For public observers - redacted

Lead team presentation

Cerliponase alfa for treating neuronal ceroid lipofuscinosis type 2

2nd Evaluation Committee Meeting
Highly Specialised Technology, 25 April 2018

Lead team: Ron Akehurt, Shehla Mohammed, Mark Sheehan

Companies: BioMarin

Chair: Peter Jackson

Evidence review group: The University of York

NICE team: Thomas Paling, Raisa Sidhu, Sheela Upadhyaya

Cerliponase alfa (BioMarin)
authorised under 'exceptional circumstances'

Marketing authorisation	Indicated for treatment of neuronal ceroid lipofuscinosis type 2 (CLN2) disease, also known as tripeptidyl peptidase 1 (TPP1) deficiency
Mechanism of action	Recombinant human tripeptidyl peptidase 1, which is an enzyme replacement therapy
Administration & dose	Cerliponase alfa is supplied as a sterile solution (30 mg/ml) for intracerebroventricular (ICV) infusion to the cerebrospinal fluid (CSF). The ICV access device must be implanted prior to the first infusion. The recommended dose of cerliponase alfa for children over the age of 2 is 300mg administered every other week, given by ICV over approximately 4.5 hours
Price	The list price of a pack of cerliponase alfa (consisting of two 150mg vials) is £20,107. The company has proposed a confidential commercial access agreement.
Treatment length	Lifetime treatment duration, subject to clinical judgement

Decision problem

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

ECD preliminary recommendation

*Cerliponase alfa is **not recommended**, within its marketing authorisation, for treating neuronal ceroid lipofuscinosis type 2 (CLN2), also known as tripeptidyl peptidase 1 (TPP1) deficiency*

Recap of ECD considerations
Nature of the condition

- CLN2 is a rapidly progressive and relentless condition leading to:
  - deterioration and then loss of speech and walking ability
  - movement disorders
  - pain
  - progressive dementia
  - loss of vision
  - progressive difficulties with swallowing, constipation, hydration, respiratory function and sleep disturbance
  - need for gastrostomy feeding
  - Complete reliance on carers 6 years of age; average age of death 10 years
- Significant unmet need; no effective treatment options
- CLN2 severely affects lives of families, carers and siblings
  - emotional distress from caring for a child with a life-limiting debilitating condition; noted findings of a study that suggested quality of life for carers is lower when disease is severe than when child has died
  - struggle to provide a normal life for siblings without condition
  - parents become full-time carers – financial burden

Recap of ECD considerations
Clinical

- Diagnosis is challenging, but earlier diagnosis is critical to stabilising disease earlier in its course if an effective treatment is available
  - could allow diagnosis in younger asymptomatic siblings
  - enable parents to make informed reproductive choices
- CLN2 clinical rating scale focuses on motor and language domains, but excludes vision and seizure domains
  - acceptable instrument but broader measures (including vision and seizure domains) presented also considered
- Cerliponase alfa effective in the short term in slowing progression of disease in 2 key functional domains (motor and language)
  - long-term effect of cerliponase alfa on seizure control is uncertain
  - insufficient evidence to suggest treatment prevents vision loss

Recap of ECD considerations
Clinical

- In the absence of evidence it is not possible to predict long-term effects of cerliponase alfa. Assumptions of disease stabilisation, and late stabilisation in particular, were associated with substantial uncertainty. These included:
  - *early stabilisers, that is patients who did not have an unreversed CLN2 score point decline after week 16, were assumed to have no further decline after week 16*
  - *late stabilisers, that is patients having an unreversed CLN2 score points decline after week 16, were assumed not to have a decline after week 96*
- Plausible that patients would have further progression of disease with an associated mortality risk
- The effect of CLN2 on mortality due to effects in other body systems is unknown, as there is no information long-term causes of mortality
  - but, given the severity of CLN2, unrealistic to assume that patients who had cerliponase alfa would have same life expectancy as the general population
- Cerliponase alfa associated with at least an initial improvement in quality of life

