

**NATIONAL INSTITUTE FOR HEALTH AND
CARE EXCELLENCE**

Managed Access Agreement

**Elosulfase alfa for treating
mucopolysaccharidosis type IVa**

Date of Agreement	
NHS England	Signed Dame Barbara Hakin – National Director Commissioning Operations
BioMarin Europe Limited	Signed Guy Eggleton, Executive Director, Sales & Marketing Operations EUMEA
BioMarin International Limited	Signed James Lennertz, VP & General Manager
Clinical Expert	Signed Professor Chris Hendriksz - Adult Inherited Metabolic Disorders Consultant Transitional Metabolic Medicine, Salford Royal Foundation NHS Trust
Patient Organisation	Signed Christine Lavery, Group CEO MPS Society UK
NICE	Signed Professor Carole Longson / Sir Andrew Dillon

1 Purpose of agreement

- 1.1 The objectives of the document as a whole are to embody a set of auditable measures that will be used to assess the compliance of this “Managed Access Agreement” in England and to ensure that all relevant stakeholders have a common understanding that such measures have the agreement and backing of all involved and will therefore be enforced. This common perspective is aimed to support concerns raised by the NICE Committee in their evaluation; communicated in the second consultation document (see link below), and final guidance.

<https://www.nice.org.uk/guidance/indevelopment/gid-mucopolysaccharidosiselosulfasealfaid744/documents>

- 1.2 This Managed Access Agreement has been drawn up by NHS England, BioMarin Europe Limited (the “Market Authorisation Holder” or “MAH”), and patient community experts and clinicians.
- 1.3 For the avoidance of doubt, the parties intend this Managed Access Agreement to be legally enforceable between them.
- 1.4 A Commercial in confidence ancillary agreement containing certain terms relating to the supply of Vimizim agreed between the licensed owner of Vimizim (BioMarin International Limited) and NHS England is appended to this Agreement at Appendix D.

2 Background

- 2.1 The NICE evaluation has developed positive recommendations conditional on a Managed Access Agreement being developed and agreed by key stakeholders in the use of elosulfase alfa in the NHS in England.

3 Commencement and period of agreement

3.1 This Managed Access Agreement shall take effect on the date of publication of the Guidance. Subject to clause 3.2, it will remain in force until the earlier of: (i) publication of a NICE HST of elosulfase alfa or; (ii) a maximum of 5 years. For the avoidance of doubt, this Managed Access Agreement shall expire automatically on the 5th anniversary of its term if it has not expired earlier as a result of the publication of a NICE HST of elosulfase alfa. The MAH will provide the relevant data required for the review of the guidance on the product performance during the fourth year of this Managed Access Agreement. NICE will reissue guidance to the NHS in England based on a review of the data during the fifth year of this Managed Access Agreement. For the purposes of this clause, “**Guidance**” means the guidance expected to be published by the National Institute for Health and Care Excellence in December 2015 in relation to the use of elosulfase alfa.

3.2 This Managed Access Agreement shall terminate automatically on the termination or expiry of the commercial agreement relating to the funding of elosulfase alfa and entered into between the BioMarin International Limited and NHS England.

4 Patient eligibility

4.1 To receive treatment, patients must sign up to the ‘Managed Access Patient Agreement’ included in Appendix A to this Managed Access Agreement, and NHS England and the MAH will use reasonable endeavours to ensure that this requirement (and the other eligibility criteria specified in this clause 4) are reflected in their contracts with those clinical services providers who purchase elosulfase alfa from the MAH.

- 4.2 Patients are required to attend their clinics three times a year for assessment.

Children under the age of 5 may not be able to complete all baseline and subsequent assessments. Clinically relevant assessments should be attempted at least once every 12 months until the age of 5, at which point all assessments become compulsory. There may also be other patients i.e. those with cognitive impairments, who are not able to complete a full set of tests at appointed visits. In such cases, clinicians will be expected to make all possible efforts to gather as much of the required data as possible.

- 4.3 Elosulfase alfa will not be started if any of the following apply:-

- 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 has a lung capacity (FVC) of less than 0.3 litres and require ventilator assistance; or
- The patient is unwilling to comply with the associated monitoring criteria:
- All patients are required to attend their clinics three times a year for assessment.
- All patients will sign up to the 'Managed Access Patient Agreement' as seen in the appendix to this Managed Access Agreement.

