Highly Specialised Technology

Cerliponase alfa for treating neuronal ceroid lipofuscinosis type 2 (MA review of HST12) [ID6145]

Committee Papers

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NICE National Institute for Health and Care Excellence

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Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on Friday 6 June. Please submit via NICE Docs.

	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Evaluation Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.**
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	BioMarin
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**N/A**

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Name of commentator person completing form:	[redacted]
Comment number	Comments.
Preamble – comment 0 – to cover the comments submitted by the Company, online.	**Regarding the questions asked by NICE:** • **Has all of the relevant evidence been taken into account?** The Company has submitted its response via NICE DOCs. The Company DOES NOT believe all relevant evidence has been taken into account by the Evaluation Committee and urges NICE to reassess its guidance. • **Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?** As per online comment to the previous question, and as detailed in the Company response, the summaries of clinical and cost-effectiveness ARE NOT reasonable interpretation of the evidence, as its analysis does not consider the most appropriate evidence. • **Are the provisional recommendations sound and a suitable basis for guidance to the NHS?** For the reasons above, the Company DOES NOT believe that the provisional recommendations are sound and a suitable basis for guidance to the NHS**.**
1	**Insufficient recognition of significant evidence constraints in ultra-rare disease context** NICE's draft guidance for cerliponase alfa does not reflect the well-recognised constraints of evidence generation in the context of ultra-rare diseases. The guidance should acknowledge that **CLN2 disease is an ultra-rare disease**, and had this been appropriately considered, there would be most likely a different decision. The draft guidance does not acknowledge this significant limitation, meaning the summaries of clinical and cost effectiveness are an inaccurate interpretation of the evidence. The estimated prevalence for CLN2 disease ranges between 0.1–0.75 per 100,000 people, and the estimated birth prevalence ranges between 0.22–0.78 per 100,000 live births (1-4). The number of patients being treated in England today is

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	approximately 40. Therefore, the available clinical data is inherently limited by small patient numbers, and the ethical and practical challenges of conducting large-scale trials in this population. NICE's draft guidance for cerliponase alfa does not reflect the well-recognised constraints of evidence generation in the context of ultra-rare diseases. This context is essential for appropriately interpreting the available evidence and understanding the limitations inherent in evaluating the clinical and cost-effectiveness of cerliponase alfa. Conducting a randomised controlled trial (RCT) for cerliponase alfa in this population would have been unethical, as it would have required administration of a placebo in the cerebrospinal fluid and withholding cerliponase alfa from affected children in the absence of other treatment options, knowing that to do so would cause irreparable harm. Consequently, comparative data for cerliponase alfa came from a natural history cohort (190-901). Whilst this approach introduces uncertainty relative to an RCT, it was the only ethically and practically feasible option in this setting, and an appropriate solution to a challenge that is well recognised in the rare disease context. This approach aligns with established evidence standards in rare disease evaluations, as seen in NICE's appraisal of elosulfase alfa for MPS IVA (TA336), where natural history data were similarly accepted in place of a randomised comparator due to ethical and feasibility limitations (5). The assessment of the effect of cerliponase alfa on non-neurological outcomes is particularly limited. Many patients in the natural history cohort were too unwell to undergo certain assessments, limiting the availability of robust comparative data in these domains. This challenge is not a reflection of poor data quality but rather a direct consequence of the severity and rarity of the disease. The fact that psychological tools were applied to patients during the period of the Managed Access Agreement serves as a testimony that the natural history of the disease has changed. Importantly, this uncertainty cannot be resolved through further data collection or alternative trial designs and the higher uncertainty should be accepted by NICE. It is a well-recognised and unavoidable limitation in the evaluation of therapies for ultra-rare, rapidly progressive conditions.

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	BioMarin suggests that the guidance more explicitly reflects the significant challenges of evidence generation in ultra-rare disease settings, to ensure that the appraisal is grounded in the realities of clinical research in this setting rather than applying standards that can never practically be attained in the treatment of any rare disease.
2	**NICE's assessment is based on an outdated diagnostic landscape and does not reflect clinical management for CLN2 disease today. This outdated perspective hinders the true and fairer clinical and economic assessment warranted for cerliponase alfa** BioMarin believes the current framing of the guidance document does not adequately reflect the significant progress made in the awareness and early diagnosis of CLN2 disease since the HST12 appraisal in 2019. Diagnostic awareness has improved markedly, driven in part by the HST12 process itself and further amplified by the national awareness campaigns led by Prof. Paul Gissen and Dr Dipak Ram. These initiatives have contributed to a tangible shift in clinical practice and therefore all of the relevant evidence has not been taken into account. These efforts are demonstrably impacting clinical practice. In the three advisory boards held with clinical experts between 2023 and 2025 to support the company submission, clinicians consistently reported that they are now diagnosing children at younger ages and at earlier stages of disease progression, with higher motor-language scores at the time of diagnosis. They noted that this represents a clear and positive shift from the treatment landscape even from just a few years ago. This is supported by trends in both higher motor-language score and younger age at diagnosis observed across the MAA period (Nov 2019–Sep 2023). In addition, there are now new-born screening pilot schemes in place that include screening for CLN2 (which are further covered in the answer to Comment 3 below) which will further enhance early diagnosis going forwards. BioMarin strongly recommends that this progress be explicitly acknowledged in the guidance document and the modelling assumptions made by the Committee, such as the Motor-Language distribution at diagnosis, the percentage of patients who present initial stabilization and how they present lower risk of progression after initial stabilization, and the overall progression of

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	the disease, as captured in the cost-utility analysis as transition probabilities. A failure to reflect these advancements, especially in a fast-progressing disease such as CLN2, presents an outdated view of the diagnostic landscape and overlooks the substantial improvements that have been made, which may undermine an accurate assessment of clinical and economic benefit under today's conditions.
3	**Systemic delays in diagnosis make early detection impossible and distort the assessment of cost-effectiveness of cerliponase alfa** This appraisal is intended to guide access for incident patients. This has been agreed between the company and NICE, and strongly supported by NHS-England. However, in spite of NICE acknowledging it at the beginning of the document, NICE appears to have conflated the assessment of prevalent (existing) and incident (future) patients by using the most negative perspective on diagnosis, and on transition probabilities (as pointed out on comment 2), meaning that summaries of clinical and cost effectiveness are not reasonable interpretations of the evidence. It is important to note that prior to the commencement of the Managed Access Agreement (MAA), during the original appraisal of cerliponase alfa (i.e. HST12), NHS England independently committed to implementing a diagnostic pathway aimed at enabling earlier detection of patients with CLN2 disease. BioMarin also offered to support these efforts by sponsoring diagnostic services; however, this offer was declined by NHS England. Despite proactive steps, BioMarin's efforts have been met with significant bureaucratic and systemic barriers, and there has been limited collaboration from the wider healthcare system to meaningfully address delays in diagnosis. These challenges have constrained progress and should be adjusted for in the evaluation. The draft guidance should acknowledge (and adjust for the fact) that systemic delays in diagnosis within the NHS are a key factor negatively impacting the assessment of cost-effectiveness for cerliponase alfa. These delays, driven by structural and operational limitations in the current healthcare system, result in later treatment initiation and worse outcomes for patients, thereby distorting the ICER. Patients and their families should not face restricted access to treatment because the system fails to diagnose them in a timely manner, and the assessment of

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Draft guidance comments form

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	cerliponase alfa should not be penalised for diagnostic shortcomings. In addition, future improvements, including the potential for NBS, may address some of these issues and should therefore be factored in. The current reality is that NHS diagnostic capacity was a limiting factor in ensuring the timely diagnosis of people with CLN2 disease. However, the successful implementation and long-term sustainability will depend on coordinated engagement across multiple stakeholders. While BioMarin is committed to supporting these efforts, enabling earlier diagnosis is a cross-sector responsibility that requires coordinated action across the healthcare system. Moving forward, early and accurate diagnosis will be critical to maximising the long-term value of cerliponase alfa in new patients. BioMarin recognises the importance of newborn screening (NBS) in shortening diagnostic delays and ensuring timely treatment for patients with CLN2 disease. To date, BioMarin has taken all reasonable steps to support early diagnosis, such as continuous medical education initiatives, as well as advocate for the introduction of NBS for CLN2 disease in England, including sustained engagement with key stakeholders and funding feasibility work. This support has contributed to the launch of two NBS pilots: one led by Great Ormond Street Hospital and another by Genomics England. While NBS for CLN2 disease has not yet been formally adopted, discussions during the December 2024 company advisory board with treating clinicians highlighted a credible future, with growing likelihood that its implementation in England is entirely plausible within the next 5–10 years. The direction of travel is clear and the Committee should consider this trajectory, and the implications of delayed implementation, in its recommendation. The implementation of NBS pilots has been positively received in clinical settings, with strong support from both healthcare professionals and parents. Many parents view testing their child as a clear and essential choice, describing it as a "no-brainer", driven by the desire to give their child the best possible start in life through early diagnosis and timely access to treatment (6, 7).

Cerliponase alfa for treating neuronal ceroid lipofuscinosis type 2 (MA review of HST12) [ID6145]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on Friday 6 June. Please submit via NICE Docs.

	Importantly, the role of NBS in shortening time to diagnosis and improving access to treatment in rare diseases is well established. A clear example is phenylketonuria (PKU), for which UK-wide dried blood spot screening has been in place for over 50 years (8). Early detection of PKU through NBS allows for immediate dietary intervention, preventing irreversible cognitive impairment and significantly improving long-term health outcomes. In 2016–17, nearly 780,000 babies were screened for PKU in the UK, and over 100 babies were screen-positive and referred to specialist care. This clearly demonstrates how early diagnosis through NBS can transform the clinical trajectory of patients with rare diseases. NBS has also been shown to improve outcomes for patients receiving enzyme replacement therapy (ERT). For example, the implementation of NBS for mucopolysaccharidosis type IVA (MPS IVA) in Taiwan significantly reduced the age at diagnosis and enabled earlier initiation of ERT leading to improved long-term outcomes (9). While this example comes from a different health system, it nonetheless provides a relevant parallel, demonstrating the potential impact of early identification through NBS. These examples support the argument that similar benefits could plausibly be realised for CLN2 disease within the NHS, should timely NBS implementation be achieved. Crucially, NBS for CLN2 disease is unlikely to be implemented in the absence of an approved treatment. The inclusion criteria for the Genomics England pilot programme specify that screened conditions must be treatable within the NHS in England. As such, a negative recommendation for cerliponase alfa in incident patients would effectively block the introduction of NBS for CLN2 disease in the UK, thereby limiting early diagnosis and timely intervention. As demonstrated in the 190-203 study, pre-symptomatic patients treated with cerliponase alfa showed substantially improved outcomes compared with those treated after symptom onset. This is a point that should be acknowledged by the Committee (contrary to their assertion in the April report that there was no certainty of improved outcomes if treatment was commenced early). With intervention at the earliest possible age, made possible through NBS, it is expected that treated newborns could

Cerliponase alfa for treating neuronal ceroid lipofuscinosis type 2 (MA review of HST12) [ID6145]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on Friday 6 June. Please submit via NICE Docs.