Recap of ECD considerations

Value for money

Issue	Conclusion
Discount rate	Insufficient justification for deviation from 3.5%
Vision loss	Incorporation of a disutility and additional costs associated with blindness appropriate
Transition probabilities	Using individual patient data from clinical study report more robust
Starting distribution	The distribution of patients across the 10 modelled health states should reflect severity of disease at diagnosis from study 190-901. The company's assumption of early diagnosis was too optimistic
Disease stabilisation	Assuming partial stabilisation may be reasonable, that is: cerliponase alfa patients achieving stabilisation by week 16 would remain stable for the entire time horizon of the model but late stabilisers would continue experiencing disease progression after week 96
Mortality	Incorporating the impact of neurological progression-related mortality and extra-neurological progression-related mortality appropriate
Beyond direct health benefits	Recognised full impact was not quantified but unlikely to reduce ICER sufficiently

Recap of ECD considerations

Value for money

Issue	Conclusion
Utility values	EQ-5D-3L values estimated from company utility study accepted
	Applying differential utility for on/off treatment inappropriate as it overestimates treatment benefit
	For less severe health states, adjusting utility values for those over the age of 18 appropriate as they exceeded those of the adult general population
	Carer and sibling disutility should be stopped after 30 years
Results	Based on committee's preferred assumptions, incremental QALYs gained – 4.34 ICER [redacted] per QALY gained.
Asymptomatic subgroup	Lower ICERs for this subgroup plausible but above what could be considered cost-effective. No clinical evidence available for this population.
Managed access agreement	Welcome consideration of a managed access agreement including clinical criteria and commercial agreements

ECD consultation responses

- Consultee comments from:
  - BioMarin
- Clinical and patient experts:
  - Batten Disease Family Association
  - UCL Great Ormond Street Institute of Child Health
- Web comments from (n=21):
  - Parents, carers and the public
- No comment response from:
  - Department of Health

ECD consultation comments
Patient group (I)

- Committee did not fully consider benefit of cerliponase alfa not captured in trial
- Treatment allows near normal life, maintaining levels of ability and giving children more independence:
  - ability to drink, eat and swallow
  - no loss of bladder or bowel control
  - gain in strength – can sit up, walk, run, swim – allows interaction and play
  - reduction in seizures
  - less disrupted sleep, improved appetite, weight gain and better energy
  - calmer and more tolerant
  - capable of attending schooling
- Treatment has stabilised children whose disease had already progressed
- *'Being diagnosed and treated at 3 years has allowed our child to retain and even learn new skills, they have no movement disorders and have had no seizures'*
- Children continue to learn and develop, which is suggestive of a long term effect
- Hope that children may live into adulthood and enjoy a meaningful and happy life

ECD consultation comments
Patient group (II)

- Vision:
  - patients treated with cerliponase alfa will likely maintain their visual processing ability, meaning they can better make sense of what they are seeing → positive impact on functional vision
  - if motor abilities are maintained children better able to use remaining vision
  - variation in the additional costs associated with complete vision loss, affected by quality and availability of local support services
  - results in an animal model of CLN2 suggest that TPP1 protein delivered via cerebrospinal fluid (CSF) may protect retinal ganglion cells, preservation of the remainder of the retina will require delivery of normal TPP1 more directly to the retina (via the vitreous body)
  - intravitreal injections have been successful in halting retinal deterioration in dogs
  - BDFA is also funding a 3 year research programme on gene therapy for retinal disease in CLN2 disease in animal models
- Mortality:
  - drawing conclusions about mortality risk from CLN3 patients is inappropriate

ECD consultation comments
Patient group (III)

- CLN2 rating scale too broad and does not account for all treatment benefits
  - insensitive to important changes in motor capability
  - language scale difficult to score with young children
  - seizure control, vision, movement disorders and pain should carry more weight
- Children perform tasks differently at home compared to in hospital, this could have an adverse effect on a child's score on the rating scale
- PedsQL and EQ-5D-5L are not sensitive to changes in quality of life for patients and families impacted by CLN2
- Costs for patients not on treatment are significantly higher than in model
  - proxy of young adult with a severe brain injury is inappropriate
- Emotional strain of CLN2 can have an adverse effect on relationships
- There have been further CLN2 diagnoses since compassionate use places were filled, meaning there are patients not receiving treatment and will lose many of their current abilities at a rapid rate
- Helpless feeling knowing there is an effective treatment which is essential to maintaining the quality of life of children and families which cannot be accessed
- Managed Access Agreement will address lack of long term clinical data

