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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

HIGHLY SPECIALISED TECHNOLOGY EVALUATION

Asfotase alfa for treating paediatric-onset hypophosphatasia(review of HST6) [ID3927]

Evaluation Committee Meeting – 12 October 2022
1st Committee meeting

The following documents are made available to the Committee:

1. **Final Scope and Final Matrix of Consultees and Commentators**

2. **Company submission** from Alexion Pharma

3. **Clarification letters**
   - NICE request to the company for clarification on their submission
   - Company response to NICE's request for clarification

4. **Patient group, professional group and NHS organisation submission** from:
   - Metabolic Support UK (YouTube video available https://www.youtube.com/watch?v=UxjzZcywlBM
   - NHS England

5. **Expert personal perspectives** from:
   - Mel Williams – patient expert, nominated by Metabolic Support UK

6. **Evidence Review Group report – post factual accuracy check** prepared by Kleijnen Systematic Reviews

7. **EAG comment on the company's response to the EAG report**

Please note that the appendices to the company's submission and company model will be available as a separate file on NICE Docs for information only.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Highly specialised technology evaluation

Asfotase alfa for treating paediatric-onset hypophosphatasia (review of HST6) [ID3927]

Document B

Company evidence submission

June 2022

File name	Version	Contains confidential information	Date
		Yes/no	

Contents

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Abbreviations

AA	Asfotase alfa
ADHD	Attention deficit hyperactivity disorder
AE	Adverse event
ALP	Alkaline phosphatase
BAMF	Brief Assessment of Motor Function
BIA	Budget impact analysis
BMI	Body mass index
BOT-2	Bruininks-Oseretsky Test of Motor Proficiency, 2nd Edition
BPAP	Bilevel positive airway pressure
BPI-SF	Brief Pain Inventory Short Form
BSC	Best supportive care
BSID-III	Bayley Scales of Infant and Toddler Development®, 3rd Edition
CADTH	Canadian Agency for Drugs and Technologies in Health
CBT	Cognitive behavioural therapy
CDC	Centers for Disease Control and Prevention
CHAQ	Child Health Assessment Questionnaire
CHAQ-DI	Child Health Assessment Questionnaire Disability Index
CHS	
CI	Confidence interval
COVID-19	Coronavirus disease 2019
CPAP	Continuous positive airway pressure
CRD	Centre for Reviews and Dissemination
CSR	Clinical study report
DEXA	Dual energy X-ray absorptiometry
DMD	Duchenne muscular dystrophy
DSU	Decision Support Unit
EC	European Commission
EMA	European Medicines Agency
EOI	Events of interest
ERG	Evidence Review Group
ERT	Enzyme replacement therapy
ETP	Extension treatment period
GI	Gastrointestinal

GP	General practitioner
G-tube	Gastrostomy tube
GJ-tube	Gastrostomy jejunostomy tube
HAQ-DI	Health Assessment Questionnaire-Disability Index
HDU	High dependency unit
HIPS	Hypophosphatasia Impact Patient Survey
HOST	Hypophosphatasia Outcomes Study Telephone interview
HPP	hypophosphatasia
HR	Hazard ratio
HRG	
HRQL	Health-related quality of life
HST	Highly specialised technology
HTA	Health technology assessment
IAR	Injection associated reactions
ICER	Incremental cost-effectiveness ratio
ICU	Intensive care units
IQR	Interquartile range
ISR	Injection site reaction
IV	Intravenous
LEFS	Lower Extremity Functional Scale
LFU	Last follow-up
LTV	Long-term ventilation
LY	Life years
LYG	Life years gained
MAA	Managed access agreement
Max	Maximum
MCID	Minimum clinically important difference
MCS	Mental Component Summary
MIMS	Monthly Index of Medical Specialities
Min	Minimum
MRI	Magnetic resonance imaging
N/A	Not applicable
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NICU	Neonatal intensive care unit

Nobs	Number of observations/participants
NSAID	Nonsteroidal anti-inflammatory drugs
ONS	Office for National Statistics
OS	Overall survival
PAS	Patient access scheme
PCS	Physical Component Summary
PDMS-2	Peabody Developmental Motor Scales, 2nd edition
PEA	Phosphoethanolamine
PedsQL	Paediatric Quality of Life Inventory
PHQ-9	Patient Health Questionnaire-9
PICU	Paediatric intensive care unit
PK	Pharmacokinetic
PLP	Pyridoxal 5'-phosphate
PODCI	Paediatric Outcomes Data Collection Instrument
POSNA	Paediatric Orthopaedic Society of North America
PPi	Inorganic pyrophosphate
PRO	Patient reported outcome
PROMIS-29	Patient-Reported Outcomes Measurement Information System
PSA	Probabilistic sensitivity analysis
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
PTP	Primary treatment period
QALY	Quality-adjusted life year
QoL	Quality of life
RAPID3	Routine Assessment of Patient Index Data 3
RGI-C	Radiographic Global Impression of Change
RSS	Rickets Severity Score
SAE	Serious adverse events
SC	Subcutaneous
SD	Standard deviation
SE	Standard error
SEE	Standard error of the estimate
SF-10	10-item Short-Form Health Survey for Children
SF-32v2	36-item Short-Form Health Survey version 2
SL	Severity level

SLR	Systematic literature review
SmPC	Summary of product characteristics
SPPB	Short Physical Performance Battery
TEAE	Treatment-emergent adverse event
TNSALP	Tissue non-specific alkaline phosphatase
TRAE	Treatment-related adverse events
TSD	Technical Support Document
TTO	Time trade-off
TUG	Timed Up and Go
VAS	Visual analogue scale
VFS	Ventilator-free survival
WPAI-SHP	Work Productivity and Activity Impairment – Specific Health Problem
6MWT	6-Minute Walk Test
6MWTP	6-minute walk test percent of predicted

B.1. Decision problem, description of the technology and clinical care pathway

B.1.1. Decision problem

The submission covers the technology's full marketing authorisation for this indication, as summarised in Table 1.

