

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Data Collection Agreement

Cerliponase alfa for treating CLN2 Disease

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Version history

Version	Published	Summary of updates	Approver(s)
1.0	November 2019	First release	NHSE, BioMarin, NICE
2.0	March 2023	Modification to clinical data collection and assessments to be conducted	NHSE, BioMarin, NICE

1 Purpose of data collection agreement

- 1.1 The evaluation committee has made a positive recommendation within the context of a Managed Access Agreement (MAA) for cerliponase alfa for treating neuronal ceroid lipofuscinosis type 2 HST12.
- 1.2 The purpose of this agreement is to describe the uncertainties identified by NICE's technology appraisal committee, patient eligibility criteria, arrangements intended to capture the data that may address these uncertainties.

2 Commencement and period of agreement

2.1 The commencement and period of this agreement are consistent with the terms of Section 3 of the MAA.

3 Area(s) of clinical uncertainty

3.1 Committee considered the key uncertainties were:

- Long-term disease stabilisation; and
- Improvements in Motor and Language (ML) score starting distribution.

Assumptions based on these clinical data are currently very uncertain and have a substantial impact on the cost-effectiveness estimates.

3.2 The committee considered that there were several further areas of clinical uncertainty that could benefit from further data, including: CLN2 clinical rating scores over time; the frequency and severity of tonic-clonic seizures; myoclonus and dystonia control; visual acuity; extra-neurological symptoms; cause of mortality; and, if possible, measures of quality of life.

4 Source(s) of data

4.1 Data will be collected from all patients who start or receive treatment with cerliponase alpha during the term of this MAA. Patients who stop treatment during the MAA period will also continue to be monitored for disease deterioration and supported with other clinical measures.

4.2 There will be two data collection streams. The first will be the clinical data collected by the treating clinician, and will include clinical, safety and efficacy data. The second will be the Quality of Life (QoL) data collected by MPS Commercial.

- 4.3 The data that will be collected are summarised in table 1 below.
- 4.4 Sources of data that could resolve the key uncertainties identified by committee include:
- BioMarin’s clinical data collection (including neurodevelopmental data) on clinical trial, extended access¹ and new patients under this MAA;
 - Patient reported outcome (PRO) data collected by MPS Commercial.
- 4.5 The clinical, patient reported outcomes and neurodevelopmental (cognitive) assessment data that will be collected, and the frequency of collection, are summarised in table 1 (overleaf).

¹ Ongoing follow-up of patients already receiving cerliponase alfa to collect data concerning long-term disease stabilisation. This should include patients treated outside England within the clinical trial and extension studies as well as clinical registries held within other countries.

Table 1: Outline of assessments to be collected for patients

Clinical data

Assessments	Rationale	Frequency	Collected by	Electronic repository
Total CLN2 disease rating scales	Primary measure of disease progression	6 mthly	Clinician	Secure share-point site (excel)
Weill Cornell Disease Rating Scale	Measure of progression for movement disorder and myoclonus	6 mthly	Clinician	Secure share-point site (excel)
Visual Assessment Test	Functional vision domain (part of CLN2 rating scale)	6 mthly	Clinician	Secure share-point site (excel)
Missed infusions	Compliance with MAA	3mthly	Clinician	Secure share-point site (excel)
ECG, 12-lead	Heart function test	6 mthly	Clinician	Secure share-point site (excel)
EEG, standard	Brain electrical activity	6 mthly	Clinician	Secure share-point site (excel)
Brain MRI	Observation of preserved brain tissue	12 mthly	Clinician	Secure share-point site (excel)
██████████	██████████	12 mthly	Clinician	Secure share-point site (excel)
██████████	██████████	12 mthly	Clinician	Secure share-point site (excel)
██████████	██████████	12 mthly	Clinician	Secure share-point site (excel)

A standard 12-lead ECG, including heart rate, rhythm, intervals, axis, conduction defects, and anatomic abnormalities, will be performed within 15 (±5) minutes after infusion end.

Updates to clinical data to be collected, March 2023

Assessments	Original Rationale	Original Frequency	Proposed change	Rationale for amendment
ECG, 12-lead	Heart function test EMA recommended an ECG during infusion every 6 months as some patients with CLN2 with CLN2 disease may develop conduction disorders or heart disease	6 mthly	ECGs should continue to be collected after infusion, but do not need to be undertaken within 15 minutes of the infusion.	Centres report there is a substantial burden in collecting ECG within 15 minutes of infusion end. To date, no relevant cardiac safety concerns have been identified in clinical and post-marketing data collection that indicate ECGs needs to be collected within 15 minutes post infusion in all patients. Retain assessment to assess any potential “extra-neurological symptoms”.
EEG, standard	Brain electrical activity New EEG activity may be suggestive of new seizure activity	6 mthly	Remove requirement for EEGs in all patients, at all time points. EEGs to continue to be undertaken if judged to be clinically appropriate.	Feedback from patient and clinical experts is that EEGs are a substantial burden on patients. Feedback from stakeholder is that the data collected to date will not provide new information for decision-making. No new data that is not also captured elsewhere is expected to be collected.
Brain MRI	Observation of preserved brain tissue	12 mthly	No change	Continue to perform and assess MRIs as practiced currently, with the

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			Qualitative MRIs will continue to be completed annually until the end of the MAA.	assessment of “atrophy progressed yes/no”. This data is informative for monitoring disease progression. A more detailed quantification of brain atrophy by MRI analyses has been discussed but is not considered feasible as part of current service provision.
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Patient reported outcomes

