NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Proposed Managed Access Agreement

Asfotase alfa for treating paediatric-onset hypophosphatasia

Date of Agreement	TBD
NHS England	Signed _____ John Stewart Acting National Director of Specialised Commissioning
NICE	Signed _____ Professor Carole Longson / Sir Andrew Dillon
Alexion Pharma UK Ltd.	Signed _____ Sara Trafford-Jones, General Manager
Clinical Expert	Signed _____ Dr Nick Shaw, Consultant Paediatric Endocrinologist, University of Birmingham, Birmingham children's hospital, also on behalf of Professor Nick Bishop and professor Zulf Mughal
Patient Organisation	Signed _____ Lindsay Weaver, Executive Director, CLIMB

1 Purpose of agreement

1.1 The objectives of the document are to set out the agreed terms and conditions according to which patients will be entitled to access the drug called asfotase alfa (Strensiq®) in paediatric-onset hypophosphatasia (**HPP**). It also describes a set of auditable measures that will be used as an evidence base in this ultra-rare disease and to assess the compliance with this Managed Access Agreement in England and to ensure that all relevant stakeholders have a common understanding that such measures have the commitment of all involved and will be applied. This common perspective is aimed to address uncertainties raised by the NICE Committee in their evaluation of asfotase alfa for paediatric-onset HPP.

1.2 This Managed Access Agreement (**MAA**) is entered into between the National Institute for Health and Care Excellence (**NICE**), NHS England, Alexion Pharma UK Ltd (**Alexion UK**), the Clinical Expert named on page 1 and the patient organisation CLIMB (Children Living with Inherited Metabolic Diseases).

1.3 For the avoidance of doubt, the parties intend this MAA to be legally enforceable between them.

1.4 A commercial in confidence ancillary agreement containing certain terms relating to the supply of asfotase alfa agreed between the licensed owner of asfotase alfa (Alexion UK) and NHS England is appended to this Agreement at Appendix D.

2 Background

2.1 HPP is an inherited, metabolic disease of bone mineralization characterized by persistently low activity of the enzyme alkaline phosphatase (**AlP**) leading to hypo-mineralisation with radiological findings that may include rickets/osteomalacia, irregularity of the

provisional zone of calcification, physeal widening, metaphyseal flaring/fraying, metaphyseal radiolucencies, or abnormal structure of the bone architecture.

2.2 Patients presenting below one year of age will have either perinatal or infantile HPP, which may constitute a medical emergency. The predominant feature is failure of adequate mineralization and development of the ribcage, leading to respiratory compromise as a result of biomechanical failure. Vitamin B6 dependent seizures may also be a feature.

2.3 Juvenile patients may present with impaired skeletal development (short stature or waddling gait), impaired mobility and inability to perform activities of daily living, requiring the use of mobility devices, or home adaptations. Recurrent low trauma fractures or poorly healing fractures and severe, intractable bone and joint pain are predominant symptoms in adults whose disease onset was in childhood.

2.4 Any patient with a clinical presentation consistent with a diagnosis of paediatric-onset HPP and persistently low AlP, should be referred to one of the national HPP expert centres for clinical assessment for potential therapy under this MAA.

3 Commencement and period of agreement

3.1 This MAA shall take effect on the date of publication by NICE of the first final Guidance for asfotase alfa (the **Effective date**). It will remain in force until the earlier of: (i) publication of new guidance following a subsequent NICE HST review of asfotase alfa or; (ii) a maximum of 5 years from the effective date. For the avoidance of doubt, this MAA shall expire automatically on the 5th anniversary of its term if it has not expired earlier as a result of the publication of new guidance following a subsequent NICE HST review of asfotase alfa.

3.2 Alexion UK will provide all relevant data in accordance with its obligations in clause 5 of this MAA and the terms of Appendix E (Data Collection and Sharing) that will be required for the review of the Guidance during the fourth year of the term of this MAA. NICE will reissue guidance to the NHS in England based on a review of the data during the fifth year of the term of this MAA.

3.3 For the purposes of this clause 3, "**Guidance**" means the guidance expected to be published by NICE on [date] in relation to the use of asfotase alfa.