ECD consultation comments
Clinical Experts

- Clear treatment effect demonstrated in the clinical trial
- Patients on ERT for 6 months or more maintain level of function, and in many cases learn new motor and language skills
- Treated patients have stable seizures and do not develop progressive myoclonus, progressive spasticity or movement disorders
  - large improvement in quality of life for patients and families
- Assuming risk of heart, liver and pancreatic complications in CLN2 based on CLN3 is misinformed. Primarily, significant differences in phenotypes. Also, even for CLN3:
  - no evidence of pancreatic or liver failure at any age
  - cardiac disease does not develop by the age of 14
- Better proxy may be milder forms of CLN2 – no evidence of extra-neuronal disease
- MRI scans find no deterioration of the brain after 1 year of enzyme replacement
- No evidence of any cardiac structural or rhythm abnormalities identified in the trial or in the expanded access program
- '[decision] not surprising given the health economic evaluation, anticipated cost of the technology and NICE criteria. We have an ethical duty to continue their [children on trials] treatment within the NHS as long as the treating physicians and families believe such treatment is in the child's best interests.'

ECD consultation comments
BioMarin (I)

- Company has developed diagnostic programmes aimed at supporting early diagnosis of CLN2 disease
  - committee should have taken into account the impact of earlier diagnosis in health state starting population
  - historical control population at diagnosis unrepresentative of current incident population as some patients were recruited 40 years before first genetic test to aid CLN2 diagnosis
  - DEM-child data base shows there has been a trend towards earlier diagnosis of CLN2: ML score of >4 (70% in 2008 vs 27% pre-1998)
- Evidence of a reduction in non-tonic-clonic seizures not considered. Additionally, clonic-tonic seizures that have the greatest impact on patient quality of life – not clear in ECD
- Never claimed treatment prevented vision loss, evidence suggests a slowing of vision loss
  - 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
- Disagree that vision domain of Hamburg scale not the most appropriate scale
  - validated measure for measuring visual function in CLN2 patients

ECD consultation comments
BioMarin (II)

- Committee accept treatment improves quality of life, but disregard these benefits in their assessment of cost-effectiveness
- Acknowledgement that there is limited long-term evidence and that assumptions about long-term disease stabilisation are associated with uncertainty, but:
  - 96 week trial data presented for all patients, 129 week and 145 week data submitted for some patients – longer term data is being captured
  - safety and efficacy data is still being collected, which will be made available to NHSE as part of any future MAA
  - uncertainty is not surprising given this is the first treatment for CLN2
- Lack of long term data does not imply no long term benefit
  - only 1 of 20 patients with data post 96 weeks had an unreversed decline in M/L score at last observation compared to their week 96 score
  - there were some fluctuations in scores between Week 96 and week 129 in 2 other patients, their actual score was the same – no unreversed decline
  - cannot reasonably be concluded that the mean trend indicated further decline
- Additionally, uncertainty also applied to committee's preferred assumptions
  - 'absence of data cannot and should not be construed solely to the benefit of one opinion'

ECD consultation comments
BioMarin (III)

- Development of new epileptiform activity in treated CLN2 patients is not indicative of neuronal progression or worsening of seizures
- Conclusions on mortality are misinformed:
  - CLN3 is not a suitable proxy
  - extra-neurological mortality not relevant – no evidence in literature or in practice; also, cerliponase alfa delivered via ICV has been shown to go into the blood stream at concentrations similar to the blood concentration seen in atypical patients who live longer with no presentation of cardiovascular or extra-neurological complications → plausible that this concentration in the blood should be sufficient to protect from any future risk of extra-neurological complications.
  - limited evidence of cardiac abnormalities
- Disagree with conclusion mixed measures repeat models (MMRM) makes better use the available data
  - using the first and last point simple regression method to estimate decline was pre-defined in the analysis plan
  - regulators agreed the company approach was acceptable
  - MMRM models require significant assumptions

