of the other observed clinical benefits in the economic evaluation. 1.1.4.3 The Committee concluded that measures to support earlier diagnosis were important (section 4.2 ECD), but then fails to take into account the real-life trend towards earlier diagnosis over time in the economic evaluation. 1.1.5 The company acknowledges that there is uncertainty associated with the long-term benefits of cerliponase alfa, as well as assumptions about long-term disease stabilisation and mortality. However, in choosing to adopt the ERG's preferred economic scenario in its entirety without challenge, the Committee is acting inconsistently with the totality of the evidence. 1.1.5.1 Firstly, the Evaluation Committee noted that the ERG's analysis was similarly associated with considerable uncertainty; 1.1.5.2 Secondly, at the meeting on 17th January, the ERG admitted that the	

Consultee	Comment	Response
	scenarios it presented were likely to be 'unduly pessimistic'. The company concurs with this view. It is completely unrealistic for the ERG to conclude that cerliponase alfa treatment generates as few as [redacted] QALYs (undiscounted), even taking into account the inevitable uncertainty. 1.1.5.3 Thirdly, the Committee fails to make any concession whatsoever in the economic evaluation for the positive treatment effects that it itself has accepted and which are noted elsewhere in the ECD. 1.1.6 In summary, therefore, it is, particularly concerning and, in the company's opinion, entirely unreasonable that the Committee has chosen to adopt the ERG's scenario in full and without question. 1.2 In this response, the company puts forward two alternative scenarios for consideration which address the concerns about the uncertainty associated with the long term clinical effectiveness of cerliponase alfa that have been raised by NICE. The assumptions used in these scenarios provide a much more credible, objective and reliable basis for decision-making than any of the ERG's preferred scenarios. 1.3 For all of these reasons, the company does not believe that the Committee's provisional recommendations are either a sound or suitable basis for guidance on the use of cerliponase alfa in the context of national commissioning by NHS England	
BioMarin	2. Page 3. Section 1.2. Why the Committee made these recommendations "Clinical evidence suggests that, in the short term, cerliponase alfa improves quality of life, and slows the deterioration of motor and language function. However, there is no long-term clinical evidence, so assumptions about long-term disease stabilisation and mortality are associated with substantial uncertainty." Company response: The company is pleased to note the Committee's	Comment noted. The company considered that the further evidence submitted following consultation supported a trend towards long-term disease stabilisation. The committee agreed that the evidence showed that the substantial benefits with cerliponase alfa continued to be observed. However, it concluded that the additional evidence submitted after consultation did not change its conclusion that the assumptions about disease stabilisation, and late stabilisation in particular, were

Consultee	Comment	Response
	acknowledgement that the clinical evidence showed that cerliponase alfa improved patient quality of life and slows the deterioration of motor and language function. The company acknowledges that there is limited long-term evidence of benefit and that assumptions about long-term disease stabilisation are associated with uncertainty, but it is neither true to say that there is no long-term clinical evidence nor that the lack of abundance of the same means that there is no long-term benefit. The company provided 96-week data on the efficacy and safety of cerliponase alfa for all patients treated in studies 190-201 and 190-202. These patients continue to be followed up in study 190-202 for a period of up to 5 years. Where available, the company submitted data to NICE for up to 145 weeks of treatment for some patients, but this evidence was not taken into account by the Committee. In addition to Study 190-202, and as part of its ongoing commitments to the European Medicines Agency (EMA) and the US Food and Drug Administration (FDA), the company is in the process of initiating a 10 year study to provide long-term evidence on the safety and efficacy of cerliponase alfa treatment, as well as a neurological outcomes study investigating the effect of cerliponase alfa on long-term outcomes. The data from these three studies will be made available to NHS England and reported back as part of any future Managed Access Agreement (MAA). Thirdly, the company acknowledges that assumptions about long-term disease stabilisation and mortality are associated with considerable uncertainty. This is hardly surprising given that cerliponase alfa is the first ever treatment for the disease and untreated patients historically die around 10 years of age on average. It is not, however, reasonable to penalise the patients for the fact that this treatment is pioneering. Unfortunately, the assumptions put forward by the ERG on these topics are largely unsound and based on limited or questionable evidence of little or no	associated with substantial uncertainty. Please see section 4.12 of the Final Evaluation Document (FED)

Consultee	Comment	Response
	relevance to CLN2 disease. The ERG report includes a number of statements which are either factually incorrect or which lack validity. The company refutes the suggestion that the ERG's assumptions on long-term disease stabilisation and mortality constitute a reasonable interpretations of the body of evidence submitted and asserts that the uncertainty around long-term outcomes must apply equally to the ERG's preferred approach as it does to company's submitted base case. Insofar as the Committee has based its conclusions about the long-term benefits of cerliponase alfa treatment, mortality risk and extra-neuronal pathology on a flawed ERG report, its provisional recommendations cannot be considered a sound or reasonable basis for decision-making in the context of national commissioning.	
BioMarin	3. Pages 7-8. Section 4.2 Diagnosis "The committee concluded that measures to support earlier diagnosis are important." The Committee heard from clinicians and parents that CLN2 diagnosis is a lengthy and difficult process and that earlier diagnosis is critical to stabilising the disease earlier in its course. The committee also heard about a number of measures designed to support earlier diagnosis. Given these conclusions, the Committee's decision not to take into account the impact of earlier diagnosis when considering the health states of the starting population for the economic evaluation is inexplicable (see section 4.20, modelling assumptions). BioMarin has developed diagnostic programmes that are aimed at supporting early	Comment noted. The evaluation committee has taken into account all factors that may affect its decision. The committee recognised that children diagnosed and treated earlier in the pathway may have better outcomes. However, it concluded that implementing the early diagnosis campaign would be feasible, but there are substantial administrative barriers to implementation. Please see sections 4.13 and 4.14 of the FED.

Consultee	Comment	Response
	diagnosis of CLN2 disease. In accordance with the NICE Epilepsy Guide (Services for the diagnosis and management of the epilepsies in adults, children and young people: commissioning guide, 26th February 2013), BioMarin will be supporting general paediatricians or paediatricians with a special interest in neurology by providing enzyme tests whenever there is a suspicion of CLN2 disease (i.e. patients presenting between the ages of 2-4 with unprovoked seizures and history of language delay). BioMarin will offer at no cost to the NHS epilepsy gene panels in cases when a definitive diagnosis is more difficult to achieve (for example, unprovoked seizures but without clear history of language delay). These gene panel would cover over 190 potential epilepsy causing mutations, supporting earlier care for patients suffering epilepsies of an unknown origin.	
BioMarin	4. Page 9. Section 4.4 Clinical trial evidence "The committee recognised the limitations of developing an evidence base for an ultra-rare disease and was satisfied that it had been presented with the best available evidence". Company response: The company accepts that there is limited clinical effectiveness data available beyond 96 weeks of treatment and therefore that there is inevitable uncertainty associated with estimates of the long-term risk and benefits of treatment. We welcome NICE's acknowledgement that the best available evidence was presented. However, this acknowledgement makes it even more perplexing that the Committee chose to accept the ERG's assumptions (which were, in part, based on inaccurate inferences) and pessimistic scenario over the totality of the clinical trial data, expert clinical and caregiver testimony submitted to it.	In the absence of any long-term evidence and the positive short-term experience with cerliponase alfa, the committee considered that assuming partial stabilisation may be reasonable and concluded that it would consider this scenario in its decision making. The company considered that the further evidence submitted following consultation supported a trend towards long-term disease stabilisation. The committee agreed that the evidence showed that the substantial benefits with cerliponase alfa continued to be observed. However, it concluded that the additional evidence submitted after consultation did not change its conclusion that the assumptions about disease stabilisation, and late stabilisation in particular, were associated with substantial uncertainty. Please see sections 4.12 and 4.21 of the FED

Consultee	Comment	Response
BioMarin	5. Page 10. Section 4.6 Rate of decline in CLN2 scores in the natural history population "The ERG noted that estimates of mean decline in the natural history controls varied depending on the statistical method used, with more sophisticated methods such as the repeated measures mixed effects model resulting in lower estimates (a 1.29 to 1.46 point decline per 48 weeks). The ERG explained that the more sophisticated statistical methods were superior to the company's simplistic approach because they made better use of all the available data points. The committee concluded that all available data should be used when possible. It agreed that the mixed effects model used by the ERG was more appropriate to estimate the rate of decline in CLN2 scores in the natural history population." Company response: The company disagrees with the ERG's assertion that a 'more sophisticated' repeated measures mixed effect model is preferable to the company's approach and is therefore a more appropriate method for estimating the rate of decline in CLN2 patients. Basing the responder analysis on a 2-point change in the CLN2 rating scale (as shown by 1st and last point and simple regression methods) was the pre-defined approach in the clinical trial Statistical Analysis Plan. Secondly, both the FDA and EMA agreed that the company's approach was a suitable approach to statistical analysis. The mixed measures repeated model (MMRM) is based on significant assumptions, whereas the regression analysis carried out by the company was based on the actual data observed in the clinical trial programme. We note that committee's	On balance the committee agreed that the using the MMRM was a more appropriate method to estimate mean decline in the natural history population. The committee also took into account a number of analyses on CLN2 clinical rating scale scores conducted by the company when assessing the clinical effectiveness of cerliponase alfa. Please see sections 4.6 and 4.7 of the FED

Consultee	Comment	Response
	conclusion that “all available data should be used when possible”. The assumptions incorporated into the MMRM are significant and not in line with the observed data. Some sources of inaccuracy in the ERG assumptions include: • Significant data imputation methods were used for the MMRM analyses – carry forward post-baseline and carry backward to baseline; • Modelling was performed to the first ML scale score of 0; • For the analysis from age 36 months onwards, many subjects had ML scale scores of 6 at age 36 months; and • For the analysis from age of diagnosis, a relatively high proportion of the follow-up is for the ML scale score transition from 1 to 0 (which has a relatively slower rate of decline than the transitions from 5 to 1.	
BioMarin	6. Page 12. Section 4.8 Results Seizures “The Committee noted the improvement in scores in the seizure domain…The ERG highlighted that the seizure domain of the Hamburg scale reflects only the frequency of tonic-clonic seizures and does not take into account other seizure types…The committee concluded that the long-term effect of cerliponase alfa on seizures remained uncertain”. The company welcomes the Committee’s acknowledgement that evidence was presented on the reduction in tonic-clonic seizures. However, it is not true to say that evidence relating to other types of seizure does not exist; the company presented evidence of a reduction in the frequency and severity of other types of seizure, but this evidence appears to have been ignored by the ERG and, therefore, by the Committee.	Comment noted. The committee concluded that seizure control with treatment, with a subsequent effect on quality of life, was plausible. However, the long-term effect of cerliponase alfa on seizures remained uncertain. Please see section 4.9 of the FED.

Consultee	Comment	Response
	Specifically, seizure data from Schulz was presented as part of the company's submission, but has not been taken into account. These data showed that: • Twenty-two subjects in the cerliponase clinical trials (92%) reported a medical history of epilepsy or seizures; • Twenty-three subjects (96%) experienced one or more seizures during the study; • An improvement was seen in the grand-mal seizure subscore from baseline to 96 weeks (increasing from 1.7 points to 2.3 points); • 88% of seizures were mild to moderate (Grade 1 or 2) in severity; • A decrease in seizure frequency and severity was observed over time (Schulz, A. Intracerebroventricular Enzyme Replacement Therapy with Cerliponase Alfa in Children with CLN2 Disease: Results from an Ongoing Multicenter Extension Study. Presentation held at 14th annual WORLD symposium, February 5-9 in San Diego, CA) The patient perspective was in line with this clinical evidence but, again, this has largely been ignored by the Committee. Finally, and notwithstanding the data summarised above about other types of seizure, there was a clear acceptance in the ERG report that it is the clonic-tonic seizures that have the greatest impact on patient quality of life; this is not made clear in the ECD.	
BioMarin	7. Page 12. Section 4.8 Results Vision "Vision: the company stated that patients treated with cerliponase alfa had a slower	Comment noted. The committee acknowledged comments from the company, but on balance agreed that there was not sufficient evidence to

Consultee	Comment	Response
	decline in vision (as measured by the vision domain in the Hamburg rating scale) than untreated patients. The ERG noted that baseline vision scores were higher for the cerliponase alfa group, so the comparability of the groups was limited. Company response: As stated in its response to the ERG report, the company does not, and never has, claimed that treatment with cerliponase alfa can prevent vision loss. The company has only ever maintained that cerliponase alfa can slow the progression or rate of decline of characteristic aspects of CLN2 disease, inter alia, by preventing the deterioration of motor and language function, reducing the frequency of seizures and by slowing down the rate or progression of visual impairment. These claims are based on the clinical trial results in study 190-201/202. The company submitted clinical trial data on the vision and seizure domains of the Hamburg scale; these data are suggestive of a durable treatment effect of cerliponase alfa in CLN2 patients, which is not specific to any one domain. The company maintains that the clinical trial results indicate that cerliponase alfa can, and appears to, delay the rate of progression of visual impairment; the decline in visual domain scores of cerliponase treated patients in the 201/202 study was significantly less than that observed in the 1:1 matched natural history cohort. However, this was never a primary endpoint or a symptom targeted by the company for proof of the efficacy of cerliponase alfa. The company does not know for certain the physiological mechanism underlying the treatment effect observed; however, it is likely that this might be a result of the effect on the central components of the brain.	suggest that cerliponase alfa delayed vision loss. Please see section 4.9 of the FED.
BioMarin	8. Pages 12-13. Section 4.8 Results Vision	Comment noted. The committee acknowledged comments from the company, but on balance agreed that there was not sufficient evidence to

Consultee	Comment	Response
	"The ERG also noted that the vision domain of the Hamburg scale may not have been the most appropriate scale to measure deterioration in vision because the scale wording necessitates a certain level of motor function (for example, grabbing objects). It stated that other more specialised ophthalmological endpoints would have been more appropriate for assessing vision decline." Company response: The company recorded visual function measures showing the impact of cerliponase alfa on the visual domain scores as part of the total CLN2 (MLVS) scale (Table C24 of the company submission) and as a separate score (response to the clarification question A10 and A11). The vision domain score of the total CLN2 scale (Hamburg scale) is a validated measure for measuring visual function in CLN2 patients. In addition, the company is currently investigating the impact of intravitreal applications of TPP1 directly into the retina in animal models. Results so far have shown a clear prevention of retina damage and stabilisation of retinal function as assessed using electro-retinography tests, in dog models treated with intravitreal delivery of TPP1 compared to untreated dogs who continued to progress (Sinclair et al 2018, "Intravitreal enzyme replacement therapy attenuates retinal disease progression in a canine model of neuronal ceroid lipofuscinosis type 2 (CLN2)" presented at WORLD congress, San-Diego, USA Feb 5 – 9 2018).	suggest that cerliponase alfa delayed vision loss. Please see section 4.9 of the FED.
BioMarin	9. Page 13. Section 4.8 Results Vision "The committee concluded that there was insufficient evidence to suggest that cerliponase alfa would prevent vision loss in people with CLN2."	Comment noted. The committee acknowledged comments from the company, but on balance agreed that there was not sufficient evidence to suggest that cerliponase alfa delayed vision loss. Please see section 4.9 of the FED.

Consultee	Comment	Response
	Company response: Please refer to the previous response in point 7 above, the company never states that treatment will prevent vision loss, but the evidence shows a slowing down of vision loss.	
BioMarin	10. Page 14. Section 4.10 Long-term effectiveness "The ERG stated that there were a number of limitations related to these assumptions: • These definitions were determined after the studies, which was inappropriate because differences in response may be due to sampling error rather than a genuine difference in response patterns to cerliponase alfa treatment. • Trial data were not sufficiently long enough (96 weeks) to make long-term judgements about disease stabilisation. • Long-term trends in CLN2 scores implied that scores will continue to decline for late stabilisers beyond 96 weeks, so contradicting the assumption that disease stabilises in all patients..." Company response: [redacted]	Comment noted. The committee considered all evidence relating to the long-term effectiveness of cerliponase alfa. It recognised the limitations of developing an evidence base for an ultra-rare disease, and acknowledged concerns about using data from people with CLN3 disease as a proxy. The committee agreed that the evidence showed that the substantial benefits with cerliponase alfa continued to be observed. However, it concluded that the additional evidence submitted after consultation did not change its conclusion that the assumptions about disease stabilisation, and late stabilisation in particular, were associated with substantial uncertainty. Please see section 4.12 of the FED

Consultee	Comment	Response
	[redacted] The fluctuations seen in some scores over time do not contradict the claim in the company submission that patients would not see an unreversed decline in CLN2 score. The fluctuations (improvement followed by a decline) between week 96 and last observed follow-up may reflect the impact of temporary illness, which could have a temporal impact on their ability to walk or talk at that point. In addition, slope analyses provided by the company suggest that, on average, patients receiving cerliponase alfa see their ML scores stabilise after Week 96; [redacted]	

Consultee	Comment	Response
	[redacted]	
BioMarin	11. Page 14. Section 4.10 Long-term effectiveness "Relative to baseline, there was a trend of new epileptiform activity on electroencephalogram, suggesting that disease progression had not halted completely." Company response: As stated in the company's factual accuracy check of the ERG report, the ERG's conclusions that electroencephalogram (EEG) and magnetic resonance imaging (MRI) evidence suggested that disease progression was not halted in treated CLN2 patients are incorrect. The development of new epileptiform activity in treated CLN2 patients is not indicative of neuronal progression or worsening of seizures as asserted by the ERG. According to several world-leading experts in the management of CLN2 disease consulted by the company, the development of new epileptiform activity could be due to a number of reasons: 1. EEG findings are in no way correlated with the clinical picture. Clinical experts have reported been able to eliminate seizures or significantly reduce their frequency and severity without seeing a correlated change in EEGs (i.e. still observing the development of epileptiform activity). This could be as a result of difficulties in distinguishing from EEG readings what is a seizure, versus movement disorder or dystonia. 2. Given that CLN2 patients have epilepsy (with a life-long risk of seizures), development of abnormal epileptiform activity is to be expected, even when their	Comment noted. The committee concluded that exploring the effect of continued neurological progression-related mortality was appropriate, but incorporating extra-neurological mortality risk was not. It was satisfied with the approach of including the mortality risk of patients TBI, adjusted for comorbidities present before TBI occurred was acceptable. See FED section 4.15.

Consultee	Comment	Response
	seizures are well-managed by anti-epileptic drugs. 3. The development of epileptiform activity could also be as a result of detection (unmasking) of previously existing seizure types that are not obvious to patients who regularly experience generalised tonic-clonic seizures. In addition, children with CLN2 may have hundreds of seizures (of different types; focal, atonic, absent, etc.) a day, which in the past were difficult to differentiate even in EEG outputs due to the very rapid deterioration of natural history patients. 4. The EEG readings might be influenced by the time of the assessment and also a change in medication. In conclusion, the company believes that the ERG's conclusions about new epileptiform activity cannot be considered a reasonable interpretation of the evidence on this topic and the Committee was wrong to place such weight on them.	
BioMarin	12. Page 15. Section 4.10. Long-term effectiveness "The committee agreed that, in the absence of any evidence, it was not possible to predict the long-term effects of cerliponase alfa. It concluded that the assumptions of disease stabilisation, and late stabilisation in particular, were associated with substantial uncertainty." Company response: The company acknowledges that assumptions of disease stabilisation are associated with substantial uncertainty, but does not believe that the Committee has fully taken into account all the relevant evidence presented. For example, MRI showed significant slowing of brain loss, which could be attributed to debulking of lysosomal storage disorders (LSDs) as opposed to disease progression. [redacted]	Comment noted. The ERG stated Long-term trends in CLN2 scores (data academic in confidence) implied that scores will continue to decline for late stabilisers beyond 96 weeks, so contradicting the assumption that disease stabilises in all patients. The committee agreed that the evidence showed that the substantial benefits with cerliponase alfa continued to be observed. However, it concluded that the additional evidence submitted after consultation did not change its conclusion that the assumptions about disease stabilisation, and late stabilisation in particular, were associated with substantial uncertainty. Please see sections 4.11 and 4.12 of the FED

Consultee	Comment	Response
	[redacted] The ERG noted that this is indicative of long-term stabilisation of disease. There is no suggestion that this evidence has been taken into account by the Committee.	
BioMarin	13. Page 16. Section 4.12 Mortality "The committee was aware that, by assuming long-term disease stabilisation (see section 4.10), the company implicitly assumed that patients treated with cerliponase alfa would have the same life expectancy as the general population. The ERG stated that this was unrealistic and considered that mortality related to neurological progression as well as extra-neurological mortality was relevant. The committee agreed that, because it had concluded that that the assumption around late stabilisation was very uncertain (see section 4.10), it was plausible that patients would have further progression of disease with an associated mortality risk." Company response: The company acknowledges the uncertainty around late stabilisation of disease, further disease progression and associated mortality risk. However, the Committee has apparently concluded that this uncertainty does not apply to the opinions and conclusions of the ERG on these topics, many of which are unsound, based on very little evidence and/or run contrary to the body of expert opinion. In short, an absence of data cannot and should not be construed solely to the benefit of one opinion and the detriment of another – it needs to remain, at worst, inconclusive for both sides. Specifically,"The ERG explained that, while death usually occurs because of complications from neurological degeneration, the expression of TPP1 is not limited	Comment noted. The committee was aware that the EMA had not dismissed concerns about cardiac impairment. However, the committee heard strong testimonies that there was no experience of extra-neurological progression in patients having cerliponase alfa. The committee acknowledged that, without longer-term data, the effect of CLN2 on mortality because of effects in other body systems was completely unknown. It agreed that extra-neurological mortality, was not supported by the trial evidence nor the clinical experts. The committee concluded that, exploring the effect of continued neurological progression-related mortality was appropriate, but incorporating extra-neurological mortality risk was not. Please see section 4.15 of the FED.

Consultee	Comment	Response
	to the central nervous system and that untreated accumulation of ceroid lipofuscin may lead to pancreatic, intestinal, cardiac and hepatic impairment". The company challenges this on three grounds; 1. CLN3 disease is not a suitable or reliable proxy for CLN2 disease; 2. Extra-neurological mortality is not a relevant factor when considering mortality risk in CLN2 patients; and 3. The ERG's conclusions regarding cardiac abnormalities and increased mortality risk are erroneous and based on extremely limited evidence of questionable relevance. 1. CLN3 disease is not a suitable or reliable proxy for CLN2 disease • The ERG's conclusions of an increased significant risk of death to CLN2 patients from heart, liver and pancreatic complications assume that CLN3 disease is a reliable proxy for CLN2 disease. This is not the case. As the company made clear in its response to clarification questions and the ERG report, CLN3 disease is a very different disease to CLN2 in terms of causality, pathology, clinical manifestation and progression; CLN3 disease is not an appropriate analogue from which to draw conclusions applicable to CLN2 disease. 2. Extra-neurological mortality is not a relevant factor when considering mortality risk in CLN2 patients • There is no evidence of extra-neuronal mortality complications in CLN2 patients, including those with atypical presentations and Scar 7 (which has	

Consultee	Comment	Response
	TPP1 deficiency and is a variant of CLN2 disease) who have lived up until the age of 73 (Sun et al., Hum. Mutat. 34: 706-713 and Breedveld et al. Med. Genet. 41: 858-866, 2004) • In addition, clinical experts experienced in the treatment of CLN2 patients (with and without cerliponase alfa) and consulted by the company have confirmed that they have not identified any extra-neuronal pathology in any of their patients in clinical practice and nor is it something they would expect to see in the near future. This was detailed in the company response to the clarification question A11, the company response to the ERG report and was also supported by the clinical expert at the 17th January meeting (Section 4.12 ECD), who confirmed that no extra-neurological effect has been seen in patients currently being followed. • Extra-neurological complications and related mortality are infrequent in other NCL diseases, including CLN3 disease (for which only a few patients have died from extra-neurological complications). This is clear from the Østergaard paper relied upon by the ERG (Østergaard et al., 2011) in which only 54% of CLN3 patients (and not all of them, as claimed by the ERG) experienced cardiac complications, most of which were mild and potentially easily treatable. Of these subjects, only 20% died of cardiac complications; the remaining 80% died of neurological complications. • As mentioned in our factual accuracy check to the ECD report, cerliponase alfa delivered in the brain via ICV has been shown to go into the blood stream at concentrations (1.0 – 1.9 ug/mL) that are similar to concentrations of other systematically delivered enzyme replacement therapies (ERTs) such as elosulfase afa and galsulfase. These concentrations are similar to	

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	the blood concentration seen in atypical patients who live longer with no presentation of cardiovascular or extra-neurological complications (Kohan et al. Gene 2013 516: 114 – 128, Kohan et al Clin Biochem 2005: 38: 492 – 494). Although not a perfect comparison (as tissue concentration of enzyme does not always correlate with blood concentration), we feel it is plausible that this concentration in the blood should be sufficient to protect from any future risk of extra-neurological complications. This is supported by evidence from other LSDs such as MPS IIIB, in which ICV delivery of the enzyme has been shown to result in reduction of storage material in the peripheral organs (such as reduced liver size) (Muschol et al 2018. "ICV-administered BMN 250 (NAGLU-IGF2) is well tolerated and reduces heparan sulfate accumulation in the central nervous system of subjects with Sanfilippo Syndrome Type B (MPS IIIB)" Platform presentation at WORLD congress, San-Diego, USA Feb 5 – 9 2018) • The company acknowledges the potential for retinal damage leading to vision loss as an extra-neuronal pathology, but would reiterate that there is virtually no other evidence of any other form of extra-neuronal pathology (including cardiac dysfunction) in any of the phenotypes of CLN2 patients. • The Committee itself acknowledged that, in the absence of longer-term data, the effect of CLN2 on mortality due to effects in other body systems is completely unknown (section 4.12 ECD, pages 16-17). It is, therefore, surprising that the Committee has adopted the ERG's conclusions on this topic in full. 3. The ERG's conclusions regarding cardiac abnormalities and increased mortality	

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	risk are spurious, and based on extremely limited evidence of questionable relevance. • The ERG has concluded (i) that cardiac abnormalities observed in animal models and ECG observations in the clinical trial programme are suggestive of possible cardiac developments in CLN2 patients at a later stage, (ii) that all CLN2 patients will start to develop significant heart abnormalities by the age of 14, as seen in CLN3 patients, and (iii) that these cardiac abnormalities will result in CLN2 patients dying on average at the age of 27 years. These three conclusions are based on either very limited or no credible evidence and are untrue. • Firstly, the three publications (Fukumura et al., Hoffman et al., Østergaard et al.) relied upon by the ERG in support of these statements included only one CLN2 patient. That patient's diagnosis of CLN2 could not be confirmed, as it was not carried out according to current clinical practices (i.e. genetic testing was carried out on only one allele, not two). • Secondly, there is no evidence to support the ERG's claim that all CLN2 patients will develop cardiac abnormalities, or that these abnormalities will result in early death. The cardiac complications identified are easily managed with anti-arrhythmia drugs and/or a pacemaker. In the case reported in the Fukumura paper, the CLN2 patient's family declined to have the cardiac complications treated due to the patient being in the advanced stages of neurological disease. • The ERG's narrative that cardiac complications and mortality occur in all CLN3 patients is also untrue. In the Østergaard paper, which the ERG relied	

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	upon, only 54% of patients were identified as having some evidence of cardiac abnormalities, most of which were mild. Only 20% of the deaths in CLN3 patients were due to cardiac failure; the remaining 80% were due to complications sequelae to neurological complications. • The animal models referred to by the ERG used gene therapy to treat CLN2 disease, not enzyme replacement therapy or cerliponase alfa; these models are not appropriate predictors of future outcomes in CLN2 disease in humans. There is some evidence in the literature of some vectors used in gene therapy causing immune response in animals, which might explain the complications seen in the animal model. • Finally, the investigators in the cerliponase alfa clinical trial programme concluded that the small number of ECG abnormalities observed were not clinically significant. • In spite of these concerns, at the ERG's request, the company modelled a conservative scenario a modelled scenario exploring the impact of assuming an increase in all-cause mortality due to involvement of extra-neuronal pathology, and disutility associated with continued vision loss in CLN2 patients as they grow older. The results of this scenario indicated that these assumptions - even if correct - had a small impact on the ICER. • The Committee also accepted the ERG's conclusions that patients with CLN2 disease have an increased mortality risk due to their neuro-disability compared to the general population. The ERG assumed this to be in-line with that seen in patients with traumatic brain injury. Specifically, the ERG assumed that: • Patients with ML scores of 6 and 5 will have the same mortality risk (1.44	

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	times greater than the general population) as patients with traumatic brain injury with minor injury severity score. • Patients with ML score of between 2 and 4 will have the same mortality risk (2.00 times greater than the general population) as patients with traumatic brain injury with moderate injury severity score. • Patients with ML score of 1 and 0 will have the same mortality risk (9.92 times greater than the general population) as patients with traumatic brain injury with severe injury severity score. No explanation has been given as to why traumatic brain injury is considered a relevant comparator for CLN2 disease, nor is there any evidence to support it.	
BioMarin	14. Pages 20-21. Section 4.20 Model assumptions (health state distribution) "The distribution of patients across health states at the start of the model was based on the population expected to have treatment for CLN2 in the UK. For this, the company assumed that patients will be diagnosed in an earlier health state in the future, with most patients (about 80%) starting treatment in heath states 1 and 2 (CLN2 score 6 and 5 respectively). The ERG highlighted that this differed substantially from the trial, which included 16% of patients with a CLN score of 5 or 6. The company explained that it intended to implement a campaign to support earlier diagnosis. The ERG highlighted that the assumption of earlier diagnosis had a considerable impact on the quality-adjusted life years (QALYs) gained in the model but that there was little evidence to show how this could be achieved. The committee discussed the details of the company's programme (commercial in confidence). It supported initiatives to enable earlier diagnosis because it recognised	The committee discussed analyses in which the company's proposed early diagnosis campaign improved the starting distribution of patients. However, it did not consider the company's presented scenario plausible because it would need the uptake and effect of the early diagnosis campaign to be greater than it currently expects. The committee preferred a starting population based on the company's alternative scenario, in which 60% of patients starting in health states 1 and 2 (ML score of 6 – 20%, 5 – 40%, 4 – 25%, 3 – 10% or 2 – 5%) (see section 4.23). Please see sections 4.23, 4.27, 4.33 and 4.36 of the FED

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	that any gains from treatment would be larger if treatment was started in early stages of the disease. However, it considered that the company's assumptions around diagnosis in the model were too optimistic. In its exploratory analyses, the ERG reflected the distribution of patients from the natural history study 190-901, and the committee concluded that this was appropriate." Company response: The company disputes the Committee's conclusion that it was appropriate for the ERG, in its exploratory analyses, to reflect the distribution of patients from the natural history study 190-901 when distributing patients across the health states in the economic model at diagnosis/onset. In response to a clarification question on this point, the company pointed out that the historical control population at diagnosis was unrepresentative of the current incident population due to the age of the cohort – some patients were recruited into the natural history cohort (the DEM-CHILD database) as far back as the 1960's, some 40 years before the first genetic test to aid diagnosis of CLN2 disease was developed. To provide an accurate portrait of the incident population the company provided information on the starting population from the historical control data restricted to patients born after the year 2000. Nevertheless, results from the DEM-child natural history study have shown that there has been a trend towards earlier diagnosis of CLN2 disease even after the year 2000, [redacted] As such the distribution of patients across health states is likely to be different in the present day. The ERG has failed to take this trend into account; consequently, the distribution of patients across health states in the ERG's	

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	exploratory analyses cannot be considered a sound basis for decision-making.	
BioMarin	15. Page 22. Section 4.21 Model assumptions "The ERG presented analyses exploring the impact of incorporating neurological progression-related mortality and extra-neurological progression-related mortality, and the committee concluded that this was appropriate." Company response: As noted above in several places, the company is surprised that the Committee has concluded that the ERG analyses are appropriate, in view of the fact that: • Expert clinical evidence supported the fact that there is no evidence of extra-neuronal pathology in CLN2 patients; • Several of the ERG's assertions about mortality risk are not supported by credible or relevant evidence, or are simply incorrect; • Assumptions about CLN3 disease and traumatic brain injury being relevant proxies for mortality risk and long-term outcomes in CLN2 patients are flawed; and • The Committee itself concluded that (section 4.12) the effect of CLN2 on mortality due to effects in other (non-neurological) body systems is "completely unknown".	Comment noted. The committee was aware that the EMA had not dismissed concerns about cardiac impairment. However, the committee heard strong testimonies that there was no experience of extra-neurological progression in patients having cerliponase alfa. The committee acknowledged that, without longer-term data, the effect of CLN2 on mortality because of effects in other body systems was completely unknown. It agreed that extra-neurological mortality, was not supported by the trial evidence nor the clinical experts. The committee concluded that, exploring the effect of continued neurological progression-related mortality was appropriate, but incorporating extra-neurological mortality risk was not. Please see section 4.15 of the FED.
BioMarin	16. Pages 22-23. Section 4.22-4.23 Utility Values "The committee noted that the utility data collected in the clinical studies (190-201/202) were not included because utility values were not available for all health	Comment noted. The committee concluded that a utility benefit for people treated with cerliponase alfa, beyond that on slowing disease progression, was plausible. See section 4.29 of the FED.

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	states and no utility values were available for patients having standard care. The utility values for the base case were derived from a utility study commissioned by the company, in which vignettes describing the health states for both cerliponase alfa and standard care were developed...The committee concluded that applying differential utility values for patients who had or had not had treatment was inappropriate". In sections 1.2 and 4.13 of the ECD, the Committee acknowledges that cerliponase alfa treatment improves patient quality of life. Perversely, the Committee then decides to exclude this improvement in quality of life from further consideration when calculating utility values for treated patients in the economic analysis. In section 4.22, the Committee considers two alternative sources of utility values: the clinical trials and a utility study containing patient vignettes submitted by the company. The Committee decided that neither source was particularly robust. Moreover, the Committee notes that there is no utility value associated with standard care in the trials, while the ERG speculates that utility values in less severe health states were very high. As a result, the Committee concludes that applying differential utility values for treated and untreated patients was "inappropriate". No reason is given for this conclusion, which clearly flies in the face of the Committee's previous acknowledgement that a quality of life improvement was observed with treatment, and so introduces a disconnect between the Committee's clinical findings and the quantification thereof in the economic evaluation. Regrettably, the company is left with the impression that it was difficult for the ERG and Committee to quantify the quality of life improvement and as such disregarded it entirely.	
BioMarin	17. Company's alternative modeling scenarios	Comment noted. Please see response below,

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	The Committee has accepted the ERG's preferred scenario as the basis for its decision-making in its totality. While the company acknowledges the limited evidence base and the uncertainty associated with long-term assumptions about the stabilisation of disease, there is no basis on which the Evaluation Committee can reliably conclude that the ERG's analyses and preferred scenario are any more appropriate than those of the company, or that the perceived absence of long-term data should automatically lead to a conclusion that there no long-term stability. As previously stated, the uncertainty in the evidence base does not mean that the ERG's preferred scenario is any more certain or definitive than that of the company. The company therefore puts forward two alternative scenarios, applying different assumptions to the ERG preferred scenario accepted by the Committee, which provides a less pessimistic and more reliable basis for decision-making and which attempts to address some of the Committee's concerns about the uncertainties associated with the evidence base. These scenarios are presented in the Appendix but the key assumptions are summarised below. In some cases, the company has reluctantly used the ERG's preferred assumption for pragmatic reasons in order to move the discussion forward, despite continued reservations from both the company and the clinical community about the validity or relevance of these assumptions. Scenario 1 1. Starting population in the model – the ERG's analyses use the natural history cohort from study 190-901 as the starting population for the model; the ERG has distributed patients according to baseline ML score accordingly. This approach is unduly pessimistic, because the pattern of diagnosis has changed over time and	incorporating committee's preferred analysis. Comment noted. The committee concluded the most appropriate starting population was based on the company's alternative scenario in which 60% of patients starting in health states 1 and 2 (ML score of 6 – 20%, 5 – 40%, 4 – 25%, 3 – 10% or 2 – 5%).

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	even since 2000. The company has altered the patient distribution to reflect diagnostic improvements over time, resulting in a greater proportion of CLN2 patients being diagnosed at an earlier stage of disease. The rationale for why this is a more appropriate distribution than that applied by the ERG has already been described in the company's response to section 4.20 of the ECD (see paragraph 14 above). 2. Partial disease stabilisation – The ERG has assumed that CLN2 patients who 'stabilise early' will continue to maintain that stabilisation over time. The company agrees with that assumption. The Committee accepted the ERG assumption that all patients who are 'late stabilisers' will continue to progress at the same rate after 96 weeks of treatment. The company does not agree with this second assumption. The evidence from the clinical trials suggests that there is a trending towards disease stabilisation (with a mean decline of 0.27 over a 96 week period, [redacted]), for all patients. As such, the company does not agree with the assumption that all late stabilisers will continue to progress at the same rate, but rather that approximately 20-25% of late stabilisers will progress at a reduced rate of decline. The company has applied this alternative assumption in its alternative model scenario. 3. Extra-neurological mortality risk – As stated previously, the company does not accept that there is an additional risk of mortality associated with extra-neurological complications for CLN2 patients. However, it does acknowledge the	See section 4.23 of the FED. Comment noted. The committee considered that in the absence of long-term evidence and the positive short-term experience with cerliponase alfa, assuming partial stabilisation may be reasonable and concluded that it would consider the company's alternative scenario in its decision making (disease stabilisation for 74% of late stabilisers who had cerliponase alfa). See section 4.21 of the FED. Comment noted. The committee concluded that incorporating extra-neurological mortality risk was not appropriate. It was satisfied with the approach

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	limited evidence base on this topic and the Committee's conclusion that the effect of extra-neuronal pathology on long-term outcomes is unknown. In order to try to account for the uncertainty in the long-term mortality of CLN2 patients, therefore, the company has reluctantly applied the mortality risk of patients with traumatic brain injury (TBI) from the paper identified by the ERG as a pragmatic way of moving forward, despite its strong reservations about the validity of this comparison.	of including the mortality risk of patients with traumatic brain injury, adjusted for comorbidities present before TBI occurred was acceptable. Please see section 4.15 of the FED.
	4. Utility values – The ERG has applied the same utility values to patients in both arms of the model, i.e. it has assumed that there is no difference in health-related quality of life between treated and untreated patients. The Committee has contradictorily accepted this assumption. When reviewing the clinical evidence, the Committee concluded that cerliponase alfa reduced the frequency and severity of seizures and did improve patient quality of life in the short-term (section 1.2, 4.8 ECD). It is, therefore, extraordinary that the Evaluation Committee has chosen to completely disregard its own findings on quality of life improvements for the purposes of the cost-effectiveness analysis. The company acknowledges that there is uncertainty as to the magnitude and duration of the quality of life benefit but some difference in utility must be expected between treated and untreated patients, especially as seizure domains are not captured by the M/L score and patients experience a reduction in seizures while maintaining their M/L score, both points which the Committee has accepted. For the purposes of alternative Scenario 1, therefore, the company has applied a utility increment of 0.1, being the smallest change in quality of life that a patient would identify as clinically relevant (i.e. the smallest minimal clinically important difference,	Comment noted. The committee concluded that a utility benefit for people treated with cerliponase alfa, beyond that on slowing disease progression, was plausible. See FED section 4.29.

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	or MCID) to patients in health states 2-6 (i.e. with a baseline M/L score of 1 to 5) in the cerliponase alfa-treated arm of the model to account for the reduction in frequency and severity of grand-mal seizures. In addition, and in accordance with clinical opinion, an additional utility increment of 0.1 (giving a total increment of 0.2 for cerliponase alfa arm) was also added to patients in health states 5 and 6 (i.e. M/L scores 1 and 2) to reflect the reductions in pain and myoclonus that patients experience on treatment. Scenario 2 1. Starting population in the model – the company used the same distribution of patients and proportions per health state as submitted in the original company submission base case. 2. Partial disease stabilisation – the company has adopted the same assumption as for Scenario 1. 3. Extra-neurological mortality risk – In scenario 2, the company has applied the mortality risk of patients with TBI from the paper identified by the ERG, albeit with some modifications to correct for the errors made by the ERG. These adjustments represent the additional mortality risk that might be associated with neuro-disability and disease progression in CLN2 patients on the pragmatic basis that there is no other suitable proxy for comparison. Instead of applying an unadjusted mortality risk factor of 1.44 times greater than the general population for the early heath states, as the ERG did, the	Comment noted. The committee concluded the most appropriate starting population was based on the company's alternative scenario in which 60% of patients starting in health states 1 and 2 (ML score of 6 – 20%, 5 – 40%, 4 – 25%, 3 – 10% or 2 – 5%). See section 4.23 of the FED. Comment noted. The committee considered that in the absence of long-term evidence and the positive short-term experience with cerliponase alfa, assuming partial stabilisation may be reasonable and concluded that it would consider this scenario in its decision making (disease stabilisation for 74% of late stabilisers who had cerliponase alfa). See section 4.21 of the FED. Comment noted. The committee concluded that incorporating extra-neurological mortality risk was not appropriate. It was satisfied with the approach of including the mortality risk of patients with traumatic brain injury, adjusted for comorbidities present before TBI occurred was acceptable. Please see section 4.15 of the FED.

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	company has applied a factor of 1.12, which adjusts for comorbidities present before the TBI occurred. In patients with more severe disease, the company applied a risk factor of 10.30 times greater than the general population (cf. ERG factor of 9.92) of for the same reason. 4. Utility values – the company approach to utilities is the same as that submitted in the original company submission base case. By applying these revised assumptions in the model, the number of undiscounted QALYs associated with cerliponase alfa treatment increase from [redacted] (estimated by the ERG) to [redacted] in Scenario 1 (discounted QALYs increase from [redacted]) and to [redacted] (discounted QALYs [redacted]) in Scenario 2). These alternative scenarios are being put forward by the company as part of ongoing confidential discussions with NICE and NHS England with regard to a MAA in the context of national commissioning. A separate submission will be made to NICE in confidence detailing the clinical and financial aspects of the MAA, with Scenarios 1 and 2 described above forming the basis of that submission. Addendum not reproduced in the ECD comments table. See addendum of the manufacturer response to ECD for further details].	Comment noted. The committee concluded that a utility benefit for people treated with cerliponase alfa, beyond that on slowing disease progression, was plausible. See FED section 4.29. Comment noted. After publication of the Evaluation Consultation Document, new commercial offer was provided by the company (details deemed to be commercial in confidence). QALYs gains are also commercial in confidence, therefore cannot be reported here.
Batten disease family associate	Please see our comments below from the Batten disease family Association, (BDFA) (Registered charity in England and Wales 1084908-Scotland SC047408) as the only UK patient organisation representing patients and families affected by this devastating disease. Based on our 20-year experience of dealing with this condition the BDFA would like to draw the Committee's attention to what we see as omissions	

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	and potential errors in the understanding of the condition CLN2 disease, a late infantile form of Neuronal Ceroid Lipofuscinosis commonly known as Batten disease, and the benefits of Cerliponase Alfa. We are particularly concerned that the committee did not fully include the benefits of cerliponase alfa treatment that had not been adequately captured in the trial data and drew heavily on data from CLN3 disease. The committee has therefore drawn damaging conclusions about the likely disease progression for treated patients from this data, which are not accurate. To date 14 different types of NCL have been identified and characterised according to the gene affected. (NCL Batten disease second edition- edited by Sara E Mole, Ruth E Williams and Han H. Goebel, Oxford Uni Press) Whilst there is definite synergy in the overall disease characteristics and symptoms it is widely documented and clinically accepted that comparisons within disease types should not be used to make extrapolations on life expectancy and disease progression. Overall, patients with CLN3 disease, juvenile will definitely not have the same progression as CLN2 disease. CLN2 disease results in a known enzyme deficiency and CLN3 disease, a deficiency in a membrane bound protein (function currently not identified) located in the lysosome, which is not the same disease as CLN2. We would also like to inform the Committee that since the last meeting (17th January 2018) another two children in the UK have been diagnosed with CLN2 disease. There are a further four children in the UK who have been diagnosed since the Compassionate Use places were filled and therefore are unable to receive treatment. The committee stated, “It was convinced that cerliponase alfa offers an effective treatment option” Without this treatment, these children will lose many of their	Comment noted. The committee recognised the limitations of developing an evidence base for an ultra-rare disease and was satisfied that it had been presented with the best available evidence. Please see section 4.4 of the FED

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	current abilities at a rapid rate. In Section 1.2, the Committee stated that 'Clinical evidence suggests that, in the short term cerliponase alfa improves quality of life, and slows down the deterioration of motor and language function.' However, there were questions around the long-term effectiveness of the drug. We recognise that at present we do not have long-term trial data past the stage of 96 weeks. The clinical trial 190-201/202 is scheduled to continue until 2020, allowing for the collection and evaluation of data from 23 patients worldwide. The BDFA is working closely with NHS England on a Managed Access Agreement, which would collect data on the effectiveness of treatment for 7 years. The BDFA is committed to working with the company to collect data from all children on treatment to measure the effectiveness of this drug in the long term. All patients on the clinical trial in the UK have been receiving treatment for between 3 years 3 months (159 weeks) and 4 years 1 month (212 weeks). You will see in the Appendices that the families whose children have been on the clinical trial report that the abilities of their children have stabilised when receiving treatment. Parents report that their children have a very good quality of life and that little has changed for them since commencing treatment, in contrast to what they were led to expect at diagnosis. Two of the UK children aged between 7 and 8 years old on the clinical trial, who were able to walk unaided prior to starting treatment, are still able to do so. A third child, aged 8, who has been receiving treatment for 4 years 1 month (212 weeks), was able to walk with support prior to the start of treatment and is still mobile using a walker. The fourth child aged 7, can walk a few steps independently but prefers to use her wheelchair and can independently propel herself to where she wants to go. A child without treatment would be expected to lose the ability to walk	Comment noted. The committee considered all the available evidence relating to the long-term effectiveness of cerliponase alfa. It noted that cerliponase alfa could be expected to be used for decades, and that the results could not show whether the disease would remain stabilised over that period of time. The committee concluded that cerliponase alfa would likely provide long-term benefits. However, assumptions of disease stabilisation and late stabilisation in particular, were associated with substantial uncertainty and it accounted for this in its preferred analysis. Please see sections 4.11, 4.12, 4.21 and 4.22 of the FED.

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	at age 5. Parents of these children told us that they were able to learn new skills and those who were talking prior to starting the clinical trial have developed their vocabulary and the complexity of their sentences. This development would not be expected for children not receiving the treatment who would be likely to lose all speech capacity by the age of 5 years old. Similarly, parents of patients receiving treatment on the clinical trial outside of the UK report their children are able to walk with support, ride bikes, attend mainstream education, communicate and have the ability to increase their skills. Children can still attend school and are learning new skills and information. In Section 2.2, the EDC states that the life expectancy of CLN2 is around 8 years to early adolescence This information is incorrect. The youngest child to die from CLN2 in the UK was 5 years old and many children have died at 6 years old. In Section 4.5, the Committee stated that 'the CLN2 clinical rating score was an acceptable instrument to inform efficacy outcomes in the short term..' The BDFA facilitated a focus group of 13 family members with children on treatment. They all had children aged between 5 and 16 years old. Their time on treatment varied between 9 months (36 weeks) and 4 years 1 month (212 weeks). The parents explained that the CLN2 disease rating scale does not take into account all the benefits that are seen on treatment, especially as the Visual and Seizure scores are rarely utilised. Parents discussed that the points on this scale are too broad and therefore children on and off treatment could have the same CLN2 disease rating scale score but significantly different abilities. Visual and Seizures	Comment noted. The committee recognised that there is a distribution in the life expectancy of people with CLN2. It heard from clinical experts that the average life expectancy of people with CLN2 is around 10 years, but acknowledged that many children will die before this. Please see section 4.1 of the FED.

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	scores should carry more weight as these aspects of CLN2 have a huge impact on the child's quality of life, e.g. ability to access education and other activities. The CLN2 disease rating scales are too broad and require more granularity to fully capture the impact on children's quality of life. Looking at the motor scale as an example, there is a large gap between a child who is completely immobile, who would score a 0 on the scale, and a child who is showing no unaided walking or only crawling, who would score a 1 on the scale. In addition to this scale, parents felt it important to acknowledge a child's ability to sit, reach for items of interest, hold toys and devices, turn their head towards sounds, laugh, smile and participate in activities as this is something of importance to parents and families, not just the ability to walk or crawl. Parents asked for recognition and consideration of their children's cognition, learning and understanding as children who are only able to say a few words may understand a lot more than they are able to vocalise. A score for pain is also required as many children who are not receiving treatment experience pain on a daily basis whereas parents of patients on treatment have not expressed concerns about pain. There is a clear need to develop a measure for clinicians to understand this key issue as pain has a huge impact on quality of life Similarly, movement disorders, which are another key symptom of the disease, are not reflected in the CLN2 disease rating scale. Children, who are not receiving treatment, are affected by movement disorders throughout their day and during the night and this can be painful and disturb sleep. Parents of children on treatment report them to be significantly less troubled by movement disorders, such as dystonia and chorea, than their peers who are not receiving treatment. The parents agreed that the language scale was difficult to score as with all young	Comment noted. Comment noted. The committee considered acceptability of CLN2 rating and concluded that, the CLN2 clinical rating score was an acceptable instrument to inform efficacy outcomes in the short term, but that it would also consider any broader measures presented in its considerations of clinical effectiveness. Please see section 4.5 of the FED. The committee also recognised that generic measures of health related quality of life were not sensitive to all aspects of CLN2 disease. However, it acknowledged the significant burden of CLN2 on people with the condition and their families, and took this into consideration in its decision making.

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	children, affected or unaffected develop at different stages and have more than one way of communicating. Some children with CLN2 disease retain the ability to point, make gestures and use other means of communication even when they have very few spoken words Parents noted that the seizure scale was not clear enough. There are many different seizures associated with CLN2 disease and they need to break this scale down into types of seizures. As the committee noted the current scale only considers tonic-clonic seizures. Parents whose children receive treatment have not only reported fewer tonic-clonic seizures but also experience far fewer alternative types of seizures, such as myoclonic seizures. Parents whose children do not receive treatment report that their children have many myoclonic seizures throughout the day and this can be very distressing for both the child and the parents. These types of seizures in children with CLN2 disease are very difficult to treat. In order for the more accurate and informative data to be collected, parents suggested that assessments could be done, where possible, outside of the hospital setting. Most children are more relaxed in a home or school setting. The use of technology such as video could be employed to ensure that tasks that children often perform in the home but would not do in the hospital can be recorded and evaluated as part of the overall assessment process. For example, a child may be able to use a walker at home but they would not be able to do this during the assessment, unless the parent can transport their walker into the hospital. Parents identified that this could have a potentially adverse effect a child's overall score on the rating scale. Parents commented that children who have reduced vision might be more confident with their mobility in familiar environments e.g. school and home. In Section 4.8, the committee concluded that the long-term effect of celiponase alfa	

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	on seizures remained uncertain Parents and professionals have seen a significant reduction in seizures for those on the treatment. Although it was noted by a clinical expert that children on treatment remain on medication for epilepsy this is a minimal amount compared to those who have not received treatment. Patients on the trial have MDT meetings twice a year, which the BDFA are invited to attend, and many of the medication doses have remained the same for a long period of time for these patients. The BDFA attends similar meetings for patients not receiving treatment and observes that this is not the case; with many types of seizures being reported on a daily basis. Parents report that tonic-clonic seizures and the associated hospital admissions have an adverse impact on the child and family's quality of life. As the ERG stated and as previously discussed the CLN2 disease rating scale only captures the tonic-clonic seizures and does not take into account the many other different types of seizures that affect these children. Parents with children receiving treatment do report occasional absences and myoclonic jerks but consider these to be minimal in comparison to untreated CLN2 patients. In section 4.22, the committee concluded that applying differential utility values for patients who had or had not had treatment was inappropriate. These variations capture the many benefits seen by families with children on treatment. These benefits are not captured by current Quality of life metrics. As discussed previously, parents believe that these quality of life assessments should always be undertaken in conjunction with the CLN2 disease rating scale assessments. Families in the focus group looked at both the Paediatric Quality of Life Inventory (PedsQL) and the EQ-5D-5L and identified that neither one was	Comment noted. The committee heard the evidence showed that treatment with cerliponase alfa slows the deterioration of myoclonus-related symptoms. The committee concluded that the long-term effect of cerliponase alfa on seizures remained uncertain. However, it agreed that some seizure control with treatment, with a subsequent effect on quality of life, was plausible. Please see section 4.9 of the FED.

Consultee	Comment	Response
	detailed enough or had the appropriate domains to reflect the quality of life for children with CLN2 disease. One parent said; "*The questionnaires PedsQL and EQ-DD-5L are inappropriate for children with CNL2 Batten Disease. For children who are at the lower end of the rating scale, points 3 and below, using this questionnaire they would be deemed not to have a good quality of life purely based on the simple fact that the questions being asked do not give a true reflection on what quality of life actually is. As it is a tick questionnaire with no opportunity given to explain the answers, practitioners reading the questionnaires will only see the answers given to them rather that seeing all the things a child who can't walk and talk can still achieve.* *There is no mention about attending school, or classes or activities. As there is also no mention of activities, which children enjoy doing with or without help. Seizures have not been included along with feeding, tasting, swallow and vision.* *It would be appalling to put this type of questionnaire in place to assess a child's quality of life with CNL2 Batten Disease."* Parents requested that there should be many more areas of assessment in the Quality of Life assessments such as 'non-verbal interaction and gesturing, pain, cognition, sleep pattern and feeding and swallowing.' Parents also asked if multidisciplinary school reports and evidence of overall ability to take part in a broad range of activities could be part of these assessments to have a wider and more comprehensive evaluation. The BDFA has the knowledge, professional expertise, and experience to work with families to assist them and to work with BioMarin to improve quality of life assessments. This would ensure that assessments better reflect and capture the data needed to meet the needs of all concerned, most notably the patients with	Comment noted. The committee concluded that a utility benefit for people treated with cerliponase alfa, beyond that on slowing disease progression, was plausible. Please see section 4.29 of the FED.

Consultee	Comment	Response
	CLN2 disease, the treatment provider and health care regulators. The BDFA would be happy to work with the company on these quality of life assessments to ensure that they meet the needs of patients with CLN2. In section 4.18, the Committee has not adequately taken into account the costs for children who are not receiving treatment and has solely focussed on patients on treatment. The use of costs for caring for a person with an acquired brain injury is an inappropriate proxy for children with CLN2 disease. The BDFA asked parents on treatment how many hours care a week they received from health or social care. One child on treatment, aged 7, who has been on treatment for 1 year 3 months (64 weeks), receives 20 hours per week. A CLN2 disease affected child, of comparable age, not receiving treatment would expect to receive 100-120 hours per week, provided by highly skilled or trained nurses. A bereaved grandmother, who also works in the NHS, estimated that in the end of life stages for a child with CLN2 disease the medication cost to the NHS is in the region of £2000 per month. Her grandson spent many weeks of his life in a High Dependency Unit, had numerous ambulance trips to hospital and A&E admissions. Over the course of a lifetime of a child with CLN2 disease who is not on treatment, they will have had 2-3 wheelchairs, 1-2 walkers, a standing frame, specialist beds, housing adaptations, numerous slings, 2-3 bath seats, SATs monitors, cough assist machines, hoists, numerous pairs of splints for their hands and their feet, neck collars, suction machines. As the disease progresses so quickly, often equipment arrives too late and it is no longer useful. This is why a child will require 2-3 wheelchairs in the space of just a few years.	Comment noted. The annual cost of caring for a young adult with a severe acquired brain injury was used as a proxy for residential care costs. These costs were included in the model to capture the cost of people with CLN2 who were entering adulthood and could no longer be cared for at home. Caregiver costs and productivity losses are captured in the health state costs. Please see section 4.20 of the FED.

Consultee	Comment	Response
	Patients being treated are not losing their skills rapidly unlike untreated children. Their equipment is therefore lasting longer and there is more time for professionals to react and provide exactly what is needed in a useful timeframe and cost effective way. Most of the patients on treatment do not require the use of a wheelchair, or a standing frame. They can sleep in a normal bed. None of the children on treatment in the UK use a cough assist machine or suction machines compared to children of the same age untreated who would need access to this equipment aged 7, although in some circumstances this might be earlier. Parents whose children are on treatment do not have to fight for health and social care support as minimal support is needed, often allowing family members to remain in employment. The ERG assumed that the cost of care for a patient with CLN2 would be similar to costs for a young adult with a severe acquired brain injury. We do not believe that this is a fair comparison. Firstly, a person with an acquired brain injury may have a rapid change of symptoms that could take place in a matter of hours. Patients with CLN2 disease may deteriorate but this would be over a longer period of time, as the disease symptoms and expected progression is well documented. Patients with acquired brain injuries would, by definition of the condition, need all the care support and equipment immediately. Patients on treatment with CLN2 would need the care and equipment gradually if the disease did progress. Patients on treatment would not be expected to deteriorate so rapidly as to need 24-hour support without advanced warning. If, as is suggested by the current evidence, disease progression has stabilised they would and could, for a much longer period, live more independent lives than those not receiving treatment. The report also does not adequately take into account the impact on the wider family. Many parents of affected children have to cease employment to care for their	The committee discussed the impact of cerliponase alfa beyond its direct health benefits. It was aware of the very large impact of CLN2 on families,

Consultee	Comment	Response
	children and have to rely on state benefits. Parents are far more at risk of physical and mental health issues as a direct consequence of the burden of caring for their children. These issues, such as back injuries from lifting or depression and stress related health issues due to the lack of sleep, will require medical intervention at some point and necessitate further support measures to be provided at considerable cost by the health care and benefit system. In section 4.8 “The Committee incorrectly concluded that there was insufficient evidence to suggest that cerliponase alfa could prevent or slow vision loss in patients with CLN2.” We recognise that there is currently little data as to whether ERT slows down the deterioration in vision. One parent has reported that their child, aged 7, who has been on treatment for 3 years 6 months (162 weeks), can still navigate their way round an IPad, selecting videos they would like to watch on You Tube independently and being able to find the ‘Skip’ button to skip through the adverts independently. They have not seen evidence in the 3 years she has been on the treatment that her vision has deteriorated. As per the data on the natural history of the disease we would expect that a child aged seven, not receiving treatment, would be functionally blind. Many other parents tell us that their child is able to navigate their iPad well, and also, without assistance, find their own toys and play with them. Children with CLN2 disease have a considerable visual memory and progressively going blind is a very different situation compared to being blind since birth. Children with CLN2 are usually able to navigate their way around familiar environments even if they have no remaining vision. The BDFA work with Qualified Teachers for the Visually Impaired across the UK, and we also work closely with	including the emotional effect on carers, family relationships and siblings with the disease. It noted that there is a substantial financial impact on families. The committee heard from parents that treatment with cerliponase alfa completely changed their experience of having children with CLN2. This, in turn, allowed parents to work and provide a normal childhood for siblings without the disease. The committee considered that some of these aspects, such as productivity losses and disutilities, were included in the economic analysis. However, it recognised that the full effect of benefits beyond direct health benefits had not been quantified. The committee also recognised that considering these in a qualitative manner would not be sufficient to affect its recommendation, given the difference between its estimate of a most plausible ICER and the threshold level considered to be cost effective. Please see section 4.38 of the FED. Comment noted. The committee acknowledged comments from the company, but on balance agreed that there was not sufficient evidence to suggest that cerliponase alfa delayed vision loss. Please see section 4.9 of the FED.

Consultee	Comment	Response
	schools. Children can now use many different communication aids to access literacy and numeracy in school. Many children use objects of reference to ask for particular items or tasks. Barbara Cole, the BDFA Education Advisor and Qualified Teacher for the Visually Impaired, who has over 30 years of experience working with children and young people with Batten Disease reports: "*Visual processing is affected by the condition and children will CLN2 disease find it increasingly difficult to make sense of what they are seeing. It is likely that the patients that are treated with cerliponase alfa will maintain their visual processing ability and this will have a positive impact on their functional vision.* *There may be areas of good retinal function and good visual acuity that are retained late in the disease progression. Children are unable to make use of these areas late in the disease progression as they are unable to move their heads or position themselves. If their motor abilities are maintained, they are more able to use their remaining vision more effectively.* *Children with CLN2 disease had normal vision and retain visual memories in their long-term memory. Even when vision is lost, visual memories can support learning and independence skills, especially if the disease progression and resulting dementia is stabilised.* *Children with CLN2 disease vary in the rate of visual loss in the progression of the disease. Complete blindness occurs in the later stages of progression. The proportion of the patients having cerliponase alpha who are completely blind may be relatively low. The additional costs associated with blindness have been estimated in the general population, including the elderly who are affected by age related conditions resulting in sight loss. The government spend has been relatively low*	

Consultee	Comment	Response
	compared with other disabling conditions. Adaptive skills can be learnt and people can adapt to vision loss over time. There will be a variation in the additional costs associated with complete vision loss and this will be affected by the quality and availability of local support services, many of which are provided by charities such as the RNIB. *It may be possible to access records to establish better evidence of the maintenance of visual functioning of children treated with cerliponase alfa. This could include functional vision assessments by teachers of the visually impaired. The Hamburg scale wording necessitates a certain level of motor function and is a relatively crude measure of functional vision."* Rahul Dubey, a parent of a child on treatment, who is also a clinician, would like to share some very important and critical evidence about some very successful experimental research in the area of treating retinal disease in CLN2 patients. "*The following two landmark papers from animal model experimental studies, supports the fact that Intracerebral ERT slows the progression of vision loss in CLN2 patients by preserving the white matter visual pathways and preserving the ganglion cell layer of retina. In the first paper titled "Enzyme replacement therapy delays pupillary light reflex deficits in a canine model of late infantile neuronal ceroid lipofuscinosis" published in Experimental Eye Research 125 (2014) 164-172; the study concluded that "in some of the dogs treated with rhTPP1, there were substantial delays in the appearance and progression of Pupillary Light Reflex (PLR) deficits compared with untreated or vehicle treated affected dogs. These findings indicate that CSF administration of TPP1 can attenuate functional impairment of neural pathways involved in mediating the PLR but does not prevent loss of retinal responses detectable with ERG." In the second paper "Intracerebroventricular gene therapy*	

Consultee	Comment	Response
	that delays neurological disease progression is associated with selective preservation of retinal ganglion cells in a canine model of CLN2 disease; published in Experimental Eye Research 146 (2016) 276-28; the conclusion was that "in the affected dogs that received TPP1 gene therapy to the CSF and survived an average of 80 weeks, retinal ganglion cell axons were present in numbers comparable to those of normal Dachshunds of similar age. The selective preservation of the retinal ganglion cells suggests that while TPP1 protein delivered via the CSF may protect these cells, preservation of the remainder of the retina will require delivery of normal TPP1 more directly to the retina, probably via the vitreous body." In context to these studies, it is of paramount importance to say that rtTPP1 ERT has successfully been trialled in animal dog models in the form of intravitreal injections (injection directly in the posterior chamber of eyes, which is in direct contact with retina) and has been tremendously successful in halting the progression of retinal disease and structure, demonstrated by sequential Electroretinograms (ERG). Finally the following experimental study must be noted to understand how far we are with a breakthrough treatment for the eyes "Intracerebroventricular gene therapy that delays neurological disease progression is associated with selective preservation of retinal ganglion cells in a canine model of CLN2 disease" published in Experimental Eye Research 146 (2016) 276e282. "In this novel study, a single *injection of the autologous bone marrow derived stem cells transduced with a TPP1 expression construct (TPP1 gene) at an early stage in the disease progression, substantially inhibited the development of disease-related retinal function deficits and structural changes. No adverse effects of the treatment were detected. These findings indicate that ex vivo gene therapy using autologous stem cells is an effective means of achieving sustained delivery of therapeutic compounds to tissues such as the retina for which systemic administration would be ineffective."* The	

Consultee	Comment	Response
	BDFA is also funding a 3 year research programme on gene therapy for retinal disease in CLN2 disease in animal models. All these research papers are important for the panel to take into consideration while reviewing their decision. In section 4.12 the Committee concluded, from incorrect information from the ERG, that although cerliponase alfa is effective in the short term in treating the key neurological aspects of CLN2, there is a possible risk of death from pancreatic, intestinal, cardiac and hepatic impairment, which may develop in the future as seen in patients with CLN3 disease. The BDFA along with the patient community consider this statement to be unfair and based on inappropriate extrapolation from CLN3 disease patient data rather than clinical expertise in CLN2 disease. As highlighted at the outset the committee seems to have based their discussion around an incorrect assumption about the progression of the disease beyond the age at which children currently die based on clinical features of CLN3 disease patients. CLN2 and CLN3 disease are completely different diseases and have different effects on patients due to the different disease progression. The first symptom of CLN3 disease is vision loss. This can begin between 5-8 years old. Patients then may not have any other symptoms for several years. It is a much slower deterioration with CLN3 disease although it must be noted the effects of the disease are still just as devastating. We estimate the population of patients diagnosed with CLN3 disease in the UK to be around 50- 60 children and young people. In our experience, none of these young people have been diagnosed with heart abnormalities by the age of 14. The earliest we know that there have been cardiac problems for a young person with	Comment noted. The committee concluded that exploring the effect of continued neurological progression-related mortality was appropriate, but incorporating extra-neurological mortality risk was not. Please see section 4.15 of the FED.