3.4 This MAA shall terminate automatically on the termination or expiry of the commercial agreement relating to the funding of afostase alfa and entered into between Alexion UK and NHS England.

4 Patient eligibility

4.1 To receive asfotase alfa treatment, patients must first sign up to the Managed Access Patient Agreement included in Appendix A to this MAA. NHS England and Alexion UK will use reasonable endeavours to ensure that this requirement, and the other eligibility criteria specified in this clause 4, is reflected in their contracts with those clinical services providers who purchase asfotase alfa from Alexion UK.

4.2 All patients must have a diagnosis of paediatric-onset HPP (regardless of current age) confirmed by one of the national HPP expert centres, according to national guidelines. Treatment with asfotase alfa must only be initiated by the expert centre.

4.3 Patients receiving asfotase alfa must attend clinic every three months as a condition of ongoing treatment.

4.4 Patients aged 5 or over can only start treatment once a full set of baseline assessments has been obtained. These baseline assessments are set out in Appendix C.

4.5 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 (see Appendix C).

4.6 There may also be other patients, such as those with cognitive impairments, who will not be able to complete a full set of baseline assessments 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. Reasonable adjustments will be made for patients who are unable to comply with the assessments by reasons of cognitive impairment or other behavioral issues or challenges completing assessment.

4.7 Asfotase alfa therapy must not be started if any of the following conditions apply:

1. asfotase alfa is contraindicated for any reason; or
2. the patient is diagnosed with an additional progressive life-limiting condition where treatment with asfotase alfa would not provide long- term benefit such as terminal cancer or catastrophic brain injury; or
3. the patient or guardian (which may include family/carer) is unwilling to comply with associated monitoring criteria as defined in Appendix C or refuses to sign the consent form contained in Appendix A.

4.8 The start and stop criteria to be applied are set out in Appendix B to this MAA.

4.9 Any patient for whom treatment is stopped should continue to be followed-up on a 6-month basis for consideration of treatment restart where clinically indicated. Data for such patients should continue to be entered in the Global HPP Registry where relevant. Patients should be restarted on therapy immediately with signs of worsening disease.

5 Data collection and monitoring

5.1 Data will be collected from all patients who start treatment during the term of this MAA. The schedule of assessments in Appendix C contains details of the data that will be recorded.

5.2 Data will be entered into a Managed Access Agreement database designed specifically for this purpose

5.3 Alexion will allow NHS England access to this database for checking of data validity and completeness and audit purposes and any other purpose as states in Appendix E – Data collection and sharing agreement

5.4 As part of this MAA, Alexion UK will constitute and maintain for the duration of this agreement a National (UK) HPP Advisory Board. Membership of this Advisory Board must include HPP physician experts, an elected patient organisation member, the Alexion UK Medical Director, and a representative appointed by NHS England. The Advisory Board will oversee the operation of the Managed Access Agreement database in England and the provision of data to NHS England to enable full audit of this MAA. Requests for analysis or data extracts from the HPP Global Registry may be made via the UK coordinator for the HPP Global Registry, who will also be a member of the UK HPP Advisory Board.

5.5 Alexion UK shall procure that the Advisory Board will grant NHS England access to the with relevant data extracts from the Global HPP Registry database to allow it to assess the clinical impact of asfotase alfa on patient outcomes. The Global HPP Registry is guided and governed overall by an international Scientific Advisory Board (SAB) comprising key international experts.

5.6 For avoidance of doubt, this National (UK) HPP Advisory Board is separate from the clinical panel required under this agreement to

assess patient eligibility and patient start or stop criteria. The clinical panel required for this purpose will be constituted and maintained by NHS England and NICE. This clinical panel will have no commercial function.

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 designated HPP centre in England. Travel and associated costs will be at the patient's expense.

7 Ownership of the data

7.1 By agreeing to take part in the MAA, patients in England will be required to consent to have their demographic and clinical data collected by their treating clinician and entered into a database (the **MAA Database**). Each patient will own their specific data but aggregated data will be owned by the sponsor of the Global HPP Registry, Alexion Pharmaceuticals Inc. The Global HPP Registry contains two databases: the global HPP database and the MAA Database.

