National Institute for Health and Care Excellence

Health Technology Evaluation

Nusinersen and risdiplam for treating spinal muscular atrophy (review of TA588 and TA755) ID6195
Response to stakeholder organisation comments on the draft remit and draft scope

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Comment 1: the draft remit and proposed process

Section	Stakeholder	Comments [sic]	Action
Appropriateness of an evaluation and proposed evaluation route	BioMarin	BioMarin agrees with the decision to evaluate cerliponase alfa via the Highly Specialised Technologies (HST) process.	Thank you for your comment.
	Manchester University Hospital NHS Foundation Trust	The highly specialised technology evaluation route would be appropriate.	Thank you for your comment.
	BDFA	The 5-year MAA, which followed on from the clinical trial, for this treatment is coming to an end in November 2024. As there are no other treatment alternatives suitable for children with CLN2 Batten disease we consider this appraisal to be significant to the families whose children receive it.	Thank you for your comment.
Wording	BioMarin	BioMarin agrees that the wording is appropriate.	Thank you for your comment.

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	BDFA	The wording is appropriate.	Thank you for your comment.
Timing issues	BioMarin	Apart from cerliponase alfa, there are no treatments licensed or otherwise approved to treat CLN2 disease. Cerliponase alfa received a positive recommendation within the context of a five-year Managed Access Agreement (MAA) in 2019 (HST12), which will end in November 2024.	Thank you for your comment.
	Manchester University Hospital NHS Foundation Trust	This evaluation should be considered urgent as there are patients currently on treatment under a managed access agreement, and there have been a number of new diagnoses at our centre just in the last few months.	Thank you for your comment. Comment noted.
	Genetic Alliance	Currently there are no treatments available for the condition and significant unmet need. We have heard that families who have received this treatment through a managed access agreement are worried about the uncertainty over the future availability of this treatment, not only for their own children but for the whole community. The evaluation is of particular urgency due to the speed at which the condition progresses with only a few years from onset of symptoms to the development of a vegetative state. For this reason it is important that patients in the UK are able to access the treatment as soon as possible if approved.	Thank you for your comment. Comment noted.
	BDFA	All other medications used during the rapid progression of Batten disease are aimed at symptom management rather than preventing progression. Currently there are children who have been receiving this treatment as part of	Thank you for your comment. Comment noted.

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		the clinical trial and the MAA. There are also children who started after the MAA came into effect. All of them are highly anxious that delays to the final decision will have an impact on the treatment of their children and those who are diagnosed during the evaluation process. Given the speed of disease progression without this treatment, this evaluation is of high urgency to ensure continuity of care.	

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	BioMarin	BioMarin considers the content of the background section to be accurate.	Thank you for your comment.
	Manchester University Hospital NHS Foundation Trust	Suggest in background section (page 1, paragraph 2) amending wording to 'symptoms in children with CLN2 *typically* start to arise in the second year of life' – as there are attenuated forms Life expectancy is *typically* around 6-13 years, although children with attenuated forms may live longer Suggest removal of reference to Parkinsonian symptoms: typical neurological symptoms are epilepsy, spasticity and dystonia.	Thank you for your comment. Your suggestions have been included in the scope.
	BDFA	The background information has not discussed sleeping difficulty experienced by the children which is distressing for the whole family. The background information does not fully address the enormous burden on the families caring for children with this condition.	Thank you for your comment. The scope has been amended to highlight the burden on

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			families. Patient experience is valued by committee for decision making and therefore detailed patient experiences are welcomed in submissions and are highlighted at the appraisal committee meetings. The scope background provides an overview of the condition and treatment.
Population	BioMarin	BioMarin considers the population appropriately defined.	Thank you for your comment. Comment noted.
	Manchester University Hospital NHS Foundation Trust	Yes. There are some attenuated patients who may be diagnosed outside of the typical age range, who should still qualify for treatment with cerliponase.	Thank you for your comment. Comment noted.
	BDFA	Yes	Thank you for your comment.
Subgroups	BioMarin	BioMarin considers the following subgroups are not appropriate and should not be considered in this evaluation:	Thank you for your comment. The scope

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		• **IVT patients.** Intravitreal (IVT) administration was initially included in the MAA statistical analysis plan (SAP) due to a cerliponase alfa safety study conducted by Great Ormond Street Hospital. However, as this study was comprised of only two patients, both of whom started the trial with a very progressed baseline CLN2 condition, BioMarin do not believe there is sufficient or robust data to consider this subgroup. Moreover, BioMarin believe that this subgroup is not appropriate as the IVT route of administration is not expected to be used in clinical practice. • **Age at treatment initiation.** BioMarin do not consider age at treatment initiation to be an appropriate subgroup. Due to the predictive nature of CLN2 progression, BioMarin recognise that age is considered a proxy marker for CLN2 score. However, a proportion of atypical patients (~14% in the MAA cohort), who develop CLN2 at a later age are included in the MAA cohort. The age of patients with atypical CLN2 does not correlate well with their CLN2 score. Therefore, age at treatment initiation is unlikely to be fully reflective of CLN2 score and this subgroup is not considered appropriate. BioMarin considers CLN2 clinical rating scale baseline score is a superior determinant, and reflective of patient outcomes; subgroup and scenario analyses based on baseline CLN2 score will therefore be considered.	has been updated to reflect the change requested, the subgroups IVT patients and age at treatment initiation listed in the draft scope are removed.
	GOSH	Consider including stage of disease progression	Thank you for your comment. The scope has been updated to include stage of disease progression.