Start Criteria

All of the following are required before treatment is started:

- All patients must have a confirmed diagnosis of MPSIVA as per the diagnosis criteria recommended in Wood et al. (2012)

- All patients must have confirmed enzymatic test, elevated urinary Keratan Sulfate and mutation analysis.
- In addition patients aged 5 and over can only start once a full set of baseline assessments has been obtained, and they have signed the Managed Access Patient Agreement.

Stop Criteria

Patients will cease enzyme therapy if any of the following apply:

- The Patient is non-compliant with assessments for continued therapy (non-compliance is defined as fewer than three attendances for assessment in any 14 month period);
- The Patient fails to meet 4 of the 5 criteria as defined below under naïve responder or long term trial patient.
- The Patient is unable to tolerate infusions due to infusion related severe adverse events that cannot be resolved.

Patients who are taken off treatment will continue to be monitored for disease deterioration and supported with other clinical measures. These patients should continue to be assessed to allow gathering of important information.

5 Data collection and monitoring

- 5.1 Data will be collected from all patients who start during the term of this Managed Access Agreement.
- 5.2 The MAH has been asked by the European Medicines Agency to enroll all patients into a 12 year disease registry to continue to gather information about this ultra-rare condition. The purposes of this registry are to: (i) characterise and describe the MPS IVA population as a whole, including the heterogeneity, progression and

natural history of MPS IVA; (ii) to evaluate the long-term effectiveness and safety of Vimizim (elosulfase alfa); (iii) to help the MPS IVA medical community with the development of recommendations for monitoring subjects and reports on subject outcomes to optimise subject care; (iv) to collect data on other treatment paradigms, evaluate the prevalence of their use and their effectiveness; (v) to characterise the effects of 5 years of elosulfase alfa treatment in subjects under 5 years of age; and (vi) to collect additional data to: (a) help broaden knowledge of identified and potential risks of elosulfase alfa, as well as increase the size of the safety database and possibly provide new information on use in identified subgroups (pregnancy, hepatic and renal impairment, cardiac impairment); and (b) to help evaluate long-term effectiveness of elosulfase alfa. The MAH will provide access for NHS England to this database to assist it in assessing the clinical impact of elosulfase alfa on this disease. As part of this Managed Access Agreement the MAH agrees to NHS England appointing a representative to sit on the registry advisory board.

5.2A The MAH grants NHS England a fully paid-up non-exclusive licence to access the data collected and held under clause 5.2 above and to use such data for the purpose of assessing the clinical effectiveness of elosulfase alfa.

5.3 A distinction has been made between those patients who are naïve to treatment and the cohort of patients who have been on treatment in England or those who become the commissioning responsibility of NHS England.

5.4 Treatment of Naïve Responder (for patients who have never received treatment)

NHS England and the MAH will use reasonable endeavours to ensure that the requirements detailed in this clause 5.4 and in

clauses 5.5, 5.6 and 5.7 are reflected in their contracts with those clinical services providers who purchase elosulfase alfa from the MAH.

A responder following the first year of treatment for a treatment naïve patient will demonstrate at least four out of five of the following otherwise they will have to stop treatment with Enzyme Replacement Therapy (ERT):-

1. Improvement of 6 minute walking test (6MWT) or 25ft Ambulation Test of at least 10% improvement over baseline, or stabilization after plateauing to a 10% improvement. Baseline will be a single 6MWT test performed according to American Thoracic Society guidelines and applied at a time the patient is in suitable condition that the test is not confounded by other health issues e.g. chest infection, cold etc. If a patient has had any minor surgery in the previous 3 months or major surgery in 6 months they will still take the test but it will be repeated. 6MWT will not be performed within 2 hours of respiratory function testing or any endurance assessments. The following will also be recorded in all patients over the age of 5 at both start and end of 6MWT- heart rate, oxygen saturation, respiratory rate and Borg scale. These values are required to support the validity and effort of 6MWT but only the total distance will be used for determining the stop point.
2. Improvement in FVC or FEV-1 measured with standard spirometry of 5% over baseline in the first year or stabilization after the first year. Both are standard measures and the best values from 3 attempts will be used to determine the stop criterion but improvement in either FVC or FEV-1 will be sufficient as both measure different aspects of

respiratory disease. Pulmonary Function Testing should not be done within 2 hours of endurance testing and if the patient is on any inhaler this should be used as appropriate. The other tests should be delayed if the patient is unwell (a respiratory rate higher than normal or a temperature greater than 38 degrees centigrade).

