Public observer slides – redacted

Lead team presentation

Cerliponase alfa for treating neuronal ceroid lipofuscinosis type 2

1st Evaluation Committee Meeting
Highly Specialised Technology, 17 January 2018

Lead team: Ron Akehurt, Shehla Mohammed, Mark Sheehan

Company: BioMarin

Chair: Peter Jackson

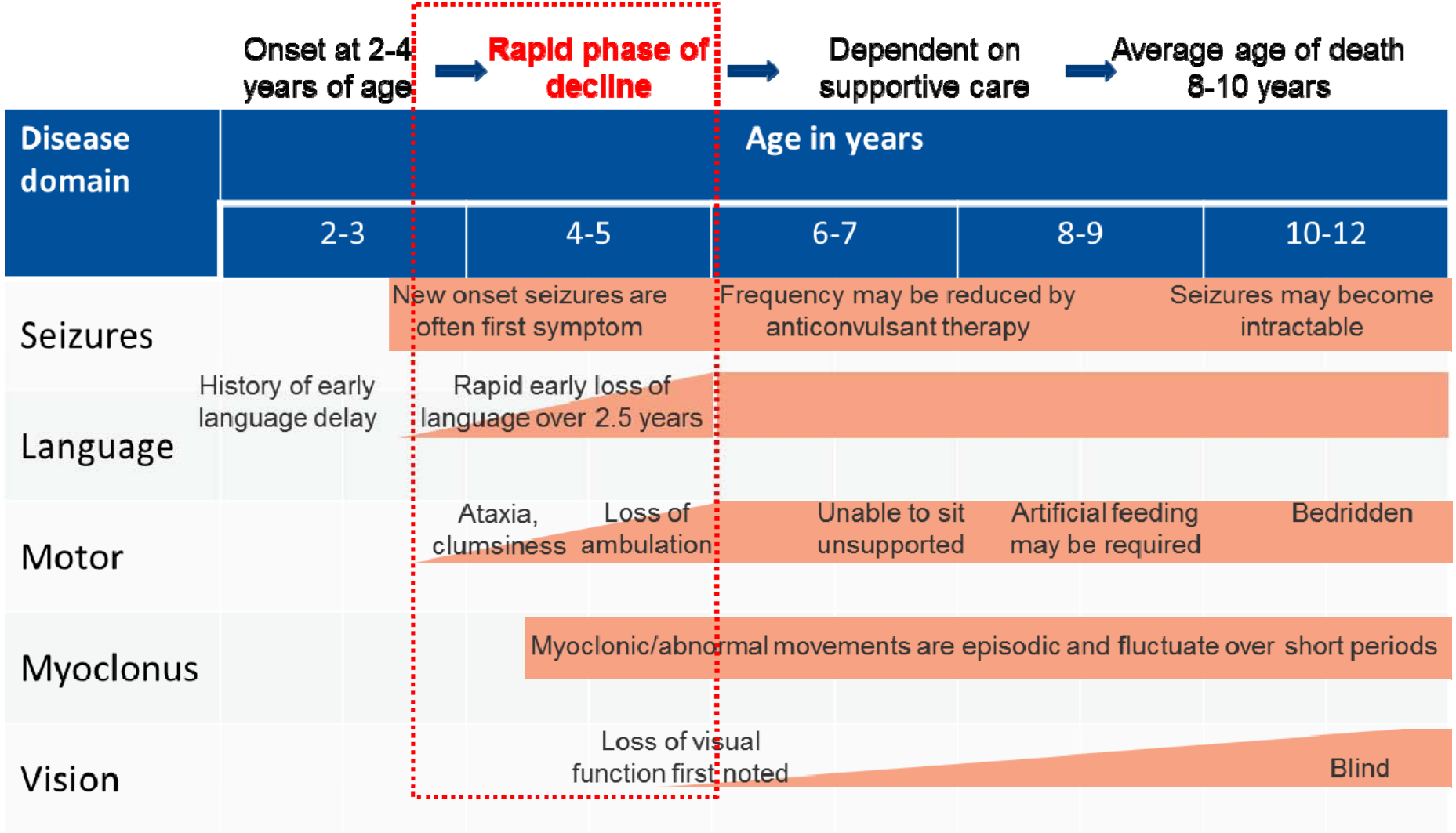
Evidence review group: The University of York