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	Manchester University Hospital NHS Foundation Trust	For age of treatment initiation, our experience is that patients treated earlier in their course of disease may do better in terms of seizure control etc. This may be better assessed in terms of pre-symptomatic or early symptomatic patients, given the existence of attenuated patients. Please clarify what IVT therapy refers to? If intravitreal therapy, then there is limited evidence around its efficacy to date, and should not be considered as a separate subgroup.	Thank you for your comment. The scope has been updated to reflect the change requested, the subgroups IVT patients and age at treatment initiation listed in the draft scope are removed. The scope has been updated to include stage of disease progression.
	BDFA	There are two major subgroups within the population; those that start treatment after symptoms have led to a diagnosis (delayed diagnosis) and their siblings who are identified pre-symptomatically (early diagnosis). There is a third subgroup, referred to as atypical CLN2. IVT patients should not be considered as a subgroup. These were involved in a small safety study only which was not powered to assess efficacy. The efficacy will depend on the vision of the children at the start of the injections and was not addressed as part of this safety study.	Thank you for your comment. The scope has been updated to reflect the change requested, the subgroups IVT patients and age at treatment initiation listed within the draft scope are removed.
Comparators	BioMarin	BioMarin agree that the appropriate comparator is established clinical management without cerliponase alfa, including managing the symptoms and complications associated with CLN2.	Thank you for your comment.

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	Manchester University Hospital NHS Foundation Trust	Yes	Thank you for your comment.
	BDFA	Yes	Thank you for your comment.
Outcomes	BioMarin	BioMarin considers the outcomes listed appropriate to capture the most important health related benefits and safety of cerliponase alfa. However, it is important to note that not all of the listed outcomes are measured in cerliponase alfa's clinical trial studies or captured in the MAA (e.g., WISC-V). Nevertheless, BioMarin will present all the evidence available for the outcomes captured.	Thank you for your comment. Comment noted.
	Manchester University Hospital NHS Foundation Trust	Suggest amending "electrocardiogram, 12-lead" to "12-lead electrocardiogram" for clarity. We would suggest that assessment of seizure burden should also take into account need for hospital admission, or status epilepticus. The investigations listed under safety outcomes are not useful measures of safety for this intervention and population. They are clinical outcomes, but not helpful measures of efficacy.	Thank you for your comment. The scope has been updated to reflect the change requested. Need for medical care (including hospitalisation, emergency care and primary and secondary care appointments, and concomitant medication) has been added to the scope and safety outcomes has

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			been removed from the scope.
	BDFA	CLN2 Batten disease is a devastating diagnosis for the families. There is complex symptomology that impacts patients, carers, siblings, and the wider family unit. The listed outcomes do not capture the associated mental and physical health aspects within the health-related quality of life outcomes, for the carers, parents, siblings, and extended family. The aim of our submission is to provide a review of the wider benefits in addition to the needs of the affected child.	The scope has been updated to include the outcome health-related quality of life (for patients and carers and including impact on families such as social and mental health and impact on siblings). This may be informed by quality-of-life measures including PedsQL, EQ-5D, and CLN2-QoL.
Equality	BioMarin	BioMarin have not identified any issues relating to equity or equality that are relevant to this evaluation. CLN2 is an ultra-rare, multi-systemic, and life-limiting disease for which there are no current treatment options other than cerliponase alfa, and the management of symptoms and palliative care. BioMarin supports treatment	Thank you for your comment. Comment noted.

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		for all patients who can benefit, and any limitation needs to be considered by NHS England, English Clinical and Patient Experts. Given the rapidly progressing nature of CLN2 disease, the accompanying loss of function across all domains, deteriorating health-related quality of life, and poor survival prognosis, early diagnosis and treatment is vital for all patients, as is early and comprehensive access to multi-disciplinary supportive and palliative care.	
	Manchester University Hospital NHS Foundation Trust	Patients from ethnic minority backgrounds may access healthcare less well and may be diagnosed later, and may therefore be at risk of not qualifying for treatment.	Thank you for your comment. Comment noted.
Other considerations	BioMarin	BioMarin believes the costs associated with diagnostic testing for CLN2 should be excluded from the analysis. CLN2 disease can be definitively diagnosed either through demonstration of deficient tripeptidyl peptidase 1 (TPP1) enzymatic activity or through identification of causative mutations in each allele of the *TPP1/CLN2* gene, with most clinicians in the UK and worldwide making the decision to start treatment on the basis of the enzyme test only. As the symptoms of CLN2 are very severe and debilitating, in order to establish the cause of these, BioMarin expects that the enzymatic tests would be carried out by the NHS irrespective of the availability of treatment. Therefore, no additional tests are required to identify patients eligible for treatment with cerliponase alfa and there is no population of people with CLN2 who would not otherwise be tested.	Thank you for your comment. Comment noted. This has been included in the scope to allow for the possibility for diagnostic tests prior to starting cerliponase alfa which would not otherwise be carried out. It is anticipated that diagnostic testing will be determined during the appraisal.