Assessments	Rationale	Frequency	Collected by	Electronic repository
██████████	██████████	6 mthly	Administered by MPS Commercial	Secure share-point site (excel)
██████████	██████████	6 mthly	Proxy reported by parents of patients or person responsible for patient	Secure share-point site (excel)
██████████	██████████	6 mthly		Secure share-point site (excel)

Neurodevelopmental assessment tools

Assessments	Rationale	Frequency	Collected by	Electronic repository
Bayley Scales of Infant Development III	Age appropriate development tool	12 mthly	Psychologist in centre	Secure share-point site (excel)
Wechsler Preschool and Primary Scale of Intelligence (WPPSI-IV or WISC-V)	Age appropriate development tool	12 mthly	Psychologist in centre	Secure share-point site (excel)
Vineland Adaptive Behaviour Scales	Age appropriate development tool	12 mthly	Psychologist in centre	Secure share-point site (excel)

Updates to neurodevelopmental assessment tools, March 2023

Assessments	Original Rationale	Frequency	Proposed change in patients whose vision is 6/60 or worse on Snell scale or if clinically the child’s vision does not seem appropriate for the assessment (e.g., the child is no longer looking at pictures in books)	Rationale for amendment
Bayley Scales of Infant Development III	Age appropriate development tool	12 mthly	Exclude. Applies to all developmental ages.	No longer informative with vision impairment.
Wechsler Preschool and Primary Scale of Intelligence (WPPSI-IV)	Age appropriate development tool	12 mthly	Adapt: Direct measure depending on developmental (not chronological) age. <ul style="list-style-type: none"> 2:6-3:11 year level start information subtest from Item 5; 4-6 year level start information subtest 	Some items in subtest no longer informative with vision impairment. Other items in the subtests should continue to be collected as clinical expert opinion is that these will still provide meaningful data.

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			<p>from Item 5 and similarities subtest from Item 5.</p> <p>If the child can complete items from 5 onwards they should be given credit for the items which aren't administered.</p>	
Vineland Adaptive Behaviour Scales	Age appropriate development tool	12 mthly	<p>Adapt:</p> <p>Vineland-III Comprehensive Parent Interview.</p> <p>Only Receptive and Expressive Communication scales (exclude Written Communication, Daily Living, Socialisation and Motor Skills).</p>	Some domains no longer informative with vision impairment.
WISC-V	(New)	(New)	<p>Over 6 years development level (not chronological age). Direct measure with child. Use Similarities subtest, Digit Span subtest and Vocabulary subtest from Item 5.</p> <p>If the child can complete items from 5 onwards they should be given credit for the items which aren't administered.</p>	<p>WISC-V is being used in practice for those who reach a developmental level beyond the WPPSI-IV – both are Wechsler scales of intellectual ability.</p> <p>Some items in subtest no longer informative with vision impairment.</p> <p>Other items in the subtests should continue to be collected as clinical expert opinion is that these will still provide meaningful data. The child is given credit for items 1-4 which aren't administered.</p>

4.6 All data, whether collected by the treating physicians or the MPS Commercial will be entered into an excel spreadsheet, contained on the BioMarin SharePoint site. The data will be entered by the treating clinician and/or the MPS Society in a pseudonymized format. The information entered onto the database will utilize the patient's MAA identification number and not their name. The following data will also be included:

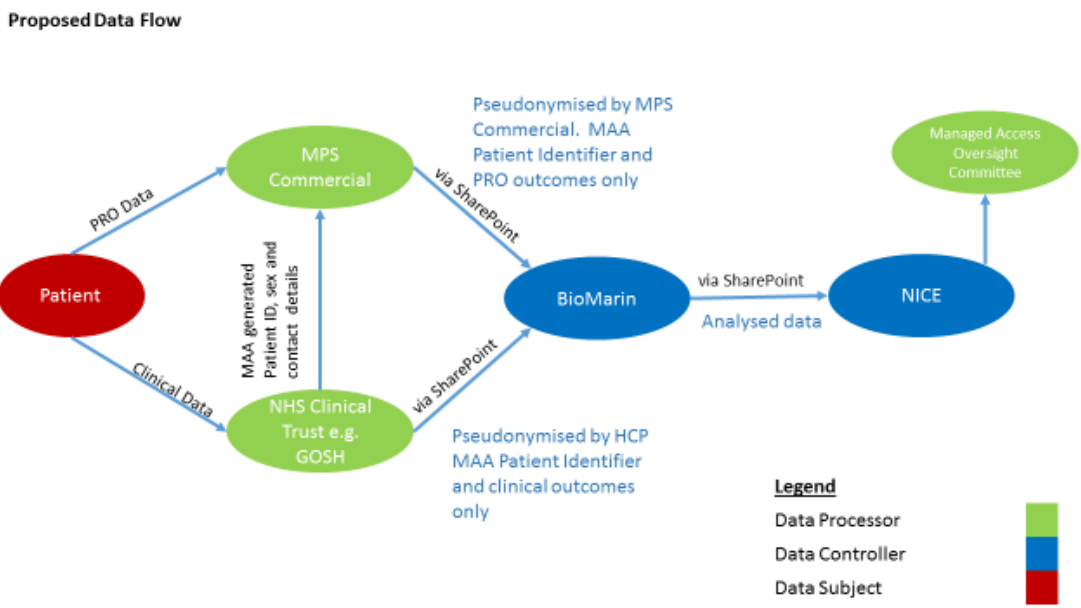
- Initials
- Age at diagnosis
- Sex

4.7 The treating clinician will provide the following data to the MPS Commercial so that the Clinical and Patient Reported Outcomes can be properly linked under one Patient Identifier:

- MAA generated Patient Identifier
- Name
- Contact details including phone number, email and postal address
- Sex
- Former trial patient status and/or Extended Access Programme status

4.8 The treating clinician will be responsible for the timely collection of the clinical outcomes and will send these to BioMarin (the "Company") for analysis every six (6) months.