Consultee	Comment	Response
	CLN3 in the UK is 26. The BDFA work closely with Heather House, a residential home that accommodates many young people with CLN3 disease. We asked manager, Sarah Kenrick to comment on the committee's conclusions: "*I have worked with young adults with CLN3 disease from mid-teens to end of life since 1990. In this time I have seen only 1 individual die due to liver complications.* *I have seen only 2 individuals die of sudden cardiac arrest, both females. 1 aged 20 who was admitted to the service I worked in, she had acute malnutrition due to eating difficulties and was refeeding at the time so this was probably a causative factor. The other aged 26 with advanced disease but no significant features relating to cardiology.* *We did have 3 men die, 1 aged 26, 1 aged 28 and 1 aged 30 who all showed weakened cardiac output in the last 2 weeks at the end of life, but these also had chest complications (infections and reduced air entry) so we cannot say that they died directly of cardiac arrest, rather it was part of the dying process.* *We have 2 men with pacemakers; 1 fitted last year at age 30 and 1 4 years ago at age 28, both showed increased agitation and distress for some months prior to cardiology team involvement, both are well and stable now.* *I think the issue is the treatment will not prevent death, all of us will die, and the treatment is not a cure, but to prevent treatment because people with a different disease (CLN3) may die of liver failure (extremely rare in my experience) or cardiac arrest.* *The treatment enables children with CLN2 disease to live longer lives with a real degree of quality, being able to walk, talk, actively participate, contribute and learn.*	

Consultee	Comment	Response
	To say that this should not be offered because CLN3 patients die sometimes of potentially preventable organ failure is akin to saying patients with Bowel cancer should not be treated because the incidence of survival for prostate cancer is low." In the UK there are two CLN2 confirmed patients with atypical phenotypes. This has not been taken into consideration anywhere in the ECD. One of these patients receives ERT treatment. She presented with mobility problems, language problems and some learning difficulties. She is now 16 years old and has never had seizures, is able to mobilise independently at home and school and with support in the community and her vision remains unaffected. The other patient is in her teens and still has a good quality of life. There are many other issues for families who are not receiving treatment that the EDC fails to fully recognise. There is a high rate of separation in families because of the pressures of caring. This has a huge effect on siblings as not only do they have to deal with their sibling's diagnosis but they also have to deal with family breakdowns. Many families tell us that the disease has a detrimental effect on siblings. Many become young carers, have anxiety issues, sleep disturbance and miss out on time with parents. They also miss out on holidays, spend a lot of time in hospitals and have had to cope at a young age with the death of a sibling. They have then had to deal with the aftermath of this and make sense of what has happened to their siblings. Families spend too much time fighting against "the system" and trying to engage professionals to get the equipment, care and support they need to the detriment of family life. Children on treatment do not have as many unexpected hospital admissions or associated appointments. They do not need access to the same quantity of equipment. Families stay together because they can spend more time together.	Comment noted. The committee discussed the impact of cerliponase alfa beyond its direct health benefits. It was also aware of the large impact of CLN2 on families, including the emotional effect on carers, family relationships and siblings with the disease. The committee considered that some of these aspects, such as productivity losses and disutilities, were included in the economic analysis. However, it recognised that the full effect of benefits beyond direct health benefits had not been quantified. The committee also recognised that considering these in a qualitative manner would not be sufficient to affect its recommendation, given the difference between its estimate of a most plausible ICER and the threshold level considered to be cost effective. Please see section 4.38 of the FED.

Consultee	Comment	Response
	Siblings lead a more normal life because their siblings are healthier for longer. There are so many benefits to the treatment. The ECD failed to note that children who are no longer mobile can still have a good quality of life. These children can still go outside and join in with activities. They can still go to school, go swimming, and go on bike rides. They are still able to enjoy TV despite not being able to see. They can still play with their siblings and enjoy family outings. They are still able to enjoy going on holiday, going on the swings and are still able to do many things that normal unaffected children can do. Often only minimal support and/or adaptions are needed for them to be able to participate. Being in a wheelchair does not mean that there is a decline in a child's quality of life; they may just need more support to be able to do the activities that they enjoy doing. The families feel that the impact of vision loss on quality of life has been unfairly judged. The BDFA and the Batten disease community do not agree with the current NICE recommendation. We have had a number of responses from families, not only in the UK, as listed in the appendices of this document. 90% of the families on treatment have submitted comments. We have had 9 submissions from families on treatment outside the UK. The BDFA also received 15 submissions from families who are not receiving treatment which include bereaved families. From working with families receiving treatment, and those who are not, we have been able to see first-hand that this treatment has a significant benefit to patients. We have the experience and, we believe, the expertise to support the process and we wish to work with NHS England to produce a fair Managed Access Agreement for all. Batten disease is a rapidly progressing disease and timely intervention is essential.	Comment noted. The evaluation committee considered evidence submitted by the company, the views of people with the condition, those who represent them and clinical experts, NHS England and a review by the ERG. The committee recognised that CLN2 is a serious and debilitating condition, and that cerliponase alpha could be a

Consultee	Comment	Response
	There is a very limited time for each newly diagnosed child and an ever decreasing window of opportunity to provide a treatment which can make a meaningful difference to children affected by this devastating disease. Children can lose their skills very quickly, sometimes in days or weeks, which cannot be regained. For those children and their families we hope that NICE, NHS England and BioMarin will come together to reach an agreement. We know of four children who have been recently diagnosed with CLN2 disease and, by prolonging the process, it is very possible that they may not be eligible for treatment when an agreement is reached. We urge the committee to reverse the decision not to fund this treatment. We would like to draw the committee's attention to the statements in the appendices from families whose children have not received treatment and those families where their children have sadly died. We are grateful for all the families who have contributed but we would like to acknowledge those families who are bereaved or are not receiving treatment and thank them for sharing their difficult and painful experiences and being able to be so honest as to the effects of CLN2 disease on their children. The BDFA works closely with other patient organisations within the UK. We have received the following support from Climb: "Climb is an umbrella patient organisation for all Inherited Metabolic Disorders. We have experience of the HST process and an interest in improving patient access to treatments and services that can improve their outcomes. In support of the BDFA, Climb would urge the committee to take into account all of the above points made by patient experts and alter its current view regarding the treatment of CLN2 Batten Disease and the benefits of Cerliponase Alfa.	potentially promising treatment. Clinical evidence suggests that, in the short term, cerliponase alfa improves quality of life, and slows the deterioration of motor and language function. However, there is no long-term clinical evidence available, so assumptions about long-term disease stabilisation and mortality are associated with substantial uncertainty. Furthermore, the cost-effectiveness estimates are all much higher than the range that NICE considers acceptable for highly specialised technologies that met the criteria for a QALY weight of 3.0. Please see section 4 of the FED for the committee's consideration of the evidence.

Consultee	Comment	Response
	We are particularly keen to reiterate the error the committee have made in making a comparison between CLN2 and CLN3 in respect of their data. If the committee have made their recommendations with this in mind, then this is wholly inaccurate."	
The Department of Health and Social Care	No comment.	Comment noted

Comments received from clinical specialists and patient experts

Nominating organisation	Comment	Response
UCL	Dear HST Evaluation Committee members I am providing my comments for the consultation process. First of all, it is disappointing to me as a clinician looking after the patients with CLN2 disease that the use of cerliponase alfa enzyme replacement therapy is not recommended for use in treating this disease despite quite clear treatment effect demonstrated in the clinical trial, which was accepted by the HST evaluation committee at the panel meeting. Moreover, it does not appear from the summary of the meeting that basic mistakes made by the ERG in their evaluation of the effect of cerliponase alfa (accepted by the ERG at the meeting) were taken into consideration. The speaker for the ERG said it himself: "We got it wrong". These were their last words. Hence it was frustrating to see no mention of this in the summary and no clear recommendation at least for the managed access agreement in the ECD document, which would address the question about long-term	Comment noted. The evaluation committee has taken into account all factors that affect its decision. It considered that clinical evidence suggests that, in the short term, cerliponase alfa improves quality of life, and slows the deterioration of motor and language function. However, there is no long-term clinical evidence available, so assumptions about long-term disease stabilisation and mortality are associated with substantial uncertainty. Furthermore, all the cost-effectiveness estimates are substantially above the range NICE normally considers acceptable for highly specialised technologies that met the criteria for a QALY weight of 3.0. Therefore the committee decided that cerliponase alfa does not appear to provide value for money within the context of a highly specialised service, and cannot be recommended for use in the NHS. Please see section 1 of the FED.

Nominating organisation	Comment	Response
	effect on the arrest of disease progression. In my personal practice I look after 10 patients with CLN2 disease on cerliponase alfa. 4 of these patients have been on this drug for at least 3.5 years and the other 6 for more than 10 months. I have also looked after 6 patients who were not on cerliponase alfa and I have attended meetings where numerous cerliponase alfa treated and untreated CLN2 patients from other centres were presented. Compared to the untreated patients who progressively loose skills after the onset of the disease, CLN2 patients in my care treated with the enzyme replacement for more than 6 months maintain their level of functioning and in many cases learn new motor skills and develop complex language. Moreover, the treated patients' seizures stabilise (many have not had any seizure episodes for years) and we are able to reduce their antiepileptic therapy, patients do not develop progressive myoclonus that is a real problem for the untreated patients. Treated patients do not develop progressive spasticity and do not have deteriorating movement disorder. The difference between the treated and untreated patients is so dramatic that the decision of NICE HST evaluation committee is staggering but clearly is based on the ERG studies that quite unfortunately were completely misleading. As a result of this poorly informed assessment by the ERG there is a delay in providing life-saving therapy for new patients with CLN2 disease who are being diagnosed in the UK. Unfortunately, this decision does not take into consideration the urgency of the need for starting therapy early. As a direct result of this decision the newly diagnosed children will not	Comment noted. The committee agreed that substantial benefits had been shown with cerliponase alfa in the short term for treating the key neurological aspects of CLN2. However, although cerliponase alfa would likely provide long-term benefits, assumptions of disease stabilisation, and late stabilisation in particular, were associated with substantial uncertainty. Please see sections 4.10 and 4.11 of the FED.

Nominating organisation	Comment	Response
	benefit and loose skills, they will not be able to walk, talk and enjoy life as much as they would if the treatment was started. I provide specific comments to 3 conclusions made by NICE. 1. NICE concluded that there is a significant risk of heart, liver and pancreatic complications as seen in CLN3 disease. In fact, it is suggested that in CLN3 disease all patients develop heart abnormalities by the age of 14 and therefore surviving CLN2 patients will do the same. It is important to recognise that whilst there are similarities between CLN2 and CLN3 deficiencies (specifically both diseases cause seizures, retinopathy and brain atrophy with the resulting motor and cognitive deficits), there are also significant differences in the phenotype of the two disorders caused by deficiencies of two different proteins with completely different functions. However, even for the CLN3 phenotype I have consulted with my colleagues in the UK and abroad and none of them believe that all CLN3 patients develop cardiac disease by the age of 14 and they certainly do not develop pancreatic or liver failure at any age. There is one report of a CLN2 patient (who has no confirmed molecular or enzyme diagnosis in the case report) who survived for many years on artificial ventilation and developed cardiac rhythm abnormalities aged 22. I have a confirmed report from a Turkish colleague Dr Meral Topcu who has a classical CLN2 patient on artificial ventilation aged 24 who has no extraneuronal disease manifestations. A much more appropriate proxy example for a CLN2 patient on enzyme replacement treatment would be the milder forms of CLN2 deficiency	Comment noted. The committee recognised the limitations of developing an evidence base for an ultra-rare disease and was satisfied that it had been presented with the best available evidence. The committee was aware that the EMA had not dismissed concerns about cardiac impairment, although this related more to potential adverse effects of treatment. Therefore, the committee agreed that extra-neurological mortality, although plausible, was not supported by the trial evidence nor the clinical experts. It concluded that exploring the effect of continued neurological progression-related mortality was appropriate, but incorporating extra-neurological mortality risk was not. Please see sections 4.4 and 4.15 of the FED

Nominating organisation	Comment	Response
	(confirmed by molecular and enzyme studies) where the onset of disease is still in the childhood but the patients are surviving into their 50s and 60s (see references below). These patients have no evidence of extraneuronal disease. 1. Breedveld, G. J., van Wetten, B., te Raa, G. D., Brusse, E., van Swieten, J. C., Oostra, B. A., Maat-Kievit, J. A. A new locus for a childhood onset, slowly progressive autosomal recessive spinocerebellar ataxia maps to chromosome 11p15. (Letter) J. Med. Genet. 41: 858-866, 2004. 2. Dy, M. E., Sims, K. B., Friedman, J. TPP1 deficiency: rare cause of isolated childhood-onset progressive ataxia. Neurology 85: 1259-1261, 2015. 3. Sun, Y., Almomani, R., Breedveld, G. J., Santen, G. W. E., Aten, E., Lefeber, D. J., Hoff, J. I., Brusse, E., Verheijen, F. W., Verdijk, R. M., Kriek, M., Oostra, B., Breuning, M. H., Losekoot, M., den Dunnen, J. T., van de Warrenburg, B. P., Maat-Kievit, A. J. A. Autosomal recessive spinocerebellar ataxia 7 (SCAR7) is caused by variants in TPP1, the gene involved in classic late-infantile neuronal ceroid lipofuscinosis 2 disease (CLN2 disease). Hum. Mutat. 34: 706-713, 2013. 2. Very little was commented by NICE about the benefits of treatment with cerliponase alfa beyond the stabilisation of deterioration in motor abilities and language. Whilst motor and language domains were used as primary endpoints in the	

Nominating organisation	Comment	Response
	clinical trial, seizures, myoclonus and vision domains were assessed and the data was presented to NICE. I presented the data at the British Paediatric Neurology Association meeting in January 2018 to a room full of Paediatric Neurologists (many with experience of looking after patients with CLN2 disease) who were stunned to see the effect of this drug on reducing the seizures and preventing progression of the myoclonus and spasticity, which is reflected in the overall motor abilities. The effect of the above on improving quality of life for the patients would be enormous. In addition, this would provide a massive improvement in the quality of life of the families. In addition to the improvement in generalised tonic clonic seizures (our longest treated patient has not had any seizures for more than 3 years) the patients have improvement and no further progression in myoclonus and absence seizures. Although the EEG still shows baseline abnormalities our patients have improvement in the EEG as reported by our neurophysiology department. Furthermore, our radiologists report no further deterioration of the brain MRI scans for CLN2 patients after the first year on enzyme replacement therapy. These reports are slightly different to the averaged results from all the patients on BioMarin trial. No normal controls were used in the trial and therefore it is difficult to know whether the reported 3.3% reduction in cerebral volume between weeks 48 and 96 lie within the normal variation for the children of this age. We do know that brain continues to solidify during childhood which is seen as overall reduction in volume. 3. NICE focused on the ECG abnormalities that were reported in the "Adverse Events" for the trial and invariably deemed clinically not significant	Comment noted. The committee agreed that treatment with cerliponase alfa would result in some benefit beyond improvements in motor and language function. In terms of seizures, the committee heard that the evidence showed that treatment with cerliponase alfa slows the deterioration of myoclonus-related symptoms. The committee concluded that the long-term effect of cerliponase alfa on seizures remained uncertain. However, it agreed that some seizure control with treatment, with a subsequent effect on quality of life, was plausible. In terms of vision, the committee looked at the trial results and concluded that there was insufficient evidence to suggest that cerliponase alfa would prevent vision loss in people with CLN2. Please see section 4.9 of the FED.

Nominating organisation	Comment	Response
	by the clinical staff. This was a particularly frustrating conclusion of the NICE since bradycardias reported by the ECG machines were in fact normal rhythm associated with normal sleep of the children. The ERG should have dismissed all of the reports as they were not significant. Even after I explained this to the ERG at the NICE meeting they still brought up another report (also deemed not significant) of the "possible cardiac hypertrophy" which was initially reported as possibly related to the drug as it appeared soon after the infusion (a very unlikely possibility). Again, this was an ECG report which was not confirmed by the echocardiography and shown to be wrong. It is important to accept the following: there is no evidence of any cardiac structural or rhythm abnormalities identified in the trial or in the expanded access program. Saying this, I can emphasise that we, of course, be keen to continue carefully monitoring patients on therapy for any possible new cardiac problems.	Comment noted. The committee discussed the ERG's interpretation that new electroencephalography (EEG) activity could be suggestive of new seizures activity. The clinical experts confirmed that EEG activity is not interpreted in this way. Please see sections 4.9 of the FED.
Patient expert	I am writing to you as a mother of four children, two of whom have CNL2 Batten Disease. Both [redacted] and [redacted] are receiving the drug Cerliponase Alfa at Great Ormond Street hospital, London. [redacted] started treatment in November 2016, aged five, [redacted] started in February 2017, aged three. As you are aware both [redacted] and [redacted] are doing incredibly well on the treatment. On reading the Evaluation Consultation Document for Cerliponase Alfa for treating neuronal ceroid lipofuscinosis type 2 I have concerns that not all aspects of the treatment have been taken into account.	Comment noted. Thank you for sharing this information about the experiences of you and your family. The evaluation committee considered evidence submitted by the company, the views of people with the condition, those who represent them and clinical experts, NHS England and a review by the ERG. The committee recognised that CLN2 is a serious and debilitating condition, and that cerliponase alpha could be a potentially promising treatment. Clinical evidence suggests that, in the short term, cerliponase alfa improves quality of life, and slows the deterioration of motor and language function. However, there is no long-term clinical evidence available, so assumptions about long-term disease stabilisation and mortality

Nominating organisation	Comment	Response
	The committee recognised that CNL2 Disease is a devastating condition associated with a very poor quality of life and a very short life expectancy which until now had significant unmet needs in terms of effective treatment options. The committee acknowledged that the aim of this treatment is to maintain function for as long as possible and to improve quality of life. Whilst children are receiving this treatment there is a possibility as research continues that a cure will be found. I recognise that the company have concentrated gathering evidence to show the positive impact this treatment is having on motor and language skills but they have not included other aspects such as seizure control, movement disorders and swallow function, as well as the impact treatment is having on quality of life. [redacted] is seven years old, sadly before this treatment was available to [redacted] he had lost his ability to walk and talk. Before treatment [redacted] lost his abilities rapidly. Doctors had warned that it would be fast but nothing could prepare our family for how fast the disease took over our little boy's body. In the space of just a few months [redacted] went from being a little boy who could run like the wind, climb the tallest trees and kick a football as hard as his two older brothers to a little boy who could no longer stand on his own two feet. We cannot describe the pain which we felt as parents watching the confusion on our sons face as he fell over time and time again, wiping those tears from his face as he became frustrated. When children with Batten disease begin to lose these abilities they are of sound mind. This is something that has not been discussed, how do these	are associated with substantial uncertainty. Furthermore, the cost-effectiveness estimates are all much higher than the range that NICE considers acceptable for highly specialised technologies that met the criteria for a QALY weight of 3.0. Please see section 4 of the FED for the committee's consideration of the evidence. Comment noted. The committee considered the treatment benefit associated with cerliponase alfa beyond improvements in motor and language function. Please see section 4.9 of the FED. Comment noted. Thank you for sharing this information about the experiences of you and your

Nominating organisation	Comment	Response
	children feel when they are aware they are losing skills but are not at an age to understand why? [redacted] is not like healthy children of his age that are CNL2 free but nor is he like other children of his with CNL2 Disease that are not receiving this treatment. As we are all aware CNL2 Disease progresses rapidly, but this treatment has stabilised [redacted]. I understand that some may question how we can prove this as [redacted] has already lost his gross motor skills and can no longer speak recognisable words. Before treatment [redacted] was experiencing all types of seizures daily, many which required hospital admissions. In the last sixteen months [redacted] has had one tonic clonic seizure and no other seizure of any type. [redacted] does not suffer from movement disorders and his medication intake for a child of his age and weight is at the lower range. Amazingly [redacted]s swallow is still safe and he can still enjoy his favourite foods such as McDonalds fries, crisps, and toast, this is something that is rarely seen in a child of his age. Since [redacted] has been diagnosed with CNL2 Disease he has not had a chest infection and his oxygen is 99% in air, we truly believe that this is the result of the treatment he has been receiving. I know from research that is very common for children with this disease to have recurrent chest infections which they cannot recover from, some of these infections lead to the child needing oxygen at home and untimely these infections can cause death.	family. The evaluation committee considered evidence submitted by the company, the views of people with the condition, those who represent them and clinical experts, NHS England and a review by the ERG. The evaluation committee has taken into account all factors that affect its decision.

Nominating organisation	Comment	Response
	The disease can also affect a child's ability to sleep, some researchers say this is due to the child's loss of vision meaning the brain does not know the difference between night and day and therefore it does not release the hormone needed to stimulate sleep, others say it is due to pain and movement disorders. Both [redacted] and [redacted] do not have trouble sleeping, both sleep between ten to twelve hours a night which is the recommended amount of sleep for a child of their age. They do not take medication to help them sleep. An important factor I have picked up on throughout my involvement in the NICE process is how quality of life is measured. It is a huge concern as parents that it may be seen that children who cannot walk and talk do not have a good quality of life. On the trial and the extended access program children are assessed using a rating scale which has been adapted by the pharmaceutical company from the Hamburg and Weill Cornell scales. I feel that it is extremely important that the committee members know that there is a huge difference between children, who have been rated a zero. A child with the score of zero has been defined as a child who is immobile and has no language. A child who is at end of life care who is experiencing constant seizures, excruciating pain, needing many different types of medications to keep them as stable as possible; a child who is requiring oxygen daily; a child who is being fed small amounts via pumps and IVs because their body is shutting down and can no longer cope digesting food is being rated at the same scale as a child like our little boy [redacted] who can	Comment noted. The committee considered acceptability of CLN2 rating and concluded that, the CLN2 clinical rating score was an acceptable instrument to inform efficacy outcomes in the short term, but that it would also consider any broader measures presented in its considerations of clinical effectiveness. Please see section 4.5 of the FED. The committee also recognised that generic measures of health related quality of life were not sensitive to all aspects of CLN2 disease. However, it acknowledged the significant burden of CLN2 on people with the condition and their families, and took this into consideration in its decision making.

Nominating organisation	Comment	Response
	still attended a main stream school where he accesses the curriculum alongside his peers, he takes part in PE lessons, school trips and school plays. Each week he attends swimming lessons and enjoys having his friends over for tea. He can interact, make sounds and communicate via body language. [redacted] loves fast rides and laughs his little head off, he hates anything messy and rolls his eyes and pulls his hands away from paints and play dough as he does not like them. [redacted] enjoys tasting foods and playing with his siblings. He does not experience pain and his seizures are very well controlled, resulting in a huge reduction in hospital admissions. In addition to this the only extra outside care [redacted] receives is a carer who has been put in place for [redacted] to attend school, due to [redacted] needing to be hoisted in and out of his chair. The school did not have qualified members of staff in place for this. [redacted] enjoys spending time in his standing frame as well as attending local and professional football matches in all weathers. [redacted]'s health has been stable since starting the treatment, he does not require equipment such as a SATs monitor, suction machine or oxygen cylinders at home. It is very clear that [redacted] does have a Very Good Quality of Life despite the fact he is in a wheelchair. I think that it is unrealistic and extremely unfair to group children who are in completely different stages of the disease together with the same score of zero. When measuring quality of life in a child with CNL2 Batten Disease, I	Comment noted. Cerliponase alfa was appraised within its marketing authorisation which is not restricted by the severity of disease. The company proposed a managed access arrangement to target people who would benefit most from cerliponase alfa treatment. However, for the agreement to be implemented, it would need to be shown that cerliponase alfa could plausibly be cost effective in the context of a highly specialised technology. Please see sections 4.38 and 4.39 of the FED

Nominating organisation	Comment	Response
	believe that the questionnaires given to parents from the PedsQL and the EQ-5D-5L/EQ-5D-3L are very difficult to answer when the questions are not pacific to a child with this type of disease. I think that these questionnaires would benefit from having an area that parents can write comments, this would also help to gather more evidence rather than it being a simple tick box answer. Our perfect little girl [redacted] was diagnosed with Batten Disease 30th March 2015 at two years of age. [redacted] was tested for this disease due to the recent diagnosis of her older brother [redacted]. She had no symptoms of the disease, [redacted] had hit all her milestones, was fully toilet trained and was enjoying life as a 'normal' happy, healthy toddler. Over a year after [redacted]'s confirmed diagnosis in February 2017, [redacted] started receiving treatment on the extended access program at Great Ormond Street Hospital in London. [redacted] is one of the youngest Children in the world to be receiving this treatment and even more importantly the only symptom of Battens Disease [redacted] had shown was a seizure two months prior to starting treatment, which was associated with a sickness bug. As far as we have been made aware by professionals this treatment had never been given to a child at this stage in the disease before. Our daughter is a first, [redacted] is days away from celebrating her fifth birthday. Batten Disease should have taken over her little body, destroying her abilities, taking away her childhood. Instead [redacted] is a healthy, extremely lively, happy little girl. [redacted] attends a mainstream school along with her three big brothers. She	Comment noted. The committee recognised that generic measures of health related quality of life were not sensitive to all aspects of CLN2 disease. However, it acknowledged the significant burden of CLN2 on people with the condition and their families, and took this into consideration in its decision making. Comment noted. Thank you for sharing this information about the experiences of you and your family. The committee heard from parents that treatment with cerliponase alfa completely changed their experience of having children with CLN2. This was because children remained healthy, able to live a normal life and attend mainstream school and activities. However, it recognised that the full effect of benefits beyond direct health benefits had not been quantified. The committee also recognised that considering these in a qualitative manner would not be sufficient to affect its recommendation, given its estimate of a most plausible ICER. Please see section 4.38 of the FED.

Nominating organisation	Comment	Response
	participates in all classroom activities, she enjoys mark making and is able to play independently as well as being able to interact appropriately with her peers. [redacted] is learning new words daily and is able to speak in five to six word sentences which is recognisable to strangers. Recently [redacted] has been able to learn simple phonic sounds which she can retain and can also make the correct animal sounds when asked. She is able to count to ten and school has reported that she is beginning to count objects in order. The committee recognised that onset of symptoms in CNL2 Batten Disease present themselves between the ages of two and four, it is also stated in the report produced that a rapid phase of decline is expected in children ages four to five. During this period the report quotes that children should be experiencing seizures, there should be a rapid loss of language, as well as ataxia, clumsiness, loss of ambulation, myoclonic/abnormal movements and the start of vision loss function. This description does not describe our little girl. Not only is our daughter not losing skill, she is retaining her skills and even more incredibly [redacted] is learning new skills. [redacted] is able to understand instructions and is aware of the world around her, for example, she will stop at the side of the road as she understands it is not safe to cross without an adult. She understands danger and also knows age appropriate right from wrong, i.e. she knows it is wrong to hurt another person. Outside of school [redacted] attends dance, gymnastics and swim classes as well as being able to go round to her friend's house to play. She has also been	

Nominating organisation	Comment	Response
	able to take part in professional dance shows with a local dance company, Dance at the Smithy Dance and Theatre School. [redacted] has no health problems and has recently been accessed by the physiotherapists at Great Ormond Street Hospital, the report produced by GOSH states that [redacted] has no problems with her balance, she has no muscle or joint problems. [redacted] does not suffer from any movement disorders or myoclonic jerks neither is she on any medications for these. [redacted] is able to walk, run, jump and climb. She is able to stand from sitting whilst holding objects therefore not needing to use her hands to assist her to stand. [redacted] is able to use an age appropriate scooter and is learning to ride a bike. The Physiotherapy assessment also looked at how [redacted] placed her feet as she walked and the speed in which she walked at, the reports shows that [redacted]'s results are that of a healthy child. Since starting treatment [redacted] has not experienced any types of seizures. [redacted] was started on an anti-seizure medication before the enzyme therapy was started, this has not been increased at any stage and is a very low dose. Given the fact that [redacted] has gained weight and age it would have been expected that the medication would have had to have been increased to control seizures, however this has not been the case and instead a discussion has been had with health professionals regarding removing the medication if no seizure present themselves over the next twelve months. To have this discussion in itself is remarkable as most children [redacted]'s age would be adding in many medications to try gain seizure control. Importantly [redacted] has not lost any bladder or bowel control, she is in knickers	

Nominating organisation	Comment	Response
	and is dry both day and night, she does not experience any accidents. [redacted] is able to live her life just like any other healthy four-year-old thanks to the early administration of the enzyme replacement therapy. This leads onto the extreme importance of early diagnosis. The earlier in which this treatment can be administered to a child with CNL2 Batten Disease the better the outcome. For this to happen health professionals need to be educated on the signs and symptoms of Batten disease, not just the doctors but health visitors also as these are the professionals parents of young children will turn to first if their child is experiencing language problems or struggling to meet milestones. Due to the lack of knowledge and experience of CNL2 Batten Disease of those health professionals which we encountered led to the deterioration in [redacted]s condition. The lack of support that we were given when [redacted] was diagnosed lead to us having to fight along with the BDFA to gain compassionate use of the treatment. This again delayed treatment for both [redacted] and [redacted] with consequent further deterioration in [redacted]s condition before treatment could be given. As a family we are doing our upmost to raise the awareness of this disease, encouraging members of the public to share our journey. The impact of this treatment does not just impact on [redacted] and [redacted]'s quality	Comment noted. The evaluation committee has taken into account all factors that may affect its decision. The committee recognised that children diagnosed and treated earlier in the pathway may have better outcomes. However, it concluded that implementing the early diagnosis campaign would be feasible, but there are substantial administrative barriers to implementation. Please see sections 4.13 and 4.14 of the FED.

Nominating organisation	Comment	Response
	of life but it has improved the quality of life for the whole family unit. We also have two older children aged nine and ten, both boys are healthy yet watching their younger brother decorate so quickly has obviously affected them emotionally. They have had to watch their little brother experience horrendous seizures, and even witnessed their father performed CPR on [redacted]. Before treatment started our older boys would not know if we would be at home when they returned home from school or if we would yet again be in hospital with [redacted] because of another seizure. They spent their time being ferried from one relative to another as [redacted]'s condition worsened. They could not spend time with their friends outside of school or join in with after school activities. Instead they found themselves having to grow up extremely quickly, learning basic first aid and having the knowledge to call the emergency services. The severity of the disease also affected myself and my husband's ability to work. [redacted] was self-employed and had to give up work to help myself care for the children. Financially we struggled as we had no wage entering the household. Life was extremely hard; stress levels were high as well as our emotions. Since [redacted] and [redacted] started treatment our life's have complete changed. As this therapy has stabilised [redacted], improving his symptoms, our life has adapted to a new norm. Our children can now take part in after school activities, both our older boys are committed members of an established football club. They no longer worry about hospital admissions and most importantly they do not have to witness daily seizures and other health	Comment noted. Thank you for sharing this information about the experiences of you and your family. The committee discussed the impact of cerliponase alfa beyond its direct health benefits. It was aware of the very large impact of CLN2 on families, including the emotional effect on carers, family relationships and siblings with the disease. It noted that there is a substantial financial impact on families. The committee heard from parents that treatment with cerliponase alfa completely changed their experience of having children with CLN2. This, in turn, allowed parents to work and provide a normal childhood for siblings without the disease. The committee considered that some of these aspects, such as productivity losses and disutilities, were included in the economic analysis. However, it recognised that the full effect of benefits beyond direct health benefits had not been quantified. The committee also recognised that considering these in a qualitative manner would not be sufficient to affect its recommendation, given the difference between its estimate of a most plausible ICER and the threshold level considered to be cost effective. Please see section 4.38 of the FED.

Nominating organisation	Comment	Response
	related issues, instead they can spend quality time with their brother and sister playing and creating memories. [redacted] has been able to return to work part time and we have recently booked a family holiday aboard. Life has improved immensely for us all. During the meeting on the 17th January 2018, the subject mortality was disused. The ERG had compared CNL2 patients receiving Cerliponase Alfa with CNL3 patients where currently there is no treatment. We believe that it is unrealistic to compare these two types of Batten Disease, as two different genes are affected. Stating that children receiving enzyme replacement therapy will experience shorter life expectancy because of cardiac, pancreatic and hepatic impairment unless enzyme replacement therapy is administer systemically is based on option and not evidence. It is unfair that this has been taken into account when making a decision to fund treatment for CNL2 Batten Disease. Since diagnosis [redacted] has had a number of ECGs all which have been normal both off and on treatment. Last month [redacted] also had a ECG which has also been reported as normal. Without continuing children on this therapy there will never be any long term evidence to say if this treatment continues to work in the long term. It would be unethical to remove treatment from patients that is showing huge benefits to their health and quality of life.	Comment noted. The committee recognised the limitations of developing an evidence base for an ultra-rare disease and was satisfied that it had been presented with the best available evidence. Please see section 4.4 of the FED Comment noted. The recommendation is not intended to affect treatment with cerliponase alfa that was started in the NHS before this guidance was published. People having treatment outside this recommendation may continue without change to the funding arrangements in place for them before this guidance was published, until they and their NHS clinician consider it appropriate to stop. This decision should be made jointly by the clinician, and the child and the child's parents or carers. Please see section 1.2 of the FED

Nominating organisation	Comment	Response
Clinical expert (consultant neurologist)	Has all of the relevant evidence been taken into account? I believe so Are the summaries of the criteria considered by the committee, and the clinical and economic considerations reasonable interpretations of the evidence? I believe so Are the provisional recommendations sound and a suitable basis for guidance on the use of cerliponase alfa in the context of national commissioning by NHS England? Yes at the current time, but the landscape is changing rapidly and further information is very likely to become available. The evidence should be reviewed again within 3-5 years. Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity? The draft guidance from NICE not to recommend cerliponase alfa as a treatment for CLN2 disease within its marketing authorisation will be disappointing for families and advocacy groups, but not surprising given the health economic evaluation, anticipated cost of the technology and NICE criteria. We have a duty to those children and families who have volunteered altruistically to participate in the clinical trials of this technology, including UK families. They have willingly taken on unknown risks and the burdens of trial participation in the hope that this will benefit not only their	Comment noted Comment noted Comment noted. The guidance on this technology will be considered for review 3 years after publication. Please see section 5 of the FED. Comment noted. The evaluation committee has taken into account all factors that affect its decision. It considered that clinical evidence suggests that, in the short term, cerliponase alfa improves quality of life, and slows the deterioration of motor and language function. However, there is no long-term clinical evidence available, so assumptions about long-term disease stabilisation and mortality are associated with substantial uncertainty. Furthermore, all the cost-effectiveness estimates are substantially above the range NICE normally

Nominating organisation	Comment	Response
	own children but those diagnosed in the future. My view is that we have an ethical duty to continue their treatment within the NHS as long as the treating physicians and families believe such treatment is in the child's best interests. It will be important to monitor the progress of these treated children closely in order to gain as much information as possible to inform future policy and practice, so that they do not feel participation was wasted.	considers acceptable for highly specialised technologies that met the criteria for a QALY weight of 3.0. Therefore the committee decided that cerliponase alfa does not appear to provide value for money within the context of a highly specialised service, and cannot be recommended for use in the NHS. Please see section 1 of the FED.

Comments received from commentators

None.

Summary of comments received from members of the public

Theme	Response
Without treatment people with CLN2 disease decline quickly	Comment noted. The committee recognised that CLN2 is a devastating condition associated with poor quality of life and a very short life expectancy. Please see section 4.1 of the FED.
Disease progression is delayed or stopped in people who received cerliponase alfa	Comment noted. The committee noted that substantial benefits had been shown with cerliponase alfa in the short term for treating the key neurological aspects of CLN2. The committee also considered long-term effectiveness of cerliponase alfa. It noted that cerliponase alfa could be expected to be used for decades, and that the results could not show whether the disease would remain stabilised over that period of time. It therefore concluded that cerliponase alfa would likely provide long-term benefits. However, assumptions of disease stabilisation and late stabilisation in particular, were associated with substantial uncertainty. Please see sections 4.7, 4.8, 4.9, 4.10, 4.11, 4.12, 4.21 and 4.22 of the FED.
Seizures are controlled by cerliponase alfa	Comment noted. The committee agreed that some seizure control with treatment was plausible. However, long-term effect of cerliponase alfa on seizures remained uncertain. Please see section 4.9 of the FED.

Theme	Response
Cerliponase alfa improves the quality of life of people with CLN2 disease	Comment noted. It concluded that treatment with cerliponase alfa was associated with at least an initial improvement in quality of life. It further concluded that a utility benefit for people treated with cerliponase alfa, beyond that on slowing disease progression, was plausible. Please see sections 4.16 and 4.29 of the FED.
Cerliponase alfa leads to improved development (e.g. process language quicker, movement, better cognitive funtion, ability to eat and swallow)	Comment noted. The committee acknowledged the substantial benefits shown with cerliponase alfa in the short term for treating the key neurological aspects of CLN2. Please see section 4.10 of the FED.
Cerliponase alfa has an acceptable adverse event profile	Comment noted. The committee heard from clinical experts that cerliponase alfa is not associated with adverse events that could not be easily managed. Please see section 4.10 of the FED
CLN3 has different pathology and etiological process – difficult to compare and draw conclusion for CLN2 from observations in CLN3 disease	Comment noted. The committee recognised the limitations of developing an evidence base for an ultra-rare disease and was satisfied that it had been presented with the best available evidence. Please see section 4.4 of the FED
No evidence to support reduced mortality at 96 months	Comment noted. The committee concluded that, although cerliponase alfa would likely provide long-term benefits, assumptions of disease stabilisation, and late stabilisation in particular, were associated with substantial uncertainty. Please see sections 4.8, 4.21 and 4.22 of the FED. .
EEG findings not necessarily indicate continued neuronal progression	Comment noted. The committee discussed the ERG's interpretation that new electroencephalography (EEG) activity could be suggestive of new seizures activity. The clinical experts confirmed that EEG activity is not interpreted in this way. Please see sections 4.9 of the FED.
Earlier diagnosis is feasible due to routine genetic testing	Comment noted. The committee recognised that children diagnosed and treated earlier in the pathway may have better outcomes. However, it concluded that there are substantial administrative barriers to implementation of an early diagnosis campaign proposed by the company. Please see sections 4.13 and 4.14 of the FED.

Theme	Response
Cardiac conduction abnormalities are not issues with cerliponase alfa treatment	Comment noted. The committee was aware that the EMA had not dismissed concerns about cardiac impairment, although this related more to potential adverse effects of treatment. Therefore, the committee agreed that extra-neurological mortality, although plausible, was not supported by the trial evidence nor the clinical experts. It concluded that exploring the effect of continued neurological progression-related mortality was appropriate, but incorporating extra-neurological mortality risk was not. Please see section 4.15 of the FED.
Traumatic brain injury may not be a good proxy for estimating long term effects of neuro-disability	Comment noted. The committee considered that in the absence of evidence or an alternative proxy, traumatic brain injury was acceptable for modelling purposes.
Managed access agreement would be beneficial	Comment noted. The committee agreed that a managed access agreement would be appropriate and the proposed data collection could address the key clinical uncertainties that it had identified. However, cerliponase alfa could not be recommended within the context of a highly specialised services. Please see section 4.39, 4.40 and 4.42 of the FED.
No other treatments available, if patients stay on treatment long-term results will become available	Comment noted. The committee is aware that there are currently no treatments available to treat the underlying cause of the condition and data collection could address the key clinical uncertainties that it had identified. It was aware of the very large impact of CLN2 on families. However, cerliponase alfa could not be recommended within the context of a highly specialised services. Please see sections 4.1, 4.38, 4.39, 4.40 and 4.42 of the FED.

Highly Specialised Technology Evaluation

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

Company's Responses to Evaluation Consultation Document

Supplied 5th March 2018

1. Summary of company comments

1.1 The company is confused and perturbed by the NICE Evaluation Committee's ("the Committee") provisional recommendations and considers them to be flawed for a number of reasons:

1.1.1 The Committee concludes that all of the treatment benefits associated with cerliponase alfa are fully captured in the slowing of decline in motor and language scale (M/L) scores only. This conclusion is at odds with the evidence presented by the company, patient and clinical experts, which clearly identify additional treatment-related benefits over and above M/L scale scores including, but not limited to, improvements in the reduction of frequency and severity of seizures, reduction in myoclonus, improved wellbeing and reductions in vision loss, when compared to standard of care alone.

1.1.2 The Committee has clearly based its conclusions about the long-term benefits of cerliponase alfa treatment and several other topics (including the interpretation of M/L scale score progression and decline, EEG and cardiac abnormalities, the importance of extra-neuronal pathology) on, at best misleading or unreliable evidence put forward by the Evidence Review Group (ERG) and, at worst, incorrect or false evidence. In particular, the company is concerned that the ERG's perspective on the following topics has created a completely misleading or false narrative about neuronal ceroid lipofuscinosis type 2 (CLN2) patients:

1.1.2.1 Utilisation of CLN3 disease as a proxy for predicting long-term outcomes and mortality risk for CLN2 patients, despite these being totally different diseases in terms of causation, pathology and course of disease;

1.1.2.2 Concluding that all CLN2 patients will die of extra-neuronal complications when the published evidence does not support this conclusion, with neurological

complications being the main cause of death in all CLN2 patients and even CLN3 patients (of which only about 20% have been reported to die of extra-neuronal pathology);

1.1.2.3 It is wholly inappropriate and inaccurate to compare people experiencing traumatic brain injury and CLN2 patients to make assumptions about the mortality risk associated with neuro-disability;

1.1.2.4 Incorrectly assuming that all of the treatment benefits of cerliponase alfa are fully captured in the slowing of decline in M/L scale scores, thereby ignoring the benefits observed on the vision and seizure domains.

1.1.3 The ERG's narrative and conclusions on these topics form the main basis of the ERG's preferred modeling scenario, but do not accurately reflect the clinical evidence submitted. Nor does this correlate with the body of expert opinion in the UK and from other clinician experts in the management of CLN2 disease, and does not reflect their understanding of CLN2 and their experiences in real-life clinical practice. The company has to question, therefore, why and on what basis the Committee has chosen to give so much weight to the ERG's conclusions.

1.1.4 The company welcomes the Committee's acceptance that cerliponase alfa treatment leads to clinical benefit and improves patient quality of life in the short-term. It is, therefore, all the more inexplicable that the Committee has chosen to completely disregard those same benefits when considering cost-effectiveness. Specifically:

1.1.4.1 In sections 1.2 and 4.13 of the Evaluation Consultation Document (ECD), the Committee acknowledges that cerliponase alfa treatment improves quality of life. This improvement is not, however, taken into account at all when calculating utility values for treated patients in the ERG's economic analyses.

1.1.4.2 The Committee accepted that, in the short-term, cerliponase alfa treatment is associated with improvements in M/L function and physical health, as well as reductions or slowing of progression on the seizure, pain, vision and myoclonus domains (see sections 1.2, 4.8, 4.9, 4.19 of the ECD). In spite of these findings, the Committee erroneously and perversely concludes that all of the treatment benefits associated

with cerliponase alfa are fully captured in the slowing of decline in M/L scores only, and fails to take account of any of the other observed clinical benefits in the economic evaluation.

1.1.4.3 The Committee concluded that measures to support earlier diagnosis were important (section 4.2 ECD), but then fails to take into account the real-life trend towards earlier diagnosis over time in the economic evaluation.

1.1.5 The company acknowledges that there is uncertainty associated with the long-term benefits of cerliponase alfa, as well as assumptions about long-term disease stabilisation and mortality. However, in choosing to adopt the ERG's preferred economic scenario in its entirety without challenge, the Committee is acting inconsistently with the totality of the evidence.

1.1.5.1 Firstly, the Evaluation Committee noted that the ERG's analysis was similarly associated with considerable uncertainty;

1.1.5.2 Secondly, at the meeting on 17th January, the ERG admitted that the scenarios it presented were likely to be 'unduly pessimistic'. The company concurs with this view. It is completely unrealistic for the ERG to conclude that cerliponase alfa treatment generates as few as 5.89 QALYs (undiscounted), even taking into account the inevitable uncertainty.

1.1.5.3 Thirdly, the Committee fails to make any concession whatsoever in the economic evaluation for the positive treatment effects that it itself has accepted and which are noted elsewhere in the ECD.

1.1.6 In summary, therefore, it is, particularly concerning and, in the company's opinion, entirely unreasonable that the Committee has chosen to adopt the ERG's scenario in full and without question.

1.2 In this response, the company puts forward two alternative scenarios for consideration which address the concerns about the uncertainty associated with the long term clinical effectiveness of cerliponase alfa that have been raised by NICE. The assumptions used in these scenarios provide a much more credible, objective and reliable basis for decision-making than any of the ERG's preferred scenarios.

1.3 For all of these reasons, the company does not believe that the Committee's provisional recommendations are either a sound or suitable

basis for guidance on the use of cerliponase alfa in the context of national commissioning by NHS England

1.4 The company's comments on specific sections of the ECD are given below.

2. Page 3. Section 1.2. Why the Committee made these recommendations

"Clinical evidence suggests that, in the short term, cerliponase alfa improves quality of life, and slows the deterioration of motor and language function. However, there is no long-term clinical evidence, so assumptions about long-term disease stabilisation and mortality are associated with substantial uncertainty."

Company response: The company is pleased to note the Committee's acknowledgement that the clinical evidence showed that cerliponase alfa improved patient quality of life and slows the deterioration of motor and language function. The company acknowledges that there is limited long-term evidence of benefit and that assumptions about long-term disease stabilisation are associated with uncertainty, but it is neither true to say that there is no long-term clinical evidence nor that the lack of abundance of the same means that there is no long-term benefit. The company provided 96-week data on the efficacy and safety of cerliponase alfa for all patients treated in studies 190-201 and 190-202. These patients continue to be followed up in study 190-202 for a period of up to 5 years. Where available, the company submitted data to NICE for up to 145 weeks of treatment for some patients, but this evidence was not taken into account by the Committee.

In addition to Study 190-202, and as part of its ongoing commitments to the European Medicines Agency (EMA) and the US Food and Drug Administration (FDA), the company is in the process of initiating a 10 year study to provide long-term evidence on the safety and efficacy of cerliponase alfa treatment, as well as a neurological outcomes study investigating the effect of cerliponase alfa on long-term outcomes. The data from these three studies will be made available to NHS England and reported back as part of any future Managed Access Agreement (MAA).

Thirdly, the company acknowledges that assumptions about long-term disease stabilisation and mortality are associated with considerable uncertainty. This is hardly surprising given that cerliponase alfa is the first ever treatment for the disease and untreated patients historically die around 10 years of age on average. It is not, however, reasonable to penalise the patients for the fact that this treatment is pioneering. Unfortunately, the

assumptions put forward by the ERG on these topics are largely unsound and based on limited or questionable evidence of little or no relevance to CLN2 disease. The ERG report includes a number of statements which are either factually incorrect or which lack validity.

The company refutes the suggestion that the ERG's assumptions on long-term disease stabilisation and mortality constitute a reasonable interpretations of the body of evidence submitted and asserts that the uncertainty around long-term outcomes must apply equally to the ERG's preferred approach as it does to company's submitted base case.

Insofar as the Committee has based its conclusions about the long-term benefits of cerliponase alfa treatment, mortality risk and extra-neuronal pathology on a flawed ERG report, its provisional recommendations cannot be considered a sound or reasonable basis for decision-making in the context of national commissioning.

3. Pages 7-8. Section 4.2 Diagnosis

"The committee concluded that measures to support earlier diagnosis are important."

The Committee heard from clinicians and parents that CLN2 diagnosis is a lengthy and difficult process and that earlier diagnosis is critical to stabilising the disease earlier in its course. The committee also heard about a number of measures designed to support earlier diagnosis.

Given these conclusions, the Committee's decision not to take into account the impact of earlier diagnosis when considering the health states of the starting population for the economic evaluation is inexplicable (see section 4.20, modelling assumptions).

BioMarin has developed diagnostic programmes that are aimed at supporting early diagnosis of CLN2 disease. In accordance with the NICE Epilepsy Guide (*Services for the diagnosis and management of the epilepsies in adults, children and young people: commissioning guide, 26th February 2013*), BioMarin will be supporting general paediatricians or paediatricians with a special interest in neurology by providing enzyme tests whenever there is a suspicion of CLN2 disease (i.e. patients presenting between the ages of 2-4 with unprovoked seizures and history of language delay). BioMarin will offer at no cost to the NHS epilepsy gene panels in cases when a definitive diagnosis is more difficult to achieve (for example, unprovoked seizures but without clear history of language delay). These gene panel would cover over 190 potential epilepsy causing mutations, supporting earlier care for patients

suffering epilepsies of an unknown origin.

4. Page 9. Section 4.4 Clinical trial evidence

"The committee recognised the limitations of developing an evidence base for an ultra-rare disease and was satisfied that it had been presented with the best available evidence".

Company response: The company accepts that there is limited clinical effectiveness data available beyond 96 weeks of treatment and therefore that there is inevitable uncertainty associated with estimates of the long-term risk and benefits of treatment. We welcome NICE's acknowledgement that the best available evidence was presented. However, this acknowledgement makes it even more perplexing that the Committee chose to accept the ERG's assumptions (which were, in part, based on inaccurate inferences) and pessimistic scenario over the totality of the clinical trial data, expert clinical and caregiver testimony submitted to it.

5. Page 10. Section 4.6 Rate of decline in CLN2 scores in the natural history population

"The ERG noted that estimates of mean decline in the natural history controls varied depending on the statistical method used, with more sophisticated methods such as the repeated measures mixed effects model resulting in lower estimates (a 1.29 to 1.46 point decline per 48 weeks). The ERG explained that the more sophisticated statistical methods were superior to the company's simplistic approach because they made better use of all the available data points. The committee concluded that all available data should be used when possible. It agreed that the mixed effects model used by the ERG was more appropriate to estimate the rate of decline in CLN2 scores in the natural history population."

Company response: The company disagrees with the ERG's assertion that a 'more sophisticated' repeated measures mixed effect model is preferable to the company's approach and is therefore a more appropriate method for estimating the rate of decline in CLN2 patients.

Basing the responder analysis on a 2-point change in the CLN2 rating scale (as shown by 1st and last point and simple regression methods) was the pre-defined approach in the clinical trial Statistical Analysis Plan. Secondly, both the FDA and EMA agreed that the company's approach was a suitable approach to statistical analysis.

The mixed measures repeated model (MMRM) is based on significant assumptions, whereas the regression analysis carried out by the company was based on the actual data observed in the clinical trial programme. We note that committee's conclusion that "all available data should be used when possible".

The assumptions incorporated into the MMRM are significant and not in line with the observed data. Some sources of inaccuracy in the ERG assumptions include:

- Significant data imputation methods were used for the MMRM analyses – carry forward post-baseline and carry backward to baseline;
- Modelling was performed to the first ML scale score of 0;
- For the analysis from age 36 months onwards, many subjects had ML scale scores of 6 at age 36 months; and
- For the analysis from age of diagnosis, a relatively high proportion of the follow-up is for the ML scale score transition from 1 to 0 (which has a relatively slower rate of decline than the transitions from 5 to 1.

6. Page 12. Section 4.8 Results Seizures

"The Committee noted the improvement in scores in the seizure domain…The ERG highlighted that the seizure domain of the Hamburg scale reflects only the frequency of tonic-clonic seizures and does not take into account other seizure types…The committee concluded that the long-term effect of cerliponase alfa on seizures remained uncertain".

The company welcomes the Committee's acknowledgement that evidence was presented on the reduction in tonic-clonic seizures. However, it is not true to say that evidence relating to other types of seizure does not exist; the company presented evidence of a reduction in the frequency and severity of other types of seizure, but this evidence appears to have been ignored by the ERG and, therefore, by the Committee.

Specifically, seizure data from Schulz was presented as part of the company's submission, but has not been taken into account. These data showed that:

- Twenty-two subjects in the cerliponase clinical trials (92%) reported a medical history of epilepsy or seizures;
- Twenty-three subjects (96%) experienced one or more seizures during the study;
- An improvement was seen in the grand-mal seizure subscore from baseline to 96 weeks (increasing from 1.7 points to 2.3 points);
- 88% of seizures were mild to moderate (Grade 1 or 2) in severity;

- A decrease in seizure frequency and severity was observed over time (Schulz, A. Intracerebroventricular Enzyme Replacement Therapy with Cerliponase Alfa in Children with CLN2 Disease: Results from an Ongoing Multicenter Extension Study. Presentation held at 14th annual WORLD symposium, February 5-9 in San Diego, CA)

The patient perspective was in line with this clinical evidence but, again, this has largely been ignored by the Committee.

Finally, and notwithstanding the data summarised above about other types of seizure, there was a clear acceptance in the ERG report that it is the clonic-tonic seizures that have the greatest impact on patient quality of life; this is not made clear in the ECD.

7. Page 12. Section 4.8 Results Vision

"Vision: the company stated that patients treated with cerliponase alfa had a slower decline in vision (as measured by the vision domain in the Hamburg rating scale) than untreated patients. The ERG noted that baseline vision scores were higher for the cerliponase alfa group, so the comparability of the groups was limited.

Company response: As stated in its response to the ERG report, the company does not, and never has, claimed that treatment with cerliponase alfa can prevent vision loss. The company has only ever maintained that cerliponase alfa can slow the progression or rate of decline of characteristic aspects of CLN2 disease, inter alia, by preventing the deterioration of motor and language function, reducing the frequency of seizures and by slowing down the rate or progression of visual impairment. These claims are based on the clinical trial results in study 190-201/202.

The company submitted clinical trial data on the vision and seizure domains of the Hamburg scale; these data are suggestive of a durable treatment effect of cerliponase alfa in CLN2 patients, which is not specific to any one domain.

The company maintains that the clinical trial results indicate that cerliponase alfa can, and appears to, delay the rate of progression of visual impairment; the decline in visual domain scores of cerliponase treated patients in the 201/202 study was significantly less than that observed in the 1:1 matched natural history cohort. However, this was never a primary endpoint or a symptom targeted by the company for proof of the efficacy of cerliponase alfa. The company does not know for certain the physiological mechanism underlying the treatment effect observed; however, it is likely that this might be a result of the effect on the central components of the brain.

8. Pages 12-13. Section 4.8 Results Vision

"The ERG also noted that the vision domain of the Hamburg scale may not have been the most appropriate scale to measure deterioration in vision because the scale wording necessitates a certain level of motor function (for example, grabbing objects). It stated that other more specialised ophthalmological endpoints would have been more appropriate for assessing vision decline."

Company response: The company recorded visual function measures showing the impact of cerliponase alfa on the visual domain scores as part of the total CLN2 (MLVS) scale (Table C24 of the company submission) and as a separate score (response to the clarification question A10 and A11). The vision domain score of the total CLN2 scale (Hamburg scale) is a validated measure for measuring visual function in CLN2 patients.

In addition, the company is currently investigating the impact of intravitreal applications of TPP1 directly into the retina in animal models. Results so far have shown a clear prevention of retina damage and stabilisation of retinal function as assessed using electro-retinography tests, in dog models treated with intravitreal delivery of TPP1 compared to untreated dogs who continued to progress (Sinclair et al 2018, "Intravitreal enzyme replacement therapy attenuates retinal disease progression in a canine model of neuronal ceroid lipofuscinosis type 2 (CLN2)" presented at WORLD congress, San-Diego, USA Feb 5 – 9 2018).

9. Page 13. Section 4.8 Results Vision

"The committee concluded that there was insufficient evidence to suggest that cerliponase alfa would prevent vision loss in people with CLN2."

Company response: Please refer to the previous response in point 7 above, the company never states that treatment will prevent vision loss, but the evidence shows a slowing down of vision loss.

10. Page 14. Section 4.10 Long-term effectiveness

"The ERG stated that there were a number of limitations related to these assumptions:

- ***These definitions were determined after the studies, which was inappropriate because differences in response may be due to sampling error rather than a genuine difference in response***

patterns to cerliponase alfa treatment.

- ***Trial data were not sufficiently long enough (96 weeks) to make long-term judgements about disease stabilisation.***
- ***Long-term trends in CLN2 scores implied that scores will continue to decline for late stabilisers beyond 96 weeks, so contradicting the assumption that disease stabilises in all patients...”***

Company response: [redacted]

The fluctuations seen in some scores over time do not contradict the claim in the company submission that patients would not see an unreversed decline in CLN2 score.

The fluctuations (improvement followed by a decline) between week 96 and last observed follow-up may reflect the impact of temporary illness, which could have a temporal impact on their ability to walk or talk at that point.

In addition, slope analyses provided by the company suggest that, on average, patients receiving cerliponase alfa see their ML scores stabilise after Week 96; [redacted]

11. Page 14. Section 4.10 Long-term effectiveness

"Relative to baseline, there was a trend of new epileptiform activity on electroencephalogram, suggesting that disease progression had not halted completely."

Company response: As stated in the company's factual accuracy check of the ERG report, the ERG's conclusions that electroencephalogram (EEG) and magnetic resonance imaging (MRI) evidence suggested that disease progression was not halted in treated CLN2 patients are incorrect.

The development of new epileptiform activity in treated CLN2 patients is not indicative of neuronal progression or worsening of seizures as asserted by the ERG. According to several world-leading experts in the management of CLN2 disease consulted by the company, the development of new epileptiform activity could be due to a number of reasons:

1. EEG findings are in no way correlated with the clinical picture. Clinical experts have reported been able to eliminate seizures or significantly reduce their frequency and severity without seeing a correlated change in EEGs (i.e. still observing the development of epileptiform activity). This could be as a result of difficulties in distinguishing from EEG readings what is a seizure, versus movement disorder or dystonia.
2. Given that CLN2 patients have epilepsy (with a life-long risk of seizures), development of abnormal epileptiform activity is to be expected, even when their seizures are well-managed by anti-epileptic drugs.
3. The development of epileptiform activity could also be as a result of detection (unmasking) of previously existing seizure types that are not obvious to patients who regularly experience generalised tonic-clonic seizures. In addition, children with CLN2 may have hundreds of seizures (of different types; focal, atonic, absent, etc.) a day, which in the past were difficult to differentiate even in EEG outputs due to the very rapid deterioration of natural history patients.
4. The EEG readings might be influenced by the time of the assessment and also a change in medication.

In conclusion, the company believes that the ERG's conclusions about new epileptiform activity cannot be considered a reasonable interpretation of the evidence on this topic and the Committee was wrong to place such weight on them.

12. Page 15. Section 4.10. Long-term effectiveness

"The committee agreed that, in the absence of any evidence, it was not possible to predict the long-term effects of cerliponase alfa. It concluded that the assumptions of disease stabilisation, and late stabilisation in particular, were associated with substantial uncertainty."

Company response: The company acknowledges that assumptions of disease stabilisation are associated with substantial uncertainty, but does not believe that the Committee has fully taken into account all the relevant evidence presented.

For example, MRI showed significant slowing of brain loss, which could be attributed to debulking of lysosomal storage disorders (LSDs) as opposed to disease progression. [redacted] The ERG noted that this is indicative of long-term stabilisation of disease.

There is no suggestion that this evidence has been taken into account by the Committee.

13. Page 16. Section 4.12 Mortality

"The committee was aware that, by assuming long-term disease stabilisation (see section 4.10), the company implicitly assumed that patients treated with cerliponase alfa would have the same life expectancy as the general population. The ERG stated that this was unrealistic and considered that mortality related to neurological progression as well as extra-neurological mortality was relevant. The committee agreed that, because it had concluded that that the assumption around late stabilisation was very uncertain (see section 4.10), it was plausible that patients would have further progression of disease with an associated mortality risk."

Company response: The company acknowledges the uncertainty around late stabilisation of disease, further disease progression and associated mortality risk. However, the Committee has apparently concluded that this uncertainty does not apply to the opinions and conclusions of the ERG on these topics, many of which are unsound, based on very little evidence and/or run contrary to the body of expert opinion. In short, an absence of data cannot and should not be construed solely to the benefit of one opinion and the detriment of another – it needs to remain, at worst, inconclusive for both sides.

Specifically,***"The ERG explained that, while death usually occurs because of complications from neurological degeneration, the expression of TPP1 is not limited to the central nervous system and that untreated***

accumulation of ceroid lipofuscin may lead to pancreatic, intestinal, cardiac and hepatic impairment".

The company challenges this on three grounds;

1. CLN3 disease is not a suitable or reliable proxy for CLN2 disease;
2. Extra-neurological mortality is not a relevant factor when considering mortality risk in CLN2 patients; and
3. The ERG's conclusions regarding cardiac abnormalities and increased mortality risk are erroneous and based on extremely limited evidence of questionable relevance.

1. CLN3 disease is not a suitable or reliable proxy for CLN2 disease

- The ERG's conclusions of an increased significant risk of death to CLN2 patients from heart, liver and pancreatic complications assume that CLN3 disease is a reliable proxy for CLN2 disease. This is not the case. As the company made clear in its response to clarification questions and the ERG report, CLN3 disease is a very different disease to CLN2 in terms of causality, pathology, clinical manifestation and progression; CLN3 disease is not an appropriate analogue from which to draw conclusions applicable to CLN2 disease.

2. Extra-neurological mortality is not a relevant factor when considering mortality risk in CLN2 patients

- There is no evidence of extra-neuronal mortality complications in CLN2 patients, including those with atypical presentations and Scar 7 (which has TPP1 deficiency and is a variant of CLN2 disease) who have lived up until the age of 73 (Sun et al., Hum. Mutat. 34: 706-713 and Breedveld et al. Med. Genet. 41: 858-866, 2004)
- In addition, clinical experts experienced in the treatment of CLN2 patients (with and without cerliponase alfa) and consulted by the company have confirmed that they have not identified any extra-neuronal pathology in any of their patients in clinical practice and nor is it something they would expect to see in the near future. This was detailed in the company response to the clarification question A11, the company response to the ERG report and was also supported by the clinical expert at the 17th January meeting (Section 4.12 ECD), who confirmed that no extra-neurological effect has been seen in patients currently being followed.