Additional evidence

The company has presented the following additional evidence for consideration:

- 2 scenarios incorporating alternative assumptions
- A managed access agreement proposal
- A commercial offer – commercial in confidence to be discussed in part 2

Alternative scenarios

Company presented 2 alternative scenarios varying some assumptions

	Committee preferred ECD assumptions	Company Scenario 1	Company Scenario 2
Starting population	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%	As per base case ML 6 – 40%, ML 5 – 40%, ML 4 – 10%, ML 3 – 5%, ML 2 – 5%, ML 1 – 0% ML 0 – 0%
Late stabilisers	100% (of late stabilisers) continue to progress at same rate after 96 week	20-25% continue to progress after 96 week but at reduced rate of decline	Same as company scenario 1
Extra-neuro and neuro-disability related mortality	Mortality risk of patients with traumatic brain injury (TBI)	Disagree, but apply same assumption as ERG	Mortality risk of patients with TBI but adjusted for comorbidities present before TBI occurred
Utilities	Standard of care utility values in both arms (using EQ-5D-3L data)	As ERG but with additional utility benefit of: 0.1 for HS 2-4 and 0.2 for HS 5-6	As per base case i.e. taken from utility studies
Undisc QALYs	5.89	29.73	32.80
Disc QALYs	4.34	12.22	13.20

ERG comment
Starting population

- Key driver of cost-effectiveness
- Company suggest their alternative scenarios are more realistic representations of current and future practice on the basis that (i) there's been a trend toward earlier diagnosis (DEM-CHILD data), (ii) the introduction of [redacted] will lead to further earlier diagnosis
  - highly speculative; no attempt to extrapolate improvements in diagnosis observed in the DEM-CHILD data, nor does it link potential benefits of any future campaign to reduce time in diagnosis
  - trends towards earlier diagnosis in the DEM-CHILD cohort are observed in 27 people born after 2000, therefore limiting the meaningfulness of any conclusions drawn
  - magnitude of benefit resulting from an early diagnosis campaign is significantly uncertain

ERG comment

Disease stabilisation and long-term effectiveness

- Company present scenario relaxing stabilisation assumption by assuming 74% stabilise (100% in original base case) and 26% continue to experience disease progression (at a slower rate than on standard care)
- This assumption is more reasonable than the base-case, however it is still subject to considerable uncertainty given limited long-term evidence.
- Plausible that all patients will continue to progress, because:
  - proportion of patients experiencing a decline in CLN2 rating scale increases with the length of follow-up
  - one patient experiences a decline in CLN2 score post week 96
  - EEG examinations in study 190-201/202 show new epileptiform activity in [redacted] of patients, suggestive of continued progression
  - MRI measurements show reductions in brain volume *n.b. company suggest this could be attributed to debulking of lysosomal storage disorders (LSDs) as opposed to disease progression*
  - non-human studies only show a slowing, not halting, of progression of symptoms
- Assuming very slow progression (1 point per 10 years) would have a large impact on patients life and significantly impacts cost-effectiveness

ERG comment
Health state utilities

- Company's alternative scenarios assume
  - cerliponase alfa patients with CLN2 scores of 3, 4 and 5 experience a 0.1 point improvement in quality of life, to account for improved seizure control.
  - patients with CLN2 scores of 0, 1 and 2 experience 0.2 point improvement to account for improved seizure control, reduced pain and reduced severity of myoclonus
- Assumed quality of life benefits for health states 2,3,5,6 and 7 are larger than in the original base case
- Magnitude of benefit is arbitrary, with no evidence presented in support. Related evidence of patients with uncontrolled epilepsy suggests a quality of life benefit of 0.1 is at the upper limit for seizure control
- No evidence to support quality of life improvements in myoclonus and pain, benefits are supported by parent observation and clinical input
- ERG present a scenario with a reduced quality of life gain, based on the quality of life studies in people with epilepsy, with pain and myclonus benefits removed

ERG comment
Mortality

- The ERG is satisfied with the company's alternative approach in ECD response scenario 2