- 4.9 MPS Commercial will be responsible for the timely collection of the patient reported outcomes and will send these to the Company for analysis every six (6) months
- 4.10 The Company will be responsible for the analysis of the collated pseudonymised data and share interim and final analyses with NICE for the purposes of the reconsideration of the clinical impact of cerliponase alfa on CLN2 disease and to members of the Managed Access Oversight Committee to monitor data collection and for quality assurance.
- 4.11 Blueteq’s system data is owned by NHS England. NHS England is responsible for implementing Blueteq data collection and use of these data. NHS England will be able to share Blueteq data for the purposes of a NICE guidance review, subject to data sharing agreements between NHS England and parties to this agreement.
- 4.12 The Company will share the pseudonymised data with members of the Managed Access Oversight Committee for review every six (6) months.



5 Patient eligibility

- 5.1 To receive treatment, patients or their guardians must sign up to the 'Managed Access Patient Agreement' included in Appendix A to this Data Collection Agreement.
- 5.2 The starting and stopping criteria will apply to patients who start on treatment during the term of this MAA.
- 5.3 All patients who transfer from the clinical trial and expanded access programme will be deemed to be eligible at the beginning of the MAA and will be subject to the stopping criteria only.
- 5.4 Patients must attend clinics two times a year for assessment.
- 5.5 Treating clinicians must ensure that their patients are made aware of the start and stop criteria for receiving treatment with cerliponase alfa.
- 5.6 Baseline assessments will be established as follows:
- For clinical trial and expanded / compassionate access programme patients and for patients who start treatment under this MAA aged over 3 years – the baseline for assessment will be taken at the first infusion received by the patient;
 - For patients who start receiving cerliponase alfa before the age of 3 years - the baseline assessment will be the first assessment conducted after their third birthday and conducted within 6 months of their third birthday.
- 5.7 Patients who have been travelling abroad to receive individual treatments can join the MAA so long as they meet the MAA eligibility criteria. Where a patient/family has been residing abroad to receive treatment, they can join the MAA so long as they meet the MAA eligibility criteria and their treating centre confirms that

they are eligible for NHS treatment. Patients who have been receiving treatment privately can join the MAA so long as they meet the MAA criteria and their NHS clinician is content that the proposed ongoing NHS treatment is clinically appropriate in light of the privately funded treatment that the patient has received. In all these cases, it is for the patient/family to ensure that there is an appropriate handover between the organisation currently treating the patient and the NHS treating centre in England.

5.8 Starting criteria for NEW patients

Note: These starting criteria apply only for new patients who start treatment under the MAA for cerliponase alfa for treating CLN2 disease only and not to patients who transfer from the clinical trial and expanded access programme

All of the following criteria must be met before treatment can be started:

- All patients must have a confirmed diagnosis of CLN2 on the basis of clinical information and enzymatic activity test.
- The patient is not diagnosed with an additional progressive life limiting condition where treatment would not provide long term benefit, e.g. cancer or multiple sclerosis.
- The patient has a CLN2 Rating Scale ML Score of 2 or above.
- A complete set of baseline assessments to confirm eligibility will be performed and recorded in the patient's clinical notes at the time of the first infusion. For patients who start receiving cerliponase alfa before the age of 3 years, the baseline assessment will be the first assessment conducted after their third birthday and conducted within 6 months of their third birthday.

5.9 Stopping criteria applicable to all patients (including children under the age of 3 years)

All patients will cease therapy with cerliponase alfa, if any of the following apply:

- The patient is non-compliant with assessments for continued therapy (non-compliance is defined as fewer than two attendances for assessment in any 14-month period excluding medical reasons for missed dosages); OR
- The patient is unable to tolerate infusions due to infusion related severe adverse events or any other clinical concerns that cannot be resolved and have been discussed with NHS England or the Managed Access Oversight Committee; OR
- The patient is diagnosed with an additional progressive life limiting condition where treatment would not provide long term benefit e.g.; cancer or multiple sclerosis; OR
- The patient meets the stopping criteria as defined below in sections 5.10 and 5.11.

5.10 Stopping criteria for new patients aged 3 years and over who start treatment under this MAA or have been receiving treatment for less than 18 months

Patients aged 3 years and over, who have been receiving treatment for less than 18 months will be stopped if both of the following non-response criteria are met:

- A loss of more than two points (i.e. 3 or more points) on the CLN2 Rating Scale ML Score from baseline within eighteen months of the first infusion and a total CLN2 rating scale score of less than 2:

- A loss is defined as a decline in CLN2 rating scale ML score that has persisted for 3 or more infusions (i.e. after 6 weeks).

AND

- During the first eighteen months of treatment, a reduction in proxy reported patient quality of life of:
 - ≥ 15 points on the PedsQL total score (which is three times the minimal clinically important difference²); AND
 - 0.23 drop in utility as measured by the EQ5D-5L AND
 - decline in CLN2 quality of life assessment of ≥ 15 points.

In the case of temporary illness, patients should be retested twice within 12 weeks to ensure that the decline is not solely due to a temporary illness.