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		Therefore, the costs associated with diagnostic testing for CLN2 are not relevant to the economic analysis.	
Questions for consultation	BioMarin	• *Do you consider that the use of cerliponase alfa can result in any potential substantial health-related benefits that are unlikely to be included in the QALY calculation?* Yes, BioMarin recognise that NICE's preferred outcome measure in economic evaluations is the QALY. However, capturing all benefits associated with cerliponase alfa is not quantifiable and therefore is not included in the QALY. Treatment with cerliponase alfa stabilises the progression of CLN2, minimising the need for constant revisions of care. Therefore, cerliponase alfa is likely to have significant benefits to patients other than health, including education, mental health, and societal contributions. Additional benefits should be considered for carers and the families of patients who will be able to benefit society by improved employment and family life. Caregivers are generally the parents of children with CLN2. Caring for a child with CLN2 can have a large impact on caregiver mental health; parent representatives have described feelings of isolation, time anxiety, and anxiety for the future. CLN2 also has a large impact on siblings of affected children with siblings experiencing psychological effects and major anxieties. Treatment with cerliponase alfa can alleviate such pressures and anxieties by stabilising disease progression, and stabilising symptoms. Ultimately, treatment will have a significant qualitative effect on patients with CLN2, their caregivers, and their families.	Thank you for your comments. The HRQoL of carers and families of patients has been added as an outcome to the scope.

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		• *Do you think that costs and treatments should be analysed separately for existing and new patients? Should this be done by age?* Yes, BioMarin notes the significant steps made in early diagnosis for CLN2 since HST12 and as a result, CLN2 score at diagnosis is likely to differ between new and existing patient populations. Earlier diagnosis is in large, a direct result of improved CLN2 awareness across the UK. Since HST12, several additional specialist UK treatment centres have opened, leading to increased CLN2 awareness for healthcare professionals, and easier access to cerliponase alfa treatment. Furthermore, press coverage during the previous appraisal increased awareness for CLN2. Moreover, the BDFA charity is continuously working to improve awareness via fundraising and outreach events. Age is considered a proxy indicator of CLN2 score. However, as noted in comment 2 (subgroups), age is unlikely to be fully reflective of CLN2 score. BioMarin do not believe that costs and treatments should be analysed by age.	
	BDFA	Where do you consider cerliponase alfa will fit into the existing care pathway for neuronal ceroid lipofuscinosis type 2? There isn't an existing care pathway for these patients. The appropriate patient pathway for children diagnosed with CLN2 should ensure that patients with first presenting symptoms, which occur in a rather unfirm sequence (Nickel M. et al Lancet Child Adolesc Health. 2018 Aug;2(8):582-590.), enter the healthcare system where the first contact with the treating physician will result in high level of disease suspicion, rapid access to diagnostic tools and early diagnosis. Since this pathway does not exist, we continue to observe	Thank you for your comments. NICE would welcome the inclusion of this research on patient perspectives in your submission for this evaluation.

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		delayed diagnosis in these children. The best chance that the CLN2 patient stand, once diagnosed at any stage, is to have rapid access to treatment with cerliponase alfa. There is strong evidence that treatment with cerliponase alfa provides clinical benefits when initiated at any stage of the disease. Cerliponase alfa should be available to all eligible children alongside therapies used to manage the disease. Do you consider that the use of cerliponase alfa can result in any potential substantial health-related benefits that are unlikely to be included in the QALY calculation? We have received reports from our families that treatment with cerliponase alfa results in a wide range of benefits, not just those related to slowing of disease progression as measured on the Hamburg scale. We will endeavour to show this in our submission with data from our parent survey. Please identify the nature of the data which you understand to be available to enable the committee to take account of these benefits. We have completed a qualitative research involving families of children diagnosed with CLN2 which demonstrate significant impact of the disease on QoL and activities of daily living of family members. We are currently reconducting a survey to gain feedback on additional benefits from treatment with cerliponase alfa that are not captured in the Managed Access Agreement.	

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		Do you think that costs and treatments should be analysed separately for existing and new patients? Should this be done by age? No. Everyone should have equal access to treatment whether existing or new. Should any outcomes currently listed under "safety outcomes" be instead listed under clinical outcomes? No	