- Extra-neurological complications and related mortality are infrequent in other NCL diseases, including CLN3 disease (for which only a few patients

have died from extra-neurological complications). This is clear from the Østergaard paper relied upon by the ERG (Østergaard et al., 2011) in which only 54% of CLN3 patients (and not all of them, as claimed by the ERG) experienced cardiac complications, most of which were mild and potentially easily treatable. Of these subjects, only 20% died of cardiac complications; the remaining 80% died of neurological complications.

- As mentioned in our factual accuracy check to the ECD report, cerliponase alfa delivered in the brain via ICV has been shown to go into the blood stream at concentrations (1.0 – 1.9 ug/mL) that are similar to concentrations of other systematically delivered enzyme replacement therapies (ERTs) such as elosulfase afa and galsulfase. These concentrations are similar to the blood concentration seen in atypical patients who live longer with no presentation of cardiovascular or extra-neurological complications (Kohan et al. Gene 2013 516: 114 – 128, Kohan et al Clin Biochem 2005: 38: 492 – 494). Although not a perfect comparison (as tissue concentration of enzyme does not always correlate with blood concentration), we feel it is plausible that this concentration in the blood should be sufficient to protect from any future risk of extra-neurological complications. This is supported by evidence from other LSDs such as MPS IIIB, in which ICV delivery of the enzyme has been shown to result in reduction of storage material in the peripheral organs (such as reduced liver size) (Muschol et al 2018. "ICV-administered BMN 250 (NAGLU-IGF2) is well tolerated and reduces heparan sulfate accumulation in the central nervous system of subjects with Sanfilippo Syndrome Type B (MPS IIIB)" Platform presentation at WORLD congress, San-Diego, USA Feb 5 – 9 2018)
- The company acknowledges the potential for retinal damage leading to vision loss as an extra-neuronal pathology, but would reiterate that there is virtually no other evidence of any other form of extra-neuronal pathology (including cardiac dysfunction) in any of the phenotypes of CLN2 patients.
- The Committee itself acknowledged that, in the absence of longer-term data, the effect of CLN2 on mortality due to effects in other body systems is completely unknown (section 4.12 ECD, pages 16-17). It is, therefore, surprising that the Committee has adopted the ERG's conclusions on this topic in full.

3. The ERG's conclusions regarding cardiac abnormalities and increased mortality risk are spurious, and based on extremely limited evidence of questionable relevance.

- The ERG has concluded (i) that cardiac abnormalities observed in animal models and ECG observations in the clinical trial programme are suggestive of possible cardiac developments in CLN2 patients at a later stage, (ii) that *all* CLN2 patients will start to develop significant heart abnormalities by the age of 14, as seen in CLN3 patients, and (iii) that these cardiac abnormalities will result in CLN2 patients dying on average at the age of 27 years. These three conclusions are based on either very limited or no credible evidence and are untrue.

- Firstly, the three publications (Fukumura et al., Hoffman et al., Østergaard et al.) relied upon by the ERG in support of these statements included only one CLN2 patient. That patient's diagnosis of CLN2 could not be confirmed, as it was not carried out according to current clinical practices (i.e. genetic testing was carried out on only one allele, not two).

- Secondly, there is no evidence to support the ERG's claim that all CLN2 patients will develop cardiac abnormalities, or that these abnormalities will result in early death. The cardiac complications identified are easily managed with anti-arrhythmia drugs and/or a pacemaker. In the case reported in the Fukumura paper, the CLN2 patient's family declined to have the cardiac complications treated due to the patient being in the advanced stages of neurological disease.

- The ERG's narrative that cardiac complications and mortality occur in all CLN3 patients is also untrue. In the Østergaard paper, which the ERG relied upon, only 54% of patients were identified as having some evidence of cardiac abnormalities, most of which were mild. Only 20% of the deaths in CLN3 patients were due to cardiac failure; the remaining 80% were due to complications sequelae to neurological complications.

- The animal models referred to by the ERG used gene therapy to treat CLN2 disease, not enzyme replacement therapy or cerliponase alfa; these models are not appropriate predictors of future outcomes in CLN2 disease in humans. There is some evidence in the literature of some vectors used in gene therapy causing immune response in animals, which might explain the complications seen in the animal model.

- Finally, the investigators in the cerliponase alfa clinical trial programme concluded that the small number of ECG abnormalities observed were not clinically significant.

In spite of these concerns, at the ERG's request, the company modelled a conservative scenario a modelled scenario exploring the impact of assuming an increase in all-cause mortality due to involvement of extra-neuronal

pathology, and disutility associated with continued vision loss in CLN2 patients as they grow older. The results of this scenario indicated that these assumptions - even if correct - had a small impact on the ICER.

The Committee also accepted the ERG's conclusions that patients with CLN2 disease have an increased mortality risk due to their neuro-disability compared to the general population. The ERG assumed this to be in-line with that seen in patients with traumatic brain injury. Specifically, the ERG assumed that:

- Patients with ML scores of 6 and 5 will have the same mortality risk (1.44 times greater than the general population) as patients with traumatic brain injury with minor injury severity score.
- Patients with ML score of between 2 and 4 will have the same mortality risk (2.00 times greater than the general population) as patients with traumatic brain injury with moderate injury severity score.
- Patients with ML score of 1 and 0 will have the same mortality risk (9.92 times greater than the general population) as patients with traumatic brain injury with severe injury severity score.

No explanation has been given as to why traumatic brain injury is considered a relevant comparator for CLN2 disease, nor is there any evidence to support it.

14. Pages 20-21. Section 4.20 Model assumptions (health state distribution)

"The distribution of patients across health states at the start of the model was based on the population expected to have treatment for CLN2 in the UK. For this, the company assumed that patients will be diagnosed in an earlier health state in the future, with most patients (about 80%) starting treatment in heath states 1 and 2 (CLN2 score 6 and 5 respectively). The ERG highlighted that this differed substantially from the trial, which included 16% of patients with a CLN score of 5 or 6. The company explained that it intended to implement a campaign to support earlier diagnosis. The ERG highlighted that the assumption of earlier diagnosis had a considerable impact on the quality-adjusted life years (QALYs) gained in the model but that there was little evidence to show how this could be achieved. The committee discussed the details of the company's programme (commercial in confidence). It supported initiatives to enable earlier diagnosis because it recognised that any gains from treatment would be larger if treatment was started in early stages of the disease. However, it considered that the company's assumptions around diagnosis in the model were too optimistic. In its exploratory analyses, the ERG reflected the distribution of patients from

the natural history study 190-901, and the committee concluded that this was appropriate."

Company response: The company disputes the Committee's conclusion that it was appropriate for the ERG, in its exploratory analyses, to reflect the distribution of patients from the natural history study 190-901 when distributing patients across the health states in the economic model at diagnosis/onset. In response to a clarification question on this point, the company pointed out that the historical control population at diagnosis was unrepresentative of the current incident population due to the age of the cohort – some patients were recruited into the natural history cohort (the DEM-CHILD database) as far back as the 1960's, some 40 years before the first genetic test to aid diagnosis of CLN2 disease was developed.

To provide an accurate portrait of the incident population the company provided information on the starting population from the historical control data restricted to patients born after the year 2000. Nevertheless, results from the DEM-child natural history study have shown that there has been a trend towards earlier diagnosis of CLN2 disease even after the year 2000, [redacted] As such the distribution of patients across health states is likely to be different in the present day. The ERG has failed to take this trend into account; consequently, the distribution of patients across health states in the ERG's exploratory analyses cannot be considered a sound basis for decision-making.

15. Page 22. Section 4.21 Model assumptions

"The ERG presented analyses exploring the impact of incorporating neurological progression-related mortality and extra-neurological progression-related mortality, and the committee concluded that this was appropriate."

Company response: As noted above in several places, the company is surprised that the Committee has concluded that the ERG analyses are appropriate, in view of the fact that:

- Expert clinical evidence supported the fact that there is no evidence of extra-neuronal pathology in CLN2 patients;
- Several of the ERG's assertions about mortality risk are not supported by

credible or relevant evidence, or are simply incorrect;
- Assumptions about CLN3 disease and traumatic brain injury being relevant proxies for mortality risk and long-term outcomes in CLN2 patients are flawed; and
- The Committee itself concluded that (section 4.12) the effect of CLN2 on mortality due to effects in other (non-neurological) body systems is "completely unknown".

16. Pages 22-23. Section 4.22-4.23 Utility Values

"The committee noted that the utility data collected in the clinical studies (190-201/202) were not included because utility values were not available for all health states and no utility values were available for patients having standard care. The utility values for the base case were derived from a utility study commissioned by the company, in which vignettes describing the health states for both cerliponase alfa and standard care were developed...The committee concluded that applying differential utility values for patients who had or had not had treatment was inappropriate".

In sections 1.2 and 4.13 of the ECD, the Committee acknowledges that cerliponase alfa treatment improves patient quality of life. Perversely, the Committee then decides to exclude this improvement in quality of life from further consideration when calculating utility values for treated patients in the economic analysis.

In section 4.22, the Committee considers two alternative sources of utility values: the clinical trials and a utility study containing patient vignettes submitted by the company. The Committee decided that neither source was particularly robust. Moreover, the Committee notes that there is no utility value associated with standard care in the trials, while the ERG speculates that utility values in less severe health states were very high. As a result, the Committee concludes that applying differential utility values for treated and untreated patients was "inappropriate". No reason is given for this conclusion, which clearly flies in the face of the Committee's previous acknowledgement that a quality of life improvement was observed with treatment, and so introduces a disconnect between the Committee's clinical findings and the quantification thereof in the economic evaluation. Regrettably, the company is left with the impression that it was difficult for the ERG and Committee to quantify the quality of life improvement and as such disregarded it entirely.

17. Company's alternative modeling scenarios

The Committee has accepted the ERG's preferred scenario as the basis for

its decision-making in its totality. While the company acknowledges the limited evidence base and the uncertainty associated with long-term assumptions about the stabilisation of disease, there is no basis on which the Evaluation Committee can reliably conclude that the ERG's analyses and preferred scenario are any more appropriate than those of the company, or that the perceived absence of long-term data should automatically lead to a conclusion that there no long-term stability. As previously stated, the uncertainty in the evidence base does not mean that the ERG's preferred scenario is any more certain or definitive than that of the company.

The company therefore puts forward two alternative scenarios, applying different assumptions to the ERG preferred scenario accepted by the Committee, which provides a less pessimistic and more reliable basis for decision-making and which attempts to address some of the Committee's concerns about the uncertainties associated with the evidence base.

These scenarios are presented in the Appendix but the key assumptions are summarised below. In some cases, the company has reluctantly used the ERG's preferred assumption for pragmatic reasons in order to move the discussion forward, despite continued reservations from both the company and the clinical community about the validity or relevance of these assumptions.

Scenario 1

1. *Starting population in the model* – the ERG's analyses use the natural history cohort from study 190-901 as the starting population for the model; the ERG has distributed patients according to baseline ML score accordingly. This approach is unduly pessimistic, because the pattern of diagnosis has changed over time and even since 2000. The company has altered the patient distribution to reflect diagnostic improvements over time, resulting in a greater proportion of CLN2 patients being diagnosed at an earlier stage of disease. The rationale for why this is a more appropriate distribution than that applied by the ERG has already been described in the company's response to section 4.20 of the ECD (see paragraph 14 above).

2. *Partial disease stabilisation* – The ERG has assumed that CLN2 patients who 'stabilise early' will continue to maintain that stabilisation over time. The company agrees with that assumption.

   The Committee accepted the ERG assumption that all patients who are 'late stabilisers' will continue to progress at the same rate after 96 weeks of treatment. The company does not agree with this second

assumption. The evidence from the clinical trials suggests that there is a trending towards disease stabilisation (with a mean decline of 0.40 in ML score after the 1st 48 weeks of treatment, compared to a mean decline of 0.27 over a 96 week period, [redacted], for all patients. As such, the company does not agree with the assumption that all late stabilisers will continue to progress at the same rate, but rather that approximately 20-25% of late stabilisers will progress at a reduced rate of decline. The company has applied this alternative assumption in its alternative model scenario.

3. *Extra-neurological mortality risk* – As stated previously, the company does not accept that there is an additional risk of mortality associated with extra-neurological complications for CLN2 patients. However, it does acknowledge the limited evidence base on this topic and the Committee's conclusion that the effect of extra-neuronal pathology on long-term outcomes is unknown.

   In order to try to account for the uncertainty in the long-term mortality of CLN2 patients, therefore, the company has reluctantly applied the mortality risk of patients with traumatic brain injury (TBI) from the paper identified by the ERG as a pragmatic way of moving forward, despite its strong reservations about the validity of this comparison.

4. Utility values – The ERG has applied the same utility values to patients in both arms of the model, i.e. it has assumed that there is no difference in health-related quality of life between treated and untreated patients. The Committee has contradictorily accepted this assumption.

   When reviewing the clinical evidence, the Committee concluded that cerliponase alfa reduced the frequency and severity of seizures and *did* improve patient quality of life in the short-term (section 1.2, 4.8 ECD). It is, therefore, extraordinary that the Evaluation Committee has chosen to completely disregard its own findings on quality of life improvements for the purposes of the cost-effectiveness analysis.

   The company acknowledges that there is uncertainty as to the magnitude and duration of the quality of life benefit but some difference in utility must be expected between treated and untreated patients, especially as seizure domains are not captured by the M/L score and patients experience a reduction in seizures while maintaining their M/L score, both points which the Committee has accepted. For the purposes of alternative Scenario 1, therefore, the company has applied a utility increment of 0.1, being the smallest change in quality of life that

a patient would identify as clinically relevant (i.e. the smallest minimal clinically important difference, or MCID)[1] to patients in health states 2-6 (i.e. with a baseline M/L score of 1 to 5) in the cerliponase alfa-treated arm of the model to account for the reduction in frequency and severity of grand-mal seizures. In addition, and in accordance with clinical opinion, an additional utility increment of 0.1 (giving a total increment of 0.2 for cerliponase alfa arm) was also added to patients in health states 5 and 6 (i.e. M/L scores 1 and 2) to reflect the reductions in pain and myoclonus that patients experience on treatment.

Scenario 2

1. *Starting population in the model* – the company used the same distribution of patients and proportions per health state as submitted in the original company submission base case.

2. *Partial disease stabilisation* – the company has adopted the same assumption as for Scenario 1.

3. *Extra-neurological mortality risk* – In scenario 2, the company has applied the mortality risk of patients with TBI from the paper identified by the ERG, albeit with some modifications to correct for the errors made by the ERG. These adjustments represent the additional mortality risk that might be associated with neuro-disability and disease progression in CLN2 patients on the pragmatic basis that there is no other suitable proxy for comparison.

   Instead of applying an unadjusted mortality risk factor of 1.44 times greater than the general population for the early heath states, as the ERG did, the company has applied a factor of 1.12, which adjusts for comorbidities present before the TBI occurred. In patients with more severe disease, the company applied a risk factor of 10.30 times greater than the general population (cf. ERG factor of 9.92) of for the same reason.

4. *Utility values* – the company approach to utilities is the same as that submitted in the original company submission base case.

By applying these revised assumptions in the model, the number of undiscounted QALYs associated with cerliponase alfa treatment increase from 5.89 (estimated by the ERG) to 29.73 in Scenario 1 (discounted QALYs

[1] Chen et al. Qual Life Res. 2016 Jun;25(6):1585-96

increase from 4.34 to 12.22) and to 32.80 (discounted QALYs 13.20) in Scenario 2).

These alternative scenarios are being put forward by the company as part of ongoing confidential discussions with NICE and NHS England with regard to a MAA in the context of national commissioning. A separate submission will be made to NICE in confidence detailing the clinical and financial aspects of the MAA, with Scenarios 1 and 2 described above forming the basis of that submission.

Appendix: Alternative company scenarios

	ERG assumption	Company Scenario 1	Company Scenario 2
Starting population based on the 190-901 cohort;	ML 6 – 4% ML 5 – 11% ML 4 – 44% ML 3 – 19% ML 2 – 19% ML 1 – 0% ML 0 – 4%	ML 6 – 20% ML 5 – 40% ML 4 – 25% ML 3 – 10% ML 2 – 5% ML 1 – 0% ML 0 – 0%	Original base case in company submission, i.e. ML 6 – 40% ML 5 – 40% ML 4 – 10% ML 3 – 5% ML 2 – 5% ML 1 – 0% ML 0 – 0%
Transition probabilities for cerliponase alfa patients	As calculated by the ERG	As calculated by the ERG	As calculated by the ERG
Partial disease stabilisation for cerliponase alfa patients	Early stabilisers – stabilised Late stabilisers – continue to progress at same rate after 96 week	Early stabilisers – stabilised Late stabilisers – continue to progress, but at a slightly reduced rate	Early stabilisers – stabilised Late stabilisers – continue to progress, but at a slightly reduced rate
Extra-neurological and neuro-disability-related mortality	Neuro-disability-related mortality risk assumed using following risk factors: Health States 1-2: 1.44x that of general population Health States 3-5: 2x that of general population Health States 6-9: 9.92x that of general population	Neuro-disability-related mortality risk assumed using following risk factors: Health States 1-2: 1.44x that of general population Health States 3-5: 2x that of general population Health States 6-9: 9.92x that of general population	Neuro-disability related mortality risk factors applied with the following modifications: • Health States 1–2: 1.12x that of general population (adjusted ratio from ERG article) instead of 1.44 (unadjusted ratio used by ERG) • Health States 3-5: 2x that of general population (no change as article only reported unadjusted values) • Health States 6-9: 10.30x that of general population (adjusted ratio

			from ERG article) instead of 9.92 (unadjusted ratio used by ERG)
Vision	All patients go blind over time, and incur related support costs and disutility	ERG assumption applied	ERG assumption applied
Utility values using EQ-5D-3L data	Utilities are the same for both treatment arms using EQ-5D-3L data - Standard of care utility values used in both arms	Standard of care utility values used in both arms but with an additional utility benefit of: • 0.1 for patients in Health States 2–4 (ML score 3–5) to reflect the minimal clinically important difference (MCID) that patients will obtain due to improvements in seizures; and • 0.2 for patients in Health State 5 and 6 (ML score 1 and 2) to reflect MCID for improvements in seizures, pain, myoclonus and vision domains.	Utility values applied as per the base case in the original company submission, i.e. utility values taken from the utility studies
	Age-adjusted utilities are applied	ERG assumption applied	ERG assumption applied
	Carer and sibling disutility are removed after 30 years	ERG assumption applied	ERG assumption applied
Resource use	Additional resource use items are included (ECG, psychiatric support, residential care)	ERG assumption applied	ERG assumption applied
Discount rate	3.5% for costs and benefits	3.5% for costs and benefits	3.5% for costs and benefits
Undiscounted QALYs	5.89	29.73	32.80
Discounted QALYs	4.34	12.22	13.20

Highly Specialised Technologies (HST)

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

Response to ERG questions on company ECD response and MAA scheme

Question 1: On page 20 (point 2) of the company's response to the ECD it states that evidence from the clinical trials suggests that there is a trending towards disease stabilisation as the rate of decline in CLN2 score is falling over time. In support of this statement three figures are reported giving the mean rate of decline over different time periods. The wording of this paragraph is somewhat ambiguous and we would like verify that we are interpreting this paragraph correctly. Our interpretation of these figures reported is as follows:

- A mean decline of 0.27 points between week 0 (300mg baseline) and week 48 for all patients enrolled in the trial excluding patient [redacted];
- A mean decline of 0.40 points between weeks 48 and 96 for all patients enrolled in the trial excluding patient [redacted];
- [redacted].

Company response

The interpretation of the figures about the rate of decline is incorrect. Instead the mean rates of declines are as follows:

- A mean decline of 0.40 points between week 0 (300mg baseline) and week 48 for all patients enrolled in the trial excluding patient [redacted];
- A mean decline of 0.27 points between weeks 0 (300mg baseline) and week 96 for all patients enrolled in the trial excluding patient [redacted];
- [redacted]

The company acknowledges the ERG's concerns that the wording of the aforementioned paragraph in the company response ECD was somewhat ambiguous, and may have contributed to the misinterpretation.

Can you also clarify whether these figures have be rounded at all as the ERG can generate figures close to these, but not the precisely the same numbers?

The figures have been rounded to the nearest two decimal points. It is not clear what approach the ERG is using to estimate the rate of decline. For the avoidance of doubt the company will like to clarify that as per the statistical analytical plan (which was included in the submission) the rate of decline was estimated using the following algorithm:

The rate of decline is calculated as follows:

1) Identify a starting point and an ending point, where a “point” is a bivariate observation comprised of (1) a CLN2 score and (2) a time-point.
2) Determine the slope of the line connecting the two points:

$$\text{Slope} = \frac{(\text{Ending CLN2 score}) - (\text{Starting CLN2 score})}{(\text{Ending date}) - (\text{Starting date})}$$

3) Calculate the rate of decline as the negative of the line’s slope, scaled to a 48-week time period:

$$\text{Rate of decline} = (-1) \times (48 \times 7) \times \text{Slope}$$

Also attached to this response is the individual patient efficacy listings which provides CLN2 score per time point for each patient. We hope that this will enable the ERG reproduce these figures.

Question 2: [redacted]?

Company response

[redacted]

Question 3: In the company's response to the ECD, it states that a slight change was made to the ERG' s partial stabilisation scenario: a reduction to the rate of decline. The ERG are, however, not able to identify any change to this scenario. Can you confirm whether this has been altered and specify in more detail what has been changed in the executable model?

Company response

The company confirms that no change was made to the ERG's partial stabilisation scenario. Although no change was made to the scenario, the company does not believe this aligns with the results from the clinical trials. The evidence from the clinical trials suggests that there is a trending towards disease stabilisation (with a mean decline of 0.40 in ML score during the 1st 48 weeks of treatment, compared to a mean decline of 0.27 over a 96 week period, [redacted]. Although the company ***does not*** believe that 'late stabilisers' will continue to progress at the same rate after 96 weeks of treatment, in order to arrive at a potential agreeable scenario with the committee, the company decided against applying the reduced rate of disease progression for late stabilisers, in its alternative model scenario.

Highly Specialised Technology Evaluation

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

Company's Responses to Evaluation Consultation Document

(Commercial Offering Errata: Confidential for HST Committee Viewing Only)

Supplied 10th April 2018

Further to the company response to the Evaluation Consultation Document, the company proposes the following draft confidential commercial offering for consideration as part of the ongoing evaluation of cerliponase alfa. Specifically the elements of the commercial offering being proposed by the company include:

[redacted] Further details of the rationale and anticipated benefits of this programme is outlined in Appendix 1 of this document.

[redacted] The duration of the commercial offering will be 5 years which we assume will be the duration of a potential NICE positive guidance. This offering will be valid only if there is a positive NICE guidance

Presented below is a revised cost-effectiveness results taken into consideration the proposed commercial offering. The results are provided for a 5 year time horizon to reflect the duration of the proposed commercial offering. What can be noted is that the range of ICERs in the offer range from [redacted] dependent on the associated scenario and estimation on the uptake of the epilepsy genetic panels.

5 year time horizon		Company Submission (Base case)	ECD Response Scenario 1	ECD Response Scenario 2
	ICER	[redacted]	[redacted]	[redacted]
	QALYs (Undisc)	3.79	3.38	3.48
Commercial offering (Conservative Scenario)	ICER	[redacted]	[redacted]	[redacted]
	QALYs (Undisc)	5.21	4.74	4.84
Commercial offering (Optimistic Scenario)	ICER	[redacted]	[redacted]	[redacted]
	QALYs (Undisc)	8.5	7.91	8.00

Appendix 1

IMPACT OF NO COST GENE PANEL CAMPAIGN

BioMarin will be offering a series of programmes to support the early diagnosis of CLN2 disease. Specifically BioMarin will be providing at no cost [redacted] an epilepsy gene panel in patients with onset of un-provoked seizure at age of 2 – 4 years of age, and neuro-developmental co-morbidity is suspected. [redacted].

Currently gene panels are used in diagnosing of patients who do not have sufficiently recognisable or distinctive symptoms for a diagnosis to be made using other methods including enzyme testing for specific diseases. In the case of patients with early onset seizures and neurodevelopment comorbidities, these are mainly used as a 2nd or even 3rd line due to a perceived lack of cost-effectiveness. The current 1st line tests include EEG, Brain - MRI as well as blood and cerebro-spinal fluid tests (Mercimek-Mahmutoglu et al. 2015)[1]. These tests are useful in raising suspicion but are not diagnostic. Evidence from the literature suggests that the diagnostic yield rate using these tests in patients with epilepsy are quite low, with gene panels or specific gene or metabolic enzyme tests often required later for a diagnosis to be made. Based on discussions with the organisation of paediatric epilepsy network (OPEN), it is anticipated that providing a gene panel at no-cost to the NHS will result in gene panels being used as 1st line, provided it is done in partnership with the existing medical genetics team. In this way the process can potentially move from late confirmation of diagnosis to earlier screening and diagnosis.

Using gene panels as 1st line will result in earlier diagnosis of CLN2 disease and other diseases such as GLUT-1 deficiency and Lennox Gestaut, which are often diagnosed late or misdiagnosed due to their non-specific symptoms and rarity. The earlier diagnosis of these diseases have several benefits including reducing the diagnostic odyssey and associated anxiety of not knowing what the condition is; better and more targeted disease management, e.g. patients with GLUT-1 deficiency could be put on ketogenic diet which will reduce the seizure severity and frequency; and reduction of costs of investigative diagnostic tests that will be accrued if gene panel use is delayed.

Detailed below are the steps undertaken to model the impact of introducing the no-cost gene panel offering within the health economic model.

[1] Mercimek-Mahmutoglu et al, Epilepsia 2015; 56(5): 706 - 715

1. Step 1: Estimation of number of gene panels used

The gene panel campaign will be targeted mainly at paediatrician with specialist interest in epilepsy who are the main specialists responsible for diagnosing and managing epilepsy. As per the NICE guidance, all patients aged 2 – 4 years presenting with unprovoked seizure will be referred to see a paediatrician with specialist interest in epilepsy within 2 weeks of the incident. The annual number of gene panels used are estimated as follows:

- Based on the hospital episode statistics data 2016 -17; 4995 patients (across all age groups) will have a 1st paediatric epilepsy appointment for the first time, of which 1009 patients will be aged 2 – 4 years of age[2].

- Assuming [redacted] [3]of patients presenting with seizures have unprovoked seizures with presumed or diagnosed neuro-developmental comorbidities present, then potentially [redacted] will be eligible every year for the gene panel.

- We have assumed that the uptake of this service during the 1st year will be low (due to necessary time to promote this offering as well as ensure it's integrated within the existing clinical genetics service) and range between [redacted].

  [redacted].

2. Step 2: Estimation of cost savings and benefits due to earlier use of gene panel

The cost savings **per CLN2 patient diagnosed** as a result of the introduction of the gene panel campaign will consist of:

I. Total cost of NHS gene panels avoided due to patients using the BioMarin gene panels

[2] Estimated that 20.2% of paediatric epilepsy 1st appointments are due to patients aged 2- 4 years based on the hospital episodes statistics database.
[3] Table 1, Andell et al. Epilepsy Research (2015) 113, 140—150; 68% of patients with 1st unprovoked seizures had no presumed or diagnosed neurodevelopment comorbidity present

II. Total costs of additional diagnostic tests (such as MRI and EEG) that will be incurred as a result of delayed use of gene panels

III. Costs calculated in I and II are divided by the number of new CLN2 diagnosis per year (which is currently estimated as 5 based on known incidence numbers)

Summarised in the table below are the potential annual cost savings **per patient diagnosed** due to the gene panel.

A	B	C = (B x £800)**/5**[4]	D = B X 30%[5]	E = (D X £115)**/5**	F = (D X £448)**/5**	G = C+E+F
Scenario	Gene panels used	Total cost	Number of patients with positive diagnosis	MRI Total Costs avoided (MRI = £115)	EEG Total Costs avoided (EEG = £488)	Total Costs Avoided
Conservative	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Optimistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

It has also been assumed that earlier diagnosis of epilepsies will result in improvement in quality of life for patients and their family. Evidence from the literature has indicated that a ≥1 month diagnostic delay is associated with poorer outcomes (such as reduced IQ scores, vineland-adaptive scores which persist for several years) in patients with epilepsy (Berg et al. Epilepsia. 2014 Jan; 55(1): 123–132).[6]

Although there is a significant body of qualitative evidence in the literature on the quality of life benefit on patients and their families of early diagnosis of rare diseases including those presenting with seizures, we were unable to find a quantitative estimate. Hence in the absence of quantitative data, to reflect this improvement in quality of life, we have assumed an improvement of 0.03 for each patient diagnosed early using the gene panel in the conservative scenario and 0.05 in a more optimistic scenario.

Summarised in the table below are the potential additional QALYs that will be gained due to the gene panel campaign. **The QALYs are divided by the number of new CLN2 diagnosis per year (which is currently estimated as 5 based on known incidence numbers) to get QALY gained per CLN2 patient diagnosed.**

[4] Cost of gene panel at medical genetics lab in Great Ormond Street Hospital (GOSH).
[5] Diagnostic yield rate with gene panels are between 10% and 45% depending on the age of patients and the number of genes on the panel. We've conservatively estimated 30% given the BioMarin gene panel will have more than 190 genes (compared to ~ 70 for NHS gene panels)
[6] Berg et al. Epilepsia. 2014 Jan; 55(1): 123–132.

A	B	C	D = B X 30%[7]	E = (C X D)/5
Scenario	Gene panels used	**Utility benefit grossed over 1st 5 years[8] (discounted at 3.5% per year)**	Number of patients with positive diagnosis	Total number of QALYs gained
Conservative	[redacted]	[redacted]	[redacted]	[redacted]
Optimistic	[redacted]	[redacted]	[redacted]	[redacted]

[7] Diagnostic yield rate with gene panels are between 10% and 45% depending on the age of patients and the number of genes on the panel. We've conservatively estimated 30% given the BioMarin gene panel will have more than 190 genes (compared to ~ 70 for NHS gene panels)

[8] Optimistic scenario assumes 0.03 QALY due to early diagnosis and 0.05 QALY for optimistic

BATTEN DISEASE FAMILY ASSOCIATION
Together we WILL make a difference
Registered Charity In England and Wales 1084908 - Scotland SC047408

NICE Evaluation of Cerliponase Alfa for Treating CLN2 Disease, Late Infantile Batten Disease.

Highly Specialised Technologies Evaluation Consultation Response

Please see our comments below from the Batten disease family Association, (BDFA) (Registered charity in England and Wales 1084908-Scotland SC047408) as the only UK **patient organisation representing patients and families affected by this devastating disease. Based on our 20-year experience of dealing with this condition the BDFA would like to draw the Committee's attention to what we see as omissions and potential errors in the understanding of the condition CLN2 disease, a late infantile form of Neuronal Ceroid Lipofuscinosis commonly known as Batten disease, and the benefits of Cerliponase Alfa.**

We are particularly concerned that the committee did not fully include the benefits of cerliponase alfa treatment that had not been adequately captured in the trial data and drew heavily on data from CLN3 disease.

The committee has therefore drawn damaging conclusions about the likely disease progression for treated patients from this data, which are not accurate. To date 14 different types of NCL have been identified and characterised according to the gene affected. (NCL Batten disease second edition- edited by Sara E Mole, Ruth E Williams and Han H. Goebel, Oxford Uni Press) Whilst there is definite synergy in the overall disease characteristics and symptoms it is widely documented and clinically accepted that comparisons within disease types should not be used to make extrapolations on life expectancy and disease progression. Overall, patients with CLN3 disease, juvenile will definitely not have the same progression as CLN2 disease. CLN2 disease results in a known enzyme deficiency and CLN3 disease, a deficiency in a membrane bound protein (function currently not identified) located in the lysosome, which is not the same disease as CLN2.

We would also like to inform the Committee that since the last meeting (17th January 2018) another two children in the UK have been diagnosed with CLN2 disease. There are a further four children in the UK who have been diagnosed since the Compassionate Use places were filled and therefore are unable to receive treatment.

The committee stated, "It was convinced that cerliponase alfa offers an effective treatment option" Without this treatment, these children will lose many of their current abilities at a rapid rate.

In Section 1.2, the Committee stated that 'Clinical evidence suggests that, in the short term cerliponase alfa improves quality of life, and slows down the deterioration of motor and language function.' However, there were questions around the long-term effectiveness of the drug.

We recognise that at present we do not have long-term trial data past the stage of 96 weeks. The clinical trial 190-201/202 is scheduled to continue until 2020, allowing for the collection and evaluation of data from 23 patients worldwide. The BDFA is working closely with NHS England on a Managed Access Agreement, which would collect data on the effectiveness of treatment for 7 years. The BDFA is committed to working with the company to collect data from all children on treatment to measure the effectiveness of this drug in the long term.

All patients on the clinical trial in the UK have been receiving treatment for between 3 years 3 months (159 weeks) and 4 years 1 month (212 weeks). You will see in the Appendices that the families whose children have been on the clinical trial report that the abilities of their children have stabilised when receiving treatment. Parents report that their children have a very good quality of life and that little has changed for them since commencing treatment, in contrast to what they were led to expect at diagnosis. Two of the UK children aged between 7 and 8 years old on the clinical trial, who were able to walk unaided prior to starting treatment, are still able to do so. A third child, aged 8, who has been receiving treatment for 4 years 1 month (212 weeks), was able to walk with support prior to the start of treatment and is still mobile using a walker. The fourth child aged 7, can walk a few steps independently but prefers to use her wheelchair and can independently propel herself to where she wants to go. A child without treatment would be expected to lose the ability to walk at age 5.

Parents of these children told us that they were able to learn new skills and those who were talking prior to starting the clinical trial have developed their vocabulary and the complexity of their sentences. This development would not be expected for children not receiving the treatment who would be likely to lose all speech capacity by the age of 5 years old.

Similarly, parents of patients receiving treatment on the clinical trial outside of the UK report their children are able to walk with support, ride bikes, attend mainstream education, communicate and have the ability to increase their skills. Children can still attend school and are learning new skills and information.

In Section 2.2, the EDC states that the life expectancy of CLN2 is around 8 years to early adolescence

This information is incorrect. The youngest child to die from CLN2 in the UK was 5 years old and many children have died at 6 years old.

In Section 4.5, the Committee stated that 'the CLN2 clinical rating score was an acceptable instrument to inform efficacy outcomes in the short term..'

The BDFA facilitated a focus group of 13 family members with children on treatment. They all had children aged between 5 and 16 years old. Their time on treatment varied between 9 months (36 weeks) and 4 years 1 month (212 weeks).

The parents explained that the **CLN2 disease rating scale does not take into account all the benefits that are seen on treatment, especially** as the Visual and Seizure scores are rarely utilised. Parents discussed that the points on this scale are too broad and therefore children on and off treatment could have the same CLN2 disease rating scale score but significantly different abilities. Visual and Seizures scores should carry more weight as these aspects of CLN2 have a huge impact on the child's quality of life, e.g. ability to access education and other activities.

The CLN2 disease rating scales are too broad and require more granularity to fully capture the impact on children's quality of life. Looking at the motor scale as an example, there is a large gap between a child who is completely immobile, who would score a 0 on the scale, and a child who is showing no unaided walking or only crawling, who would score a 1 on the scale. In addition to this scale, parents felt it important to acknowledge a child's ability to sit, reach for items of interest, hold toys and devices, turn their head towards sounds, laugh, smile and participate in activities as this is something of importance to parents and families, not just the ability to walk or crawl.

Parents asked for recognition and consideration of their children's cognition, learning and understanding as children who are only able to say a few words may understand a lot more than they are able to vocalise. A score for pain is also required as many children who are not receiving treatment experience pain on a daily basis whereas parents of patients on treatment have not expressed concerns about pain. There is a clear need to develop a measure for clinicians to understand this key issue as pain has a huge impact on quality of life

Similarly, movement disorders, which are another key symptom of the disease, are not reflected in the CLN2 disease rating scale. Children, who are not receiving treatment, are affected by movement disorders throughout their day and during the night and this can be painful and disturb sleep. Parents of children on treatment report them to be significantly less troubled by movement disorders, such as dystonia and chorea, than their peers who are not receiving treatment.

The parents agreed that the language scale was difficult to score as with all young children, affected or unaffected develop at different stages and have more than one way of communicating. Some children with CLN2 disease retain the ability to point, make gestures and use other means of communication even when they have very few spoken words

Parents noted that the seizure scale was not clear enough. There are many different seizures associated with CLN2 disease and they need to break this scale down into types of seizures. As the committee noted the current scale only considers tonic-clonic seizures. Parents whose children receive treatment have not only reported fewer tonic-clonic seizures but also experience far fewer alternative types of seizures, such as myoclonic seizures. Parents whose children do not receive treatment report that their children have many myoclonic seizures throughout the day and this can be very distressing for both the child and the parents. These types of seizures in children with CLN2 disease are very difficult to treat.

In order for the more accurate and informative data to be collected, parents suggested that assessments could be done, where possible, outside of the hospital setting. Most children are more relaxed in a home or school setting. The use of technology such as video could be employed to ensure that tasks that children often perform in the home but would not do in the hospital can be recorded and evaluated as part of the overall assessment process. For example, a child may be able to use a walker at home but they would not be able to do this during the assessment, unless the parent can transport their walker into the hospital. Parents identified that this could have a potentially adverse effect a child's overall score on the rating scale. Parents commented that children who have reduced vision might be more confident with their mobility in familiar environments e.g. school and home.

In Section 4.8, the committee concluded that the long-term effect of celiponase alfa on seizures remained uncertain

Parents and professionals have seen a significant reduction in seizures for those on the treatment.

Although it was noted by a clinical expert that children on treatment remain on medication for epilepsy this is a minimal amount compared to those who have not received treatment. Patients on the trial have MDT meetings twice a year, which the BDFA are invited to attend, and many of the medication doses have remained the same for a long period of time for these patients. The BDFA attends similar meetings for patients not receiving treatment and observes that this is not the case; with many types of seizures being reported on a daily basis. Parents report that tonic-clonic seizures and the associated hospital admissions have an adverse impact on the child and family's quality of life.

As the ERG stated and as previously discussed the CLN2 disease rating scale only captures the tonic-clonic seizures and does not take into account the many other different types of seizures that affect these children. Parents with children receiving treatment do report occasional absences and myoclonic jerks but consider these to be minimal in comparison to untreated CLN2 patients.

In section 4.22, the committee concluded that applying differential utility values for patients who had or had not had treatment was inappropriate.

These variations capture the many benefits seen by families with children on treatment. These benefits are not captured by current Quality of life metrics. As discussed previously, parents believe that these quality of life assessments should always be undertaken in conjunction with the CLN2 disease rating scale assessments. Families in the focus group looked at both the Paediatric Quality of Life Inventory (PedsQL) and the EQ-5D-5L and identified that neither one was detailed enough or had the appropriate domains to reflect the quality of life for children with CLN2 disease.

One parent said; "*The questionnaires PedsQL and EQ-DD-5L are inappropriate for children with CNL2 Batten Disease. For children who are at the lower end of the rating scale, points 3 and below, using this questionnaire they would be deemed not to have a good quality of life purely based on the simple fact that the questions being asked do not give a true reflection on what quality of life actually is. As it is a tick questionnaire with no opportunity given to explain the answers, practitioners reading the questionnaires will only see the answers given to them rather that seeing all the things a child who can't walk and talk can still achieve.*
There is no mention about attending school, or classes or activities. As there is also no mention of activities, which children enjoy doing with or without help. Seizures have not been included along with feeding, tasting, swallow and vision.
It would be appalling to put this type of questionnaire in place to assess a child's quality of life with CNL2 Batten Disease."

Parents requested that there should be many more areas of assessment in the Quality of Life assessments such as 'non-verbal interaction and gesturing, pain, cognition, sleep pattern and feeding and swallowing.' Parents also asked if multidisciplinary school reports and evidence of overall ability to take part in a broad range of activities could be part of these assessments to have a wider and more comprehensive evaluation.

The BDFA has the knowledge, professional expertise, and experience to work with families to assist them and to work with BioMarin to improve quality of life assessments. This would ensure that assessments better reflect and capture the data needed to meet the needs of all concerned, most notably the patients with CLN2 disease, the treatment provider and health care regulators.

The BDFA would be happy to work with the company on these quality of life assessments to ensure that they meet the needs of patients with CLN2.

In section 4.18, the Committee has not adequately taken into account the costs for children who are not receiving treatment and has solely focussed on patients on treatment.

The use of costs for caring for a person with an acquired brain injury is an inappropriate proxy for children with CLN2 disease.

The BDFA asked parents on treatment how many hours care a week they received from health or social care. One child on treatment, aged 7, who has been on treatment for 1 year 3 months (64 weeks), receives 20 hours per week. A CLN2 disease affected child, of comparable age, not receiving treatment would expect to receive 100-120 hours per week, provided by highly skilled or trained nurses.

A bereaved grandmother, who also works in the NHS, estimated that in the end of life stages for a child with CLN2 disease the medication cost to the NHS is in the region of £2000 per month. Her grandson spent many weeks of his life in a High Dependency Unit, had numerous ambulance trips to hospital and A&E admissions.

Over the course of a lifetime of a child with CLN2 disease who is not on treatment, they will have had 2-3 wheelchairs, 1-2 walkers, a standing frame, specialist beds, housing adaptations, numerous slings, 2-3 bath seats, SATs monitors, cough assist machines, hoists, numerous pairs of splints for their hands and their feet, neck collars, suction machines. As the disease progresses so quickly, often equipment arrives too late and it is no longer useful. This is why a child will require 2-3 wheelchairs in the space of just a few years.

Patients being treated are not losing their skills rapidly unlike untreated children. Their equipment is therefore lasting longer and there is more time for professionals to react and provide exactly what is needed in a useful timeframe and cost effective way. Most of the patients on treatment do not require the use of a wheelchair, or a standing frame. They can sleep in a normal bed. None of the children on treatment in the UK use a cough assist machine or suction machines compared to children of the same age untreated who would need access to this equipment aged 7, although in some circumstances this might be earlier. Parents whose children are on treatment do not have to fight for health and social care support as minimal support is needed, often allowing family members to remain in employment.

The ERG assumed that the cost of care for a patient with CLN2 would be similar to costs for a young adult with a severe acquired brain injury. We do not believe that this is a fair comparison. Firstly, a person with an acquired brain injury may have a rapid change of symptoms that could take place in a matter of hours. Patients with CLN2 disease may deteriorate but this would be over a longer period of time, as the disease symptoms and expected progression is well documented. Patients with acquired brain injuries would, by definition of the condition, need all the care support and equipment immediately. Patients on treatment with CLN2 would need the care and equipment gradually if the disease did progress. Patients on treatment would not be expected to deteriorate so rapidly as to need 24-hour support without advanced warning. If, as is suggested by the current evidence, disease progression has stabilised they would and could, for a much longer period, live more independent lives than those not receiving treatment.

The report also does not adequately take into account the impact on the wider family. Many parents of affected children have to cease employment to care for their children and have to rely on state benefits. Parents are far more at risk of physical and mental health issues as a direct consequence of the burden of caring for their children. These issues, such as back injuries from lifting or depression and stress related health issues due to the lack of sleep, will require medical intervention at some point and necessitate further support measures to be provided at considerable cost by the health care and benefit system.

In section 4.8 "The Committee incorrectly concluded that there was insufficient evidence to suggest that cerliponase alfa could prevent or slow vision loss in patients with CLN2."

We recognise that there is currently little data as to whether ERT slows down the deterioration in vision. One parent has reported that their child, aged 7, who has been on treatment for 3 years 6 months (162 weeks), can still navigate their way round an IPad, selecting videos they would like to watch on You Tube independently and being able to find the 'Skip' button to skip through the adverts independently. They have not seen evidence in the 3 years she has been on the treatment that her vision has deteriorated. As per the data on the natural history of the disease we would expect that a child aged seven, not receiving treatment, would be functionally blind.

Many other parents tell us that their child is able to navigate their iPad well, and also, without assistance, find their own toys and play with them. Children with CLN2 disease have a considerable visual memory and progressively going blind is a very different situation compared to being blind since birth.

Children with CLN2 are usually able to navigate their way around familiar environments even if they have no remaining vision. The BDFA work with Qualified Teachers for the Visually Impaired across the UK, and we also work closely with schools. Children can now use many different communication aids to access literacy and numeracy in school. Many children use objects of reference to ask for particular items or tasks.

Barbara Cole, the BDFA Education Advisor and Qualified Teacher for the Visually Impaired, who has over 30 years of experience working with children and young people with Batten Disease reports:

"*Visual processing is affected by the condition and children will CLN2 disease find it increasingly difficult to make sense of what they are seeing. It is likely that the patients that are treated with cerliponase alfa will maintain their visual processing ability and this will have a positive impact on their functional vision.*

There may be areas of good retinal function and good visual acuity that are retained late in the disease progression. Children are unable to make use of these areas late in the disease progression as they are unable to move their heads or position themselves. If their motor abilities are maintained, they are more able to use their remaining vision more effectively.

Children with CLN2 disease had normal vision and retain visual memories in their long-term memory. Even when vision is lost, visual memories can support learning and independence skills, especially if the disease progression and resulting dementia is stabilised.

Children with CLN2 disease vary in the rate of visual loss in the progression of the disease. Complete blindness occurs in the later stages of progression. The proportion of the patients having cerliponase alpha who are completely blind may be relatively low. The additional costs associated with blindness

have been estimated in the general population, including the elderly who are affected by age related conditions resulting in sight loss. The government spend has been relatively low compared with other disabling conditions. Adaptive skills can be learnt and people can adapt to vision loss over time. There will be a variation in the additional costs associated with complete vision loss and this will be affected by the quality and availability of local support services, many of which are provided by charities such as the RNIB.

It may be possible to access records to establish better evidence of the maintenance of visual functioning of children treated with cerliponase alfa. This could include functional vision assessments by teachers of the visually impaired. The Hamburg scale wording necessitates a certain level of motor function and is a relatively crude measure of functional vision."

Rahul Dubey, a parent of a child on treatment, who is also a clinician, would like to share some very important and critical evidence about some very successful experimental research in the area of treating retinal disease in CLN2 patients. "*The following two landmark papers from animal model experimental studies, supports the fact that Intracerebral ERT slows the progression of vision loss in CLN2 patients by preserving the white matter visual pathways and preserving the ganglion cell layer of retina.*

In the first paper titled ***"Enzyme replacement therapy delays pupillary light reflex deficits in a canine model of late infantile neuronal ceroid lipofuscinosis****" published in Experimental Eye Research 125 (2014) 164-172; the study concluded that "in some of the dogs treated with rhTPP1, there were substantial delays in the appearance and progression of Pupillary Light Reflex (PLR) deficits compared with untreated or vehicle treated affected dogs.* ***These findings indicate that CSF administration of TPP1 can attenuate functional impairment of neural pathways involved in mediating the PLR but does not prevent loss of retinal responses detectable with ERG."***

*In the second paper "****Intracerebroventricular gene therapy that delays neurological disease progression is associated with selective preservation of retinal ganglion cells in a canine model of CLN2 disease****; published in Experimental Eye Research 146 (2016) 276-28; the conclusion was that "in the affected dogs that received TPP1 gene therapy to the CSF and survived an average of 80 weeks, retinal ganglion cell axons were present in numbers comparable to those of normal Dachshunds of similar age.* ***The selective preservation of the retinal ganglion cells suggests that while TPP1 protein delivered via the CSF may protect these cells, preservation of the remainder of the retina will require delivery of normal TPP1 more directly to the retina, probably via the vitreous body."***

In context to these studies, it is of paramount importance to say that rtTPP1 ERT has successfully been trialled in animal dog models in the form of intravitreal injections (injection directly in the posterior chamber of eyes, which is in direct contact with retina) and has been tremendously successful in halting the progression of retinal disease and structure, demonstrated by sequential Electroretinograms (ERG).

*Finally the following experimental study must be noted to understand how far we are with a breakthrough treatment for the eyes "****Intracerebroventricular gene therapy that delays neurological disease progression is associated with selective preservation of retinal ganglion cells in a canine model of CLN2 disease"*** *published in Experimental Eye Research 146 (2016) 276e282. "In this novel study, a single*

injection of the autologous bone marrow derived stem cells transduced with a TPP1 expression construct (TPP1 gene) at an early stage in the disease progression, substantially inhibited the development of disease-related retinal function deficits and structural changes. No adverse effects of the treatment were detected. These findings indicate that ex vivo gene therapy using autologous stem cells is an effective means of achieving sustained delivery of therapeutic compounds to tissues such as the retina for which systemic administration would be ineffective."

The BDFA is also funding a 3 year research programme on gene therapy for retinal disease in CLN2 disease in animal models. All these research papers are important for the panel to take into consideration while reviewing their decision.

In section 4.12 the Committee concluded, from incorrect information from the ERG, that although cerliponase alfa is effective in the short term in treating the key neurological aspects of CLN2, there is a possible risk of death from pancreatic, intestinal, cardiac and hepatic impairment, which may develop in the future as seen in patients with CLN3 disease.

The BDFA along with the patient community consider this statement to be unfair and based on inappropriate extrapolation from CLN3 disease patient data rather than clinical expertise in CLN2 disease.

As highlighted at the outset the committee seems to have based their discussion around an incorrect assumption about the progression of the disease beyond the age at which children currently die based on clinical features of CLN3 disease patients.

CLN2 and CLN3 disease are **completely different diseases** and have different effects on patients due to the different disease progression. The first symptom of CLN3 disease is vision loss. This can begin between 5-8 years old. Patients then may not have any other symptoms for several years. It is a much slower deterioration with CLN3 disease although it must be noted the effects of the disease are still just as devastating.

We estimate the population of patients diagnosed with CLN3 disease in the UK to be around 50- 60 children and young people. In our experience, none of these young people have been diagnosed with heart abnormalities by the age of 14. The earliest we know that there have been cardiac problems for a young person with CLN3 in the UK is 26.

The BDFA work closely with Heather House, a residential home that accommodates many young people with CLN3 disease. We asked manager, Sarah Kenrick to comment on the committee's conclusions:

"*I have worked with young adults with CLN3 disease from mid-teens to end of life since 1990. In this time I have seen only 1 individual die due to liver complications.*

I have seen only 2 individuals die of sudden cardiac arrest, both females. 1 aged 20 who was admitted to the service I worked in, she had acute malnutrition due to eating difficulties and was refeeding at the time so this was probably a causative factor. The other aged 26 with advanced disease but no significant features relating to cardiology.

We did have 3 men die, 1 aged 26, 1 aged 28 and 1 aged 30 who all showed weakened cardiac output in the last 2 weeks at the end of life, but these also had chest complications (infections and

reduced air entry) so we cannot say that they died directly of cardiac arrest, rather it was part of the dying process.

We have 2 men with pacemakers; 1 fitted last year at age 30 and 1 4 years ago at age 28, both showed increased agitation and distress for some months prior to cardiology team involvement, both are well and stable now.

I think the issue is the treatment will not prevent death, all of us will die, and the treatment is not a cure, but to prevent treatment because people with a different disease (CLN3) may die of liver failure (extremely rare in my experience) or cardiac arrest.

The treatment enables children with CLN2 disease to live longer lives with a real degree of quality, being able to walk, talk, actively participate, contribute and learn. To say that this should not be offered because CLN3 patients die sometimes of potentially preventable organ failure is akin to saying patients with Bowel cancer should not be treated because the incidence of survival for prostate cancer is low."

In the UK there are two CLN2 confirmed patients with atypical phenotypes. This has not been taken into consideration anywhere in the ECD. One of these patients receives ERT treatment. She presented with mobility problems, language problems and some learning difficulties. She is now 16 years old and has never had seizures, is able to mobilise independently at home and school and with support in the community and her vision remains unaffected. The other patient is in her teens and still has a good quality of life.

There are many other issues for families who are not receiving treatment that the EDC fails to fully recognise. There is a high rate of separation in families because of the pressures of caring. This has a huge effect on siblings as not only do they have to deal with their sibling's diagnosis but they also have to deal with family breakdowns. Many families tell us that the disease has a detrimental effect on siblings. Many become young carers, have anxiety issues, sleep disturbance and miss out on time with parents. They also miss out on holidays, spend a lot of time in hospitals and have had to cope at a young age with the death of a sibling. They have then had to deal with the aftermath of this and make sense of what has happened to their siblings. Families spend too much time fighting against "the system" and trying to engage professionals to get the equipment, care and support they need to the detriment of family life.

Children on treatment do not have as many unexpected hospital admissions or associated appointments. They do not need access to the same quantity of equipment. Families stay together because they can spend more time together. Siblings lead a more normal life because their siblings are healthier for longer. There are so many benefits to the treatment.

The ECD failed to note that children who are no longer mobile can still have a good quality of life. These children can still go outside and join in with activities. They can still go to school, go swimming, and go on bike rides. They are still able to enjoy TV despite not being able to see. They can still play with their siblings and enjoy family outings. They are still able to enjoy going on holiday, going on the swings and are still able to do many things that normal unaffected children can do.

Often only minimal support and/or adaptions are needed for them to be able to participate. Being in a wheelchair does not mean that there is a decline in a child's quality of life; they may just need more support to be able to do the activities that they enjoy doing. The families feel that the impact of vision loss on quality of life has been unfairly judged.

The BDFA and the Batten disease community do not agree with the current NICE recommendation. We have had a number of responses from families, not only in the UK, as listed in the appendices of this document. 90% of the families on treatment have submitted comments. We have had 9 submissions from families on treatment outside the UK. The BDFA also received 15 submissions from families who are not receiving treatment which include bereaved families.

From working with families receiving treatment, and those who are not, we have been able to see first-hand that this treatment has a significant benefit to patients. We have the experience and, we believe, the expertise to support the process and we wish to work with NHS England to produce a fair Managed Access Agreement for all.

Batten disease is a rapidly progressing disease and timely intervention is essential. There is a very limited time for each newly diagnosed child and an ever decreasing window of opportunity to provide a treatment which can make a meaningful difference to children affected by this devastating disease.

Children can lose their skills very quickly, sometimes in days or weeks, which cannot be regained. For those children and their families we hope that NICE, NHS England and BioMarin will come together to reach an agreement.

We know of four children who have been recently diagnosed with CLN2 disease and, by prolonging the process, it is very possible that they may not be eligible for treatment when an agreement is reached. We urge the committee to reverse the decision not to fund this treatment.

We would like to draw the committee's attention to the statements in the appendices from families whose children have not received treatment and those families where their children have sadly died. We are grateful for all the families who have contributed but we would like to acknowledge those families who are bereaved or are not receiving treatment and thank them for sharing their difficult and painful experiences and being able to be so honest as to the effects of CLN2 disease on their children.

The BDFA works closely with other patient organisations within the UK. We have received the following support from Climb: "*Climb is an umbrella patient organisation for all Inherited Metabolic Disorders. We have experience of the HST process and an interest in improving patient access to treatments and services that can improve their outcomes.*

In support of the BDFA, Climb would urge the committee to take into account all of the above points made by patient experts and alter its current view regarding the treatment of CLN2 Batten Disease and the benefits of Cerliponase Alfa.

We are particularly keen to reiterate the error the committee have made in making a comparison between CLN2 and CLN3 in respect of their data. If the committee have made their recommendations with this in mind, then this is wholly inaccurate."

Appendix

UK CLN2 Families on Treatment Comments:

Parent of child on for Treatment 3 years 3 months (159 weeks)

[redacted] has been on the trial since December 2014. 3 years. [redacted] has had no change in his abilities. He is better each day. He can speak better, he walks fine, his eyesight is perfect. He hasn't had a seizure for 2 years exactly. He can swim very confidently and has used the toilet on numerous occasions. His memory is amazing. He can count to 15 and knows his shapes, colours and part of the alphabet. He helps to dress and undress. He brushes his own teeth and washes his own hands. The only things that keep us from living a normal daily life is that [redacted] wears nappies, drinks from a baby bottle and has medication every morning and night. Thankfully, with [redacted] not having seizures and a great balance with his medication we lead a pretty normal life.

We travel from Liverpool to London every two weeks for infusion. It is very tiring on us all but thankfully, [redacted] is a delight to travel with and with routine, it doesn't bother him at all. Having a strong family and good partner we all deal with it pretty well. This treatment has given not only [redacted] a quality of life but us all. [redacted] shows so much strength and shocks a lot of people when explained he has this awful condition.

[redacted] is a very happy, pleasant and very energetic child and he pulls us away from any dark place we may fall to. He loves to play with his friends in school and his cousins. He is very sociable and only shows how strong he is and that we all can smile at. [redacted] is a walking, talking little boy who is living proof this treatment is working and when caught at the right time can show amazing results.

We are all extremely proud of [redacted] and how far he has come and showed a lot of people hope. [redacted] goes to a special needs school 5 days a week (unless having treatment) full time.

[redacted] has no problems after his treatment. He is sedated but tends to wake from it after an hour and sits happily with snacks and an Ipad. He loves to play after his treatment and there never any concerns that he is drowsy or has any effects from his infusion. Being on the original trial [redacted] has to have 24 hour observations then can go home. [redacted] is always back to school the next day after returning home. Never as a family did we think that [redacted] would be the child he is. There is no doubt in our minds that this treatment is working and is giving him a life of a child without battens.

Parents of child on treatment, 3 years 7 months (166 weeks)

[redacted] has been on the trial from July 2014 in Rome and later transferred to Great Ormond Street

[redacted] has pretty much maintained all his skills since he began treatment. He is still able to walk, run, jump and play. He's a little more unstable, but that is also due to his missing eyesight (which is not covered by the treatment. He does very sophisticated playing by himself, including imaginative storytelling and singing. He has not really lost any vocabulary - he has actually gained some as he is constantly learning new things in school.

As a parent, the single most important thing is that he is able to enjoy himself, play and be happy. The trial has kept him on his feet - he is able to eat unaided, attend school and be part

of advanced red activities such as field trips, swimming, and music classes. He is a very happy boy who is incredibly loving and caring with a sharp sense of humour.

Without the trial, he would be dead or dying by now. The trial gives us hope and it gives us quality time with our child. He is able to play and interact with his brother [redacted] which in turn helps [redacted] develop. [redacted] is mobile enough to be let loose in the park and play in the playground, with some oversight. He does not yet need a proper wheelchair, so we are able to get him around town without too much hassle. He loves museums and public transportation, so we do a lot of that. We function as a real family. With him being happy and lucid, you can at times even forget what a cruel condition he has. Without the trial, there would be nothing but darkness.

[redacted] goes to [redacted] school every day where he has friends and does his most favourite activities. He loves going to school He is part of music therapy there and goes swimming and ice-skating among many things. He even goes to school straight after his infusion at GOSH. (He also loves going to the hospital :-) We have a nanny to help take care of him and his brother on weekdays. He is pretty easy to take care of as he very rarely has seizures and is mostly happy.

The trial has changed everything for us. [redacted] is completely stable and is pretty high functioning for a kid with a mortal brain disorder. He is the most loving kid - I invite any NICE legislator to spend an hour with him. Maybe meet him at the Transport Museum, as that is his favourite place. Or to watch Sarah and Duck with him at our house.

The uncertainty surrounding the availability of the trial in the UK is incredibly nerve wrecking and depressing. If his treatment is taken away, he will very quickly deteriorate and will not survive.

Parent of child on treatment, 1 year 2 months (60 weeks)

[redacted] has been lucky enough to have been receiving enzyme treatment now since 21st December (2016). She's now had 30 enzymes resulting in some amazing and beautiful differences.

Since being on them she has not declined in anything at all, if anything she has amazed us and her doctors, teachers, friends and family just how well and how much she needs them.

[redacted] eats more and its a lot easier to swallow for her, which that in itself is amazing after 17 months on being diagnosed, she smiles giggles and says new little words 100 percent more. She even has a 3 worded sentence, and yes everyone understands it, (I did that), all gone, and go bow bows are all understood. Her vocabulary is astounding us on a daily basis. Frustration is a no no anymore. More like normal 5 year old moods now, we love these though.

[redacted] is in a special school, which she absolutely loves, by our choice of course, she's never been ill and needed to come home ever since being in her school since September 2017 when she started there. She attends 5 full days a week and never has a snooze never mind a sleep there.

Being on compassionate use of these amazing and much needed enzymes, has brought our family lives so much closer as we've got a lot of our baby girl learning an smiling again. We know it's no cure but we definitely know it's doing our baby girl the world of good. When princess [redacted] smiles then we no it's a good day.

Parents of two children on Treatment 1 year 3 months (64 weeks) and 1 year 1 month (56 weeks).

[redacted]

[redacted] was diagnosed with Late Infantile Batten Disease in February 2015.

He started enzyme replacement therapy at Great Ormond Street Hospital, London in November 2016.

Due to the drug not being available until late 2016 the disease unfortunately was able to progress in [redacted], taking away his ability to stand, walk unaided and limited [redacted] to only a few single words, before treatment started.

[redacted] has now been receiving treatment for just over a year. At the age of seven [redacted] has been able to retain a safe swallow meaning he does not dribble and can still eat the foods that he enjoys, this is almost unheard of for a child of this age with CNL2 Batten Disease.

[redacted] attends a mainstream school, where he is able to access the curriculum alongside his peers. [redacted] has many friends and is a well-known loved little boy. He has recently participated in his Christmas show on stage where he performed as the brightest star in the sky.

[redacted] loves to be around people especially his friends, he reacts, reaches out, laughs and smiles with them. [redacted] attends swimming lessons once a week and a sensory class, which enables [redacted] to explore and interact using all of his senses.

[redacted] is still able to support his own weight when sitting on all fours for a short amount of time and enjoys listening to his favourite programs, films and storybooks where he will often laugh along. [redacted] particularly enjoys using his standing frame to interact with others at eye level.

Before treatment, [redacted] was experiencing seizures daily, some, which were extremely distressing, and life threatening. Since starting treatment fifteen months ago [redacted] has only had one tonic clonic seizure, which was associated with [redacted] being sick and bringing up his medication. [redacted] has not experienced any other type of seizure since he started treatment including absent seizures. [redacted] does not suffer from movement disorders nor does he experience myoclonic jerks. Alongside this [redacted] overall health has scientifically improved, reducing the amount of hospital admissions. It is important to understand that before treatment [redacted] would get extremely agitated, upset and would cry out in pain. This would affect his ability to function in activities and had an effect on feeding resulting in dramatic weight loss. Since starting on treatment the difference in [redacted] has been incredible, he is like a different child. He no longer gets upset, he never cries and loves to play and experience new things. [redacted] enjoys eating again, which in turn has improved his weight meaning professionals no longer class his weight as a worry or concern.

[redacted] is still able to sleep in a normal bed and does not require any oxygen or suction day or night nor does he require any medical monitoring equipment.

[redacted] has two healthy older brothers and a younger sister who sadly also has Batten Disease. As you can imagine as a family of six and two dog's life is busy. All our boys are football crazy and we often take them to open aired football matches. It is priceless to watch [redacted] eyes light up when he hears the crowd. He will wave his arms around as supporters around him chant and cheer, [redacted] will often let out screams of excitement.

We are a family who live life to the full. We often go out for the day, to the Zoo, the ice cream farm, or even a meal out with friends. [redacted] favourite is when we go to places with rides he's a little thrill seeker who will laugh his way around a ride whilst we are clinging on for dear life!