5.11 Stopping criteria for existing patients aged 3 years and over who are currently on treatment, who have been receiving treatment for over 18 months

Patients who are 'currently on treatment' are defined as: (i) clinical trial patients; (ii) extended access programme; (iii) patients who started on treatment during the term of the Managed Access Agreement and have been receiving treatment for over 18 months.

These patients should be stopped from receiving further treatment due to non-response, if they meet the following criteria:

² The accepted minimal clinically important difference (MCID) is 4.5 points for the PedsQL™ [Varni et al. *Ambul Pediatr.* 2003 Nov-Dec; 3(6):329-41]

³ A minimal clinically important difference of 0.24 based on distribution methods has been estimated. Walters SJ, Brazier JE. *Qual Life Res.* 2005;14:1523–32.

- A loss of more than one point (i.e. 2 or more points) on the CLN2 Rating Scale ML Score, in the previous twelve months and a total CLN2 rating scale score of less than 2;
 - A loss is defined as a decline in CLN2 rating scale ML score that has persisted for 3 or more infusions (i.e. after 6 weeks)

OR

- Progression to an unreversed score of 0 on the CLN2 Rating Scales ML Score
 - Patients with a score of 0, should be retested twice within 12 weeks to ensure that the decline is not solely due to a temporary illness.

AND

- A reduction in proxy reported patient quality of life in the previous twelve-month treatment window of
 - ≥ 15 points on the PedsQL total score (which is three times the minimal clinically important difference⁴);AND
 - 0.2⁵ drop in utility as measured by the EQ5D-5L AND
 - Decline in CLN2 quality of life assessment of ≥ 15 points

5.12 If a patient is ill prior to an assessment, then the patient needs to be reassessed within 12 weeks and subsequent measures need to be considered from this point.

⁴ The accepted minimal clinically important difference (MCID) is 4.5 points for the PedsQL™ [Varni et al. *Ambul Pediatr.* 2003 Nov-Dec; 3(6):329-41]

⁵ A minimal clinically important difference of 0.24 based on distribution methods has been estimated. Walters SJ, Brazier JE. *Qual Life Res.* 2005;14:1523–32.

6 Patient Appeal Process

6.1 If a patient (or patient's parents or person responsible for a patient) feels the assessments have been performed incorrectly or information not gathered appropriately, they have the right for a repeat set of assessments to be carried out at another lysosomal storage disease reference centre in England with appropriate experience of treating patients with cerliponase alfa. Travel and associated costs will be at the patient's expense.

6.2 Reasonable adjustments will be made for patients who are unable to comply with the assessment by reasons of challenges completing assessments. These patient's stop criteria will be defined on a case by case basis, subject to a recommendation to a validation panel which will be convened by NHS England.

6.3 A patient (or patient's parents or person responsible for a patient) may withdraw consent for participation in the MAA at any time without prejudice. Withdrawal of participation in the MAA will effectively stop access to cerliponase alfa treatment. A patient may inform their physician of their decision to withdraw consent at any time and accordingly, the patient's cerliponase alfa treatment shall cease.

7 Data Protection

7.1 Patient data collected as part of this MAA will be in accordance with all applicable data protection legislation, including but not limited to, the General Data Protection Regulation.

7.2 The Company is the joint Data Controller with NICE. The NHS Trust and MPS Commercial are Data Processors, along with the Managed Access Oversight Committee. BioMarin will carry out all Data Controller obligations, in particular:

- Maintain a Record of Processing

- Report any Data Breaches to the relevant Supervisory Authority

7.3 As part of this agreement all parties agree to abide by the terms of the Data Processing Agreement set out at Appendix B.

8 Data analysis plan

8.1 The Company is responsible for ensuring relevant data required for the NICE reconsideration of guidance for cerliponase alpha for treating neuronal ceroid lipofuscinosis type 2 is available during the fourth year of this agreement.

8.2 This responsibility will include the development of a data analysis plan within 6 months following the commencement of this agreement, for review at the first Managed Access Oversight Committee meeting.

9 Ownership of the data

9.1 The analysed data will be owned by the Company but shared with NHS England, the BDFA and NICE for the purpose of assessing the benefit of the treatment. The data collected by MPS Commercial will be owned by the Company and shared with NHS England and NICE.

9.2 This data shall be stored for no more than 5 years following the completion of the Managed Access Agreement guidance review by NICE. In the event that the guidance review does not take place data will be stored for no more than ten years from the MAA start date.

9.3 By agreeing to take part in the MAA patients will be asked to acknowledge that their demographic and clinical data will be collected and shared with the Company by their treating clinician, in

addition to patient reported outcomes (QoL questionnaires) collected by MPS Commercial.

9.4 The clinical data will be collected by healthcare professionals at the expert treatment centres who have undertaken the relevant training prescribed by NHS England.

10 Funding for data collection and analysis

10.1 The Company will be expected to pay direct and associated costs for:

- Collection and entry of data into a specified database;
- Database management – including quality assurance;
- Data analysis;
- Costs associated with accessing and linking data to other sources (if applicable);
- Any other costs identified that are relevant to data collection and analysis associated with the uncertainties identified by the NICE appraisal committee.

10.2 The company shall be required to provide NICE and NHSE assurance that separate agreements concerning the resources required to operationalise data collection and analyses have been agreed with relevant third parties within 3-months of the publication of the Managed Access Agreement for cerliponase alfa for treating CLN2 disease.

10.3 The relevant terms of these agreements should be presented to the MOAC for review at its first meeting (i.e. no later than 6 months after the commencement of this agreement).