3. Stabilization defined as no adverse change in the numerical value in two of the following three measures:
 - (1) the score of Quality of Life as measured by utility derived from EQ5D-5L scores OR caregiver burden as measured by MPS HAQ Caregiver Domain,
 - (2) Beck depression score and
 - (3) Adolescent Pediatric Pain Tool (APPT) or Brief Pain Inventory (BPI) pain score depending on age.
4. Reduction from baseline in uKSSs of 20%
5. Decline in ejection fraction of less than 10% from baseline as measured by echocardiogram.

5.5 Patients who are currently on treatment

Patients who are 'currently on treatment' are defined as: (i) clinical trial patients; (ii) patients otherwise already receiving treatment and have become a commissioning responsibility of NHS England; and (iii) patients who started on treatment during the term of the Managed Access Agreement and have been receiving treatment for over 12 months. To remain on treatment patients must fulfil four out of five of the response criteria:-

1. 6MWT and 25ft Ambulation Test remains 5% above baseline value at start of treatment with same limitations as for treatment naïve patients
 2. FVC and FEV-1 remain 2% above baseline at start of treatment
 3. uKS levels remain reduced at least 20% from baseline value
 4. Stabilization is defined as no adverse change in the numerical value in two of the following three measures:-
 - (a) the score of Quality of Life as measured by utility derived from EQ5D-5L scores OR caregiver burden as measured by MPS HAQ Caregiver Domain;
 - (b) Beck depression score; and
 - (c) Adolescent Pediatric Pain Tool (APPT) or Brief Pain Inventory (BPI) pain score depending on age.
 5. Decline in ejection fraction of less than 10% from baseline as measured by annual echocardiogram
- 5.6 Patients will also cease to qualify for treatment if they have a lung function (FVC) of less than 0.3L and require ventilator assistance.
- 5.7 Patients will cease to qualify for treatment if they miss more than 3 infusions in any 14 month period, excluding medical reasons for missing dosages.

Outline of assessments to be made

Assessments	Baseline	Month 4	Month 8	Month 12	Measures	Response
6MWT or 25ft ambulation	x	X		X	Time and Metres /Feet completed	RR, HR, Borg scale and saturations before and after
FVC	x		X		Total value in ML	Best value of 3 attempts
FEV1	x				Total value in ML	Best value of 3 attempts
uKS	x	x		x	% change from baseline Corrected for creatinine	Single lab analysis
EQ5 DL	x			x	Numerical value	Administered by MPS Society
MPS HAQ caregiver	x			x	Numerical value	Administered by MPS Society
Beck score	x		X		Numerical value	Administered by MPS Society
BPI/APTT	x	X	X	x	Random Day before and after infusion	Administered by MPS Society
Cardiac echo	x			x	Ejection fraction as a percentage	Record operator and single operator ideal
Missed infusions		X	X	x	Numerical value Missed Medical reason missed	
Weight	x	x	x	x	Numerical value	
Antibody titres	x		X	x		

6 Patient Appeal Process

- 6.1 If 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 LSD reference centre in England. 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 cognitive impairment or other behavioural issues or challenges completing assessments. These patient's stop criteria will be defined by individual agreement between the clinician and NHS England.

7 Ownership of the data

- 7.1 By agreeing to take part in the Managed Access Agreement patients will be asked to consent to have their demographic and clinical data collected by their treating clinician. The data will be owned by the MAH but shared with NHS England and NICE for the purpose of assessing the benefit of the treatment. The MAH will be responsible for the timely collection and analysis of the data and submitting the relevant reassessment report to NICE in the fourth year of this Managed Access Agreement.
- 7.2 The data will be collected by the clinicians at the expert centres who have undertaken the relevant training prescribed by NHS England.