[redacted] life is obviously more challenging than a healthy child of his age but [redacted] never complains, he never cries and he is always a happy, smiling little boy who has taught us how life should truly be lived.

[redacted]

[redacted] was diagnosed with Late Infantile Batten Disease in March 2015. [redacted] had no symptoms of the disease; she was tested due to the recent diagnoses of her older brother.

In February 2017 at the age of three [redacted] started receiving enzyme replacement therapy at Great Ormond Street Hospital, London. [redacted] is one of the youngest children in the world to be receiving this treatment and even more importantly the only symptom of Batten Disease [redacted] had shown before treatment started was a seizure two months prior to starting treatment, which was associated with a sickness bug.

[redacted] is now a days away from turning five and she is thriving. [redacted] attends a mainstream school. She participates in all classroom activities, she enjoys mark making and is able to play independently. [redacted] is learning new words daily and is able to speak in five to six word sentences, which is recognisable to strangers. Recently [redacted] has been able to learn simple phonic sounds, which she can retain and can make the correct animal sounds when asked. She is able to count to ten and is starting to count objects.

Not only is [redacted] not losing skill and retaining them, she is also learning new skills.

[redacted] is able to understand instructions and is aware of the world around her. For example, she will stop at the side of a road as she understands it is not safe to her to cross the road without an adult. She understands danger and knows right from wrong, for example, she knows it is not nice to hurt others.

Outside of school, [redacted] attends dance, gymnastics and swim classes as well as being able to go for tea at her friends' houses after school.

Recently [redacted] participated in a dance production, Cinderella. This production was five shows over the space of three days. Healthy children the same age as [redacted] were struggling to keep up with the professionalism of the show along with the late nights but [redacted] fed off the excitement and had the time of her life.

[redacted] has no health problems and has recently been accessed by the physiotherapists at Great Ormond Street Hospital; the report states that [redacted] has no problems with her balance. It also states that she has no muscle or joint problems. [redacted] does not suffer from any movement disorders or myoclonic jerks. [redacted] is able to walk, run, jump and climb. She is able to stand from sitting whilst holding objects therefore not needing to use her hands to assist her to stand. [redacted] is able to use an age appropriate scooter and is learning to ride a bike. The Physiotherapy assessment also looked at how [redacted] placed her feet as she walked and the speed in which she walked at, the report shows that [redacted] results are of that of a healthy child.

Since starting treatment, [redacted] has not experienced any types of seizures. [redacted] is able to live her life just like any other healthy four-year-old thanks to the early administration of the enzyme replacement therapy.

Importantly [redacted] has not lost any blander or bowel control, she is in knickers and is dry both day and night, she does not experience any accidents.

[redacted] is a happy, fun, loving, caring none stop little girl who loves to run, dance, sing and climb. We often refer to [redacted] as the little girl dressed in her princess dress with a bow in her hair who you will find playing in a puddle full of mud or half way up a tree.

Parent of child on treatment: 3 years 6 months (162 weeks)

[redacted] has been on treatment since September 2014, for 3 years and 6 months

[redacted] has not had a Tonic clonic seizure for over two years now, her myoclonic jerks have disappeared and she rarely has absences. [redacted] is able to feed herself dry food, which she likes, such as nuts and crisps, evidence that her fine motor skills are very much intact. Whilst [redacted] does have difficulty walking unaided, she uses a wheelchair and is able to push herself around either in the flat or on the street with her hands. [redacted] can walk on her knees well which shows that it is not an issue with balance but rather the tightening of her muscles that prevent her walking.

[redacted] is able to operate the Ipad well and can navigate Youtube to watch her favourite programs and video clips. She is happiest when she has an Ipad and given the circumstances, we let her enjoy herself as much as possible. Whilst [redacted] is visually impaired, she can see much in her environment and likes to play with small figurine toys, such as putting them in and out of containers and boxes. She is able to skip ads and choose clips on the Ipad, showing that there is still much detail she can pick up on.

[redacted] remembers many of the people she meets, and has strong relationships with her grandmothers who she does not see very often. She also likes it when my family friends come over, many of whom she remembers.

[redacted] likes to go swimming and because of her difficulties in walking, this is an ideal exercise for her. She likes to play in water and splash about and she is very happy when she does this. [redacted] also likes tactile play, such as being picked up and she likes it when people help her to jump up and down. Supported, [redacted] can do many things, such as walking down the street in her walking frame and helping with preparing meals, such as pressing down the blender or helping to put rubbish in the bin.

[redacted] also likes to organise things, such as when we go through her toys and put them into different categories, as well as her snack cupboard. [redacted] does not like clutter and things lying around, and will often push small objects away to keep the place tidy and clutter free. [redacted] is able to keep her environment the way she likes it.

[redacted] likes going for walks around London and seeing and meeting new people, as well as playing instruments such as blowing horns and whistles. She also likes to strum her ukulele. [redacted] has many friends at school who make her happy and whom she makes happy. She plays with them, eats with them and participates in many activities with them which, as a parent is very important to know.

[redacted] **does not** have a feeding tube even though she is now seven and is regularly gaining weight. Even though she is spoon fed, she is able to swallow well and with certain foods such as rice and spaghetti, she will even feed herself. [redacted] is very big and robust.

Compared to [redacted] peers who are not getting treatment, the impact on [redacted] life has been monumental. Bluntly, [redacted] may very well have passed away by now as many of her peers have.

Whilst we do not know [redacted] life expectancy now, judging on the impact of the treatment, there is much hope that she may live into adulthood and enjoy and meaningful and happy life with us. Whilst [redacted] may not be able to get a job and will always need support, there are huge ways she contributes to society and her community. She makes others happy, she brings people an incredible amount of pleasure and joy- this is not limited to her blood relatives but to everyone she meets. I don't think this should be taken lightly when assessing the treatment- people can be of value in many ways.

[redacted] can be an active member of the community given the right support, and I feel that with our input (the parents) working in tandem with the local authority and the BDFA, [redacted] can spend many years engaged in meaningful activities that enrich many people's lives. This treatment gives [redacted] the opportunity to lead the life [redacted] and only [redacted] is entitled to live.

It would be a false to say this treatment has not put a strain on our family life, I'm not a liar. However, [redacted] is our child and we would do anything to keep her alive. Yes, it is hard work, but that is why we have organisations like the BDFA, SEND schools and local authorities to support us. Regardless of whether someone has a child with Batten disease or not life can often be a struggle- this is just part of the human condition. All parents would welcome this struggle because it means we still have our child and we still have hope.

We spend a lot of time in hospital, but the thought of not spending time in hospital is terrifying and makes me extremely uncomfortable. I would choose a life of regular hospital visits a 1000 times over a life without [redacted] What is more, [redacted] likes going to hospital in England because there are a lot of toys and people make her feel special. If going to hospital with [redacted] is taken out of the equation because the treatment is not available, then our quality of life plummets so far it is beyond words. I want to make clear that for us, spending a lot of time is hospital is a positive and not a negative.

Similarly, although we cannot go on holiday for longer than a week or so, if you contrast this with a child who is no longer with us then a one week holiday is much preferred.

In essence, what I am trying to say it that although there are struggles- it would be unrealistic to say there weren't, these are **GOOD** struggles, struggles that we want to have and struggles that have now become normal. I believe the information in the above 3 sections illustrates just how much positivity can come out of this.

[redacted] goes to school full time, and takes part in many activities outside of school. She goes to children's parties, Christmas parties, theatre trips, she goes to the playground, she goes to farms, the seaside, aquariums, trips out on the train. The list is endless- with the right support she can participate in all the things mainstream children can do and she is happy during these activities.

She has an overnight stay every two weeks at hospital to receive the treatment, where she has hospital teachers and extra sensory entertainers come in to engage her, she is very happy when this happens. There is also a play specialist at hospital, which dedicates a certain amount of time to playing with her.

Whilst [redacted] doesn't like needles and the observations of vital statistics, this is becoming less and less during the trial and the rest of the time she is mostly happy. Hospital has become the norm and we are happy for this to be the case, as I have mentioned above.

I feel [redacted] life should not be judged solely on how 'useful' she is to society, but also on her basic human rights; to be happy to the best of her ability, to live a life free from persecution and to live a life where her intrinsic value is recognised literally and not just through lip service. When [redacted] is

given this treatment, she is able to be happy and if the treatment is not given to her and children like her then their basic human right is being violated. If there is a treatment that has been shown to work in the short term, then it has to be a moral and political imperative to give the treatment to the child to find out how well it works in the long term. Anything less would be wrong and incredibly unfair.

Parents of two children on treatment, one on sibling trial. Time on treatment for [redacted]: 1 year 1 month (60 weeks)

We were blessed with our three children and as any parents among you reading this will understand the immediate feeling of overwhelming love and insurmountable desire to keep them safe from harm, forever. We have painfully had to come to terms with the fact we cannot do this.

We would give anything to be able to just grab our coats on a whim and go out to the park or walk our dog somewhere adventurous, nothing spectacular, just simple pleasures, are things that are sadly now out of our reach due to this condition.

Our days are very different, no longer are they carefree and full of excitement, our days and weeks are now planned around hospital appointments, meetings with various healthcare professionals, everything has to be tightly orchestrated with lots of preparation and forward planning to ensure we have everything covered for the care of [redacted] as she is fully reliant on us for every aspect of her daily routine.

Having three small children is a challenge in itself, juggling school runs, meals, after school clubs, play dates, school activities, general doctors / dentist appointments, food shopping, housework….

Now try to imagine all of the normal stresses and strains on top of having to care for a child with additional complex needs who is fully reliant on you, cannot speak or walk, needs medication twice a day to control her seizures. In addition, having a 2 year old who can be quite demanding and also needs your attention. To have to listen and hold yourself together when your 7 year old son asks if he sister is going to die, or if she will ever be able to walk or talk again. Then playing with his littlest sister, [redacted] who is currently perfect and saying "I don't want [redacted] to ever lose her abilities because I want to be able to play with her".

Before Batten Disease started to take away our beautiful girl's abilities, [redacted] was always running around the garden and acting silly with her big brother. She was a daredevil and loved to climb. We were never to know that she would lose her mobility and would never be able to do this with her little sister when she came along. It is truly heart breaking for us to watch and acknowledge.

She had a very short attention and concentration span and school struggled to manage her in a mainstream class environment. She moved to [redacted] school which is a specialist school in [redacted] in November 2016 and they have been a huge source of support and care for [redacted]

Since [redacted] has been having the infusions everyone has noticed an improvement, friends & family regularly comment on how much better [redacted] is now, compared to this time last year, before treatment had begun.

We have seen with our own eyes that this treatment has not only stabilised [redacted] condition, but it has actually improved her. [redacted] is proof that Brinuera works.

Before [redacted] started her enzyme replacement therapy in January 2017, she used to get agitated, very easily. So much so that we stopped going out as a family for fear that she would have a meltdown and be uncontrollable, crying and screaming. It was a very stressful experience.

She is so much calmer, much more receptive to new experiences. Since treatment, we have started to go out again as a family, because she is far more tolerant of new environments that she ever has been. Ourselves, family and friends have all commented on the huge improvement they see in [redacted], she is brighter, happier and much more alert.

We have got a part of our life back thanks to Brinuera. It has had a measurable impact on [redacted] enjoyment and engagement at school and she is now far more interactive and responsive in her lessons. When [redacted] first joined [redacted] School in November 2016 on a part time basis and is now attending full time only being away from school when she attends GOSH for her treatment.

[redacted] class teacher described how when [redacted] first joined her class, she appeared quite agitated, making lots of guttural vocal sounds and frequent repetitive hand movements. [redacted] is now much more settled and the class rarely hear the vocal sounds related to her agitation and the hand movements are only observed occasionally.

[redacted] has made really good progress with her acceptance of touch – initially she found it difficult to tolerate any touch based activities but again, they have seen a significant change in this and she is now much more tolerant of Story Massage sessions, TacPac and physio stretches.

[redacted] is also beginning to demonstrate a greater awareness of what is going on around her in regular and familiar small group activities. [redacted] loves seeing her photograph in circle time, looking towards an adult when they call her name and taking part in her favourite songs and rhymes with support, she always shows us that she is enjoying something by smiling or giggling or even an excited scream.

When [redacted] first started at [redacted] staff also noted that her emotional responses e.g., smiling were very fleeting and [redacted] would not tend to repeat the smile during the activity, however we are now observing that [redacted] is sustaining her happy reactions for longer periods of time.

The teacher's final comment was "[redacted] is a lovely happy little girl who really enjoys coming to school, being with her friends and taking part in a variety of activities in her therapeutic curriculum. She lights up our day with her smile".

It is not only [redacted] general character & responses that have improved, but [redacted] physiotherapist at school feels that it is a very positive sign that [redacted] has maintained her level of mobility over the last year since commencing school. One of the most significant points they mentioned was that fact that [redacted] has needed a very limited amount of intervention, which is something they have not experienced with children with Batten Disease in the past.

She continues to be very motivated to use her Cavalier walker at home and school for independent mobility and to walk with the facilitation of one adult. She has maintained good head control and postural control in her trunk only requiring a basic seat set up with feet supported and a lap belt for safety[redacted] also continues to have full range of movement in her upper and lower limbs. All the team have also commented on her being more content and happy to be handled and touched when previously she was unhappy with this. She gives lovely eye contact now and is very responsive to familiar adults and children in her class group.

[redacted] is not showing any symptoms at yet and we hope with all of our hearts that she never does. It is very difficult to see the difference in our daughters. [redacted] is chatting away and beginning to count, she is such an independent little lady who can already newly 2yrs old, can put her own coat, shoes and socks on. She is developing amazing well and in a lot of areas, she is exceeding. We cannot express the hope that this treatment has given to us.

[redacted] has paved the way becoming the youngest child in the world to be given this treatment, so she is the hope for the future.

We are all full of hope and optimism that she could potentially beat Batten Disease, because she is having the treatment so early, before symptoms have begun, we are all hoping and praying that she may never develop the symptoms like her big sister…. because of this treatment being given to her so early in her precious life.

Some brave and beautiful children, of a similar age to [redacted], are sadly longer with us because there has been no treatment before this. You could not have a harsher awakening to what would lie ahead for our children if the NHS deny this remarkable treatment for CNL2 type Battens.

We are living in a country whose brave children and families have given themselves up to be part of the trials to assess if the drug works….yet, having contributed to the successful results culminating in the drug being licensed, they may be excluded from feeling the benefits of this treatment.

The facts are:

We know there is a drug in existence, which has been proven to work.
We know this drug is available to children in other parts of the world right now.
Yet, even though our families have contributed to trials, we may be denied access to the thing we were helping to assess.
Batten Disease is a rare condition so monetary concerns should be quashed because it is only going to be prescribed to a minority, thus not being a financial burden to the NHS.

Having listened to the facts, we hope and pray NICE and NHS England make the right decision.

Parent of child on treatment, 9 months (36 weeks)

We as parents would like to share the life story of our 5-year-old son, who is on the Extension study of the BMN190 – 201/202 programme sponsored by Biomarin Company. He was diagnosed with CLN2 Batten Disease on 31st March 2017, which is almost a year ago. We were completely devastated with this news and lost all hope. [redacted] was a very normal child until about 18 months when he achieved all his milestones in time and had already started to speak few single syllable words like Papa (dad), Baba (granddad), Mamma (mum).

However by about 2 years of age he started to lose his words and regressed. He was also not playing very well in the park as he used to and would just go around running aimlessly rather than getting onto swings or slides. He was referred to ENT and Speech & Language. ENT diagnosed him with Glue ears, however his hearing was within normal limits so no intervention was done. Speech & Language raised the suspicion of Autism Spectrum Disorder (ASD). While we were still getting to term with the ASD bit, he started having funny turns (seizures) when he was 2 years and 9 months. After the third episode this was confirmed to be a seizure and he was diagnosed to have ASD associated epilepsy. His epilepsy transformed from Complex partial / Focal seizures to Myoclonic / Atonic jerks which finally got controlled after trying three different antiepileptic's. We spent over 2 years between

various therapists such as SALT, OT, ENT, Community Paediatricians, Neurologists and finally we saw a Child Psychiatrist in Children and Adolescent Mental Health Services in (CAMHS) in Salford in Manchester in May 2016, when [redacted] was 3 years and 4 months and he was labelled to be on the severe end of the ASD. At that time his IQ was found to be equivalent to 18 months. [redacted] mental development seems to have stopped at 18 months. Both of us are medical professionals, I am a Neurosurgeon and working in NHS as a Consultant, while [redacted] is a Dentist but full time mum and carer for [redacted] now. It probably did help to some extent to understand what [redacted] was going through although it was frustrating that there were very little I could do even as clinician to help him.

We were still trying to provide as much support to him in Nursery with one to one teaching assistant and doing lot of activities with him at home, but he never picked up any verbal speech except very occasional single syllable words. It was only just before [redacted] 4th Birthday that that his balance started to get worse and he started to fall quite a lot. Initially it was put down to epilepsy and a second antiepileptic was added but despite this his balance never got better. This is when his Neurologist, who has a huge experience in batten disease, tested him and diagnosed him with CLN2 Batten disease. He was 4 years and 3 months then.

There are no words that could really describe well enough how our lives had completely been destroyed. With a small ray of hope shown to us, [redacted] was referred to Great Ormond Street Hospital Metabolic team for an assessment and possibility of being referred to Hamburg, Germany to be considered for a place in the Sibling trail, which was soon starting. Since [redacted] was not a sibling of an affected child hence he did not fit the criteria, however, with god's grace and Biomarin's support, he was given an extra place in GOSH on the extension study.

It was 1st June 2017 that [redacted] got his first infusion and has received 9 months of ICV ERT till date.

We would like to emphasize his strengths and areas where we have seen any improvement.

1) Cognition - Improved – He can now understand single and double word commands. He understands words like sit down, stand up, please, No, Clap, Lets go, TV, Peppa Pig, iPAD. He is now not rolling out of his changing mat when laid down for nappy change, which he used to do until recently.

2) Vocabulary – Retained – [redacted] has managed to retain most of his receptive vocabulary and is still able to identify a number of alphabets and associated objects by pointing, along with atleast 10-15 animals and birds, Sun, Moon, objects like Car, bus, etc.

3) Communication – Improved – [redacted] can communicate his desires by pointing his finger or looking at the object. He makes choices in his foods while having meals and is very clear when he wants yogurt or rice or water.

Very recently he has started to come to either of us when he has soiled which is a big step for us as previously we had keep checking on the times after meals. There are some you tube videos, when played, he would look at us and gesture in a way that he wants us to sing with it and there is excellent eye to eye contact and loads of giggle and smiles with it. He used to watch some very weird videos on you tube which we would discourage him but in the last couple of months he has completely lost interest in them and is more interested in ABC, numbers and Shapes videos, which are more in keeping with his mental development.

4) Motor Skills – Stabilised – There has been no significant change in his crude and fine motor skills since last 6 months. [redacted] is comfortably able to switch and navigate into apps and his games and

able to play the ones he likes. He is exceptionally good in finding his favourite Nursery rhyme videos on Youtube and enjoys them thoroughly.

He can hold a beaker or baby bottle and can drink himself, he can hold biscuit and take a bite or two. His hand to mouth co-ordination is still very good.

His mobility has somewhat slightly deteriorated in these 10 months but within the limits expected as per the trial data. He can still walk unassisted comfortably up to 10 -15 steps in straight line but get shaky on turning. Part of his problem is Hypotonia which is exacerbated by one of his antiepileptics which has muscle relaxant action. We are already in the process of reducing that by introducing another antiepileptic in its place.

5) Seizures: [redacted] has not had any generalised tonic clonic seizures ever. His seizure were atypical, more so in keeping with genetic epilepsy and transformed into atonic jerks or drop attacks in the first few months. However, for nearly 14 months, even from before the diagnosis of Batten disease the jerks and drop attacks have been well controlled. There multiple vacant episodes during the day in the past, which were possibly absences. In fact his absence episodes, which have been checked by the neurologist and confirmed to be absences and not absence seizures, have dramatically reduced in last 3 months.

6) Energy Levels – **Significantly improved** – [redacted] used to previously sleep in Nursery almost routinely last year even he was attending Nursery only for 3 hours and now 2 days in a week he attends full day and remainign3 days half days and he is only sleeping short spells very occasionally. He can cope very well all day without any sleep and does not sleep at home in the evening either.

7) Sleep – Dramaticlly improved – [redacted] now sleeps much more easily within minutes of being in bed. He used to wriggle for hours prior to the treatment was started and would sleep short periods and keep waking up several times. We had to seek help with melatonin occasionally. Now I can't even remember when we last used melatonin. He is completely off it and sleeps through the night in the correct posture on a normal bed without any interruption. His sleep is much deep as well, until about 4 months he used to wake up even with slightest sound in or outside his room but now ther are days when we would have to wake him up like any normal 5 year old.

8) Appetite – Significantly Improved – [redacted] had not gained any weight for nearly 2 years prior to his diagnosis. I ma pleased to say that he has put on 5 KG in last 9 months since he has been on treatment. His appetite is very good, he enjoys his means thoroughly. He likes all kind of food and in fruits banana is his favourite.

9) Eating & Swallowing – Stabilised – [redacted] had slight swallowing issues quite early after his diagnosis and needed a thickener with thin fluids. He only needs that with water and milk and that has not progressed. He has not had any aspiration or chest infections.

10) School – **Positive Feedback overall** - [redacted] attends two full days and 3 half days in a special school. He started with half days in September last year in reception and from Dec he went to 2 full days and is doing very well. He is making good progress as per his teachers. He is lot more interactive. He has developed friends and shares toys and books with them. He attends Swimming session twice in a week and thoroughly enjoys that. He does cycling on an automated machine for exercise once a week and is starting to synchronize his rhythm more with the machine. The feedback from the physios is very positive.

Lastly, all I would say is that this treatment can't be judged alone on the basis of evidence given through the trial, which although very strong, still does not cover all the aspects of the child's life. An

overall view of the child's progress on treatment can only be achieved by collecting evidence from all the professionals engaged with the child in school, in community and patient (in this case parent reported) outcome measures. This treatment is very much working and is he lifeline for this extremely vulnerable group of children and under no circumstances it should be turned down.

Parents of child (atypical phenotype) on Treatment, 1 year (52 weeks)

Treatment:

- We are pleased that [redacted] has no adverse effects from the treatment and that the infusions themselves don't cause her any discomfort or anxiety. [redacted] has no other regular medication and we hope that by continuing this treatment that will remain the case.

What it means to us as a family:

- [redacted] is far from a typical teenage lifestyle, but for her to be able to continue to enjoy the quality of life that she currently has is very precious to us as a family.
- Whilst the level of physical assistance that [redacted] currently needs is challenging, by having this treatment to manage her condition we can continue to give her that support without having to rely on others outside of her immediate family. That is much better for us as a family and for [redacted]
- At the moment, we feel like a normal family, albeit managing the challenges of [redacted] condition. If [redacted] condition were to deteriorate in any way we believe that it would quickly make it very difficult for us to maintain that normality.

Effects on Scarlet:

- Halting the degenerative nature of [redacted] condition means that she maintains an otherwise healthy and relatively active lifestyle as well as her own personality and is able to participate in family life.

Further comments are:

- [redacted] has a place at [redacted] College in September on a Foundation Course, 3 days a week. She is looking forward to this. The course involves some English and Maths, working with money, cooking, meal planning, shopping and life skills.
- [redacted] is hoping to attend a day centre for the other two days a week. The day centre grows fruit and vegetables, cares and looks after some large and small animals, goes on trips to the swimming baths, bowling, cinema and various other outings. She will also have the opportunity to go on holidays with other young people.
- [redacted] currently swims independently twice a week, which she enjoys – she recently swam 22 lengths without stopping.
- During the summer months [redacted] goes horse riding with a disability group.
- [redacted] is also due to start Music Therapy with the Amber Trust shortly. We feel this will benefit her greatly as she loves to sing and enjoys music very much.

- All these activities keep [redacted] busy, active, stimulated and sociable. She still continues to learn new things and has a good quality of life. She especially loves holidays and short breaks. Last year she tried surfing in Cornwall and loved it. We are revisiting this year where she will again have surfing lessons. She continues to have new exciting experiences in life.
- We are hoping that [redacted] can maintain all these activities as she grows older. The treatment will enable her to do this.
- It is important to us that other children who have this diagnosis can also live their lives to the fullest. An early diagnosis is essential to achieving this and a treatment will help them maintain it.

Grandparents of two children on treatment

Before and in the months following [redacted] diagnosis in September 2016 she was losing the ability to walk, eat unaided and was extremely frustrated. [redacted] would bang her head on whatever surface was nearby and make grunting sounds it was so heart breaking to watch. [redacted] could not maintain eye contact and despite patiently playing with toys/books/bricks etc. [redacted] would just throw them away.

Since [redacted] has been receiving the enzyme replacement therapy, the change in her is absolutely amazing. She no longer bangs her head or grunts she is a happy smiling wee girl who is now much more aware of the world around her and can make eye contact with you. An example of this is watching out the train window on the way to London rather than staring straight ahead at the DVD player. She will now hold her dolly or flip a couple of pages in her book she would never have done this before. When we would take [redacted] out before she was receiving treatment we had to have an ipad or device for her to watch her beloved films or she would have a meltdown. Now [redacted] is happy to sit in a café etc without the DVDs and enjoys her surroundings. [redacted] is also much happier being cuddled and likes having her hair and face stoked which she did not like before treatment began.

Although [redacted] does require assistance with her meals I have a short video showing [redacted] feeding herself unfortunately file is too big to send as attachment.

[redacted] is a perfectly healthy little girl with no symptoms of this dreadful disease and the hope for the future is by receiving this life changing treatment so early she will never develop any symptoms .

This treatment works! Our hope for the future is for early diagnosis and treatment for all children, which we believe, will change the future of batten disease.

Grandparents of two children on treatment.

We are [redacted], [redacted] Nanna and Grandad. We are a very tight knit family and have a lot to do with our grandchildren especially [redacted] who sleeps over at our house on a regular basis. The fact that [redacted] was not diagnosed with CLN2 until after he was showing symptoms we were noticing a depreciation in him and very often he would be admitted to hospital with his awful seizures and infections. He also looked so thin and poorly. Since [redacted] has been

receiving the enzyme treatment, it has made a remarkable difference to the quality of his life. [redacted] looks so well and healthy, and has gained weight. [redacted] is so loveable and since this treatment is always happy and smiling. [redacted] has a wonderful and wicked sense of humour, when we talk to him about things he has done especially when he put Grandads slippers in the toilet when he was very young, he laughs his head off, he finds it hilarious and he certainly remembers everything. [redacted] has a marvellous memory and he is so on the ball with everything, nothing gets past him, which can only be due to his ongoing enzyme treatment. [redacted] loves being out and about especially in the sunshine and he loves going on holiday especially on an aeroplane. He loves the thrill of taking off and landing just as he does love all the big rides in a theme park. [redacted] just loves life. Our beautiful grand-daughter [redacted] is so loving life to the full thanks to being on the enzyme treatment. She has only had one seizure since being diagnosed and none since receiving the treatment. [redacted] is so energetic she never keeps still always on the go. [redacted] has a wonderful sense of humour and is funny always making people laugh. [redacted] goes to school, gymnastics, dancing and swimming and she loves to swim with [redacted] who also loves the water. The first thing [redacted] does when she comes home from school is run to [redacted] and put her arms around him and kiss him, they are inseparable. [redacted] is so well and healthy and this is all thanks to her being on the enzyme treatment. We do not agree with the decision by nhs England and NICE not to fund this treatment, to quote an old saying the proof is in the pudding, is certainly true. This treatment does work and ongoing treatment is essential to maintain quality of life for our grandchildren, which also impacts on all our family especially [redacted] 2 older brothers, everybody's quality of life is better. The children deserve to be on this treatment, they have done nothing wrong in life. They are innocent and pure. They have not asked the NHS for operations after botched up surgery abroad. They are not alcoholics or drug addicts, they have not smoked cigarettes. They have not made wrong decisions in their life. They love life and should be given the chance to live it first and foremost and not be given a death sentence. Thank you for reading regards [redacted].

Aunt to two children on treatment.

I am writing in relation to the decision by NICE to pull treatment from children receiving enzyme therapy.

I am the Aunty of [redacted].

As I'm sure you're aware [redacted] was diagnosed with CLN2 battens disease in February 2015 one month later [redacted] was diagnosed.

I remember prior to treatment being commenced [redacted] was having seizures regularly. He was being hospitalised on a regular basis. His speech and mobility deteriorated by August 2015. At a family gathering [redacted] was having to hold on to his uncles hands to stand. [redacted] was 4 years and 7 months old.

Fast forward to now and [redacted] is 4 years and 11 months old. She has been on enzyme treatment for over 1 year and is running, dancing, swimming. She recognises names and puts words together. Without this I truly believe she would be losing her mobility by now. With treatment being given sooner to [redacted] Ido not believe he would have deteriorated as rapidly as he did.

With treatment, we still see cheeky [redacted]. He smiles he laughs and loves life.

[redacted] loves his family and his family adore him! I can not bare to think of the time before [redacted] started enzyme treatment. It is not fair to him or to us. We can not go back to [redacted] having seizures so regular it almost became "the norm" that should never be "a normal" childhood for any child. Nor his parents or his siblings. This treatment has allowed time and memories to be made and a "normal childhood" not just for [redacted] and [redacted] but his two older brothers who have suffered and will suffer if this treatment is taken away.

I appreciate the incredibly hard decision NICE has had to make. But this drug works! The children are all the results that are needed!

Thank you for taking the time to read this.

I hope it makes a difference.

– Auntie and Uncle to two children on treatment.

Dear NICE Committee,
I wish to make a statement regarding your recent decision to not recommend funding for cerliponase alfa. My nephew and niece both have CLN2 Late Infantile Batten Disease. I believe that early diagnosis and early access to treatment supports the effectiveness of the drug. [redacted] who is receiving the drug at an earlier age than her brother [redacted] did, is showing extremely positive signs. She is thriving at her mainstream school and enjoys sharing new words she has learnt. She has also began to follow more complex demands involving two or three part sequences. [redacted] lives a comfortable and happy life, he interacts with those around him and participates in sensory activities. He continues to swallow and maintains control of seizures. I believe if [redacted] had access to the drug earlier, he would not have lost his motor ability at such rapid rate. [redacted] is still able to run around and take part in dancing and gymnastics. A huge difference thanks to cerliponase alfa. Both children only attend hospital for their infusion treatments at Great Ormond Street Hospital, the drug is keeping them well. Before treatment started, [redacted] attended hospital on urgent basis, attending A&E due to illness and uncontrollable seizures. This is not the case anymore thanks to cerliponase alfa.
In order to gain more research and evidence, children must have access to the drug. Long-term data is not possible without children receiving cerliponase alfa.
Other European countries are already receiving cerliponase alfa. It is inhumane to keep a working drug from children. Please follow suit and do not let the children and families suffering with Batten Disease in this country down.
I beg you to reconsider your decision.

Families on treatment outside the UK

[redacted]

On June 11th 2009, we welcomed our second daughter [redacted]. A perfectly healthy 7 lbs 1 oz baby girl, huge brown eyes, rosy cheeks and full pink lips. [redacted] developed typically, met all her milestones and even met some early. She was walking at 7 months old! [redacted] is our little ray of sunshine, she brings joy with her 100 watt smile on the darkest of days. She's our silly, happy, free spirited yet strong willed child.

[redacted] was born on July 8th of 2010, a perfectly healthy and plump 7 lbs 8 oz bundle of joy. His sisters welcomed him with lots of hugs and kisses, they were so happy to have him as part of our family. A total mommy's boy. He is the happiest, sweetest, most caring and loving little boy I have ever met. Gives the best cuddles in the world, we have officially named him a professional cuddler.

Things were going well until [redacted] had their first seizure in January of 2013. Oddly enough, they had their first seizure in the same month just 3 weeks from each other. Numerous labs, scans, tests and 48 hour EEGs determined that [redacted] both had epilepsy. Breakthrough seizures and the fact that they are siblings had our neurologist wanting to do further testing. The anti epileptic drugs were not working and they continued to have hundreds of seizures a day. We had genetic testing done in August of 2013 but nothing could have prepared us for the answers we received on November 14th of 2013.

[redacted] were diagnosed with Neuronal Ceroid Lipofucinosis or Late Infantile Batten Disease. It means that our children are lacking the enzyme responsible for clearing the cells in their brain so in turn the cells die and that is how skills are lost. Our children's fate included losing their ability to walk, talk, eat by mouth and losing their eyesight. We were sent home and told to enjoy the rest of their lives as they may not even make it to 10 years of age. Relieved to finally have answers to what was happening to our children but devastated by what it was, our world came crashing down on us that day. All the hopes and dreams we had for our children were now gone. Nothing at all made sense or mattered.

A couple days after receiving this news, after countless hours of frantically researching online, we found a family who also had two children with Batten disease. They told us about a clinical trial that at the time was only available in Germany, it was an enzyme replacement trial. At the time, there wasn't any evidence or information out there that this enzyme replacement therapy was even making a difference but there wasn't a doubt on our minds that we wanted to enrol our children in it. We remained in touch with the clinicians and doctors in Germany as they informed us that they will be opening a trial site in the United States, that was perfect since the US it is our native country.

In December of 2014 [redacted] became one of the first 3 children in the US to receive this enzyme replacement drug. Unfortunately, there were only 3 slots open and [redacted] wasn't able to participate. This tore our hearts out as we wanted to give our children the same chance.

At the start of December 2014, [redacted] started to struggle putting sentences together, she was starting to lose her ability to walk, she wasn't wanting to eat and she was now very weak. She was seizing every 20-40 minutes all day long and the rescue seizure medications had now stopped working. The

seizures began to take a huge toll on her little body. We watched, waited, hoped and prayed that these enzyme infusions can at least give us an extra year with our girl as she was rapidly declining.

A few months into treatment we noticed that the seizures were now shorter in duration, not as intense and not as frequent. She developed an appetite like we've never seen before. She was happy again and her speech became more clear. She became more confident and started taking more and more steps on her own.

When [redacted] started treatment, [redacted] was happy as can be, running, jumping, spelling words on his iPad and scarfing down as much food as he can fit in his little belly. [redacted] ended up starting treatment 19 months after [redacted] and he was then such a completely different boy. He was no longer able to walk, play on his iPad, eat by mouth and he was experiencing around 300 seizures a day. His body started to shut down

It's been a little over 3 years since [redacted] first infusion and she's doing great! She has stabilized and made some gains. She hasn't had a seizure in 2 years! We threw her a party and celebrated a milestone that we never thought we would get a chance to do. She is still able to eat by mouth and see. She is super strong and her happy self again.

For [redacted], it has been 18 months and he has also stabilized. He is able to give those amazing cuddles that only he knows how to give. He is taking steps in his gait trainer and is able to eat by mouth again. He is happy and getting stronger each day.

As their parents, it's always been important for us to do all that we can for our children, give them the best quality of life and make as many memories as possible. With Brineura, we are able to do all of these things. I can honestly say that [redacted] are still enjoying life and that they wouldn't be here today without this enzyme replacement therapy.

Just like we wanted [redacted] to have the same chance as his sister [redacted], we want our dear friends overseas to have the same chance for their children and family. Please reconsider your decision, it makes a world of a difference for many people.

Thank you for taking your time to read this.

[redacted]

I am mother of four kids. Two of them have NCL2. My son [redacted], he died two years and half ago in age of almost 10. And [redacted] she is 7 years old[redacted] is part of Clinical Trial in Hamburg since three and half years.

Three years after I found out my son's diagnose my daughter got first seizure. Thanks to her brother we found out for diagnose very quickly and six months after diagnose we started with treatment.

I and my husband also didn't' t have any doubts to treat or not. If you see one child suffering and dying you would do anything to save your child.

I saw my son dying in these age, age of [redacted]. It was a miracle to catch the moment see him laughing. But moments like this are not rarity in [redacted] life. She is one happy young girl. She cannot walk alone, but she has a walker and walk independently, she can ride a bicycle, she can speak, she

knows how to turn off candles on her birthday cake, she chooses dress that she likes, she can paint, play with blocks and toys. These are things maybe small for us but for parents they are whole world.

Please do not allow that any child suffer any more from this disease. Every child needs a medicine.

It is hard to imagine daily life of disabled child but also parent of disabled child. Kids need medicine. Do not allow that you will be one day written as someone who refused to treat kids. I as a mother of two kids I know the difference I can say that this medicine works.

At age of 5 my son was already bedridden, and m daughter of 7 she is still able to walk with help, eat, swallow, speak. She doesn't have problem with constipation, with sleeping, with vision. Maybe this sounds stupid but all above mentioned thing make huge problem to kids and to parent to find out the way to help. If it is possible to help. Because sometimes you are just helpless. And this is the worst feeling that one parent can experienced. Do not allow this to happen any more child or parents.

I hope and I know that you will change your decision.

Regards from Hamburg from Croatian family from Bosnia and Hetzegowina.

[redacted]

Dear NICE committee,
I am the mother of an Australian boy with late infantile batten disease. He is presently 5 years and 2 months old. He has been receiving cerliponase alfa every fortnight since he was 3 years and 10 months (November 2016). We had been told that around 5 years of age, he would lose the ability to walk and talk and eat. However, on this treatment, he continues to run, walk, climb with assistance, speak (in single and two word utterances), communicate, toilet independently and, most importantly, live a very happy life. He attends mainstream kindergarten and has now been seizure free since July 2016. I have no doubt that cerliponase alfa is sustaining his life quality.
In order to access this treatment on the compassionate use trial, my family had to leave our home, our jobs and our family and friends and move to the other side of the world (literally) to Rome, Italy where we didn't speak the language and we didn't know anybody. Don't make your citizens go through that. This treatment is now the 'standard of care' in the USA and parts of Europe. Why should children in the United Kingdom be entitled to anything less?
I implore you to reconsider your decision to fund this drug. It is working.

[redacted]

Hi, my name is [redacted]. My daughter [redacted] has received 18 infusions of Brineura, she turned 4 this past October. [redacted] was 2 weeks shy of her 3rd birthday when she had her first seizure; she started a seizure med right away because the seizure lasted over 10 minutes. In Feb 2017 [redacted] started having "drop" seizures. They were so bad at some points that she couldn't hold our hand and walk, she was falling all the time, she started wearing a helmet at school for safety precautions. Our neurologist suggested genetic testing because of this change in her seizures. We received [redacted] diagnosis 1 day after Brineura was approved in the US. That same day we were on the phone with Dr. Emily De Los Reyes, we scheduled a consultation to see if [redacted] was a good fit to be in the next round of clinical trials for Brineura[redacted] met the criteria, she was still walking and talking, Dr. Emily started making her phone calls. We were making the 8 hour drive home when we

received the call that another child had filled the spot in the trial. Regardless we knew [redacted] had to get this treatment whether she was in the trial or not. Her port placement was scheduled for June 2nd and her first infusion was on June 20th. Altogether, we made 7 trips to Ohio between May and July. [redacted] received her first 4 infusions at Nationwide Children's hospital until a site closer to our home in New York was ready for us. [redacted] is doing great by CLN 2 standards. She has not regressed in any areas and is continuing to learn new words. She had started stuttering the week before her port was placed and after 2 infusions the stuttering had pretty much stopped. [redacted] does not just walk, she runs! She goes to school 5 days a week and loves every minute of it. Her teachers and therapists keep a close eye on her to note any changes they see, they have yet to report any regression in skills, even with missing so much school to receive her infusions. Brineura has given our happy little girl more time to be the fun loving kid that she is. We are forever grateful that we received our diagnosis so quickly and we were able to start Brineura earlier than most kids. Our [redacted] can still run and jump, she loves the playground and bouncy houses and dancing along to Mickey' hot dog song. She wouldn't be able to do that without Brineura. It's unbelievable to me that children anywhere could be denied this treatment because it is too expensive. It would be one thing to wait it out for the long-term data if the drug came with adverse effects, but the only outcomes have been positive thus far. I believe the current data and outcomes should be more than enough to show that Brineura is effective and should be made available to all children.

[redacted]

My 12 year old son [redacted] was diagnosed with CLN2 November 2016. He was 10 years old had steadily been losing his mobility prior to diagnosis, and he seemed to lose even more once he was diagnosed.
So quickly, that he went from walking on his own, occasionally using a wall to sturdy himself to needing a walker within a 30 day period.
It actually frightened me to see how quickly he was losing his ability to walk, talk and use his fine motor coordination.
He was so fortunate to be the only child in Canada to receive treatment. To this day, he remains the only child in Canada to receive treatment. His are performed biweekly at Sick Kids Hospital in Toronto.
I know that there exists no long-term results to help prove the effectiveness of the Brineura. Sadly, the only reason for this is that no child has lives that long yet.
I can in 100% honesty tell you that almost immediately.. as soon as he started treatment in July 2017, his deterioration plateaued.
He has had a number of baseline tests run with SickKids hospital and so far, he has showed no further decline with his mobility, Speech, coordination and cognitive ability.
My husband and I agree that at home, we have also not seen any further decline.

Given how quickly CLN2 was taking over our son, there is honestly no way his decline could have been stopped over these past 8 months through any other means than with this medication.
I would be honoured to answer any questions you may have.
I know without a doubt, that Brineura is saving my son's life.

I think it's important to note that although it did run quickly through his body, we were fortunate that his treatment started before he lost his ability to walk, talk, eat on his own, attend school and actively participate in his extended family life.

As a result, today he is still walking with a walker and talking (although he does slur his words).

We see this as his chance to rebuild.. ground zero for him. We are alongside with him as he works himself daily with Physiotherapy, Occupational Therapy and Speech Therapy.

I sincerely hope you will reconsider your decision and permit the other CLN2 children to receive treatment.
You can never possibly know the feeling of hope a medication like this brings to and entire family and community.

[redacted]

My name is [redacted], my son was diagnosed with cln2 battens disease in June 2017. He stopped walking by then after almost 2 years of seizures. Before treatment started he cried for hours and hours in pain and never smiled or moved around. He had multi grand mall seizures a day. Once treatment started in October 2017 we noticed immediate change. His seizures became less and less. He smiled after his first treatment. Every treatment since he shows better days. Treatment is giving him a better quality of life. He is now clapping and playing peek a boo. [redacted] crawls on the floor which he was not doing before treatment because he was so very sick and in pain. This treatment is giving us more time and a better quality of life for him. I really truly believe he wouldn't be here today without treatment. Please reconsider your decision to fund this for UK families. It's the cruellest most disgusting disease that takes so much from the children and from families. This treatment works! Please please please help these kids and their families. Thank you for taking the time to read this. I have attached some pictures of my happy boy with cln2 battens disease. Before treatment, he did not smile.

[redacted]

I have one child, my son [redacted], and he has CLN2. My son has been receiving these treatments for a few months now. I have noticed significant changes with this treatment in this short amount of time. My son just turned 4 and he is on his 6th ERT. He has zero adverse reactions while receiving the treatment and he just gets better after each treatment. My son is still walking and saying a few words. He is in speech therapy and occupational therapy to maintain where he is at. Prior to his diagnosis and treatment, [redacted] was declining quickly, he was 2 when we started noticing his speech deteriorating and at 3 he started having seizures; within that year he had needed assistance most of the time with walking and his eating habits were poor, he was eating MAYBE 1 meal a day, my son was very foggy; he was distant. After receiving these ERT's, he is MUCH more aware, he laughs, copies words we say and is completely engaged in everything. Each day he says a new word or words I haven't even heard him say before. His eating habits have improved GREATLY, he has been eating 3 whole meals a day and sometimes even asks for a snack in between!!! , now, HE HAS A QUALITY OF LIFE!!!!!! HE HAS A PIECE OF CHILDHOOD BACK!!! All children should be able to have this. Every child should be able to be aware, and laugh, and communicate, and MOVE. Please re-consider your decision and give these children a chance at life as I do not know where my son would be without them!

[redacted]

My name is [redacted] and I am writing to you as a parent whose child [redacted] is currently receiving Brineura in a clinical trial in USA.

Our story is similar to so many others, our daughter [redacted] grew up like any other child although we had noticed a delay in speech but as do so many other parents. When [redacted] was 3 1/2 she suffered her first of many seizures. At first the diagnosis was epilepsy but we knew it was something more than this. We were fortunate that the neurologist that saw [redacted] had another patient with Battens disease and knew what to test for, so within 4 months and just before her 4th birthday we had the devastating news that our daughter had late infantile Battens disease. At the time of [redacted] diagnosis we were told that there was no cure or treatment for this disease this is when our world came crashing down around us. This disease takes a huge toll on the child, the family and the community involved. After doing some research we found out about a trial that was being undertaken in 4 countries around the world and we were extremely fortunate to be accepted on a two year clinical trial in Ohio, America in May 2017. However, this meant leaving behind all our friends and family in Australia and moving the family to America. This was hard for us to do especially as we knew nobody and needed support, but as a parent of a child with a life threatening illness you are not going to sit back and just watch your child die a painful and slow death when their is treatment available. Any parent would fight and do whatever they can to give their child the life they deserve and Brineura is the answer!

[redacted] has now had 20 infusions and has tolerated the drug very well with no side effects. I have seen first hand in my own child and other children on the study how this treatment has slowed down the dreadful effects of Battens disease and significantly improved their quality of life. [redacted] is five years old and has not had a seizure in over a year, she is walking with some assistance, is able to communicate her needs to us and can still speak words and is learning new words all the time. [redacted] attends preschool and loves to socialise and play with her friends. She is included and does all the same activities that her peers do. In August she will be starting kindergarten in a mainstream school.

I think it is unethical and unfair to deny a drug which could be lifesaving and has proven to enhance the quality of life for these children. I understand that the pharmaceutical company is charging a lot of money for this drug but you can't put a price on the lives of these children. They deserve a chance and a fight for life.

We ask that you really listen to these families and all the evidence that has been put in front of you and make the right decision to fund this drug for the children currently on Brineura and for any new children diagnosed with late infantile Batten Disease. How helpless some of these families must feel knowing that there is a treatment available to help their child but they cannot access the drug due to its cost and because the government have denied funding.

[redacted]

I have come to understand that NICE is not approving Brineura (Cerliponase Alfa) at this time for new patients in the UK, and as a parent of a 5 year old CLN2 boy, who is receiving this medicine, I cannot fathom how this decision was made. The reason that I am writing this letter is that the BDFA

has reached out through the BDSRA here in the US, specifically to families receiving treatment, and asked us to share our experiences with you considering your current decision to decline funding this treatment. Both the BDFA and the BDSRA have been instrumental in lifting families like mine when they are struck with the terrible news of diagnosis, no matter if CLN1, CLN2, CLN3, etc. There are several points the BDFA asked us to touch on: long-term evidence of success, some confusion over CLN3 heart issues in unrelated CLN2 cases, rebuttal of EEG findings long term, and prevention of vision loss. I am not a scientist, so I will present you with anecdotal evidence of treatment success I have seen with my own eyes.

To truly understand the benefit of treatment, one must put themselves in the role of CLN2 parent 5 years ago, and compare/contrast against a CLN2 parent today, to see how morally abject the decision to decline funding this life-altering treatment really is. Parents, whose children were born prior to 2010 and diagnosed with CLN2, were told to go home and hug their children, there is nothing that could be done to help with the quality of life. Several of these same parents vowed to change that dynamic, and started raising money for research and communicating with the medical research community. These parents pressed on, even when it was apparent their own child was too far progressed to benefit from a radical new way to treat this disease. Through their tireless work, they changed the course of CLN2 Batten history.

As a result, just a few short years later, my son is proof against the historical progression of the disease that Cerliponase Alfa is delivering the results it claims. As a quick background, [redacted] had his first seizure in Nov 2015, diagnosis of CLN2 Batten took a year (Nov 16), and he was admitted into expanded access for Brineura in May 2017. Yesterday he received his 22nd enzyme infusion. In the 10 months since he started treatment, we have seen a tremendous improvement in his quality of life against the progression of the disease. After his first infusion, he was more aware of his surroundings, by the 6th infusion, he was stabilizing and now he is doing things he hadn't done in the previous year, such as taking steps independently, crawling up the stairs, holding his sippy cup and drinking independently, playing ball with his unaffected twin sister and trying to say words we hadn't heard in a long time. Some people take for granted these tiny acts, or dismiss them as insignificant. I am here to tell you how beautiful it is for my child to entertain himself without worrying about a seizure, or a fall, or a black eye. There were times of constant crying and anguish because he can't communicate his issue to me in a way I could understand, and now there is peace in our house and peace within him. Peace, when his gaze locks onto me from across the living room, and he crawls his way over to me and crawls up on my lap to sit with me. Peace, amid the chaos of physical therapy appointments twice a week, gymnastics for his sister, Brineura treatments every fortnight, waiting for the school bus, all the normal tasks of raising children with working parents, yet multiplied by a factor of 10 because of CLN2.

We know that this is a treatment for this disease, and we still search for a cure, which may be as simple as identifying the disease at birth and beginning treatment as early as possible. We know what the historical path of this disease is, and today, we have a chance to change history. My wish is that in addition to NICE providing access to Brineura for that incredibly small percentage of the population that needs it, CLN2 is one of the conditions that is screened upon birth. This morning, I met a CLN2 child who just turned 4 and is receiving her 3rd enzyme infusion. I can tell you unequivocally that I am jealous of where this child is in relation to my own. The key difference is that she has not progressed as far as my son in this disease since they were fortunate to receive a diagnosis in half the time that ours took. I pray that you not stand in the way of progress for those affected by this terrible disease, look no further than [redacted], children of your countrymen, as the living proof needed to move forward with approval.

Comments from Untreated Families

[redacted] Bereaved Grandparent CLN2

In 2007, our 5th grandchild was born. A beautiful healthy baby born into a family where he was to be welcomed and loved.
[redacted] was a delightful child, sociable, chatty, he loved Peppa Pig and playing with his cousins. We would struggle to get him indoors as he just loved playing out in the garden. His grandad was his favourite person in the whole world.
As [redacted] grew, we began to notice that things weren't quite as they should. We would teach him a new word, but a week later he had forgotten it. He forgot the punchline to his 'that's not my monkey' story, he was struggling to ear, and he began to fall, to black out, to bump his head, to regress.
I don't need to tell you the symptoms and signs of Batten Disease, but we had never heard of it, we didn't know it's devastating consequences for [redacted]. We could only watch as it robbed him of everything that was good, his mobility, his voice, his sight, his laugh and his ability to cuddle.
Aged almost 5, [redacted] was given a death sentence. We were told that he had Battens CLN2, no treatment, no cure.
Our son ,[redacted] daddy, sat up each night for hours, he trawled the internet looking for hope. There was none. Research was in the early stages, with drug companies reluctant to invest in treatment for such a rare disease.
[redacted] lived until the 19th of December 2013. He was 6 years old. We miss him ever hour of every day.

Over the last few years we have watched the development of a drug that could offer hope to families like ours. A drug trial that could slow down the progress of Battens, a drug that couldn't cure....yet, but there was tentative hope, priceless, terrifying, but the most amazing hope.
There was also envy, sadness, and anger that this hope had come too late for [redacted], and for the many other children who have lost the fight; those were ineligible for trials and for those who had a different type than CLN2.
We followed the journey of [redacted] as they participated in the trials.
[redacted] reminds us so much of [redacted] is just a little dot, who could not be moved by her joy for life, and be happy that they were given this chance.
How amazing that [redacted] continued to dance and that [redacted] continued to laugh. The disease regression has visibly slowed. The children's lives were undoubtedly exceeding their prognosis.

Still, The shadow of [redacted] loomed, as we saw [redacted] pass milestones that he never reached. But the joy in the laughter of those two children, soothed our souls and gave us a belief that families will not go through what we did, that children won't die in convulsive pain, blind, immobile and unable to communicate.

To hear the news today. That NICE are not recommending this treatment, that they are questioning its effectiveness, is a knockout punch to the hearts of Battens families.
I can only speak as a grandparent of seven. Number 5 is missing and so very very missed.

[redacted] **Parent of CLN8 child**

Every child has a right to life, however short or limited that might be. It's our job as parents, carers, professionals and most importantly as human beings to stand up and help them fight for that right on their behalf. This treatment represents science and human spirit coming together to speak up for those children and families affected.

My son [redacted] has CLN8 so is not directly benefiting from this life changing treatment...at the moment.

The treatment represents the beginning. The beginning of something that is already proving to help affected children with CLN2. The beginning of a journey where the continued successful use of the treatment will lead to further research to make the treatment more accessible and more affordable. Research that will also lead to other potential treatments being created to treat other, and ultimately all, variants of this debilitating condition, including CLN8.

Let's not stall this journey in its infancy because of short sightedness or economic shrewdness

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[redacted] **CLN2 Parent of 2 affected children.**

I have had 2 children with CLN2 who did not access the treatment. Batten disease progresses incredibly fast. In the space of 3 months leading up to her 5th birthday, my daughter lost all her speech and ability to walk and stand unaided. She passed away aged 6 1/4 unable to see, eat, hold her head up, even hold a toy. She died directly of battens disease as she went into constant seizure. The fact that there are 7 year olds on the treatment still walking and talking is incredible proof that this treatment significantly slows down the disease progression and relieves burdens on families to provide around clock care. My son lost his ability to walk **overnight** aged 4 1/2. He is now 7 1/2 and cannot move his body intentionally, hardly at all. He is completely tube fed and his digestive system is slowing down. He requires full-time care including overnight. He is on 10 regular daily medications and the ketogenic diet just to keep him alive by managing the symptoms but none of them slow the disease down and it will take his life in the next few years. I cannot work as he hardly attends school, my marriage broke down and I am reliant on benefits to live. The impact of the horror of this disease on all aspects of life cannot be overestimated.

If NICE wishes to see more evidence, why can the drug not be funded now and reviewed in 5 years time when the longer term effects are known? It is keeping children alive and they will die once taken off it.

[redacted] **Bereaved Parents CLN2**

We are absolutely devastated to hear the news of NICE's decision, regarding treatment for CLN2. Please find below what this decision means to us.

Our beautiful daughter [redacted] was diagnosed with CLN2 Batten Disease in Jan 2014. The BioMarin trial were recruiting for new patients at the time and, after being told that there was no treatment, no cure for our little girl, we finally had some hope. A delay in the trial taking on the next patient coincided with [redacted] having a rapid decline, meaning that she no longer qualified for the trial. We no

longer had any hope. We knew our daughter would die, but we were completely unaware of how horrific the journey our daughter was to take, would be.

After losing the ability to walk, talk, sit and swallow, [redacted] lost her sight. Her little brother was 6 weeks old when we received diagnosis, and grew up seeing his sister getting more poorly each day.

When [redacted] was 6.5 years, Batten Disease started to affect her brainstem. Her heart would race to 275bpm then plummet to 20bpm. We would cuddle her, thinking that our daughter was leaving us. On 26th Jan 2017, I was at home alone with [redacted]. We had spent the morning cuddling on the sofa, watching Cinderella when I suddenly noticed that [redacted] had stopped breathing. She was conscious and aware of what was happening. She had lost the ability to breathe, whilst still awake. I rang my husband, who was at work at the time, so that [redacted] could hear her Daddy's voice as she started to slip away.

I will always wonder if I made the right decision that day. I called an ambulance and started to resuscitate my daughter. With hind sight, it was part of our plan for [redacted] to die at home. A DNR was in place. But I wasn't ready to say goodbye, I didn't want to be by myself when our daughter died. For 12 minutes, I desperately resuscitated [redacted]. During this time, our son [redacted], now aged 3, came home from preschool and saw me resuscitating his big sister. After 12 minutes, [redacted] started to breath again. We went to hospital, where [redacted] stopped breathing a further 5 times that evening. After a week in hospital, we thought [redacted] was improving, breathing-wise, however to our horror, her gut stopped working. She could no longer absorb anything through her stomach. Her kidneys had stopped working, and so IV fluids weren't an option. We knew at this point that we had to say our final goodbyes.

[redacted] lived for almost a week with no fluids. A drain was attached to her gastrostomy to try and stop the bile escaping out of her nose. As the dehydration kicked in, [redacted] beautiful big brown eyes started to blister and bubble. Despite increasing Diamorphine and midazolam via syringe driver, [redacted] suffered terribly during her final days.

[redacted] now has counselling, he has for nearly a year. He was having panic attacks that 'the angels would come down and take him away too'. He remembers everything that he saw his big sister go through and this will no doubt affect him for the rest of his life.

We now have the ability to prevent this horrific disease progression for children with Batten Disease. By the time [redacted] was 5, she could no longer sit up unaided. She died aged 6. There are children older than [redacted] on the trial who are not only still alive, but walking and talking. They deserve the chance to live. They deserve to have the horrific final disease progression to be delayed as long as possible. They deserve the time that Brineura will buy them, whilst scientists find a cure. Science is advancing every day. There are labs across the globe working on a cure for Battens as we speak. These children deserve the chance to be alive when a cure is finally found.

No child should go through what [redacted] did. No child should see any of the things that [redacted] witnessed. Please do the right thing and give these children the chance to live. Let's give them the chance to grow up with their siblings.

[redacted] – Bereaved Parent CLN2

My son [redacted] was born in 1990 , the most beautiful perfect little boy .. he met his milestones , was walking by 11 months , was talking and counting g at 2 , did everything and more than any other boy his age , at almost 3 he suffered a seizure , we were in a bus going into Liverpool city Center , and I noticed he was blinking a lot but wasn't sure what was wrong , we stepped off the bus and he became very ill and started to shake , I got straight back into a cab , to hospital by the time he got there he was in a full blown seizure , he he was diagnosed a few months later , after which he deteriorated rapidly , he loved football , and stilled kicked a ball around with his brother and sisters even when he could barely walk , when he could no longer walk , he crawled around wracking the ball with his hand , he struggled to talk , but with shear force and determination he tried his best to still communicate using , all his strength to control his muscles to get a single word out , these children know what is happening to them , they fight with everything they have , to do as much as they can till the very end , and we as parents watch powerless, with equal amounts of heartache and pride, I have watched [redacted] Journey on this trial treatment and I am truly amazed .. especially with [redacted] .. of course we don't know the long term effects , just as we do t with many other drugs.. but these children have limited time with us anyway .. so give us 6-7 years maybe a little more of our children living a full and active life , the cost to the NHS is undoubtedly going to be high anyway given the amount of time our children spend in hospital , in intensive care , requiring Home adaptions , support in the community and medication , surely it would be best to spend this money in maki g the lives of our children and their families worth living , [redacted] , mother of [redacted] born in 1990, and who we sadly lost in 2000

[redacted] – Parent of CLN2 child

[redacted], our precious baby girl.

We won't ever forget the day [redacted] was diagnosed. Every little detail is imprinted in our minds. Walking into the hospital, we were expecting bad news. We thought [redacted] would have problems walking, her legs were weak or maybe she suffered from severe epilepsy. They were the worst case scenarios in our head. Terminal illness, [redacted] dying. Them thoughts hadn't even occurred to us. Battens disease. We had never even heard of it, we spent hours and hours researching on it, looking for advice, any chance of a cure or maybe it was a misdiagnosis.
Nothing. No hope.
Watching [redacted] deteriorate on a daily basis is difficult, not being able to explain to her what is happening and not being able to help her. It's unbearable.
Our beautiful baby girl, unable to walk, talk, and eat. Unable to sleep and suffering from frequent seizures and myclonic jerks. Is this the life she deserves? Would things be different if she suffered from a more common, well known disease? Unlucky [redacted], you didn't get to choose. You have no control over any of this, yet you have to bear a great burden.
We heard about the clinical trial, [redacted] had already deteriorated, was it worth it? We hadn't thought about what was yet to come. More frequent seizures. Myclonic jerks causing her excruciating pain. Worsening physical condition. Loss of eyesight.
We had to get [redacted] the treatment. A four year old girl having to go through all that. It was too cruel. Finding out the trial had ended and there were no more spaces available for compassionate use. It broke our heart but didn't deter us because it had been proven to halt further deterioration, it had helped alleviate symptoms. So obviously NICE were going to approve the treatment and [redacted] would be starting the treatment very soon, under the NHS.

The thought that NICE wouldn't recommend it, hadn't even occurred to us. How could they be so cruel? How could they refuse to help us ease the pain and suffering of our children?
To help control their seizures and give them a better quality of life...?
How do we explain to our son, whilst he watches his sister deteriorate and die...?
[redacted] is a beautiful and happy little girl. She loved playing outside, she loved eating, she loved singing. This treatment has given us a glimmer of hope.
Surely there will be more children diagnosed with Battens, this awful disease won't just end after the loss of these current children suffering. There needs to be more research on the disease, there is need to find a cure. The closest thing to a cure at the moment is the trial. It has shown very positive results in just a few years. Wouldn't it make more sense to allow the treatment on the NHS and hopefully wait to see the long term affects too. Expenses do come into it but what are the costs involved for a child with Battens anyway.
Just looking at the story of [redacted]. [redacted] is doing absolutely fine, she is able to walk, talk and eat. So all the things a normal child her age would do. Does that not save on NHS costs? Surely there is a huge difference in the amount of time and money spent on her and her brother. Speech therapy, mobility vehicles, equipment for home, equipment for school, schooling at a specialist school, home adaptations, medications. Obviously it doesn't cover the cost of the treatment but it can reduce pressure on other departments within the NHS. There are so many advantages in starting the treatment.
The NHS was set up to help everybody. It feels as if this decision is doing the opposite. Instead of helping to try and eliminate the disease, they seem to be eliminating any chance of a cure.

This is the step needed to ensure funding for drugs that are not commercially viable.

[redacted] bereaved parents CLN2
To Whom it may concern

As parents of a child who died of Late Infantile Battens Disease, we are devastated by the decision made by NICE not to fund the new treatment that has been proven to slow down the disease and let the children benefit from a prolonged quality of life.

Our daughter never had this option and we feel strongly that cerliponase alfa should be reconsidered for the following reasons:

1. This disease is terminal and progresses very rapidly. Not only is this heart-breaking for the parents, siblings and the rest of the family and friends, but it is so rapid that the NHS often fails to provide support quickly enough to help the children and family.
2. This pioneering treatment gives hope to the family. Recent trials have proven its effectiveness.
3. Some families, like the [redacted], sometimes have more than one child with the disease, as the symptoms rarely manifest until the child is over 2 years of age.
4. As parents of a child with CLN2 ([redacted] 07/01/97-03/01/08), like the other families on the trial, we chose not to have any other children with the disease, as we were able to make an informed decision and chose to terminate 2 pregnancies than watch any more of our children suffer as [redacted] did. [redacted] family do not have this choice, as they already have another child that has been diagnosed with the disease but has no symptoms yet. We really feel their heartache and could not imagine watching another child suffer the way [redacted] did. To give you an idea what it is like having a child with Battens, I will provide details

of our personal experience. This is not an easy option for us to recount and still makes me cry just writing about it.

[redacted] was born on 7th January 1997 and progressed well, reaching the usual development markers easily. [redacted] had her first partial seizure just after her 3rd Birthday. I had noticed before Christmas that she had become increasingly clingy, whereas she had previously been a confident independent toddler. She also showed signs of deterioration in mental capacity and possibly visual problems. For example, I noticed she was unable to do jigsaw puzzles that she had previously been able to complete easily. The following month (February 2000), [redacted] had a generalised seizure which was very frightening. Seizures became more frequent and then she began to have mobility problems. She went to a Special Needs School at 4 years of age, as she was unable to walk far and was unstable and kept hurting herself. She was unable to go to the toilet independently and became doubly incontinent. She lost her vision quite rapidly, which was very distressing for her and us. Just before [redacted] 7th birthday, she became increasingly ill and the local hospital lacked expertise to care for her. She was eventually given full time care at The Children's Trust in [redacted], as she needed 24-hour support. I am sure that these nurses could give you first-hand information to verify the amount of care and expertise children like [redacted] require. Having cared for one child with Battens Disease, I have suffered from the physical consequences of the lack of support given. The sleep deprivation and the child's inability to weight bear really takes its toll on your body. To give you an example of [redacted] rapid progression, we had a hoist and kept having to return slings as they weren't appropriate by the time assessment, funding agreement by panel and order had arrived. Another time, I actually paid up front for a walking frame for [redacted], so that we reduced the delay. It still took too long and by the time it arrived, it was too late. This was understandably heart-breaking for us as a family.