NICE team: Thomas Paling, Raisa Sidhu, Sheela Upadhyaya

Disease background

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

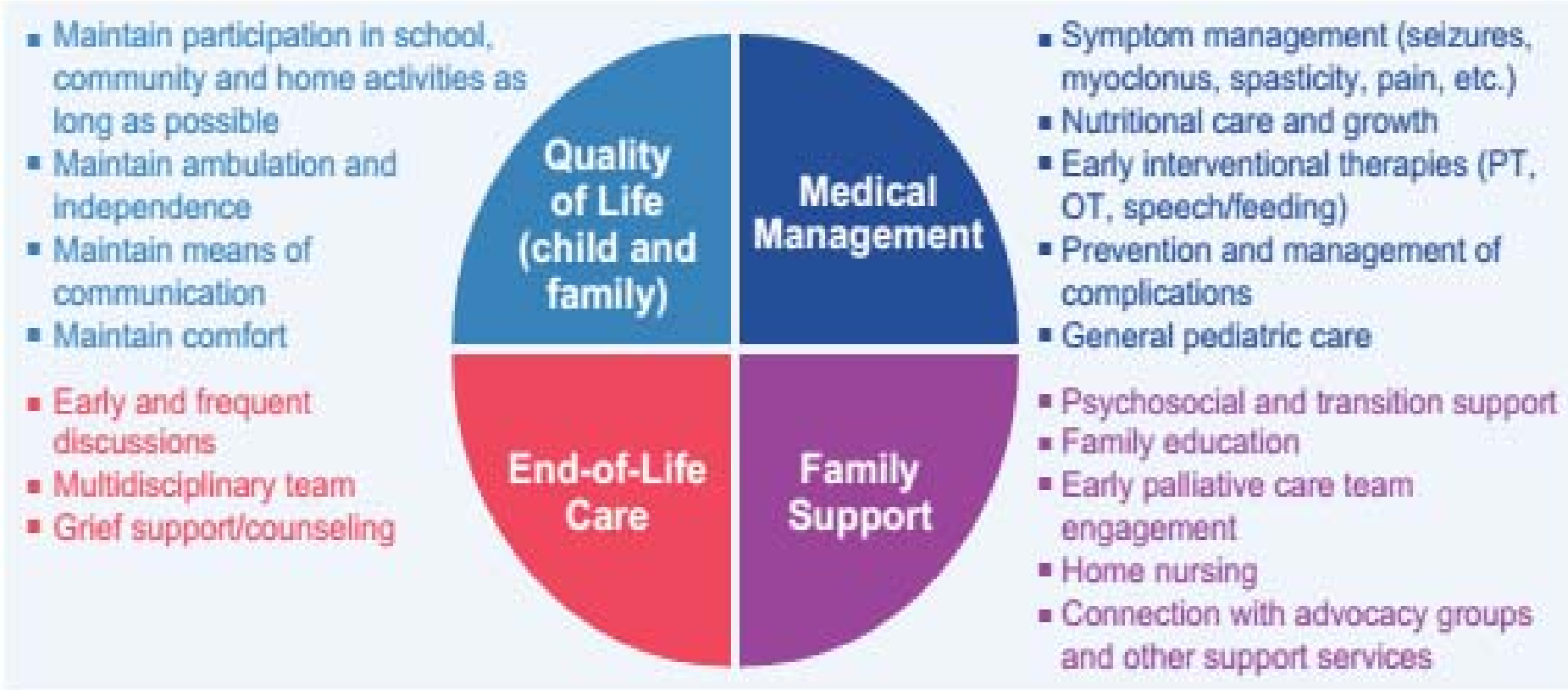
Course of CLN2 disease



The rapid progression of the disease means that by the age of 6, most children will be completely dependent on families and carers for all of their daily needs

Current treatment options

- Current management is limited to symptomatic relief and supportive care, guided by principles of paediatric palliative care; no clearly defined pathway



- No current treatment options address underlying cause of disease, namely, TPP1 enzyme deficiency
- Uncertainty in best practice for treatment

Cerliponase alfa

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
List price	The price of a pack of cerliponase alfa (consisting of two 150mg vials) is £20,107.00
Treatment length	Lifetime treatment duration, subject to clinical judgement

Source: Company submission

Decision problem

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

ERG comment:

- Clinical evidence in company submission is derived from a narrower population of children aged >3 with mild-to-moderate disease and 'stable' seizures