8 Exit strategy

- 8.1 If at the end of the 5 year Managed Access Agreement: (i) NICE does not recommend elosulfase alfa for NHS funding, NHS England funding for elosulfase alfa will cease to be available for all patients and treatment will cease (in which case cessation shall be

managed between the MAH and NHS England to ensure it is effected in a controlled manner); (ii) NICE recommends elosulfase alfa for NHS funding, further funding from NHS England will not be automatic and will be conditional on the agreement of commercial terms in relation to such funding between NHS England and the MAH.

- 8.2 The cessation of funding under this Managed Access Agreement and the conditionality of further funding as specified in clause 8.1 above apply notwithstanding any desire which patients and their NHS clinicians may have for continued treatment with elosulfase alfa. NHS England and the MAH shall use their reasonable endeavours to ensure that any patient being treated with elosulfase alfa which is funded by NHS England under this Managed Access Agreement is made aware of these funding limitations and accepts them when they sign the Patient Agreement on the terms set out in the Appendix.

9 Ongoing Review of this Agreement

- 9.1 The measures determined to be used are based on best current information. It would be expected that more knowledge will be gained over the next few years; hence a reassessment of the criteria by all signatories to this Managed Access Agreement will be reassessed three years from the start of this Managed Access Agreement and adjusted accordingly. NHS England shall conduct an interim review at the end of the second year, and the other parties, in a reasonably timely manner, shall furnish NHS England with all information and data requested by NHS England in connection with such review.
- 9.2 A body of NHS England, the MAH, the NICE Observational Data Unit, clinical experts and patient organisation representatives will

meet annually to consider how the prescribed criteria are working. They will meet under the chairmanship of NICE.

10. Funding

The MAH has registered a confidential patient access price with the Department of Health, and has agreed further commercial arrangements with NHS England to respond to the NICE committee's concerns. These arrangements set out in the ancillary agreement apply for the duration of the Managed Access Agreement.

11. Counterparts

- 11.1 This Agreement may be executed in any number of counterparts, each of which when executed and delivered shall constitute a duplicate original, but all the counterparts together shall constitute one agreement.
- 11.2 Transmission of the executed signature page of a counterpart of this Agreement by (a) fax or (b) email (in PDF, JPEG or other agreed format) shall take effect as delivery of an executed counterpart of this Agreement. If either method of delivery is adopted, without prejudice to the validity of the agreement thus made, each Party shall provide the others with the original of such counterpart as soon as reasonably possible thereafter.
- 11.3 No counterpart shall be effective until each Party has executed and delivered at least one counterpart.

Appendix A

Enzyme Replacement Therapy (ERT) Elosulfase alfa (Vimizim) for Mucopolysaccharidosis Type IVA Managed Access Patient Agreement

NICE have approved reimbursement of Elosulfase Alfa, licensed as Vimizim®, subject to the collection of auditable measures that will be used to assess the compliance of a Managed Access Agreement in England and to ensure that all relevant stakeholders have a common understanding that such measures have the agreement and backing of all involved and will therefore be enforced.

The NICE Managed Access Agreement includes:-

- A protocol that sets out the clinical criteria for starting and stopping treatment with elosulfase alfa.
- Assurance from BioMarin Europe Limited (the “Marketing Authorisation Holder” or “MAH”) that it will collaborate with the MPS Society and NHS England to collect your anonymized data and continue to support the MPS IVA registry. The data will be used by NICE to inform a review no more than 5 years after publication of the guidance.
- Agreement between the licensed owner of Vimizim and NHS England to set the total costs of elosulfase alfa during data collection, which is in addition to the discount in the patient access scheme, in order to manage financial risk.

1. Patient Eligibility

The clinical community and MPS Society feel it is appropriate and right that all patients have access to elosulfase alfa (Vimizim) in England. The only exception from starting elosulfase alfa in confirmed cases of MPSIVA will be where:-

- 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
- Patient / Parent are unwilling to comply with the associated monitoring criteria:
 - The patient has a lung capacity (FVC) of less than 0.3 litres and require ventilator assistance; or
 - The patient is unwilling to comply with the associated monitoring criteria:

- All patients are required to attend their clinics three times a year for assessment within a 14 month period.
- All patients will sign up to this 'Managed Access Patient Agreement'.