Managed access agreement (I)
Start criteria

- All required
  - Confirmed CLN2 diagnosis, based on clinical info and enzymatic activity test
  - No diagnosis of an additional progressive life limiting condition where treatment would not provide long term benefit
  - CLN2 score ≥ 2
  - Patient is willing to comply with monitoring
  - Patients must have baseline assessments and have signed the MAA to start

Managed access agreement (II)
Stopping criteria

- Patients aged under 3 excluded from stopping criteria as natural decline in functional endpoints is not seen at this point
- Stop if any of the following apply:
  - Non-compliance (fewer than 2 attendances in 14 months, excluding medical reasons for missed doses)
  - Meets stopping criteria for new patients (treatment naïve) or meets stopping criteria for patients on treatment
  - Unable to tolerate infusions
  - Patient is diagnosed with with an additional progressive life limiting condition where treatment would not provide long term benefit
- Stop criteria for patients aged 3 or more who are treatment naïve:
  - A loss of 3 or more points on the CLN2 ML scale from baseline, in 18 months of treatment, and a total CLN2 rating scale score < 2

  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; and 0.2 drop in EQ5D-5L; and decline in CLN2 QoL assessment of ≥ 15 points
- Retest patients twice in 12 week in the case of temporary illness

Managed access agreement (III)
Stopping criteria

- Stop criteria for patients currently on treatment
  - A loss of 3 or more points on the CLN2 ML scale from baseline, in previous 12 months of treatment, and a total CLN2 rating scale score < 2

  OR

  - Progression to an unreversed score of 0 on the CLN2 Rating Scales ML Score

  AND

  - During the first eighteen months of treatment, a reduction in proxy reported patient quality of life:
    - ≥ 15 points on the PedsQL total score; and 0.2 drop in EQ5D-5L; and decline in CLN2 QoL assessment of ≥ 15 points

- Retest patients twice in 12 weeks in case of temporary illness
- Patients taken off treatment will continue to be monitored

ERG comment

Managed access agreement: stopping rule

- Stopping rule described is unlikely to apply to many (if any) patients
  - would require patients to experience a rate of decline equivalent to those on standard care
  - the stopping rule only protects the NHS from treatment failure, but does not address the uncertainty whether cerliponase can provide long term stabilisation of disease progression in some or all patients.
- The stopping rule relating to progression of disease and falling quality of life was not applied in the company's economic analysis. However, it would be challenging to apply using a markov model.
  - memoryless nature of the model makes it inappropriate to use this model structure as it would overestimate the proportion of patients covered by the stopping rule

Key issues for consideration

- What assumptions and inputs does the committee consider to be most plausible regarding:
  - starting distribution of patients in the model
  - utility values
- Is the committee satisfied with the incorporation of extra-neurological mortality as per the company's alternative scenario?
- Does the committee consider that the MAA proposals will result in data collection to address current uncertainties?
- Are the start and stop criteria in the proposed managed access agreement appropriate?
  - Have all stakeholders been involved in agreeing the criteria?

Slides for public – Contains no ACIC

NICE National Institute for Health and Care Excellence

Cerliponase alfa for treating neuronal ceroid lipofuscinosis type 2

Chair's presentation

3rd appraisal committee meeting
Highly Specialised Technologies, 19 September 2018
Lead team: Ron Akehurt, Shehla Mohammed, Mark Sheehan
ERG: The University of York
NICE technical team: Orsolya Balogh, Thomas Strong, Sheela Upadhyaya
Company: BioMarin

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Price	The list price of a pack of cerliponase alfa (consisting of two 150mg vials) is £20,107. The company has proposed a confidential commercial access agreement
Treatment length	Lifetime treatment duration, subject to clinical judgement

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

[redacted]

Recap: evaluation history

- **January 2018: 1st Evaluation Committee meeting**
  - *Cerliponase was **not recommended***
  - *ECD released*

- **April 2018: 2nd Evaluation Committee meeting**

Committee considered comments received during consultation, draft managed access agreement (MAA) and a new commercial offer proposed by the company