11 Monitoring arrangements

- 11.1 NICE will convene a Managed Access Oversight Committee with representation from NICE, the Company, NHS England, the BDFA, MPS Commercial and expert treatment centres.
- 11.2 The Managed Access Oversight Committee exists to oversee the operation of all aspects of the MAA and to address issues that may arise throughout the MAA term. The Managed Access Oversight Committee are responsible for monitoring the implementation of the MAA and recommending actions to support its operation. A detailed description of the Managed Access Oversight Committee function will be available in a Terms of Reference document produced by NICE.
- 11.3 The Managed Access Oversight Committee will meet at 6-monthly intervals throughout the MAA period.

APPENDIX A: MANAGED ACCESS PATIENT AGREEMENT

Cerliponase alfa (Brineura) for treating neuronal ceroid lipofuscinosis type 2

Managed Access Patient Agreement

NICE has recommended as an option cerliponase alfa, licensed as Brineura®, for treating neuronal ceroid lipofuscinosis type 2 (CLN2) subject to the collection of further data. Cerliponase alfa will be available via the NHS in England as part of a Managed Access Agreement.

A Managed Access Agreement is an agreement between NICE, NHS in England and the drug company. If you and / or your parent / guardian decides that you would like to start treatment with cerliponase alfa, you will be asked to sign this document to show that you understand what you need to do as part of this agreement.

The NICE Managed Access Agreement includes:

- A data collection agreement outlining how your data will be collected, stored, protected, analysed and used to inform a NICE guidance review of the conditional recommendation for cerliponase alfa. The NICE guidance review of cerliponase alfa is expected to start in the 4th year of the agreement.
- Clinical criteria for starting and stopping treatment with cerliponase alfa, developed jointly with clinicians and patient representatives.
- An agreement between BioMarin UK Ltd (the Company) and NHS England on a financial arrangement for the total costs of cerliponase alfa throughout the duration of the managed access

agreement. This is not information that is given to the general public.

1. Patient Eligibility

Experts in Batten disease, in collaboration with the Batten Disease Family Association (BDFA), have developed clinical criteria to identify patients who are eligible to start treatment, as well as those patients who should stop treatment because they are not receiving sufficient benefit. Not every child with CLN2 Batten disease will be eligible for the treatment.

Your treating clinicians at the Lysosomal Storage Disease treatment centre must provide full details about the eligibility criteria to you and answer any questions you may have about these if they are not clear. In addition to the clinical criteria, you (and / or your parent / guardian) must sign this Managed Access Patient Agreement before you can start receiving treatment. In signing this agreement, you are confirming that you have read this document and understand the requirements of the agreement, including the need to attend clinics for assessments, at least 2 times within each 12 month period (an additional grace period of 2 months will be added to account for unforeseen barriers to attending clinics).

If you (or your parent / guardian) feels the assessments have been performed incorrectly or information not gathered appropriately, you have the right to request a second opinion at the Lysosomal Storage Disease treatment centre. If you (or your parent / guardian) decide to go to a Lysosomal Storage Disease treatment centre that is not your usual centre, you will be responsible for paying your travel and associated costs.

2. Access to treatment and data collection

The clinical criteria in this Managed Access Agreement have been used because they formed part of the phase III clinical trial and have been the basis on which the European licence for cerliponase alfa was granted.

A distinction has been made between those patients who are new to treatment and the group of patients who have been on treatment in England prior to the start of this Managed Access Agreement.

Allowance is also made for children under the age of 3, as natural decline in functional endpoints is not measurable at this point. Children who start treatment with cerliponase alfa therapy before the age of 3 will be excluded from the stopping criteria mentioned until they reach the age of 3, at which point the stopping criteria for patients “currently on treatment” will apply.

3. Start Criteria⁶

- Patients must have a confirmed diagnosis of CLN2 on the basis of clinical information and enzymatic activity tests;
- The patient is not diagnosed with an additional progressive life limiting condition where treatment would not provide long term benefit e.g.; cancer or multiple sclerosis;
- The patient has a CLN2 Rating Scale ML Score of 2 or above;
 - CLN2 ML score is calculated by an assessment of your / your child’s motor and language skills, it is measured using the categories and scores in the table below:

Category	Score	Description
Motor	3	Walks normally
	2	Frequent falls, ataxia, independent walk > 10 steps
	1	No unaided gait
	0	Immobile, mostly bedridden

⁶ The start and stop criteria have been independently developed by clinical experts and patient advocacy group in discussions with patient families. BioMarin have not endorsed these criteria
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Language	3	Normal
	2	Loss of word, intelligible but abnormal speech
	1	Some comprehension, mostly unintelligible speech
	0	Unintelligible or no speech

- Patients can only start once a full set of baseline criteria has been obtained;
- Patients will be expected to attend their clinic two times a year for assessment within a 14 month period;
- Patients and / or their parent / guardian will be informed about the strict requirement for attendance as set out in this Managed Access Patient Agreement document;
- The patient (and parent / guardian) is willing to comply with the associated monitoring criteria;
- The patient and / or their parent / guardian must sign this Managed Access Patient Agreement to confirm they have read and understood the terms of the Managed Access Agreement.

In the event of the patient being unable to agree to the above criteria, the implementation of the stop criteria will be discussed with the patient and / or parent / guardian.