Table 1: The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Intervention	AA	AA	N/A
Population	Patients with paediatric-onset hypophosphatasia	Patients with paediatric-onset hypophosphatasia	N/A
Comparator(s)	Best supportive care	Best supportive care	N/A
Outcomes	• Mortality • Radiographic response • Severity of rickets • Pain • Respiratory function • Craniosynostosis and intracranial pressure • Growth • Tooth loss • Cognitive development and motor skills • Adverse effects of treatment • Health-related quality of life (for patients and carers)	• Mortality • Radiographic response • Bone mineralisation • Severity of rickets • Pain • Respiratory function • Growth • Tooth loss • Cognitive development and motor skills • Adverse effects of treatment • Health-related quality of life (for patients and carers)	• Bone mineralisation added: Outcome not included in the NICE final scope document, but was included in the AA clinical trials (i.e. bone biopsy and DEXA) • Craniosynostosis and intracranial pressure removed: Outcome included in the NICE final scope document, but not measured in the AA clinical trials. This was because these outcomes are related to the underlying disease and not with a causality association with AA

Subgroups to be considered	• Patients with infantile-onset hypophosphatasia • Patients with childhood-onset hypophosphatasia	• Patients with infantile-onset hypophosphatasia • Patients with childhood-onset hypophosphatasia	• N/A
Key: AA, asfotase alfa; DEXA, dual energy X-ray absorptiometry; N/A, not applicable; NICE, National Institute for Health and Care Excellence.			

B.1.2. Description of technology being evaluated

The summary of product characteristics and the European public assessment report for asfotase alfa (AA) are provided in Appendix C.

A summary description of AA is provided in Table 2.

Table 2: Technology being evaluated

UK approved name and brand name	▼Asfotase alfa (AA; Strensiq®)
Mechanism of action	AA is a human recombinant TNSALP-Fc-deca-aspartate fusion protein ERT.[1] It is a soluble glycoprotein comprised of 2 identical polypeptide chains, each with a length of 726 amino acids made from the catalytic domain of human TNSALP, the human immunoglobulin G1 Fc domain and a deca-aspartate peptide domain used for bone targeting. AA targets the underlying causes of HPP, a deficiency of TNSALP activity, by replacing the defective enzyme and reducing the accumulation of extracellular substrates, thereby preventing or reversing bone mineralisation defects.[2-6] It reverses the pathophysiological mechanism of HPP by normalising values of PPi and PLP, restoring phosphate homeostasis and removing PPi, the inhibitor of bone mineralisation. Restoring normal TNSALP substrate activity leads to renewed bone development and improvements in rickets and growth.
Marketing authorisation/CE mark status	AA received marketing authorisation from the EMA on 28 August 2015, which has been converted to a national GB license on 1 January 2021. It is the only approved treatment for HPP and is indicated for long-term ERT in patients with paediatric-onset HPP to treat the bone manifestations of the disease.[1] A black triangle warning features in the SmPC.[1] AA is subject to additional monitoring, which will allow quick identification of new safety information.
Indications and any restriction(s) as described in the summary of product	The indication under appraisal is:

characteristics (SmPC)	'for long-term ERT in patients with paediatric-onset HPP to treat the bone manifestations of the disease'.[1]
Method of administration and dosage	2 pharmaceutical formulations of AA are approved: • 40 mg/ml solution for injection: containing 18 mg (0.45 ml), 28 mg (0.7 ml) and 40 mg (1.0 ml) • 100 mg/ml solution for injection: containing 80 mg (0.8 ml) Both strengths are a clear, slightly opalescent or opalescent, colourless to slightly yellow, aqueous solution; pH 7.4. A few small translucent or white particles may be present. The recommended dosage regimen is 2 mg/kg of body weight administered subcutaneously 3 times per week, or a dosage regimen of 1 mg/kg of body weight administered subcutaneously 6 times per week.[7] The maximum volume of medicinal product per injection should not exceed 1 ml. If more than 1 ml is required, multiple injections may be administered at the same time.[7]
Additional tests or investigations	No additional tests will be needed for selecting or monitoring patients over and above what is currently used.
List price and average cost of a course of treatment	• 18 mg/0.45 ml = £12,700.80 per 12 pack • 28 mg/0.7 ml = £19,756.80 per 12 pack • 40 mg/1 ml = £28,224.00 per 12 pack • 80 mg/0.8 ml = £56,448.00 per 12 pack • Average cost of treatment varies by patient age and weight. The model currently assumes an average cost of treatment per year (at list price) ranging from [redacted].
Patient access scheme (if applicable)	A simple discount patient access scheme has been proposed to NHS England (pending approval) offering asfotase alfa at a price equating to a [redacted] discount on the approved list price. At the proposed PAS price, asfotase alfa pack costs are as follows: • 18mg/0.45ml = £5,600.88 per 12 pack • 28mg/0.7ml = £8,712.48 per 12 pack • 40mg/1ml = £12,446.40 per 12 pack • 80mg/0.8ml = £24,892.80 per 12 pack Average cost of treatment by patient age and weight (at PAS price) as per the model ranges from [redacted]

Key: AA, asfotase alfa; EMA, European Medicines Agency; ERT, enzyme replacement therapy; HPP, hypophosphatasia; N/A, not applicable; PLP, pyridoxal 5'-phosphate; PPi, inorganic pyrophosphate; SmPC, summary of product characteristics; TNSALP, tissue non-specific alkaline phosphatase.