2. Access to treatment and data collection

The criteria in this Managed Access Patient 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 Vimizim was granted.

A distinction has been made between those patients who are naïve to treatment and the cohort of patients who have been on treatment in England or those who will be applicable to have commissioning from NHS England

Allowance is also made for children under the age of 5 that may not be able to do some assessments but they should be attempted at least once every 12 months until the age of 5 at which point they become compulsory.

It is expected that all patients, who are appropriate for homecare delivery, will receive infusions via home care delivery. This is expected to follow the clinically appropriate initial hospital infusions at the commencement of treatment.

3. Start Criteria

- Patients must have a confirmed diagnosis of MPSIVA as per the diagnosis criteria recommended in Wood et al. (2012)
- Confirmed enzymatic test, elevated uKS and mutation analysis for all patients
- Patients can only start once a full set of baseline criteria has been obtained.
- Patients / Parents will be expected to attend their clinic three times a year for assessment within a 14 month period.
- Patients / Parents will be informed about the strict requirement for attendance as set out in this patient agreement document, an appendix to the Managed Access Agreement.

In the event of the patient being unable to maintain the above criteria, the implementation of the stop criteria will be discussed with the Patient / Parent.

4. Stop Criteria

Patients will become ineligible for further treatment where:-

- The patient is non-compliant with assessments for continued therapy where non-compliance is defined as fulfilling fewer than three attendances for assessment in any 14 month period.
- The patient fails to meet 4 of the 5 criteria as defined in Appendix B under naïve responder or long term trial patient.
- The patient is unable to tolerate infusions due to infusion related severe adverse events that cannot be resolved.
- Patients who are taken off treatment will continue to be monitored for disease deterioration and supported with other clinical measures. These patients should continue to be assessed to allow gathering of important information.

If you feel that you or your child will be able to comply with the above please fill in your details below and sign for reimbursed treatment to begin.

If you meet the start criteria for elosulfase alfa and choose to receive elosulfase alfa your clinician will be monitoring you or your child for demonstrable benefit, outlined in Appendix B attached.

The Managed Access Agreement (and therefore agreed funding for elosulfase alfa) expires 5 years after NICE's recommendations being published in 2016, or following a further review should this be sooner. At year four a comprehensive review will look at the benefits of elosulfase alfa, collectively. Any funding beyond such 5-year term will be conditional on NHS England agreeing the terms of such funding with BioMarin, the manufacturer of elosulfase alfa. Accordingly, there are currently no arrangements to enable access to Elosulphase alpha to be available as part of standard NHS care following the expiry of the managed access agreement. Any continued access to Elosulphase alpha beyond this point will be subject to consideration by NICE and publication of further recommendations. If NICE does not recommend Elosulphase Alpha in its further review at that time patients will discontinue NHS treatment with Elosulphase Alpha.

You or the parents of the child must sign this Managed Access Patient Agreement as part of the start criteria for treatment.

Please note. By signing this document you are agreeing to the MPS Society performing the Quality of Life study required as part of this Managed Access Patient Agreement in addition to all collected data from your monitoring visits to hospital to be entered into the MPS IVA registry (MARS registry). This is a commercial registry and if you object to your data being collected into this database your treating clinician may be able to offer an alternative non-commercial registry. Although researchers hope the data collected will lead to better future patient outcomes, it is your right to opt out from the data collection and you will still be offered treatment. By agreeing to your information being entered into the registry you also explicitly consent to that information being used to fulfil the purposes of the registry.

The purposes of the registry are to: (i) characterise and describe the MPS IVA population as a whole, including the heterogeneity, progression and natural history of MPS IVA; (ii) to evaluate the long-term effectiveness and safety of Vimizim (elosulfase alfa); (iii) to help the MPS IVA medical community with the development of recommendations for monitoring subjects and reports on subject outcomes to optimise subject care; (iv) to collect data on other treatment paradigms, evaluate the prevalence of their use and their effectiveness; (v) to characterise the effects of 5 years of elosulfase alfa treatment in subjects under 5 years of age; and (vi) to collect additional data to: (a) help broaden knowledge of identified and potential risks of elosulfase alfa, as well as increase the size of the safety database and possibly provide new information on use in identified subgroups (pregnancy, hepatic and renal impairment, cardiac impairment); and (b) to help evaluate long-term effectiveness of elosulfase alfa.