7.2 Alexion UK grants NHS England a free of charge non-exclusive license to access the raw data on the MAA Database and to receive an annual report from the Global HPP Registry [performed by Alexion UK under clause 7.1 above] in order to assess the clinical effectiveness of asfotase alfa in accordance with Appendix E (Data collection and sharing).

7.3 The data will be collected by the clinicians at the designated HPP centres who have undertaken the relevant training prescribed by NHS England and performed by the Global HPP Registry or Alexion,

subject to such centres registering as participating sites in the Global HPP Registry.

7.4 Alexion UK will be responsible for the timely analysis of the data and submitting the relevant reports to NICE and NHS England.

8 Exit strategy

8.1 If at the end of the five year term of this MAA (i) NICE does not recommend astofase alfa for NHS funding, NHS England funding for astofase alfa will cease to be available for all patients and treatment will cease (in which case cessation will be managed between Alexion and NHS England to ensure it is effected in a controlled manner) (ii) NICE recommends astofase alfa for NHS funding then astofase alfa will be commissioned in England according to the prevailing arrangements between NICE and NHS England at that time. 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 Alexion UK

8.2 The cessation of funding under this MAA 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 astofase alfa. NHS England and Alexion shall use their reasonable endeavours to ensure that any patient being treated with astofase alfa which is funded by NHS England under this MAA is made aware of these funding limitations and accepts them when they sign the Managed Access Patient Agreement (as set out in Appendix A).

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 MAA will be performed three years from the start of the term of this MAA and adjusted accordingly. NHS England may conduct an interim review at the end of the second year, and in that case, the other parties, in a reasonably timely manner, shall furnish NHS England with all information and data requested by NHS England connection with such review.

9.2 A body of NHS England, Alexion UK, 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

10.1 Alexion UK, as the Market Authorisation Holder for asfotase alfa, has registered a confidential patient access scheme with the Department of Health and has agreed further commercial in confidence arrangements with NHS England to respond to the NICE committee's concerns. These arrangements will be set out in the ancillary agreement and apply for the duration of the MAA.

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.

Appendices:

Appendix A – Managed Access Patient Agreement
Appendix B – Start and Stop criteria
Appendix C – Schedule of clinical assessments
Appendix D – Commercial Access Agreement
Appendix E – Data collection and sharing appendix

Appendix A:

Asfotase alfa (Strensiq®) for Treating Paediatric-onset Hypophosphatasia

Managed Access Patient Agreement and Informed Assent Form

The National Institute for Health and Care Excellence (**NICE**) has approved asfotase alfa, brand name Strensiq®, for patients who have been diagnosed with childhood-onset hypophosphatasia (**HPP**) who meet the starting rules outlined in a Managed Access Agreement.

What is a Managed Access Agreement?

An MAA is a way that doctors and the NHS can assess the long term benefits of a new medicine by collecting agreed test results over a given period of time in patients who have certain symptoms of HPP. It is an agreement between NICE, NHS England, Alexion Pharma UK Ltd (the distributer of Strensiq® in the UK), doctors who are experts in treating HPP (**HPP Specialists**) and the patient organisation CLIMB.

The MAA describes who can receive treatment with asfotase alfa and how information will be collected to understand how patients being treated with asfotase alfa respond to treatment in the same way that patients did in clinical trials. It allows patients to start being treated while at the same time allowing more information to be collected on how well the medicine works. An MAA is needed because NICE and NHS England need to understand more about the long term benefits of asfotase alfa. The MAA is managed by NHS England in consultation with selected HPP specialists.

Since you will be treated with asfotase alfa, your information will need to be collected under the MAA. This is a condition of receiving treatment with asfotase alfa in England. Thanks to this information, the NICE guidance can be looked at again after five years, and a further decision can be made on whether NHS should continue to pay for patients to receive this medicine in England.

This Managed Access Patient Agreement sets out:

- Rules for starting and stopping treatment with asfotase alfa.
- An explanation of the MAA database and how it will work.