B.1.3. Health condition and position of the technology in the treatment pathway

B.1.3.1. Overview of HPP

Hypophosphatasia (HPP) is a rare, chronic, metabolic disease characterised by insufficient bone mineralisation, which can lead to premature death (in newborns and infants) and a range of skeletal and systemic complications.[8] In the musculoskeletal system, skeletal deformities, premature tooth loss, fractures, impaired bone healing, muscle weakness, unusual gait and chronic debilitating pain can occur.[9-19] These symptoms can lead to gross motor and cognitive developmental delays, reduced physical function, impaired mobility, the need for ambulatory assistance and the need for respiratory support.[9-11, 13-18] Additionally, patients can experience a variety of systematic complications including fatigue, failure to thrive, impaired renal function, craniosynostosis, seizures and respiratory failure in patients with infantile-onset HPP.[9-18] In those most severely affected by HPP (perinatal- and infantile-onset), mortality ranges from 50–100% within 1 year and survival beyond 1 year of age comes with significant co-morbidities with impact on patients' quality of life (QoL).[20-23]

The first clinical manifestation of HPP can occur as early as in utero or as late as in adult life, and age at onset often determines which clinical manifestations patients may experience (e.g. rickets-like features are only present in children).[16] Further details on clinical manifestations of HPP are provided in Section B.1.3.3.1.

The traditional clinical description of HPP is based on categorising the disease by age of onset:

- Perinatal-onset (onset in utero or at birth)
- Infantile-onset (onset between 0–6 months of age)
- Juvenile-onset (also referred as childhood onset; onset between 6 months to 18 years of age)
- Adult-onset (onset ≥ 18 years of age)
- Odonto-HPP (only dental clinical symptoms)

More recent studies have suggested that the traditional clinical description is limited in its utility. Studies suggest that disease description by age of symptom onset does not account for the progression of disease as patients age, the considerable overlap of symptomatology across all ages and how disease presentation changes and may accumulate over a patient's lifetime.[11, 16] The traditional clinical description does not consider that diagnosis is often delayed, which leads to underdiagnosis and creates confusion when it comes to classification.[11, 22, 24, 25] For example, adults may not have been diagnosed until adulthood despite having symptoms during childhood, which means that they have paediatric-onset HPP, whereas others may have true adult-onset HPP. Nonetheless, most publications follow this traditional clinical description when discussing patients with HPP, and the Alexion clinical programme for AA also used this to describe patients.

Paediatric-onset HPP is a rare disease that presents before the age of 18 years and includes patients with perinatal-, infantile- or juvenile-onset HPP, as shown above. Due the rarity of the disease, estimates of the prevalence and incidence for paediatric-onset HPP in England are limited. A 10-year study of 20 European countries reported an estimated birth prevalence of perinatal-/infantile-onset HPP of 1 in 300,000 live births.[26] Another study estimated an incidence of HPP of 0.8 per 1,000,000 for children under age 18 and 2.8 per 1,000,000 for children under age 1 using a survey method in 2003.[27]

After NICE approved AA in August 2017[7], Alexion initiated the UK managed access agreement (MAA) data collection that included all UK patients with HPP treated with AA.[28] As of [redacted], a total of [redacted] patients had been enrolled into the UK MAA Database and [redacted] patients had received AA treatment. Of these patients, [redacted] patients received AA treatment in England. After excluding patients who had received AA prior to MAA enrolment, the annual estimate of new perinatal- or infantile-onset patients and juvenile-onset patients observed in the MAA were approximately 2 and 5 patients, respectively.

B.1.3.2. Aetiology and pathophysiology of HPP

The underlying cause of HPP is missing or deficient tissue non-specific alkaline phosphatase (TNSALP), encoded by the *ALPL* gene.[8] Since the initial

characterisation of the *ALPL* gene in 1988, over 400 mutations have been identified, resulting in a range of TNSALP activity, with more mutations likely to be identified. These are predominantly missense mutations, which indicates a strong allelic heterogeneity in the disease.[29, 30] Some mutations decrease gene expression, while others have a dominant-negative effect.[22, 31] In a Global HPP Registry sponsored by Alexion, *ALPL* pathogenic variant analysis was performed on 172 participants.[11] Among these patients, 218 variants were reported, the majority of which were missense variants (73.9%), which confirms findings from previous publications.

In patients with HPP, loss-of-function mutations in *ALPL* cause a deficiency in TNSALP enzymatic activity, which leads to accumulation of its known substrates: inorganic pyrophosphate (PPi), pyridoxal 5'-phosphate (PLP) and phosphoethanolamine (PEA). This results in deficient bone mineralisation, leading to the skeletal defects and systemic complications that are characteristic of HPP.[11, 13, 16, 18] High extracellular levels of PPi inhibit bone mineralisation by blocking hydroxyapatite crystal formation.[32-34] Consequently, calcium and PPi accumulate in the bloodstream, causing disturbances in calcium/phosphate homeostasis.[24] This can disrupt bone formation and skeletal mineralisation, with secondary effects on respiratory function and muscular/rheumatologic symptoms. Dysregulation of PLP, the principal form of circulating vitamin B_6, in the central nervous system has been associated with pyridoxine-responsive seizures in the most severely affected patients.[8, 10] The clinical consequences of PEA accumulation are not currently known, but the biomarker has been used as a diagnostic marker for HPP.[35]

B.1.3.3. Burden of HPP

B.1.3.3.1. Clinical manifestations of HPP

As discussed in Section B.1.3.1, the loss or reduced functionality of *ALPL* associated with HPP has the potential to affect multiple organ systems. As such, the clinical manifestations of HPP can vary considerably between individuals and may include skeletal abnormalities, muscle weakness, ambulatory difficulties, respiratory insufficiencies such as asthma, pain, neurological, articular, renal and dental manifestations.[8, 16] The exact manifestations exhibited will vary by patient and may

change as the patient ages, depending on whether the disease manifested itself before or after 6 months of age, and on disease progression over a patient's lifetime.