Data collected will be shared with NHS England, NICE and the MAH and may be stored both inside and outside of the EU on static databases and portable devices (including being stored in the United States of America). Research papers and other scientific findings may be developed and published based on information provided in the registry and by signing below you understand and consent to your data being used for such scientific and academic purposes.

*Patient/Parent Name: _____ Name of Clinician: _____

Signature: _____ Signature of Clinician: _____

Date: _____ Date: _____

(Please note that the informed assent form wording will be adjusted according to the age of the child as per Appendix C)

Appendix B

Start and Stop Criteria

Eligibility

1. To receive treatment, patients must sign up to the 'Managed Access Patient Agreement' included in Appendix A to this Managed Access Agreement.
2. Patients are required to attend their clinics three times a year for assessment.
3. Children under the age of 5 may not be able to complete all baseline and subsequent assessments. Clinically relevant assessments should be attempted at least once every 12 months until the age of 5, at which point all assessments become compulsory. There may also be other patients, i.e, those with cognitive impairments, who are unable to complete a full set of tests at appointed visits. In such cases, clinicians will be expected to make all possible and reasonable efforts to gather as much of the required data as possible.
4. Elosulfase alfa will not be started if any of the following apply:-
 - 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 has a lung capacity (FVC) of less than 0.3 litres and require ventilator assistance; or
 - The patient is unwilling to comply with the associated monitoring criteria:
 - All patients are required to attend their clinics three times a year for assessment.

- All patients will sign up to the 'Managed Access Patient Agreement' as seen in the appendix to this Managed Access Agreement.

Start Criteria

All of the following are required before treatment is started:

- All patients must have a confirmed diagnosis of MPSIVA as per the diagnosis criteria recommended in Wood et al. (2012)
- All patients must have confirmed enzymatic test, elevated uKS and mutation analysis for all patients
- In addition patients aged 5 and over can only start once a full set of baseline assessments has been obtained, and they have signed the Managed Access Patient Agreement.

Stop Criteria

Patients will cease enzyme therapy if any of the following apply:

- The Patient is non-compliant with assessments for continued therapy (non-compliance is defined as fewer than three attendances for assessment in any 14 month period);
- The Patient fails to meet 4 of the 5 criteria as defined below under naïve responder or long term trial patient.
- The Patient is unable to tolerate infusions due to infusion related severe adverse events that cannot be resolved.

Patients who are taken off treatment will continue to be monitored for disease deterioration and supported with other clinical measures. These patients should continue to be assessed to allow gathering of important information.

Treatment of Naïve Responder (for patients who have never received treatment)

A responder following the first year of treatment for a treatment naïve patient will demonstrate at least four out of five of the following otherwise they will have to stop treatment with ERT:-

1. Improvement of 6 MWT or 25ft Ambulation Test of at least 10% improvement over baseline, or stabilization after plateauing to a 10% improvement. Baseline will be a single 6MWT test performed according to American Thoracic Society guidelines and applied at a time the patient is in suitable condition that the test is not confounded by other health issues e.g. chest infection, cold etc.... If a patient has had any minor surgery in the previous 3 months or major surgery in 6 months they will still take the test but it will be repeated. 6MWT will not be performed within 2 hours of respiratory function testing or any endurance assessments. The following will also be recorded in all patients over the age of 5 at both start and end of 6MWT- heart rate, oxygen saturation, respiratory rate and Borg scale. These values are required to support the validity and effort of 6MWT but only the total distance will be used for determining the stop point.
2. Improvement in FVC or FEV-1 measured with standard spirometry of 5% over baseline in the first year or stabilization after the first year. Both are standard measures and the best values from 3 attempts will be used to determine the stop criterion but improvement in either FVC or FEV-1 will be sufficient as both measure different aspects of respiratory disease. Pulmonary Function Testing should not be done within 2 hours of endurance testing and if the patient is on any inhaler this should be used as appropriate. The other tests should be delayed if the patient is unwell (a

respiratory rate higher than normal or a temperature greater than 38 degrees centigrade).