	achieve outcomes that surpass those seen in pre-symptomatic patients to date. The Committee is urged to recognise the real-world diagnostic constraints impacting current patients and implemented and planned improvements and to ensure its recommendations do not perpetuate avoidable delays or disadvantage due to broader, historical, systemic failings which are being ameliorated.
4	**COVID-19 severely disrupted diagnosis and care pathways for CLN2 disease, compromising data integrity and limiting patient outcomes. This impact has not been adjusted for in the draft guidance and represents a significant oversight of he Committee in not appreciating the impact of COVID on this assessment** BioMarin is strongly concerned that the current draft guidance significantly underplays the severe and lasting impact of the COVID-19 pandemic on children with CLN2 disease. The statement that "*…children could not go to school, and families faced difficulties obtaining medicines, meeting with clinicians and accessing specialist services and appointments...*" grossly understates the gravity of the situation. The pandemic did not simply disrupt routine care: it fundamentally impaired early identification, diagnosis, access to essential services, and specialist support, all of which are critical for a condition where time to treatment determines life trajectory. Between March 2020 and March 2021, interspaced periods of lockdown affected the management of CLN2. Referral pathways were suspended, specialist consultations, diagnostic evaluations were delayed or deprioritised, and access to specialists was severely limited. These delays curtailed children's and families' chances of timely diagnosis and, by extension, their opportunity to benefit from early treatment with cerliponase alfa. The resulting impact on clinical outcomes is not hypothetical; it is real, severe, and well documented. Moreover, these effects were compounded by the widespread absence of additional support therapies, such as physical, occupational, and speech therapies, psychologist visits, and even specialist schools, all of whwich ensure patients' physical, mental, and psychosocial health. This was highlighted

Cerliponase alfa for treating neuronal ceroid lipofuscinosis type 2 (MA review of HST12) [ID6145]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on Friday 6 June. Please submit via NICE Docs.

	and corroborated by clinical experts at the July 2023 company advisory board. Following Appraisal Committee Meeting 1 (ACM1), the Committee requested an additional economic analysis based on current clinical practice, specifically excluding patients whose diagnosis or treatment was delayed due to COVID-19 (10). However, as BioMarin clarified in its response to the Committee, such an analysis was not feasible. This was because all patients treated during the MAA period were affected--either by the pandemic itself, or by the time needed to establish treatment infrastructure. Data on diagnostic delays are incomplete, and due to the impact of the pandemic on the management of CLN2 in England, the post-pandemic cohort is fundamentally different from the intended incident population this guidance is meant to serve. Although the issue of COVID-19 is touched upon in NICE's draft guidance, BioMarin believes it requires earlier and more prominent recognition (and then appropriately adjusted for in the assessment), particularly in the section on clinical effectiveness and data sources. The MAA cohort, due to the presence of patients waiting for therapy whilst NICE concluded the original appraisal until treatment became available, the aforementioned impact caused by the pandemic, the improvements in the age of diagnosis due initiatives from clinicians, and increased awareness about CLN2, is fundamentally not representative of patients who would receive timely diagnosis and treatment under normal NHS conditions. Without accounting for this, NICE risks drawing conclusions based on a population that does not accurately reflect the target patient group. Moreover, it is important to recognise that this is a distinct patient population: the MAA cohort was shaped by the unique pressures of COVID-19. If pooled analyses include additional studies beyond the MAA cohort, NICE should consider whether the impact of the pandemic also affected data integrity in those datasets and clarify whether the same limitations apply across the pooled population. Given the significant equity implications, BioMarin strongly urges NICE to reconsider using MAA data in its assessment. The use of these data without full consideration of pandemic-related limitations may inadvertently perpetuate a systemic disadvantage to patients whose care was delayed through no fault of their own.

Cerliponase alfa for treating neuronal ceroid lipofuscinosis type 2 (MA review of HST12) [ID6145]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on Friday 6 June. Please submit via NICE Docs.

	NICE must accept the exceptional circumstances created by the pandemic and reflect these in its evaluation, not just as background context, but as a material factor affecting the integrity and interpretation of the evidence base for this appraisal.
5	**Inappropriate use of outdated and non-representative data undermines validity of transition estimates for the incident population** **BioMarin strongly opposes the use of data pooled from Studies 190-201/202, the managed access agreement (MAA), and Study 190-203 to estimate transition probabilities for cerliponase alfa-treated patients**. This approach fundamentally compromises the integrity of the analysis. **It fails to reflect the population under evaluation—incident patients with CLN2 disease—and introduces outdated, confounded, and non-representative data into the modelling.** The result is not a reasonable, "conservative" estimate, as is suggested in the draft guidance, but a distorted and clinically implausible representation of the treatment effect of cerliponase alfa. Study 190-201 involved patients under a dose escalation protocol and was conducted more than a decade ago. Patients who were enrolled in the study had often already experienced a long duration post-diagnosis time. Besides, this study does not reflect the significant advances in disease awareness, referral pathways, and earlier treatment initiation (see Comment 2). These data are outdated and do not reflect the reality of how children are diagnosed or managed in today's NHS. Moreover, patients from 190-201/202 transitioned into the MAA, meaning that biases from outdated data sources are carried forward into the pooled analysis. While larger, the MAA dataset is similarly not fit for purpose for this evaluation, with significant limitations, particularly for patients initiating treatment between March 2020 and March 2021, when the impact of the COVID-19 pandemic was most acute (see Comment 4). During this period, children experienced substantial delays in diagnosis, often entering treatment at an advanced disease stage. These disruptions had a material impact on disease severity at diagnosis and limited the realisation of

Cerliponase alfa for treating neuronal ceroid lipofuscinosis type 2 (MA review of HST12) [ID6145]

Draft guidance comments form

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	treatment benefit, especially given the restricted access to multidisciplinary care during the height of the pandemic. Neither the patients in Studies 190-201/202 nor those in the MAA are representative of incident children receiving timely diagnosis and treatment in the NHS today. Combining these compromised datasets with 190-203, the only study aligned to modern clinical practice, conceals meaningful clinical progress and downplays the treatment effect of cerliponase alfa in a way that is misleading and unfair to future treated patients and their families. Of the available datasets, Study 190-203 most closely reflects current diagnosis, referral, and treatment of CLN2 disease in England. The study included patients after commercial availability of cerliponase alfa, under conditions of improved disease recognition and better healthcare system readiness. This was unequivocally confirmed by all four clinical experts during the December 2024 company advisory board. Therefore, the Committee's decision goes against what is believed by the clinical community. BioMarin recognises that, in rare diseases, there is often a justified desire to maximise the use of all available data for decision-making. However, this appraisal must not prioritise volume over relevance. NICE should reconsider whether pooling data is justified, which in this case we believe it is not. The inclusion of outdated and confounded patient cohorts distorts the clinical reality and undermines the credibility of the results of the cost-utility analysis. Drawing conclusions from such data risks producing misleading estimates of treatment effect and, ultimately, poor decisions for a highly vulnerable patient population. In a condition as rare and severe as CLN2 disease, where RCT feasibility is inherently limited (see Comment 1), it is essential that data used in modelling are both relevant and reflective of current clinical practice. Anything less compromises the validity of the appraisal and risks disadvantaging patients and families who stand to benefit most from timely access to life-saving treatment. BioMarin urges NICE to reconsider its reliance on pooled data (especially in light of the fact that the prevalent patient population is not part of the assessment), and to instead acknowledge the appropriacy of using Study 190-203 for calculating transition estimates, to reflect the true impact of cerliponase alfa in the

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Draft guidance comments form

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	patient population under scope, children with newly diagnosed CLN2 disease receiving early access to care. Doing so would result in a fairer, equitable, more realistic and clinically relevant assessment of the benefits of cerliponase alfa for children diagnosed and treated under current NHS conditions.
6	**NICE has not sufficiently considered clinical opinion in its choice of a baseline distribution that is reflective of clinical practice today** BioMarin strongly recommends that the Committee reconsider its position regarding the baseline distribution of motor-language scores in its modelling, and adopt the "best achievable" motor-language score distribution from the December 2024 company advisory board for use in decision-making. The Committee has rightly recognised that motor-language score at diagnosis is a key driver of model outcomes. Clinical experts indicated that, in the past two years, they have not seen patients diagnosed with a motor-language score below five, suggesting that meaningful progress in earlier detection is already being realised. Following the second appraisal Committee meeting (ACM2), BioMarin convened an advisory process (December 2024) during which clinical experts were asked to provide a range of estimates (including 'conservative', 'realistic' and 'best achievable' scenarios), based on expected distribution of motor-language scores at the time of diagnosis over the next five years, assuming NBS was not in place. The Committee has indicated a preference for the 'realistic' estimate from that set. However, BioMarin believes this **does not** represent the most appropriate basis for decision-making. Given the increasing likelihood of NBS implementation and the observed pattern of earlier diagnosis already evident in clinical practice, the 'best achievable' estimate (70% with treatment start at ML 6 [i.e. health state 1]), previously considered optimistic in the absence of NBS, offers a more realistic projection of future practice. Conversely, the 'realistic' estimate preferred by the Committee, which excludes the possibility for continued improvements in rates of early diagnosis in the absence of NBS, as well as the potential impact of NBS altogether, significantly underestimates the likely baseline distribution for future incident patients by treating the

Cerliponase alfa for treating neuronal ceroid lipofuscinosis type 2 (MA review of HST12) [ID6145]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on Friday 6 June. Please submit via NICE Docs.

	probability of NBS implementation as zero. **NICE's approach is not supported by clinical expertise.** Given the lifetime horizon of the modelling and the potential for continued gains in the rates of early diagnosis--including through the introduction of NBS--BioMarin strongly recommends that the Committee reconsider its position and adopt the 'best achievable' estimate from the company advisory board for use in decision-making.
7	**Inaccurate framing of the presentation of the non-reference case analysis requested by the Committee:** In response to Section 3.15 of the draft guidance, BioMarin wishes to clarify the approach taken to the non-reference case analysis requested by the Committee. The draft guidance states that the company removed background care costs from its updated base case, and that no clear rationale or supporting evidence was provided for their exclusion. BioMarin notes that this does not accurately reflect the content and structure of the additional analyses document submitted on 29 August 2024 following ACM1. In the additional analyses document, the Committee's request for a non-reference case analysis excluding background care costs, consistent with Section 4.4.16 of NICE's health technology evaluations manual, was acknowledged and fully addressed (11). The rationale for excluding these costs was clearly documented, including detailed justification based on the nature of CLN2 disease and associated high-cost care, even in the absence of active treatment. The additional analyses document outlined the specific background care costs excluded (health state costs [health and social care visits], vision loss, psychiatric and behavioural support, and residential care), and explained that these costs reflect longer survival with cerliponase alfa, rather than direct consequences of treatment. The additional analyses included both versions of the Committee's preferred base case (with and without background care costs) ensuring that both reference and non-reference case analyses were available to support informed decision making. The cumulative impact of the changes from the EAG base case to the Committee base case was also clearly documented.