4. Stop Criteria⁷

4.1 Stopping criteria applicable to all patients (including children under the age of 3 years)

All patients will cease therapy with cerliponase alfa, if any of the following apply:

- Patients will cease to qualify for treatment if they miss more than 2 infusions in any 14 month period, excluding medical reasons for missing dosages;
OR
- The patient is unable to tolerate infusions due to infusion related severe adverse events or any other clinical concerns that cannot be resolved and have been discussed with NHS England or the Managed Access Oversight Committee;
OR
- The patient is diagnosed with an additional progressive life limiting condition where treatment would not provide long term benefit e.g.; cancer or multiple sclerosis;
OR
- The patient meets the stopping criteria as defined below in sections 4.2 and 4.3.

⁷ The start and stop criteria have been independently developed by clinical experts and patient advocacy group in discussions with patient families. BioMarin have not endorsed these criteria
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4.2 Stopping criteria for new patients (those who have never received treatment)

This section applies only to those who start treatment at the age of 3 or more. The criteria for which new patients should be stopped from treatment due to non-response to treatment are:

- A loss of more than two points (i.e. 3 or more points) on the CLN2 Rating Scale ML Score from baseline, during the first eighteen months of treatment and a total CLN2 rating scale score of less than 2;
 - A loss is defined as a decline in CLN2 rating scale ML score that has persisted for 3 or more infusions (i.e. after 6 weeks)

AND

- During the first eighteen months of treatment, a reduction in Quality of Life (QoL) specifically:
 - ≥ 15 points on the PedsQL total score (which is three times the minimal clinically important difference⁸); and
 - 0.2⁹ drop in utility as measured by the EQ5D-5L and
 - Decline in CLN2 quality of life assessment of ≥ 15 points

For more information on QoL questionnaires please see section 4.4 of this document.

In the case of temporary illness, patients should be retested twice within 12 weeks to ensure that the decline is not as a result of temporary illness.

⁸ The accepted minimal clinically important difference (MCID) is 4.5 points for the PedsQL™ [Varni et al. *Ambul Pediatr.* 2003 Nov-Dec; 3(6):329-41]

⁹ A minimal clinically important difference of 0.24 based on distribution methods has been estimated. Walters SJ, Brazier JE. *Qual Life Res.* 2005;14:1523–32.

4.3 Stopping criteria for Patients who are currently on treatment

Patients who are 'currently on treatment' are defined as: (i) clinical trial patients; (ii) extended access programme patients; and (iii) patients who started on treatment during the term of the Managed Access Agreement and have been receiving treatment for over 18 months.

The criteria for which patients "currently on treatment" should be stopped from treatment due to non-response are:

- A loss of more than one point (i.e. 2 or more points) on the CLN2 Rating Scale ML Score, in a twelve months treatment window and a total CLN2 rating scale score of less than 2;
 - A loss is defined as a decline in CLN2 rating scale ML score that has persisted for 3 or more infusions (i.e. after 6 weeks)

OR

- Progression to an unreversed score of 0 on the CLN2 Rating Scales ML Score
 - Patients with a score of 0, should be retested twice within 12 weeks to ensure that decline is not as a result of temporary illness.

AND

- A reduction in proxy reported patient quality of life in a 12 month treatment period of
 - ≥ 15 points on the PedsQL total score (which is three times the minimal clinically important difference¹⁰); and
 - 0.2¹¹ drop in utility as measured by the EQ5D-5L and

¹⁰ The accepted minimal clinically important difference (MCID) is 4.5 points for the PedsQL™ [Varni et al. *Ambul Pediatr.* 2003 Nov-Dec; 3(6):329-41]

¹¹ A minimal clinically important difference of 0.24 based on distribution methods has been estimated. Walters SJ, Brazier JE. *Qual Life Res.* 2005;14:1523–32.

- Decline in CLN2 quality of life assessment of ≥ 15 points

For more information on QoL questionnaires please see section 4.4 of this document.

Patients will cease to qualify for treatment if they miss more than 2 infusions in any 14 month period, excluding medical reasons for missing dosages.

If a patient is ill prior to an assessment, then the patient needs to be reassessed within 12 weeks and subsequent measures need to be considered from this point.

If you meet the start criteria for cerliponase alfa and choose to receive cerliponase alfa your clinician will be monitoring you or your child for benefits that can be measured and recorded.

The Managed Access Agreement (and therefore agreed funding for cerliponase alfa) expires after 5 years. NICE will review the guidance on this technology to align publication of a final decision with the end of the Managed Access Agreement in 5 years. Any funding beyond such 5-year term will be conditional on NHS England agreeing the terms of such funding with BioMarin, the manufacturer of cerliponase alfa.

Accordingly, there are currently no arrangements to enable access to cerliponase alfa to be available as part of standard NHS care following the expiry of the Managed Access Agreement. Any continued access to cerliponase alfa beyond this point will be subject to consideration by NICE and publication of further recommendations. If NICE does not recommend cerliponase alfa following a guidance review, then patients will discontinue NHS treatment with cerliponase alfa.

You or the parents / guardian of the child must sign this Managed Access Patient Agreement to confirm that you have read and understood the terms of the Managed Access Agreement.