Clinical expert comments

- Cerliponase alfa is a step-change in the management of CLN2
- Treatment aims to prevent disease progression and stabilise disease
- A significant response would be: maintained developmental skills (motor, language and cognitive) for at least six months from initiation of treatment when deteriorating function would be expected without disease modifying therapy
- Rate of expected disease progression based on motor and language skills has slowed significantly for those treated with cerliponase alfa
- Epileptic seizures continue and life expectancy may still be shortened, but if progressive neurodisability can be prevented, delayed or slowed, the consequent problems (necessity for a tube feeding, aspiration pneumonia and spinal scoliosis) may be mitigated, and life-expectancy increase
- Visual impairment is an important clinical factor not modified by treatment – hugely important to quality of life
- Treatment is more effective before symptom onset or at an early disease stage
- After 1st year of treatment with cerliponase alfa there has been no further loss of skills in any of the patients
  - Benefit on medium and long term quality of life and survival is unknown

Clinical expert comments

- Infusions well tolerated with minimal adverse effects
- Catheter blockage and infection are main predictable adverse events with increased risks of both if the treatment is delivered outside centres of expertise
- What investment would be needed to introduce cerliponase alfa?
  - A diagnostic pathway early in the course of disease
  - Specialist multidisciplinary teams with expertise in delivery of cerebro-ventricular infusions of enzyme replacement therapy and the management of symptoms of CLN2 disease
  - Psychological and emotional support for families attempting to make decisions regarding initiation of therapy
  - Care pathway and protocol/guideline for long term monitoring of patients; response to therapy, adverse events, and emerging extra-CNS disease
  - Long term monitoring of cardiac, pancreatic and gut function
  - Need for an ethical framework for decision making regarding eligibility criteria for treatment
- QALYs don't capture the benefits from a retained ability to communicate and enjoy their environment in patients with limited mobility and speech

NHS England comments

- Patients with CLN2 would be directed to Lysosomal Storage Disease (LSD) expert centres to access the technology
- Pathways in LSD centres are well defined for those with LSDs which are treatable with disease modifying drugs or which are predominantly metabolic
  - CLN is somewhat different as a primarily neurological disorder with an unremitting degenerative course
- Cerliponase alfa requires the insertion of the intra cerebral conduit for drug delivery
- Estimated that there are 10 CLN2 patients eligible for treatment

Clinical evidence summary

Trial name	Type	Location, duration and numbers	Primary outcome(s)
190-201 **Pivotal study**	Phase 1/2, open-label, including dose escalation phase	• United States, Germany, Italy, United Kingdom • 48 weeks • 23 patients (aged 3 to 16)	• Adapted CLN2 rating scale • Safety
190-202 **Ongoing**	Extension to study 190-201	• Up to 240 weeks • 23 patients	• Motor & language changes • Safety
190-901 **Compari-son**	Natural history study, retrospective	• Germany, Italy (DEM-CHILD database) • 41 untreated patients (23 matched to 190-201/202)	• Motor & language changes
Unpublished			
190-502	Expanded access scheme, open label	• UK • 5 patients (≥2 years)	• Safety & tolerability
190-203	Phase 2, open label No data reported	• Younger siblings of participants in 190-201 (≤17 years) • Up to 5 patients • 96 weeks	• Adverse events • Motor and language changes • Immunogenicity

CLN2 clinical rating scale

Primary outcome in key trials

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

- Used in clinical trials; adapted from Hamburg and Weill Cornell scales
- Motor and language domains best track the progression of CLN2 disease, a 1-point change on the summary motor-language score is clinically meaningful

ERG comment:

- EMA ad-hoc experts meeting confirmed that CLN2 clinical rating scale was an acceptable primary outcome
- Limitation: not assessing all the domains from Hamburg/Weill Cornell scales
- Expression of TPP1 is not limited to the central nervous system

⊙ ***Is the CLN2 clinical rating scale an appropriate outcome measure?***

Study 190-201/202

ERG comments

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

⊙ ***Is the study 190-201/202 population generalisable to English clinical practice?***