3. Stabilization defined as no adverse change in the numerical value in two of the following three measures:
 - (4) the score of Quality of Life as measured by utility derived from EQ5D-5L scores OR caregiver burden as measured by MPS HAQ Caregiver Domain,
 - (5) Beck depression score and
 - (6) Adolescent Pediatric Pain Tool (APPT) or Brief Pain Inventory (BPI) pain score depending on age.
4. Reduction from baseline in uKSs of 20%
5. Decline in ejection fraction of less than 10% from baseline as measured by echocardiogram.

Patients who are currently on treatment

Patients who are 'currently on treatment' are defined as: (i) clinical trial patients; (ii) patients otherwise already receiving treatment and have become a commissioning responsibility of NHS England; and (iii) patients who started on treatment during the term of the Managed Access Agreement and have been receiving treatment for over 12 months. To remain on treatment patients must fulfil four out of five of the response criteria:-

1. 6MWT and 25ft Ambulation Test remains 5% above baseline value at start of treatment with same limitations as for treatment naïve patients
2. FVC and FEV-1 remain 2% above baseline at start of treatment
3. uKS levels remain reduced at least 20% from baseline value

4. Stabilization is defined as no adverse change in the numerical value in two of the following three measures:-

(d) the score of Quality of Life as measured by utility derived from EQ5D-5L scores OR caregiver burden as measured by MPS HAQ Caregiver Domain;

(e) Beck depression score; and

(f) Adolescent Pediatric Pain Tool (APPT) or Brief Pain Inventory (BPI) pain score depending on age.

5. Decline in ejection fraction of less than 10% from baseline as measured by annual echocardiogram

- Patients will also cease to qualify for treatment if they have a lung function (FVC) of less than 0.3L and require ventilator assistance.
- Patients will cease to qualify for treatment if they miss more than 3 infusions in any 14 month period, excluding medical reasons for missing dosages.

Outline of assessments to be made

Assessments	Baseline	Month 4	Month 8	Month 12	Measures	Response
6MWT or 25ft ambulation	x	X		X	Time and Metres /Feet completed	RR, HR, Borg scale and saturations before and after
FVC	x		X		Total value in ML	Best value of 3 attempts
FEV1	x				Total value in ML	Best value of 3 attempts
uKS	x	x		x	% change from baseline Corrected for creatinine	Single lab analysis
EQ5 DL	x			x	Numerical value	Administered by MPS Society
MPS HAQ caregiver	x			x	Numerical value	Administered by MPS Society
Beck score	x		X		Numerical value	Administered by MPS Society
BPI/APTT	x	X	X	x	Random Day before and after infusion	Administered by MPS Society
Cardiac echo	x			x	Ejection fraction as a percentage	Record operator and single operator ideal
Missed infusions		X	X	x	Numerical value Missed Medical reason missed	
Weight	x	x	x	x	Numerical value	
Antibody titres	x		X	x		

Appendix C

Informed assent form wording according to patient age

Name of Patient _____

I understand the conditions of the Managed Access Programme and the Managed Access Patient Agreement (including the circumstances in which NHS access to the treatment will cease)

Signature of Patient (if over 18) _____

Date _____

If patient is under 18 with informed assent

I have explained the details of the Managed Access Programme and the Managed Access Patient Agreement (including the circumstances in which NHS access to the treatment will cease) to (insert name) _____

who understands the conditions and likely benefits of the treatment

Signature of parent or guardian _____

Date _____

I (insert name) _____ understand the treatment and the conditions of the Managed Access Programme and the Managed Access Patient Agreement (including the circumstances in which NHS access to the treatment will cease) which my parents / guardian have explained to me.

Signature of Patient _____

Date _____

If patient is under 18 without informed assent

I understand the conditions of the Managed Access Programme and the Managed Access Patient Agreement (including the circumstances in which NHS access to the treatment will cease) and the likely benefits of treatment for my child.

Signature of parent or guardian _____

Date _____

Name of Clinician: _____

Signature of Clinician: _____

Date: _____

Appendix D

Ancillary Agreement between BioMarin and NHS England

(The ancillary agreement contains commercial-in-confidence information and has been redacted from the managed access agreement)