Clinical manifestations can be severe across all populations and result in high mortality among patients with perinatal- and infantile-onset disease. This is primarily a result of respiratory insufficiency, but is also due to B_6-responsive seizures when the condition is left untreated.[16, 36] The variety of clinical manifestations and the rarity of HPP contribute to delays in diagnosing HPP, which often leads to initial misdiagnosis as well as underdiagnosis.[11, 22, 24, 25] Patients with paediatric-onset HPP are often misdiagnosed, with adults experiencing an average diagnostic delay of 24.5 years. This leads to ineffective disease management that may exacerbate clinical manifestations.[11]

Analysing patients in the Global HPP Registry highlighted that, for the 323 children enrolled, the most commonly affected body systems/manifestations were dental (56.0%) followed by skeletal (45.2%), muscular (34.4%) and constitutional/metabolic (34.1%).[13] For children presenting with ≥ 3 baseline signs and symptoms, the most common signs and symptoms were early loss of primary teeth (47.9%), bone deformity (46.7%), weakness (39.4%) and gross motor delay (36.4%).

Of the 398 adults with HPP enrolled in the Global HPP Registry, 213 had paediatric-onset HPP (114 treated, 99 untreated) and 141 had adult-onset HPP (2 treated and 139 untreated).[10] The most commonly affected body systems/manifestations in treated adults with paediatric-onset HPP at baseline were pain (83.3%), dental (71.9%), skeletal (65.8%), constitutional/metabolic (53.5%), and muscular (48.2%). In untreated adults with paediatric-onset HPP, the most commonly affected body systems/manifestations at baseline were dental (78.8%), pain (65.7%), skeletal (49.5%), constitutional/metabolic (32.3%), and muscular (27.3%).

As described in Section B.1.3.1, the traditional clinical description of HPP is based on categorising disease by age of onset. Even within these categories, clinical subtypes can overlap and vary, as infantile- and juvenile-onset HPP share some signs and symptoms.[11, 16] Table 3 provides an overview of the potential clinical manifestations according to the traditional clinical description of HPP.

Table 3: Overview of potential clinical manifestations by the traditional clinical description

Clinical form by time of onset	Bone signs and symptoms	Physical signs and symptoms	Dental signs
Perinatal HPP (in utero and at birth), usually lethal	• Hypomineralisation • Osteochondral spurs • Marked shortening of long bones • Rachitic chest deformities	• Respiratory complications • Hypoplastic lungs • Apnoea • Seizures	Not relevant to developmental stage
Prenatal benign HPP (in utero),	• Bowed, shortened long bones • Benign post-natal • Spontaneous improvement of skeletal defects	• Not reported	Not relevant to developmental stage
Infantile (< 6 months of age)	• Craniosynostosis • Hypomineralisation • Rachitic ribs • Hypercalciuria • Presence of open fontanelles • Non-traumatic fractures • Deformities of long bones • Short stature in adulthood	• May appear normal • Respiratory insufficiencies • Increased cranial pressure • Seizures (vitamin B_6-responsive) • Muscle weakness/hypotonia • Hypercalcaemia (irritability, poor feeding, anorexia, vomiting, hypotonia, polydipsia, hypercalciuria) • Organ calcification (e.g. nephrocalcinosis)	Premature loss of deciduous teeth

Clinical form by time of onset	Bone signs and symptoms	Physical signs and symptoms	Dental signs
Juvenile (≥ 6 months–18 years of age)	• Hypomineralisation • Short stature • Skeletal deformity • Bone pain/fractures • Rickets • Focal bone defects in long bones • Spontaneous remission of bone symptoms has been reported	• Chronic muscle pain • Waddling gait • Delayed walking • Intracranial hypertension • Failure to thrive • Secondary metabolic inflammation • Hyperprostaglandinism	• Premature loss of deciduous teeth • Premature loss of permanent teeth (in older aged children)
Adult (≥ 18 years of age)	• Stress fractures (e.g. metatarsal, tibia) • Chronic bone pain • Osteomalacia • Osteoarthritis • Recurring/pseudofractures of femur • Chondrocalcinosis	• Chronic muscle and joint pain • Muscle weakness • Arthropathy with or without chondrocalcinosis • Enthesopathy • Impaired ambulation • Foot pain • Thigh pain	• Dental history may reveal premature loss of deciduous teeth • Severe caries • Premature loss of permanent teeth
Odonto-HPP (any age)	Loss of alveolar bone	Biochemical markers similar to those with mild HPP	• Exfoliation (incisors) • Reduced dentin thickness • Enlarged tooth pulp chambers • Dental caries

Key: HPP, hypophosphatasia.
Sources: Conti et al. 2017[8] ; Schmidt et al. 2017[37]; Whyte et al. 2017.[38]