  - *Cerliponase was **not recommended***
  - *No guidance was published*

- **September 2018: 3rd Evaluation Committee meeting**

Company submitted additional evidence

[redacted]

Additional evidence submitted by BioMarin

- The company has presented the following additional evidence for consideration in public:
  - Further details on additional data to be collected as part of the MAA
  - Further follow-up results from study 190-202
  - Updated assumptions to base-case

- The company has presented the following confidential additional evidence for consideration in part 2:
  - Clinical evidence to support cost savings and quality of life benefits resulting from the early diagnosis of patients with child onset epilepsy
  - All cost-effectiveness results

[redacted]

Recap of ECD: *Nature of the condition*

CLN2 is a rapidly progressive and relentless condition leading to:	
Deterioration and then loss of speech and walking ability	Progressive difficulties with swallowing, constipation, hydration, respiratory function and sleep disturbance
Movement disorders	Loss of vision
Pain	Need for gastrostomy feeding
Progressive dementia	Reliance of carers and early mortality

- Significant unmet need; no effective treatment options
- Diagnosis is challenging, earlier diagnosis is critical to stabilising disease earlier in its course if an effective treatment is available
- CLN2 clinical rating scale focuses on motor and language domains, but excludes vision and seizure domains
- Cerliponase alfa effective in the short term in slowing progression of disease in 2 key functional domains (motor and language)
  - Long-term effect of cerliponase alfa on seizure control uncertain
  - Insufficient evidence to suggest treatment prevents vision loss

[redacted]

Recap of ECD: Clinical

- Stabilisation of disease progression plausible for proportion of patients, but associated with substantial uncertainty. Committee assumed:
  - *Early stabilisers assumed to have no further decline after week 16*
  - *26% of late stabilisers would have slow disease progression after week 96*
- Given the severity of CLN2, treated patients will have shorter life expectancy than general population, but no information on long-term causes of mortality
  - Progression of disease should be associated with higher mortality risk
  - Causes of mortality should be captured in any data collection arrangement
  - Excluding extra-neurological mortality risk reasonable
- Treatment with cerliponase alfa could result in some additional utility benefit beyond that achieved through delaying disease progression

[redacted]

Recap of ECD: Economic (I)

Issue	Conclusion
Discount rate	Insufficient justification for deviation from 3.5%
Vision loss	Incorporation of a disutility and additional costs associated with blindness appropriate
Transition probabilities	Using individual patient data from clinical study report more robust
Starting distribution	60% of patients assumed to start treatment in health states 1 and 2 (CLN2 score 6 and 5 respectively)
Disease stabilisation	Late stabilisers (26%) would continue to progress after week 96, at a slower rate those receiving standard care; remaining proportion (74%) stabilising
Mortality	Incorporating the impact of neurological progression-related mortality and excluding extra-neurological progression-related mortality appropriate
Beyond direct health benefits	Recognised full impact was not quantified but unlikely to reduce ICER sufficiently

[redacted]

Recap of ECD: Economic (II)

Issue	Conclusion
Utility values	EQ-5D-3L values estimated from company utility study accepted
	Applying utility increment of 0.045 in health states 2 to 6
	For less severe health states, adjusting utility values for those over the age of 18 appropriate
	Carer and sibling disutility should be stopped after 30 years
Managed access agreement	MAA would be welcomed, but the proposed agreement required refinement to ensure it is fit for purpose

[redacted]

New evidence: Disease stabilisation and longer-term follow-up data (I)

- Newly available follow-up data for patients enrolled in the 190-202 study

	Mean value (SD); N=23 (except Week 169, N=21)		Mean change vs previous 24-week period*
	[redacted]	[redacted]	
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]
LRO	[redacted]	[redacted]	

Source: ERG response to additional evidence Table 1

Key: LRO - Last recorded observation; * calculated by ERG

[redacted]

- **ERG comment**: not possible to assess whether patients experiencing a decline in CLN2 score were patients who **previously experienced a decline**; or patients who had **otherwise been stable up to this point** (latter is more plausible)

New evidence: Disease stabilisation and longer-term follow-up data (II)

Company:

- [redacted]
- [redacted]
- [redacted]
  - ERG note that this [redacted] than the committee's preferred assumption from ECM2

ERG comment:

- Potentially over-optimistic given evidence of [redacted]
- ERG presents ***alternative scenario analysis***: [redacted]

[redacted]

Does the follow-up evidence generated from the 190-202 trial indicate that there is a trend to stabilisation for late stabilisers?