⊙ ***Is it reasonable to assume earlier diagnosis than observed in the trial?***

Study 190-901: Natural history study

- Patients in 190-201/202 were matched to 190-901 population using 1:1 matching algorithm (n=22), based on their CLN2 clinical rating scale score and age within 12 months
- Baseline analysis found that first CLN2 symptoms commonly manifest around 3 years of age, unprovoked seizures and language difficulties are most common, and diagnosis is at ~5 years age, nearly 2 years from onset of symptoms
- Disease progression at time of diagnosis is variable, with Hamburg Motor-Language scale scores most commonly in the 2-4 range
- Analysis of rate of decline of CLN2 clinical rating scale confirmed rapid progression of disease:
  - Mean points lost per 48 weeks: 2.09 (first and last points method)
- The time taken to lose 2 points on the CLN2 clinical rating scale at different stages of disease was also estimated in the 190-901 population, as an alternative way to measure the rate of decline
  - the mean time for a 2-point decline was less than a year for all categories except for those with CLN2 scores of 5 & 4

Study 190-901: Natural history study
ERG comment

- There are differences between baseline CLN2 rating scores between matched natural history (NH) population and source population → scores may not be compared against same outcome in the natural history population, but against estimated or imputed outcome data
- Origin of study 190-901 data is unclear, unable to replicate analyses
- NH patients had lower average vision score (more advanced disease)
- Estimates of mean decline in the natural history controls varied depending on the statistical method used
  - The more sophisticated mixed effects models of repeated measures data resulted in a substantially lower estimate of mean decline (per 48 weeks)
    1. autoregressive variance: 1.29 points (95% CI 1.03 to 1.54)
    2. unstructured variance: 1.46 points (95% CI 1.12, 1.79)
    3. main analyses: 2.09 points (95% CI 1.79 to 2.40)
  - Mixed effects model (1 & 2) are likely to have greater validity because it made better use of the data reported over time

⊙ ***How should rate of decline be estimated in the NH population?***

Summary of analyses

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

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

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

Analyses of the secondary endpoints include:

- Hamburg scale analysis
- Health-related quality of life measures (carers and toddlers)

Early vs. late Stabilisers

- 'Early stabilisers' experienced no further unreversed declines after 16 weeks.
  - Assumed in the model to experience no further decline after 16 weeks
- 'Late stabilisers' experienced any unreversed point decline after 16 weeks
  - Assumed in the model to experience no further decline after 96 weeks

ERG comment:

- Post-hoc categories; could be sampling error rather than genuine reflection of patterns of response
- 96 weeks follow up insufficient to make long terms judgements on stabilisation
- Some patients classified as early stabilisers had fluctuations in CLN2 score suggesting disease may not be stable
- Plotting mean CLN2 score for 'late stabilisers' suggests late stabilisation is unlikely as there is a trend of decreasing scores from week 48 to week 96
  - Contradiction to the assumption of disease stabilisation
- Relative to baseline, all patients appeared to experience new epileptiform activity
  - Evidence that disease progression has not halted

⊙ ***Is 'early' or 'late' disease stabilisation (as defined) possible with cerliponase alfa treatment?***

Responder analysis
Study 190-201; 48 weeks

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

Baseline CLN2 clinical rating scale score

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

65%

87%

Responder analysis
Study 190-201/202; 96 weeks

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

ERG comment:

- The number of patients experiencing no change or improvement in score reduced at week 96 from 15 patients to [redacted], [redacted], or [redacted](inconsistent reporting)

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Change in CLN2 score

Study 190-201/202; 96 weeks

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

Figure redacted – academic in confidence

- CLN2 score includes language and motor domains (ML)
- CLN2 total score includes seizure and vision domains as well as language and motor

ERG comments

Change in CLN2 clinical rating scale

Follow up time (weeks)	CLN2 score (ML): Mean (SD)	Absence of unreversed decline from baseline: n (%)	Absence of unreversed 2-point decline from baseline: n (%)	Decline in CLN2 points per 48 weeks: mean (SD)
Baseline	[redacted]	[redacted]	[redacted]	[redacted]
16	[redacted]	[redacted]	[redacted]	[redacted]
48	[redacted]	[redacted]	[redacted]	[redacted]
96	[redacted]	[redacted]	[redacted]	[redacted]
Last follow up	[redacted]	[redacted]	[redacted]	[redacted]
ERG extracted mean CLN2 scores from study 190-201/202				

- Decline in CLN2 scores for cerliponase alfa patients slows over time as shown both in mean rate of decline and mean CLN2 score
- Fewer patients experience no decline in the later periods, therefore caution is needed when interpreting long-term benefits
  - Contradicting assumption of disease stabilisation, slope analyses suggest on average patients receiving cerliponase alfa continue to experience further declines in CLN2 score after week 96