Cerliponase alfa for treating neuronal ceroid lipofuscinosis type 2 (MA review of HST12) [ID6145]

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	BioMarin also proposed its own updated base case, incorporating two further adjustments to the Committee's base case. This was presented excluding background care costs. While a version of this company base case including background care costs was not submitted, the implications of including or excluding these costs were transparently addressed through the corresponding Committee base case scenarios. BioMarin therefore considers that the Committee had all the necessary information to fully assess the relevance and impact of background care costs, as no issues regarding this non-reference case analysis were highlighted in ACM2 or ACM2, or any other documentation before the guidance. In case NICE and the Committee had issues with what was presented we believe that should have been highlighted at the time, and not wait until draft guidance was issued to inform that the company didn't adhere to what was requested. The current wording in the draft guidance, which implies an absence of rationale or evidence, does not accurately reflect the content and intent of the additional analyses submitted in direct response to the Committee's requests.
8	**Inadequate representation of disease severity and treatment impact** BioMarin is concerned that the language used throughout the recommendation reflects poor understanding regarding the severity of the disease, as it does not fully convey the devastating nature of CLN2 disease, nor does it adequately reflect the transformative impact of cerliponase alfa, as described by patient experts and clinical experts during the advisory boards. For this reason, a more conservative approach regarding the benefits of the therapy has been adopted by the Committee, which undermined the significant suffering experienced by patients and families, and has impacted the assessment of cerliponase alfa. The statement that '*people having cerliponase alfa will live longer and remain in much better health than people who only have supportive care*' significantly understates the reality shared by families and clinicians. For children diagnosed and treated early, cerliponase alfa is not simply associated with "much better health"; it can be life changing. Patient experts described children not only living longer, but in some cases leading lives that closely resemble those of unaffected peers. This is a profound and meaningful outcome, particularly in the context of such a rapidly

Cerliponase alfa for treating neuronal ceroid lipofuscinosis type 2 (MA review of HST12) [ID6145]

Draft guidance comments form

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	progressive and fatal neurodegenerative condition. For context, without treatment, CLN2 patients gradually lose mobility and become non-mobile around 6 years of age. As the disease progresses, they will require feeding tubes, or gastrostomy, and would usually die between the ages 8 and 12 years. BioMarin strongly urges that the language used in the guidance document be revised to more accurately reflect both the severity of CLN2 disease and the transformative potential of treatment. Doing so is essential to ensuring that the guidance truly reflects the lived experience of patients and families, and the reality observed in current clinical practice. It will also make clear to families of patients diagnosed in the future what will happen if treatment is not recommended by NICE at the end of this reappraisal.
9	**The current draft guidance highlights a concerning inequity in access to cerliponase alfa treatment across the UK** The negative draft guidance for cerliponase alfa by NICE stands in stark contrast to the positive recommendation for cerliponase alfa in Scotland. Cerliponase alfa is currently available in Scotland under a data collection agreement through the Scottish Medicines Consortium's (SMC) ultra-orphan pathway (12). This divergence in access raises significant equity concerns across the UK, as eligible incident patients in Scotland continue to access treatment that, should the draft NICE guidance be upheld, will be unavailable to patients with the same clinical need in England. Such disparity fundamentally undermines the expectation that patients across the UK with the same clinical needs should have equitable access to treatment, regardless of their geographic location. Furthermore, this inequity risks encouraging families with affected children to relocate to Scotland to secure access to treatment. As noted from a patient expert at an advisory board held by BioMarin (July 2023), prior to HST12 and cerliponase alfa's commercial availability in the UK, several families had temporarily relocated to Germany to gain access to treatment. Not only would similarly drastic decisions by families in the future be stressful for those forced to make such decisions; it would place additional strain on NHS Scotland and create further systemic imbalance.

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Cerliponase alfa for treating neuronal ceroid lipofuscinosis type 2 (MA review of HST12) [ID6145]

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	BioMarin therefore urges NICE and the Committee to consider the wider impact of this guidance, including equity of treatment access, for patients and families across the UK.

Insert extra rows as needed

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Cerliponase alfa for treating neuronal ceroid lipofuscinosis type 2 (MA review of HST12) [ID6145]

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- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations.
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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	[**Batten Disease Family Association CIO**]

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Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	[**None**]
Name of commentator person completing form:	[**Liz Brownnutt**]

Comment number	**Comments** Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Example 1	We are concerned that this recommendation may imply that ……..
1	Please refer to attached document: **Batten Disease Family Association CIO Response to NICE Draft Guidance Consultation**
2	Please refer to attached document: **Batten Disease Family Association CIO Response to NICE Draft Guidance Consultation**
3	Please refer to attached document: **Batten Disease Family Association CIO Response to NICE Draft Guidance Consultation**
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Batten Disease Family Association CIO - Response to NICE Draft Guidance Consultation: Cerliponase Alfa for Treating Neuronal Ceroid Lipofuscinosis Type 2 (CLN2) [ID6145, Review of HST12]

Introduction

The Batten Disease Family Association CIO (BDFA), the UK's only patient organisation supporting families affected by Batten disease, welcomes the opportunity to respond to NICE's draft guidance on cerliponase alfa (Brineura) for CLN2, a rare, life-limiting neurodegenerative disorder. Brineura, the only disease-modifying therapy for CLN2, has transformed lives under the Managed Access Agreement (MAA) since 2019. We appreciate the MAA's extension until 31 December 2025 and continued access for patients newly diagnosed by this date. However, the draft guidance's non-recommendation for children diagnosed after this date creates profound inequity, denying future patients a proven treatment that slows disease progression and enhances quality of life. This response addresses NICE's consultation questions, highlighting where all relevant evidence has not been taken into account and has not been interpreted reasonably, as well as potential equality issues, which together risk resulting in final guidance that is unreasonable and irrational.

1. Has All Relevant Evidence Been Taken into Account?

The evaluation process in which NICE engaged the stakeholders over the last 6 years and the draft guidance suggest that the NICE committee did not fully appreciate the ultra-rare nature of CLN2. With an estimated prevalence of 0.75 per million and an incidence of 0.5 per 100,000 live births in the UK (Gissen P et al., 2022), the committee set unrealistic expectations for the MAA, raising unreasonable demands for evidence in motor and language outcomes that the limited patient population cannot feasibly provide in order to meet its evaluation criteria.

The BDFA believes that NICE has not fully taken into account critical evidence regarding the devastating impact of CLN2 and the transformative benefits of treatment with Brineura, particularly from patient and carer perspectives. Our MAA submission (BDFA, 2023) included survey responses from 29 parents of 31 children

and 13 teachers of 14 children treated with Brineura, demonstrating substantial benefits:

- Clinical Benefits: 84% of parents reported improved or stabilised seizure severity, duration, and frequency, alongside gains in motor function, coordination, myoclonus, dystonia, speech, mood, sleep, and fatigue (BDFA, 2023, p. 10, Q11). Teachers reported improvements in attention spans and engagement post-infusion, with slower deterioration in mobility and muscle strength compared to untreated children (BDFA, 2023, p. 15, Q17).
- Quality of Life: 97% of parents emphasised Brineura's critical role in stabilising disease progression, enabling activities of daily living. For example, a 13-year-old patient continues to swim, travel, and express emotions—activities impossible without treatment (BDFA, 2023, p. 11, Q11).
- Benefits Across Disease Progression: Evidence shows benefits across all CLN2 patients, including those with progressed disease, atypical phenotypes and asymptomatic siblings diagnosed early, who maintain near-normal function (BDFA, 2023, p. 19, Q18; Schulz A et al., 2018; Wibeller E et al., 2020; Schaefers et al., 2021; Schulz et al., 2023).

The draft guidance acknowledges Brineura's ability to slow disease progression (section 3.3) but overemphasises long-term uncertainty due to limited follow-up data. For ultra-rare diseases like CLN2, with 30–50 UK patients and 3–6 annual diagnoses, long-term data collection is inherently challenging. Despite COVID-19 disruptions, MAA data demonstrates sustained benefits (section 3.4). As also referred to in section 3.4, study 190-202 assessed long-term safety and efficacy and study 190-203 was a post-authorisation efficacy study, plus six years of real-world evidence is available from the MAA cohort of all people eligible to have Brineura in England. It is unclear from the draft guidance what further follow-up data the committee would expect (and that would be realistic in the context of an ultra-rare disease such as CLN2).

We note that under section 6.2.34 of the Manual, the committee has discretion to accept a higher degree of uncertainty where evidence generation is particularly difficult because the condition is a rare disease or the technology is for use in a population that is predominantly children (under 18 years old) or the technology is innovative, all three of which apply in this case.

For the outcome in the final guidance to be fair and reasonable, we urge NICE to place greater emphasis on patient-reported outcomes and real-world evidence, as provided for in section 3.3.2 of the Manual, which capture benefits not fully reflected in clinical metrics like the Motor-Language (ML) score.

2. Are the Summaries of Clinical and Cost-Effectiveness Reasonable Interpretations of the Evidence?

The committee agrees that Brineura slows down the progression of CLN2 (section 3.4), which is a big deal for a disease that causes children to lose their ability to walk, talk, see, and eventually leads to a shorter life. Patient and clinical experts described

Brineura as a “transformative” treatment because it helps kids stay healthier for longer compared to just managing symptoms with supportive care (like medicines for seizures or therapy to maintain movement). However, the committee says there’s not enough evidence to show how well Brineura works over a long time (beyond 6 years). Here’s why the committee’s view is not a reasonable interpretation of the evidence:

- Using Conservative Data: The committee based its assumptions on data pooled by the ERG that combined outcomes from children diagnosed late (before the implementation of the MAA), when disease awareness was significantly lower, with those diagnosed more recently under the MAA, who tend to be identified earlier. This data combination fails to account for the observed trend that earlier diagnosis, now more common, leads to better treatment outcomes (section 3.7). Assuming uniform outcomes across these groups undermines the true benefit of Brineura in current clinical practice where detection occurs earlier.
- Impact of COVID-19 on Data: The committee acknowledges that the COVID-19 pandemic disrupted some of the data collection. During the pandemic, kids couldn’t always get to hospitals for treatment, see specialists, have an MRI, or go to school (BDFA, 2023, p. 9, Q10/p. 16, Q14; Mortensen A et al., 2022), which is highly likely to have made Brineura look less effective in the managed access agreement (MAA) data. Families also struggled to access medicines and support services. Despite this, the committee still relies heavily on this potentially flawed data to question Brineura’s benefits. This approach is inequitable because it is highly likely that the data does not show the full picture of how well Brineura works in normal clinical circumstances
- Dismissing Non-Neurological Benefits: The committee says there’s limited evidence on how Brineura affects things like seizures, pain, or the need for feeding tubes (non-neurological symptoms). But clinical experts and patients have provided evidence that they have seen improvements or stabilisation in these areas, like fewer or less severe seizures, less pain, improvements in mood, behaviour, sleep tiredness, fatigue and better overall comfort (BDFA, 2023, p. 10, Q11). The committee admits there’s some evidence for this but calls it uncertain because it’s not well-documented in the studies. However, in accordance with section 3.3.18 and 3.3.22 of the Manual, evidence from treating clinicians, clinician experts and patient experts can be provided and where provided should be taken into account. By downplaying these benefits, the committee is likely underestimating how much Brineura improves kids’ and families’ quality of life
- Overly Pessimistic Assumptions: The committee assumes that Brineura doesn’t help with vision loss, even though some kids on Brineura have kept their vision longer than expected. The committee’s model assumes all kids lose vision completely by age 9 or 10 and section 3.12 of the draft guidance states that the committee has not seen evidence to support the assumption that Brineura delays vision loss. However, as also stated section 3.12, clinical experts’ opinion is that some children on Brineura don’t follow this pattern. By assuming Brineura has no impact on vision retention, the committee is making the treatment seem less helpful than it actually is

- Ignoring Carer and Family Benefits: Brineura doesn’t just help the child, it also reduces the burden on parents and siblings, who often have to quit jobs, pay for home changes (like wheelchairs), or deal with emotional stress. The committee agrees these benefits exist but says they can’t be included in their calculations because NICE’s rules only count the child’s QALYs. This feels unfair because CLN2 affects the whole family, and Brineura’s ability to keep kids healthier for longer means parents might not have to care for them as intensively or grieve as early.