Despite being very proud and independent, I had to reluctantly admit that my health was deteriorating and I was unable to cope with the lack of sleep, without support. Many times the support require for her growing needs was reactive rather than proactive. This was in part due to the speed of deterioration, which I have already mentioned. The decision to accept the place at the Children's Trust was not easy, as it was recognising the fact that we were unable to meet the needs of our daughter – 24 hour care.

[redacted] died just before her 11th birthday and was finding it difficult to breathe, so needed oxygen and was using morphine to help with her pain management. As I hope you can imagine, this traumatic situation has left and indelible mark on our memory. I do not think I would have had the strength to watch another child deteriorate so rapidly and suffer the same fate.

After [redacted] death we donated brain tissue in the hope that [redacted] suffering would lead to improvements in the treatment of this disease and hopefully a cure eventually.

Any parent who has lost a child from this disease will be familiar with our story. Although we still have no cure, slowing down the disease would give these children a chance to maintain their skills for longer, thus leading to improved quality of life. It would also help the NHS provide for these children more effectively as would give more time to organise support. At the moment, the natural speed of the disease aggravates the situation and is a huge strain on the whole family.

We beg you to reconsider your decision.

[redacted] **bereaved parent CLN2**

[redacted] **– Late Infantile Batten Disease**

Date of Birth 10.11.2009

Date of Death 21.11.2009

I would very much like to express my concern regarding the decision made my NICE on the decision for ten drug Cerliponase Alfa to not be funded by the NHS

[redacted] was born a healthy child, the 2nd treasured child to me and his father.

[redacted] development progressed well until nearly his 3rd birthday where he turned blue in the back of the car. Over 2 very long painful years we watched [redacted] health rapidly decline where he lost every single ability from walking, talking, eating, becoming blind and 24/7 bedridden.

As a parent, how do you accept this? How do you come to terms with all of this? You don't, you battle on looking after your child to the best of your best abilities whilst watching your family be torn apart by an exceptionally cruel, rare genetic disease.

[redacted] was age 3 to 5 in the lead up to his diagnosis was regularly blue lighted to hospital, air lifted not once but **twice**. Multiple MRI scans, lumbar punctures, skin biopsies taken under anaesthetic.

In all of this, I've no idea how were coping, the extreme stress was life shattering.

We finally had [redacted] diagnosis just before his 5th birthday of Late Infantile Battens Disease. It was the most horrendous time any family should never experience.

[redacted] health took a rapid turn for the worse the day after his 7th birthday where he went to a routine appointment at [redacted] General Hospital for a Platelet transfusion, during this procedure his left lung collapsed and he was transferred to a children's ward at [redacted] Royal Hospital.

On arrival [redacted] went into cardiac arrest where we witnessed our treasured sons chest be pumped brutally. **This is something NO PERSON should EVER witness**. [redacted] was swiftly transferred via Intensive Care Ambulance to [redacted] Children's Hospital to be placed on the highest level of Intensive care with the help of an Oscillator machine.

Over 10 long days [redacted] poorly body ballooned to an unrecognizable size because of the air being pumped into him, chest drains were inserted into his sides to try & bring the pressures of air down in him.

After 10 days we had to make a decision no parent should ever make to have his life support switched off.

[redacted] passed away in our arms and was transferred to our local children's hospice to be placed in their special bedroom.

It's been 8 years since [redacted] has passed away. I have no shame in admitting I had to have urgent counselling to help me to get my head around what had happened. Witnessing your child being resuscitated left me with extreme anxiety and Post Traumatic Stress

I won't discuss the effects on his brother or father as it goes without saying. Its life changing for everyone in the family, extended and also for our friends too.

My marriage also broke down with [redacted] illness and death playing a significant contributing factor with all the stress and grief being dealt with.

To now know batten families personally and witness that a drug has been discovered and now not being funded by the NHS that can prevent all of the above is as brutal to me as reliving it all over again.

Please do understand the amazing effects this drug is having on the children receiving this. I can compare my son with them. By the age of 5 [redacted] was permanently in a wheelchair and had to rely on 24/7 care being PEG fed. The children on this drug are mobile, verbal and feeding normally.

I urge this decision to be turned around for the drug to be funded.

It would be exceptionally irresponsible of our country to not fund this drug. Its amazing progress for not only Batten Disease but also for all rare diseases and should be the perfect example of the work and research so many scientists have been working desperately hard to achieve.

I really hope common sense prevails for all of the families.

PLEASE NO MORE [redacted]

[redacted] bereaved parent CLN2

My name is [redacted] and I lost two beautiful daughters to Battens Disease in 2004 and 2006, [redacted], both aged 8.

Since reading the news about the treatment that [redacted] are receiving I haven't stopped crying. Firstly because it is too late to help my daughters but secondly because there is a potential cure out there which is obviously benefitting [redacted] and they may get the treatment taken away from them. I fought so hard to try and find a cure for my girls and we did take them to new York for a clinical trial which unfortunately didn't work, but this was the start of finding a cure and if children can now be treated on the NHS and live a longer life, then my girls helped this cure to be found and they didn't die for no reason.

Unless you have lost a child yourself no one can understand what you go through and each day is so hard to get through. To take away the treatment that [redacted] are receiving is the most heart-breaking decision that could be made as it is quite clearly helping both of them. As a Battens parent I know you would do anything to help your children and I am 100% behind [redacted].

[redacted] – bereaved parent, CLN3

'Both my children had CLN3 (Juvenile Batten Disease) and I lost my beautiful daughter at the age of 23 and my smiley, handsome son at the age of 26. Watching your 2 children deteriorate and die of

this evil disease has to be the worst thing a parent ever has to go through and is only beaten by what my children had to go through. They were both loved and well cared for but they went to hell and back and there was never any hope that there would be a cure.

This new drug gives the whole Batten community hope. Even though CLN2 is in so many ways different to CLN3, it gives hope where there was none.

And from a practical perspective, surely it is short term thinking not to fund this drug, which is already giving good results and will hopefully encourage continuing research into finding a cure for all forms of this devastating disease. Providing the care required is , of course, expensive and the devastating effects has a ripple effect throughout families. This drug is already showing promising results is improving children lives so surely longer term, medical and care costs will decrease.

Please reconsider your decision and give hope and life to our children.

[redacted] Mother to [redacted] CLN2 age 8, diagnosed just after turning 5.

[redacted] was not on the treatment, however since seeing the delay in the disease in many of the children that we know on the trial I would definitely put him on this trial as I do believe the benefits to quality of life and extending life are priceless. I do see that the children on the trial are retaining their skills for so much longer than my son who has declined rapidly over the last 2 years.

I do believe that this treatment should be available to all children with CLN2 and this treatment given at the earliest opportunity it will change the lives of the affected children and also their families, who will be able to enjoy more experiences with their children and siblings.

[redacted] condition has deteriorated rapidly over the last 2 years and at the age of 8 he can no longer walk, talk, eat, see or communicate, and to keep any of these skills for longer is something you can't put a price on. He has had 2 life threatening chest infections in the last year which has resulted in him now being reliant upon oxygen. He has seizures everyday some of which last for an hour or more. All of these things could be very different had [redacted] been on this treatment.

It is very disappointing that this decision has been made for all newly diagnosed children, so that their is no hope for them. And those on the trial that this will be withdrawn, which is ultimately going to shorten their lives.

I do hope that this decision will be overturned, as some of the reasons given, for example referring to long term results are bizarre when this is a new treatment and the costs if they live to adulthood all of which are unknown at present, until the treatment is given long term.

[redacted] – Bereaved Grandparent CLN2

[redacted] Born 08/11/08. Died. 29/10/2016

I cared for my grandson [redacted] who suffered from Late Infantile NCL. For the last year of his life I took long term sick from my employment as a palliative care specialist nurse. I literally could not

leave his side or the house during that time due to his complicated medical needs. He died just before his 8th birthday.

I am not going to describe the suffering this brave little boy had to endure. The heartbreak of watching a healthy, bright young lad lose all his abilities. The need to deep suction him up to 20 times a day to prevent him choking. The ridiculous amounts of medications needed to attempt to control his tonic clonic seizures, his atonic seizures, his dystonia, his myoclonic seizures, his hyperkinetic movements. No, I am not going to describe any of them as I assume the Committee of NICE are, by now, well aware of the symptoms of Late Infantile Batten disease. The Committee would have researched the disease in depth before they decided that they would not be supporting continued funding for enzyme therapy. So it is obvious the suffering Batten children have to endure is of no consequence to it's members.

It is, therefore, all about the cost. And ,yes, it is very costly. But NICE are being extremely short sighted. Funding this therapy will prove cost effective if NICE members consider the long term benefits. For example, at present:

1) these children can need in excess of £2000 every month in essential medication
2) these children spend weeks of every year in HDU settings
3) these children require highly specialist careers in the community
4) these children require custom made equipment

The above is just a small example of what caring for these children costs the NHS as the disease rapidly results in total dependency. And this stage of the disease usually continues for years.

It may appear that I am providing evidence to support NICE's recommendation. NICE may believe that as these children are draining the NHS by withdrawing funding and ensuring these children die sooner rather than later they will no longer be a financial burden on resources. Of course NICE will deny that this is the reason but few of us affected by Batten Disease will think otherwise. But NICE would be WRONG.

The enzyme therapy has proved without fear of contradiction that it not only slows the progression of the disease but by doing so it has drastically reduced the cost of treating and controlling the symptoms . So saving hundreds of thousands of pounds . NICE may then argue that eventually each child receiving the therapy will succumb to the final stage of the disease and the financial burden is only delayed not eradicated. Can NICE prove that? NO. And there is strong evidence in medical research, that when enzyme trials are allowed to continue they often advance to the point where diseases are , if not cured, easily controlled. It is very feasible that this therapy could result in preventing the disease from become symptomatic in the future . Are NICE really sure that preventing medical advances and so reducing financial burdens on the NHS is the way forward?

I have been an experienced nurse for many decades and witnessed how much money is wasted by the NHS through waste and bad management. Do not let this decision be another example of bad judgement

[redacted] – Parent of CLN3

In response to the decision from NICE regarding the treatment for CLN2 children, I think the decision needs looking at very closely and it needs to be overturned to a "Yes"

Yes, we will fund the treatment to allow these innocent children to live their lives to their full potential. Every child deserves this chance. I am a mother of a child who has s different form of

Battens Disease (CLN3), there also is no cure but also no treatment as yet either, this doesn't give other Batten families much hope of future funding if other successful treatments are developed. Imagine being told there is treatment available but your child cannot receive it, it's like receiving your child's death sentence all over again.

This treatment is improving the quality of life of children with this devastating disease. To not continue with this treatment is robbing children and their families of experiencing so many memories. There is solid evidence that this treatment is slowing down the progression of the disease and giving these children quality of life. How can this treatment not be continued ?

[redacted] Parents of child with CLN2

As parents of a little girl with LINCL we were very downhearted with the decision of NICE not to recommend the funding for the use of cerliponase alfa. I was amazed to find that £2.41mil of the NHS' budget was spent on drink addiction prescriptions and a massive £500mil on drug addicts (namely methadone) in 2010. This figure rises yearly at a rate of approximately 1.5%. The NHS is funding prescriptions to prolong the lives of people who have had a chance at life and chose (for what ever reason) not to live. These children (like my daughter) did not have a chance and did not choose this condition either however NICE have decided not to fund a drug that has shown great results at slowing this horrible disease down if it is diagnosed early enough which could be enough to prolong the lives of our children until a cure could be found. Yes it is very expensive (at present) however there are only a handful of children with LINCL that could be treated with this drug and there will always be cases like ours where we have been let down by the NHS in missed opportunity to diagnose the condition to the point we felt it was too late to start on the trial. The cost of a handful of lives is expensive, but we feel that the cost of the drug could and probably would be negotiated down and would be a mere drop in the ocean of the money keeping drug addicts and alcoholics alive. Although there is no long term results for this drug, there is plenty of long term results for many of the treatments available on the NHS that many of the British public agree aren't worth the money that is spent, drug abuse being one of the most expensive and least successful long term treatments (there is no such thing as a cured addict). Unfortunately for us the diagnosis came too late but please give family's like ours a better chance of a brighter future and make this drug available for whoever is lucky enough to catch this disease early enough.

Her MRI was misread, she had microcephaly, the pattern of the seizures and progression of her seizures, the MRI (AT SECOND VIEWING OF THE SAME MRI) actually showing moderately atrophic cerebellum, developmental delay, and the terrible condition of her movement and myoclonic jerking by September (month of diagnosis). [redacted] was let down and we were let down. Always being told it was difficult epilepsy and drug related. The test for batten disease was sent off around May/June 2016 yet it took till September to give us the results by which time [redacted] had lost most of her abilities. 3 days prior to this we were told "not to worry" that she was "too good" to have anything sinister going on and she was given a drug called phenytoin which is known to mimic and increase the symptoms of batten disease even though no test results had been received. We hope in future diagnosis is made earlier for families and that Carbamazapine and phenytoin are not given to children with epilepsy until they have been tested for batten disease.

[redacted] **Parent CLN2**

I'm writing in response to the NICE decision that funding Brineura "is not a good use of resources." I can't imagine that anyone recommending this has ever had any member of their family affected by Batten Disease.

It is a cruel and relentless disease, I know so because my nearly 7 year old son suffers from CLN2. He is a distinctly different child than he was 2.5 years ago when we first received his diagnosis and learned what cerliponase alfa is, and how it can slow the progression of this horrific condition by more than 90% as compared to children without treatment over the same time frame.

We tried to gain access through a clinical trial but were unfortunately unable to secure treatment. Now that it's an approved treatment - which works so well it was fast tracked to help more children sooner - it's painfully unbearable to know that some children still won't get it based on cost.

I won't make this a lengthy email, I hope this is all that's needed to aid in a proper decision being made. My son hasn't been able to receive treatment and is declining rapidly, I have met other children who have been on treatment and there is a remarkable difference in their abilities as compared to my own child. This treatment was fast tracked for approval, as already mentioned, because of its outstanding results. We can't wait and see what the long term effects are! There is no long term presently for children with CLN2, their only hope to live a longer life is through treatment with Brineura. Research is still being done, there may be something even more effective uncovered in the near future; to deny Brineura is to deny any hope of ever getting better for these children. Please grant them a chance at life. Give their families more time with them.

Letter from a Head Teacher

To whom it may concern

I am writing to you regarding the recent decision by NICE to recommend to the NHS to not fund Brineura, the treatment for Batten's Disease CLN2.

I have been working with children with learning difficulties for 29 years and as the headteacher of a school for children with profound and multiple learning difficulties, have significant experience of children with life limiting conditions and the impact that this has on both the child's and family's life.

At [redacted] School we currently have two children with Batten's Disease Type 2 and one child with Batten's Disease Type 3. During my time at the school we have also worked with two other children with Batten's Disease. As a result, we have relevant experience and an understanding of how the condition is likely to develop and significant information on pupil's attainment during their lives. Some of this information is anecdotal.

Currently the two children who attend [redacted] School who have Batten's Disease Type 2 are part of the clinical trials based at Great Ormond Street Children's Hospital. Having worked with these children during their time at the school it would appear that the current trial is having some impact. Although, in one child's case they have lost some of their physical skills, I have to report that these children are still making academic progress. Both of the children are able to communicate effectively, in some cases this is a little idiosyncratic, and are able to make choices and have some

control over their lives and the world around them. In fact, it would appear that they are making progress that I would not normally have expected children with this condition to make. They are able to have, within their limited understanding of the world, a fulfilling and meaningful life.

With regards to the families that we work with, I believe that the trial provides parents with some hope and an expectation that their child will experience a fulfilling life, even if this is for a short period of time. This has allowed the families to continue to work together to provide meaningful experiences. This is not always something that I have experienced, as the lack of hope can affect parents and siblings considerably.

Based on what I believe is reasonable experience of Batten's Disease, I would like to petition NICE to reconsider their assessment and to look more widely at the impact that this trial is having on the children, their parents and their siblings.

Yours faithfully [redacted]

Public Comments

[redacted]

I have no medical knowledge whatsoever but what I do have is three small children who I would fight till the very end for.

It's quite clear the infusions have been working from seeing [redacted] on a daily basis via their page. [redacted] seem to be rarely Ill these days where at one point they were always in and out of hospital for one reason or another.

The treatment is quite clearly working, if a treatment is working why pull it for other children diagnosed or yet to be diagnosed.

These children deserve the world for what they are going through you wouldn't wish it on your worst enemy, if this treatment gives them a better quality of life than the suffering they have to endure, the decision needs to be changed.

[redacted]

To say I am disappointed by the decision is an understatement.
I am a supporter of [redacted] Army & help to raise awareness & funds whenever I can. Having seen the difference between [redacted] at the same age is astonishing & I am convinced that the infusions are having a positive effect on [redacted]. To deny the funding is to condemn them & other sufferers to an early death with lots of suffering along the way.
I hope that this decision can be reversed very soon as it seems very unfair that children in the USA & other parts of Europe have access to these drugs.

[redacted]

I have been following [redacted] on Facebook for sometime and have seen how the clinical trial has slowed down the progression, particularly for [redacted], who by now should have shown some kind of decline, however, miraculously she appears to be thriving and hitting milestones [redacted] seems to be maintaining and hasn't showed any further progression since the trial.

If it was your child you would do anything as a parent to give them a better quality of life and to not see them suffer unnecessarily.

I am against the ruling and think it is unjust and is cruel to prevent children from having the best life they can. It isn't just about extending their lives, it is about allowing them to lead a better quality of life without the unnecessary suffering, which the trial has proved!

I hope and pray that this is not the final decision and that people are listened to and more evidence is found or to extend the trial to get a more accurate portrait of how it helps long term.

[redacted]

In response to NICE recommending not to fund the drug for CLN2 batten's disease..

I am in complete and utter shock that they are recommending not to fund this drug, it is currently proving that it is slowing down and prolonging the lives of those children who have been diagnosed with the disease. NICE need to think about the families of those with this disease and how horrible it must be as a parent to find out your child has a life limiting disease and there is a drug out there to slow down the progression, yet the NHS wont fund it. They need to imagine how they would feel if they had a child who was born with batten's disease.. if one of the panel members went on to have a child with this condition and she had agreed not to fund the treatment, she would be completely heartbroken with the fact that she could have said yes to the treatment and given her child a better quality of life.

It does not make sense as to why they would choose not to fund this drug when it is clearly slowing down the progression of the illness. If one of the reasons is because they don't know if it will prolong their lives after 12-13 then the only way they are going to know is if they continue to fund the drug. Companies will happily pour millions of pounds into helping people quit smoking yet not to fund a drug which will help children live longer with a better quality of life.

SMOKING IS A CHOICE.. BATTEN'S DISEASE ISN'T.

[redacted]

To Whom It May Concern,

I am utterly disappointed and frustrated at your decision to not fund treatment for CLN2 Batten Disease. [redacted] is PROOF that this treatment program works on these kids, extends their lives AND gives them better quality of life to live!

Other kids in the United States are receiving this treatment and are also seeing the positive effects. [redacted]. These kids are benefiting from this treatment and you are halting other children from receiving it by not funding it.

I am heartbroken for all the lives you are throwing away with this decision. I hope and pray that you come to your senses, reverse your decision, and fund this treatment for these children who have done nothing to deserve what this awful disease does to them.

[redacted]
NICE/NHS,

I've recently become aware of the devastating decision you have made to not fund the one and only treatment available to families affected by battens disease.

I 'follow' many children's journeys via Facebook - I've only met one of these amazing children and her family. She sadly gained her angel wings at the young age of just 5 years old. This little girl had no access to treatment, it's heartbreakingly too late for her. The family I am now most in contact with is the [redacted] family who have 4 gorgeous children, two of which [redacted] have been diagnosed with battens disease. The two little ones plus [redacted] (mum and dad) travel to Great Ormond Street Hospital in London from their home in [redacted] every 2 weeks to receive the treatment that very wrongly only a handful of children in the UK are able to access following a diagnosis. The positive results and effect this treatment has had on both [redacted] is incredible - more so with [redacted] due to her accessing the drug while she was still very young and showing little sign of the disease progressing. [redacted] is turning 5 next month and is living her little life to the fullest and how every single child should do! She is still learning new words, forming sentences, eating as much 'choc choc' as she can fit in her little mouth, attending school & a dance class, running riot causing mayhem and jumping in muddy puddles! Looking at it from this point of view is devastating as beautiful little [redacted] who I was lucky enough to meet had deteriorated to the stage where she was fully dependant on her brave parents & siblings, was tube fed, could no longer walk & talk, had no vision and often required oxygen and suctioning to breathe. As [redacted] didn't have access to treatment this resulted in her passing away a month after she turned 5 years old - which is the same age as [redacted] is now!

This treatment needs to be funded. Treatments and help for people who are addicted to drugs, smoking, alcohol etc, are available so why isn't a treatment for battens funded?! People CHOOSE to smoke, drink and take illegal drugs and substances. Children with battens DO NOT GET A CHOICE - they have no say! They didn't ask for battens disease so therefore deserve treatment to be available to them! I work in a playgroup for children under 5 who have complex health needs and disabilities. A couple of our children including [redacted] have so cruelly been taken from us far too young due to battens disease. Not only does it affect the child but also their families, siblings and friends too.

EVERY child deserves a chance in life and to enjoy childhood. Please re consider funding this one and only treatment - it really does have amazing results and would be incredible to be able to offer families a treatment once they've received the dreaded diagnosis of battens disease.

Thank you for taking the time to read my view on your decision.

[redacted]

To whom it may concern,

I can’t begin to even understand why the decision has been made to not license the Cerliponase Alpha treatment. As a carer of a child with CLN2 who hasn’t been able to receive the treatment due to the progression of the disease but also a friend of three children who have been able to receive the treatment, I have seen first-hand the affects the drug has had on the children. One of these children who has been receiving the treatment on the compassionate use is 5 years old and has had 1 seizure; they are still walking and talking and interacting like an average 5 year old however children not receiving this treatment at 5 years old have experienced multiple seizures, they are unsteady on their feet relying on a pushchair or a wheelchair for longer journeys. The decision made by the NICE guidelines is truly heart breaking.

I would like you to imagine, you find out your pregnant and the pregnancy goes without complications. You give birth to a happy and healthy baby, they are hitting their milestones like any toddler. They then hit 3 years old and have a seizure, lasting a lengthy time, the ambulance have to

be called. You don't know how to help your baby, you then get the devastating diagnosis that your child has Late Infantile Batten Disease. All those milestones they hit they look eventually leaving them fully dependent on yourself, incontinent, unable to walk, talk and see. Your baby's body eventually gives up between the ages of 6 and 10. You have to bury your baby. Then think back to that time when you had to the power to say YES and license the treatment that could have prolonged your child's life.

This might only be a thought for you but this is the reality of many families, this is the reality of the boy I care for. I've already had to attend his big sisters funeral in 2015 and inevitably I will have to attend his. I will then attend another 3 funerals of children who have been robbed of their childhood. Those three children's life could have been prolonged but now they're having to be taken off the drug and parents, carers, families and friends will have to see the rapid decline of their treasured family member or friend.

As a third year learning disability student nurse myself I have spent my time throughout my studying raising awareness in different placements and in university about Batten Disease, all different strands of it. More people are becoming aware and more people are praying the treatment gets licensed but yet again it is another area we are lagging behind the USA in and other parts of Europe. Yet again children in the UK are losing out because of the NHS. I fully understand the NHS is under strain in the current economic climate but this is an area that money is needed to be put into, the results are showing that. Do we have to wait until another 50 children die before we realise what we've missed out on?

The NHS is putting its money into helping people quit smoking via smoking cessation, nicotine replacement therapy.

The NHS is putting its money into helping people lose weight via gastric band/bypass surgery, free gym memberships for 12 weeks.

These are choices.

People choose to make these decisions that hinder their life yet you can give all your money to helping them but when a disease takes over a child's life you can't seem to find the money to put into treatment for that.

I am utterly disgusted and completely broken with the result of this. It make me question: Do I really want to be part of the NHS when they can't seem to put their patients first? Is person-centred planning not part of your ethos as a health service. This saddens me immensely.

[redacted]

Hello,

I have just seen your post on Facebook asking for feedback with regards to the fact that NICE will no longer fund the treatment for CLN2.

I don't have first hand experience of Battens Disease, but I have a good friend who's children were diagnosed with CLN3 this time last year. I can think of nothing more horrific for your child to be diagnosed with than Battens Disease. My friend and her family are understandably devastated. Her friends, myself included, are also devastated and are doing all we can to raise money and awareness of this awful condition. I believe all children with Battens should be given a chance of prolonging their lives and I have seen, through the power of social media, how well [redacted] are doing on the trial. I believe that this trial gives hope to everyone affected by Battens. To give people a glimmer of hope and then to take it all away is criminal.

I'm not sure how much use my comments are, but seeing how much a diagnosis can affect a family, I would love to think that one day an affected individual could be given the chance of a prolonged life, or maybe even a cure, when a diagnosis is first made.

[redacted]

[redacted] have been receiving drug therapy on a clinical trial at Great Ormond Street hospital to help slow down the symptoms of Late Infantile Battens Disease.

The NHS NICE has now refused to pay £350.000 a year it would cost per child. A report regarding this decision explained that they didn't know enough about this new drug and the long term effects was one of the reasons for refusing this drug.

The positive results so far is that is has slowed down this disease. The parents desperately want their children to continue on this drug so that this disease can be slowed down and their children can have quality of life. This is their only chance to help both children.

[redacted]

I have been following [redacted] for a while now having learned of the terminal disease and it's complications through this family. I struggle to understand how N.I.C.E can make such a decision on little children's lives knowing the full implications of this disease.

Not only is the decision at the moment going to affect the mums and dads and the sufferers other siblings have to grow up watching every part of life been stripped away from them, how will this affect the other children who properly can't understand what's going on themselves?

In [redacted] case their brothers know they need the treatment and they take a back seat. How is it fair, knowing this condition is terminal to not let these children have the treatment which is proving to stabilise them and help them develop and live near normal life with their families for the little time they have left ? Why let them die in this way.

I have three healthy boys and I cannot begin to imagine the complications something like this would have on us , it would tear anybody's world apart.
We help many children in this world through charities fundraising etc why not help our own and give these families the drugs their children need to better enable their little lives.

[redacted]

I want to challenge the decision by NICE not to fund treatment for children in England with CLN2. I have witnessed first hand the benefits to 2 children on compassionate use of the drug. Quality of life has improved and a slowing down of the progression of the disease. Please do what you can as the official representatives of parents and children affected by this devastating disease. Not to have access to treatment in England when European countries have approved and fund treatment is a human rights issue. Everyone should have the basic right to receive treatment when there is an effective drug. How else are we going to move forward with research and treatment of CLN2?

[redacted]
FAO N.I.C.E - RE: Funding CNL2 Battens Disease Treatment

Without the use of this continued treatment, for those already on it, will be like switching off their life support without giving them the full chance to breathe alone! This treatment is not just prolonging lives of children that 'are going to die anyway'! It's not prolonging the inevitable, its giving them LIFE!! Because you've seen the results for yourself! It IS slowing down, in some cases HALTING & possibly even reversing the progression of this disease!

If their treatment is stopped now not only will it cause unnecessary suffering for these beautiful, innocent children, but there will be no way of knowing what it's long term effects are!!!? Stopping this treatment will be giving them a death sentence! It WILL NOT be giving them a dignified death either! It will be cruel, slow, painful, antagonising death; and one that will affect the whole family & beyond!

So it is without a doubt in the bests interests of these children to, at the very least, allow the treatment be granted to remain in place for those already on it for whom this drug IS being proven effective for, to continue; if not only for the greater good of that child BUT more importantly for medical research purposes itself!

[redacted], for example, is one of only TWO children, In the WORLD, who has been fortunate enough to start this treatment BEFORE the more serious side effects & symptoms of the disease took a hold & having suffered only one seizure prior to treatment. In doing so [redacted]4) is able to live the life of a normal 4 year old child. [redacted] has been able to go to pre-school & progress (like her peers) to mainstream school & more! She CAN still laugh, play, see, eat, hear, speak and LEARN & continues to grow & develop, hitting all her milestones, at the same rate as the national level statistics indicate!

Without this treatment she would now be most likely unable to talk or walk unaided (at best) or be wheelchair bound or worse!

Why you would want to stop such pioneering research for these children is beyond astonishing! You can SEE the results for yourself! She is here, living, breathing, PROVING to you that this treatment IS BENEFICIAL to her & Battens Disease sufferers as a whole!

[redacted] (7), [redacted]'s older brother, hasn't been quite so Lucky as to receive the treatment as early into diagnosis as his sister, BUT the improvements & benefits that being on this treatment have given him thus far are incredible & are making massive differences for him, his sister & his entire family. Proven, positive results which are improving his quality of life & those of his siblings & family extensively!

It is my opinion & belief that NICE have made errors in their initial reports, with regards to this treatment & the funding of it, which needs to be rectified immediately.

Whilst it's appreciated that there are only approx. 5-6 children diagnosed with this disease in the UK per year, that in itself shows that the cost of this treatment, as a whole, will be minimal in comparison to the amount the NHS fund, as a whole, on other drugs; therefore should balance itself out!

For example, Cancer treatments. Treatments that are NOT denied to any patient regardless of cause and/or diagnosis; even if it will only prolong life short term!

If the CNL2 treatment is allowed to continue & progress then that in itself will enable further progression which may well result in a CURE for this cruel disease! And judging by the rate of progress for this particular drug then it seems highly likely statistically.

When more drugs trials & research are available it is PROVEN to increase further development of drugs & it's usage & in doing so is more likely to allow the discovery of a cure that could be administered very early on thus reducing costs & further strains on the NHS as a whole!

[redacted], for example, have been seizure free for over 12 months now BECAUSE of THIS treatment. This in itself has reduced the strain on a struggling NHS by freeing up Ambulance time, hospital time & bed space! Without this drug [redacted] would have had 999 response treatment, I'd estimate of at least a minimum of 3 times weekly. They would have required overnight hospital care (usually longer) & a hospital bed, & beds for their parents, multiple times a week - do the maths for the costs of those figures per week & what does that amount too? EVERY life is valuable, more so that of a child that has not yet had the chance to live & grow!

If Europe & the US have granted this treatment why on earth are the UK saying no! These children have no choice about having this disease, they didn't ask for it! They didn't put themselves at risk to get it! It is NOT a lifestyle choice yet they're not having a fair chance at survival & it is extremely unfair! This is not just extending the life of the majority of these children it's actually halting the progression of their disease, allowing those fortunate enough to get it early enough to remain SYMPTOM FREE!!

Compare the MINIMAL amount of use this drug is going to be used, due to the rarity of it, in comparison to say SMOKING RELATED DISEASES! Those patients Who are given unlimited access to treatments, when they are well informed of the risks to their health if they continue to smoke, yet do it anyway!? It's their fault! Their lifestyle choice! If they want to continue to put their lives at risk why should they get funded treatment when these helpless children don't!? They're even funded to help quit!! So WHY aren't these children being funded to help quit this disease?

We HAVE to be the voice for these children! We MUST STOP their unnecessary suffering!

NICE, STOP thinking about the cost of the treatment & the low statistical rate of number of children affected each year & think outside of the box here! This is one terminal illness that actually could be cured, or at the very least controlled, effectively & in a very short space of time!
You CAN reduce the fatalities in the UK from 5-6 diagnosed deaths a year to ZERO so action it!

Whilst being on the treatment [redacted] has been seizure free! He is still able to attend mainstream school! He can still eat (albeit small amounts), chew and swallow! He can still respond to your voice & his surroundings! He still enjoys the company of his friends & family! He still loves to hear stories

& listen to others chatting with him! He is still AWARE! He can still smile & laugh - despite all that he has lost so far! He is comfortable & pain free! He HAS made a difference to the Battens community! He IS raising world wide awareness! He IS proving that fundamental research is VITAL! And he is loved & respected, more than words can say by a WHOLE town, neighbouring towns & areas, a nation & millions of people all over the world including PRINCE HARRY!

Without this treatment he would be subject too immense pain & suffering!

NICE, pull yourselves together & agree to the funding of this treatment in the UK! There might not be enough evidence for long term usage yet, because no one has had the opportunity to use it long term yet, but so far there are no negatives! Give these children a chance, give this drug a chance to PROVE that it IS extremely beneficial!

Granted, at this moment in time, sadly it may be too late for those too far advanced to benefit from this treatment at present. BUT please, please help those who can be proven to be treated quickly & effectively when given access to this drug promptly!

Use the evidence you've been given from those few Battens sufferers who have been given a chance to trial this drug effectively in the UK, AND the positive results from the EU & US users statistics & the benefits for children being given this drug; especially those who are already seeing huge benefits from receiving it now & those who have been given treatment before the onset of the disease has had natural chance to progress & destroy their abilities one by one!

It is not only the children with Battens that are benefiting from the use of this drug but also their entire families, friends, neighbours, colleagues, teachers, local health care providers etc (the list goes on).

Myself and our neighbourhood are privy to this! [redacted] family have mine & their whole towns support with this & we are all behind them 100% & will do everything possible to get their children the treatment they need and deserve!

In being able to receive this treatment these children are able to live in comfort, pain free & lead as normal a life as possible. Spending precious, valuable time with their friends & families. Going to school, like all children should be able too. Go on holiday. Play with friends. Learn, grow, develop! Everything every child should be entitled too!

With this treatment their siblings don't have to witness their parents performing life saving techniques on their brother or sister on a daily basis, whilst they're heavily convulsing & stopping breathing at the dinner table/in the bath/at school/in bed/watching tv/doing their homework!! They're not having to call 999 because their parents are unable too as they're trying to administer life saving drugs & perform CPR on their youngest children! They're not having to help administer drugs to their younger siblings because there's no one else there to help do so! They're not seeing and hearing the blue lights & wailers of the ambulances thundering down their street every day/week/month/year! They're not having to see the looks of desperation on their parents/friends/relatives/neighbours/strangers faces when people are struggling to comprehend & deal with the daily devastation that a life involving Battens throws at them. Never knowing when the cruelty & dangers of Battens will strike!

BECAUSE this treatment has STOPPED all of that! THIS TREATMENT is allowing them ALL to live relatively normal childhoods! It is taking the pressure off other innocent children who are also suffering at the effects of Battens!

Yes their younger brother is still severely disabled but he's improving! And he certainly isn't getting worse! And they're able to see their little sister grow up with them normally, as they should!

Yes their lives have been turned upside down & they all know nothing will ever be completely normal, YET! And they'll still have to live with hospital appointments & tests etc but this is the BEST line of hope & progress they've had in years & you're wanting to take that away from them!? Why? Think of the mental health & well being of the other siblings & family members also! And all the added stresses and strains this new fight is now causing!

It's not fair NICE!
The proof is out there! Utilise it!
Children's lives are priceless!
Please help them!

[redacted]

My family & myself cannot understand why children in the UK are being deprived of this treatment that gives so much hope for their futures, when so much money is being spent in the form of foreign aid that a lot of the times is not being used correctly & does not reach the people it was intended for.

What price do they put on children's lives!

[redacted]

I am writing in support of the petition for the Enzyme Therapy treatment which is currently being given to the two [redacted] children as well as other Batten suffers.

[redacted] has ceased having seizures and has a far better quality of life since beginning the treatment. He is a happy little boy who gives so much to so many he comes into contact with. He smiles and laughs and is healthier. Do not take this from him. [redacted] has benefitted from this treatment enormously - she has come on leaps and bounds - is talking (non-stop), walking and running - her scooter is her favourite mode of transport at the moment - she is eating and all in all a normal 5 year old. If the treatment were to be discontinued from [redacted] goodness knows what will happen to her.

When NICE stated that 'it is the long term situation of greatest interest' this cannot be. The trial has only been going for over a year and the life expectancy of all Battens children is 10 - 12 years so long term is not an option. Perhaps in the future but these children cannot wait that long. Their lives are important and they are entitled to the best shot at life. They MUST be given a chance to lead as normal a childhood as possible.

Please, please pursue this case fort the continued use of the enzyme therapy. Implore you to pursue this vigorously.

4th March 2018

Dear HST Evaluation Committee members
I am providing my comments for the consultation process.

First of all, it is disappointing to me as a clinician looking after the patients with CLN2 disease that the use of cerliponase alfa enzyme replacement therapy is not recommended for use in treating this disease despite quite clear treatment effect demonstrated in the clinical trial, which was accepted by the HST evaluation committee at the panel meeting.

Moreover, it does not appear from the summary of the meeting that basic mistakes made by the ERG in their evaluation of the effect of cerliponase alfa (accepted by the ERG at the meeting) were taken into consideration. The speaker for the ERG said it himself: "We got it wrong". These were their last words. Hence it was frustrating to see no mention of this in the summary and no clear recommendation at least for the managed access agreement in the ECD document, which would address the question about long-term effect on the arrest of disease progression.

In my personal practice I look after 10 patients with CLN2 disease on cerliponase alfa. 4 of these patients have been on this drug for at least 3.5 years and the other 6 for more than 10 months.
I have also looked after 6 patients who were not on cerliponase alfa and I have attended meetings where numerous cerliponase alfa treated and untreated CLN2 patients from other centres were presented.

Compared to the untreated patients who progressively loose skills after the onset of the disease, CLN2 patients in my care treated with the enzyme replacement for more than 6 months maintain their level of functioning and in many cases learn new motor skills and develop complex language. Moreover, the treated patients' seizures stabilise (many have not had any seizure episodes for years) and we are able to reduce their antiepileptic therapy, patients do not develop progressive myoclonus that is a real problem for the untreated patients. Treated patients do not develop progressive spasticity and do not have deteriorating movement disorder. The difference between the treated and untreated patients is so dramatic that the decision of NICE HST evaluation committee is staggering but clearly is based on the ERG studies that quite unfortunately were completely misleading. As a result of this poorly informed assessment by the ERG there is a delay in providing life-saving therapy for new patients with CLN2 disease who are being diagnosed in the UK. Unfortunately, this decision does not take into consideration the urgency of the need for starting therapy early. As a direct result of this decision the newly diagnosed children will not benefit and loose skills, they will not be able to walk, talk and enjoy life as much as they would if the treatment was started.

I provide specific comments to 3 conclusions made by NICE.

1. NICE concluded that there is a significant risk of heart, liver and pancreatic complications as seen in CLN3 disease. In fact, it is suggested that in CLN3 disease all patients develop heart abnormalities by the age of 14 and therefore surviving CLN2 patients will do the same.

It is important to recognise that whilst there are similarities between CLN2 and CLN3 deficiencies (specifically both diseases cause seizures, retinopathy and brain atrophy with the resulting motor and cognitive deficits), there are also significant differences in the phenotype of the two disorders caused by deficiencies of two different proteins with completely different functions. However, even for the CLN3 phenotype I have consulted with my colleagues in the UK and abroad and none of them believe that all CLN3 patients develop cardiac disease by the age of 14 and they certainly do not develop pancreatic or liver failure at any age. There is one report of a CLN2 patient (who has no confirmed molecular or enzyme diagnosis in the case report) who survived for many years on artificial ventilation and developed cardiac

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rhythm abnormalities aged 22. I have a confirmed report from a Turkish colleague Dr Meral Topcu who has a classical CLN2 patient on artificial ventilation aged 24 who has no extraneuronal disease manifestations.
A much more appropriate proxy example for a CLN2 patient on enzyme replacement treatment would be the milder forms of CLN2 deficiency (confirmed by molecular and enzyme studies) where the onset of disease is still in the childhood but the patients are surviving into their 50s and 60s (see references below). These patients have no evidence of extraneuronal disease.

1. Breedveld, G. J., van Wetten, B., te Raa, G. D., Brusse, E., van Swieten, J. C., Oostra, B. A., Maat-Kievit, J. A. **A new locus for a childhood onset, slowly progressive autosomal recessive spinocerebellar ataxia maps to chromosome 11p15. (Letter)** J. Med. Genet. 41: 858-866, 2004.
2. Dy, M. E., Sims, K. B., Friedman, J. **TPP1 deficiency: rare cause of isolated childhood-onset progressive ataxia.** Neurology 85: 1259-1261, 2015.
3. Sun, Y., Almomani, R., Breedveld, G. J., Santen, G. W. E., Aten, E., Lefeber, D. J., Hoff, J. I., Brusse, E., Verheijen, F. W., Verdijk, R. M., Kriek, M., Oostra, B., Breuning, M. H., Losekoot, M., den Dunnen, J. T., van de Warrenburg, B. P., Maat-Kievit, A. J. A. **Autosomal recessive spinocerebellar ataxia 7 (SCAR7) is caused by variants in TPP1, the gene involved in classic late-infantile neuronal ceroid lipofuscinosis 2 disease (CLN2 disease).** Hum. Mutat. 34: 706-713, 2013.

2. Very little was commented by NICE about the benefits of treatment with cerliponase alfa beyond the stabilisation of deterioration in motor abilities and language.

Whilst motor and language domains were used as primary endpoints in the clinical trial, seizures, myoclonus and vision domains were assessed and the data was presented to NICE. I presented the data at the British Paediatric Neurology Association meeting in January 2018 to a room full of Paediatric Neurologists (many with experience of looking after patients with CLN2 disease) who were stunned to see the effect of this drug on reducing the seizures and preventing progression of the myoclonus and spasticity, which is reflected in the overall motor abilities. The effect of the above on improving quality of life for the patients would be enormous. In addition, this would provide a massive improvement in the quality of life of the families.
In addition to the improvement in generalised tonic clonic seizures (our longest treated patient has not had any seizures for more than 3 years) the patients have improvement and no further progression in myoclonus and absence seizures. Although the EEG still shows baseline abnormalities our patients have improvement in the EEG as reported by our neurophysiology department. Furthermore, our radiologists report no further deterioration of the brain MRI scans for CLN2 patients after the first year on enzyme replacement therapy. These reports are slightly different to the averaged results from all the patients on BioMarin trial. No normal controls were used in the trial and therefore it is difficult to know whether the reported 3.3% reduction in cerebral volume between weeks 48 and 96 lie within the normal variation for the children of this age. We do know that brain continues to solidify during childhood which is seen as overall reduction in volume.

3. NICE focused on the ECG abnormalities that were reported in the "Adverse Events" for the trial and **invariably deemed clinically not significant by the clinical staff**.

This was a particularly frustrating conclusion of the NICE since bradycardias reported by the ECG machines were in fact normal rhythm associated with normal sleep of the children. The ERG should have dismissed all of the reports as they were not significant. Even after I explained this to the ERG at the NICE meeting they still brought up another report (also deemed not significant) of the "possible cardiac hypertrophy" which was initially reported as possibly related to the drug as it appeared soon after the infusion (a very unlikely possibility). Again, this was an ECG report which was not confirmed by the echocardiography and shown to be wrong. It is important to accept the following: **there is no evidence of any cardiac structural or rhythm abnormalities identified in the trial or in the expanded access program.**

Saying this, I can emphasise that we, of course, be keen to continue carefully monitoring patients on therapy for any possible new cardiac problems.

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UCL Great Ormond Street Institute of Child Health
Consultant in Paediatric Metabolic Diseases
Great Ormond Street Hospital for Children.

Has all of the relevant evidence been taken into account?
I believe so

Are the summaries of the criteria considered by the committee, and the clinical and economic considerations reasonable interpretations of the evidence?
I believe so

Are the provisional recommendations sound and a suitable basis for guidance on the use of cerliponase alfa in the context of national commissioning by NHS England?
Yes at the current time, but the landscape is changing rapidly and further information is very likely to become available. The evidence should be reviewed again within 3-5 years.

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

The draft guidance from NICE not to recommend cerliponase alfa as a treatment for CLN2 disease within its marketing authorisation will be disappointing for families and advocacy groups, but not surprising given the health economic evaluation, anticipated cost of the technology and NICE criteria. We have a duty to those children and families who have volunteered altruistically to participate in the clinical trials of this technology, including UK families. They have willingly taken on unknown risks and the burdens of trial participation in the hope that this will benefit not only their own children but those diagnosed in the future. My view is that we have an ethical duty to continue their treatment within the NHS as long as the treating physicians and families believe such treatment is in the child's best interests. It will be important to monitor the progress of these treated children closely in order to gain as much information as possible to inform future policy and practice, so that they do not feel participation was wasted.

28/02/2018

I am writing to you as a mother of four children, two of whom have CNL2 Batten Disease.

Both [redacted] and [redacted] are receiving the drug Cerliponase Alfa at Great Ormond Street hospital, London. [redacted] started treatment in November 2016, aged five, [redacted] started in February 2017, aged three.

As you are aware both [redacted] and [redacted] are doing incredibly well on the treatment. On reading the Evaluation Consultation Document for Cerliponase Alfa for treating neuronal ceroid lipofuscinosis type 2 I have concerns that not all aspects of the treatment have been taken into account.

The committee recognised that CNL2 Disease is a devastating condition associated with a very poor quality of life and a very short life expectancy which until now had significant unmet needs in terms of effective treatment options. The committee acknowledged that the aim of this treatment is to maintain function for as long as possible and to improve quality of life. Whilst children are receiving this treatment there is a possibility as research continues that a cure will be found.

I recognise that the company have concentrated gathering evidence to show the positive impact this treatment is having on motor and language skills but they have not included other aspects such as seizure control, movement disorders and swallow function, as well as the impact treatment is having on quality of life.

[redacted] is seven years old, sadly before this treatment was available to [redacted] he had lost his ability to walk and talk. Before treatment [redacted] lost his abilities rapidly. Doctors had warned that it would be fast but nothing could prepare our family for how fast the disease took over our little boy's body. In the space of just a few months [redacted] went from being a little boy who could run like the wind, climb the tallest trees and kick a football as hard as his two older brothers to a little boy who could no longer stand on his own two feet. We cannot describe the pain which we felt as parents watching the confusion on our sons face as he fell over time and time again, wiping those tears from his face as he became frustrated.

When children with Batten disease begin to lose these abilities they are of sound mind. This is something that has not been discussed, how do these children feel when they are aware they are losing skills but are not at an age to understand why?

[redacted] is not like healthy children of his age that are CNL2 free but nor is he like other children of his with CNL2 Disease that are not receiving this treatment.

As we are all aware CNL2 Disease progresses rapidly, but this treatment has stabilised [redacted]. I understand that some may question how we can prove this as [redacted] has already lost his gross motor skills and can no longer speak recognisable words.

Before treatment [redacted] was experiencing all types of seizures daily, many which required hospital admissions. In the last sixteen months [redacted] has had one tonic clonic seizure and no other seizure of any type. [redacted] does not suffer from movement disorders and his medication intake for a child of his age and weight is at the lower range. Amazingly [redacted]s swallow is still safe and he can still enjoy his favourite foods such as McDonalds fries, crisps, and toast, this is something that is rarely seen in a child of his age.

Since [redacted] has been diagnosed with CNL2 Disease he has not had a chest infection and his oxygen is 99% in air, we truly believe that this is the result of the treatment he has been receiving.

I know from research that is very common for children with this disease to have recurrent chest infections which they cannot recover from, some of these infections lead to the child needing oxygen at home and untimely these infections can cause death.

The disease can also affect a child's ability to sleep, some researchers say this is due to the child's loss of vision meaning the brain does not know the difference between night and day and therefore it does not release the hormone needed to stimulate sleep, others say it is due to pain and movement disorders.

Both [redacted] and [redacted] do not have trouble sleeping, both sleep between ten to twelve hours a night which is the recommended amount of sleep for a child of their age. They do not take medication to help them sleep.

An important factor I have picked up on throughout my involvement in the NICE process is how quality of life is measured.

It is a huge concern as parents that it may be seen that children who cannot walk and talk do not have a good quality of life.

On the trial and the extended access program children are assessed using a rating scale which has been adapted by the pharmaceutical company from the Hamburg and Weill Cornell scales. I feel that it is extremely important that the committee members know that there is a huge difference between children, who have been rated a zero.

A child with the score of zero has been defined as a child who is immobile and has no language. A child who is at end of life care who is experiencing constant seizures, excruciating pain, needing many different types of medications to keep them as stable as possible; a child who is requiring oxygen daily; a child who is being fed small amounts via pumps and IVs because their body is shutting down and can no longer cope digesting food is being rated at the same scale as a child like our little boy [redacted] who can still attended a main stream school where he accesses the curriculum alongside his peers, he takes part in PE lessons, school trips and school plays.

Each week he attends swimming lessons and enjoys having his friends over for tea. He can interact, make sounds and communicate via body language. [redacted] loves fast rides and laughs his little head off, he hates anything messy and rolls his eyes and pulls his hands

away from paints and play dough as he does not like them. [redacted] enjoys tasting foods and playing with his siblings. He does not experience pain and his seizures are very well controlled, resulting in a huge reduction in hospital admissions. In addition to this the only extra outside care [redacted] receives is a carer who has been put in place for [redacted] to attend school, due to [redacted] needing to be hoisted in and out of his chair. The school did not have qualified members of staff in place for this. [redacted] enjoys spending time in his standing frame as well as attending local and professional football matches in all weathers.

[redacted]'s health has been stable since starting the treatment, he does not require equipment such as a SATs monitor, suction machine or oxygen cylinders at home.

It is very clear that [redacted] does have a Very Good Quality of Life despite the fact he is in a wheelchair.

I think that it is unrealistic and extremely unfair to group children who are in completely different stages of the disease together with the same score of zero.

When measuring quality of life in a child with CNL2 Batten Disease, I believe that the questionnaires given to parents from the PedsQL and the EQ-5D-5L/EQ-5D-3L are very difficult to answer when the questions are not pacific to a child with this type of disease. I think that these questionnaires would benefit from having an area that parents can write comments, this would also help to gather more evidence rather than it being a simple tick box answer.

Our perfect little girl [redacted] was diagnosed with Batten Disease 30th March 2015 at two years of age. [redacted] was tested for this disease due to the recent diagnosis of her older brother [redacted]. She had no symptoms of the disease, [redacted] had hit all her milestones, was fully toilet trained and was enjoying life as a 'normal' happy, healthy toddler.

Over a year after [redacted]'s confirmed diagnosis in February 2017, [redacted] started receiving treatment on the extended access program at Great Ormond Street Hospital in London. [redacted] is one of the youngest Children in the world to be receiving this treatment and even more importantly the only symptom of Battens Disease [redacted] had shown was a seizure two months prior to starting treatment, which was associated with a sickness bug.
As far as we have been made aware by professionals this treatment had never been given to a child at this stage in the disease before. Our daughter is a first, [redacted] is days away from celebrating her fifth birthday. Batten Disease should have taken over her little body, destroying her abilities, taking away her childhood. Instead [redacted] is a healthy, extremely lively, happy little girl.

[redacted] attends a mainstream school along with her three big brothers. She participates in all classroom activities, she enjoys mark making and is able to play independently as well as being able to interact appropriately with her peers. [redacted] is learning new words daily and is able to speak in five to six word sentences which is recognisable to strangers. Recently [redacted] has been able to learn simple phonic sounds which she can retain and can also make the correct animal sounds when asked. She is able to count to ten and school has reported that she is beginning to count objects in order.

The committee recognised that onset of symptoms in CNL2 Batten Disease present themselves between the ages of two and four, it is also stated in the report produced that a rapid phase of decline is expected in children ages four to five. During this period the report quotes that children should be experiencing seizures, there should be a rapid loss of language, as well as ataxia, clumsiness, loss of ambulation, myoclonic/abnormal movements and the start of vision loss function. This description does not describe our little girl.
Not only is our daughter not losing skill, she is retaining her skills and even more incredibly [redacted] is learning new skills.

[redacted] is able to understand instructions and is aware of the world around her, for example, she will stop at the side of the road as she understands it is not safe to cross without an adult. She understands danger and also knows age appropriate right from wrong, i.e. she knows it is wrong to hurt another person.

Outside of school [redacted] attends dance, gymnastics and swim classes as well as being able to go round to her friend's house to play. She has also been able to take part in professional dance shows with a local dance company, Dance at the Smithy Dance and Theatre School. [redacted] has no health problems and has recently been accessed by the physiotherapists at Great Ormond Street Hospital, the report produced by GOSH states that [redacted] has no problems with her balance, she has no muscle or joint problems. [redacted] does not suffer from any movement disorders or myoclonic jerks neither is she on any medications for these. [redacted] is able to walk, run, jump and climb. She is able to stand from sitting whilst holding objects therefore not needing to use her hands to assist her to stand. [redacted] is able to use an age appropriate scooter and is learning to ride a bike. The Physiotherapy assessment also looked at how [redacted] placed her feet as she walked and the speed in which she walked at, the reports shows that [redacted]'s results are that of a healthy child.

Since starting treatment [redacted] has not experienced any types of seizures. [redacted] was started on an anti-seizure medication before the enzyme therapy was started, this has not been increased at any stage and is a very low dose. Given the fact that [redacted] has gained weight and age it would have been expected that the medication would have had to have been increased to control seizures, however this has not been the case and instead a discussion has been had with health professionals regarding removing the medication if no seizure present themselves over the next twelve months. To have this discussion in itself is remarkable as most children [redacted]'s age would be adding in many medications to try gain seizure control.

Importantly [redacted] has not lost any bladder or bowel control, she is in knickers and is dry both day and night, she does not experience any accidents.

[redacted] is able to live her life just like any other healthy four-year-old thanks to the early administration of the enzyme replacement therapy.

This leads onto the extreme importance of early diagnosis. The earlier in which this treatment can be administered to a child with CNL2 Batten Disease the better the outcome.

For this to happen health professionals need to be educated on the signs and symptoms of Batten disease, not just the doctors but health visitors also as these are the professionals parents of young children will turn to first if their child is experiencing language problems or struggling to meet milestones.

Due to the lack of knowledge and experience of CNL2 Batten Disease of those health professionals which we encountered led to the deterioration in [redacted]s condition.
The lack of support that we were given when [redacted] was diagnosed lead to us having to fight along with the BDFA to gain compassionate use of the treatment. This again delayed treatment for both [redacted] and [redacted] with consequent further deterioration in [redacted]s condition before treatment could be given.

As a family we are doing our upmost to raise the awareness of this disease, encouraging members of the public to share our journey.

The impact of this treatment does not just impact on [redacted] and [redacted]'s quality of life but it has improved the quality of life for the whole family unit.

We also have two older children aged nine and ten, both boys are healthy yet watching their younger brother decorate so quickly has obviously affected them emotionally.
They have had to watch their little brother experience horrendous seizures, and even witnessed their father performed CPR on [redacted].

Before treatment started our older boys would not know if we would be at home when they returned home from school or if we would yet again be in hospital with [redacted] because of another seizure. They spent their time being ferried from one relative to another as [redacted]'s condition worsened. They could not spend time with their friends outside of school or join in with after school activities. Instead they found themselves having to grow up extremely quickly, learning basic first aid and having the knowledge to call the emergency services. The severity of the disease also affected myself and my husband's ability to work. [redacted] was self-employed and had to give up work to help myself care for the children. Financially we struggled as we had no wage entering the household. Life was extremely hard; stress levels were high as well as our emotions.

Since [redacted] and [redacted] started treatment our life's have complete changed. As this therapy has stabilised [redacted], improving his symptoms, our life has adapted to a new norm. Our children can now take part in after school activities, both our older boys are committed members of an established football club. They no longer worry about hospital admissions and most importantly they do not have to witness daily seizures and other health related issues, instead they can spend quality time with their brother and sister playing and creating memories. [redacted] has been able to return to work part time and we have recently booked a family holiday aboard. Life has improved immensely for us all.

During the meeting on the 17th January 2018, the subject mortality was disused. The ERG had compared CNL2 patients receiving Cerliponase Alfa with CNL3 patients where currently there is no treatment. We believe that it is unrealistic to compare these two types of Batten Disease, as two different genes are affected. Stating that children receiving enzyme

replacement therapy will experience shorter life expectancy because of cardiac, pancreatic and hepatic impairment unless enzyme replacement therapy is administer systemically is based on option and not evidence. It is unfair that this has been taken into account when making a decision to fund treatment for CNL2 Batten Disease.

Since diagnosis [redacted] has had a number of ECGs all which have been normal both off and on treatment. Last month [redacted] also had a ECG which has also been reported as normal. Without continuing children on this therapy there will never be any long term evidence to say if this treatment continues to work in the long term.

It would be unethical to remove treatment from patients that is showing huge benefits to their health and quality of life.

Lucy Carroll, mother of [redacted] and [redacted] Carroll.

Comments on the ACD Received from the Public through the NICE Website

Name	[redacted]
Role	Carer
Other role	[redacted] and Mother of son with CLN2
Organisation	
Location	USA
Conflict	None
Notes	
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	I am writing from the US on behalf of all of our fellow Batten families in the UK. Our son [redacted] started the Brineura trial in December, 2014 as the first child to receive the infusion in the US. Prior to his diagnosis in August of that same year, we were going through the challenge that all Batten families have tackled, trying to figure out what was going on with our child. [redacted]'s seizures began in May, 2013, on Mother's Day of all days. The diagnosis of epilepsy was horrifying, but not surprising as it was in my husband's family. The next step was looking at [redacted]'s delays and trying to determine whether he was Autistic or if the seizures were affecting his development. Our worst nightmare came true though when we were notified of the CLN 2 diagnosis and by the grace of the BDSRA we were connected with [redacted] and Nationwide Children's to begin the trial. Our main goal of the trial was for [redacted] to continue to be [redacted]. He was doing fine with his gross motor skills, was extremely delayed with his speech and fine motor, but we could understand what he was saying for the most part and he could maneuver the Ipad easily to play Angry Birds. We did not even consider his seizures improving, we just hoped they would not get worse. Improvement and development was simply a dream to us at that time. We knew the path this disease would take and we simply wanted more time with our son than Batten would allow. We now sit here looking at where [redacted] was in comparison to where he is now. Batten families often post pictures showing their children running, laughing, singing, and playing, with the comment, "I miss this so much!". We, on the other hand, are one of the first, if not the very first family in this country with a child with Batten Disease that can talk about the improvements over the last two years, so let's do that. In the first year and two months of [redacted]'s epilepsy diagnosis, he had 13 seizures, some of which would keep him unconscious for upwards of 8 to 10 minutes. [redacted] currently has been seizure-free since April of 2017. [redacted] continues to take the same two meds as he has been for the past three years, which is unheard of for a child with CLN 2 and we even decreased one of those meds last month. Developmentally, it is always difficult to measure a child like [redacted] because he cannot sit for the typical

	standardized measures. We were able to see a comparison on the Peabody Developmental Motor Scales from an evaluation in October of 2015 to April of 2016. Over that 6 months period, [redacted]'s raw scores on the Stationary and Object Manipulation improved and his Locomotion score remained the same. As you all know, according to the natural history of Batten, [redacted]'s scores should not be staying the same or improving. [redacted] processes language quicker than he ever has and responds to us with answers to questions. He is able to get all his needs and wants met, even to the point of manipulating us to get those wants met. Although we have only described a snapshot of [redacted]'s life and improvements, it speaks volumes to this treatment. On Christmas Day in 2013, [redacted] had a seizure Christmas morning. We just watched a video this week from Christmas Day in 2015 and [redacted] was excited about the new toys he got and actually showed them to his Dad and I. That was also the first year that [redacted] actually told Santa what he wanted for Christmas. These are milestones that, although they may have hit them at one point in their younger days, children with Batten disease will not continue to meet. When we received this terrible diagnosis, my husband and I would wake up every morning terrified of what skill [redacted] would lose. That is the life that all families dealing with Batten Disease live. We now wake up wondering what new skill, new word, new piece of his personality [redacted] is going to show us. Thank you so much for all your time, hard work, and dedication to improving the lives of so many people in your country, but please do not forget about our Batten Children!

Name	[redacted] [redacted]
Role	Carer
Other role	Mum of 2 CLN2 boys
Organisation	
Location	USA
Conflict	No
Notes	
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	"I would like to speak to the efficacy of this treatment as we have first hand experience and a direct comparison to make between my two sons. My oldest son, [redacted], was diagnosed with CLN2 in April of 2015. We immediately tested our youngest, [redacted], as well when we found out this was a genetic disease. He unfortunately was found to be affected by CLN2 as well. At the time of our diagnosis, this treatment (Brineura) was unavailable to us. Prior to diagnosis, my oldest began having seizures at 3 and 1/2 years old, struggled with his vision, and was falling a lot due his muscles giving out on him. By the time we received his diagnosis at 4 and 1/2 years of age, he had lost several skills: the ability to eat by mouth, unable to walk without assistance, and had trouble saying words he used to be able to say well. As the disease progressed, his brain deteriorated and we watched our son go through the horrific stages of dementia, the organs of his body shut down, he struggled to breath on his own, and had 24/7 care provided by myself and hospice care to ensure the best quality of life as he bravely fought through this disease. We lost our son, [redacted], at the age of 6, a short year and 1/2 after diagnosis, to this cruel and swiftly moving CLN2 monster. Our youngest son, began treatment shortly after his big brother passed away as part of an early access program to the treatment. He was able to start treatment early because we found his diagnosis early, thanks to his brother. [redacted], began treatment right after he turned 3. He is now 4 and 1/2 years old... the same age his brother was when [redacted] was rapidly losing skills. [redacted] has been receiving the enzyme replacement therapy, Brineura, for 1.5 years now. As I stated a sentence ago, [redacted] is 4 years and 7 months old now. Keep this in mind as I tell you how he is doing: He still has not had a seizure (his brother started seizures at 3 and 1/2 years of age and they rapidly progressed to 100's a day). He is walking, running, jumping and even learning to ride a scooter (at this point, his brother needed assistance to even take simple steps). He eats independently by mouth (his brother was entirely g-tube fed at this point).

	He is gaining skills in speech and motor development (his brother was losing them at this age). My son's quality of life has sky-rocketed. And not just that, but his ability to learn and be in a classroom setting with other kids, play at the park like a normal child, and do everyday life as a kid should be able to do, would absolutely NOT be possible if it weren't for this treatment. When we walked into the doctor's office to receive our diagnosis nearly 3 years ago, we were told there was nothing we could do for our child. Nothing. Never in my wildest dreams did I anticipate that as a parent, I could not help my child. His future plans no longer involved little league, school and play dates. It involved hospice care, and having read and sign documents for his anticipated death. It was devastating and we will forever be broken over the loss of our son. But things are different now. It's not every day we get to have victory over a rare disease like CLN2, but Brineura is just that... a VICTORY! Now, parents get to be told they can fight back for their child. And it's not in vain. This treatment IS working. Some may think there needs to be more time to prove it's worth. I'll tell you what, this disease progresses so fast, we can see immediate results. We don't need to wait around to find out if it's truly staving off the disease. The massive difference between my boys is proof we see dynamic and incredible results that EVERY child should have access to in their fight against CLN2. I hope you can put yourselves in our shoes as you re-consider this decision. Thank you for the opportunity to be able to speak out about this. We hope and pray the right decision will be made and we will soon celebrate another victory against CLN2. "

Name	[redacted] [redacted]
Role	Carer
Other role	[redacted] [redacted]
Organisation	
Location	USA
Conflict	
Notes	
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	My daughter [redacted] [redacted] age five is currently one of six children on the clinical trial in USA receiving cerliponase alpha for Battens disease. This is a disease that is so devastating to parents to have a normal child lose all their skills and die a slow and painful death yet you have a chance to change all of this. I have met and seen first hand many children that have received this treatment and the results are amazing. These children can still walk (some with assistance) , talk and communicate, eat, have seizure control, can still participate in social activities and education with peers of same age. I understand we don't know yet if this drug can save lives but surely the fact that it gives these children a better quality of life and I have no doubt our children will outlive patients not receiving this treatment. It is so important that families have access to this drug as soon as a child is diagnosised as every day counts. This drug must be made available and with little cost to families so they can spend more time with their precious children, live in hope and we can pray for a cure. We have had to move to USA from Australia to receive treatment nobody should have to pack up and leave their home, family and friends. This drug needs to be available worldwide and it will continue to be pioneering and lead the way in enzyme replacement therapy. And our kids will prove to you all that the benefits far outweigh anything else.