Time-to-event analysis

Study 190-201/202: Time to first event

- After adjusting for baseline ML score, age, genotype and sex, compared to treated subjects, natural history patients were [redacted] times more likely to have experienced an unreversed 2-point decline in the CLN2 score (ML) ([redacted])

Figure redacted – academic in confidence

⊙ ***Does the absence of an unreversed 2-point decline in CLN2 score (ML) represent a clinically meaningful benefit?***

Slope analysis

Study 190-201/202

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

⊙ ***Does treatment with cerliponase alfa slow the rate of CLN2 disease progression?***

Hamburg scale

Domains

Hamburg scale scores at time points:	Seizures				Vision			
	Natural history controls		Cerliponase alfa		Natural history controls		Cerliponase alfa	
	Mean (SD)	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)	N
Baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 49	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 97	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Hamburg scale scores at time points:	Motor				Language			
	Natural history controls		Cerliponase alfa		Natural history controls		Cerliponase alfa	
Baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 49	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 97	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Possible scores of 0-3 on all domains: 3=normality (best) and 0=loss of function (worst)

ERG comment

Hamburg scale

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

HRQoL measures
Study 190-201/202

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

Instrument	Mean (SD) at baseline	Mean (SD) at 49 weeks	Mean (SD) at 97 weeks
PedsQL Parent Report for toddlers	60.7 (12.80)	63.3 (15.23)	54.7 (15.00)
PedsQL Family Impact Module	61.4 (14.27)	65.1 (15.46)	61.6 (15.48)
CLN2 disease-based QoL	74.2 (13.82)	81.9 (11.10)	76.8 (11.65)

HRQoL measures

Study 190-202

EQ-5D-5L:

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

ERG comments

HRQoL

PedsQL Parent report for toddlers

- Baseline to week 49 there was a mean improvement of [redacted] points
- But clinically significant reduction (+/- 4.5 points) from weeks 49 to 97 ([redacted])
- Family impact module: baseline to week 49 there was a [redacted] point increase. However, from week 49 to week 97 there was a decline of [redacted]

CLN2QL

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

EQ-5D-5L

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

⊙ ***Does cerliponase alfa improve quality of life?***
⊙ ***For patients? For carers? For siblings?***

Mortality

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

ERG comment:

- Assuming patients receiving cerliponase alfa experience general population mortality is inappropriate
- Three potential reasons why patients receiving cerliponase alfa are likely to experience shorter life expectancy than assumed by company:
  1. *Neurological progression:* Assuming all patients on cerliponase alfa stabilise after 96 weeks (late stabilisers) is overly optimistic
  2. *Extra-neurological progression:* There may be serious implications for patient morbidity and mortality associated with cardiac, pancreatic, and hepatic impairment unless ERT is administered systemically. This unrelated to neurological progression, therefore represents an additional mortality risk
  3. *Other-disease-related mortality:* Evidence from the related 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

Adverse events (AEs)

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted] related to cerliponase alfa treatment

ERG comment:

- Hypersensitivity judged by EMA to be most relevant safety concern related to cerliponase alfa
  - life threatening anaphylactic reactions from cerliponase alfa cannot yet be excluded (despite reactions so far appearing manageable)
- [redacted] of patients experienced ECG abnormalities post-baseline

⊙ ***Is cerliponase alfa a tolerable treatment option for children with CLN2 disease?***

Equality

- No equity or equality issues were raised in the submissions

Key issues for consideration
Clinical effectiveness

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

Public observer slides - redacted

Lead team presentation

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1st Evaluation Committee Meeting
Highly Specialised Technology, 17 January 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