B.1.3.3.1.1. Perinatal-onset HPP

In the traditional clinical description, perinatal-onset HPP comprises 2 subtypes: perinatal lethal or prenatal benign.[8] The perinatal benign form is extremely rare and usually accounts for less than 10% of perinatal-onset HPP cases.[39]

Perinatal lethal HPP is the most extreme form of the disease and often leads to stillbirth or death, typically within 1 year of life.[20-22] A retrospective, multinational chart review reported a median time from birth to death of 8.9 months (95% confidence interval [CI] 5.1–14.1) and a probability of death of 31% and 58% at 3 and 12 months, respectively.[21] Patients with this subtype exhibit skeletal hypomineralisation, osteochondral spurs, respiratory insufficiencies, shortened limbs, seizures, pulmonary hypoplasia and rachitic chest deformities.[20, 22, 29, 40]

By contrast, patients with the prenatal benign form typically also exhibit short and bowed limbs. However, bone mineralisation can be closer to normal and spontaneous improvements of skeletal defects may occur, especially during the third trimester. These infants may present at birth with a milder, non-lethal form of HPP.[29] One such case was described by Pauli et al. where a second trimester foetus exhibited limb shortness, mild skull hypomineralisation and angulated long bones, prompting an initial diagnosis of osteogenesis imperfecta.[41] However, biochemical confirmation of HPP, spontaneous improvement in long-bone angulation observed in the third trimester and a benign course after birth (including the lack of bone fractures, minimal osteopenia and a fully intact skull) led to the diagnosis of prenatal benign HPP.

B.1.3.3.1.2. Infantile-onset HPP

Patients with infantile-onset HPP, defined by the presentation of HPP within the first 6 months of life, may appear normal at birth, then begin to exhibit skeletal abnormalities and failure to thrive.[22] Patients may exhibit respiratory insufficiencies due to rachitic deformities of the chest. Other signs may include premature craniosynostosis, widespread demineralisation and rachitic changes in the metaphyses, and hypercalcaemia.[22, 40] Patients may also suffer from non-traumatic fracture and exhibit

HPP rickets, delayed motor movement and muscle weakness. Respiratory failure secondary to hypomineralisation of the chest is the most common cause of death in infants with HPP. Mortality rates, usually due to pulmonary complications and respiratory failure, ranges from 50–100% in the first year of life.[20, 22, 23]

B.1.3.3.1.3. Juvenile-onset HPP

Juvenile-onset HPP occurs between the ages of 6 months and 18 years, but generally presents with premature exfoliation of the deciduous teeth (before 5 years of age).[22, 42] Clinical presentation may include severe bone deformities and hypomineralisation that may require corrective surgery and impact physical function as well as QoL.[40, 43] In a retrospective chart review, children and adults with juvenile-onset HPP experienced morbidity without any changes in rickets or height Z-score through childhood and early adolescence.[43] In children with juvenile-onset HPP, radiographs of long bones often reveal focal bony defects projecting from the growth plates into the metaphysis, sometimes described as 'tongues' of radiolucency.[8, 22] Physeal widening, irregularities in the provisional zones of calcification or growth plates, and metaphyseal flaring with areas of radiolucency adjacent to areas of osteosclerosis may also be present. Craniosynostosis is also observed in some patients, and is associated with severe complications such as increased intracranial pressure, proptosis, cerebral damage and cranial malformation. Rachitic deformities, including beading of the costochondral junctions, bowed legs (i.e. 'knock knees'), and enlargement of the wrists, knees, and ankles from flared metaphysis, are common, and some patients exhibit short stature.[22] In addition, these patients may have delayed and/or abnormal walking and muscle weakness, especially in the proximal muscles of the lower extremities.[13, 22, 40] Skeletal pain and stiffness may also be present and non-traumatic fractures often occur.

Analysing patients in the Global HPP Registry highlighted that, for the 323 children enrolled, the most commonly reported clinical manifestations were early loss of primary teeth (49.2%), bone deformity (30%), failure to thrive (21.1%) and weakness (20.7%).[13] Disease presentation varies greatly in children, demonstrating that the signs and symptoms experienced by this group differs across individuals.

B.1.3.3.1.4. Adults with paediatric-onset HPP

Adults with paediatric-onset HPP generally suffer from similar HPP-related symptoms as adults with adult-onset HPP, and report a range of bone and systemic complications.[10, 15, 18]

For adults with paediatric-onset HPP, the types of manifestations experienced during childhood were often different to those experienced during adulthood, suggesting that the disease evolves over time. A retrospective chart review of 30 adults with paediatric-onset HPP found that the most common manifestations during childhood were dental (70%), skeletal (67%), muscular (37%), neurological (33%), rheumatological (30%) and developmental (23%).[44] In the same 30 patients, skeletal manifestations were most common (90%), followed by dental (77%), neurological (73%), muscular (57%) and developmental (43%) in adulthood.[44] Generally, a higher proportion of patients experienced multiple HPP manifestations in adulthood than in childhood, providing evidence that the disease burden of patients with HPP increases over their lifetime. The use of assistive devices was more frequent during adulthood compared with childhood (37% versus 10%, respectively), as well as receiving orthopaedic therapy (60% versus 20%, respectively). Assistive devices were primarily used during adulthood due to problems with pain (55%), balance (46%) and fatigue (36%).

Analysing patients in the Global HPP Registry highlighted that, for the 231 adult patients with paediatric-onset HPP, the most commonly reported clinical manifestations in treated patients at baseline were chronic bone pain (65.8%), generalised body pain (57.9%), recurrent and poorly healing fractures/pseudofractures (53.5%), early loss of primary teeth (47.4%), chronic muscle pain (46.5%) and fatigue (46.5%).[10] The most commonly reported clinical manifestations in untreated patients at baseline were early loss of primary teeth (58.6%), chronic bone pain (45.5%) and generalised body pain (40.4%).