1. Patient Eligibility

- NICE, the HPP specialists and CLIMB agree that patients in England should be able to have asfotase alfa (Strensiq®) as long as they meet the starting rules that are described in the MAA and are being treated by a specialist in HPP in a specialist HPP centre. If a patient meets the starting rules, they will be required to go to their clinic appointments for tests at three months, six months and 12 months in the first year of treatment, and a then at least every 6 months after that for a check up.

- All patients (whether by themselves or through a parent or guardian) will need to sign up to this Managed Access Patient Agreement.

2. Access to treatment and data collection

- The starting rules and regular tests in this Managed Access Patient Agreement have been developed by the clinical experts in HPP together with representatives of a patient organisation and other interested groups.

- Children under the age of 5 may not be able to do some of the tests, but they should be tried at least once every 12 months until the age of 5 at which point they must be done (see Appendix C).

- It is expected that all patients, who can have their medicine at home, will receive supply of asfotase alfa via home care delivery. Patients and parent/ guardians will get support to make sure that they are able to inject asfotase alfa safely and effectively at home.

3. Starting Rules

- All patients must have a diagnosis of childhood-onset HPP (regardless of their current age) confirmed by one of the national HPP specialist centres, according to national guidelines. Treatment with asfotase alfa must be started by the one of these centres.

- All patients who meet the starting rules for asfotase alfa will be discussed by a committee of HPP experts and a pain management expert from different hospitals before treatment is started, except in babies where HPP is needed urgently. In this situation the specialist may start treatment straight away. The committee will meet monthly by teleconference and face to face every 6 months.

- All patients, or their guardian (as applicable), must give their consent for their information needed for the MAA to be entered into the MAA database which is part of the HPP Global Registry. This is to allow the effect of the treatment to be measured.

- All patients, or their guardian (as applicable), must sign consent to keep to the rules of the Managed Access Agreement, including attending regular appointments and completing questionnaires.

Perinatal- and Infantile-onset HPP: Patients below 1 year of age with symptoms and signs of HPP should be initiated on asfotase alfa therapy as soon as is possible.

Other Patients with Childhood-Onset HPP who meet the starting rules for asfotase alfa therapy include:

1. **Children aged 1-4 with <u>ONE</u> of the following**:

    I. Have not achieved expected developmental gross motor milestones for age as demonstrated by the BAMF-Scale (Brief Assessment of Motor Function); OR

    II. Continuing or recurring musculoskeletal pain where there is **<u>significant</u>** pain that affects daily activities which:

    - Affects quality of life
    - Hasn't got better with 2 different types of painkiller which have been recommended by a national pain specialist

2. **Children aged 5-18 with <u>ONE</u> of the following**:

    I. Continuing or recurring musculoskeletal pain where there is **<u>significant</u>** pain that affects daily activities which:

    - Affects quality of life
    - Hasn't got better with 2 different types of painkiller which have been recommended by a national pain specialist

    OR

    II. Limited mobility assessed by a specialist according to the modified Bleck Ambulation Efficiency Scoring and with a Bleck score between 1-6:

Score	Description
1	Non-walker older than 2 years of age
2	Therapy walker with the use of crutches or sticks
3	Therapy walker without the use of crutches or sticks
4	Household walker with the use of crutches or sticks
5	Household walker without the use of crutches or sticks
6	Neighbourhood* walker with the use of crutches or sticks

*Neighbourhood walker defined as one who can walk less than 300m.

3. **Patients over the age of 18 years old with childhood-onset HPP**

who have <u>two</u> or more of the following:

I. Current fractures (commonly affected areas include feet, hip, spine, wrist and thigh bone) with a history of non-traumatic, recurrent or non-/ poorly-healing fractures (e.g. inability to remove fixation devices due to risk of recurrent fracture).

II. Continuing or recurring musculoskeletal pain where there is **<u>significant</u>** pain that affects daily activities which:

- Affects quality of life
- Hasn't got better with 2 different types of painkillers which have been recommended by a national pain specialist

III. Limited mobility assessed by a specialist according to the modified Bleck Ambulation Efficiency Scoring and with a Bleck score between 1-6[2]:

Score	Description
1	Non-walker older than 2 years of age
2	Therapy walker with the use of crutches or sticks
3	Therapy walker without the use of crutches or sticks
4	Household walker with the use of crutches or sticks
5	Household walker without the use of crutches or sticks
6	Neighbourhood* walker with the use of crutches or sticks

*Neighbourhood walker defined as one who can walk no more than 300m.