De novo cost-effectiveness analysis
Company base-case assumptions

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

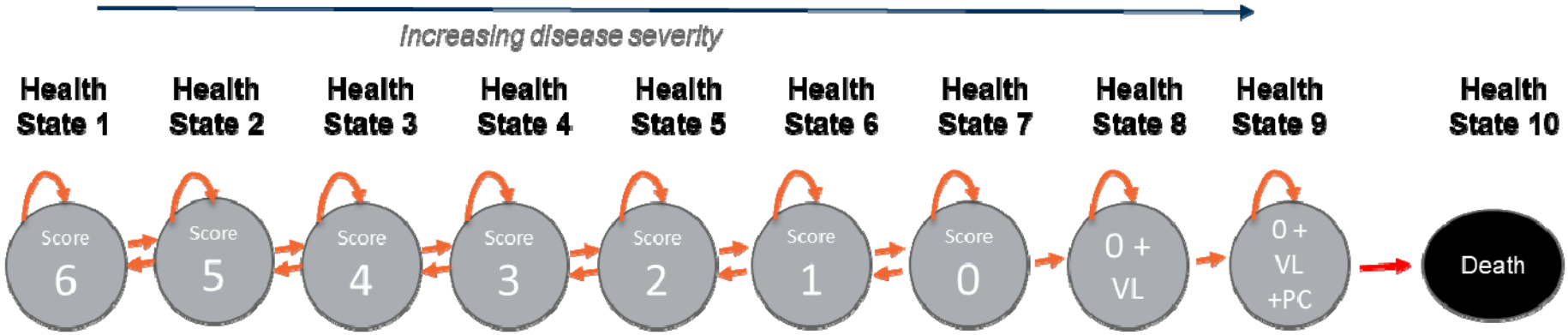
ERG comment, 1.5% discount rate is only justified when:

- Treatment restores individuals, who would otherwise die or have a very severely impaired life, to full or near full health, and when this is sustained over a very long period
- No clinical evidence to suggest that cerliponase alfa is restorative

⊙ ***Is a deviation from reference case discount rates justified?***

Model
Structure

- 10 mutually exclusive health states intended to capture the disease progression of a patient from the onset of CLN2 disease through to death



CLN2 score (motor and language), VL=vision loss, PC=palliative care

ERG comment:

- Some patients progress through the 'memoryless' model too quickly
- Model structure does not account for progressive vision loss
- Extra-neurological progression symptoms are not included (QoL impact)
- Dosing of majority of therapies used to provide symptomatic relief is based on weight and patients were assumed not to change after age 18 – lacks face validity and is unnecessary given data availability

Model
Treatment effectiveness

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

Model

Transition probabilities

- Patients receiving cerliponase alfa transition through the model using the transition probabilities calculated from the study 190-201/202 data (until week 16)
  - Early stabilisers (stabilise at week 16): [redacted] of patients in the trial experienced no further disease progression after 16 weeks, and
  - Late stabilisers (stabilise after week 96): [redacted] of patients in the trial experienced a 1-point decline on the CLN2 scale between week 16 and week 96
- Patients stop receiving treatment when they reach health state 7 (CLN2 score = 0) and switch to SoC utilities and transition probabilities

ERG comment:

- Transitional probabilities used until week 16 are based on first 24 weeks of trial data (not 16 as stated by the company) - inconsistency with clinical data
  - While these transition probabilities are only applied for a short period of time, the assumption of disease stabilisation after this period means that they are an important determinant of total costs and QALYs
- Concern that patients may remain on treatment past health state 7
  - Some patients and carers value extension of life more than quality of life
- Preferred to estimate cerliponase alfa transition probabilities from IPD in the CSR

Stabilisation assumptions
ERG comment

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

⊙ ***Are the assumptions around disease stabilisation plausible?***

Mortality

- Three types of mortality were modelled – disease related mortality, infection related mortality, and age related mortality
  - Disease related mortality depends on time in palliative state
  - No infections in the trials led to death, assumed infection related mortality =0
- Assumed constant probability of transitioning to death from health state 9
  - Patients cannot die of disease-related causes in earlier states (0-8)

ERG comment:

- Assuming general population mortality is inappropriate in the cerliponase alfa arm, because of factors not directly attributable to progression of the disease;
  1. *Neurological progression:* There is significant uncertainty relating to the late stabilisation assumption. Relaxing this assumption will reduced life expectancy for cerliponase alfa patients
  2. *Extra-neurological progression:* there may be serious implications for patient morbidity and mortality associated with cardiac, pancreatic, and hepatic impairment unless ERT is administered systemically
  3. *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

See slide 26 for the impact of additional mortality risks on the results

⊙ ***Should these additional mortality risks being included in the model?***

Model

Starting population

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

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

ERG comment
Model population

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

⊙ ***Should the starting population be based on the study 190-901 cohort? Or, is it reasonable to assume earlier diagnosis in the future?***

Utility values

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

- Values based on utility study conducted by company: vignettes describing patient experience in each arm in each health state sent to 8 clinical experts who completed EQ-5D-5L as proxy for patients; values mapped to EQ-5D-3L
- If treatment discontinued at HS7, values in cerliponase arm switch to SoC values