Updated company base-case

Company base-case includes:

- Revised transition probabilities for cerliponase alfa patients based on new longer-term follow up data
- Partial stabilisation in which early stabilisers stabilised after week 16 and late stabilisers continue to experience slow decline
  - Slower decline with trend towards stabilisation based on the new longer-term follow up data
- Incorporation of cost savings and benefits due to earlier use of gene panel
- All other committee preferred assumptions
  - ERG notes committee preferred assumptions regarding starting population and utilities are somewhat more optimistic than ERG's preferred

Cost-effectiveness estimates are confidential and will be presented in part 2

[redacted]

ERG changes to updated company base-case

- Correct a calculation error concerning uptake of the gene panel testing
- Set uptake of gene panel testing to 25% - based on clinical advice received
- Include cost savings of gene panel testing only – as gene panels will soon be standard practice

- ERG present 2 alternative base-cases:
  - **Partial stabilisation**, some patients experience slow decline with no change in the rate of over time (i.e no change to committee's previous preferred assumption)
  - **No stabilisation**, all patients experience a slow decline calculated using updated clinical data (ERG considers this scenario to be more likely)

- ERG present several scenarios which explore the impact and sensitivity of:
  - Uptake of gene panel (set to 25% in ERG base-cases)
  - Including only cost or QALY savings at one time (cost savings included in ERG base-cases)
  - Diagnostic yield of gene panel (impact removed in ERG base-cases)
  - QALY gains of gene panel (impact removed in ERG base-cases)

[redacted] ***What is the committee's preferred modelling assumption concerning long-term stabilisation?***

Managed access agreement

Recap - Managed access agreement (I)

Note: The Managed Access Agreement will only be implemented if the commercial agreement is considered sufficient by NHS England and Committee

Start criteria

- All required
  - Confirmed CLN2 diagnosis, based on clinical info and enzymatic activity test
  - No diagnosis of an additional progressive life limiting condition where treatment would not provide long term benefit
  - CLN2 score ≥ 2
  - Patient is willing to comply with monitoring
  - Patients must have baseline assessments and have signed the MAA to start

[redacted]

Recap - Managed access agreement (II)

Stopping criteria

- Patients aged under 3 excluded from stopping criteria as natural decline in functional endpoints is not seen at this point
- Stop if any of the following apply:
  - Non-compliance (fewer than 2 attendances in 14 months, excluding medical reasons for missed doses)
  - Meets stopping criteria for new patients (treatment naïve) or meets stopping criteria for patients on treatment
  - Unable to tolerate infusions
  - Patient is diagnosed with with an additional progressive life limiting condition where treatment would not provide long term benefit
- Stop criteria for patients aged 3 or more who are treatment naïve:
  - A loss of 3 or more points on the CLN2 ML scale from baseline, in 18 months of treatment, and a total CLN2 rating scale score < 2

  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; and 0.2 drop in EQ5D-5L; and decline in CLN2 QoL assessment of ≥ 15 points
- Retest patients twice in 12 week in the case of temporary illness

[redacted]

Recap - Managed access agreement (III)

Stopping criteria

- Stop criteria for patients currently on treatment
  - A loss of 3 or more points on the CLN2 ML scale from baseline, in previous 12 months of treatment, and a total CLN2 rating scale score < 2

    OR

  - Progression to an unreversed score of 0 on the CLN2 Rating Scales ML Score

    AND

  - During the first eighteen months of treatment, a reduction in proxy reported patient quality of life:
    - ≥ 15 points on the PedsQL total score; and 0.2 drop in EQ5D-5L; and decline in CLN2 QoL assessment of ≥ 15 points

- Retest patients twice in 12 weeks in case of temporary illness
- Patients taken off treatment will continue to be monitored

[redacted]

Are the starting and stopping criteria of the MAA appropriate?