4. Stopping Rules

Each year all test results will be looked at to see if asfotase alfa should be stopped by the HPP expert committee. The committee will decide to stop treatment if any of the following apply:

- Patient does not attend their appointments (misses more than one visit in any 18-month period with no attempts to rearrange; assessments missed due to medical reasons should be rescheduled as soon as possible).
- Patient is unable to tolerate asfotase alfa including continuing injection

reactions which cannot be managed with usual medicines/measures and have a significant impact on quality of life.

- Asfotase alfa treatment is no longer helping the patient.

Children, under the age of 18 years, must reach <u>two out of the three</u> following non-responder rules before discontinuing:

- Loss of height or failure to maintain growth along centile lines following one year on a stable dose
- No improvement, or did not reach the expected cut off for the test of six minute walk test (6MWT) improvement of either <25m or <10% compared to test results before treatment or a fall in Bleck score of more than one level
- No reduction in pain: failure to achieve significant reduction in frequency of dose of analgesics (pain killers) or failure to see an improvement in quality of life as measured by PedsQL

Adults, aged 18 years and over, must reach <u>one of the three</u> following non-responder criteria before discontinuing:

- No improvement, or did not reach the expected cut off for the test of six minute walk test (6MWT) improvement of either <25m or <10% compared to test results before treatment or fall in in Bleck score of more than one level
- Continued fractures over a 3 year period
- No reduction in pain: failure to achieve significant reduction in frequency of dose of analgesics or failure to achieve improvement in quality of life as measured by Brief Pain Inventory and EQ5-D-5L

5. Expiry of the Managed Access Agreement

- At the end of 5 years NICE will look again at how well asfotase alfa works in patients such as yourself. If at the end of the 5 year Managed Access Agreement: (i) NICE no longer recommends asfotase alfa for NHS funding, NHS England funded treatment will

need to stop; (ii) NICE recommends asfotase alfa for further NHS funding, then asfotase alfa will continue to be funded in England according to the arrangements between NICE and NHS England at that time.

- You understand that if NICE no longer recommends asfotase alfa for NHS funding, this could mean that your treatment with asfotase alfa will discontinue.

6. Acceptance and use of information

- You, or the parent(s)/guardian(s) of a child, must sign this Managed Access Patient Agreement to confirm that you accept and will comply with the requirements of the Managed Access Patient Agreement as part of the start criteria for treatment.
- **Please note**: By signing this document, you are agreeing to complete a Quality of Life questionnaire required as part of this Managed Access Patient Agreement. The Quality of Life survey is a very short series of questions which allow you to say how you feel the treatment is helping your daily living. Your doctor or a team member will give you the questionnaire when needed, and help you fill out the answers. You will need to fill in this questionnaire about every 3 months.
- The information collected from your tests and clinic visits will be held in a Managed Access Agreement database. You as patient (or through your guardian) will need to sign a consent form agreeing to your information being entered into the MAA database. The information collected about you and your treatment will not identify you by name, address etc. This database is part of a larger database, the Global HPP Registry and your doctor will talk to you about whether you wish to take part in the separate registry study as well.

- Information collected under the MAA will be shared with NHS England, NICE and Alexion, 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).

Informed Assent Form (Wording According to Patient Age)

To be signed by patient and/or parent or guardian **AND** clinician

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 B: Start and Stop Criteria

1. Eligibility

1.1. To receive asfotase alfa treatment, the patient/parent/carer must sign up to the Managed Access Patient Agreement included in Appendix A of this Managed Access Agreement, and NHS England and Alexion UK will use reasonable endeavours to ensure that this requirement (and the other eligibility criteria specified in this Appendix) are reflected in their contracts with those clinical services providers who purchase asfotase alfa from Alexion UK.