Name	[redacted] [redacted]
Role	Public
Other role	
Organisation	
Location	USA
Conflict	
Notes	
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	My grandson [redacted] [redacted] has ncl cln2. When he started the treatment he was going downhill quickly. The treatment stopped the diseases progression and [redacted] is still [redacted]. He is enjoying life. He runs plays and communicates with those around him. There is no doubt this treatment has saved his life. How can you not approve this treatment. How do you put a price on a child's life. Come say hello to [redacted] and it will make it a clear choice!!

Name	[redacted]
Role	
Other role	Parent of child with CLN2
Organisation	
Location	Not stated
Conflict	
Notes	
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	Dear NICE committee, I am the mother of an Australian boy with late infantile batten disease. He is presently 5 years and 2 months old. He has been receiving cerliponase alfa every fortnight since he was 3 years and 10 months (November 2016). We had been told that around 5 years of age, he would lose the ability to walk and talk and eat. However, on this treatment, he continues to run, walk, climb with assistance, speak (in single and two word utterances), communicate, toilet independently and, most importantly, live a very happy life. He attends mainstream kindergarten and has now been seizure free since July 2016. I have no doubt that cerliponase alfa is sustaining his life quality. Below is a link to a dropbox file of recent videos of my son. The videos of him running on the oval were taken on 18 February 2018. https://www.dropbox.com/sh/ypardra777cjfl4/AACPItXuOM-hWc3g4SVztBpka?dl=0 In order to access this treatment on the compassionate use trial, my family had to leave our home, our jobs and our family and friends and move to the other side of the world (literally) to Rome, Italy where we didn't speak the language and we didn't know anybody. Don't make your citizens go through that. This treatment is now the 'standard of care' in the USA and parts of Europe. Why should children in the United Kingdom be entitled to anything less? I implore you to reconsider your decision to fund this drug. It is working. If I can answer any questions, please feel free to contact me. Kind regards

Name	[redacted]
Role	Carer
Other role	Mother of CLN2 son age 4
Organisation	
Location	United states
Conflict	
Notes	
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	I wanted to comment on the decline of this treatment. My son has had 5 Brineura treatments since being diagnosed in December 2017. He has had 0 adverse reactions to this drug both during treatment and after treatment, it has only helped him. He has maintained his ability to walk and talk and within 5 treatments, he is more cognitively aware than what he had been in over a year. He has even expanded his vocabulary, when statistically, he should be losing all these skills per the progression of the disease. We have not seen him this happy and aware in over a year and with each of these treatments he only gets better!! My son does still have seizures which we control with AED's but I have heard many other children's seizures decline or disburse with these treatments, and we are hopeful this will be the case with our son, however, I am just happy we can still hold hands and walk together and that he can still call me Mommy and tell me his wants and needs. I do not know how anyone can put a cost on the quality of life and possible extension of life that these treatments give these defenseless children. Even though there are few cases a year, world wide, this is huge for our community of Batten families. We live in the US and these treatments were approved in April of 2017, without these treatments, we would have been given a death sentence, which is what you will give families without approving these treatments. Training and planning is minimal, which is why so many US hospitals are picking it up, because it is LIFE changing for these children and they want to be apart of that. Additionally, the long term benefits of these treatments can open the doors for possible treatments of other lysosomal storage disorders and gives hope for a potential cure one day. But for now, this is the best treatment and shot at a good life we can give our children. This gives us hope and the proof of the benefits in these Brineura treatments is shown with each and every child that has had them. I can not stress how important and beneficial these are to every child out there, please consider making a difference in the world by approving these for all the families in the UK.

Name	[redacted] [redacted]
Role	Carer
Other role	Father of 2 CLN2 affected children
Organisation	
Location	USA
Conflict	
Notes	
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	"I am the parent of two daughters affected by CLN2 and a third daughter that is not affected and I live in the USA, in [redacted]. My middle daughter, [redacted], passed away in November 2016 at the age of 6 years and two weeks. [redacted] was not able to receive Cerliponase Alpha, aka Brineura. [redacted] was 100% immobile by February 2016 when she was 5 years and 3 months old. She was 100% blind by 5 years 8 months and her seizure activity never slowed nor was it ever under control. I tell you all of this because I have seen firsthand the contrast between a CLN2 patient receiving Cerliponase Alpha versus a patient that does not, Every. Single. Day. For over 18 months. My youngest daughter [redacted], who is 5 years 10 months old has been on Cerliponase Alpha since September 2016 and she provides a stark contrast to her sister [redacted]. [redacted] can crawl on her own. She can name colors on her own. She can eat normal food at every meal. She has a vocabulary of over 25 words and, at times, can form two word phrases. She knows 6 to 8 colors. She knows shapes. She recognizes sounds. She still has her vision. She can walk with assistance. [redacted] has a great quality of life! My daughter [redacted] had lost 99% of all of these by the time she was 5 years 9 months old. [redacted] is older than this today. The only change in their care is Cerliponase Alpha. My family traveled 1,180 miles every other week for nine months to get [redacted] into the ""compassionate use"" care allowed by the FDA prior to the drug being approved. Each trip was departure on Wednesday and return on Saturday, or occasionally a Friday. Every other week. For nine months. I am grateful my family did not have to move, but the toll it has taken on our family is indescribable. I am writing to implore you to show support for your citizens and the medicine that is available for your people! Please do not hold back approval for any reason. The side effects, while minimal, pale in comparison to the effects of not having access to this drug. I am happy to provide videos of [redacted], should you need them. I can be contacted via phone or email at the contact info provided. Please reconsider your decision and approve access to what is now considered the standard of care around the world for

	CLN2. It is the ONLY standard of care available and there is empirical evidence to support what I, and many families around the world, have witnessed firsthand. Please show support for your citizens by approving access to this treatment."

Name	[redacted]
Role	Public
Other role	Secretary
Organisation	
Location	England
Conflict	No
Notes	
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	I implore you to allow funding of the drug for Battens disease. It is the only hope for the dear children who have been struck down with this horrifying disease. There is clear evidence that this drug makes a positive difference, of that there is no doubt. There is no price that you can put on the head of an innocent child.

Name	[redacted]
Role	NHS Professional
Other role	[redacted] Hospital de NiÃ±os de CÃ³rdoba, Argentina
Organisation	
Location	Argentina
Conflict	n/a
Notes	
Section 1 (Appraisal Committee's preliminary recommendations)	"I'm [redacted] and [redacted], [redacted] of the [redacted] section of the Hospital de Ninos de Cordoba, Argentina. Cordoba is a large city located in the center of the country with more than 3,000,000 inhabitants and our Section of Metabolic Diseases is a reference center in inherited metabolic diseases for the center, north and west of the country. Since the year 2003 we started a research program in ceroid neural lipopfuscinosis. Pediatricians, geneticists, biologists, biochemists and laboratory technicians, began to study lipopfuscinosis, from 2003 to present, 106 cases were diagnosed in our program. We followed a detailed study algorithm (Kohan et al, The Neuronal Ceroid lipofuscinosis program, A translational research experience in Argentina, Biochim Biophys, Acta (2015)) confirming the specific diagnosis of CLN1 in 2% of cases, CLN2 - 33% , CLN3 - 7%, CLN 5 - 2%, CLN 6 - 2%, CLN 7. 3%, CLN 8 - 1%. In 50% of the remaining cases we could not reach a definitive genotypic diagnosis. A large majority of our cases were represented by CLN 2 or Late Infantile Lipofuscinosis (36 patients or 33%). Within this group we could distinguish 2 different forms of evolution: A) Classic CLN-2, seen in 24 patients. They presenting seizures at 2-4 years old, delayed speech and rapid neurological deterioration, some died at 10 to 14 years, other patients are alive and under our control currently. B) Atypical form (Juvenile) seen in 12 patients. They evolved with later onset of symptoms, around 9-12 years and slower evolution. Some patients lived until 27 to 29 years, others are still alive and lucid at 23 years of age, within this group there are patients who have never had seizures and others who have normal vision. We haven`t seen cardiac compromise, myocardial hypertrophy or conduction disorders in any of our patients. On the other hand, we have not observed either hepatic or pancreatic pathology. (An integrated strategy for the diagnosis of neuronal ceroid lipofuscinosis types 1 (CLN1) and 2 (CLN2) in eleven

	Latin American patients Kohan, Guelbert et al. Clin Genet, 2009 Oct; 76 (4) : 372-82) Since FDA approved the enzyme replacement therapy for CLN2 in June 2017, we already have 4 patients treated with cerliponase alfa. The first one that started, is a child who is currently 3 years old, and it was diagnosed because a brother of 12 years old is in the terminal stages of the disease, this child began his intracerebroventricular treatment at the age of 2 years and 6 months, without symptoms only a delay in speech. He has not presented adverse events and we have been able to show progress in speech, he has a normal neurological examination for his age. The other 3 patients, 2 of them with Classic CLN2 form and one with an Atypical evolution, have not had adverse events to this medication and their seizures have disappeared. Parents notice better connection with the environment. I`m afraid that the decision of the National Institute for Health of England not to recommend the use of Cerliponase alfa for the treatment of CLN2, can harm the decision of other countries, like Argentina, in which it has been accepted. On the other hand, comparing the evolution of CLN2 with CLN3 does not correspond because they are totally different pathologies and due to different etiological processes. We expect, from our program for Neuronal Ceroid Lipofuscinosis, in Argentina, that the decision of England will be carefully revised so that these children can benefit from an effective treatment in stopping the advance of this cruel disease, for the patients and their families.

Name	[redacted]
Role	Clinical expert in NCL disorders and related degenerative brain diseases of childhood.
Other role	[redacted], retired
Organisation	[redacted],
Location	Europe
Conflict	Yes
Notes	"[redacted] is a [redacted] to Biomarin, Ltd., USA [redacted] are involved in clinical trials of cerliponase alfa, manufactured by Biomarin, Ltd."
Section 1 (Appraisal Committee's preliminary recommendations)	General Comments The negative conclusion in this report (lack of cost-effectiveness) is primarily based on the lack of data on the long-term clinical effectiveness. This criticism is well founded. Years of additional experience are direly needed. However, in the presence of objective documentation of short-term clinical effectiveness and additional substantial evidence of benefit to quality of life issues etc., denying access to such treatment in a large and developed country would leave the job of collecting the required additional experience to other countries. Leaving out UK families with CLN2 disease would not only deprive these families of short-term relief and potential long-term benefit, but would also prolong the time required to reach more definitive conclusions on the long-term results of treatment in this rare disease. In addition, some arguments used against insurance coverage are insufficient, speculative and misleading. These comments have been prepared in collaboration with Angela Schulz, MD, PhD, and Miriam Nickel, MD, who have long specific clinical experience in these diseases. They have been running a specialty clinic for NCL disorders for many years where they presently care for about 170 children per year affected with NCL and related disorders. (See ERG report p. 11) Cardiac involvement in CLN2 disease Heart disease is a typical problem of patients with CLN3 in later stages of the disease and may cause overt symptoms later in life. It is difficult to draw conclusions for CLN2 disease (caused by the deficiency of a lysosomal enzyme) from observations in CLN3 disease, a different genetic disease caused by the deficiency of a lysosomal transmembrane protein. Little is known on the heart in CLN2 disease. There is a single report on a CLN2 patient who survived, due to prolonged life-sustaining

	intensive care, unusually long and developed conduction defects and episodic bradycardia at 23 years of age (Fukumura et al., Dev Med Child Neurol. 2012;54:663-6). Although not published yet, at meetings of clinical experts around the globe many patients with an atypical (prolonged) course of CLN2 disease (mostly from Argentina and Brazil) have been described who did not show any sign of cardiac abnormalities at varying ages of 18-30 years. It appears therefore probable that cardiac involvement in CLN2 disease is very different from that observed in CLN3 disease. (See also ERG report, table 50, p. 126.) Life expectancy The assertion that in general the maximum life expectancy of CLN3 patients is 40 years is correct. However, due to profound genetic, biochemical and pathophysiological differences between CLN3 and CLN2 disease, expectations regarding life expectancy of CLN2 patients under enzyme replacement therapy are presently speculative." (See ERG report, p. 126) Traumatic Brain Injury as a model for estimating long-term effects of neuro-disability on mortality Traumatic brain injury does not appear to be a good model for estimating the long-term effects of neurodisability on mortality. Traumatic brain injury is essentially a static condition the consequences of which in regard to disability-related mortality are extremely variable. In contrast, disability-related mortality in a storage disease such as CLN2 disease, will depend on the inherent progression of the neurodegenerative process. The dynamics of this process can be expected to be halted or slowed down, but estimations of life expectancy of treated patients are speculative at this time.""Additional benefits of treatment apart from stabilizing motor and language capabilities Effects of treatment on seizures Treatment with cerliponase alfa has distinct effects on seizures. Grand mal seizures, which are treatment-resistant in natural history patients, occur less frequently and are less severe in patients receiving enzyme replacement therapy. The mitigation of seizures has a big impact on quality of life since also the number and dosage of anticonvulsive drugs can be reduced, by virtue of which common side effects of these drugs (nausea, drowsiness, weight problems,...) are avoided. In addition, hospital admissions due to grand mal seizures can be significantly reduced in number or avoided. Increased attention span and better cognitive functioning Clinicians, patient families (especially families with multiple

	CLN2-affected children where a treated child can be compared to an untreated one) and teachers report an increased attention span and better cognitive functioning in daily life aspects (school and communication skills) in patients under enzyme replacement therapy. Communication with the child, which depends on cognitive functioning, can be preserved under therapy, and this has a huge impact on daily life in the families. (See also ERG report p. 45 and 49) Impact of treatment on non-grand mal seizures and on patient's quality of life Although not documented within the scoring system, there is an impact of treatment on all seizure types, which is documented in patient's seizure diaries. Non-tonic clonic seizures are less common and less severe under treatment. This has a big impact on everyday life and activities of families and increases quality of life. New patterns of epileptiform activity seen in cerliponase alfa treated patients EEG abnormalities in natural history patients are very severe due to the rapidly progressing neurodegeneration and are clinically reflected in frequent treatment-resistant grand mal seizures. Subtle EEG abnormalities such as focal activity or EEG changes reflecting minor seizure types (focal, astatic,..) are obscured by the overall massive EEG changes seen in natural history patients . Since grand mal seizures occur less often and are less severe under enzyme replacement therapy (and less medication is needed to treat them), the underlying small seizure types are a bit more likely to show. In an otherwise progressive degenerative disease this cannot be interpreted as a worsening of function but rather seems an expression of preserved neuronal function under effective treatment. (See also ERG report p14, 71) Meaning and relevance of EEG and brain volume changes EEG (new focal and generalised epileptiform activity) and MRI findings (3.3% reduction in total cortical grey volume between week 48 and 96) do not indicate continued neuronal progression. As stated above, the EEG findings are likely indicating an alteration of previous, more severe disease symptoms. Due to the nature of this rare disease, the diagnosis of the vast majority of trial patients was made after onset of first clear symptoms which is in most cases the onset of epilepsy. Treatment was therefore initiated within the phase of rapid neurological decline. For a meaningful interpretation of the MRI data one has most

	probably to assume that, when enzyme replacement in the CSF space starts, there will be no immediate stop of the degenerative neuronal process. At this point in time, a number of neurons are dying in an irreversible process. So, for a therapeutic “rescue” to become discernible (clinically and brain volumetrically), some time is needed during which further brain tissue is lost. A look at the brain volumetric data over time clearly shows that the rapid loss of grey matter volume slows very soon after the initiation of enzyme replacement therapy, which indicates a long-term effect on brain tissue volume and neuronal stability. (See also ERG report p. 23 and 24) ECG abnormalities or heart abnormalities observed in cerliponase treated patients In 30 enzyme-treated patients, the following ECG or other heart abnormalities have been observed: one patient with intermittent rhythm abnormalities without clinical significance; two patients with a systolic murmur due to mild congenital heart abnormalities (bicuspidal aortic valve, atrial septic defect with small tricuspidal valve abnormality). All cardiac abnormalities observed during the treatment trial were not clinically significant. Such abnormalities are commonly seen in this age group of children. They are most likely not associated with treatment nor underlying disease. At this time no conclusions to long-term effects and future heart complications can be made as there are no natural history data on possible heart involvement, due to the general severity and rapid progression of the disease that leads to early death. Nevertheless, as mentioned above, at meetings of clinical experts many patients with an atypical (prolonged) course of CLN2 disease (mostly from Argentina and Brazil) have been described who did not show any sign of cardiac abnormalities at varying ages of 18-30 years.

Name	[redacted]
Role	Patient Advocacy NGO
Other role	[redacted]
Organisation	[redacted]
Location	USA
Conflict	Yes
Notes	We have a small contract to provide social services to families participating in this clinical trial for housing, school supports and other local supports needed while being relocated for several years.
Section 1 (Appraisal Committee's preliminary recommendations)	February 28, 2018 National Institute for Health and Care Excellence (NICE) National Health Service United Kingdom RE: Cerliponase Alpha Dear Committee Members: I am writing on behalf of the hundreds of families in the United States whose children have, or have lost young children to Batten disease, the most common cause of inherited childhood dementia. Children with the common CLN2 type of Batten are affected by loss of motor ability, seizures of many forms, blindness, immobilization and early death unless treated with the only FDA/EMA-approved drug, Brineura or Cerliponase Alpha. Natural history data tell us that our 4 and 5- year olds will have gone through these changes within an 18-month period. The Batten Disease Support and Research Association serves families primarily in North America, but each year helps families contacting us from 30 countries, including the U.K. Because our offices are only 15 minutes from one of the four original trial sites at Nationwide Children's Hospital, we have had the extraordinary opportunity to see many children with CLN2 Batten disease in clinical trials and post-regulatory approval. This milestone treatment has changed the course of this horrific disease and provided families with real hope. With Cerliponase Alpha, these kids are in grade school for the first time, engaging in active learning and meaningful activities with peers. Their parents hear them say words that have never been uttered before and they are still walking and laughing. These sounds of life are the reason we work each day to bring brighter futures for them and those yet to be diagnosed. We understand NICE's task of and need for reviewing medicines such as this one. While the process continues, we believe the views of families need to be considered most prominently. I know you will be receiving significant numbers of

	letters from parents and their communities during your proceedings. I hope that you will really hear about their experience and how Cerliponase Alpha has changed their lives for the better, which is what medicine and proper care is all about. Thank you for your kind consideration. Sincerely, [redacted]

Name	[redacted]
Role	Carer
Other role	
Organisation	
Location	USA
Conflict	None
Notes	I have seen improvements with my own eyes. My wish is for others who receive this terrible diagnosis to have the same access to this treatment as my son has, regardless of race, creed, social status, location, language.
Section 1 (Appraisal Committee's preliminary recommendations)	March 3, 2018 I have come to understand that NICE is not approving Brineura (Cerliponase Alfa) at this time for new patients in the UK, and as a parent of a 5 year old CLN2 boy, who is receiving this medicine, I cannot fathom how this decision was made. The reason that I am writing this letter is that the BDFA has reached out through the BDSRA here in the US, specifically to families receiving treatment, and asked us to share our experiences with you considering your current decision to decline funding this treatment. Both the BDFA and the BDSRA have been instrumental in lifting families like mine when they are struck with the terrible news of diagnosis, no matter if CLN1, CLN2, CLN3, etc. There are several points the BDFA asked us to touch on: long term evidence of success, some confusion over CLN3 heart issues in unrelated CLN2 cases, rebuttal of EEG findings long term, and prevention of vision loss. I am not a scientist, so I will present you with anecdotal evidence of treatment success I have seen with my own eyes. To truly understand the benefit of treatment, one must put themselves in the role of CLN2 parent 5 years ago, and compare/contrast against a CLN2 parent today, to see how morally abject the decision to decline funding this life-altering treatment really is. Parents, whose children were born prior to 2010 and diagnosed with CLN2, were told to go home and hug their children, there is nothing that could be done to help with the quality of life. Several of these same parents vowed to change that dynamic, and started raising money for research and communicating with the medical research community. These parents pressed on, even when it was apparent their own child was too far progressed to benefit from a radical new way to treat this disease. Through their tireless work, they changed the course of CLN2 Batten history. As a result, just a few short years later, my son is proof against the historical progression of the disease that Cerliponase Alfa is delivering the results it claims. As a quick background, [redacted] had his first seizure in Nov 2015, diagnosis of CLN2 Batten took

	a year (Nov 16), and he was admitted into expanded access for Brineura in May 2017. Yesterday he received his 22nd enzyme infusion. In the 10 months since he started treatment, we have seen a tremendous improvement in his quality of life against the progression of the disease. After his first infusion, he was more aware of his surroundings, by the 6th infusion, he was stabilizing and now he is doing things he hadn't done in the previous year, such as taking steps independently, crawling up the stairs, holding his sippy cup and drinking independently, playing ball with his unaffected twin sister and trying to say words we hadn't heard in a long time. Some people take for granted these tiny acts, or dismiss them as insignificant. I am here to tell you how beautiful it is for my child to entertain himself without worrying about a seizure, or a fall, or a black eye. There were times of constant crying and anguish because he can't communicate his issue to me in a way I could understand, and now there is peace in our house and peace within him. Peace, when his gaze locks onto me from across the living room, and he crawls his way over to me and crawls up on my lap to sit with me. Peace, amid the chaos of physical therapy appointments twice a week, gymnastics for his sister, Brineura treatments every fortnight, waiting for the school bus, all the normal tasks of raising children with working parents, yet multiplied by a factor of 10 because of CLN2. We know that this is a treatment for this disease, and we still search for a cure, which may be as simple as identifying the disease at birth and beginning treatment as early as possible. We know what the historical path of this disease is, and today, we have a chance to change history. My wish is that in addition to NICE providing access to Brineura for that incredibly small percentage of the population that needs it, CLN2 is one of the conditions that is screened upon birth. This morning, I met a CLN2 child who just turned 4 and is receiving her 3rd enzyme infusion. I can tell you unequivocally that I am jealous of where this child is in relation to my own. The key difference is that she has not progressed as far as my son in this disease since they were fortunate to receive a diagnosis in half the time that ours took. I pray that you not stand in the way of progress for those affected by this terrible disease, look no further than [redacted] and [redacted], children of your countrymen, as the living proof needed to move forward with approval.

Name	[redacted]
Role	NHS Professional
Other role	[redacted]
Organisation	
Location	Wales
Conflict	None
Notes	I have spent over twenty years telling families their children are going to die of relentlessly progressive neurological disorders such as CLN2. I have no choice but to pursue any treatments that might halt the progression of these devastating conditions. This is my duty to my patients and their families, who may be materially, emotionally and socially disadvantaged. If I don't do this; nothing will change. Other disclosures: I have accepted educational grants from BioMarin for transport and accommodation in order to receive training on the administration of Cerliponase Alfa.
Section 1 (Appraisal Committee's preliminary recommendations)	1. I have been a [redacted] at the [redacted] Hospital [redacted] since 1997. In this capacity I have been treating a child with CLN2 at our hospital since December 2017. This is the first patient in the UK to have been treated outside of a clinical trial. Funding was provided by the Welsh Health Specialist Services Commissioners (WHSSC) and this is to be reviewed 6 months after the start of treatment. I therefore have a keen interest in the outcome of this consultation 2. My main concern throughout the consultation is the failure to take into consideration that CLN2 is an extremely rare disorder with 3-6 patients per year diagnosed in the UK. Therefore the cost of treatment to the NHS; though expensive by QOLY, will be limited. The proposal to increase detection rates by genetic screening will only contribute to earlier diagnosis as the absolute numbers will remain largely unchanged in the UK. I do not believe there are many ""undiagnosed"" cases in the UK as NICE CG 137 already recommends that such children (ie early onset epilepsy before the age of 3 years) have access to paediatric neurology services. 3. In addition to the comments on the individual sections described below I would like to take issue with some of the assumptions of the ERG in relation to health related QOL: a. The extra-neurological effects of CLN2 (ie visceral, cardiac) have been compared with CLN3 which is a completely different disorder resulting in the accumulation of a different protein, battenin. I consider therefore that judgements regarding mortality and morbidity in comparison with CLN3 must be invalid and not appropriate for consideration by the committee.

	b. The committee does not appear to have consider the latest evidence that treatment has caused some improvements in seizure control in the clinical trials as evidenced by weaning of antiepileptic medications. The epilepsy related QOL must be significantly improved by the reduction in numbers of generalised seizures, as the risk of epilepsy related death is also thereby reduced. c. My patient has so far experienced a significant improvement in QOL. I know that this is anecdotal evidence but it is clear that even after 6 treatments she is calmer and happier. Before treatment she was consistently agitated and distressed for several hours every day and this has significantly improved, as has her interest in her surroundings and her engagement with wider family and school. 4. The committee has not emphasised the importance of a managed access agreement such that treatment could be administered to a narrow group of children and better outcomes would be expected long term. For example most parents of children with severe disability would choose not to treat their children and extend the duration of poor QOL. I think it would have been reasonable of NICE to reference limits for the eligibility of patients to receive treatment (pending such an agreement) rather than impose a blanket ban on any child receiving treatment (include treatment for younger asymptomatic siblings). I cannot imagine the suffering of families who have watched their elder child die only to be refused any treatment for their second. The recurrence risk is very high; 1:4 so this situation cannot be ignored. 5. Finally my experience in this area would suggest that no other treatments will come along for these patients until the development of gene therapy (already underway for other childhood neurological disorders such as spinomuscular atrophy). Children treated with cerliponase alfa have the opportunity to maintain their neurological status until such treatments are inevitably available. To my knowledge there is only one child whose treatment is being funded by the NHS (?outside of compassionate use) and that is my patient. I therefore have a keen interest in the outcome of the consultation Para 4. re the conclusion that there is no evidence to support reduced mortality (at 96 months). The age of death in CLN2 is 10-12 years; does NICE intend to wait until the current cohort of treated patient reach this age before deciding on this point? If so in the meantime many children will have missed the opportunity for life-lengthening treatment.

	The NICE committee recognise that CLN2 is a very rare disease with no treatment options apart from palliation but they have not recommended cerliponase alfa which gives these terminally ill children an opportunity of even a few years of good QOL. We have been treating our patient with ICV infusions for 6 cycles so far and this has been well tolerated. We have had to replace the device but this procedure was uneventful. Our centre already has experience in treating patients with lysosomal disease and therefore has quickly adapted to using cerliponase alfa with teamwork between medical, surgical, nursing and pharmacy specialist staff. It has gone really well and the patient's family is very satisfied with the service. If this treatment was available in all of the metabolic disease specialist centres in the UK, then no patient would have excessive distances to travel (compared to the current situation where all other patients are treated in London). re early stabilisation of disease. I know that we are at an early stage in the treatment of our patient (6 cycles) but they have already shown improvement in terms of reduced irritability and also speech development has emerged with the child learning new words. The panel compared care costs for young people with CLN2 with those of people with severe brain injury. I do not think this is justified. If patients are treated at an early stage of disease ie scores 2-4 and there condition is maintained, then they would be much more able than people with severe brain injury and the costs would be less. For example; my patient with a score of 2 can communicate verbally and non-verbal; would be able to transfer independently and remains orally fed. She has no generalised seizures. She does not require nursing care. Therefore her care needs are not those of a severely brain injured person. In addition if children are given the opportunity of early/presymptomatic treatment then their outcomes would be similar to those of visually impaired people. The committee presumed the company was too optimistic in predicting the number of children who could be diagnosed earlier in the course of the disease. I do not agree that this is the case. It is now standard practice to obtain genetic testing for all children with early onset epilepsy and most epilepsy specialists are extending this to children under the age of 3 years. Standard NHS epilepsy gene panels (eg Cardiff, GOSH and other centres) already include CLN2 and that indeed is how my patient was diagnosed. There is a lively network of clinicians with epilepsy expertise in the UK (OPEN UK) and information re

	CLN2 can be rapidly and widely disseminated. It is therefore not unreasonable to expect that cases can be diagnosed very soon after the onset of seizures." Comment is made on clinical vignettes describing improvements in seizure control; the panel should take into consideration the latest results from clinical trials which do show improvements in this area. QOL data described is based on health status assumptions which I believe to be inappropriate (see my comment on the whole document above) I would whole heartedly welcome a managed access agreement as described in this paragraph and would have hoped that the committee would reference this in its final decision.

Name	[redacted] [redacted]
Role	Parent
Other role	
Organisation	
Location	USA
Conflict	None
Notes	
Section 1 (Appraisal Committee's preliminary recommendations)	On June 11th 2009, we welcomed our second daughter [redacted]. A perfectly healthy 7 lbs 1 oz baby girl, huge brown eyes, rosy cheeks and full pink lips. [redacted] developed typically, met all her milestones and even met some early. She was walking at 7 months old! [redacted] is our little ray of sunshine, she brings joy with her 100 watt smile on the darkest of days. She's our silly, happy, free spirited yet strong willed child. [redacted] was born on July 8th of 2010, a perfectly healthy and plump 7 lbs 8 oz bundle of joy. His sisters welcomed him with lots of hugs and kisses, they were so happy to have him as part of our family. A total mommy's boy. He is the happiest, sweetest, most caring and loving little boy I have ever met. Gives the best cuddles in the world, we have officially named him a professional cuddler. Things were going well until [redacted] and [redacted] had their first seizure in January of 2013. Oddly enough, they had their first seizure in the same month just 3 weeks from each other. Numerous labs, scans, tests and 48 hour EEGs determined that [redacted] and [redacted] both had epilepsy. Breakthrough seizures and the fact that they are siblings had our neurologist wanting to do further testing. The anti epileptic drugs were not working and they continued to have hundreds of seizures a day. We had genetic testing done in August of 2013 but nothing could've prepared us for the answers we received on November 14th of 2013. [redacted] and [redacted] were diagnosed with Neuronal Ceroid Lipofucinosis or Late Infantile Batten Disease. It basically means that our children are lacking the enzyme responsible for clearing the cells in their brain so in turn the cells die and that is how skills are lost. Our children's fate included losing their ability to walk, talk, eat by mouth and losing their eye sight. We were sent home and told to enjoy the rest of their lives as they may not even make it to 10 years of age. Relieved to finally have answers to what was happening to our children but devastated by what it was, our world came crashing down on us that day. All the hopes and dreams we had for our children were now gone. Nothing at all made sense or mattered. A couple days after receiving this news, after countless hours of frantically researching online, we found a family who also had two children with Batten disease. They told us about a clinical

	trial that at the time was only available in Germany, it was an enzyme replacement trial. At the time, there wasn't any evidence or information out there that this enzyme replacement therapy was even making a difference but there wasn't a doubt on our minds that we wanted to enroll our children in it. We remained in touch with the clinicians and doctors in Germany as they informed us that they will be opening a trial site in the United States, that was perfect since the US it is our native country. In December of 2014 [redacted] became one of the first 3 children in the US to receive this enzyme replacement drug. Unfortunately there were only 3 slots open and [redacted] wasn't able to participate. This tore our hearts out as we wanted to give our children the same chance. At the start of December 2014, [redacted] started to struggle putting sentences together, she was starting to lose her ability to walk, she wasn't wanting to eat and she was now very weak. She was seizing every 20-40 minutes all day long and the rescue seizure medications had now stopped working. The seizures began to take a huge toll on her little body. We watched, waited, hoped and prayed that these enzyme infusions can at least give us an extra year with our girl as she was rapidly declining. A few months into treatment we noticed that the seizures were now shorter in duration, not as intense and not as frequent. She developed an appetite like we've never seen before. She was happy again and her speech became more clear. She became more confident and started taking more and more steps on her own. When [redacted] started treatment, [redacted] was happy as can be, running, jumping, spelling words on his iPad and scarfing down as much food as he can fit in his little belly. [redacted] ended up starting treatment 19 months after [redacted] and he was then such a completely different boy. He was no longer able to walk, play on his iPad, eat by mouth and he was experiencing around 300 seizures a day. His body started to shut down It's been a little over 3 years since [redacted]'s first infusion and she's doing great! She has stabilized and made some gains. She hasn't had a seizure in 2 years! We threw her a party and celebrated a milestone that we never thought we would get a chance to do. She is still able to eat by mouth and see. She is super strong and her happy self again. For [redacted], it has been 18 months and he has also stabilized. He is able to give those amazing cuddles that only he knows how to give. He is taking steps in his gait trainer and is able to eat by mouth again. He is happy and getting stronger each day. As their parents, it's always been important for us to do all that we can for our children, give them the best quality of life and

	make as many memories as possible. With Brineura, we are able to do all of these things. I can honestly say that [redacted] and [redacted] are still enjoying life and that they wouldn't be here today without this enzyme replacement therapy. Just like we wanted [redacted] to have the same chance as his sister [redacted], we want our dear friends overseas to have the same chance for their children and family. Please reconsider your decision, it makes a world of a difference for many people. Thank you for taking your time to read this. Sincerely, The [redacted] Family

Name	[redacted]
Role	[redacted] Batten's disease Center of Excellence, United States. [redacted] for Cerliponase alfa.
Other role	[redacted] The Ohio State University. [redacted]: Cerliponase alfa
Organisation	
Location	USA
Conflict	Yes
Notes	
Section 1 (Appraisal Committee's preliminary recommendations)	With regards to the comparison of EKG abnormalities in CLN3 patients, our center has experience with approximately 20 other children with CLN3 and none of them have EKG abnormalities. None of them have developed cardiac conduction abnormalities at the age of 14. Although both CLN2 and CLN3 are lysosomal storage disease, CLN3 has a different clinical course, symptom onset and progression. It may not be a good proxy model for long term outcomes in children with CLN2 disease. Although there are few case reports of cardiac abnormalities in children with CLN2 disease, these are largely case reports and not large cohorts. Our center's has experience with approximately 20 children with CLN2who have not been treated with cerliponase. None of them had any evidence of cardiac disease on EKG's. None of them had any evidence of liver or pancreatic dysfunction. Traumatic brain injury may not be a good proxy for estimating long term effects of neuro-disability since the mechanism of neuronal loss in different in head injury as compared to neurodegenerative disease With regards to the treatment of grand mal seizures, recent analysis of the data indicates an improvement in the generalized tonic clonic seizures. At the 96 week analysis, there was improvement in 66 percent of the children who suffered from generalized tonic clonic seizures. In the US children receiving Cerliponse alfa who are part of the original cohort of 24 children, all of them have experienced improvement of their generalized tonic clonic seizures (GTC) with 100 percent seizure control for their generalized tonic clonic seizures. Other children who have been treated with Cerliponase have also experienced improvement of their GTC. In the compassionate use protocol (all children are now receiving commercial Cerliponase) in the United States, approximately 80 percent of the children are free of any generalized tonic clonic seizures. In the 20 percent who are experiencing seizures, their seizures are shorter and the intervals between each seizure are prolonged. In fact, in one of my patients with an ML score of 1, that patient has experienced shorter duration of less than two minutes. In conclusion, this has caused significantly less hospitalizations for status

	epilepticus. Overall, the epileptiform burden in children with Epilepsy does not portend the prognosis of seizure control. Hence, “new” patterns of epileptiform activity do not indicate neurologic disease progression. To the clinician, this may indicate closer vigilance but it should not indicate advancing treatment. We treat the “child” and not the “EEG”, hence, seizure control is not based on electrophysiological parameters but rather, clinical response. In the US cohort, there is improvement of the myoclonus and atonic seizures. There will be rare provoked seizures (sleep deprivation or illness) but none required prolonged hospitalization. Although there will always be ongoing risk of seizures, we have been able to lower some of the medications. In our original children in the US, the children in the original cohort are still walking with assistance and one is still walking independently. In fact, all of them are going to school, attending birthday parties with their peers and communicating with their parents and families. Improved seizure control has allowed the children to lead more positive lives because they are not afraid to have seizures in school or with their friends. I have addressed the EEG abnormalities in the previous note. The MRI findings of cortical volume loss has also been less in the second year of therapy. The initial volume loss maybe related to "debulking" of the lysosomes. Although there is continued neuronal loss, there is persistence of clinical response as compared to neuroimaging In our current cohorts of patients receiving Cerliponase alfa, none of them had any clinically significant EKG abnormalities. None of the abnormalities were associated with any structural cardiac abnormalities and these were cleared by the cardiologists in our center.

Name	[redacted]
Role	Carer
Other role	Parent
Organisation	
Location	USA
Conflict	No
Notes	
Section 1 (Appraisal Committee's preliminary recommendations)	To Whom it May Concern: My name is [redacted] and I am a parent of two children with the CLN2 form of Batten Disease. We are very fortunate, as we live in the United States, and both of my children are receiving Brineura. My daughter, participated in the compassionate use program offered by Biomarin . As such, we travelled from [redacted] (~2200 miles or ~3540 km) every two weeks, so that she could receive treatment. My son started receiving treatment after commercialization. Today, we travel about 90 minutes, each way, every two weeks so that my children can receive treatment. I write to you today, because the CLN2 parents of your country have appealed for all parents of CLN2 children, from around the world, to send letters in support of approval of Brineura in England. Like the other parents, I could easily reiterate what you already know about those who receive Brineura. Yes, the progression of the disease has slowed (and hopefully stopped) in my children. Yes, my children have improved in certain areas (e.g., tying shoes, sitting without assistance etc.). Yes, my children, seem to feel better and are having better interactions with others. However, I feel that these are the obvious statements and I believe that others have provided you with quantitative and qualitative evidence of the benefits of Brineura. Instead, I thought that I would ask you the hard questions. My hope is that by pondering these questions, that your committee will reach the right decision and make Brineura available to your citizens. • Has your committee invited the English children and families who have been diagnosed with CLN2 after April of 2017 (the approximate date of EU and US approval) to testify as to how their lives have been impacted by the failure of England to approve Brineura? • Has your committee invited the American and European children and families who have been diagnosed with CLN2 after April of 2017 to testify as to how their lives

	have been impacted by the American and EU approval of Brineura? • If Brineura were 5 pounds per year, instead of the current list price, how would your decision differ? Would you honestly have similar concerns? What creative solutions are available to help address your concerns. Lives are depending upon your decisions. • For those English children that are denied access to Brineura, during the course of their lives, how much will the English government spend to provide care? I ask not just with respect to direct costs, but with respect to all costs, lost productivity (e.g., parents,family and friends missing work to care for their children, taking kids to appointments etc). I suspect that the overall cost will far exceed the cost of the treatment. • It may be obvious, but your decision will reach across the United Kingdom and will influence other governments' decisions across the rest of the world. • Your decision with respect to Brineura will have a direct impact on the availability of future treatments for mainstream disorders. The worldwide pharmaceutical industry is watching England. As such, many in the industry may be reluctant to invest in treatments and cures for other disorders (e.g., parkinsons, alzheimers, ALS,diabetes, cancer etc.), because they cannot recoup their investments and turn the profits necessary for their shareholders to support research and treatment development for "difficult diseases". • Finally, we all know that Brineura is not a cure. However, Brineura is an important step on the path to better CLN2 treatments and cures. We as families, fully understand that the science of treating CLN2 is complicated. As such, like any difficult task, Brineura is one step of many required for subsequent treatments and a cure. In the end, I hope that this letter will spark debate and ultimately sway you to recommend approval of Brineura. Despite the heartfelt arguments, that other parents have shared, and I reiterate, I hope that you and your colleagues appreciate the broader implications of your failure to approve this treatment. For those of us with loved ones living with this disease, your decision appears to be cruel and based on a narrow set of illogical conclusions. Personally, I shudder when I think of the pain and suffering, that this prolonged delay has caused. It is my sincere hope that you weigh the arguments made in this letter and the many others you have received and ultimately make the right decision. Please make Brineura available to the

	families of England suffering from this cruel disease. Best regards, [redacted] [redacted]

Name	[redacted]
Role	[redacted]
Other role	[redacted]
Organisation	
Location	UK
Conflict	None
Notes	
Section 1 (Appraisal Committee's preliminary recommendations)	I want to challenge the decision by NICE not to fund treatment for children in England with CLN2. I have witnessed first hand the benefits to 2 children on compassionate use of the drug. Quality of life has improved and a slowing down of the progression of the disease. Not to have access to treatment in England when European countries have approved and fund treatment is a human rights issue. Everyone should have the basic right to receive treatment when there is an effective drug. How else are we going to move forward with research and treatment of CLN2?

Name	[redacted]
Role	Carer
Other role	CLN2 Father & [redacted]
Organisation	
Location	USA
Conflict	n/a
Notes	
Section 1 (Appraisal Committee's preliminary recommendations)	I am writing you today as a father of two children who have been affected by CLN2-Batten Disease. You may be familiar with my story as I was a panelist at the FDA public meeting regarding Patient-Focused Drug Development on Inborn Errors of Metabolism in June of 2014. VIDEO LINK https://www.youtube.com/watch?v=2B240z7TJHY&t=10s VOICE OF THE PATIENT REPORT https://www.fda.gov/downloads/drugs/newsevents/ucm436454.pdf FULL TRANSCRIPT (pg 61-69) https://wayback.archive-it.org/7993/20170112082300/http://www.fda.gov/downloads/Drugs/NewsEvents/UCM403000.pdf My son lost his battle with CLN2 disease nearly 2 years ago and my 12 year old daughter progresses irreversibly towards the same fate. I am also [redacted] and [redacted] of the "[redacted] [redacted] - [redacted] [redacted] " research foundation and [redacted] [redacted] of the Batten Disease Support and Research Association in the USA. I can assure the committee that I am very qualified to share my perspective about CLN2 disease as a parent with over 10 years of experience with my own children and from having known approximately 50 other children and families affected by CLN2 disease during that time. During this time I have worked to understand this disease from many perspectives with the goal of developing multiple treatments and someday a cure for CLN2 disease using different therapeutic strategies. I was disappointed to hear of the NICE decision to NOT recommend Cerliponase Alfa for the treatment of CLN2 disease as I have gotten to know many of the families and the affected children who have been taking Cerliponase Alfa since the beginning of the clinical trials, and have watched many videos and heard many stories of disease stabilization. More importantly I have had several of these parent share stories of actual IMPROVEMENT and stories of children actually REGAINING abilities once lost in some cases. I believe our local neurologist (who is infusing several Cerliponase Alfa patients) stated it best when she said: "It's Brineura or death for these children". I would like to offer my views on the following 4 items for the committee to consider. Following that, are snippets of online chats I have had with

	parents who have had children on Cerliponase Alfa. 1. Extra-neurological progression: There may be serious implications for patient morbidity and mortality associated with cardiac, pancreatic, and hepatic impairment unless ERT is administered systemically. This unrelated to neurological progression, therefore represents an additional mortality risk. • There is no evidence that this is the case in either the published CLN2 literature or from QUALIFIED experts who have followed many CLN2 children longitudinally for several years. If the committee is seeking a qualified expert in this matter, I would offer that the only group that has legitimately done this type of longitudinal study is the German group in Hamburg: Schulz & Kohlschütter. Currently children do not live beyond the age of 12-13, NICE are basing their decision on incorrect assumptions about the progression of the disease beyond the age at which children currently die. 2. Other-disease-related mortality: Evidence from the related but not identical Batten's disease sub-type CLN3 shows that the actual cause of death for a substantial proportion of CLN3 patients was either pneumonia or infection, therefore not related to either neurological failure or extra-neurological pathology. • Basing ANY decision for CLN2 on LIMITED findings in CLN3 is scientifically inappropriate. Any qualified NCL expert in the world will tell you this. Biochemically these disease are quite different. Unless the committee is able to determine the definitive function of the CLN3 protein, any reference to CLN3 should be eliminated, and no cross-NCL consideration should applied. This is akin to cross referencing MPS3a to MPS4 or MPS7. It is simply not reasonable. 3. Although Cerliponase Alfa had a clear treatment benefit on tonic-clonic seizures in the short term, the committee concluded the long-term impact was uncertain in light of EEG findings. • This is an incorrect interpretation of the data provided by the electroencelphogram findings. This has been challenged by clinical experts not just in the UK but also worldwide. Most of the parents that I have spoken to regarding this have also commented that seizures are dramatically reduced if not eliminated once treatment began. 4. The committee concluded that there was insufficient evidence to suggest that cerliponase alfa would prevent vision loss in people with CLN2. • We know that children will continue to lose their vision and it has never been claimed that cerliponase alpha will prevent this loss. However, without treatment, children with this disease do not survive. For NICE to suggest that children with vision loss have a significantly decreased quality of life is

a statement that both myself and the visual impairment community from around the entire world would certainly challenge. Research continues worldwide into preventing vision loss in these children. As any parent would certainly tell you, if we had to choose between blindness and death, the choice is obviously blindness.

Lastly I would like to convey some of the comments other parents whose children received Cerliponase Alfa have made to me in the past. I have replaced names with "[redacted]", "[redacted] "etc.as to not reveal the children's names.

1. [redacted] continues to speak with a vocabulary of around 70 words. She says some 2 word imperatives, in particular, "Sit down" and "Wake up", she will occasionally add a name to this, such as "Sit down, dad". She continues to learn new words and is able to mimic novel words such as "Bear", "Donkey" and "Heart". In order to refer to objects such as toys she will say "this". All snacks are "Cookies" and most toys she calls "Eggs". She still says "Peppa Pig" and "Spongebob" with some clarity and after spending some time with her you learn to understand what she is saying. In comparison to her peers not on the trial, this is outstanding as most children whose onset begins at 3 years old will be non-verbal by this age.

2. [redacted] is still able to take over ten steps with close supervision. She does, however, use a self- propelling wheel chair to move around and she is able to move herself backwards and forwards with her hands. This means her gross motor function is still very much present and she is able to move travel in this fashion to a certain extent. Once again, children age 6 and above do not have this level of gross motor function and the ataxia in their limbs would prevent them from propelling themselves. In addition, the cognitive impairment would also hinder in operating a self-propelling wheel chair for non-trial children.

3. [redacted] also has good hand eye coordination for her age, and is able to navigate around Youtube on the iPad very well. This indicates that her Fine Motor skills are still very much intact, and she is able to press the small skip button in the bottom right hand corner of the screen- evidencing that her eye sight enabling her to do things. The fact that [redacted] can independently operate the iPad and correct it when Youtube stops working is indicative that not only her Fine Motor skills are far above average for a 6 Year old CLN2 child, but also that her cognitive skills are strong and she is able to solve some problems when the screen accidentally turns off, for example.

4. [redacted] is very good at knee walking and good general awareness of her environment. For example, she will know when it is time for bed. Due to her routine, she will watch her television program, and at a certain point in the show, will know that is when the day is over. She will then start walking on her knees to her bed room. For a non-trial child with an onset of 3 years old, this certainly would not be the case and they would need to be

		transferred to the bed from their sitting or lying position. This shows that [redacted] understands what happens at certain times of the day and where she should be at that time. Once again, this shows the level of cognition she has, which would be absent with non-trial children on the whole.
	5.	When we are going shopping in our local area, and she is in her wheel chair, [redacted] is very aware of her local environment. So much so, that when we get a few streets away from a shop where we buy her a magazine, she will start saying “stickers”. This is her way of saying, “take me to the shop where I can get a magazine with stickers in”. For us, this is very important, and once again evidences the level of cognition and even development that she has had over the last few years. BBBB is aware of her environment and is able to track her location relative to another place. From my knowledge of other non-trial children at 6, this absolutely does not happen.
	6.	[redacted] is able to feed herself finger food such as chips and popcorn, although we feed her meals. She is able to swallow well and does not longer have a problem with her medicine which she takes twice a day, which was becoming problematic over a year ago. WE feel that the longer [redacted] is on the trial the more effective the treatment is.
	7.	Perhaps one of the most significant aspects of the treatment is the fact that [redacted] has not had a Tonic Clonic seizure for 14 months, and we have not increased her anti-seizure medication either. Her Myoclonic jerks and absences have also decreased and these are rare occurrences, perhaps once every month or two. From my knowledge of other children, they are taking a lot more medicine than [redacted], necessarily through a feeding tube and are nevertheless regularly having many different types of seizures. [redacted] would have a Tonic Clonic seizure once every three months, even during the clinical trial, but now, despite not increasing her medication, these seizures have stopped. We can only put this down to the enzyme replacement therapy which is having a huge impact on [redacted]’s quality and quantity of life.
	8.	My son hasn't lost any abilities to improve on....he has by all means doing amazingly well. I am happy to say [redacted] is able to run and walk. His speech is coming one really well especially since he started school September last year.... I don't want to build people hopes up with [redacted] as he's never really been a child we have looked at with battens because thankfully he was diagnosed really early and started the trial less than 6 months later... I do think without a doubt [redacted] wouldn't be the child he is today without this trial....he can speak a lot more lately and his understanding is coming g though with leaps....he has a really good memory as well..... this trial is showing that its helping these children. I know [redacted] wouldn’t be the little boy he is without it “he is creative and loves to swim....I haven’t got anything negative to say about it apart from the obvious I would rather my child not have battens disease”. [redacted] sings alot and remembers words from songs and tv shows and can repeat

them back to you once or twice after he watched it.

9. I think [redacted] improved in Language! Doctors told me that they added one point for him once! But I don't know if he still has this point in his score! But for sure his language is stable! He was much more nervous when we started and I thought he couldn't follow a conversation! Now he understands almost everything! He is very awake and clear now!..... But life is much better since he didn't lose every day something new! He is still very good in walking aided". He turned 10 in December !..... Yes, he is still eating via mouth!..... Yes! It felt like an ordinary life! Ordinary with a disabled child but not like a life with an terminal ill child!

10. But [redacted] did climb up on our high bed 2 days ago. He hasn't done that in a year and half. Plus he can climb stairs again! He's been sitting on this Big Wheel for over an hour and hasn't fallen off, I had actually put it away thinking he was done with that" And he hugs his legs around my hip again when I carry him. Little things most people would not realize are things". What makes that so cool is him putting his hand in the bag and remembering what to do. He turned away 4 times before trying it.

I urge the NICE committee to reconsider and approve this life-altering treatment for the very small number of children who desperately need this medicine to survive. Progress is being made in this disease with the expectation that new gene therapies based will emerge in the not too distant future. These therapies on the horizon will be one time therapies and the expectation is that they will be less expensive when taken in aggregate over a number of years. For now these precious children have a long awaited life raft that was not available for my children.

Please do not cast these children out of this life raft based on a formula or "value added" calculations that appear to have some serious flaws. A decision to nut fund this treatment would indeed send a chilling message to our Batten community as well as the larger rare disease community which has seen an incredible increase in interest over the past decade.

Sincerely,
[redacted]
Father of 2 affected children

Name	[redacted]
Role	Carer
Other role	
Organisation	[redacted]
Location	USA
Conflict	n/a
Notes	
Section 1 (Appraisal Committee's preliminary recommendations)	Our daughter, [redacted], died from CLN2 Batten disease because there were NO options. When she was diagnosed in 2009 at the age of 4, we were handed a death sentence, an expiration date. She was only expected to live 8-12 years. Our entire world crumbled beneath our feet. The devastation of this disease took hold of our hearts, our lungs and paralyzed us. How was this going to happen to our spunky, spirited, cheeky, lovable little girl? How were we supposed to accept Bridget's fate without trying to do EVERYTHING we could? So we began to do ANYTHING we could. We initiated the Hope 4 Bridget foundation in order to raise funds to treat and find a cure for CLN2 Batten disease. We enlisted family, friends, acquaintances and strangers to help with our fundraising efforts. And in return, they came to us. We did amazing things- raising hundreds of thousands of dollars for the few scientists working on this rare disease. We supported studies and research and lab trials. We contributed monies to fund research that scientists from Biomarin used for the development of Cerliponase alfa. We were a small family foundation that brought thousands of people together because there was HOPE. We always had hope that a treatment and ultimately a cure would be developed. And now it has. We knew it would be too late for our [redacted]. But it is NOT too late for the next [redacted], or [redacted], or [redacted] or [redacted] or hundreds of others that have died because there were no options. Now there is truly hope. Don't rob other families of this right. Don't negate the 9 years we have spent fighting for our daughter, her memory and the future of Batten disease. Don't let the work of all these people and all the money we have raised go by the wayside: in the grave where our children lie. Support the treatment that these children need so desperately. Give hope to the 4 year olds who deserve a future of growing up past their 12th birthday.

Name	[redacted]
Role	Carer
Other role	
Organisation	
Location	USA
Conflict	No
Notes	
Section 1 (Appraisal Committee's preliminary recommendations)	I am the mother to a beautiful 7-year old daughter, named [redacted], with CLN2 Batten Disease. Her path looked much like the kids who came before her "normally" developing until about 3 years old when she started losing speech, skills and focus. She had her first seizure at 3½ years old and it took a long hard year of loss, seizures and doctor appointments to arrive at a heartbreaking diagnosis. She was diagnosed just one month too late to qualify for the Biomarin clinical trial in the United States. We desperately followed the progress of the trial and waited and hoped that [redacted] would be able to access treatment also. As the years slowly went by and [redacted] lost many, many skills; remarkably the kids we were friends with in the trial didn't. In fact, when we saw them every 3-4 months they seemed stronger, more alert, even making small gains in ambulation and verbalization "it was truly amazing"! When Biomarin opened expanded access to the US market in September of 2016 we were cautiously optimistic that she would qualify, she did not and we were heartbroken yet again. [redacted] was able to take steps with support but did not verbalize anything for the doctors. We waited yet again for a way to access treatment but this time it would be waiting for FDA approval. Our prayers were answered in April 2017 when the FDA approved Brineura for commercial use in the United States. We didn't have a moment to spare, in fact, we questioned if we should pursue treatment for [redacted] because at this point she was almost 7 years old and had lost so many skills, she was tube fed, no longer verbalizing anything, unable to walk and needing constant care and supervision. We decided to pursue insurance approval and take the chance that Brineura would better [redacted]'s quality of life. [redacted] had surgery to place the port in her brain in June 2017 and did wonderfully. Her first infusion took place on July 13, 2017, just 6 days after her 7th birthday. We have now had 17 infusions and these are some of the changes that we have seen • Ability to eat small amounts by mouth when previously completely tube-fed • Able to swallow better and deal with her own

	secretions • More control of head and neck, able to pick head up and move from side-to-side • Purposeful movement in arms and legs • Reduction in span between seizures from every 2-3 weeks to every 6-8 weeks • Reduction in duration of seizures from 2-2.5 minutes to 30 to 60 seconds • Substantial improvement in myoclonus • Increased alertness • More emotion “” smiling and laughing, as well as, crying to express displeasure • School reports that she is more engaged, alert and able to deal with her secretions better We feel so fortunate that our insurance in the United States is covering [redacted]’s treatment and want the same chance for our friends in the United Kingdom. We hope that you will reconsider your recommendation after reading the heartfelt responses from many of the families currently receiving treatment and those who didn’t have a chance to access treatment for their children. We truly feel Brineura is making a difference in [redacted]’s life and most certainly giving us the hope of more time with our lovely daughter, until a cure can be found. Thank you for your time and consideration. [redacted] [redacted]

Name	Mrs [redacted]
Role	Public
Other role	
Organisation	
Location	UK
Conflict	
Notes	
Section 1 (Appraisal Committee's preliminary recommendations)	Without the use of this continued treatment, for those already on it, will be like switching off their life support without giving them the full chance to breathe alone! This treatment is not just prolonging lives of children that "are going to die anyway'! It's not prolonging the inevitable, its giving them LIFE!!, because you've seen the results for yourself! It IS slowing down, in some cases HALTING & possibly even reversing the progression of this disease! If their treatment is stopped now not only will it cause unnecessary suffering for these gorgeous children but there will be no way of knowing what it's long term effects are!!!? Stopping this treatment WILL be giving them a death sentence! It WILL NOT be giving them a dignified death either! It will be cruel, slow, painful, antagonising death; and one that will effect the whole family & beyond! So it is without a doubt in the bests interests of these children to, at the very least, that the treatment be granted to remain in place for those whom this drug IS already being given & more over being proven to be effective treatment for these patients & for their treatment to continue; if not only for the greater good of that child BUT more importantly for medical research purposes itself! [redacted], for example, is one of only TWO children, In the WORLD, who has been fortunate enough to start this treatment BEFORE the more serious side effects & symptoms of the disease took a hold & having suffered only one seizure prior to treatment. In doing so [redacted] (4) is able to live the life of a normal 4 year old child. [redacted] has been able to go to pre-school & progress (like her peers) to mainstream school & more! She CAN still laugh, play, dance, see, eat, hear, speak, sing and LEARN & continues to grow & develop; hitting all her milestones, at the same rate as the national level statistics indicate! Without this treatment she would not! She would now be most likely unable to talk or walk unaided (at best) or be wheelchair bound or worse! Why you would want to stop such pioneering research for these children is beyond astonishing! You can SEE the results for yourself! She is here, living, breathing, PROVING to you that

	this treatment IS BENEFICIAL to her & Battens Disease sufferers as a whole! [redacted] [redacted] (7), [redacted]'s older brother, hasn't been quite so lucky as to receive the treatment as early into diagnosis as his sister, BUT the improvements & benefits that being on this treatment have given him thus far are incredible & are making massive differences for him, his sister & his entire family. Proven, positive results which are improving his quality of life & those of his siblings & family extensively! It is my opinion & belief that NICE have made errors in their initial reports, with regards to this treatment & the funding of it, which needs to be rectified immediately. Whilst it's appreciated that there are only approx 5-6 children diagnosed with this disease in the UK per year, that in itself shows that cost of that treatment, as a whole, will be minimal in comparison to the amount the NHS fund, as a whole, on other drugs; therefore should balance itself out! For example, Cancer treatments. Treatments that are NOT denied to any patient regardless of cause and/or diagnosis; even if it will only prolong life short term! If the CNL2 treatment is allowed to continue & progress then that in itself will enable further progression which may well result in a CURE for this cruel disease! And judging by the rate of progress for this particular drug then it seems highly likely statistically. When more drugs trials & research are available it is PROVEN to increase further development of drugs & it's usage & in doing so is more likely to allow the discovery of a cure that could be administered very early on thus reducing costs & further strains on the NHS as a whole! [redacted] & [redacted] [redacted] I, for example, have been seizure free for over 12 months now BECAUSE of THIS treatment. This in itself has reduced the strain on a struggling NHS by freeing up Ambulance time, hospital time & bed space! Without this drug [redacted] & [redacted] would have had 999 response treatment, I'd estimate of at least a minimum of 3 times weekly. They would have required overnight hospital care (usually longer) & a hospital bed, & beds for their parents, multiple times a week - do the maths for the costs of those figures per week & what does that amount too? EVERY life is valuable, more so that of a child that has not yet had the chance to live & grow! If Europe & the US have granted this treatment why on earth are the UK saying no! These children have no choice about having this disease, they didn't ask for it! They didn't put themselves at risk to get it! It is NOT a lifestyle choice yet they're not having a fair chance at survival & it is extremely unfair! This is not just extending the life of the majority of these children it's actually halting the progression of their disease,

	allowing those fortunate enough to get it early enough to remain SYMPTOM FREE!! Compare the MINIMAL amount of use this drug is going to be used, due to the rarity of it, in comparison to say SMOKING RELATED DISEASES! Those patients Who are given unlimited access to treatments, when they are well informed of the risks to their health if they continue to smoke, yet do it anyway!? It's their fault! Their lifestyle choice! If they want to continue to put their lives at risk why should they get funded treatment when these helpless children don't!? They're even funded to help quit!! So WHY aren't these children being funded to help quit this disease? We HAVE to be the voice for these children! We MUST STOP their unnecessary suffering! NICE, STOP thinking about the cost of the treatment & the low statistical rate of number of children affected each year & think outside of the box here! This is one terminal illness that actually could be cured, or at the very least controlled, effectively & in a very short space of time! You CAN reduce the fatalities in the UK from 5-6 diagnosed deaths to ZERO so action it! Whilst being on the treatment [redacted] has been seizure free! He is still able to attend mainstream school! He can still eat (albeit small amounts), chew and swallow! He can still respond to your voice & his surroundings! He still enjoys the company of his friends & family! He still loves to hear stories & listen to others chatting with him! He is still AWARE! He can still smile & laugh - despite all that he has lost so far! He is comfortable & pain free! He HAS made a difference to the Battens community! He IS raising world wide awareness! He IS proving that fundamental research is VITAL! And he is loved & respected, more than words can say by a WHOLE town, neighbouring towns & areas, a nation & millions of people all over the world including PRINCE HARRY! Without this treatment he would be subject too immense pain & suffering! NICE, pull yourselves together & agree to the funding of this treatment in the UK! There might not be enough evidence for long term usage yet, because no one has had the opportunity to use it long term have they? How can they when it is such a new drug!? But so far there are no negatives! Give these children a chance, give this drug a chance to PROVE that it IS extremely beneficial & a worthwhile treatment for the UK to provide! Granted, at this moment in time, sadly it may be too late for those too far advanced to benefit from this treatment at present.

	BUT please, please help those who can be proven to be treated quickly & effectively when given access to this drug promptly! Please, at the very least, allow those few children who have been fortunate enough to start treatment already, continue! Stopping treatment will only make matters worse & their deaths will be on your hands! Use the evidence you've been given from those few Battens sufferers who have been given a chance to trial this drug effectively in the UK, AND the positive results from the EU & US users statistics & the benefits for children being given this drug; especially those who are already seeing huge benefits from receiving it now & those who have been given treatment before the onset of the disease has had natural chance to progress & destroy these children's abilities one by one! THEY ARE REMAINING SYMPTOM FREE!! It is not only the children with Battens that are benefiting from the use of this drug but also their entire families, friends, neighbours, colleagues, teachers, local health care providers etc (the list goes on). Myself and our neighbourhood are privy to this! The [redacted] family have mine & their whole towns support with this & we are all behind them 100% & will do everything possible to get their children the treatment they need and deserve! In being able to receive this treatment these children are able to live in comfort, pain free & lead as normal a life as possible. Spending precious, valuable time with their friends & families. Going to school, like all children should be able too. Go on holiday. Play with friends. Learn, grow, develop! Everything every child should be entitled too! With this treatment their siblings don't have to witness their parents performing life saving techniques on their brother or sister on a daily basis, whilst they're heavily convulsing & stopping breathing at the dinner table/in the bath/at school/in bed/watching tv/doing their homework!! They're not having to call 999 because their parents are unable too as they're trying to administer life saving drugs & perform CPR on their youngest children! They're not having to help administer drugs to their younger siblings because there's no one else there to help do so! They're not seeing and hearing the blue lights & wailers of the ambulances thundering down their street every day/week/month/year! They're not having to see the looks of desperation on their parents/friends/relatives/neighbours/strangers faces when people are struggling to comprehend & deal with the daily devastation that a life involving Battens throws at them. Never knowing when the cruelty & dangers of Battens will strike!