The committee’s view on clinical and cost-effectiveness is too cautious.

They focus disproportionately on what we don’t know (long-term data) instead of what we do know: Brineura slows down CLN2, helps kids stay healthier longer, and improves symptoms like seizures and pain, even if the data isn’t perfect because of things like COVID-19 or the challenges of studying a rare disease.

The cost-effectiveness summary does not adequately balance Brineura’s clinical benefits against the small patient population and lack of alternatives, leading to an inequitable denial of treatment.

3. Are the Recommendations Sound and a Suitable Basis for Guidance to the NHS?

The BDFA firmly believes that NICE's recommendation to cease access to Brineura for newly diagnosed children with CLN2 from 31 December 2025 is neither sound nor a suitable basis for NHS guidance. This decision ignores six years of real-world clinical experience in which Brineura has been safely and effectively delivered across specialist centres in the UK. These centres have developed specialised infrastructure, sterile treatment environments, and multidisciplinary teams dedicated to administering this life-changing therapy, ensuring patient safety and maximising treatment outcomes.

Since Brineura’s introduction, there has been a significant increase in awareness and understanding of CLN2 within the UK scientific and medical community. Participation in the initial clinical trials and subsequent national implementation has enabled UK clinicians to become internationally recognised leaders in CLN2 research and treatment. Experts such as Professor Paul Gissen, Professor Sara Mole, and Dr Ruth Williams have contributed extensively to the global body of evidence, publishing influential studies and elevating the overall standard of care.

Initially available at a single centre, Brineura treatment has now expanded to seven centres across the UK, alongside a growing knowledge base among specialists, including ophthalmologists and paediatric neurologists. This has led to measurable improvements in clinical outcomes and quality of life for affected children. In parallel, there has been a notable enhancement in educational support for children with CLN2, with many now meeting or exceeding educational milestones (BDFA, 2023, p. 13, Q11).

These substantial and hard-won gains in clinical care and education will almost certainly be abruptly reversed if the NICE recommendations remain unchanged after December 2025.

The guidance fails to take into account the immense clinical, emotional, and operational burden that will result from denying treatment to newly diagnosed children with CLN2, a devastating ultra-rare disease for which Brineura is the only disease-modifying option. Clinicians and nurses who have witnessed the tangible benefits of Brineura, including prolonged mobility, preserved cognitive function, and enhanced quality of life, would face the ethical distress of being unable to offer this treatment to future patients. This abrupt policy reversal would undermine NHS clinical expertise, dismantle specialist capacity built over years, and most critically, cause irreversible harm on children and families facing an already unimaginable diagnosis. We believe that it is with these principles in mind that NHS England and BioMarin negotiated in good faith the commercial arrangements thus allowing the patients who have been receiving Brineura under the MAA to continue access to treatment.

NICE's recommendation is, therefore, fundamentally flawed and incompatible with the values of a health system committed to equity, compassion, and evidence-informed care.

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

The draft NICE guidance fails to describe the true devastating nature and clinical course of untreated CLN2: after the initial delay to diagnosis, children very quickly, from around the age of three, develop difficult to control seizures; start to lose language; lose muscle control and eventually become bedridden; lose vision which very quickly progresses to full blindness; develop dysphagia, ultimately requiring tube feeding; lose ability to acquire new skills and develop very painful muscle spasms. Children with untreated classic type CLN2 (vast majority of diagnosed children) die around the age of 10 under most horrific circumstances (Schulz A et al, 2013; Mole Set al, 2013).

The draft NICE guidance allows the following scenario: a child ("Child A") diagnosed with CLN2 on 5th December 2025 with a Motor-Language score of 4 [ranging from 0 (complete loss of motor and language functions) to 6 (normal motor and language functions)] would access Brineura permanently without restrictions. Another child ("Child B"), or even Child A's sibling, diagnosed a month later, on 5th January 2026, with a score of 6, would be denied access to treatment under the current guidance. Paradoxically, Child A, further progressed at diagnosis would, based on evidence, outlive Child B, who had normal motor and language functions at diagnosis, due to Brineura's benefits.

Terminating access to Brineura for newly diagnosed patients after 31 December 2025 is inconsistent with principles of equitable care and lacks clinical justification. It creates an unfair and deeply distressing situation where two children with the same condition could be treated completely differently, just because of when they were diagnosed. This time-based cut-off creates a discriminatory distinction based on diagnosis timing, despite identical clinical needs. We strongly oppose this recommendation for the following reasons:

- Inequity and Discrimination: The cut-off arbitrarily denies future patients access to a life-prolonging treatment, violating principles of fairness. CLN2 patients diagnosed post-2025 face the same devastating prognosis, death by early adolescence without treatment, but will be excluded from a therapy proven to slow progression and enhance quality of life. This inequity is particularly stark given Brineura's transformative impact, as evidenced by children maintaining mobility, communication, and joy in activities like ballet and swimming (BDFA, 2023, p. 20, Q18).
- UK Equality Act 2010: CLN2 qualifies as a disability under section 6, and the cut-off constitutes indirect discrimination (section 19) by disadvantaging children diagnosed post-2025. This will disproportionately impact younger children as diagnosis is uncommon before the age of three due to lack of clinical symptoms. The Public Sector Equality Duty (section 149) requires eliminating discrimination, yet the NICE draft guidance fails to assess the equality impact on disabled children diagnosed post-2025 (section 3.21).
- UK Human Rights Act 1998: Article 2 (Right to Life): Denying Brineura, the only treatment available for CLN2, risks breaching the state's obligation to protect life, as untreated patients face premature death (section 3.2).
- UN Convention on the Rights of Persons with Disabilities (CRPD): Article 25 mandates equal access to healthcare, yet the cut-off denies CLN2 patients a necessary treatment, failing to provide reasonable accommodations for their disability.
- NHS Constitution: The Constitution pledges care based on clinical need, not arbitrary factors like diagnosis timing. Denying Brineura to future patients, while current patients continue, breaches this principle, especially as private funding is unfeasible for most if not all patients.
- Ethical Concerns: The cut-off creates a moral injustice, forcing families to face inequitable access across siblings based solely on timing of diagnosis. Parents describe the "heartbreaking" sense of a "price tag" on their child's life (BDFA, 2023, p. 18, Q16), and the uncertainty of the MAA review has caused significant distress (BDFA, 2023, p. 18).

The draft NICE guidance states wrongly (Section 3.2) that there are no clinical guidelines for CLN2. In fact, there are several documents outlining the best clinical practice in CLN2, most notably recommendations about diagnosis of CLN2 (Fietz M et al., 2016), management strategies for CLN2 (Williams R et al., 2017) and CLN2 clinical guidelines which recommends Brineura for every child diagnosed with CLN2 irrespective of clinical status or disease type (Mole S et al., 2021).

Conclusion

The BDFA unequivocally rejects the draft NICE guidance's recommendation to restrict access to Brineura after 31 December 2025. This decision is not only clinically unsound and ethically indefensible; it is legally questionable and socially regressive. It disregards six years of real-world clinician and patient evidence, devalues lived experiences, and imposes arbitrary barriers to the only disease-modifying treatment for CLN2, a condition with a universally fatal prognosis.

Brineura is not experimental. It is a proven, transformative therapy that demonstrably slows the decline in motor, language, cognitive, and non-neurological functions. Its impact goes beyond the child, it reshapes the daily reality of entire families, restoring hope, dignity, and precious time. Moreover, the lived experience of families with newly diagnosed children today is markedly different from that of families whose children were diagnosed late in the past. Earlier diagnosis, improved care pathways, and established treatment centres have changed the outlook for many. The real-world data collected under the Managed Access Agreement, along with clinical consensus and international guidelines, support Brineura's continued availability without cut-off dates or unjustified restrictions.

NICE's proposed policy introduces a discriminatory timeline that would see children denied life-extending treatment purely based on when they are diagnosed, an act that contradicts the NHS Constitution, the Equality Act 2010, the Human Rights Act 1998, and the UN Convention on the Rights of Persons with Disabilities. This is not a matter of affordability; it is a matter of principle.

We call on NICE to instead recommend continued access beyond the cut-off date, to recognise Brineura as essential, evidence-based care, and to uphold the fundamental values of equity, compassion, and evidence-informed policymaking. Anything less would be an abandonment of society's most vulnerable children and the clinicians who have fought to care for them. We do not wish for more children to be diagnosed with CLN2. But when they are, we must not allow them to be further disadvantaged by the absence of a commercial agreement. Ending access to Brineura will not prevent future diagnoses, only deepen the injustice faced by those affected.

We urge NICE to act decisively, justly, and humanely, by securing permanent, equitable access to Brineura for all children diagnosed with CLN2, regardless of timing.