Caregiver and sibling disutility

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

- Clinical experts estimated caregiver disutility in health states 1 and 2
- Additional disutility was added to the model to represent the impact on quality of life felt by siblings unaffected directly by CLN2 disease
  - Applied across all but the first two health states, in line with guidance from clinical experts
  - A -0.09 decrement is applied to the midpoint of the remaining seven health states to the average number of unaffected siblings in a family with CLN2 disease; value obtained from a report on the challenges of living with and caring for a child affected by CLN2 disease

ERG comment
Health-related quality of life

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

Adverse event disutility and proportions

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

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

- Proportion of patients suffering from adverse events (treatment-related) was based on common AEs from Study 190-201
- An infection rate of 0.45% for each performed ICV infusion is assumed
- No treatment-related AEs are applied for SoC

ERG comment:

- Focus on most frequent adverse events rather than the most severe
- Number of serious adverse events not included in company's base-case analysis, but impact likely to be small given infrequency

Treatment cost

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

ERG comment:

- Additional monitoring costs associated with treatment should be included in the model given the assumption of life-long treatment for responders

Health state costs

- Health state costs include costs of: specialist clinicians, nurses, GPs, Community paediatrician, Speech/language therapist, Physiotherapist, Family Support Worker, Ophthalmologist, Health Visitor, Occupational therapist, Caregiver costs, Critical care bed days, Hospitalisation days, Palliative care, Educational Support, and Family and caregiver productivity losses

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

ERG comment:

- Results insensitive to changes in cost estimates because of the large QALY gains arising due to assumed disease stability and continued survival
- Important cost items were excluded, relating to progressive symptoms

QALY weighting

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

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

Company base case results

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

ERG comment:

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

Company alternative base case results

- Applying differential discount rates (1.5% for benefits and 3.5% for costs)
  - Discounting health benefits at a lower rate than costs will take into account any potential increase in the future value of health effects

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

Company scenario analysis (1)

Scenario	Inc costs	Inc QALYs	ICER (£/QALY)
Company base-case (corrected, see s70)	[redacted]	30.20	[redacted]
1:Starting population of patients evenly split across health states 1-2	[redacted]	33.77	[redacted]
2: All patients starts in health state 1	[redacted]	38.16	[redacted]
3: Using PedsQL utility values from the trial, mapped to EQ-5D, with the assumption of the same utility values across both arms of the treatment	[redacted]	32.35	[redacted]
4: Utility values for cerliponase alfa arm assumed to be the same as the SoC arm, from the utility study	[redacted]	27.65	[redacted]
5: Patients stop receiving cerliponase alfa treatment at health state 6	[redacted]	30.22	[redacted]
6: Treated with cerliponase alfa until death	[redacted]	30.42	[redacted]
7: No caregiver or sibling disutility is applied in the model, for the cerliponase alfa arm	[redacted]	32.22	[redacted]

Company scenario analysis (2)

Scenario	Inc costs	Inc QALYs	ICER (£/QALY)
8: Discount rate of 3.5% for costs and benefits	[redacted]	18.42	[redacted]
9: Discount rate of 3.5% for costs, 1.5% for benefits	[redacted]	30.42	[redacted]
10: Reduced price, due to price evolution and PPRS rebate	[redacted]	30.42	[redacted]
11: Time horizon of 75 years	[redacted]	29.28	[redacted]
12: Societal perspective used	[redacted]	30.42	[redacted]
13: Optimistic scenario - All patients starts in health states 1-2, no caregiver or sibling disutility applied to the cerliponase alfa arm, 50% reduction in progressive symptoms, differential discount rate	[redacted]	35.01	[redacted]
14: Pessimistic scenario - Utility values for cerliponase alfa arm assumed to be the same as the standard care arm, from the utility study, discount rate of 3.5% for costs and benefits	[redacted]	16.78	[redacted]

Deterministic sensitivity analysis

Company submission

Figure redacted – commercial in confidence

The company varied each parameter value by ±15%.