4.4 Further information on Quality of Life (QoL) questionnaires

QoL questionnaires are a way of gathering information to understand a patient or carers ability to enjoy normal life activities. Within the Managed Access Agreement, QoL questionnaires will aim to collect important information from patients and their carers on outcomes that might not be collected by other medical tests. The information that will be collected in these questionnaires may include:

- Inability to undertake daily activities
- Feeding
- Washing
- Pain
- Fatigue
- Speech and other forms of communication
- Impaired sleep or daytime sleepiness
- Weight changes
- Problems with digestion
- Psychological impact
- Loss of earnings and productivity (employment)
- Ability to participate in society – continue education and employment
- Impact on family

5. Data Protection and Sharing

For the purposes of this Managed Access Agreement, BioMarin International Limited (“the Company”) which holds the Marketing Authorisation for Cerliponase Alpha and NICE are Joint Data Controllers with NICE. The NHS Trust and MPS Commercial are Data Processors, along with the Managed Access Oversight Committee. All information relating to you collected as part of this Managed Access Agreement will be kept in strict medical confidence. This includes information about your identity, your physical or mental health or condition, your ethnic origin, test and lab results, and information about the treatments you received (“Personal Information”).

Your Personal Information must be collected and shared with certain authorised people in order to comply with this Managed Access Agreement.

This information will be recorded in the following types of records:

- i. The clinical team will record information in your medical records.
- ii. Some of the information from your medical records will be transferred onto a secure database managed by the Company. The information entered into the database will not identify you by name, but rather by a Managed Access Agreement patient identification number.
- iii. The clinical team will provide the Patient Organisation with your name and contact details and your Managed Access Agreement generated patient identification number so that the data they collect can be linked to you.
- iv. The Patient Organisation will record information directly into the same database as per ii) above.

There will be a list that links your name with your Managed Access Agreement generated patient identification number, but your treating clinician and the

Patient Organisation will keep the list in a secure place, separate from your medical records.

Your treating clinician and MPS Commercial will share your coded Personal Information in the database with BioMarin in the United States. BioMarin may share the reports with service providers supporting them in relation to this Managed Access Agreement. These service providers may be established in the United States or other countries that do not provide the same level of privacy protection or where you do not have the same level of legal compensation. NHS England, NICE, MPS Commercial and the Company will take the necessary steps to ensure the security of the data when transferred or stored outside of the European Economic Area.

The following people will have access to data on the database:

- Your clinician and their team;
- People working for MPS Commercial
- People working for the NHS England and NICE

The information contained on the database shall be stored for no more than 5 years following the completion of the Managed Access Agreement guidance review by NICE. In the event that the guidance review does not take place data will be stored for no more than ten years from the MAA start date.

Your Personal Information will be used to:

- (i) characterise and describe the CLN2 population as a whole, including the heterogeneity, progression and natural history of CLN2;
- (ii) to evaluate the long-term effectiveness and safety of cerliponase alfa;

- (iii) to help the CLN2 medical community with the development of recommendations for monitoring patients and reports on patient outcomes to optimise subject care;
- (iv) to collect data on other treatment patterns, evaluate the frequency of their use and their effectiveness;
- (v) to characterise the effects of long term treatment of cerliponase alfa treatment in subjects; and
- (vi) to collect additional data to:
 - a. help broaden knowledge of identified and potential risks of cerliponase alfa, as well as increase the size of the safety database and possibly provide new information on use in identified subgroups (pregnancy, hepatic (relating to the liver), renal impairment (problems relating to the kidneys), and cardiac impairment (problems relating to the heart)); and
 - b. to help evaluate long-term effectiveness of cerliponase alfa.

The legal basis for the processing (including transfer) of yours / your child's data is it is in the legitimate interests of the Joint Controllers to establish a framework to test the effectiveness of cerliponase alfa and further processing of medical information is necessary for the purposes of the management of health or social care systems and services.

If you do not provide your / your child's data then you will not be able to participate in the Managed Access Agreement and will not be able to receive treatment with cerliponase alfa.

The law gives you the right of access, correction and deletion, subject to limitations provided for in law and the right to lodge a complaint with a Supervisory Authority. If you decide that you or your child would like to withdraw from the Managed Access Agreement, please speak to your clinician at the Lysosomal Storage Disease treatment centre in the first instance.

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Research papers and other scientific findings may be developed and published based on information provided in the database. In such instances, any data shared will not use your name or identify you.

BioMarin has appointed a Data Protection Officer, Nicola Fowler who can be contacted at: EUMEAPrivacyQueries@BMRN.com in the event of queries relation to the processing of your data or in the event you wish to exercise your rights in relation to your data.

Please sign below to confirm that you have read the Managed Access Patient Agreement and understand the requirements of the Managed Access Agreement.

If the patient is under 18 and providing informed assent, this signature is to confirm that the parent or guardian has explained the details of the Managed Access Patient Agreement to their child.

If patient is over 18:

Patient Name: _____

Signature of patient: _____

Date: _____

If patient is under 18 with informed assent:

Patient Name: _____

Signature of patient: _____

Signature of parent or guardian: _____

Date: _____

If patient is under 18 without informed assent:

Patient Name: _____

Signature of parent or guardian: _____

Date: _____

APPENDIX B – DATA PROCESSING AGREEMENT

DATA PROCESSING AGREEMENT

Purpose: This Data Protection Agreement (“Agreement”) establishes minimum data protection standards for NHS treatment centres and MPS Commercial (“Service Providers”) in connection with its performance of services for BioMarin International Limited and/or Affiliate(s) (“BioMarin”) or to the extent it otherwise has access to Personal Data (defined below). This Agreement overrides, supersedes and replaces all and any other data protection language contained in any other agreements between the parties and shall govern all and any disputes or issues arising between the parties that concern data protection matters.