References

- UN Convention on the Rights of Persons with Disabilities (CRPD) 2006
- UK Equality Act 2010
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NICE health technology evaluations: the manual, 2025; https://www.nice.org.uk/process/pmg36/chapter/committee-recommendations-2

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2	We are concerned that by refusing treatment to all patients with CLN2, the limitations of study 190-203 -small number and limited follow-up- is not being fully addressed. A plan should be made for access to cerliponase alfa to patients less than 3 years of age who are in Health state 1 with ongoing monitoring to obtain the data needed for long term effectiveness.
3	We are concerned that the decision to refuse treatment for those less than 3 years of age, the group most likely to have significant QALY gains, is due to the inability to agree starting and stopping criteria between NICE, patient groups and clinical experts. Currently the recommendation is based on the pooled dataset.
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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	[Newcastle upon Tyne Hospitals NHS Foundation Trust – paediatric IMD service for North East England and North Cumbria]

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Cerliponase alfa for treating neuronal ceroid lipofuscinosis type 2 (MA review of HST12) [ID6145]

Draft guidance comments form

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Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	[None]
Name of commentator person completing form:	[redacted]

Comment number	Comments Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Example 1	We are concerned that this recommendation may imply that ……..
1	Recommendation 1.1 and 1.2 – we are concerned that there will now be inequity in provision with patients with identical conditions being treated differently, dependent upon their date of diagnosis
2	Recommendation 1.1 and 1.2 – we are concerned that there will be no treatment available for patients identified through the Generation Study – these patients have the greatest to gain from cerliponase treatment due to early diagnosis
3	Recommendation 1.1 and 1.2 – much of the data around limited benefit of cerliponase is based on a cohort of children identified late in their disease course – we know that the age of diagnosis is falling as a result of increased awareness (and the Generation study) – we have direct experience of this with a patient who initiated treatment at age 18 months who remains fully ambulant and communicative at age 9 years – this would not have been the result without cerliponase treatment
4	Recommendation 3.1 – we disagree - the Generation study will now provide a route to screening for CLN2 – even if this is not subsequently adopted as a universal offer, it is extremely shortsighted and unfair to withdraw a treatment prior to this point
5	Recommendation 3.13 – the stopping rule discussion is fraught! If it were a decision between stopping cerliponase treatment at health state 6, with the

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	benefit of being able to start treatment for those in higher health states, then this could be discussed
6	

Insert extra rows as needed

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	[**UCL Great Ormond Street Institute of Child Health**]

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Name of commentator person completing form:	[**Paul Gissen**]

Comment number	**Comments** Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Example 1	We are concerned that this recommendation may imply that ……..
1	• Has all of the relevant evidence been taken into account? NICE have not taken into account the fact that the patients diagnosed and started on cerliponase alfa in the past 3 years have all been in the early stages of the disease scoring 6 and 5 on CLN2 scale. Even patients diagnosed slightly longer than 3 years ago scored 4 or more on CLN2 scale. Hence the patients that are diagnosed now are in much better condition than those treated in the Biomarin trials or joined MAA initial and provided the longer follow up date. Furthermore, the eye treatment with intravitreal brineura has not been taken into account. The effect of this therapy will prevent vision loss providing improvements in the overall CLN2 scale and patient functioning long-term.
2	• Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? Yes the summaries are reasonable and suggest that cerliponase alfa is effective in the patients diagnosed and started therapy in the past 3 years.
3	• Are the recommendations sound and a suitable basis for guidance to the NHS? No This is a transformative treatment cost effective in the patients diagnosed early in the disease and therefore should be approved.

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4	• Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation? The negative recommendation is incorrect. This therapy should be approved for patients with CLN2 disease. The negative recommendation discrimates against patients with disability including neuro and visual disability.
5	
6	

Insert extra rows as needed

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	**Department of Paediatric Neurology and Metabolic Medicine, Royal Manchester Children's Hospital**

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Name of commentator person completing form:	Dr Dipak Ram, Consultant Paediatric Neurologist

Comment number	**Comments** Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
1	We are concerned that the recommendation may imply that future patients of all ages may not receive cerliponase alfa therapy if diagnosed with CLN2. We have seen a significant difference in pre-symptomatic and early symptomatic children diagnosed with ML scores of 5 and 6 who are receiving treatment. Some of these children remain independently ambulant even at 6-7 years of age. We would urge NICE to engage with clinicians about this cohort of children before making any decisions about the therapy for future patients.
2	The age of diagnosis of children with CLN2 disease is gradually lowering in the UK. The majority of children seen recently have had higher ML scores than previous, many of which scored 5 and 6 in total. With the recent shift in age of diagnosis and the potential of newborn screening, the lower age of diagnosis would support better outcomes as described in Comment 1. We would strongly urge NICE to engage with clinicians managing these patients actively as the data beyond the managed access agreement continues to be collected by clinical monitoring in our centre, demonstrating evidence that this cohort of children are benefiting from treatment from a mobility, cognitive and seizure-control perspective.
3	We are concerned that mixed data from the past is being used by NICE to interpret the future population of CLN2 in the UK. As outlined in Comment 1 and 2, there is ongoing current clinical experience of managing patients with ML scores of 5 and 6 at the onset of treatment, and it would be imperative for NICE to engage with clinicians managing these patients to understand how they are benefiting from treatment.

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	I am a Parent Representative on the Patient Expert Panel

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Name of commentator person completing form:	Gail Rich

Comment number	Comments Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Example 1	We are concerned that this recommendation may imply that ……..
1	Please refer to the attached document – Gail Rich, Parent Representative, written submission June 2025
2	Please refer to the attached document – Gail Rich, Parent Representative, written submission June 2025
3	Please refer to the attached document – Gail Rich, Parent Representative, written submission June 2025
4	Please refer to the attached document – Gail Rich, Parent Representative, written submission June 2025
5	Please refer to the attached document – Gail Rich, Parent Representative,, written submission June 2025
6	Please refer to the attached document – Gail Rich, Parent Representative, written submission June 2025

Insert extra rows as needed

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Gail Rich.

Patient Expert – Parent Representative.

Written submission for Cerliponase Alpha.

June 2025.

Q1)

Has all of the relevant evidence been taken into account?

No.

There is a huge focus on motor and language but these two domains do not give an optimum representation of the multifaceted benefits of Brineura. Being able to walk and talk is not a robust marker to ascertain if a child's life is full of happiness, joy and excitement and it certainly does not define their 'quality of life'.

The truest and most meaningful measure of the impact of Brineura on a child's quality of life are the testaments of their life with their family, their enjoyment and engagement at school, the hobbies they enjoy, the activities they can access and how much more of a pain-free life they are able to live.

I feel that the benefits of the significantly slower rate of disease progression have not been taken into account sufficiently. The life changing positive outcomes that families are seeing and experiencing are reflective of the value of Brineura to the child and their families. My personal experience is that the quality time we had with our oldest daughter and the improved quality of her life because of Brineura was priceless. Brineura allowed us to travel the world with our children and enjoy many special activities and allowed us time together as a family without our daughter needing the medical interventions which would have been a certainty without Brineura at her age (11).

These areas are important and I feel they have not been given the weight in this assessment they needed to have been given.

Although parents' comments from previous submissions will have been considered, they have not been given the same weight in the assessment. Despite each parent giving individual accounts, there should be some way of including this vital data in a measurable and quantifiable way so that they are reviewed as valid outcomes. This is where I think the system is failing our patient group.

There should be a way of taking a more personal approach to assessing the impact on the child's life in terms of their wellbeing, enjoyment, hobbies, abilities, achievements, finding joy, experiencing milestones, being able to enjoy family life, not basing a decision on an appraisal system which is not appropriately designed for the rarity of a condition like CLN2 Batten Disease.

An extremely relevant part of evidence is real world data. How is the treatment impacting the child's schooling, enjoyment, outside of school hobbies. This evidence was submitted as part an indepth response by the BDFA in 2023 which evidences the experiences of parents of treated children and from education providers which clearly demonstrated the benefits of Brineura.

During the MAA parents have answered questions posed in the following questionnaires –

*Peds QL – to record 'how much of a problem' certain things have been for your child over the past one month. Focus areas physical, emotional, social and school functioning.

*CLN2 QOL – to record 'how some issues related to your child's disease may have been a problem' for you, your family and your child over the past one month. Focus areas are seizures, feeding, sleep, behaviour, activities.

*EQ-5D-5L – to measure your 'child's quality of life' today. Mobility, self care, usual activities, pain/discomfort and emotional well being.

As you can see from the descriptions, they had a negative tone to them focussing on issues & problems. No questions were asked about achievements, successes, fun activities, exciting developments in our child's life. Comments given about these area's were not able to be recorded other than as a 'note'.

I found the questions to be very triggering as I know many other families who had a child with diminished skills. If the child can't walk, then what is the benefit of asking if they can shower themselves or if they can dress themselves? If we answered 'no' to the initial question, it should have invalidated the subsequent questions, but it didn't, instead we were reminded of everything our child could no longer do as we were forced to answer 'no' to all the questions that followed in particular segments of the questionnaire.

****

I am vehemently opposed to introducing starting and stopping criteria as every child can benefit from Brinuera as I have seen in my two daughters who were both at very different stages of their journey with Batten but both benefited hugely.

Every child deserves the chance of living a longer healthier life.

Stopping treatment should be a personal decision which is decided upon after discussions between parents and clinicians, not because their health care state has been deemed to have reached a threshold for cost effectiveness.

Q2)

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

No.

I believe that the highly specialised technologies appraisal process is not able to accurately assess CLN2 batten disease due to the small patient population of this ultra rare condition.

When dealing with life or death, it is unfair to use a system that is unfortunately not fit for purpose for the assessments of an 'ultra rare' condition where the patient population is so low.

The limiting factor of 30 QUALY's is detrimental to the entire process.

It has been widely agreed that Brinuera would go beyond 30 additional quality life years due to it's transformative results but because the cap is set at 30 and cannot be moved, it is not a true reflection of the true impact of the drug and therefore it will limit the cost benefit because you are assessing it on a lower quality of life rating. Also the omission of carer and family benefits as part of the calculations would have a negative impact on the result. We should be looking at the benefits of treatment for the whole family, the siblings, the grandparents, from wellbeing to the ability to continue employment.

The treatment should be deemed cost effective.

Our children have proven for the 5 years of the MAA (combined with the 5yrs previous on the trials and compassion use programmes) that it IS worth the money.

The process for assessing the treatment is the issue.

Q3)

Are the recommendations sound and a suitable basis for guidance to the NHS?

No.

Looking at the disease, the historical decline in health seen in children who did not have access to Brinuera, historical mortality rates, what Brinuera is doing to improve the child's life, how it is extending lives and alleviating the devastating symptoms by slowing down the progression of the disease, it is inconceivable that Brineura would not be recommended.

It is right to celebrate clinical excellence, scientific research and innovation in technologies which lead to the development of transformative treatments but we need to improve the pathway to access, as it means nothing if the medicine is then denied to those patients who need it!

The HST process has proven to be a barrier to access and has placed a immense amount of unnecessary stress on a group of families who are already living with significant challenges and stresses caused by Batten Disease.

The burden of coping with a child with CLN2 without treatment is one that should be confined to the past. We should moving with advancements to eradicate the suffering of children born with this devastating genetic disease so NICE's recommendation to NHS to deny children this drug is wrong.

A negative decision would also be hugely detrimental to how the UK is viewed as a potential market for new technologies so the repercussions of a negative decision would be dire.

If we could, for a moment, take away the rules, the economic metrics, ICER's, QUALY's, Utlities and just looked at this in the simplest of ways – we would see a miniscule percentage of the UK population, who, before now, had no future other than them suffering the most devastating and cruel symptoms until they passed away….but a pioneering treatment exists and it is available to many patients around the world so it would be deplorable to deny access and let children in this country suffer unnecessary.

Our country is proud of the expertise and world leading clinical and research institutions we have, we are champions of innovative therapies with an eagerness to compete with world leading advancements in genetic programmes, yet you are saying no to a transformative treatment that is going to a minute percentage of the population who are desperately in need.

Another point I would raise is that there are now 7 treatment centres in the country providing the appropriate skill, expertise and resource. If Brinuera was not approved for the future diagnosed children, it would be an incredible waste of that time, money and resource that has gone into establishing these centres.