	BECAUSE this treatment has STOPPED all of that! THIS TREATMENT IS allowing them ALL to live relatively normal childhoods! It is taking the pressure off other innocent children who are also suffering at the effects of Battens! Yes their younger brother is still severely disabled but he's improving! And he certainly isn't getting worse! And they're able to see their little sister grow up with them normally, as they should! Yes their lives have been turned upside down & they all know nothing will ever be completely normal, YET! And they'll still have to live with hospital appointments & tests etc but this is the BEST line of hope & progress they've had in years & you're wanting to take that away from them!? Why? Think of the mental health & well being of the other siblings & family members also! And all the added stresses and strains this new fight is now causing! It's not fair NICE! The proof is out there! Utilise it! Children's lives are priceless! Please help them! If the drugs company thought it was beneficial to the patient on compassionate use then in my opinion that speaks volumes! [redacted] [redacted]

Early Diagnosis of CLN2 Disease Service Provision

Project Initiation Document

June 2018

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Early Diagnosis of CLN2 disease.

Company sponsored service provision

Supplied 03rd July 2018

Purpose of Document

The aim of this document is to define the service provision BioMarin (the company) proposes to provide for the early diagnosis of CLN2 disease. It also outlines the approach the company will undertake to ensure it is successfully implemented within the existing services. Finally, this document sets the basis by which the company will engage with the relevant stakeholders to align on the proposed service provision.

The service provision

The company will be offering [redacted] to support the early diagnosis of CLN2 disease. Specifically the company will be providing [redacted] at no cost [redacted]:

[redacted]

- an epilepsy gene panel in patients with onset of un-provoked seizure at age of 2 – 4 years, and in whom neuro-developmental co-morbidity has been diagnosed or suspected as reflected by any one of the following signs/symptoms: history language delay or regression, motor impairments or regression (such as ataxia, abnormal gait, etc), or an EEG or MRI abnormality indicative of a genetic cause of epilepsy.

[redacted]

[redacted]

[redacted]

[redacted]

Rationale for service provision

CLN2 disease, commonly presents non-specifically with seizures and a history of language development delay at 2–4 years of age. However diagnoses occurs on average at 5 years old: a full 2 years after average seizure onset and after significant neurodegeneration, by which point the patient has had significant irreversible neuro-cognitive functional decline. [1, 2] Given the potential for cerliponase alfa to stabilise disease progression, earlier identification of patients will likely maximise health gains the patient may have.

Patient general diagnostic journey is to initially present at general hospitals paediatric centres with development delay (e.g. language delay) and with initial seizures be seen in hospitals with paediatric departments and EEG centres. As such these centres will be the target for education and implementation of the additional early diagnosis service offering. Patient's diagnosis is often held back at this stage whilst paediatricians apply standard anti-epileptic drugs and

[1] Nickel M, Jacoby D, Lezius S, et al. Natural history of CLN2 disease: quantitative assessment of disease characteristics and rate of progression. Poster session presented at: The 12th Annual WORLD Symposium; February – March 2016;San Diego, CA.

[2] 4. Schulz, A., Miller, N., Mole, S.E., and Cohen-Pfeffer, J.L. Neuronal ceroid lipofuscinosis-2 (CLN2) natural history and path to diagnosis: International experts' current experience and recommendations on CLN2 disease, a type of Batten disease, resulting from TPP1 enzyme deficiency. Eur J Paediatr Neurol. 2015; 19: S119.

are referred late to tertiary centres who can conduct gene panel tests after refractory epilepsy.

Data from the US has shown that earlier diagnosis of CLN2 patients (as well as other conditions) is possible using epilepsy gene panels. In a recently published poster[3], of 176 gene panels used, 4 CLN2 diagnosis and 12 other definitive genetic conditions (Rett Syndrome, Dravet Syndrome, Epileptic encephalopathy etc) were made, thus yielding a diagnostic rate of 7%. The 4 CLN2 patients were diagnosed 1–2 years earlier than reported average (11.5 months from seizure onset to diagnosis versus 2–3 years).

The proposed service provision by the company is aimed at supporting early diagnosis of CLN2 disease. As outlined above, the company will offer at no cost to the NHS, epilepsy gene panels for the earlier identification of CLN2 patients. These gene panel would cover over 190 potential epilepsy causing mutations, supporting earlier care for patients.

Currently gene panels are used in diagnosing of patients who do not have sufficiently recognisable or distinctive symptoms for a diagnosis to be made using other methods including enzyme testing for specific diseases. In the case of patients with early onset seizures and neurodevelopment comorbidities, these are mainly used as a 2nd or even 3rd line due to a perceived lack of cost-effectiveness. The current 1st line tests include EEG, Brain - MRI as well as blood and cerebro-spinal fluid tests (Mercimek-Mahmutoglu et al. 2015)[4]. These tests are useful in raising suspicion but are not diagnostic. Evidence from the literature suggests that the diagnostic yield rate using these tests in patients with epilepsy are quite low, with gene panels or specific gene or metabolic

[3] Miller N et al. Behind The Seizure™: A No-cost, 125-gene Epilepsy Panel for Pediatric Seizure Onset Between 2–4 Years. Presented at the ACMG Annual Clinical Genetics Meeting: April 10–14, 2018, Charlotte, NC

[4] Mercimek-Mahmutoglu et al, Epilepsia 2015; 56(5): 706 - 715

enzyme tests often required later for a diagnosis to be made.

Based on discussions with the organisation of paediatric epilepsy network (OPEN) and CLN2 clinical experts, it is anticipated that providing [redacted] gene panel at no-cost to the NHS will result in earlier diagnosis of CLN2 patients, provided it is done in partnership with the existing medical genetics team to maximise the rate of uptake. In this way the process can potentially move from late confirmation of CLN2 diagnosis to earlier screening and diagnosis.

The earlier use of [redacted] gene panels will result in earlier diagnosis of CLN2 disease. It could also result in earlier diagnosis of other diseases such as Dravet syndrome, Rett Syndrome, GLUT-1 deficiency and Lennox Gestaut, which are often diagnosed late or misdiagnosed due to their non-specific symptoms and rarity. The earlier diagnosis of these diseases have several benefits including reducing the diagnostic odyssey and associated anxiety of not knowing what the condition is; better and more targeted disease management, e.g. patients with GLUT-1 deficiency could be put on ketogenic diet which will reduce the seizure severity and frequency; and reduction of costs of investigative diagnostic tests that will be accrued if gene panel use is delayed.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Managed Access Agreement

Cerliponase alfa for treating CLN2 Disease

Date of Agreement	TBC
NHS England	John Stewart
BioMarin	James Lennertz
BDFA	Harriet Lunnemann
Clinical lead	Professor Paul Gissen
NICE	Sir Andrew Dillon

1 Purpose of agreement

1.1 The objectives of the document as a whole are to embody a set of auditable measures that will be used to assess the compliance of this "Managed Access Agreement" in England and to ensure that all relevant stakeholders have a common understanding that such measures have the agreement and backing of all involved and will therefore be enforced.

1.2 This Managed Access Agreement has been drawn up by NHS England, BioMarin International Limited (the "Market Authorisation Holder" or "MAH"), BioMarin United Kingdom Limited (the "authorised seller") and NICE with the engagement of patient community experts and clinicians, and seeks to satisfy the requirements outlined below.

1.3 For the avoidance of doubt, the parties intend this Managed Access Agreement to be legally enforceable between them. The patient organisation and clinician signatories will use their best endeavours to commend the Agreement to their patients and colleagues and encourage compliance with the Agreement.

1.4 A Commercial in confidence ancillary agreement containing certain terms relating to the supply of Brineura® (cerliponase alfa) agreed between the licensed owner of cerliponase alfa (BioMarin Europe Limited) and NHS England is appended to this Agreement at Appendix B).

2 Background

2.1 The NICE evaluation has developed positive recommendations conditional on a Managed Access Agreement (MAA) being developed and agreed by key stakeholders in the use of cerliponase alfa in the NHS in England.

2.2 This MAA includes the following:

- A statement that sets out the clinical criteria for starting and stopping treatment with cerliponase alfa.
- Agreement between the MAH and NHS England on a financial arrangement for the total costs of cerliponase alfa throughout the duration of the managed access agreement.
- Agreement between the MAH and NHS England that ensures patients started on cerliponase alfa during the term of the Managed Access Agreement should be able to continue treatment until they and their NHS clinicians consider it appropriate to stop.

3 Commencement and period of agreement

3.1 This agreement shall take effect on the date of publication of the Guidance. It will remain in force until the earlier of: (i) publication of a reissued NICE HST guidance for cerliponase alfa or; (ii) for a maximum of 5 years. The MAH will provide the relevant data required for the review of the guidance on the product performance during the fourth year of the agreement. NICE will reissue guidance to the NHS in England based on a review of the data during the fifth year of the agreement.

4 Patient eligibility

4.1 To receive treatment, patients or their guardians must sign up to the 'Managed Access Patient Agreement' included in Appendix A to this Managed Access Agreement.

4.2 Patients are required to attend their clinics two times a year for assessment.

4.3 Children under the age of 3 will be excluded from the stopping criteria as natural decline in functional endpoints is not seen at this point. However, it is important to collect data in this population to support the future evaluation and research in children under 3.

4.4 Patients must be made aware of the start and stop criteria for receiving cerliponase alfa treatment:

4.5 Start Criteria[1]

All of the following are required before treatment is started:

[1] The start and stop criteria have been independently developed by clinical experts and patient advocacy group in discussions with patient families. BioMarin have not endorsed these criteria

- All patients must have a confirmed diagnosis of CLN2 on the basis of clinical information and enzymatic activity test
- The patient is not diagnosed with an additional progressive life limiting condition where treatment would not provide long term benefit e.g.; cancer or multiple sclerosis;
- The patient has a CLN2 Rating Scale ML Score of 2 or above.
- The patient is willing to comply with the associated monitoring criteria
- In addition, all patients can only start once a complete set of baseline assessments has been obtained, and they have signed the Managed Access Patient Agreement.

4.6 Stop Criteria[2]

Patients will cease therapy with cerliponase alfa, if any of the following apply:

- The Patient is non-compliant with assessments for continued therapy (non-compliance is defined as fewer than two attendances for assessment in any 14 month period excluding medical reasons for missed dosages);
- The Patient meets the stopping criteria as defined below in sections 4.7. and 4.8.
- The Patient is unable to tolerate infusions due to infusion related severe adverse events or other clinical concerns that cannot be resolved.

[2] The start and stop criteria have been independently developed by clinical experts and patient advocacy group in discussions with patient families. BioMarin have not endorsed these criteria

- The patient is diagnosed with an additional progressive life limiting condition where treatment would not provide long term benefit e.g.; cancer or multiple sclerosis

4.7 Stopping criteria for new patients (those who have never received treatment)[3]

This section applies only to those who start treatment at the age of 3 or more and who have not received treatment prior to the time at which this agreement comes into effect. The criteria for which new patients should be stopped from treatment due to non-response to treatment are:-

- A loss of more than two points (i.e. 3 or more points) on the CLN2 Rating Scale ML Score from baseline, during the first eighteen months of treatment and a total CLN2 rating scale score of less than 2;
    - A loss is defined as a decline in CLN2 rating scale ML score that has persisted for 3 or more infusions (i.e. after 6 weeks).

AND

- During the first eighteen months of treatment, a reduction in proxy reported patient quality of life of
    - ≥ 15 points on the PedsQL total score (which is three times the minimal clinically important difference[4]); and

[3] The start and stop criteria have been independently developed by clinical experts and patient advocacy group in discussions with patient families. BioMarin have not endorsed these criteria

[4] The accepted minimal clinically important difference (MCID) is 4.5 points for the PedsQL™ [Varni et al. Ambul Pediatr. 2003 Nov-Dec; 3(6):329-41]

0.2[5] drop in utility as measured by the EQ5D-5L and decline in CLN2 quality of life assessment of ≥ 15 points.

In the case of temporary illness, patients should be retested twice within 12 weeks to ensure that the decline is not as a result of temporary illness

4.8 Stopping criteria for Patients who are currently on treatment[6]

Patients who are 'currently on treatment' are defined as: (i) clinical trial patients; (ii) extension study; (iii) patients otherwise already receiving treatment for more than 12 months and have become a commissioning responsibility of NHS England; and (iv) patients who started on treatment during the term of the Managed Access Agreement and have been receiving treatment for over 18 months.

The criteria for which patients "currently on treatment" should be stopped from treatment due to non-response are:-

- A loss of more than one point (i.e. 2 or more points) on the CLN2 Rating Scale ML Score, in the previous twelve months treatment window and a total CLN2 rating scale score of less than 2;
    - A loss is defined as a decline in CLN2 rating scale ML score that has persisted for 3 or more infusions (i.e. after 6 weeks)
- OR

[5] A minimal clinically important difference of 0.24 based on distribution methods has been estimated. Walters SJ, Brazier JE. Qual Life Res. 2005;14:1523–32.

[6] The start and stop criteria have been independently developed by clinical experts and patient advocacy group in discussions with patient families. BioMarin have not endorsed these criteria

- Progression to an unreversed score of 0 on the CLN2 Rating Scales ML Score
    - Patients with a score of 0, should be retested twice within 12 weeks to ensure that decline is not as a result of temporal illness.

AND

- A reduction in proxy reported patient quality of life in the previous twelve month treatment window of
    - ≥ 15 points on the PedsQL total score (which is three times the minimal clinically important difference[7]); and
    - 0.2[8] drop in utility as measured by the EQ5D-5L and
    - Decline in CLN2 quality of life assessment of ≥ 15 points

4.9 If a patient is ill prior to an assessment, then the patient needs to be reassessed within 12 weeks and subsequent measures need to be considered from this point.

4.10 Patients who are taken off treatment will continue to be monitored for disease deterioration and supported with other clinical measures. These patients should continue to be assessed to allow gathering of important information.

5 Data collection and monitoring

5.1 Data will be collected from all patients who start during the term of this Managed Access Agreement. [redacted]

[7] The accepted minimal clinically important difference (MCID) is 4.5 points for the PedsQL™ [Varni et al. Ambul Pediatr. 2003 Nov-Dec; 3(6):329-41]

[8] A minimal clinically important difference of 0.24 based on distribution methods has been estimated. Walters SJ, Brazier JE. Qual Life Res. 2005;14:1523–32.

[redacted]

5.1.1 [redacted]

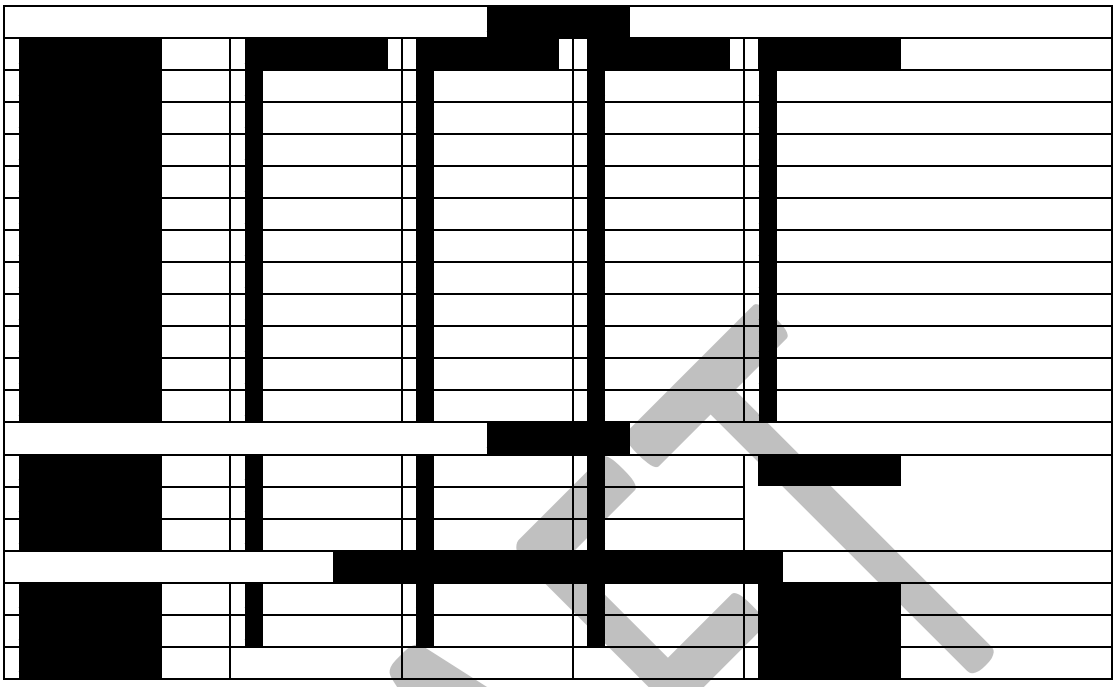
5.1.2 The treating clinician will be responsible for the timely collection of the anonymized clinical outcome and quality of life data and disseminate to NHS England.

5.1.3 The data will then be collated and anonymized by NHS England and sent to the MAH for analysis every six (6) months.

5.1.4 The MAH will be responsible for the analysis of the collated data and will provide access for NHS England to the results to assist it in assessing the clinical impact of cerliponase alfa on CLN2 disease.

5.2 [redacted]

[redacted]



[redacted]

[redacted]

[redacted]

[redacted]

6 Patient Appeal Process

6.1 If a patient (or patient's parents or person responsible for a patient) feels the assessments have been performed incorrectly or information not gathered appropriately, they have the right for a repeat set of assessments to be carried out at another LSD reference centre in England. Travel and associated costs will be at the patient's expense.

6.2 Reasonable adjustments will be made for patients who are unable to comply with the assessment by reasons of challenges completing assessments. These patient's stop criteria will be defined by individual agreement between the clinician and NHS England.

7 Ownership of the data

7.1 By agreeing to take part in the Managed Access Agreement patients will be asked to consent to have their demographic and clinical data collected by their treating clinician. The MAH will be responsible for the timely analysis of the data and submitting the relevant reassessment report to NICE in the fourth year of this agreement. The Analysed data will be owned by the MAH but shared with NHS England and NICE for the purpose of assessing the benefit of the treatment.

7.2 The data will be collected by the clinicians at the expert centres who have undertaken the relevant training prescribed by NHS England.

8 Funding

8.1 The treatment will be funded by NHS England from publication of the NICE guidance and the start of this Managed Access Agreement.

8.2 The MAH has registered a confidential patient access price with the Department of Health, and has agreed further commercial

arrangements with NHS England. These confidential arrangements, set out in the ancillary agreement (Appendix B), apply for the duration of the MAA. [redacted]

8.3 The Managed Access Agreement and therefore funding for cerliponase alfa expires after 5 years. At year four a comprehensive review will look at the benefits of cerliponase alfa, collectively. The MAH, NHS England and NICE then have the opportunity to renegotiate terms for another Managed Access Agreement as an option if a NICE positive evaluation cannot be given.

8.4 Patients will be informed about the duration of this Managed Access Agreement in the Managed Access Patient Agreement.

9 Exit strategy

9.1 If at the end of the 5 year Managed Access Agreement NICE does not recommend cerliponase alfa for NHS funding, NHS England funding for cerliponase alfa will cease to be available for all patients.

10 Ongoing Review of this Agreement

10.1 The measures determined to be used are based on best current information. It would be expected that more knowledge will be gained over the next few years; hence a reassessment of the criteria by all signatories to this agreement will be reassessed three years from the start of this agreement and adjusted accordingly.

10.2 A body of NHS England, the MAH, clinical experts and patient organization representatives will meet annually to consider how the prescribed criteria are working. They will meet under the chairmanship of NICE.

Signed by	**NHS England** **John Stewart**
Signed by	**Company** **James Lennertz, VP & General Manager**
Signed by	**Patient organisation** **Harriet Lunnemann**
Signed by	**Clinical Experts Group** **Professor Paul Gissen**
Signed by	**NICE** **Professor Carole Longson / Sir Andrew Dillon**

Appendix A

Enzyme Replacement Therapy (ERT) Cerliponase alfa (Brineura) for CLN2 Managed Access Patient Agreement

NICE have approved reimbursement of Cerliponase Alfa, licensed as Brineura®, subject to the collection of auditable measures that will be used to assess the compliance of a Managed Access Agreement in England and to ensure that all relevant stakeholders have a common understanding that such measures have the agreement and backing of all involved and will therefore be enforced.

The NICE Managed Access Agreement includes:-

- A protocol that sets out the clinical criteria for starting and stopping treatment with cerliponase alfa.
- Assurance from BioMarin International limited (the "Marketing Authorisation Holder" or "MAH"), and BioMarin United Kingdom Limited ("BUKL" – the authorized seller), that it will collaborate with the BDFA and NHS England to collect your pseudonymized data. The data will be used by NICE to inform a review no more than 5 years after publication of the guidance.
- Agreement between the MAH and NHS England on a financial arrangement for the total costs of cerliponase alfa throughout the duration of the managed access agreement.
- Agreement between the MAH and NHS England that ensures patients started on cerliponase alfa during the term of the Managed Access Agreement period should be able to continue treatment until they and their NHS clinicians consider it appropriate to stop.

1. Patient Eligibility[9]

The clinical community and BDFA feel it is appropriate and right that all patients have access to cerliponase alfa (Brineura®) in England.

- Cerliponase alfa will be added to existing standard treatment.
- Patients must be made aware of the start and stop criteria for receiving cerliponase alfa treatment and are required to attend their clinics 2 times for assessment within a 14 month period.
- All patients or their guardians must sign up to the 'Managed Access Patient Agreement' to receive treatment.

2. Access to treatment and data collection

- The criteria in this Managed Access Agreement have been used because they formed part of the phase III clinical trial and have been the basis on which the European licence for Brineura was granted.
- A distinction has been made between those patients who are new to treatment and the group of patients who have been on treatment in England prior to the commencement of this managed access agreement
- Allowance is also made for children under the age of 3, as natural decline in functional endpoints is not evaluable at this point. Children initiated on cerliponase alfa therapy before the age of 3 will be excluded from the stopping criteria mentioned until they attain the age of 3, wherein the stopping criteria for patients "currently on treatment" will apply.

[9] The start and stop criteria have been independently developed by clinical experts and patient advocacy group in discussions with patient families. BioMarin have not endorsed these criteria

3. Start Criteria [10]

- Patients must have a confirmed diagnosis of CLN2 on the basis of clinical information and enzymatic activity tests;
- The patient is not diagnosed with an additional progressive life limiting condition where treatment would not provide long term benefit e.g.; cancer or multiple sclerosis;
- The patient has a CLN2 Rating Scale ML Score of 2 or above.
- Patients can only start once a full set of baseline criteria has been obtained, and they have signed the Managed Access Patient Agreement.
- Patients / Parents will be expected to attend their clinic two times a year for assessment within a 14 month period.
- Patients / Parents will be informed about the strict requirement for attendance as set out in this patient agreement document, an appendix to the Managed Access Agreement.
- The patient is willing to comply with the associated monitoring criteria

In the event of the patient being unable to maintain the above criteria, the implementation of the stop criteria will be discussed with the Patient / Parent.

4. Stop Criteria[11]

[10] The start and stop criteria have been independently developed by clinical experts and patient advocacy group in discussions with patient families. BioMarin have not endorsed these criteria

[11] The start and stop criteria have been independently developed by clinical experts and patient advocacy group in discussions with patient families. BioMarin have not endorsed these criteria

4.1 Stopping criteria for new patients (those who have never received treatment)

This section applies only to those who start treatment at the age of 3 or more. The criteria for which new patients should be stopped from treatment due to non-response to treatment is:-

- A loss of more than two points (i.e. 3 or more points) on the CLN2 Rating Scale ML Score from baseline, during the first eighteen months of treatment and a total CLN2 rating scale score of less than 2;
    - A loss is defined as a decline in CLN2 rating scale ML score that has persisted for 3 or more infusions (i.e. after 6 weeks)

AND

- During the first eighteen months of treatment, a reduction in proxy reported patient quality of life of
    - ≥ 15 points on the PedsQL total score (which is three times the minimal clinically important difference[12]); and
    - 0.2[13] drop in utility as measured by the EQ5D-5L and
    - Decline in CLN2 quality of life assessment of ≥ 15 points

[12] The accepted minimal clinically important difference (MCID) is 4.5 points for the PedsQL™ [Varni et al. Ambul Pediatr. 2003 Nov-Dec; 3(6):329-41]

[13] A minimal clinically important difference of 0.24 based on distribution methods has been estimated. Walters SJ, Brazier JE. Qual Life Res. 2005;14:1523–32.

In the case of temporary illness, patients should be retested twice within 12 weeks to ensure that the decline is not as a result of temporary illness

4.2 Stopping criteria for Patients who are currently on treatment

Patients who are 'currently on treatment' are defined as: (i) clinical trial patients; (ii) extension study participants; (iii) patients otherwise already receiving treatment and have become a commissioning responsibility of NHS England; and (iv) patients who started on treatment during the term of the Managed Access Agreement and have been receiving treatment for over 18 months.

The criteria for which patients "currently on treatment" should be stopped from treatment due to non-response are:-

- A loss of more than one point (i.e. 2 or more points) on the CLN2 Rating Scale ML Score, in a twelve months treatment window and a total CLN2 rating scale score of less than 2;
    - A loss is defined as a decline in CLN2 rating scale ML score that has persisted for 3 or more infusions (i.e. after 6 weeks)
- OR
- Progression to an unreversed score of 0 on the CLN2 Rating Scales ML Score
    - Patients with a score of 0, should be retested twice within 12 weeks to ensure that decline is not as a result of temporal illness.

AND

- A reduction in proxy reported patient quality of life in a twelve month treatment period of

- ≥ 15 points on the PedsQL total score (which is three times the minimal clinically important difference[14]); and
- 0.2[15] drop in utility as measured by the EQ5D-5L and
- Decline in CLN2 quality of life assessment of ≥ 15 points

Patients will cease to quality for treatment if they miss more than 2 infusions in any 14 month period, excluding medical reasons for missing dosages.

If a patient is ill prior to an assessment, then the patient needs to be reassessed within 12 weeks and subsequent measures need to be considered from this point.

If you feel that you or your child will be able to comply with the above please fill in your details below and sign for reimbursed treatment to begin.

If you meet the start criteria for cerliponase alfa and choose to receive cerliponase alfa your clinician will be monitoring you or your child for demonstrable benefit.

The Managed Access Agreement (and therefore agreed funding for cerliponase alfa) expires after 5 years. At year four a comprehensive review will look at the benefits of cerliponase alfa, collectively. Any funding beyond such 5-year term will be conditional on NHS England agreeing the terms of such funding with BioMarin, the manufacturer of cerliponase alfa.

Accordingly, there are currently no arrangements to enable access to cerliponase alfa to be available as part of standard NHS care following the expiry of the MAA.

[14] The accepted minimal clinically important difference (MCID) is 4.5 points for the PedsQL™ [Varni et al. Ambul Pediatr. 2003 Nov-Dec; 3(6):329-41]

[15] A minimal clinically important difference of 0.24 based on distribution methods has been estimated. Walters SJ, Brazier JE. Qual Life Res. 2005;14:1523–32.

Any continued access to cerliponase alfa beyond this point will be subject to consideration by NICE and publication of further recommendations. If NICE does not recommend cerliponase alfa in its further review at that time patients will discontinue NHS treatment with cerliponase alfa.

You or the parents of the child must sign this Patient Managed Access Agreement as part of the start criteria for treatment.

5. Data Protection

[redacted] required as part of this Managed Access Agreement and you consent to all collected data from your monitoring visits to the hospital, [redacted] to be entered and stored into a database, for no longer than necessary for the purpose of the Agreement and in any case no more than 5 years after publication of the guidance.

The data will be entered into a commercial database. If you object to your data being collected into this database your treating clinician may be able to offer an alternative non-commercial database.

Although researchers hope the data collected will lead to better future patient outcomes, it is your right to opt out from the data collection

By agreeing to your information being entered into the database you also explicitly consent to that information being used to fulfil the purposes of the database as described below. Patient or the respective guardian can revoke their consent by informing their treating physician and this will result in them being taken off treatment

The purposes of the database are to: (i) characterise and describe the CLN2 population as a whole, including the heterogeneity, progression and natural history of CLN2; (ii) to evaluate the long-term effectiveness and safety of Brineura (cerliponase alfa): (iii) to help the CLN2 medical community with the

development of recommendations for monitoring subjects and reports on subject outcomes to optimise subject care; (iv) to collect data on other treatment paradigms, evaluate the prevalence of their use and their effectiveness; (v) to characterise the effects of long term treatment of cerliponase alfa treatment in subjects; and (vi) to collect additional data to: (a) help broaden knowledge of identified and potential risks of cerliponase alfa, as well as increase the size of the safety database and possibly provide new information on use in identified subgroups (pregnancy, hepatic and renal impairment, cardiac impairment); and (b) to help evaluate long-term effectiveness of cerliponase alfa.

Data collected will be shared with NHS England, NICE and the MAH and may be stored on static databases and portable devices, both inside and outside of the EEA, including in the United States of America, in countries which may not provide a level of data protection equivalent to countries in the EEA. NHS England, NICE and the MAH will take the necessary steps to ensure the safety of the data when transferred or stored outside of the EEA.

Research papers and other scientific findings may be developed and published based on information provided in the registry and by signing below you understand and consent to your data being used anonymously for such scientific and academic purposes.

If you feel that you and/or your child will be able to comply with the above please fill in your details below and sign for reimbursed treatment to begin.

Patient Name: _____

Parent/Carer Name: _____

Signature: _____

Date: _____

Name of Clinician: _____

Signature of Clinician: _____

Name of Clinician: _____

Date: _____

Appendix B

Ancillary Agreement between BioMarin International Limited and NHS England

(The ancillary agreement contains commercial-in-confidence information and has been redacted from the managed access agreement)

Highly Specialised Technology Evaluation

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

Company's Responses to NICE Briefing Document

Supplied 17th August 2018

Responses to issues raised in briefing document

This document provides the company's responses to the issues identified by NICE in their assessment of the clinical data and proposed managed access agreement (MAA), as outlined in their briefing document sent to NHS England and BioMarin on 16th May, 2018.

The company welcomes the committee's comment indicating satisfaction that the proposed MAA has been developed with all relevant stakeholders including patient experts, clinical experts, NHS England and the company as outlined in paragraph 10 of the briefing document.

Issue 1: Partial stabilisation – continued disease progression for late stabilisers after 96 weeks at the rate observed between week 17 and 96

Company position

The committee concluded that late stabilisers will see continued disease progression after 96 weeks at the rate observed between week 17 and 96. The company's assumption of stabilisation in all patients after 96 weeks was rejected due to insufficient data after 96 weeks. [redacted]

[redacted]. More details on the long term results as well as the steps used in updating the health economic model and the impact on the NICE preferred ICER are provided in the accompanying slide deck (dated 07th September, 2018).

Issue 2: Lack of data quantifying the "wider benefits" of early use of gene panels and inappropriate modelling of the benefits

Company position

The company acknowledges the committee's concern that there were insufficient evidence to enable quantification of the wider benefits of the early use of gene panels. As such the company has provided additional data from both "real world programs" and literature evidence that it hopes will provide greater confidence to the committee on the tangible benefits the proposed campaign will have. In addition the company has updated the approach used in modelling the benefits of the gene panel program to address the concerns the committee had. The additional data and the revised modelling approach are provided in the accompanying slide deck as well as the section in this document on integration of early diagnosis service offering.

Issue 3: Potential ethical considerations around the eligibility criteria

Company position

The company acknowledges the committee's concern about potential ethical consideration in specifying eligibility criteria (paragraph 11 of the briefing document). However as briefly mentioned during the 2nd committee meeting, the proposed starting criteria was developed by the clinical and patient experts and received the backing of family members of affected children during a focus group discussion convened by the patient organisation to survey the perspectives of the patient community on the proposed eligibility criteria.

Issue 4: Additional data to be collected as part of the managed access agreement

Company position

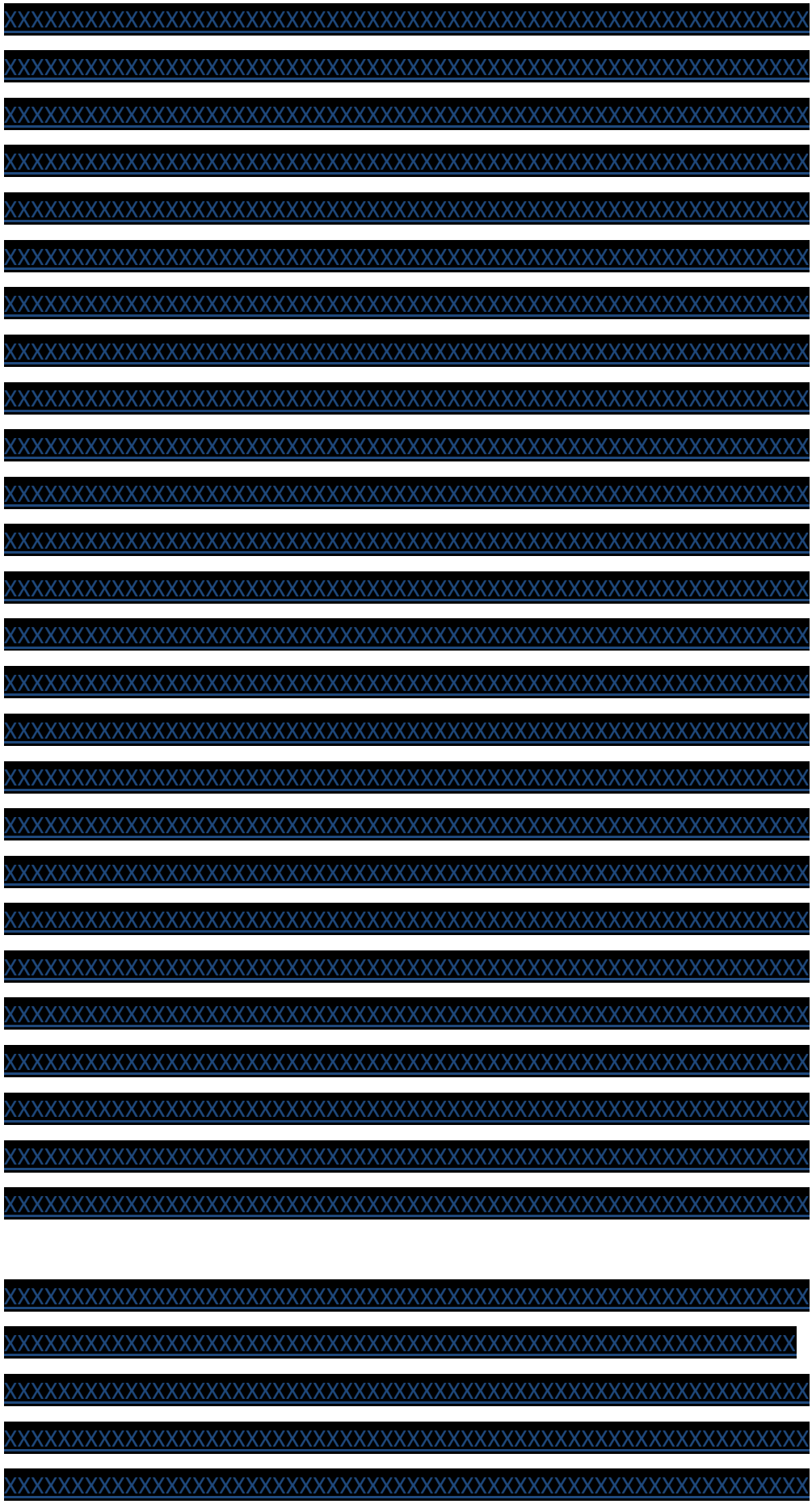
In Paragraph 14 of the briefing document, the committee recommended collection of additional outcomes (in addition to those already outlined in the proposed MAA) to address areas of perceived clinical uncertainty. The company notes that some of these outcomes were already included in the proposed MAA, but acknowledges these may not be immediately obvious. As such the MAA has been updated to provide additional clarity on what information each of the outcome assessments. Provided below is our detailed response to each of the additional outcomes recommended for collection by the committee, and the necessary updates that have been made to the MAA. [redacted] An updated table of outcome assessments to be collected as part of the MAA is in appendix 1 of the document.

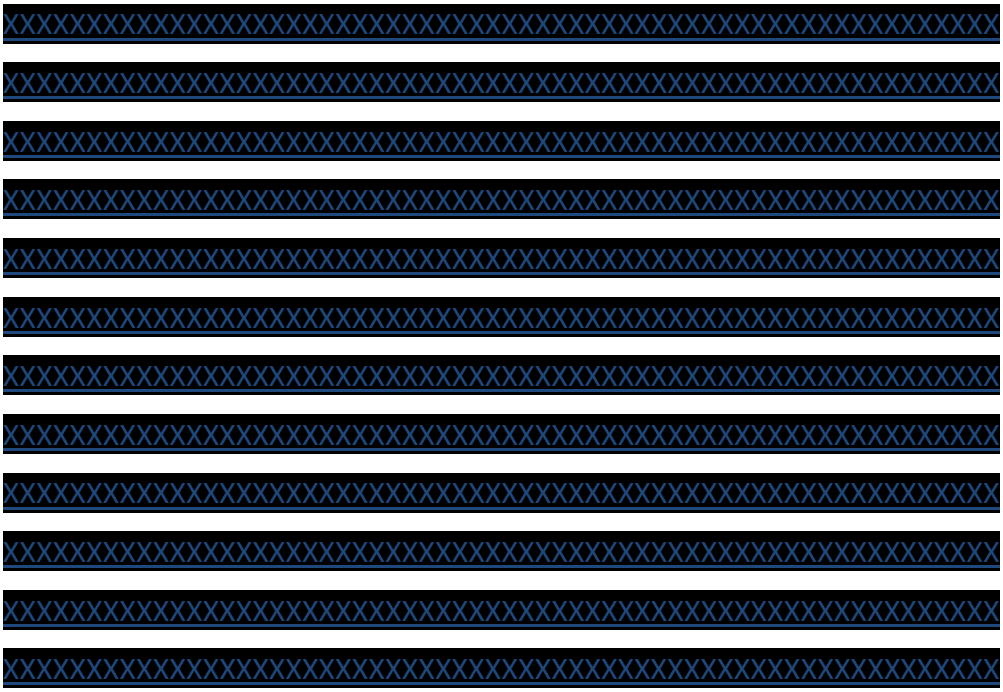
[redacted]

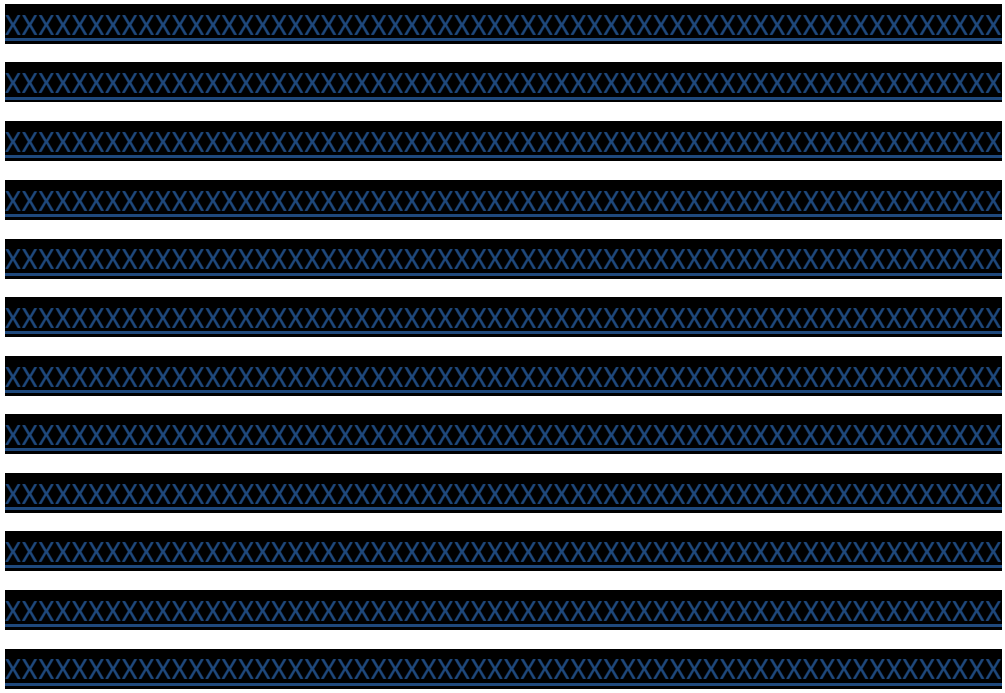
[redacted]

[redacted]

[redacted]







[redacted]

[redacted]

[redacted]

Company response

1. As part of the proposed MAA, the MAH will offer a diagnostic program aimed at supporting early diagnosis of CLN2 disease. Specifically the MAH will be providing at no cost to the NHS, [redacted] an epilepsy gene panel in patients with onset of un-provoked seizure at age of 2 – 4 years of age, and neuro-developmental co-morbidity is present or suspected.
2. [redacted] A greater description is available in the attached Project Initiation Document (PID).

3. It is anticipated that the offering will result in gene panels being used much earlier (than current practice) leading to earlier diagnosis of CLN2 disease and other diseases such as Dravet, GLUT-1 deficiency and Lennox Gestaut, which are often diagnosed late or misdiagnosed due to their non-specific symptoms and rarity.
4. The earlier diagnosis of these diseases have several benefits including (i) **improved quality of life for patients and family** due to a number of factors including reducing the diagnostic odyssey and associated anxiety of not knowing what the condition is; better and more targeted disease management, e.g. patients with GLUT-1 deficiency could be put on ketogenic diet which will reduce the seizure severity and frequency; and (ii) **cost savings to the health system,** due to direct use of these "no-cost" gene panels in lieu of "paid for" gene panels being used at a later time point in the NHS, as well as reduction of downstream investigative diagnostic tests avoided due to early gene panel use
5. 

   Further details on the early diagnosis campaign, including the offering, the potential benefits and cost savings as well as the implementation strategy and monitoring approach are contained in the Project Initiation Document.

Appendix 1

[redacted]

[redacted]				
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
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[redacted]				
[redacted]	[redacted]		[redacted]	[redacted]
[redacted]	[redacted]		[redacted]	[redacted]
[redacted]				[redacted]

Integration of early diagnosis service offering

BioMarin will be offering a series of programmes to support the early diagnosis of CLN2 disease. Specifically BioMarin will be providing at no cost [redacted] an epilepsy gene panel in patients with onset of un-provoked seizure at age of 2 – 4 years of age, and neuro-developmental co-morbidity is suspected. This gene panel offering will be rolled out in collaboration with the regional medical genetics services to ensure an efficient integration with the existing services. More details on the service offering can be found in the project initiation document in the Early Diagnosis Offering section of this document

Detailed below are the steps undertaken to model the impact of introducing the no-cost gene panel offering within the health economic model.

1. Step 1: Estimation of number of gene panels used

The gene panel campaign will be targeted mainly [redacted] As per the NICE guidance, all patients aged 2 – 4 years presenting with unprovoked seizure will be referred to see a paediatrician with specialist interest in epilepsy within 2 weeks of the incident. The annual number of gene panels used are estimated as follows:

- Based on the hospital episode statistics data 2016 -17; 4995 patients (across all age groups) will have a 1st paediatric epilepsy appointment for the first time, of which 1009 patients will be aged 2 – 4 years of age[1].
- Assuming [redacted][2] of patients presenting with seizures have unprovoked seizures with presumed or diagnosed neuro-developmental comorbidities present, then potentially [redacted] patients will be eligible every year for the gene panel.

[redacted]

[1] Estimated that 20.2% of paediatric epilepsy 1st appointments are due to patients aged 2- 4 years based on the hospital episodes statistics database.

[2] [redacted]

2. Step 2: Estimation of cost savings and benefits due to earlier use of gene panel

The cost savings **per CLN2 patient diagnosed** as a result of the introduction of the gene panel campaign will consist of:

I. Total cost of NHS gene panels / [redacted] avoided due to patients using the BioMarin gene panels or [redacted]

II. Costs calculated in I divided by the number of new CLN2 diagnosis per year (which is currently estimated as 5 based on known incidence numbers)

It has also been assumed that earlier diagnosis of epilepsies will result in improvement in quality of life for patients and their family. Evidence from the literature has indicated that a ≥1 month diagnostic delay is associated with poorer outcomes (such as reduced IQ scores, vineland-adaptive scores which persist for several years) in patients with epilepsy (Berg et al. Epilepsia. 2014 Jan; 55(1): 123–132).[3]

Although there is a significant body of qualitative evidence in the literature on the quality of life benefit on patients and their families of early diagnosis of rare diseases including those presenting with seizures, we were unable to find a quantitative estimate. Nevertheless we have estimated the potential quality of life benefit due to early treatment using Lennox Gestaut and Dravet Syndrome as proxies. In summary based on evidence from the literature, patients with Lennox Gestaut and Dravet Syndrome who respond to treatment have a utility benefit of between 0.068 and 0.212 depending on their degree of response.

[3] Berg et al. Epilepsia. 2014 Jan; 55(1): 123–132.

Based on clinical trial efficacy results for new targeted therapies such as rufinamide and stiripendol, which provides response rates, the estimated QALY benefit of treating patients with Lennox Gestaut or Dravet A syndrome is between 0.04 and 0.12 QALYS. Hence as a proxy we have conservatively assumed that patients diagnosed with Lennox Gestaut, Dravet syndrome or similar diseases through the gene panel, will accrue a QALY of 0.05 QALY in the 1st year only.

The QALYs gained due to the gene panel campaign are summed and **divided by the number of new CLN2 diagnosis per year (which is currently estimated as 5 based on known incidence numbers) to get QALY gained per CLN2 patient diagnosed.**

Early Diagnosis of CLN2 Disease Service Provision

Project Initiation Document

August 2018

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Early Diagnosis of CLN2 disease.

Company sponsored service provision

Supplied 17th August 2018

Purpose of Document

The aim of this document is to define the service provision BioMarin (the company) proposes to provide for the early diagnosis of CLN2 disease. It also outlines the approach the company will undertake to ensure it is successfully implemented within the existing services. Finally, this document sets the basis by which the company will engage with the relevant stakeholders to align on the proposed service provision.

The service provision

The company will be offering [redacted] to support the early diagnosis of CLN2 disease. Specifically the company will be providing [redacted] at no cost [redacted]:

[redacted]

- an epilepsy gene panel in patients with onset of un-provoked seizure at age of 2 – 4 years, and in whom neuro-developmental co-morbidity has been diagnosed or suspected as reflected by any one of the following signs/symptoms: history language delay or regression, motor impairments or regression (such as ataxia, abnormal gait, etc), or an EEG or MRI abnormality indicative of a genetic cause of epilepsy.

[redacted]

[redacted]

[redacted]

[redacted]

Rationale for service provision

CLN2 disease, commonly presents non-specifically with seizures and a history of language development delay at 2–4 years of age. However diagnoses occurs on average at 5 years old: a full 2 years after average seizure onset and after significant neurodegeneration, by which point the patient has had significant irreversible neuro-cognitive functional decline. [4, 5] Given the potential for cerliponase alfa to stabilise disease progression, earlier identification of patients will likely maximise health gains the patient may have.

Patient general diagnostic journey is to initially present at general hospitals paediatric centres with development delay (e.g. language delay) and with initial seizures be seen in hospitals with paediatric departments and EEG centres. As such these centres will be the target for education and implementation of the additional early diagnosis service offering. Patient's diagnosis is often held

[4] Nickel M, Jacoby D, Lezius S, et al. Natural history of CLN2 disease: quantitative assessment of disease characteristics and rate of progression. Poster session presented at: The 12th Annual WORLD Symposium; February – March 2016;San Diego, CA.

[5] 4. Schulz, A., Miller, N., Mole, S.E., and Cohen-Pfeffer, J.L. Neuronal ceroid lipofuscinosis-2 (CLN2) natural history and path to diagnosis: International experts' current experience and recommendations on CLN2 disease, a type of Batten disease, resulting from TPP1 enzyme deficiency. Eur J Paediatr Neurol. 2015; 19: S119.

back at this stage whilst paediatricians apply standard anti-epileptic drugs and are referred late to tertiary centres who can conduct gene panel tests after refractory epilepsy.

Data from the US has shown that earlier diagnosis of CLN2 patients (as well as other conditions) is possible using epilepsy gene panels. In a recently published poster[6], of 176 gene panels used, 4 CLN2 diagnosis and 12 other definitive genetic conditions (Rett Syndrome, Dravet Syndrome, Epileptic encephalopathy etc) were made, thus yielding a diagnostic rate of 7%. The 4 CLN2 patients were diagnosed 1–2 years earlier than reported average (11.5 months from seizure onset to diagnosis versus 2–3 years). [redacted]

The proposed service provision by the company is aimed at supporting early diagnosis of CLN2 disease. As outlined above, the company will offer at no cost to the NHS, [redacted] epilepsy gene panels for the earlier identification of CLN2 patients. These gene panel would cover over 190 potential epilepsy causing mutations, supporting earlier care for patients.

Currently gene panels are used in diagnosing of patients who do not have sufficiently recognisable or distinctive symptoms for a diagnosis to be made using other methods including enzyme testing for specific diseases. In the case of patients with early onset seizures and neurodevelopment comorbidities, these are mainly used as a 2nd or even 3rd line due to a perceived lack of cost-effectiveness. The current 1st line tests include EEG, Brain - MRI as well as blood and cerebro-spinal fluid tests (Mercimek-Mahmutoglu et al. 2015)[7]. These tests are useful in raising suspicion but are not diagnostic. Evidence from the literature suggests that the diagnostic yield rate using these tests in patients

[6] Miller N et al. Behind The Seizure™: A No-cost, 125-gene Epilepsy Panel for Pediatric Seizure Onset Between 2–4 Years. Presented at the ACMG Annual Clinical Genetics Meeting: April 10–14, 2018, Charlotte, NC

[7] Mercimek-Mahmutoglu et al, Epilepsia 2015; 56(5): 706 - 715

with epilepsy are quite low, with gene panels or specific gene or metabolic enzyme tests often required later for a diagnosis to be made.

Based on discussions with the organisation of paediatric epilepsy network (OPEN) and CLN2 clinical experts, it is anticipated that providing [redacted] gene panel at no-cost to the NHS will result in earlier diagnosis of CLN2 patients, provided it is done in partnership with the existing medical genetics team to maximise the rate of uptake. In this way the process can potentially move from late confirmation of CLN2 diagnosis to earlier screening and diagnosis.

The earlier use of [redacted] gene panels will result in earlier diagnosis of CLN2 disease. It could also result in earlier diagnosis of other diseases such as Dravet syndrome, Rett Syndrome, GLUT-1 deficiency and Lennox Gestaut, which are often diagnosed late or misdiagnosed due to their non-specific symptoms and rarity. The earlier diagnosis of these diseases have several benefits including reducing the diagnostic odyssey and associated anxiety of not knowing what the condition is; better and more targeted disease management, e.g. patients with GLUT-1 deficiency could be put on ketogenic diet which will reduce the seizure severity and frequency; and reduction of costs of investigative diagnostic tests that will be accrued if gene panel use is delayed.

Highly Specialised Technology Evaluation

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

Addendum to Company's Responses to NICE Briefing Document

Supplied 12th September 2018

The company is providing the following additional scenarios for consideration at the committee hearing taking place on Wednesday 19 September 2018. These scenarios have been requested by the clinical experts based on their strong opinion that the integration of the early diagnosis offering will result in future CLN2 patients diagnosed at a combined ML score of either 5 or 6.

For context below is a statement from a clinical expert[1] with their perspective on the potential outcomes of an early diagnosis campaign which provides a basis of integration of this scenario in the discussion on the 19th September.

[redacted]

This opinion is supported by recently published evidence showing the median age of first seizures in an observational cohort study of natural history patients from two independent international data sets was 37·0 months (interquartile range 35·0–42·0

[redacted]

months).[2] At this age, patients will be a score of between 5 and 6 as reflected by the natural history curve (see figure below). [1] Given the objective of the early diagnosis offering XXXXXXXXX[3] will be to diagnose patients XXXXXXXXX XXXXXXXXX, it is anticipated with this early diagnosis campaign implemented patients will be diagnosed at the score of 5 and/or 6.

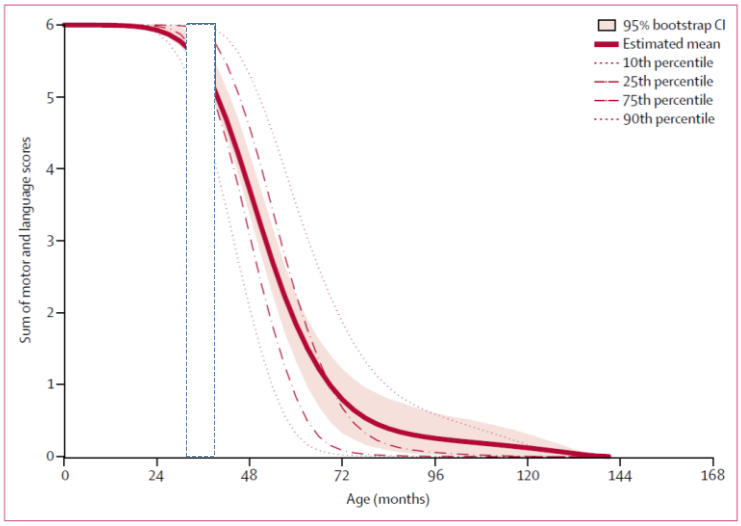

Figure 1: Longitudinal motor-language scores for CLN2 patients (n = 41). Blue dotted lines reflect interquartile age of onset of first seizures (35.0 to 42.0 months). Blue shaded rectangle indicates score of patients at onset of first seizures. Adapted from figure 4 in Nickel et al, The Lancet Child & Adolescent Health, 2018: 2 (8); 582-590

[2] Nickel et al. Disease characteristics and progression in patients with late-infantile neuronal ceroid lipofuscinosis type 2 (CLN2) disease: an observational cohort study. The Lancet Child & Adolescent Health, 2018: 2 (8); 582-590

[3] Refer to Early Diagnosis Offering Project Initiation Document (provided 17th August, 2018)

Table 1: Additional scenarios integrating benefits of early diagnosis offering. NICE preferred scenario and updated scenario (presented in August submission) added for context.

Scenario	Description	Undiscounted QALYs	XXXXXXXXX
NICE Preferred Scenario	▪Starting population is conservative early diagnosis cohort ▪No early diagnosis service offering ▪Partial stabilisation: Late stabilisers continued to progress at same rate	XXXX	XXXXXXXXX
Updated scenario	NICE preferred scenario with the following changes: ▪Starting population is conservative early diagnosis cohort ▪Early diagnosis service offering with uptake curve ▪Reduction in progression for late stabilisers after 96 weeks	XXXX	XXXXXXXXX
Additional Scenario 1	Updated scenario with following change: ▪Starting population have ML score of 6 only	XXXX	XXXXXXXXX
Additional Scenario 2	Updated scenario with following change: ▪Starting population all have ML score of 6 and 5 only (50% split)	XXXX	XXXXXXXXX
Additional scenario 3	Updated scenario with following change: ▪Starting population majority have ML score of 6 (40%) and 5 (40%). ▪20% of patients will still be diagnosed at ML score of 2 (5%), 3 (5%) and 4 (10%)	XXXX	XXXXXXXXX

DBS CLN2 Testing Metrics [redacted]
(Update- July 30 2018)

Date of preparation July 30 2018

XXXXXX XXXXXX XXXXXX XXXXXX XXXXXX XXXXXX XXXXXX XXXXXX
XXXXXX XXXXXX XXXXXX XXXXXX XXXXXX XXXXXX XXXXXX XXXXXX

Date of preparation July 30 2018

Date of preparation July 30 2018

[redacted]

[redacted]

Date of preparation July 30 2018

[redacted]

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Date of preparation July 30 2018

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[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

Date of preparation July 30 2018

THANK YOU

Cerliponase alfa for treating neuronal ceroid lipofuscinosis type 2

Company's Supplementary Information 07th September 2018

For HST evaluation only

Summary of materials provided

This slide deck

Slide deck

- Real world evidence on gene panel outcomes enabling quantification of wider benefits
- Longer term clinical trial data indicating durability of treatment efficacy
- Overview of changes to health economic model informing NICE Preferred scenario

Company response document

- Company response to briefing document from NICE addressing issues raised by committee
- Project Initiation Document providing details on Early Diagnosis Service Offering

Other documents

- Previous and Updated Health Economic Model
- Updated Managed Access Agreement

Executive Summary

We request the committee kindly reconsider the following conclusions made in it's evaluation contained in the briefing document in light of the additional evidence provided in the following slide deck

- Conclusion 1: Partial stabilisation – continued disease progression for late stabilisers after 96 weeks at the rate observed between week 17 and 96

[redacted]

  - Transition probabilities in the model has been updated to reflect slowing of disease progression in late stabilisers

- Conclusion 2: lack of data quantifying the "wider benefits" of early use of gene panels
  - Real world evidence (**slides 21-25**) from USA [redacted] where the company has run the proposed gene panel campaign, to allow the quantification of the wider benefits (proportion of gene panels with positive disease diagnosis)
  - Supported by literature evidence on (i) diagnostic yield rates of gene panels in age group of interest (**slide 27 - 29**); (ii) quality of life benefit for patients with a positive molecular diagnosis (**slide 26**)

- In addition to accompany this slide deck a word document providing complete response to the briefing document is provided

Summary of Health Economic Model Changes (1/3)

The following changes have been made on the health economic model informing NICE's preferred scenario

- Integration of longer term data showing slowing down of disease progression

[redacted]

  - Hence instead of using a constant progression rate (ERG Analysis TPs sheet I34) from week 17 onwards for late stabilisers, the following transition probabilities were used.

  i. wk 17 – 48: ERG Analysis TPs sheet G51;

  ii. wk 48 – 96: ERG Analysis TPs sheet G58;

  iii. wk 96 onwards: ERG Analysis TPs sheet G66;

[redacted]

Summary of Health Economic Model Changes (2/3)

The following changes have been made on the health economic model informing NICE's preferred scenario

- Integration of gene panel data supporting better quantification of wider benefits
  - Change 1: Previous version assumed a diagnosis yield rate of [redacted] (see cell E33 of Commercial Offering Sheet)

[redacted]

  - Change 2: Previous version assumed additional cost savings due to avoidance of MRI and EEG costs in non-CLN2 diagnosis due to earlier diagnosis using gene panel.
    - Although the company feels strongly that these cost-savings will be realisable in real settings, given the absence of specific data enabling its quantification these costs have been removed.
  - Change 3: Previous version did not include the cost-savings that will be accrued due to the company sponsored TPP1 dry blood tests that will be provided as part of the early diagnosis service offering.
    - See Cells E18 and E49 in Commercial offering Sheet.

Summary of Health Economic Model Changes (3/3)

The following changes have been made on the health economic model informing NICE's preferred scenario

Results

To view results in HE model, select relevant scenario by changing Cell N32 of Summary Page Sheet

NICE Preferred Scenario

- NICE Preferred scenario

[redacted]

Updated scenario

[redacted]

Longer Term Clinical Trial Data
(interim results from ongoing 202 study)

The information detailed in these slides are marked as academic-in-confidence

Preliminary data not validated

Longer term clinical trial data indicates a trending towards disease stabilization with an observable reduction in the rate of decline

See next slides for statistical outputs informing this table

Updated 190-202 Results: April 2018 Data Cut (1/11)

Updated 190-202 Results: April 2018 Data Cut (2/11)

Updated 190-202 Results: April 2018 Data Cut (3/11)

Updated 190-202 Results: April 2018 Data Cut (4/11)

Updated 190-202 Results: April 2018 Data Cut (5/11)

Updated 190-202 Results: April 2018 Data Cut (6/11)

Updated 190-202 Results: April 2018 Data Cut (7/11)

Updated 190-202 Results: April 2018 Data Cut (8/11)

Updated 190-202 Results: April 2018 Data Cut (9/11)

Updated 190-202 Results: April 2018 Data Cut (10/11)

Updated 190-202 Results: April 2018 Data Cut (11/11)

Epilepsy Gene Panel Testing Results
(Real World Evidence)

The information detailed in these slides are marked as academic-in-confidence

Epilepsy Gene Panel Program EU & US Results

			US Results (176 tests completed). Gene panel has 125 genes [i]			
			All Molecular Diagnosis	CLN2 Diagnosis		
Total number of MDx			12	4		
Dx Yield			6.8%	2.3%		
Age range (months)			46.1	46.3		

Diagnosis of CLN2 disease was 1-2 years earlier than reported average of diagnosis (about 5 years [ii])

Molecular Diagnosis (MDx)= Pathogenic or Likely Pathogenic findings (2 variants for Autosomal Recessive (AR) and 1 for Autosomal Dominant (AD) or X-Linked Dominant (XLD))

Ref:

i. Miller et al, ACMG 10-14 April, 2018- Charlotte NC, USA

ii. Average age of diagnosis from meta analysis of data from Poyato et al Journal of Child Neurology (2012) and Worgall et al. *Neurology* 2007;69:521–535 (n=28). Siblings were excluded.

Date of preparation July 31 2018

Molecular Diagnosis Characterisation

See next slides for details on molecular diagnosis and clinical implications

Epilepsy Gene Panel Program: EU Results (September 2017- June 2018)

All Molecular Diagnosis (n=24 over 131 samples)

AD= Autosomal Dominant, AR= Autosomal Recessive, XLD=X-Linked Dominant, CI=Complex Inheritance

Epilepsy Gene Panel Program US

All Molecular Diagnosis (n=12 over 176 samples)[i]

Gene	Inheritance	Conditions	Possible Management Implication	Number of Diagnoses (n=12)
TPP1	AR	CLN2 disease (Ceroid lipofuscinosis, neuronal [NCL, CLN2]), 2	Approved therapy for eligible patients in the US and EU	**4**
SCN1A	AD	Epilepsy, generalized, with febrile seizures plus, type 2 Epileptic encephalopathy, early infantile, 6 (Dravet syndrome) Febrile seizures, familial, 3A Migraine, familial hemiplegic, 3	Pharmacogenomic information available (PharmGKB[7]: Avoid sodium channel blockers) Interventional clinical trials open for enrollment (Stiripentol)	**1**
MECP2	XLD	Rett syndrome	Interventional clinical trials open for enrollment for Rett Syndrome, females only	**1**
SYNGAP1	AD	Mental retardation, autosomal dominant 5	No disease-altering treatment or pharmacogenomic information available (PharmGKB[7])	**3**
CHD2	AD	Epileptic encephalopathy, childhood-onset	No disease-altering treatment or pharmacogenomic information available (PharmGKB[7])	**1**
GPHN	AD/AR	Molybdenum cofactor deficiency C	No disease-altering treatment or pharmacogenomic information available (PharmGKB[7])	**1**
GRIN2A	AD	Epilepsy, focal, with speech disorder and with or without mental retardation	NMDA inhibitors (under proof of concept)8 No disease-altering treatment or pharmacogenomic information available (PharmGKB[7])	**1**

i. Miller et al, ACMG 10-14 April, 2018- Charlotte NC, USA

Date of preparation July 31 2018

AD= Autosomal Dominant, AR= Autosomal Recessive, XLD=X-Linked Dominant

Approach to estimate the quality of life benefit due to early intervention

Literature evidence indicates benefits of between 0.04 and 0.12 QALYs for patients due to early treatment

Similar QoL benefits will be observed with Rett Syndrome and other diseases that could be identified [4, 5]

	Lennox-Gestaut	Dravet Syndrome
untreated patients (i.e. uncontrolled seizures) [1, 2]	0.393	0.393
Normal responders (i.e. 50 - 75% reduction in seizures) [1, 2]	0.461	0.461
Super-responders (i.e. ≥ 75% reduction in seizures) [1, 2]	0.605	0.605
% normal responders [2, 3]	17.2%	54%*
% super-responders [2, 3]	27.9%	
Quality of life benefit due to treatment	0.07	0.04 – 0.12

1: Verdian and Yi. Seizure 2010; 19: 1 – 11. “Cost-utility analysis of rufinamide versus topiramate and lamotrigine for the treatment of children with Lennox-Gastaut Syndrome in the United Kingdom”.
2. Elliot J et al. Pharmacoeconomics. 2018 May 15. doi: 10.1007/s40273-018-0669-7 “Economic Evaluation of Stiripentol for Dravet Syndrome: A Cost-Utility Analysis.”
2. Inoue et al. Epilepsy Research (2015) **113**, 90—97. “Long-term safety and efficacy of stiripentolfor the treatment of **Dravet syndrome**: A multicenter, open-label study in Japan”
3. Kluger et al. Acta Neurol Scand 2010: 122: 202–208. “Adjunctive rufinamide in **Lennox-Gastaut syndrome**: a long-term, open-label extension Study”
4. Lane et al. Neurology. November 15, 2011; 77 (20). “Clinical severity and quality of life in children and adolescents with Rett syndrome”.