1.2. All patients must have a diagnosis of paediatric-onset HPP (regardless of current age) confirmed by one of the national HPP expert centres, according to national guidelines. Treatment with asfotase alfa must be initiated by the expert centre if agreed by the national approval committee as per below.

1.3. Patients receiving asfotase alfa are required to attend clinic at three months, six months and 12 months in the first year of treatment, and a minimum of every 6 months thereafter for assessment.

1.4. Patients aged 5 and over can only start treatment once a full set of baseline assessments has been obtained (see Appendix C).

1.5. 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 (see Appendix C).

1.6. There may also be other patients such as those with cognitive impairments, who will not be 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. 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 patients' start/stop/continuation criteria will be defined by the national approval committee.

1.7. Asfotase alfa will not be started if any of the following apply:

- Asfotase alfa is contraindicated for any reason
- The patient is diagnosed with an additional progressive life-limiting condition where treatment with asfotase alfa would not provide long-term benefit, such as terminal cancer or catastrophic brain injury
- The patient or guardian (which may include family/carer) is unwilling to comply with associated monitoring criteria as defined in Appendix D or refuses to sign the consent to abide by the conditions of the Managed Access Agreement.

2. Start Criteria

2.1. All Patients

- All patients must have a diagnosis of paediatric-onset HPP (regardless of current age) confirmed by a designated HPP centre (or member of the European Reference Network for rare bone disease if HPP centres not yet designated), with ALP activity below age and gender normal range.
- All patients considered eligible for treatment must be discussed by a national committee constituted of experts in the management of HPP, pain management specialists and commissioner representatives prior to treatment being commenced. The exception is in neonates where HPP constitutes a medical emergency. In this situation the treating clinician should inform the committee of the intention to treat but may implement treatment and then refer the case to committee to review. The committee will meet monthly by teleconference and face to face every 6 months.

- Treatment with asfotase alfa must be initiated in or under the supervision of a designated specialist centre.
- All patients must consent for their clinical data (as per this MAA) to be submitted to the Managed Access Agreement registry which is part of the Global HPP Registry

2.2. Perinatal- and Infantile-onset HPP:

Although infantile onset HPP is defined as HPP which presents up to the age of 6 months clinician consensus is that patients with symptoms and signs consistent with HPP presenting below the age of 1 year of age are most likely to have perinatal or infantile onset HPP.

All perinatal- and infantile-onset HPP cases, up to one year of age, who meet the start criteria above should be initiated on asfotase alfa therapy as soon as practical.

2.3. Other Patients with Paediatric-Onset HPP who are eligible for asfotase alfa therapy:

a) Children aged 1-4 with <u>ONE</u> of the following:

I. Have not achieved expected developmental gross motor milestones for age as demonstrated by the BAMF-Scale (Brief Assessment of Motor Function)

II. Persistent or recurrent musculoskeletal pain where there is significant disability, as described and measured by:

- The Pediatric Quality of Life (PedsQL) instrument
- Pain unresponsive to 2 different analgesic classes (according to WHO 2012 guidelines on pharmacological treatment of persisting pain in children with medical illnesses) following assessment and treatment within a designated specialised paediatric pain service (highlighting impact of pain on child and family functioning)

b) Children aged 5-18 with <u>ONE</u> of the following:

I. Persistent or recurrent musculoskeletal pain where there is **significant** pain associated disability, as described and measured by:

- The Pediatric Quality of Life (PedsQL) instrument
- Pain unresponsive to 2 different analgesic classes (according to WHO 2012 guidelines on pharmacological treatment of persisting pain in children with medical illnesses) following assessment and treatment within a designated specialised paediatric pain service (highlighting impact of pain on child and family functioning)

II. Restriction of mobility assessed by a healthcare professional according to the modified Bleck Ambulation Efficiency Scoring (Score 1-6, excluding scores 7,8, and 9)[1]:

Score	Description
1	Non-walker older than 2 years of age
2	Therapy walker with the use of crutches or sticks
3	Therapy walker without the use of crutches or sticks
4	Household walker with the use of crutches or sticks
5	Household walker without the use of crutches or sticks
6	Neighbourhood* walker with the use of crutches or sticks

*Neighbourhood walker defined as one who can walk no more than 300m.