B.1.3.3.2. Impact of HPP on quality of life

Given the different phenotypes of HPP and the varying clinical manifestations among patients, the QoL impact differs from patient to patient. Overall, patients with HPP report

poor QoL, as disease presentation consists of varying levels of functional and mobility impairment, fatigue and pain, as well as impact on emotional status, employment, school attendance and daily living, which are aspects that are usually captured by various QoL measures.[10, 14, 18, 45-47] In addition, the symptoms of HPP and necessary accommodations (including potential home modifications, frequent hospital visits, and breathing and feeding assistance in infantile-onset HPP) may be physically, emotionally and financially demanding on caregivers.[48-50] Carer burden is discussed in more detail in Section B.1.3.3.3.

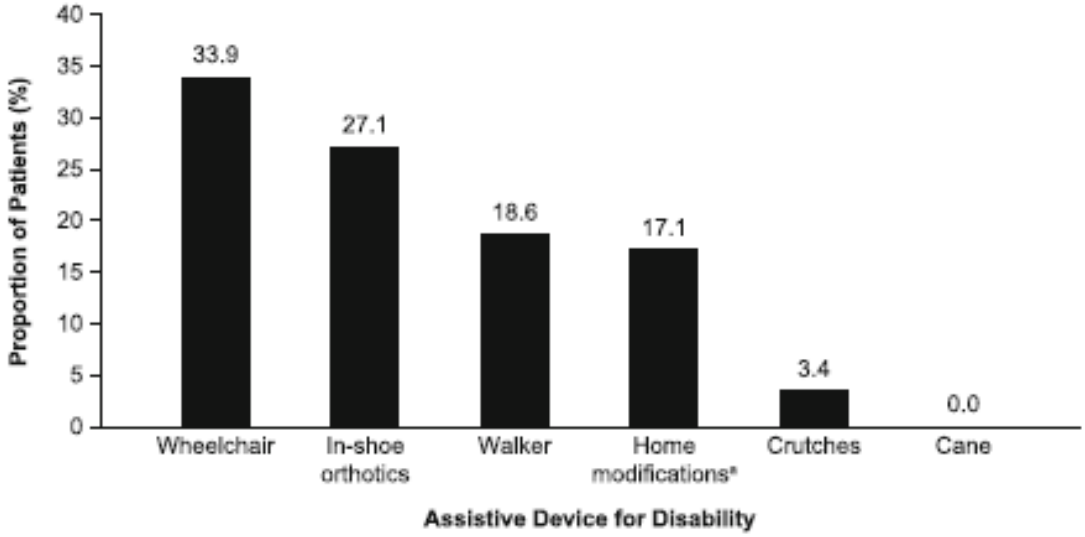
B.1.3.3.2.1. Perinatal-/infantile-onset HPP

Life with perinatal- or infantile-onset HPP is generally characterised by symptoms that lead to frequent and prolonged hospitalisation in intensive care units (ICUs). Hospitalisations are required to support and enable vital functions in patients, such as feeding, breathing and corrective surgeries (i.e. for craniosynostosis) to allow brain development and/or address skeletal deformities to allow for ambulation.[51] A study using detailed case studies and clinical expert interviews (n = 9) revealed that infant patients experienced lower QoL when on invasive ventilation (as evaluated using the EQ-5D questionnaire) compared with those who did not require ventilation assistance (score: -0.1 versus 0.2).[46]

B.1.3.3.2.2. Juvenile-onset HPP

A recent study that used patient- or caregiver-reported surveys to assess patients with juvenile-onset HPP revealed common experiences of prevalent pain (86%), muscle weakness (71%), delayed walking (59%), bowing of legs or knock knees (57%) and fractures (36%). Just over half (51%) of the children required an assistive device at some point, including a wheelchair (34%) or in-shoe orthotics (27%) (Figure 1).[14] HPP-related surgeries were also common in this population (36%), particularly skull surgeries (20.5%).