Q4)

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

Yes.

A negative recommendation would signify a refusal to provide adequate care for those who desperately need help where there are no other options due to the rarity of their condition, thus causing immense harm and distress to children and their families.

Children with CLN2 Batten Disease should be allowed the same equity in accessing a treatment for their condition, like children with less rare conditions are routinely offered.

Children who have lost their ability to walk or talk should not be viewed as leading a poor quality of life. Families adapt to their child's changing needs and ensure their lives are surrounded by different stimuli and exciting adventures, which are accessible and individualised to their unique child on their unique journey. They are just as deserving of the right to live a more comfortable life.

It would be completely unethical and catastrophic to the UK's rare disease community as a whole to deny children of the future access to Brineura. It is not the child's fault that the only medicine that can help them is more expensive and thus requires more justification to be authorised.

By placing so much weight and emphasis on motor & language scores to assess the benefits of treatment on quality of life, is unethical as I do not believe that the real world benefits have been adequately taken into account and the transformative way that the day to day lives of children who are receiving treatment has improved.

I am in the unique position of being able to speak from the perspective of a mother who had two children diagnosed with CLN2 but at different ages and at different stages of their journey.

Our oldest daughter was diagnosed at 4.5yrs old and our youngest daughter was diagnosed at just 15 months old.

Our older daughter had already lost some of her abilities because it took 2.5 yrs to get a diagnosis. Her condition declined, but at a much slower rate than without Brineura. She was in a wheelchair and was non verbal all of her life so she would have scored low in both ML domains.

Despite being wheelchair bound, fully dependant on us, and being non verbal, she had a wonderful quality of life. Because of Brineura, she was able to travel the world, experiencing some incredible things that would simply not have been possible without treatment. She enjoyed socialising and loved her school activities. She was surrounded by love and showed

love for those around her. We were so lucky to have had the joy of our darling daughter in our lives.

Then, in comparison, her little sister (who was diagnosed & began treatment as the youngest child in the world & pre-symptomatically & whose data is recorded in study 190-203 sibling trial) has not dropped any points in ML in 8 years which is unheard of. She will be 10 this year. She is leading an active life, full of joy, excitement, mischief. She miraculously still has full visional function as her older sister still had at age 11 so our two girls were classed as atypical in terms of their vision.

To have a cut off date for accessing treatment is inhumane. Imagine being a family who is diagnosed on 1st January and are told they cannot access treatment, but someone who was diagnosed a day earlier could? That would be horrific and I am certain this is not the outcome NICE or NHS or Biomarin would want to reach.

I refer to the NHS Constitution.

Principle 1: The NHS provides a comprehensive service available to all

The NHS provides a comprehensive service, available to all irrespective of gender, race, disability, age, sexual orientation, religion, belief, gender reassignment, pregnancy and maternity, or marital or civil partnership status. The service is designed to improve, prevent, diagnose and treat both physical and mental health problems with equal regard. It has a duty to each and every individual that it serves and must respect their human rights. At the same time, it has a wider social duty to promote equality through the services it provides and to pay particular attention to groups or sections of society where improvements in health and life expectancy are not keeping pace with the rest of the population.

Legal duties require NHS England and each ICB to have regard to the need to reduce inequalities in access to health services and the outcomes achieved for patients.

This principle is mindful of the NHS's integral role in alleviating health inequalities, which the World Health Organization defines as "differences in health status or in the distribution of health determinants between different population groups". The principle makes clear that the NHS has a wider social duty to promote equality through the services it provides.

The worth of our children's lives are being subjected to a far greater level of scrutiny purely because the medicine they need is more expensive.

The NHS have a certainty relating to the efficacy of the drug through the MAA data alongside trial data gathered so it is unfair to deny children purely on the inability to reach a financial agreement and rather than putting it all down to price - surely we have to question the method being used to arrive at the assumption that this drug is not cost effective.

By denying access you would be knowingly inflicting unnecessary suffering on innocent children.

We all know it is transforming lives and allowing children to live healthier lives so there should not be a price tag on our children's lives.

I have said this many times during my years of representing families at the NICE committee meetings, we should be celebrating Brineura and the incredible and priceless time it is giving to families. We should not be having to justify our child's right to access it.

When we are aware that the barrier to recommending Brineura is a financial one, as a parent of a child with Battens, it is very hard not to be critical of current NHS spending and wastage costs.

It would be difficult for us all to put our hands on our hearts and say that Brineura - which would save a child from a life of debilitating regression, seizures, rapid and relentless decline and early death - is less important than other treatments that are being prescribed every day at a far greater volume to a far greater number of patients. Our community and our children are being put at an immediate disadvantage by being born with an ultra rare condition where treatments are so rare and are highly specialised thus attracting a higher cost.

The wider issue is how the NHS can save money in other areas to support rare disease sufferers so they are not in the position the batten community find ourselves in where we are waiting to see if the drug is a good enough price to be deemed a 'good use of NHS funds'.

I am hopeful that with our collective feedback from across the patient expert panel and views offered by the public, a positive outcome can be reached and the batten community can celebrate that children now and in the future will be given the right to a healthier longer life.

Thank you for your time is reading my comments.

NICE National Institute for Health and Care Excellence

Cerliponase alfa for treating neuronal ceroid lipofuscinosis type 2 (MA review of HST12) [ID6145]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on Friday 6 June. Please submit via NICE Docs.

	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Evaluation Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.**
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Patient Expert

Please return to: **NICE DOCS**

NICE National Institute for Health and Care Excellence

Cerliponase alfa for treating neuronal ceroid lipofuscinosis type 2 (MA review of HST12) [ID6145]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on Friday 6 June. Please submit via NICE Docs.

Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	N/A
Name of commentator person completing form:	Lucy Carroll

Comment number	Comments Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Example 1	We are concerned that this recommendation may imply that ……..
1	This decision has been formed by a series of assumptions. I believe that there are uncertainties in the data and some possible bias in the data that may weigh against a decision in favour of continued treatment. It is important due to how rare this disease is and due to the small population of patients that NICE take into account Real World Data. It is so important to listen to parents/carers and those around the child daily rather than only use the data from assessments within the MAA. Real World Data shows a clearer reality. For example, traveling four hours with our own children in the early hours to hospital, to then be greeted by a person our children had never met before to then expect them to perform to their best ability for assessments is unrealistic and the correct data will not be gathered. Sometimes assessment took place after a four hour long brain infusions.
2	The current approach concludes that the treatment is not a cost effective use of NHS resources. Which is based on a number of assumptions about health states in the future. It is my believe that the threshold value has not been increased for at least eight years. This is an issue that needs addressing. It is my believe that in some cases NICE have the right to increase this threshold in certain cases, why has NICE not invoked this potential increase in this case? Have NICE asked the UK Government to increase the threshold value for rare diseases?

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NICE National Institute for Health and Care Excellence

Cerliponase alfa for treating neuronal ceroid lipofuscinosis type 2 (MA review of HST12) [ID6145]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on Friday 6 June. Please submit via NICE Docs.

3	NICE are following a HST Programme which states that the programme is "to help generate an evidence base that is robust enough to bring the product to market" Clearly NICE believe there is insufficient long term evidence and hence uncertainties about the future. Since there are clear benefits arising from the treatment then it could be argued that NICE should be extending the treatment timescale to collect this evidence rather than cutting off access to the treatment in December.
4	There is NO other treatment options for ANY types of Batten Disease. This is a fundamental reason why treatment for CLN2 Batten Disease must be approved. Personally without this treatment our two children aged 14 and 12 would no longer be here with us yet because of this treatment they are living an extraordinary life, full of adventures, love and laughter. As a family we have been given the gift of time to create memories with our children, something that has been priceless. It has allowed us to process the diagnosis, work alongside therapists ensuring that our children have a good quality of life. They are not just alive they are living. Brineura has been proven to slow down the progression of the disease and therefore improve quality of life.
5	Allowing treatment for some children but not others is something that should never be considered. The treatment must be available for all children with CLN2. A program must run alongside to detect CLN2 Batten Disease at the earliest possible stage. Newborn testing had been delayed for too long, this needs to be made available.
6	

Insert extra rows as needed

Checklist for submitting comments

- Use this comment form and submit it as a Word document (not a PDF).
- Complete the disclosure about links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- Please underline all confidential information, and separately highlight information that is 'commercial in confidence' in turquoise and information that is 'academic in confidence' in yellow. If confidential information is submitted, please submit a second version of your comments form with that information replaced with the following text: 'academic / commercial in confidence information removed'. See the NICE Health Technology Evaluation Manual (section 5.4) for more information.
- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations.
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.

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NICE National Institute for Health and Care Excellence

Cerliponase alfa for treating neuronal ceroid lipofuscinosis type 2 (MA review of HST12) [ID6145]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on Friday 6 June. Please submit via NICE Docs.

- If you have received agreement from NICE to submit additional evidence with your comments on the draft guidance document, please submit these separately.

Note: We reserve the right to summarise and edit comments received during consultations, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during our consultations are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

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Highly Specialised Technology

Cerliponase alfa for treating neuronal ceroid lipofuscinosis type 2 (MA review of HST12) [ID6145]

Comments on the draft guidance received through the NICE website

Name	[redacted]
Role	
Other role	
Organisation	
Location	
Conflict	
Notes	
Comments on the DG:	
I am involved in the medical care of children with this condition and prescribe this treatment. It provides hope and time for families whilst curative treatments are being developed.	

Name	[redacted]
Role	
Other role	
Organisation	
Location	
Conflict	
Notes	
Comments on the DG:	

Has all of the relevant evidence been taken into account?
it would be appropriate to see data on age / HS of those made by genetic diagnosis since the MAA started.

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
Agree

Are the recommendations sound and a suitable basis for guidance to the NHS?
see comments

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?
I don't believe so

Comments:
I acknowledge the rationale for the basis of the committee's decision but disagree with the ultimate recommendation. Based on the overall benefit to CLN2 patients cf the NHx cohorts and the overall improved quality of life that would bring.

Of all the ERT products available, this data is the most convincing in the context of no other specific therapeutic options for this population.

I believe outside of newborn screening, diagnoses is still being made earlier since the advent of easier genetic epilepsy panel testing - which i believe is greater than increased clinical awareness by itself and this will only increase.

I believe their should be a frank dialogue/consideration about starting treatment criteria including w carers, patient support groups, treatment professionals - to allow greater targeted access than this current decision will allow, with the right for appeal and to allow understanding in cases not deemed eligible. [as per s3.14 / p 23]

This would need to be in place until either there is a review of QALY weighting criteria for this condition or indeed a review of the drug cost by the manufacturer to make that weighting more favourable.

Name	[redacted]
Role	
Other role	
Organisation	
Location	
Conflict	
Notes	
Comments on the DG:	

Has all of the relevant evidence been taken into account?
Unfortunately there is not enough data to show the effect of disease progression on younger patients.

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
Cerliponase alfa is a novel treatment and the only intraventricular enzyme replacement therapy. Comparison of its cost against other treatments is not comparable as there is no other treatment of this kind available.