c) **Patients over the age of 18 years old with paediatric-onset HPP who have TWO or more of the following:**

I. Current fractures (most-commonly occurring in but not confined to, metatarsals, hip, vertebrae, wrist and sub-trochanteric region of femur) and a history of non-traumatic, recurrent or non-/

poorly-healing fractures (e.g. inability to remove fixation devices due to risk of recurrent fracture) characteristic of HPP

II. Persistent or recurrent musculoskeletal pain where there is **significant** pain associated disability, as described and measured by:

- Brief Pain Inventory score of 7 or above
- Pain unresponsive to 2 different analgesic classes (see WHO guidelines) following assessment and treatment within a designated specialised adult pain service

III. Restriction of mobility assessed by a healthcare professional according to the modified Bleck Ambulation Efficiency Scoring (Score 1-6, excluding scores 7, 8, and 9)[1]:

Score	Description
1	Non-walker older than 2 years of age
2	Therapy walker with the use of crutches or sticks
3	Therapy walker without the use of crutches or sticks
4	Household walker with the use of crutches or sticks
5	Household walker without the use of crutches or sticks
6	Neighbourhood* walker with the use of crutches or sticks

*Neighbourhood walker defined as one who can walk no more than 300m.

Notes prior to treatment initiation:

[1] Bleck score 7, 8, 9 would not be sufficient criteria without other functional criteria (Bleck 7: Neighbourhood walker without the use of crutches or sticks; Bleck 8: Community walker[#] with the use of crutches or sticks; Bleck 9: Community walker without the use of crutches of sticks)

[#]Community walker defined as able to walk the same distance as their age-adjusted peers, even if at a slower pace.

3. Stop Criteria

The minimum treatment period in which to define response has not been determined. A minimum treatment period of one year at a stable dose should be assumed prior to assessment for lack of response unless the patient has a severe adverse reaction to asfotase alfa or the patient is diagnosed with an additional progressive life-limiting condition where treatment with asfotase alfa would not provide long- term benefit.

A formal assessment of response will be performed after 12 months on therapy and annually thereafter.

All patients' response to treatment should be discussed and evaluated for treatment cessation by the HPP expert committee who will make the recommendation to stop treatment under any of the following conditions:

- Patient is non-compliant with monitoring criteria defined as missing more than 1 visit in any 18-month period with no attempts to reschedule; assessments missed due to medical reasons should be rescheduled as soon as possible.
- Intolerance of asfotase alfa including recurrent injection reactions which cannot be managed with standard medications/measures and have a significant impact on quality of life.
- Asfotase alfa treatment is determined as not benefiting the patient.

In **infants** presenting under the age of 1 year, with respiratory impairment or respiratory failure, treatment should continue at least for the duration of this Managed Access Agreement while further clinical data are collected unless the patient has a severe adverse reaction to asfotase alfa, the patient is diagnosed with an additional progressive life-limiting condition where treatment with asfotase alfa would not provide long- term benefit or where the patient remains on ventilatory support after 2 years of treatment.

Children, aged under 18 years, must reach two out of the three following non-responder criteria before being referred to committee for discussion and ratification of treatment discontinuation:

- Loss of height or failure to maintain growth defined as a drop of more than 5% from centile line following one year on a stable dose,;
- No improvement, or less than MCID improvement, in physical function: (6MWT improvement of either <25m or <10% over baseline)[1] or fall in in Bleck score of more than one level
- No reduction in pain as assessed by pain specialist: failure to achieve significant reduction in frequency of dose of analgesics or failure to see a Minimum Clinically Important Difference improvement in quality of life as measured by PedsQL.[2]

Adults, aged 18 years and over, should reach one of the three following non-responder criteria before discontinuing:

- No improvement, or less than MCID improvement, in physical function: (6MWT improvement of either <25m or <10% over baseline)[3] or fall in in Bleck score of more than one level
- Continued fractures over a 3 year period
- No reduction in pain: failure to achieve significant reduction in frequency of dose of analgesics or failure to achieve improvement in quality of life as measured by Brief Pain Inventory (defined as an improvement of less than 2 points) and utility derived from the EQ5D-

[1] Tomazos I et al. (2016) Determination of the Minimal Clinically Important Difference in the Six-Minute Walk Test for Patients with Hypophosphatasia. Abstract 033116 presented at ESPE.
[2] Hilliard ME et al. (2013) Identification of Minimal Clinically Important Difference Scores of the PedsQL in Children, Adolescents, and Young Adults With Type 1 and Type 2 Diabetes. Diabetes care 36: 1891–1897.
[3] Tomazos I et al. (2016) (see footnote 1).