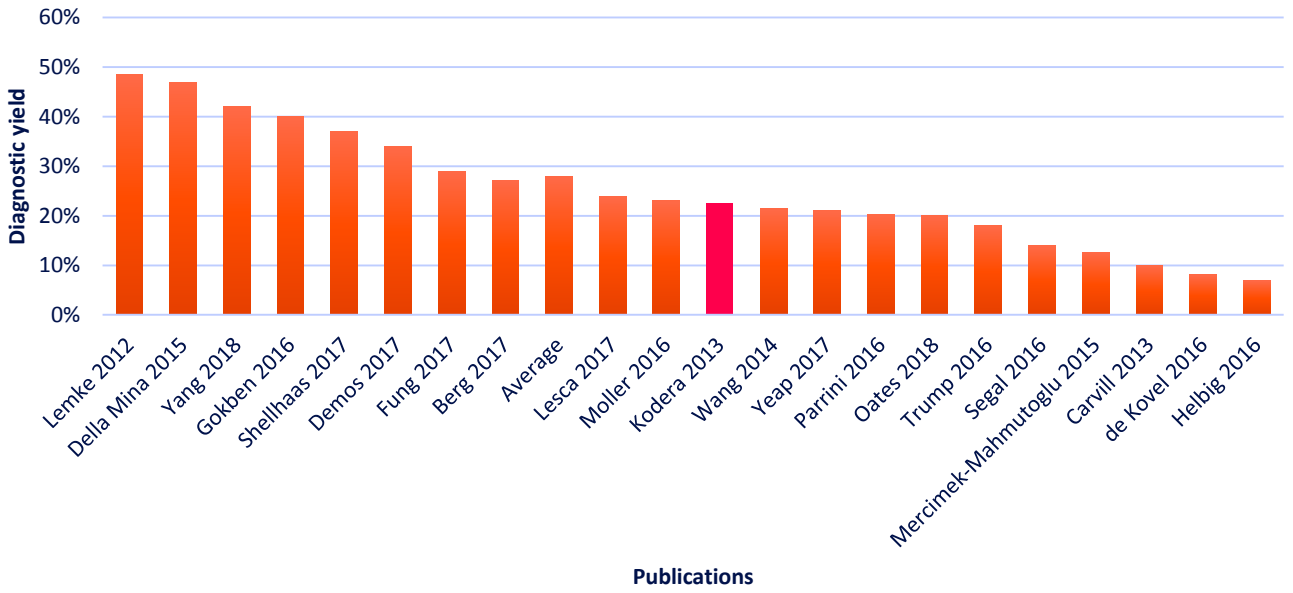
Epilepsy panel Dx yield from published literature

Date of preparation July 31 2018

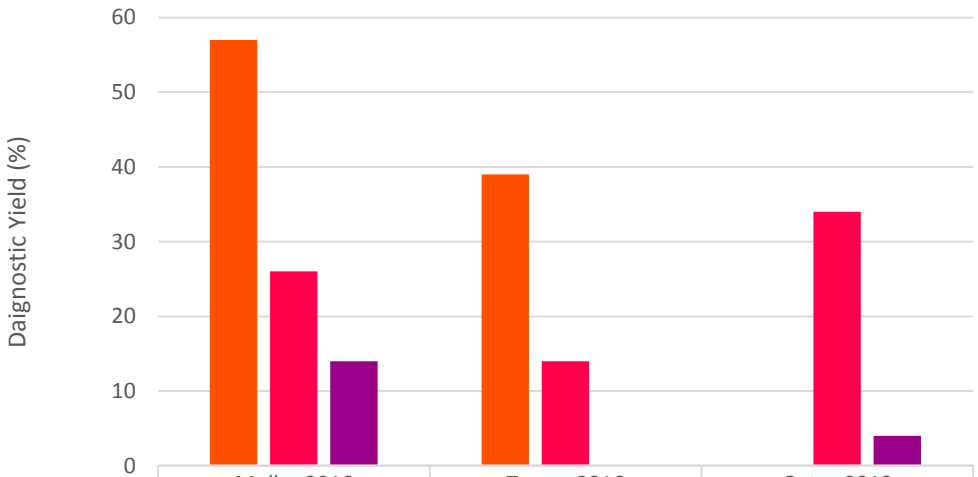
Diagnostic Yield from Epilepsy Gene Panels: Variable yield related to age of seizure onset

- **Overall diagnostic yield in published literature is generally greater than 20% (22.6% for all ages and seizure types)**
- **Higher diagnostic yield is seen in cases with earlier seizure onset.**

Diagnostic Yield of Epilepsy Gene Panels
from published literature



Diagnostic Yield of Epilepsy Gene Panels
By age of seizure onset



	Moller 2016	Trump 2016	Oates 2018
0-2 months	57	39	
<2 years	26	14	34
>2 years	14		4

Diagnostic Yield from Epilepsy Gene Panels:
Yield, population tested, number of genes tested from published literature

Publication	Diagnostic Yield	Number of Epilepsy Patients Receiving Gene Panel Testing	Number of Genes	Primarily onset <2y
Lemke 2012	48.5%	33	265	?
Della Mina 2015	47%	19	67	?
Gokben 2016	40%	30	16	Y
Demos 2017	34%	50	565	?
Fung 2017	29%	31	430	Y
Berg 2017	27.2%	114	ND	Y
Lesca 2017	24%	329	82	?
Moller 2016	23%	216	45	?
Kodera 2013	22.6%	53	35	Y
Wang 2014	21.4%	28	53	?
Yeap 2017	21%	53	36 and 66	Y
Parrini 2016	20.3%	349	30 and 95	Y
Trump 2016	18%	400	46	Y
Segal 2016	14%	49	Multiple panels used	?
Mercimek-Mahmutoglu 2015	12.7%	110	38-327	Y
Carvill 2013	10%	500	65	Y
de Kovel 2016	8.1%	360	377	?
Helbig 2016	7% (Epilepsy), 17% (Epileptic encephalopathy)	293	Exome	N
Hildebrand 2016*	0.8%	251	11	N
Yang 2018	47%	733	Exome	Y
Shellhaas 2017	37%	28	28	Y
Oates 2018	34%	16	46-102	Y
Oates 2018	4%	46	46-102	N

*Focal epilepsy only

Appendix

Epilepsy Gene Panel Program EU: Blueprint Genetics Panel and Inclusion criteria

The panel

The Comprehensive Epilepsy Panel used in this program covers 283+ genes associated with epilepsy disorders and metabolic diseases presenting with epilepsy. The panel includes coverage for all protein coding exons, exon-intron boundaries (+/-20bp) and offers coverage for certain established deep intronic variants. The panel also offers high resolution copy number variant detection for genes on the panel.

Inclusion criteria

Until April 2018

- Age: ≥24 and <60 months old
- Unprovoked seizures started after 2 year of age

After April 2018

- Age: ≥24 and ≤48 months old
- Unprovoked seizures started after 2 year of age
- One of the following signs/symptoms: history language delay or regression, motor impairments or regression (ataxia, abnormal gait, etc), EEG abnormality, MRI abnormality

Epilepsy Gene Panel Program EUMEA: Blueprint Genetics Introduction

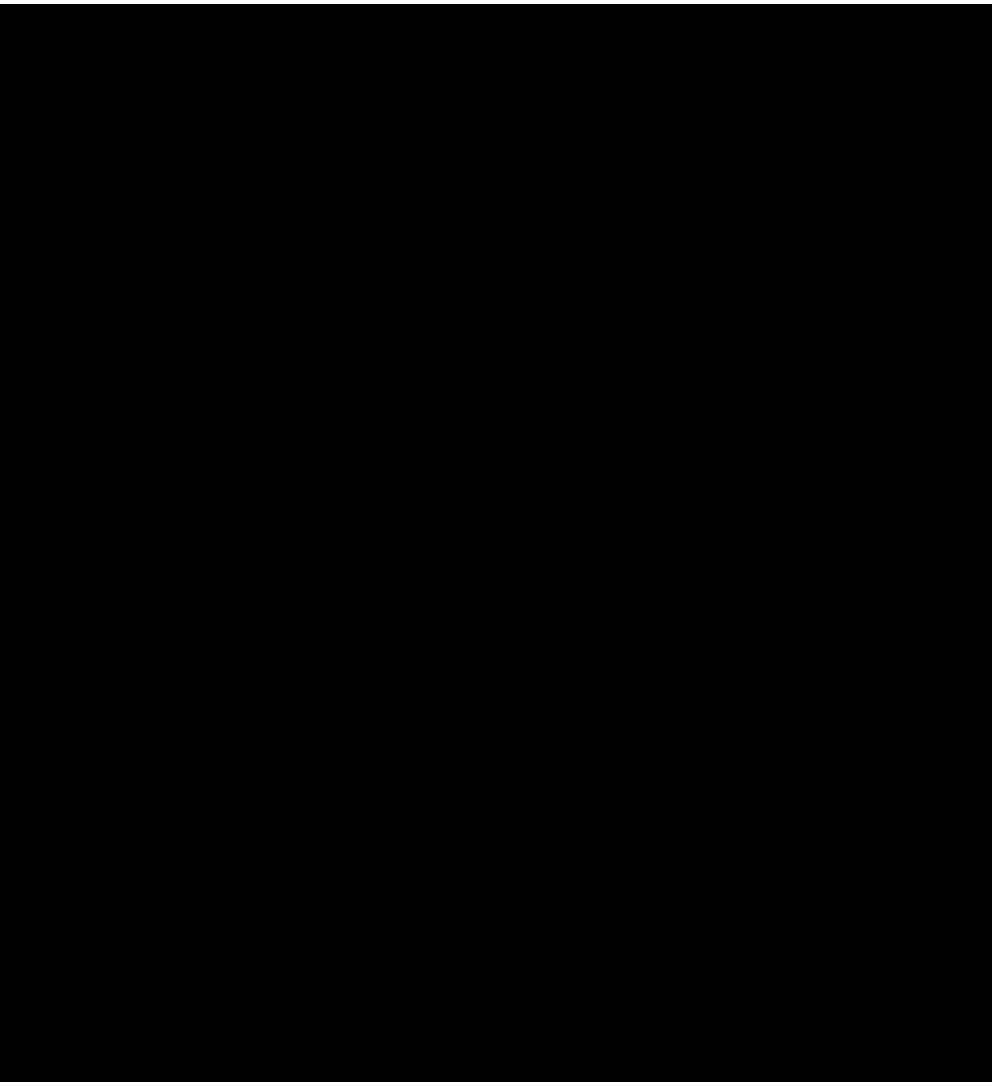
Blueprint Genetics and BioMarin collaborate to offer a no-cost 283+ gene Comprehensive Epilepsy Panel for diagnosis of the genetic cause of paediatric epilepsy in Europe and Middle East countries.

Seizures occurring in childhood may be caused by an underlying genetic disorder and applying early and accurate genetic diagnostics can shorten the diagnostic odyssey, improve the management of these patients and contribute to the understanding of paediatric onset epileptic disorders.

With this initiative, the aim is to promote early genetic testing for timely diagnosis of genetic causes of epilepsy and also of rare genetic neurodegenerative diseases presenting with epilepsy.

The initiative is part of BioMarin's service support for patients and families with rare genetic diseases such as the neuronal ceroid lipofuscinosis type 2 (CLN2) disease, a rare neurodegenerative disease presenting with epilepsy in the paediatric age.

Epilepsy Gene Panel Program EUMEA: Blueprint Genetics Results (September 2017- June 2018)



VUS Clarification Service at Blueprint

https://blueprintgenetics.com/methods-and-services/vus-clarification/

- Blueprint Genetics offer a Variant of Uncertain Significance (VUS) Clarification Service free of charge when testing of selected additional family members is likely to clarify the disease – variant association.
- The goal of the service is to gain enough additional evidence to enable re-classification of the VUS to either likely benign/benign or likely pathogenic/pathogenic. Since not all family members provide sufficient evidence for reclassification, some VUS variants or cases will not qualify for this service.
- If the variant is re-classified, an amended report will be issued for all individuals who previously tested positive for this variant.
- We will also update our interpretation and classification in public databases such as ClinVar ultimately helping other patients and families who have also tested positive for the identified variant.

Overall summary and preliminary conclusion

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

ERG commentary on the updated model, managed access agreement, and commercial agreement submitted by the company in response to the ECD

Produced by Centre for Reviews and Dissemination (CRD) and Centre for Health Economics (CHE)

Date 10/04/18

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.

Table of Contents

1 Introduction

The evidence review group (ERG) was requested by NICE to review and critique the additional evidence submitted in response to the evaluation consultation document (ECD). Due to the limited resource available, the additional work undertaken by the ERG does not constitute a formal critique of the company's resubmission and hence does not accord with the procedures and templates applied to the original submission. Further, due to the length of the companies ECD response and the substantial new evidence provided, the ERG focused its review and critique on the content of [redacted] and the company's new economic analysis. The ERG has also checked the implementation of any proposed changes, and ensured the replicability of the results presented by the company. In response to the ECD, the company provided the following:

1. Comments and critique of the evaluation consultation document;
2. Cost-effectiveness results from an amended version of the ERG's model which includes two preferred company scenarios;
3. Details of a draft managed access agreement (MAA),

[redacted]

The company also provided an updated executable models upon request, which incorporates the company's new preferred scenarios. The remainder of the report comprises four sections. In Section 2, an overview and critique of the MAA [redacted] is presented. In Section 3, an overview and critique of the ECD response is presented. In Section 4 the additional economic analysis carried out by the company is presented, along with further exploratory analysis carried out by the ERG. Section 5 presents a brief summary and the conclusions of this report.

2 Managed access scheme [redacted]

In this section, the ERG describes the new commercial offer made by the company and the proposed MAA. This includes a critique of the claimed benefits of the MAA scheme and an exploration of the implications of the MAA in terms of the eligibility of patients to receive and continue treatment with cerliponase alfa. The commercial offer and MAA proposed by the company consists of the following:

- [redacted] Starting and stopping rules, which determine eligibility to receive treatment.

Each of these individual components is considered in turn below.

[redacted]

[redacted]

Table 1 BioMarin estimates based on clinical advisor input

	BioMarin estimates
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

[redacted]

[redacted]

[redacted]

Table 2 BioMarin and ERG [redacted] based on clinical advisor input

	BioMarin estimates	ERG estimates based on clinical advisor input
[redacted]		

[redacted]

[redacted]

Table 3 Summary of cost and QALY benefits of [redacted]

	Conservative scenario	Optimistic scenario
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
Assumptions: [redacted]		

[redacted]

[redacted]

[redacted]

2.3 Stopping rule

The criteria for which new patients should be stopped from treatment due to non-response during the first eighteen months of treatment are:

- A loss of more than two points (three or more points) on the CLN2 Rating Scale ML Score from baseline, and a total CLN2 rating scale score of less than 2, AND
- A reduction in proxy reported patient quality of life.

The criteria for which patients who have been on patients currently on treatment are:

- A loss of more than one point on the CLN2 Rating Scale ML Score, in the previous twelve months treatment window and a total CLN2 rating scale score of less than 2, OR
- Progression to an unreversed score of 0 on the CLN2 Rating Scales ML Score. AND
- A reduction in proxy reported patient quality of life in the previous twelve months treatment window.

The stopping rule does not apply to children under the age of three, as natural decline in functional endpoints is not seen at this point.

The ERG considers that the stopping rule described in the MAA based on decline in response is unlikely to apply to many (if any) patients given the evidence presented in the 190-201/202 studies, as this would require that patients experience a rate of decline roughly equivalent to those on standard care. As such, the stopping rule only protects the NHS from treatment failure i.e. the treatment effect falling to zero, but does not address the uncertainty regarding whether cerliponase can provide long-term stabilisation of disease progression in some or all patients. The ERG highlights that even very

slow disease progression would have a profound impact on both patient's quality and length of life and has significant impact on the estimated cost-effectiveness of cerliponase alfa.

The stopping rule relating to progression of disease and falling quality of life was not applied in the company's economic analysis. The ERG, however, considers this likely to be either impossible or very complex, as with Markov models it is not possible to track individual patients without a large number of additional health states. Furthermore, because of the memoryless nature of the model structure, the ERG considers it inappropriate to use this economic model to estimate the proportion of patients that would be captured by the stopping rules, and that to do so would significantly overestimate the proportion of patients covered by them.

3 Response to Company's comments on the ECD

In their response, the company raised numerous concerns with the content of the ECD. It is important to note that in recognition of the significant uncertainties involved in modelling this condition and its treatment, the ERG report presented a number of alternate scenarios which drew upon expert clinical opinion and extrapolated the limited existing evidence to explore the impact of the considerable uncertainty surrounding the various issues in this appraisal. The ERG considers the caveats and emphasis on open interpretation made in the report to suitably address the company's concerns regarding the uncertainty in the ERG's presented analyses. The ERG stresses that although conservative, the ERG's critique and additional analysis is supported by expert opinion, and at present we judge to be the most plausible interpretation of all of the available evidence. The ERG also highlights that the issues raised by the company represent a minority of the corrections and adjustments to the economic model made by the ERG, and largely have a relatively insignificant effect upon the ICER.

Arguments made by the company in response to the ECD were used to support the removal of particular aspects of the ERG's adjustments to the economic model; based on these, the company presented results for two additional scenarios. These scenarios incorporate some of the alternative assumptions made by the ERG in their original analysis, maintain some of the company's original assumptions, and provide variations to the assumptions made by the ERG. The assumptions made in each scenario are summarised in Table 4, with further discussion presented below.

Table 4 Summary of key assumptions

	ERG assumption	Company Scenario 1	Company Scenario 2
Starting population	ML 6 – 4% ML 5 – 11% ML 4 – 44% ML 3 – 19% ML 2 – 19%	ML 6 – 20% ML 5 – 40% ML 4 – 25% ML 3 – 10% ML 2 – 5%	Original base case in company submission, i.e. ML 6 – 40% ML 5 – 40%

	ML 1 – 0% ML 0 – 4% Based on the 190-901 cohort	ML 1 – 0% ML 0 – 0%	ML 4 – 10% ML 3 – 5% ML 2 – 5% ML 1 – 0% ML 0 – 0%
Transition probabilities for cerliponase alfa patients	As calculated by the ERG	As calculated by the ERG	As calculated by the ERG
Partial disease stabilisation for cerliponase alfa patients*	No stabilisation	Early stabilisers – stabilised Late stabilisers – continue to progress at same rate after 96 week	ERG assumption applied
Extra-neurological and neuro-disability-related mortality	Neurodisability-related mortality risk assumed using following risk ratios: Health States 1-2: 1.44 Health States 3-5: 2.00 Health States 6-9: 9.92	ERG assumption applied	Neurodisability-related mortality risk factors applied with the following modifications, (re-estimated from ERG article): Health States 1–2: 1.12 Health States 3-5: 2.00 Health States 6-9: 10.30
Vision	All patients go blind over time, and incur related support costs and disutility	ERG assumption applied	ERG assumption applied
Utility values	Utilities are the same for both treatment arms using EQ-5D-3L data - Standard of care utility values used in both arms	Standard of care utility values used in both arms but with an additional utility benefit of: • 0.1 for patients in Health States 2 to 4 • 0.2 for patients in Health State 5 and 6	Utility values applied as per the base case in the original company submission, i.e. utility values taken from the utility studies
	Age-adjusted utilities are applied	ERG assumption applied	ERG assumption applied
	Carer and sibling disutility are removed after 30 years	ERG assumption applied	ERG assumption applied
Resource use	Additional resource use items are included (ECG, psychiatric support, residential care)	ERG assumption applied	ERG assumption applied
Discount rate	3.5% for costs and benefits	ERG assumption applied	ERG assumption applied
* Company model appears to implement the original ERG estimations of partial stabilisation but the change was not able to be identified by the ERG (late stabilisers – continue to progress, but at a slightly reduced rate)			

3.1 Starting population

The severity of disease at the initiation of treatment is a key driver of cost-effectiveness. In the company's original base-case, the distribution of patients across the health states at the initiation of

treatment were based on assumptions regarding the impact of a proposed awareness campaign, in addition to the introduction of free gene panel testing, details of which are described in the commercial offering, MAA, and supporting documents. In the ERG's critique it was noted that the benefits of any programme to identify patients early are highly uncertain, and that the logic behind the assumed distribution of patients in the company's base-analysis was 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. The ERG explored the impact of alternative distributions using recent historical data from the DEM-CHILD cohort.

In the company's response to the ECD, they dispute the Committee's conclusion that it was appropriate for the ERG to reflect the distribution of patients from the natural history study 190-901. The company's ECD response erroneously argues that the ERG included all patients from the 190-901 study when generating the starting health state distribution. While ERG used the distribution of patients born in 2000 or later with a recorded score at diagnosis, the company cited their original base-case and the additional scenario described in the response to the ECD as more realistic representations of current and future practice. The company justifies this on the basis that *i)* there has been a trend towards earlier diagnosis of CLN2 disease in recent years, and *ii)* that the introduction of a gene panel as routine testing as part of the company's commercial offering will further lead to earlier diagnosis.

With respect to the scenarios presented by the company, the ERG stands by the arguments outlined in the original report. Specifically, that the company's distribution of patients across health states appears to be highly speculative and does not formally attempt to either extrapolate the improvements in diagnosis observed in the DEM-CHILD data nor does it link potential benefits of any future campaign to the rate of progression in untreated disease, or to expected reductions in time to diagnosis.

The ERG also suggest the cited trends towards earlier diagnosis of CLN2 disease be interpreted cautiously, as there are only 27 children in the DEM-CHILD cohort born after the year 2000 with a recorded score at diagnosis. This makes it difficult to draw meaningful conclusions about trends in diagnosis, particularly when further reduced to those born post-2008, as suggested by the company in their latest scenario analysis. While the ERG acknowledges the potential for improvements in diagnosis as a result of any awareness campaign/gene panel testing programme, the magnitude of these benefits is subject to significant uncertainty. Moreover, it is unclear whether such a programme is likely to result in the significant improvements in early diagnosis assumed in the company's scenarios. The ERG also notes the significant barriers to successfully implementing gene panel testing in the UK. As described above, the clinical advisors to the ERG suggest that the number of patients

who would be eligible for a gene panel is highly uncertain, and it is unclear whether there would be any significant uptake of this option in practice.

3.2 Disease stabilisation and long-term effectiveness of cerliponase alfa

The long-term impact of cerliponase on the rate of disease progression is a key issue in determining cost-effectiveness of cerliponase alpha. The company's original base-case made the assumption that after 96 weeks all patients would be stabilised and would not experience any further disease progression. In the company's response to the ECD this assumption is relaxed and a scenario generated by the ERG adopted in which only a proportion of patients (74%) of patients are stabilised after 96 weeks. The remaining patients (26%) are assumed to continue to experience disease progression, albeit at a slower rate than on standard care. In the company also, puts forward the argument that there is an observable decline in the rate of decline after 48 weeks, though this is not modelled by the company. The figures presented by the company, however, company could not be substantiated by the ERG and were inconsistent with the reconstructed IPD used by the ERG to crate the transition probabilities.

The ERG considers that this assumption is likely to be more reasonable given the limited long-term evidence available on the effectiveness of cerliponase, but note that this assumption is still subject to considerable uncertainty. Further the ERG consider that is at least plausible that all patients will continue to experience disease progression. The ERG highlight several pieces of evidence that would support the assumption that no patient experiences long-term stabilisation:

- The proportion of patients experiencing a decline in CLN2 rating scale continues to increase as the length of follow up increases;
- One patient is documented as experiencing a decline in CLN2 rating scale post 96 weeks;
- EEG examinations conducted during the 190-201/202 study found new (focal and/or generalised) epileptiform activity in [redacted] of patients, which the ERG's clinical advisor suggested may be an indicator of continued disease progression.
- MRI measurements showed continued reductions in whole brain volume, cortical grey matter, and white matter.
- Evidence from non-human studies, showed that treatment only slowed progression of symptoms, with only modest reductions in short-term mortality.

The evidence in support of partial stabilisation is in contrast much more limited and is based largely on the fact that that not all patients appear to be continuing to progress based on the relative short follow up in the 201/202 studies. In considering the plausibility of this assumption it is also worth considering that even very slow progression of say 1 point per 10 years (compared to 2 points per year

on standard care) would still have a profound impact on a patient's life and would also have a very significant impact on the cost-effectiveness of cerliponase.

3.3 Health state utilities

In the company's original base-case it was assumed that for any given CLN2 rating score, the quality of life of patients receiving cerliponase alfa would be greater than that of patients receiving standard care. This difference in utility was justified on the basis that cerliponase would provide better control of a range of symptoms including: frequency and severity of grand-mal seizures (tonic-clonic seizures), pain, and myoclonus. In the company's original base-case the impact of these claimed benefits was estimated through the use of a set of vignettes used to elicit utility values from clinicians, which included statements indicating these benefits.

The ERG in its report questioned the empirical evidence provided by the company in support of these assumptions, noting that the evidence in support of improved seizure control focused only tonic-clonic seizures, which are only one aspect of epilepsy and that similar improvements in epileptiform activity were not observed. Furthermore, the ERG noted that the evidence provided, with respect to myoclonus, while demonstrating that the severity of myoclonus increases at slower rate in patients receiving cerliponase alfa compared with standard care, did not provide evidence by health state. As such it was unclear whether this difference was due to delays in disease progression or better symptom control. Given the weakness in the evidence provided in support of these additional benefits, the ERG took the conservative view that cerliponase alfa was unlikely to provide significant health related quality of life benefits over and above its ability to delay progression of disease.

In the company's response to the ECD the company notes the committee's acceptance that cerliponase alfa provides improved control of tonic-clonic seizures and considers this inconsistent with committee's preferred assumption of using the same utility values in patients receiving cerliponase alfa as for patients receiving standard care. The company therefore presents an alternative scenario in which it is assumed that patient with a CLN2 score of 3, 4 and 5 will experience a 0.1 point improvement in their quality of life compared with patients on standard care to account for improved seizure control. It is further assumed that patients with a CLN2 score of 0, 1 and 2 will experience a 0.2 point improvement in their quality of life compared with patients on standard care to account for improved seizure control, reduced pain and reduced severity of myoclonus.

The ERG has a number of concerns regarding the magnitude of the assumed benefits and the evidence supporting the existence of these claimed benefits.

Firstly, ERG notes that for health states 2,3,5,6 and 7 the assumed additional quality of life benefits are actually larger in the company's revised model than in the original base-case model. The reason for this difference is not given in the company's response and seems to contradict the company's focus on a smaller ranger of benefits; the need for a feeding tube and dystonia are not mentioned in the company's response.

Secondly with respect to magnitude of benefit of improved seizure control, the ERG notes that the 0.1 figure was selected only on the grounds it represents a minimally important difference, but is otherwise arbitrary. There is no evidence presented to support improvements in quality of life of this magnitude. Indeed, two recent studies assessing the quality of life of patients with uncontrolled epilepsy suggest this would represent the upper limit of the potential benefits of improving seizure control. For example, a recent UK study[1] showed an improvement in seizure control from >10 seizures a year to 1-3 seizures a year provides a QoL benefits of [redacted] QALYs per year. While another international study[2] suggests an improvement from >1 seizure a week to <1 a year implies QoL benefits of [redacted] QALYs a year. In interpreting these improvements in QoL, the ERG also note that the improvement in seizure control measures only the frequency of tonic-clonic seizures, and therefore does not necessarily indicate improved control of less severe seizure types. In addition, improvement in tonic-clonic seizure control between treatment arms was more modest than the improvements implied in the quality of life studies, representing an approximate improvement from 1-2 seizures per 3 months, to complete seizure control for 70% of patients. This would suggest that the benefits of seizure control on quality of life may be considerably lower than the [redacted] QALY improvement assumed in the company's scenario.

Thirdly, with respect to the improvements in pain and myoclonus, the ERG notes that no empirical evidence was provided to support these benefits, and inclusion of these additional quality of life benefits is supported based on parent observation and clinical opinion. Given the lack of any empirical evidence presented by the company in support of these benefits and the general lack of clinical experience of using cerliponase alfa, the ERG considers the inclusion of the utility benefits associated with pain and myoclonus somewhat speculative, and consider it highly uncertain whether these benefits would be realised in practice. The ERG also notes that magnitude of the QALY benefit is again somewhat arbitrary, and that no evidence is provided by the company to support the magnitude of the QoL gains included in the model.

Given the considerable uncertainty regarding the magnitude of any quality of life benefit in patients receiving cerliponase alfa, the ERG implemented further scenarios in which a reduced quality of life gain due to seizure control is included, based on the quality of life studies in people with epilepsy and

in which the quality of life benefits associated with reduced pain and reduced severity of myoclonus removed completely from the model.

3.4 Mortality

The company disputed the ERG's preferred scenario regarding extra-neurological and neurodisability-related mortality, stating that CLN3 disease is not a reliable proxy for CLN2 disease, extra-neurological mortality is not currently relevant when considering mortality risk in CLN2 patients, and that they did not believe traumatic brain injury to be a relevant comparison in CLN2. For further details please see the company's response to the ECD.

As discussed in the ERG report, the accumulation of lysosomal storage material in extra-neuronal tissues in human CLN2 has long been recognised. The 2017 Katz study cited in the ERG report highlights the emergence of extraneuronal pathology in animals whose neurological CLN2 disease progression is delayed through treatment with exogeneous TPP1. It was considered likely by the study authors, and by the ERG's clinical advisor, that untreated accumulation of storage material may lead to damage and dysfunction of other organs in the longer term.

This information introduced a further uncertainty into the plausibility of long-term use of ICV cerliponase alfa. To explore this uncertainty, the ERG considered the effects of extra-neuronal lysosomal storage material accumulation in CLN3, in which significant heart abnormalities develop in most patients by age 18. While the company argued that some atypical cases of CLN2 and SCAR7 disease demonstrated that patients could live to advanced ages with reduced or atypical TPP1 activity, slower-progressing phenotypes of CLN2 are not informative for the purpose of exploring extra-neurological mortality, as the rate of storage material accumulation - not the age of the patient, is the relevant factor. Because symptom onset and development is slower in CLN3 disease, the ERG deemed this an optimistic comparison for the purposes of this scenario. Again, the ERG report emphasises the significant uncertainty surrounding such comparisons, which were used as a pragmatic way of exploring the potential effects of extra-neuronal pathology raised in scientific literature and by clinicians.

While the company correctly states that very small concentrations (0.1% of CSF levels) of rhTPP1 were detected in the plasma, this exposure declined over the course of the study; thought to be due to neutralisation by anti-rhTPP1 antibodies (Vuillemenot et al, 2015[3]). Therefore any protective effect as proposed by the company is unlikely to persist, meaning the severe disease-related multiple organ damage seen in the animal models may be a cause for concern in humans.

While the company rejected the ERG's use of evidence from traumatic brain injury (TBI) patients to explore the long-term effects of loss of ambulation and increasing neurodisability on mortality, the company applied an increased mortality risk in their new scenario analyses to account for this. In health states 1-2, patients had a mortality risk 1.12x (ERG 1.44x) that of the general population, increasing to 2x (ERG 2x) in health states 3-5, and 10.30x (ERG 9.92x) in health states 6-9. The ERG was satisfied that this approach was reasonable.

4 Results of scenario analyses

This section comprises of two parts: firstly, the ERG explored the impact of the alternative assumptions described by the company in their ECD scenario analyses (Table 4) and presents the results of a number of scenario analyses based on these assumptions within the ERG base-case analysis and different starting populations. In these analyses,

[redacted]) were considered. Secondly, the ERG presents additional scenario analysis considering the new evidence and concerns raised by the in their ECD response.

4.1 Company analysis

[redacted]

[redacted]

Table 5 Results of scenario analyses (lifetime results) -with commercial discount applied

Scenario	ERG base-case population		ECD scenario 1 population		ECD scenario 2 population	
	Inc. QALYs	ICER	Inc. QALYs	ICER	Inc. QALYs	ICER
[redacted]						
ERG base-case analysis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario analyses on ERG base-case						
Partial stabilisation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Neurodisability-related mortality (company values)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Excluding extra-neurological mortality	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Alternative company utilities	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Original company utilities	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Company scenario analysis [1]			[redacted]	[redacted]	[redacted]	[redacted]
[redacted]						
Company scenario analysis (no additional benefits)			[redacted]	[redacted]	[redacted]	[redacted]
With extra cost benefits (company's optimistic scenario)			[redacted]	[redacted]	[redacted]	[redacted]
With extra cost benefits (company's conservative scenario)			[redacted]	[redacted]	[redacted]	[redacted]
With extra QALY benefits (company's optimistic scenario)			[redacted]	[redacted]	[redacted]	[redacted]

[redacted] [2]

With extra QALY benefits (company's conservative scenario)	[redacted]	[redacted]	[redacted]	[redacted]
Company's optimistic scenario (including cost and QALY benefits)	[redacted]	[redacted]	[redacted]	[redacted]
Company's conservative scenario (including cost and QALY benefits)	[redacted]	[redacted]	[redacted]	[redacted]
Scenarios conducted on the ERG base-case analysis, and combined to create the company's alternative scenario. Cost-effectiveness threshold estimated from number of incremental undiscounted lifetime QALYs. [redacted]				

[1] Set of assumptions for each company scenario summarised in Table 4.
[2] Based on the ERG-corrected calculations. Applied to the company ECD scenario.

4.2 ERG alternative analysis

In response to the ECD and the company's arguments for an alternate set of assumptions in the analysis, the ERG has considered an alternative scenario, based on the following assumptions:

- Assumptions applied in the original ERG base-case:
  - Population based on the historic cohort (study 190-901);
  - No disease stabilisation, transition probabilities estimated by the ERG;
  - Utility values are age-adjusted, and carer and sibling disutility are removed after 30 years;
  - Vision: all patients go blind over time, and incur related support costs and disutility;
  - Additional cost items (ECG, psychiatric support, residential care);
  - Discounting at 3.5%.
- Assumptions updated after ECD response:
  - CA associated with a quality of life benefit based on the improvement in seizures;
  - Neurodisability-related mortality applied, using the company-estimated risk ratios.
- [redacted] Scenario: with and without extra-neurological mortality (to reflect the lack of evidence and capture any uncertainty around the presence of this factor).

The improvement in quality of life applied by the company in their analysis was predicated on the cerliponase providing better control of a range of symptoms, including the frequency and severity of tonic-clonic seizures, pain, and myoclonus (described Section 3.3). This value was assumed to be 0.1, but not based on any evidence and may overestimate the benefit in these patients. Instead, the ERG

applied the quality of life benefits identified from an international study estimating the burden of epilepsy, to acknowledge an improvement in seizure control: an improvement from 1-3 seizures per month to 1-4 seizures per year was associated with an improvement in QoL from [redacted] to [redacted] ([redacted] increment). The ERG applied this utility benefit in HS 2 to 6 for cerliponase in the model.

[redacted]

Table 6 presents the results of the two scenarios. In both instances,

[redacted].

Table 6 Results of additional ERG analysis (lifetime results)

Scenario	Inc. QALYs	ICER
With extra-neurological mortality	[redacted]	[redacted]
Without extra-neurological mortality	[redacted]	[redacted]
Cost-effectiveness threshold estimated from number of incremental undiscounted lifetime QALYs		

5 Conclusions

The company response to the ECD included a critique of the assumptions used in the ERG's base-case which were largely accepted by the committee,

[redacted]) and a MAA which included a set of starting and stopping rules. Further, the company presents additional economic analysis considering two new scenarios using the company-preferred assumptions.

The ERG considers that the company's scenarios represent an optimistic interpretation of the available evidence, that and largely align with company's previous base-case on several key issues, namely disease stabilisation the distribution of patients at initiation of treatment and health state utilities. As such, the arguments put forward in the ERG's original report largely stand.

[redacted]

Given the results of the new scenarios present by the company which all result in ICERs [redacted] and the additional scenario analysis presented by the ERG which increase the ICER further, the ERG considers that cerliponase alfa is unlikely to represent good value to the NHS.

6 References

1. Mulhern B, Pink J, Rowen D, Borghs S, Butt T, Hughes D, et al. Comparing Generic and Condition-Specific Preference-Based Measures in Epilepsy: EQ-5D-3L and NEWQOL-6D. *Value Health* 2017;20:687-93.

2. Gupta S, Kwan P, Faught E, Tsong W, Forsythe A, Ryvlin P. Understanding the burden of idiopathic generalized epilepsy in the United States, Europe, and Brazil: An analysis from the National Health and Wellness Survey. *Epilepsy & Behavior* 2016;55:146-56.

3. Vuillemenot B, Kennedy D, Cooper JD, Wong A, Sri S, Doeleman T. Nonclinical evaluation of CNS-administered TPP1 enzyme replacement in canine CLN2 neuronal ceroid lipofuscinosis. *Mol Genet Metab* 2015;114:281-93.

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

3rd Addendum to ERG commentary on the updated model, managed access agreement, and commercial agreement submitted by the company in response to the ECD

Produced by	Centre for Reviews and Dissemination (CRD) and Centre for Health Economics (CHE)
Date	03/05/18

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.

[redacted]

- [redacted]
- [redacted]

[redacted]

[redacted] 1 [redacted]

[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]				

Results of the company analysis

The following section presents the results of a series of scenario analyses that implement [redacted].

The analyses are based on the following set of assumptions:

- Utility values age-adjusted, and carer and sibling disutility removed after 30 years
- Vision: all patients go blind over time, and incur related support costs and disutility
- Additional cost items (ECG, psychiatric support, residential care)
- Discounting at 3.5%
- Neurodisability-related mortality applied, using company-estimated risk ratios
- [redacted]
- No additional benefits included relating to commercial offer ([redacted])
- [redacted]

In addition, the assumptions described in

Table 2 are explored in a series of scenario analysis.

Table 2 Assumptions in ERG scenario analyses

Scenario	Additional assumptions
Scenario presented in Table 3	• No disease stabilisation • Cerliponase alfa was associated with a quality of life benefit based on improvement in seizures (0.046 point utility benefit in health states 2 to 6 [REF])
Scenario presented in Table 4	• Partial disease stabilisation • Cerliponase alfa was associated with a quality of life benefit based on improvement in seizures (0.046 point utility benefit in health states 2 to 6 [REF])
Scenario presented in Table 5	• Partial disease stabilisation • Cerliponase alfa was associated with a quality of life benefit based on improvement in seizures and in non-seizure symptoms (0.1 point benefit in HS 2-4 and 0.2 point benefit in HS 5-6, company-assumed values)

[redacted].

In the following scenarios, the ICER ranges from [redacted] under the most of optimistic set of assumptions regarding the clinical data in the model, to [redacted] per QALY under the most conservative assumptions.

Table 3 Results of ERG scenario analysis (lifetime results) -with [redacted] – no disease stabilisation

Scenario	Incremental	Model population based on:		
		ERG base-case scenario	Company Scenario 1	Company Scenario 2
With extra neurological mortality	ICER	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	Undiscounted QALYs	[redacted]	[redacted]	[redacted]
Without extra neurological mortality	ICER	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	Undiscounted QALYs	[redacted]	[redacted]	[redacted]
Applied to the company ECD scenario (including no additional benefits of the commercial offering [redacted]), assuming no disease stabilisation.				

Table 4 Results of ERG scenario analysis (lifetime results) -with [redacted] – partial disease stabilisation

Scenario	Incremental	Model population based on:		
		ERG base-case scenario	Company Scenario 1	Company Scenario 2
With extra neurological mortality	ICER	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	Undiscounted QALYs	[redacted]	[redacted]	[redacted]
Without extra neurological mortality	ICER	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	Undiscounted QALYs	[redacted]	[redacted]	[redacted]
Applied to the company ECD scenario (including no additional benefits of the commercial offering [redacted]), assuming partial disease stabilisation.				

Table 5 Results of ERG scenario analysis (lifetime results) - [redacted] – partial disease stabilisation and utility benefit for cerliponase patients

Scenario	Incremental	Model population based on:		
		ERG base-case scenario	Company Scenario 1	Company Scenario 2
With extra neurological mortality	ICER	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	Undiscounted QALYs	[redacted]	[redacted]	[redacted]
Without extra neurological mortality	ICER	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	Undiscounted QALYs	[redacted]	[redacted]	[redacted]
Applied to the company ECD scenario (including no additional benefits of the commercial offering [redacted]), assuming partial disease stabilisation and a health state utility benefit for cerliponase alfa patients based on additional non-seizure symptoms.				

[redacted]

[redacted]

[redacted]

ERG exploratory analysis

[redacted]

Table 6 Results of ERG scenario analyses (lifetime results): cessation of commercial agreement after five years from the time it was introduced

	Cohort of patients, time since introduction of commercial agreement					
Incremental	**Year 1**	**Year 2**	**Year 3**	**Year 4**	**Year 5**	**Average**
ICER	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Undiscounted QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]						
Applied to the company ECD scenario ([redacted]), assuming partial disease stabilisation, no extra-neurological mortality, and a health state utility benefit for cerliponase alfa patients based on additional non-seizure symptoms.						

[redacted]

Table 7 Results of ERG scenario analyses (lifetime results): cessation of commercial agreement after five years from the time it was introduced

	Cohort of patients, time since introduction of commercial agreement					
Incremental	**Year 1**	**Year 2**	**Year 3**	**Year 4**	**Year 5**	**Average**
ICER	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Undiscounted QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]						
Applied to the company ECD scenario ([redacted]), assuming partial disease stabilisation, no extra-neurological mortality, and a health state utility benefit for cerliponase alfa patients based on additional non-seizure symptoms.						

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

ERG commentary on the updated model and additional evidence submitted by the company in response to the NICE briefing document

Produced by	Centre for Reviews and Dissemination (CRD) and Centre for Health Economics (CHE)
Date	7/09/18

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.

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1 Introduction

The Evidence Review Group (ERG) was requested by NICE to review and critique the additional evidence submitted in response to the NICE briefing document. Due to the limited resource available, the additional work undertaken by the ERG does not constitute a formal critique of the company's resubmission and hence does not accord with the procedures and templates applied to the original submission. In response to the NICE briefing document, the company provided the following:

1. Comments and responses to issues raised in the NICE briefing document, including further details relating to the provision of a gene panel testing programme;
2. A slide presentation that describes new evidence form the 190-202 trial and evidence from a company sponsored [redacted].
3. Cost-effectiveness results from an amended version of the ERG's model which includes a preferred company scenario;
4. Details of a managed access agreement (MAA).

The remainder of this report comprises of four sections. In Section 2, a brief recap and overview of the [redacted]. Section 3 presents an overview of the new evidence provided regarding the updated clinical data [redacted] submitted by the company along with a critique of this evidence. Section 4 presents the results of the company's revised model, along with further exploratory analysis carried out by the ERG. Section 5 presents a brief summary and the conclusions of this report.

2 [redacted] Company response to NICE briefing document

The new evidence provided by the company primarily consisted of new longer-term follow-up data from the 190-202 trial and new evidence in support of [redacted]
This evidence was integrated into the economic model and a company preferred scenario was presented. The scenarios presented by the company were based on a previous version of the model and the following key assumptions were made:

- **Starting population:** The starting population was based on a revised distribution presented in the company's response to the ECD (ML 6 – 20%, ML 5 – 40%, ML 4 – 25%, ML 3 – 10%, ML 2 – 5% , ML 1 – 0%, ML 0 – 0%)
- **Transition probabilities for cerliponase alfa patients:** Revised and based on new longer-term follow up data.
- **Stabilisation:** Partial stabilisation scenario in which early stabilisers stabilised after week 16 and late stabilisers continue to experience slow decline.
- **Extra-neurological and neurodisability-related mortality:** Neurodisability-related mortality risk factors applied, no extra-neurological related mortality assumed.
- **Utilities:** Standard of care utility values used in both arms but with an additional utility benefit of 0.1 for patients in Health States 2 to 4 and 0.2 for patients in Health State 5 and 6.
  [redacted]

The response document also addressed a number of queries regarding the MAA and proposed data collection. The focus of the ERG's critique is upon the new evidence provided, specifically the new clinical evidence and changes made to the economic model. As described above, the company scenario analysis includes a number of changes from the ERG preferred analysis, these issues are not revisited in this report.

2.1 Disease stabilisation and long-term effectiveness of cerliponase alfa

As part of the updated model, the company provided details on the newly available follow up data for patients enrolled in the 190-202 study. This new data consisted of summary statistics (mean, median standard deviation and range) for CLN2 scores and CLN2 change from baseline only. The new data was provide for all 23 patients still enrolled in the study up to 169 weeks and for smaller number of patients up to 225 weeks. This new data, summarised in [redacted] 1, indicates that the benefits of cerliponase alfa continue to persist beyond the 96 weeks observed in the original data cut and that at least some patients continue to experience some loss of function over-time.

[redacted] 1

	Mean value (SD); N	

	ML Score	Change from baseline	Mean change vs previous 24-week period*
300 mg Baseline	[redacted]	[redacted]	[redacted]
Week 25	[redacted]	[redacted]	[redacted]
Week 49	[redacted]	[redacted]	[redacted]
Week 73	[redacted]	[redacted]	[redacted]
Week 97	[redacted]	[redacted]	[redacted]
Week 121	[redacted]	[redacted]	[redacted]
Week 145	[redacted]	[redacted]	[redacted]
Week 169	[redacted]	[redacted]	[redacted]
Last recorded observation	[redacted]	[redacted]	[redacted]

*Calculated by the ERG

Unfortunately, the provision of summary data rather than IPD or a more detailed analysis, means that it is not possible to assess whether the patients experiencing a decline in CLN 2 score were patients who had previously experienced a decline or whether they were patients who had otherwise been stable up to this point. This distinction is important as the former would be indicative of the partial stabilisation scenario, whereby a proportion of patients achieve long-term stability, while the latter would be indicate that all patients will eventually experience continuous, albeit slow, decline. The latter scenario, which the ERG considers the most plausible scenario, results in substantively more pessimistic results in the cost-effectiveness analysis and a substantially larger ICER. Given this continued uncertainty the ERG presents additional analysis in which all patients are assumed to continue to decline, using the new clinical evidence to estimate the rate of decline.

With respect to the implementation of the additional clinical evidence in the model, [redacted]

The ERG considers the approach taken by the company to implementing the new clinical data to be potentially over-optimistic given the evidence provided regarding [redacted]

[redacted]

An additional issue not addressed by the company's new model is the proportion of patients defined as late responders. In the original analysis this was based on the proportion of patients who experience a decline in CLN2 score between 16 and 96 weeks. The availability of longer follow up data, however, allows the proportion of late responders to be updated, but his has not been implemented. Due to the provision of summary data in the company's latest response, the ERG cannot implement this as a scenario analysis.

[redacted] As part of the company's response, new evidence was provided in support of claims of the benefits of

[redacted]

[redacted] The ERG discusses the evidence presented with respect to both of these claimed benefits.

[redacted]

[redacted]

[redacted]

[redacted] The current age at diagnosis was based on meta-analysis of two studies of CLN2 patients reporting age at diagnosis, Poyato et al (2012)[1] and Worgall et al (2007)[2].

[redacted]

The second concern of the ERG, is that characterising the mean age of current diagnosis as 60 months is likely too high. Specifically, the ERG notes that the 60 month figure is inconsistent with a number of alternative, and potentially more reliable, sources of data, namely, the 190-201 trial and the 190-901 natural history cohort. Data on the mean age at diagnosis of each of these studies is summarised in Table 3 along with details of the cohort upon which the figures are based.

Table 3 Summary of data on mean age at diagnosis

Study	Mean age at diagnosis	N	Description of sample
Poyato et al (2012)[1]	66 months	12	Patients recruited in Spain between 1979 and 2011
Worgall et al (2007)[2]	52 months	14	Children recruited form North America, Europe and Australia
Poyato and Worgell pooled	58 months	26	NA
190-201	[redacted]	[redacted]	Children were prevalent population with CLN 2 scores >2
190-901	[redacted]	[redacted]	Natural history cohort- sample restricted to participants born after 2005.
201 and 901 pooled	[redacted]	[redacted]	NA

*Based on mean age at enrolment

Considering the alternative sources of data, only Poyato *et al.* (2012)[1], which is the least reliable due to the age of the data included, reports a mean age greater than 5, with all three of the other studies reporting an average age at diagnosis of well below 60 months. A pooled analysis of 190-202 trial and the natural history cohort, which the ERG considers represent the most recent and reliable data, suggests that current mean age of diagnosis is only [redacted] months.

[redacted]

Thirdly, the benefits estimated above assume that all patients with CLN2 disease [redacted] This, however, may not be the case, [redacted]

Given these concerns, the ERG considers that the benefits of [redacted] This is important as it potentially brings into question how reflective the starting population used in the company analysis is, given that it assumes significant improvements in diagnosis relative to the starting distribution implied by the 190-901 natural history cohort.

[redacted]

[redacted]	[redacted]

A brief critique of each of the specific changes made to the model are provided below considering each in turn.

[redacted]

[redacted]	[redacted]

[redacted] Firstly, an uptake of [redacted] in year 5 was considered optimistic previously, and is

significantly higher than estimated by experts consulted by the ERG, who suggest a uptake figure of [redacted] may be more reasonable. The ERG, however, acknowledges that expert evidence heard at the previous committee meeting suggested that uptake would be high. Secondly, the implementation of the uptake curve has been incorrectly applied in the model, as the uptake has only been used to adjust costs and not QALY benefits, and further assumes that all of the cost savings over the first five years will be attributed to 5 patients. [redacted] To provide further evidence on the magnitude of the utility gains from early diagnosis the company presents evidence on quality of life gain in patients with two forms of severe epilepsy, Lennox-Gestaut and Dravet syndrome. The results of this review are summarised in Table 6.

Table 6 Summary of evidence supporting quality of life benefits

	Lennox-Gestaut	Dravet Syndrome
Untreated patients (i.e. uncontrolled seizures)[1, 2]	0.393	0.393
Normal responders (i.e. 50 - 75% reduction in seizures)	0.461	0.461
Super-responders (i.e. ≥ 75% reduction in seizures)	0.605	0.605
% normal responders	17.2%	54%*
% super-responders	27.9%	
Quality of life benefit due to treatment	0.07	0.04 – 0.12

The ERG considers the evidence provided by the company a useful anchor upon which to base the magnitude of the utility benefits associated with early diagnosis of childhood epilepsy, but notes a number of areas of uncertainty. It is not clear how representative Lennox-Gestaut and Dravet syndrome are of childhood epilepsy. [redacted]

[redacted]

3 Results of company and ERG scenario analysis

3.1 Company analysis

Redacted

Table 7 Company preferred base-case

Redacted

3.2 ERG alternative analysis

3.2.1 Corrections for calculation errors

To correct for the implementation errors in the company model, the ERG modified the model so that only one year's worth of benefits [redacted] are accrued to an assumed cohort of 5 patients. In such a scenario it is not possible to incorporate the effect of an uptake curve for the gene panel testing programme, and so the ERG explores a range of adoption rates: 10%, 25%, 40%, 60%, 80% and 100%. The adoption rate is applied in estimating both cost savings and QALY benefits, this is also a modification of the company base-case model where the adoption rate is incorrectly applied only to costs. The range of ICERs produced following this correction is from [redacted] per QALY assuming a [redacted] adoption rate to [redacted] assuming a [redacted] adoption rate. Because this correction is tied to the assumptions made in the model, the ERG presents the remainder of the analysis in this section assuming the most optimistic assumption of a [redacted] adoption rate.

[redacted]

Table 8 Result correcting for calculation errors

	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER	Threshold
Company base-case [redacted]						
Cerliponase alfa	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Standard care	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ERG correct base-case uptake = 10%						
Cerliponase Alfa	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Standard Care	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ERG correct base-case uptake = 25%						
Cerliponase Alfa	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Standard Care	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ERG correct base-case uptake = 40%						
Cerliponase Alfa	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Standard Care	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ERG correct base-case uptake = 60%						
Cerliponase Alfa	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Standard Care	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ERG correct base-case uptake = 80%						
Cerliponase Alfa	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Standard Care	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ERG correct base-case uptake = 100%						
Cerliponase Alfa	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Standard Care	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

[redacted]

[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

Results for each of these scenarios are presented in [redacted] 10 below. These scenarios result in ICERs ranging from [redacted] to [redacted] per QALY. [redacted]

** [redacted] 10

	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER	Threshold*
Company base-case (corrected)						
Cerliponase Alfa	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Standard Care	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 1: European cohort, includes CLN2 patients						
Cerliponase Alfa	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Standard Care	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 2: US cohort, includes CLN2 patients						
Cerliponase Alfa	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Standard Care	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 3: European and US data pooled excluding CLN 2 patients						
Cerliponase Alfa	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Standard Care	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 4: European cohort, excludes CLN2 patients						
Cerliponase Alfa	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Standard Care	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 5: US cohort, excludes CLN2 patients						
Cerliponase Alfa	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Standard Care	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

3.2.2 Magnitude of QALY benefits

The evidence provided by the company suggest that only [redacted] of patients who

[redacted]

Table 11 presents results adjusting for the proportion of patients who are able to receive active therapy. Assuming [redacted] receive a quality of life improvement the ICER is [redacted] per QALY. Assuming [redacted] receive the QALY benefit the ICER is [redacted] per QALY. [redacted].

Table 11 Results of as scenario analysis on the magnitude of QALY benefits

	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER	Threshold*
Company base-case (corrected)						
Cerliponase Alfa	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Standard Care	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 1: [redacted] of patients receive QALY benefits						
Cerliponase Alfa	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Standard Care	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 2: [redacted] of patients receive QALY benefits						
Cerliponase Alfa	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Standard Care	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

3.2.3 Inclusion of both cost and QALY savings

As noted above, the ERG considers it inappropriate for both the cost and QALY savings to be included at the same time as the cost savings relate to the provision of the gene panel testing. Table 12 therefore presents two scenarios one in which the cost benefits claimed are excluded and a second where the QALY benefits are excluded. [redacted]

Table 12 Results of exploration of impact of removing cost/QALY benefits

	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER	Threshold*
Company base-case (corrected)						
Cerliponase Alfa	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Standard Care	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 1: Cost benefits excluded						
Cerliponase Alfa	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Standard Care	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 2: QALY benefits excluded						
Cerliponase Alfa	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Standard Care	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

3.2.4 Disease stabilisation and long-term effectiveness of cerliponase alfa

As stated the above the ERG considers that considerable uncertainty remains regarding the long-term effectiveness of cerliponase alfa and presents two scenarios exploring this uncertainty. In the first, partial stabilisation is assumed such that [redacted] of patients continue to experience progressive disease,

with a constant rate of decline assumed. This contrasts with the company's preferred analysis where the rate of decline is assumed to slow over time. In the second scenario, it is assumed that all patients will continue to experience a decline in CLN 2 score over time, though at a much slower rate than on standard care. In both scenarios the rate of decline is based on mean decline post 16 weeks and incorporates the longer follow up data provided by the company. Details of how the transition probabilities were estimated are included in the appendix.

Table 13 reports the results of these two scenarios, both of which result in an increase in the ICER. In the scenario where partial stabilisation is assumed the ICER increases to [redacted] per QALY. In the scenario where no stabilisation is assumed the ICER increases [redacted] per QALY.
[redacted]

Table 13 Results alternative disease stabilisation assumptions

	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER	Threshold*
Company base-case (corrected)						
Cerliponase Alfa	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Standard Care	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 1: Partial stabilisation no slowing in the rate of decline						
Cerliponase Alfa	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Standard Care	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 2: No stabilisation						
Cerliponase Alfa	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Standard Care	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

3.2.5 ERG base-case

In response to the NICE briefing document and the company's arguments for an alternate set of assumptions in the economic analysis, the ERG has considered two alternative scenarios, based on the following assumptions regarding the impact of [redacted]:

- [redacted] equal to [redacted], in line with advice received from Prof. Deb Pal.
- Includes cost saving of testing only, on the basis that gene panel testing is soon to become standard practice in the diagnosis of child onset epilepsy that cannot be diagnosed by other means.

This scenario is explored using two alternative scenarios regarding the long-term clinical effectiveness of [redacted]: i) Partial stabilisation, some patients experience slow decline with no change in the rate of over time ii) No stabilisation, all patients experience slow decline. As stated previously, the ERG tends to favour latter scenario as the most likely. This conclusion is however based on the evidence provided in the original company submission. Further examination of the newly provided clinical evidence would be informative in determining which scenario is the most plausible. The ERG also notes that assumptions made regarding the starting population and the utilities used in the model reflect the committees preferences as outlined in the NICE briefing document rather than the ERG's which are somewhat more conservative. Table 13 reports the results of these two scenarios. In the scenario where partial stabilisation is assumed the ICER increases to [redacted] per QALY. In the scenario where no stabilisation is assumed the ICER increases [redacted] per QALY. [redacted]

Table 14 Results of alternative base-case analysis

	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER	Threshold*
Company base-case (corrected)						
Cerliponase Alfa	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Standard Care	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 1: Partial stabilisation no slowing in the rate of decline						
Cerliponase Alfa	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Standard Care	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 2: No stabilisation						
Cerliponase Alfa	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Standard Care	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

4 Conclusions

The company's response to the NICE briefing document included new longer term follow up data from the 190-202 trial and new evidence relating to a proposed [redacted] The submission also included a revised MAA document. Furthermore, the company presents additional economic analysis using company preferred assumptions.

The ERG considers that the company's scenarios represent an optimistic interpretation of the available evidence, and largely align with company's previous base-case assumptions. Importantly, the evidence generated from the 190-202 trial would have been very informative in discerning the likely long-term prognosis of patients receiving cerliponase alfa, had it been provided in full. The presentation of the results in summary form and lack of analysis from the company, however, means

the data is of limited value in this regard. With respect to the new evidence provided regarding the

[redacted]

References

1. Perez-Poyato, M. S., M. P. Marfa, et al. (2013). "Late Infantile Neuronal Ceroid Lipofuscinosis: Mutations in the CLN2 Gene and Clinical Course in Spanish Patients." Journal of Child Neurology 28(4): 470-478.

2. Worgall, S., M. V. Kekatpure, et al. (2007). "Neurological deterioration in late infantile neuronal ceroid lipofuscinosis." Neurology 69(6): 521-535.

3. Turnbull, C., R. H. Scott, et al. (2018). "The 100 000 Genomes Project: bringing whole genome sequencing to the NHS." BMJ 361: k1687.

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

Addendum two to ERG commentary on the updated model and additional evidence submitted by the company in response to the NICE briefing document

Produced by	Centre for Reviews and Dissemination (CRD) and Centre for Health Economics (CHE)
Date	24/09/18

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.

Additional scenario analysis and ERG critique

NICE requested that the ERG run additional analysis on the ERG base-case running the following scenarios:

1) Staring population ML score of 6 and 5 only (50% - 50% split).
2) Staring population ML score of 6 (40%) and 5 (40%), 4 (10%), 3, (5%), 2 (5%).

Results are presented in Table 1 and 2 respectively.

Table 1 Results of alternative base-case analysis, starting population 1

	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER	Threshold
Company base-case (corrected)						
Cerliponase Alfa	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Standard Care	[redacted]	[redacted]	N/A	N/A	N/A	
Scenario 1: Partial stabilisation no slowing in the rate of decline						
Cerliponase Alfa	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Standard Care	[redacted]	[redacted]	N/A	N/A	N/A	
Scenario 2: No stabilisation						
Cerliponase Alfa	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Standard Care	[redacted]	[redacted]	N/A	N/A	N/A	

Table 2 Results of alternative base-case analysis, starting population 2

	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER	Threshold
Company base-case (corrected)						
Cerliponase Alfa	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Standard Care	[redacted]	[redacted]	N/A	N/A	N/A	
Scenario 1: Partial stabilisation no slowing in the rate of decline						
Cerliponase Alfa	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Standard Care	[redacted]	[redacted]	N/A	N/A	N/A	
Scenario 2: No stabilisation						
Cerliponase Alfa	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Standard Care	[redacted]	[redacted]	N/A	N/A	N/A	

Considering the plausibility of the these staring populations the ERG notes that this would require substantially early diagnosis than currently and would require patients to be diagnosed at around [redacted] of age on average, see Figures 1 below. The Company's position is that this is plausible given the median time of first seizure reported in the Nickel et al paper of [redacted] months.

The ERG, however, considers that this an overly simplistic interpretation of the Nickel et paper and potentially overestimates the benefits of the a gene panel testing. In particular the ERG notes the following:

1) The figures reported in Nickel et al refer to medians not means; the ERG considers the mean to be a more appropriate measure because it better reflects the distribution of patients and more accurately estimates the average effect of the gene-panel testing. Unfortunately, the Nickel et al paper does not report mean age at first seizure onset. Based on the DEM-CHILD cohort, which makes up [redacted] of the Nickel et al cohort, however, the mean age of first seizure is [redacted] (median [redacted]). This is several months older that than the [redacted] estimate put forward by the company and would generate a mean ML(CLN2) score of ~4.5, see Figure 1. This aligns approximately with the intermediate starting population put forward by the company in the NICE briefing response document.
2) The [redacted] figure doesn't account for any delay in terms of the time to request, undertake and interpret the result of the gene panel testing. Gene panel tests are complicated to undertake and interpret and it would take at least a month for results to become available from initiation of the test. A delay of 2 or more months post first seizure therefore would therefore be entirely plausible.

Figure 1 Mean ML score by age

Redacted

Further to the above, a number of other points are relevant when interpreting the likely benefits of the gene panel-testing programme. Firstly, the results from the gene panel testing programme implemented in the US and Europe, suggest a mean age of diagnosis of between [redacted], which is considerably higher than [redacted]. Secondly, it is important to remember that the ML scoring system is a somewhat flawed tool for measuring the initial level of impairment because it is designed to measure decline. Therefore while a child may notionally be a 6 on the ML scoring system, it does not necessarily imply, as is assumed in the model that they will be in near perfect health with a normal development trajectory. [redacted]

[redacted]

24th September 2018