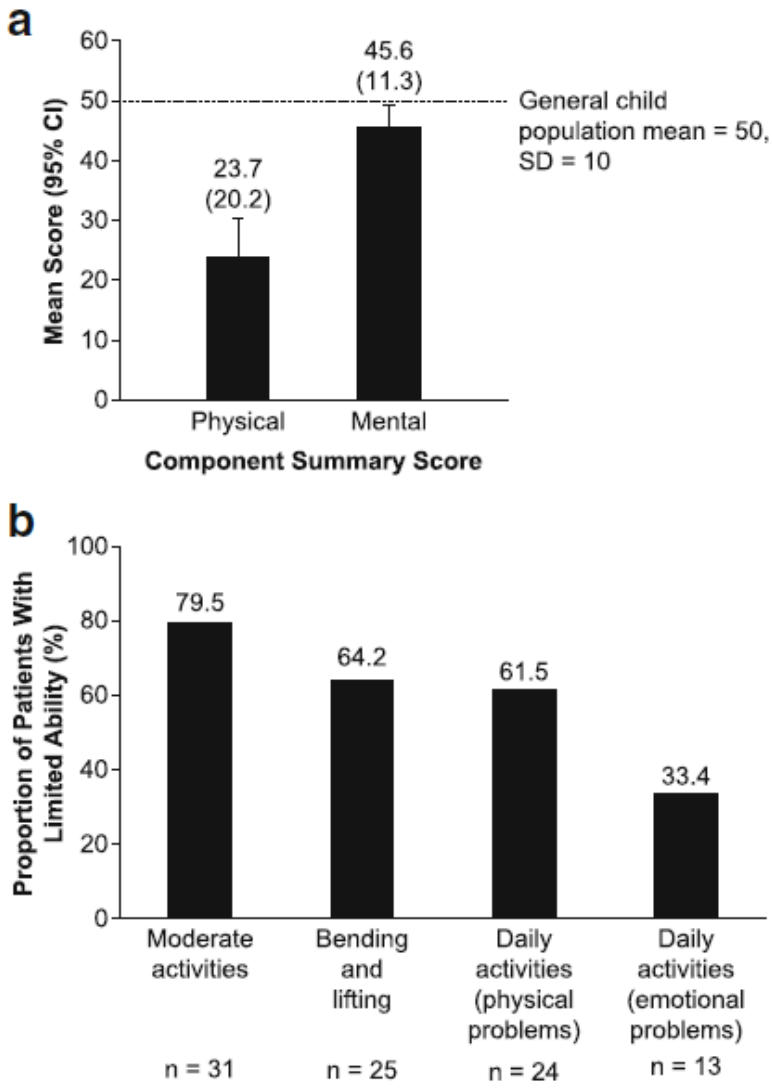
Figure 1: Proportion of patients with paediatric-onset HPP using assistive devices for disability at the time of the survey



Key: HIPS, Hypophosphatasia Impact Patient Survey; HOST, Hypophosphatasia Outcomes Study Telephone interview; HPP, hypophosphatasia.
Notes: Patients could report the use of more than 1 type of assistive device. Data presented were assessed by both HIPS and HOST unless otherwise stated (n = 59).
[a], Home modifications consisted of alterations to the kitchen, bathroom, bedroom and/or entryways. These were assessed by HIPS only (n = 44). There were 5 respondents who did not respond to this question in the survey.
Source: Rush et al. 2019.[14]

Most respondents also reported that their health impaired their physical and mental function, as measured by the 10-item Short-Form Health Survey for Children (SF-10), which was administered as part of the Hypophosphatasia Impact Patient Survey (HIPS; Figure 2a).[14] Mean (95% CI) Physical Component Summary (PCS) and Mental Component Summary (MCS) scores for paediatric-onset HPP were 23.7 (17.2, 30.3) and 45.6 (41.9, 49.3), respectively. Both of these scores were lower than the general child population mean of 50 (standard deviation [SD]: 10). 79.5% of the HIPS respondents reported that they were limited in their ability to undertake moderate activities (such as standing from a sitting position and walking); 64.2% were limited when bending and lifting; and 61.5% and 33.4% were limited in their ability to perform daily activities (such as attending school) as a consequence of their physical and/or emotional challenges, respectively (Figure 2b).

Figure 2: Impact of paediatric-onset HPP on quality of life and activities of daily living at the time of the survey



Key: HIPS, Hypophosphatasia Impact Patient Survey; HOST, Hypophosphatasia Outcomes Study Telephone interview; HPP, hypophosphatasia; MCS, Mental Component Summary; PCS, Physical Component Summary; SD, standard deviation; SF-10, 10-item Short-Form Health Survey for Children.
Notes: PCS and MCS as assessed by the SF-10 (HIPS, n = 44). Mean (SD) scores are given above each bar. Self-reported (or caregiver/family member-reported) inability to perform activities of daily living (HIPS, n = 44). Information in brackets is the reason given for the specific inability. There were 5 patients (or caregivers/family members) who did not respond to this part of the HIPS.
Source: Rush et al. 2019.[14]

A study using detailed case studies and clinical expert interviews (n = 13) revealed that reduced mobility (as assessed by the 6-Minute Walk Test [6MWT]) was associated with lower QoL, as mean EQ-5D scores for children (aged 5–12 years) varied greatly,

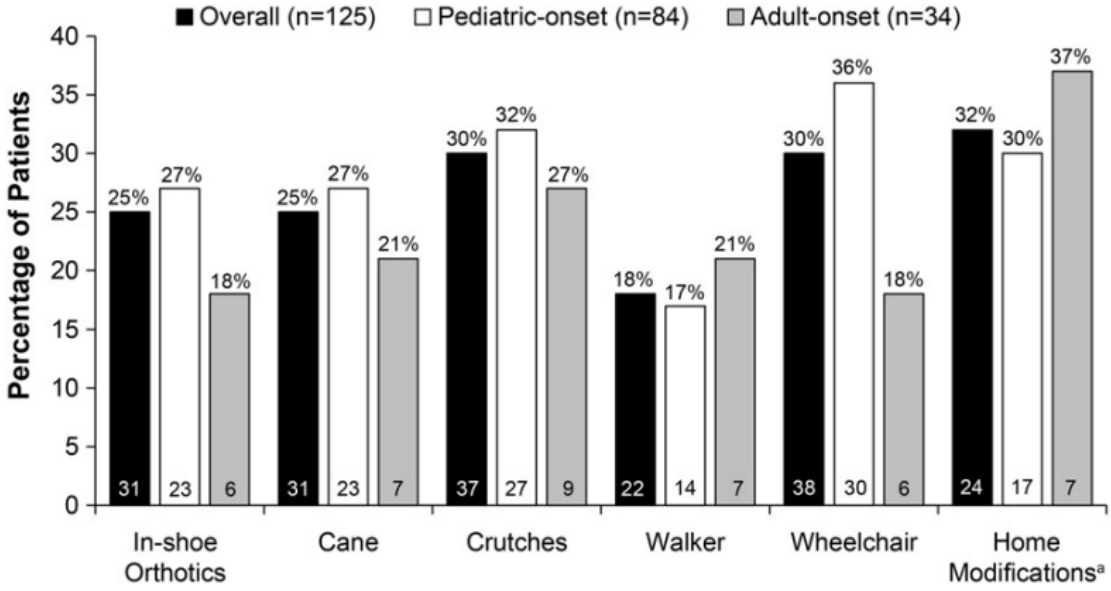
ranging from 0.838 for the highest mobility level (Level I; lowest impact on ambulation) to -0.520 for the lowest mobility level (Level IV; highest impact on ambulation).[47] The results for adolescents (13–17 years) were similar to those observed in children, with mean EQ-5D scores ranging from 0.860 (Level I; lowest impact on ambulation) to -0.523 (Level IV; highest impact on ambulation).