Are the recommendations sound and a suitable basis for guidance to the NHS?
No, the treatment not being available to newly diagnosed patients after December 2025 is not equal to all.

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?
There is unlawful discrimination based on the time of diagnosis. The unapproval of treatment for newly diagnosed patients from December 2025 will mean that newly diagnosed patients will not be able to access a treatment which has been shown to slow disease progression.

Comments:
1.1 Recommendations
There is unlawful discrimination based on the time of diagnosis. The unapproval of treatment for newly diagnosed patients from December 2025 will mean that newly diagnosed patients will not be able to access a treatment which has been shown to slow disease progression.

1.2 Recommendations
The criteria of cut off for treatment initiation is extremely concerning and disappointing for newly diagnosed CLN2 patients. With the introduction of the generation study where CLN2 is included, a newborn baby could be diagnosed with CLN2 and treatment will not be available from January 2026.

3.21 Committee discussion, equality

There are regional centres across England available for patients to access. The burden of the fortnightly inpatient hospital infusions are a lot for families.

3.1 Committee discussion, details of condition
CLN2 is currently included in the generation study where newborn babies are being screened in the study. This would improve the diagnosis of CLN2 and initiation of treatment at an earlier age.

3.2 Committee discussion, burden of the condition
It is extremely important to remember that the children with CLN2 have a great quality of life and Cerliponase alfa has extended their life expectancy. We have seen with treatment being initiated earlier that the disease burden can be less.

3.20 Committee discussion, cost-effectiveness analysis results
As the only intraventricular enzyme replacement therapy it is important that the price comparisons stipulate that there is no other treatment that it can be fully compared to.

Name	[redacted]
Role	
Other role	
Organisation	
Location	
Conflict	
Notes	
Comments on the DG:	

Has all of the relevant evidence been taken into account?
The functional data around movement and language has but there is a vast array of clinical improvements that are not recognised and therefore their impact both financially and clinically are undervalued. From seizure control, pressure injury avoidance, reduction in admission and PEG costs we have seen improvements across a much more holistic array than this reviews takes into account

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
Whilst the cost must be a challenging point for the panel the enhanced costs of caring for these children living with severe disabilities and requiring social, health and wider family support is not been calculated as reduced by keeping these children living well, more independent for longer.

Are the recommendations sound and a suitable basis for guidance to the NHS?
No, it is unreasonable and unethical to ask clinicians to withhold treatment from one group but treat another based upon an arbitrary deadline.

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?
Again, by creating a two tier system where some families receive it and others do not this creates a challenging legal and ethical position for both the clinical bodies and persons involved

Name	[redacted]
Role	
Other role	
Organisation	
Location	
Conflict	
Notes	
Comments on the DG:	

Has all of the relevant evidence been taken into account?
No. Insufficient attention and weighting has been given to the real world experiences put forward by parents, siblings, grandparents and carers describing the significant positive benefits and impacts on children and family life arising from the treatment.
Data necessary to form a well informed decision is not currently available. More time is needed for this data to form and be available for analysis.

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
No. The summaries rely on a number of unproven assumptions, preferred by the Committee, concerning the data and the number of years children will remain in each health state. It was not possible to examine and analyse any long term data because the treatment has not been available in the UK for the required length of time needed and also the population size is very small - hence the need to make so many assumptions and considerations. There is no unanimous acceptance of these preferred assumptions. (NICE 3.20). There have been a number of differing opinions and views expressed by those informing the committee. (i.e clinical experts, EAG and patient experts)
The HST programme is “intended to help generate a strong evidence base that is robust enough to being the product to market” This challenge has not been met. Uncertainties can be resolved by additional data collection and longer follow up and achieved by extending the MAA and not ending this is December as currently intended.
Bottom line here is that the decision to recommend is fundamentally dictated by the current threshold level. This figure has not been revised/increased since it was introduced (2017, 8 years?). (And it was vigorously opposed by relevant clinicians, rare disease charities and others when it was introduced). This threshold applies even when there is no doubt about clinical effectiveness. Has NICE had discussions with the UK Government towards increasing the value of the threshold? Has NICE used recent published changes to use discretion to increase this value given the uniqueness of this particular treatment and the fact that it is currently the only treatment available to these children?

Are the recommendations sound and a suitable basis for guidance to the NHS?
No. The recommendations are in the whole driven by costs rather than clinical effectiveness.

The recommendations all depend upon a significant number of assumptions, as preferred by the Committee.
There is insufficient data available; a number of unresolved uncertainties; an element of bias; and insufficient weighting given to the everyday experience of families and carers which clearly evidence real benefits.

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?
There is discrimination if the treatment is provided for some children but not others and this decision is based on uncertainty, insufficient evidence and assumptions about the likely effectiveness of the treatment.
There is also discrimination if treatment is denied for all children because it is decided that for a very small population and an ultra-rare disease the treatment is not cost effective to the NHS.

Name	[redacted]
Role	
Other role	
Organisation	
Location	
Conflict	
Notes	
Comments on the DG:	

Has all of the relevant evidence been taken into account?
Yes, the NICE appraisal of cerliponase alfa (Brineura) for treating neuronal ceroid lipofuscinosis type 2 (CLN2) did take into account all relevant evidence available at the time of the assessment.

The NICE evaluation committee considered a wide range of evidence sources, including:

Clinical trial data submitted by the manufacturer (BioMarin), specifically from three main studies: 190-201 (a single-arm open-label study), 190-202 (an extension study for long-term follow-up), and 190-901 (a natural history study for untreated patients).
Comparative analyses using matched cohorts from natural history data to provide context for the clinical trial results.
Views and experiences from people with the condition, their carers, and patient representatives.
Testimonies and input from clinical experts and NHS England.
A comprehensive review by the independent Evidence Review Group (ERG), which critiqued the submitted evidence and provided additional analyses.
Consideration of broader impacts, such as the effect on families, carers, and the healthcare system, as well as issues of equality and access.

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
The recommendations and summaries are balanced, transparent, and reflect both the strengths and limitations of the evidence. They provide a fair basis for decision-making, taking into account the clinical benefits, the rarity and severity of the condition, the lack of alternative treatments, and the high cost and uncertainties involved.

Cerliponase alfa needs to be considered for both existing patients currently benefiting from the treatment and new patients diagnosed with CLN2 disease. For existing patients, continued access ensures the maintenance of stabilized motor and language functions, preventing further decline in a condition where no alternative treatments exist. For new patients, early intervention with cerliponase alfa offers the best chance to slow disease progression, preserve functional abilities, and improve overall quality of life, addressing a critical unmet need from the point of diagnosis. Approving appraisal for both groups ensures equitable access to a potentially life-altering therapy for all children affected by this devastating condition.

Are the recommendations sound and a suitable basis for guidance to the NHS?
Yes, the recommendations are sound and a suitable basis for guidance to the NHS, particularly when viewed through the lens of a managed access agreement. While the high cost-effectiveness ratios present a challenge, the clinical benefits and lack of alternative treatments for CLN2 disease make cerliponase alfa a necessary consideration.

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

Age: Cerliponase alfa is primarily for children with CLN2. Ensure age-based eligibility criteria are clinically justified and don't unfairly exclude older children who could benefit. Age cut-offs should be evidence-based, not arbitrary.
Disability: CLN2 is a severe disability. Ensure access to cerliponase alfa and related support services is equitable, regardless of the severity of the disability or other co-existing conditions.
Race: While CLN2 affects all races, ensure that diagnostic pathways and access to treatment are equally available to all racial groups. Address any potential disparities in diagnosis or referral patterns.
Socioeconomic Status: Consider the potential for socioeconomic barriers to accessing treatment, such as travel costs to specialist centers. Ensure that financial support and logistical assistance are available to families regardless of their income.
By carefully considering these aspects, the NHS can ensure that the implementation of the recommendations for cerliponase alfa is equitable and non-discriminatory.

CONFIDENTIAL UNTIL PUBLISHED
External Assessment Group Review of the Company's Cerliponase alfa for the treatment of neuronal ceroid lipofuscinosis type 2 (CLN2) [ID6145]

Produced by	York Technology Assessment Group, University of York, Heslington, York, YO10 5DD
Authors	Ana Duarte, Senior Research Fellow, Centre for Health Economics (CHE) Mark Corbett, Research Fellow, Centre for Reviews and Dissemination (CRD) Anqian Zhou, Research Fellow, CHE Chinyereugo Umemneku-Chikere, Research Fellow, CRD Helen Fulbright, Information Specialist, CRD Natalia Kunst, Senior Research Fellow, CHE Mark Simmonds, Senior Research Fellow, CRD
Correspondence to	Mark Simmonds Centre for Reviews and Dissemination University of York Heslington Road York, YO10 5DD
Date completed	16/06/2025

OVERVIEW

The evidence assessment group (EAG) presents in this document a review of the company's response to the Draft Guidance issued after the third appraisal committee meeting (ACM3), in which cerliponase alfa was not recommended for treating neuronal ceroid lipofuscinosis type 2 (CLN2).

The company's response to draft guidance consists of comments on the evaluation process and the committee's considerations of the evidence as reported in the draft guidance. In terms of the cost-effectiveness evidence, the company expresses disagreement with the committee's preferences for the base-case analysis (see 3.20 of the draft guidance) regarding the following elements:

i) baseline distribution by health state;
ii) the assumed proportion of people who start having cerliponase alfa in health state 1 (i.e., Motor-Language [ML] score 6) and are considered 'initial stabilisers';
iii) source of evidence informing the transition probabilities; and
iv) inclusion of background costs.

The company did not, however, present any cost-effectiveness analyses, additional empirical evidence not previously considered by the committee, or proposed a change to the simple patient access scheme (PAS) consisting of a discount of [redacted] over the cerliponase alfa list price.

The EAG stresses that, under this commercial arrangement, all analyses (including the company's preferred base-case and scenario analyses) result in incremental cost-effectiveness ratios (ICERs) for cerliponase alfa vs. the standard of care (SoC) that are higher than the cost-effectiveness threshold used in the context of the Highly Specialised Technology (HST) evaluation process.

As most of the company's response relates to aspects of the committee decision or process, they do not relate to any analyses conducted by the EAG. Therefore, we respond below only to points that relate directly to our cost-effectiveness analyses.

COMPANY'S RESPONSE TO DRAFT GUIDANCE

Comment 1: Insufficient recognition of significant evidence constraints in ultra-rare disease context

It is not clear to the EAG why the company considers that the draft guidance does not sufficiently recognise the limitations of evidence generation in the context of ultra rare diseases given that we and the committee relied on comparative evidence of cerliponase alfa vs. the standard of care (SoC) from sources other than RCTs, to inform modelled treatment effects on:

- Disease progression: informed by data from people treated with cerliponase alfa in the company's clinical studies (190-203, 190-201/202, 190-506) and managed access agreement (MAA) matched to a natural history cohort (study 190-901), with additional assumptions on rate of progression after 6 years for those who initiated treatment with cerliponase alfa in health state 1 based on clinical opinion;
- Resource use associated with progressive symptoms: informed by clinical opinion;
- Health state utilities: informed by a vignette study.[1]

The EAG agrees that an RCT is infeasible for this condition, and has never suggested that one was required, nor have we criticised the use of a natural history cohort as a comparator group.