Recap - Key committee conclusions

- Proposed starting criteria of a CLN2 Rating Scale ML Score of 2 or above
  - Incorporating the majority of the CLN2 patient population in the MAA would enable the collection of efficacy data in a broad population
  - It would be very informative for a future evaluation
- Proposed stopping criteria relating to a fall in proxy reported utility scores
  - Stopping criteria was unlikely to be met as the proposed drop in instrument scores to trigger stopping treatment were relatively large
  - MAA should capture quality of life information to inform a future evaluation

[redacted]

Recap – Areas committee considered data collection could benefit

1) Measurement of CLN2 clinical rating scores over time
2) Rate of seizures in cerliponase alfa treated and untreated patients (long-term effect uncertain)
3) Myclonus control –evidence to validate that cerliponase alfa leads to improved myoclonus control
4) Visual acuity – there is insufficient evidence to support that people treated with cerliponase alfa have a slower decline in vision loss
5) Extra-neurological symptoms – the long-term impact of TPP1 expression on body systems other than the central nervous system
6) Cause of mortality –causes of mortality, particularly extra-neurological causes need to be monitored
7) Quality of life – concerns about the robustness of the vignettes to elicit utility values
8) Trends in earlier diagnosis resulting from the proposed initiatives
9) Benefits and cost savings from the implementation of the proposed gene panel testing

[redacted]

New evidence: Company updated proposal for data collection (I)

Clinical Outcome Assessments (measured at baseline and 6 monthly unless indicated)	
Assessments	**Comments**
Total CLN2 disease rating scales	Includes the four domains of motor (walking), language, vision and seizure.
Weill Cornell Disease Rating Scale	Weill Cornell evaluates gait, language, myoclonus and feeding
Visual Acuity Test	
Missed infusions	Recorded as necessary
ECG, 12-lead	
Electroencephalogram (EEG), standard awake	
Seizure Diary	As captured by the family members using a seizure diary template developed by the BDFA
Brain MRI	Baseline and yearly
Electroretinogram	Baseline and yearly
Optical Coherence Tomography	Baseline and yearly
Visual Evoke Potential	Baseline and yearly
Liver function tests	
Causes of death	Should death occur in patients, the age and cause of death should be collected by the treating physicians

[redacted]

- Company proposes updated data collection addressing all of committee's concerns

New evidence: Company updated proposal for data collection (II)

Clinical Outcome Assessments (measured at baseline and 6 monthly unless indicated)	
Assessments	**Comments**
PRO Tools	
PedsQL	Administered by the Patient Organisation. Proxy reported by parents of patients or person responsible for patient
EQ-5D-5L	
CLN2QoL	
Neurodevelopmental (cognitive) assessment tools	
Bayley Scales of Infant Development III	For patients up to the age of 3 years. Clinical psychologist. Baseline and yearly
Wechsler Preschool and Primary Scale of Intelligence (WPPSI-IV)	For patients aged 3 – 18. Clinical psychologist. Baseline and yearly
Vineland Adaptive Behaviour Scales	Administered by the clinical psychologist

- In addition company will collect data to assess the benefits and cost savings resulting from use of the gene therapy including:
  - [redacted]
  - [redacted]

For further details of data collection see draft Managed Access Agreement (confidential)

[redacted] ***Does the company's new data collection proposals address the committee's concerns?***

Key issues

- Are the starting and stopping criteria of the MAA appropriate?
- Does the company's new data collection proposals address the committee's concerns?
- Does the follow-up evidence generated from the 190-202 trial indicate that there is a trend to stabilisation for late stabilisers?
- What is the committee's preferred modelling assumption concerning long-term stabilisation?
  - [redacted] (Company preferred)
  - Partial stabilisation with constant slow decline (i.e. no change to committee's ECM2 preferred assumption)
  - No stabilisation, all patients experience slow decline (ERG preferred)

[redacted]

The company's additional evidence and economic case contain large amount of confidential information, therefore the discussion around the gene panel testing, commercial offer, company and ERG base-cases and additional work done by the ERG will continue in Part2

[redacted]