Definitions. In this Agreement:

“Data Protection Law” means all applicable laws, regulations, and requirements of regulatory guidance, in any jurisdiction, relating to data protection, privacy, and confidentiality of personal data, including the General Data Protection Regulation and any implementing, derivative or related legislation, rule, regulation, and regulatory guidance, as amended, extended and re-enacted from time to time, applicable to either party;

“Personal Data” means any information relating to an identified or identifiable natural person (“Data Subject”); an identifiable natural person is one who can be identified, directly or indirectly, in particular by reference to an identifier such as a name, an identification number, location data, an online identifier or to one or more factors specific to the physical, physiological, genetic, mental, economic, cultural or social identity of that natural person;

“Processing” means any operation or set of operations which is performed on Personal Data or on sets of Personal Data, whether or not by automated means, such as collection, recording, organisation, structuring, storage, adaptation or alteration, retrieval, consultation, use, disclosure by transmission,

dissemination or otherwise making available, alignment or combination, restriction, erasure or destruction; and

“Personal Data Breach” means a breach of security leading to the accidental or unlawful destruction, loss, alteration, unauthorized disclosure of, or access to, Personal Data transmitted, stored or otherwise Processed.

Compliance with Data Protection Law. Service Provider shall at all times comply with Data Protection Law.

Description of Processing. BioMarin is the controller and Service Provider is BioMarin’s processor in respect of all Personal Data made available to and Processed by Service Provider.

Data Processing Terms. In Processing Personal Data on behalf of BioMarin, Service Provider shall:

- Process Personal Data solely for the purpose of the services provided to BioMarin and in accordance with BioMarin’s instructions and not for any other purpose, unless required to do so by applicable EU or Member State law, in which case Service Provider shall inform BioMarin of that

legal requirement before commencing Processing unless that law prohibits such information on important grounds of public interest;

- immediately inform BioMarin if Service Provider is of the opinion that an instruction of BioMarin regarding Processing Personal Data infringes Data Protection Law;
- ensure that all agents, employees and subcontractors of Service Provider that Process Personal Data pursuant to the Agreement are subject to suitable confidentiality obligations;
- implement appropriate technical and organizational means to ensure a level of security appropriate to the risks presented by Processing;
- not disclose or transfer Personal Data to any third party without BioMarin's written prior consent except where such disclosure or transfer is to an agent or subcontractor which, prior to such disclosure, has been approved by BioMarin as an agent or subcontractor and has agreed by written contract to be bound by obligations that are no less onerous than the obligations set out in this Agreement and Service Provider shall make available to BioMarin a current list of subcontractors and shall inform BioMarin of any intended changes concerning the addition or replacement of a subcontractor; if BioMarin objects to Service Provider's change of subcontractor, BioMarin shall notify Service Provider of its objections in writing within ten [10] business days of receipt of information about the change from Service Provider and shall be entitled to terminate the Agreement with immediate effect and without liability in

the event Service Provider does not take into consideration BioMarin's objections;

- be fully responsible for all acts or omissions of its employees, agents, and subcontractors in the same manner as for its own acts or omissions;
- provide all assistance to BioMarin as reasonably necessary for BioMarin to meet its obligations in respect of Data Subject rights under Data Protection Law;
- provide all assistance to BioMarin as may be reasonably requested in performing, where required, a data protection impact assessment and in consulting with competent authorities;
- notify BioMarin, without undue delay (and in any event within 24 hours), of:

- discovering a Personal Data Breach, in which case Service Provider shall

(a) as part of such notification describe the nature of the incident and, where possible, the categories and approximate number of Data Subjects concerned and the categories and approximate number of Personal Data records concerned, and explain the impact of such Personal Data Breach upon BioMarin and the Data Subjects whose Personal Data is affected by such Personal Data Breach;

(b) in no case delay notification because of insufficient information but instead provide and supplement notifications as information becomes available; and

(c) in cooperation with BioMarin, use its best efforts to investigate such Personal Data Breach and take all necessary

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and appropriate corrective action to remedy such breach and prevent a recurrence of such breach;

- any request for information from or complaint by a supervisory authority in relation to Personal Data that Service Provider Processes for the purpose of providing the services; and
- any request to Service Provider by a Data Subject to exercise rights under Data Protection Law such as to access, rectify, amend, correct, share, delete or cease Processing his or her Personal Data;
- provide BioMarin with all information necessary to demonstrate compliance with Data Protection Law and allow BioMarin or another auditor mandated by BioMarin to audit compliance with this Agreement;
- retain Personal Data only for as long as necessary to perform the services or as required by applicable EU or Member State law. Service Provider shall, consistent with BioMarin's direction following expiration or termination of the Agreement, return or safely destroy all Personal Data that Service Provider obtained in connection with performing the services and Service Provider shall promptly notify BioMarin in writing once all such information has been returned or destroyed (as applicable in accordance with BioMarin's direction) provided that where continued storage is required by applicable law, Service Provider shall inform BioMarin of those requirements (for clarity, the provisions of this Agreement shall continue to apply to the Personal Data concerned, and Service Provider shall only Process this Personal Data to meet its legal obligations);
- Process Personal Data only within the European Economic Area. Shall the Service Provider be unable to Process Personal Data within the European Economic Area or no longer Process Personal Data within the European Economic Area, Service Provider shall notify BioMarin and request express prior written consent, and ensure that such

transfers of Personal Data outside of the European Economic Area are made only in accordance with the following:

- the transfer is to a jurisdiction deemed by the European Commission to have an adequate level of protection;
- the transfer is subject to contractual provisions approved by the European Commission such as, by way of example, the Standard Contractual Clauses, attached as Attachment 1, which the parties hereby adopt and incorporate into the Agreement, as applicable; or
- pursuant to a framework deemed adequate and approved by the European Commission.