Subgroup analysis

- Analysis of a subgroup of asymptomatic and pre-symptomatic siblings with confirmed CLN2 disease was undertaken
- The assumption was made that if patients are asymptomatic and pre-symptomatic, then all patients will start in health state 1
  - More QALYs are accrued by cerliponase alfa patients due to patients entering the model in a less severe health state and therefore are stabilised in less severe health state at the end of the trial period

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

ERG scenario analysis (1)

Scenario	Inc costs	Inc QALYs	ICER (£/QALY)
1: Patient distribution in 190-901 trial	[redacted]	18.79	[redacted]
2: Patient distribution in 190-901 trial, restricted to CLN2 score of 2+	[redacted]	19.51	[redacted]
3: Transition probabilities for cerliponase alfa estimated using IPD data in the CSR	[redacted]	30.24	[redacted]
4: Disease stabilisation for early stabilisers on cerliponase alfa	[redacted]	24.51	[redacted]
5: Neurological progression (no disease stabilisation)	[redacted]	11.81	[redacted]
6: Extra-neurological mortality	[redacted]	13.14	[redacted]
7: Other-disease related mortality	[redacted]	29.19	[redacted]
8: Vision loss in cerliponase alfa patients	[redacted]	26.61	[redacted]
9: EQ-5L-5L data to model HRQoL	[redacted]	32.55	[redacted]
10: Peds-QL data to model HRQoL	[redacted]	32.12	[redacted]

ERG scenario analysis (2)

Scenario	Inc costs	Inc QALYs	ICER (£/QALY)
11: Age-adjusted utilities	[redacted]	28.46	[redacted]
12: No carer and sibling disutility after 30 years	[redacted]	31.17	[redacted]
13: Same utility values in each arm	[redacted]	27.45	[redacted]
14: Additional ECG cost	[redacted]	30.20	[redacted]
15: Psychiatric support	[redacted]	30.20	[redacted]
16: Residential care	[redacted]	30.86	[redacted]
17: Discounting costs and QALYs at 3.5%	[redacted]	18.12	[redacted]

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Scenario analysis (3)

Cumulative impact of additional mortality risks

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

ERG preferred base-case

Combines a number of the changes to the company base-case:

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

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

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ERG exploratory analysis

Scenario	Inc costs	Inc QALYs	ICER (£/QALY)
ERG-preferred base-case	[redacted]	3.32	[redacted]
1. Partial stabilisation on cerliponase alfa (early stabilisers only)	[redacted]	4.34	[redacted]
2. No extra-neurological related mortality	[redacted]	3.84	[redacted]
3. Different utility values in each arm (EQ-5D-3L)	[redacted]	4.59	[redacted]
4. PedsQL for HRQoL	[redacted]	5.22	[redacted]
5. Stopping rule – no discontinuation of cerliponase alfa	[redacted]	3.23	[redacted]
6. Discounting at 1.5%	[redacted]	3.77	[redacted]
7. Optimistic base-case analysis - partial stabilisation, no extra-neurological mortality and HRQoL benefit for cerliponase alfa	[redacted]	8.83	[redacted]

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Subgroup analysis

ERG approach

	Total costs	Total QALYs	Inc costs	Inc QALYs	ICER	Threshold*
ERG corrected company base-case: asymptomatic and pre-symptomatic subgroup						
Cerliponase alfa	[redacted]	37.29	[redacted]	37.89	[redacted]	£300,000
SoC	£155,422	-0.60	N/A	N/A	N/A	
ERG-preferred base-case: asymptomatic and pre-symptomatic subgroup						
Cerliponase alfa	[redacted]	7.52	[redacted]	8.00	[redacted]	£106,423
SoC	£145,065	-0.48	N/A	N/A	N/A	
Optimistic base-case analysis: asymptomatic and pre-symptomatic subgroup						
Cerliponase alfa	[redacted]	15.53	[redacted]	16.01	[redacted]	£300,000
SoC	£145,065	-0.48	N/A	N/A	N/A	

*Threshold estimated using undiscounted incremental QALY values, see slide 25

- Total QALYs and incremental QALYs reported in the table are discounted

Impact of the technology beyond direct health benefits

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

Innovation

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

Key issues for consideration
Cost-effectiveness

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

Committee, projector and public observer slides - redacted

Lead team presentation

Cerliponase alfa for treating neuronal ceroid lipofuscinosis type 2

1st Evaluation Committee Meeting
Highly Specialised Technology, 17 January 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

Patient perspective
Impact of disease - patients

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

Patient perspective
Impact of disease - carers

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

Patient perspective
Diagnosis and current treatment

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

Patient perspective
Cerliponase alfa

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

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

<u>Sibling with no symptoms on sibling trial</u>
not showing any symptoms and reaching normal developmental milestones

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

Key issues for consideration

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