5L score (defined as an improvement of less than 0.15).

Any patient for whom treatment is stopped should continue to be followed-up on a 6-month basis. Data for such patients should continue to be entered in the Global HPP Registry where relevant.

Appendix C: Schedule of Clinical Assessments for Managed Access Agreement

Required assessments of response	Baseline	3 months	6 monthly	Measures	Response at 12 months vs. baseline
Under 12 months of age					
Length	X	X	X	Centimetres	Minimum of growth along centile line
Weight	X	X	X	Kilogrammes	Minimum of growth along centile line
Survival at 12 months	X	X	X		
Improvement in ventilation support	X	X	X	Use of ventilation support	If requiring ventilation support at **24** months then failure to respond
Age 1 year to 4 years					
Height (under 18 years)	X	X	X	Centimetres	If drop more than 5% from centile line then failure to respond
Weight	X	X	X	Kilogrammes	If drop more than 5% from centile line then failure to respond
BAMF Scale	X	X	X	Score	Stable or improved score

Required assessments of response	Baseline	3 months	6 monthly	Measures	Response at 12 months vs. baseline
PedsQL	X	X	X	Score	Change from baseline. If improvement less than MCID[1], then failure to respond
Age 5 years to 18 years					
Height (under 18 years)	X	X	X	Centimetres	If drop more than 5% from centile line then failure to respond
Weight	X	X	X	Kilogrammes	If drop more than 5% from centile line then failure to respond
Six-Minute Walk test (6MWT)	X		X	Distance; percent change	Improvement of 25m or 10% from baseline[2]
Bleck Score	X		X	Walking ability, Distance, use of aids; change in score	Change from baseline. If fall more than 1 level, then failure to respond
PedsQL	X	X	X	Score	Change from baseline. If improvement less than MCID[3], then failure to respond
Age 18+ (adults)					

[1] Hilliard ME et al. (2013) Identification of Minimal Clinically Important Difference Scores of the PedsQL in Children, Adolescents, and Young Adults With Type 1 and Type 2 Diabetes. Diabetes care 36: 1891–1897.
[2] Tomazos I et al. (2016) Determination of the Minimal Clinically Important Difference in the Six-Minute Walk Test for Patients with Hypophosphatasia. Abstract 033116 presented at ESPE.
[3] Hilliard ME et al. (2013) (see footnote 1).

Required assessments of response	Baseline	3 months	6 monthly	Measures	Response at 12 months vs. baseline
EQ-5D-5L	X	X	X	Score	Change from baseline. If improvement less than 0.15, then failure to respond
Brief Pain Inventory	X	X	X	Score	Change from baseline. If improvement less than 2 points, then failure to respond
Bleck Score	X		X	Walking ability, Distance, use of aids; change in score scale	Change from baseline. If fall more than 1 level, then failure to respond
6MWT	X		X	Distance; percent change	Improvement of 25m or 10% from baseline[4]

[4] Tomazos I et al. (2016) (see footnote 2).

NHS ENGLAND (1)

ALEXION PHARMA UK LIMITED (2)

Appendix D: COMMERCIAL AGREEMENT RELATING TO THE MANAGED ACCESS AGREEMENT FOR ASFOTASE ALFA

The Commercial Agreement Appendix contains highly confidential and commercial-in-confidence information and has been redacted from the managed access agreement

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NHS ENGLAND (1)

ALEXION PHARMA UK LIMITED (2)

Appendix E: Data Collection and Sharing Appendix – Asfotase Alfa Managed Access Agreement

The Data Collection and Sharing Appendix contains commercial-in-confidence information and has been redacted from the managed access agreement

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