Comment 2: NICE's assessment is based on an outdated diagnostic landscape and does not reflect clinical management for CLN2 disease today. This outdated perspective hinders the true and fairer clinical and economic assessment warranted for cerliponase alfa.

The EAG and the committee have considered the impact of earlier diagnosis of disease compared to the original HST. This includes modifying the baseline distribution across ML scores, and allowing more favourable outcomes for children diagnosed before development of symptom (i.e. at ML6 or in model heath state 1) including longer periods of initial stabilisation, and slower long-term decline.

The rationale for the committee's preferences is set out in Sections 3.7 to 3.9 of the draft guidance. We note that that the baseline ML score distribution preferred by the committee corresponds to the 'most realistic' estimate diagnosis in 5 years' time from the company's own advisory board. The committee accepted the assumption that 80% of individual who started treatment in health state 1 are 'initial stabilisers' and that these will progress at half the rate of those who start treatment with cerliponase alfa at later health states.

The EAG reiterates that cerliponase alfa did not achieve cost-effectiveness in any of these revised scenarios, including scenarios preferred by the company.

Comment 5: Inappropriate use of outdated and non-representative data undermines validity of transition estimates for the incident population

At ACM3, the EAG provided the committee with a range of cost-effectiveness analyses that included various modifications to address the concerns raised by the company here, such as basing transition probabilities on study 190-203. The EAG notes, that, although this might better represent future practice, it reduces the size of the evidence base, and hence reduces confidence in the estimated transition probabilities. Furthermore, study 190-203 could not inform the full set of transition probabilities due to the lack of data for transitions between some higher (more severe) health states, such as between health state 6 and 7. Thus, even in the analyses using study 190-203, three transitions were informed by probabilities estimated from the 'all patients' pooled dataset. The EAG also notes that cerliponase alfa was not cost-effective in any of the scenario analyses, where transition probabilities for cerliponase alfa treated patients were informed by study-190-203.

These analyses also included estimates of mean life years in health state 1 (ML6). Under the committee's preferred assumptions, expected time spent on health state 1 is 12.66 years, while for a scenario assuming the company's preferred baseline distribution (best achievable from the December 2024 advisory board) and evidence source for the transition probabilities this estimate is 27.40 years. If it assumed that 100% of patients who initiate cerliponase alfa treatment in health state 1 are 'initial stabilisers' alongside the assumptions of the latter scenario, the estimated mean life years in health state one rises to 29.98. The EAG notes that any choice of model will require this time in health state 1 to be realistic. We note that clinical experts suggested that it was possible that patient would remain in this health state up to 20 years, but this was "*likely overly optimistic*".

Comment 6: NICE has not sufficiently considered clinical opinion in its choice of a baseline distribution that is reflective of clinical practice today

The company's preferred baseline distribution is the 'optimistic' distribution from the advisory board (December 2024). The company has not provided additional evidence to support the argument that the 'optimistic' distribution from the advisory board is reflective of clinical practice in five years' time, nor any evidence as to whether cerliponase alfa would be cost-effective under this assumption.

Comment 7: Inaccurate framing of the presentation of the non-reference case analysis requested by the Committee

The company considers that the draft guidance does not accurately reflect the company's position regarding the exclusion of background costs from the cost-effectiveness analysis. This was a non-

reference analysis requested by the committee after ACM1 and which the company incorporated into their updated base-case and scenarios analyses presented at ACM2. Results for the scenario analyses were presented with and without including background costs. The company's justified the exclusion of background costs from the base-case analysis due to treatment with cerliponase alfa being associated with longer-term survival compared with SoC, resulting in increased background care costs that do not represent direct, intrinsic consequences of treatment. The committee considered that this justification did not warrant exclusion of background costs from the base-case analysis.

References

1. Gissen P, Specchio N, Olaye A, Jain M, Butt T, Ghosh W*, et al.* Investigating health-related quality of life in rare diseases: A case study in utility value determination for patients with CLN2 disease (neuronal ceroid lipofuscinosis type 2). *Orphanet J Rare Dis* 2021;**16**:217. 10.1186/s13023-021-01829-x

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External Assessment Group Additional Analyses after consultation on Final Draft Guidance

Cerliponase alfa for treating neuronal ceroid lipofuscinosis type 2 (review of HST12) [ID6145]

Produced by	York Technology Assessment Group, University of York, Heslington, York, YO10 5DD
Authors	Ana Duarte, Senior Research Fellow, Centre for Health Economics
Date completed	01/07/2025

This document presents additional cost-effectiveness analyses conducted by the External Assessment Group (EAG) at NICE's request following consultation on the Final Draft Guidance and before the fourth appraisal committee meeting (ACM4). The analyses were performed over the committee's preferred assumptions for the incident population (i.e., committee's preferred base-case analysis), which were stated in the Final Draft Guidance. Table 1 summarises the committee's and the company's preferred assumptions.

Table 1 Committee's and company's preferred assumptions for the incident population

Assumption	NICE committee	Company
BL distribution*	Realistic scenario in the company's advisory board (December 2024)	Optimistic scenario in the company's advisory board (December 2024)
HS1 (ML 6)	[redacted]	70%
HS2 (ML 5)	[redacted]	25%
HS3 (ML 4)	[redacted]	5%
HS4 (ML3)	[redacted]	0%
Source of transition probabilities	Pooled 'all patients' dataset (matched to Study 190-901)	Study 190-203 (matched to Study 190-901)
Initial stabilisation with cerliponase alfa		
Proportion of stabilisers	80% at HS1(ML6) at BL	100% at HS1(ML6) at BL
Risk reduction for initial stabilisers **	50%	75%

*the starting age assumed for the incident population is 2.625 years; ** beyond 6 years, compared to non-stabilisers treated with cerliponase alfa

Abbreviations: EAG, external assessment group; HS, health state; ML, motor language.

The additional analyses vary the following assumptions independently (analyses 1 to 3) and jointly (analyses 4 and 5):

- Source of transition probabilities for cerliponase alfa: Study 190-203;
- Baseline distribution:
    - 66.7% of patients in health state 1 (Motor language (ML) score 6 and 33.3% in health state 2 (ML score 5);
    - 70% of patients in health state 1 (Motor language (ML) score 6, 25% in health state 2 (ML score 5), and 5% in health state 3 (ML score 4), as per the company's preferred assumption.

The cost-effectiveness results for these analyses are presented alongside the committee's base case in Table 2; corresponding results for non-reference case analyses excluding background costs are shown in Table 3. All analyses in this document were conducted deterministically and are inclusive of a [redacted] patient access scheme discount over the list price of cerliponase alfa.

Table 2 Additional cost-effectiveness results

Technologies	Total costs	Total QALYs	Incr. costs	Incr. QALYs	ICER (/QALY)	CE threshold (/QALY)		LY in HS1*
						including all utilities	Including only patient utilities	
Committee's base-case analysis								
SoC	[redacted]	-0.63						0.35
Cerliponase alfa	[redacted]	9.03	[redacted]	9.65	[redacted]	[redacted]	[redacted]	12.66
Analysis 1: Transition probabilities informed by Study-190-203 for cerliponase alfa								
SoC	[redacted]	-0.50						0.49
Cerliponase alfa	[redacted]	12.26	[redacted]	12.76	[redacted]	[redacted]	[redacted]	24.77
Analysis 2: Baseline distribution – HS1 (ML6) 66.7%, HS2 (ML5) 33.3%								
SoC	[redacted]	-0.55						0.39
Cerliponase alfa	[redacted]	9.81	[redacted]	10.35	[redacted]	[redacted]	[redacted]	14.00
Analysis 3: Baseline distribution – Company's preferred assumption (HS1 (ML6) 70%, HS2 (ML5) 25%, and HS3 (ML4))								
SoC	[redacted]	-0.55						0.41
Cerliponase alfa	[redacted]	10.02	[redacted]	10.57	[redacted]	[redacted]	[redacted]	14.45
Analysis 4: Transition probabilities informed by Study-190-203 for cerliponase alfa + Baseline distribution – HS1 (ML6) 66%, HS2 (ML5) 33%								
SoC	[redacted]	-0.39						0.55
Cerliponase alfa	[redacted]	13.26	[redacted]	13.65	[redacted]	[redacted]	[redacted]	27.06
Analysis 5: Transition probabilities informed by Study-190-203 for cerliponase alfa + Baseline distribution – (HS1 (ML6) 70%, HS2 (ML5) 25%, and 5%HS3 (ML4))								
SoC	[redacted]	-0.39						0.58
Cerliponase alfa	[redacted]	13.32	[redacted]	13.71	[redacted]	[redacted]	[redacted]	27.40

*Undiscounted. **Abbreviations:** EAG, external assessment group; HS, health state; LY, life years; ML, motor language; SoC, standard of care.

Table 3 Cost-effectiveness results for non-reference case analyses excluding background costs

Technologies	Total costs	Total QALYs	Incr. costs	Incr. QALYs	ICER (/QALY)	CE threshold (/QALY)		LY in HS1*
						including all utilities	Including only patient utilities	
Committee's base-case assumptions								
SoC	[redacted]	-0.63						0.35
Cerliponase alfa	[redacted]	9.03	[redacted]	9.65	[redacted]	[redacted]	[redacted]	12.66
Analysis 1: Transition probabilities informed by Study-190-203 for cerliponase alfa								
SoC	[redacted]	-0.50						0.49
Cerliponase alfa	[redacted]	12.26	[redacted]	12.76	[redacted]	[redacted]	[redacted]	24.77
Analysis 2: Baseline distribution – HS1 (ML6) 66.7%, HS2 (ML5) 33.3%								
SoC	[redacted]	-0.55						0.39
Cerliponase alfa	[redacted]	9.81	[redacted]	10.35	[redacted]	[redacted]	[redacted]	14.00
Analysis 3: Baseline distribution – Company's preferred assumption (HS1 (ML6) 70%, HS2 (ML5) 25%, and 5%HS3 (ML4))								
SoC	[redacted]	-0.55						0.41
Cerliponase alfa	[redacted]	10.02	[redacted]	10.57	[redacted]	[redacted]	[redacted]	14.45
Analysis 4: Transition probabilities informed by Study-190-203 for cerliponase alfa + Baseline distribution – HS1 (ML6) 66%, HS2 (ML5) 33%								
SoC	[redacted]	-0.39						0.55
Cerliponase alfa	[redacted]	13.26	[redacted]	13.65	[redacted]	[redacted]	[redacted]	27.06
Analysis 5: Transition probabilities informed by Study-190-203 for cerliponase alfa + Baseline distribution – (HS1 (ML6) 70%, HS2 (ML5) 25%, and 5%HS3 (ML4))								
SoC	[redacted]	-0.39						0.58
Cerliponase alfa	[redacted]	13.32	[redacted]	13.71	[redacted]	[redacted]	[redacted]	27.40

*Undiscounted. **Abbreviations:** EAG, external assessment group; HS, health state; LY, life years; ML, motor language; SoC, standard of care.