A cross-sectional survey-based study conducted in the US included 30 patients with juvenile-onset HPP revealed that clinically significant behavioural health challenges were evident in 67% of children.[52] The most common behavioural findings included sleep disturbance and symptoms of attention deficit hyperactivity disorder (ADHD), each of which were observed in ≥ 50% of individuals. In addition, 29% of children experienced a higher than average level of pain interference during typical daily activities. Parent ratings of QoL indicated clinically meaningful impairment in overall QoL that were consistent with a major chronic health condition for 15 (50%) of the children with HPP. Sleep disturbance, pain interference, poor behavioural regulation, and mood/anxiety symptoms were associated with reduced physical and psychosocial QoL.

B.1.3.3.2.3. Adults with paediatric-onset HPP

Adults with paediatric-onset HPP often require assistive devices during adulthood.[18] The HIPS and the Hypophosphatasia Outcomes Study Telephone (HOST) survey (n = 84) illustrated that 86% of adult patients with paediatric-onset HPP reported difficulty with walking and 67% reported difficulty standing from a sitting position. These patients commonly required wheelchairs (36%) and crutches (32%), as well as home modifications (30%) such as alterations to the kitchen, bathroom, bedroom and/or entryways (Figure 3).

Figure 3: The proportion of patients with HPP employing adaptive strategies for disability at the time of the survey

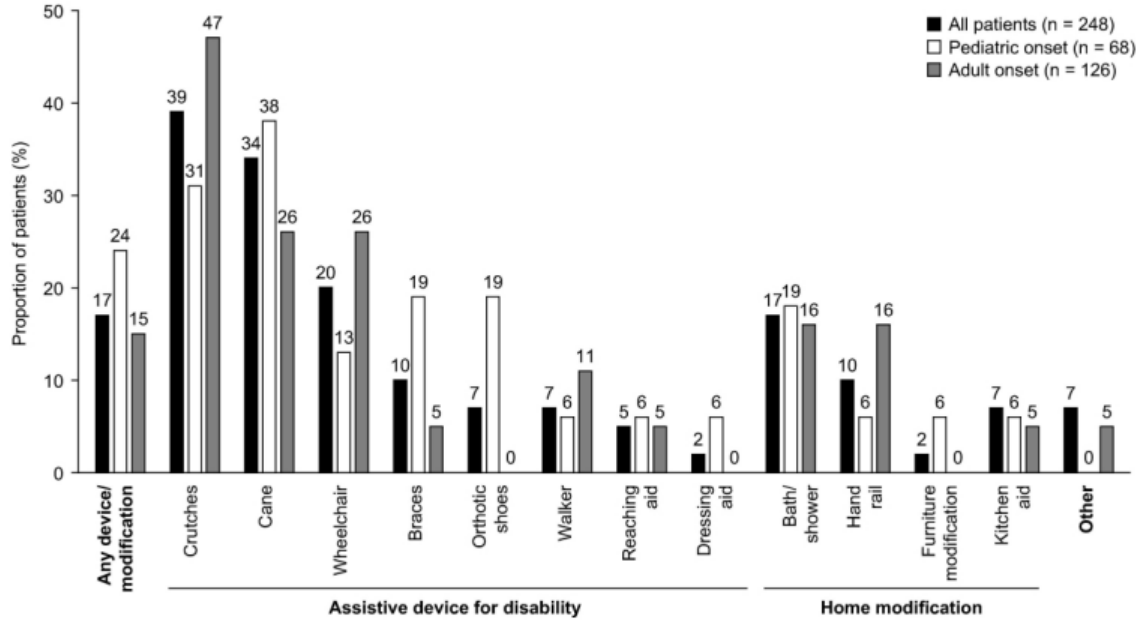


Key: HIPS, Hypophosphatasia Impact Patient Survey; HPP, hypophosphatasia.
Notes: Patients could report use of more than 1 type of adaptation. The percentage of patients in each category is given over the corresponding bar. A home modification consisted of alterations to the kitchen, bathroom, bedroom and/or entryways. Assessed on HIPS only.
Source: Weber et al. 2016.[18]

In addition, a retrospective chart review of 30 adults with paediatric-onset HPP reported that 37% used some form of assistive device.[44] In this population, the most commonly used assistive devices were canes (17%) and walkers (13%). The most common reasons for needing assistive devices were pain (55%), balance issues (46%) and fatigue (36%).

In the Global HPP Registry of adult patients with paediatric-onset HPP (n = 68), 24% of patients needed an assistive device for disability and/or home modifications (Figure 4).[15] The most frequently reported assistive devices in use were a cane (38%) and crutches (31%). Alteration to the bathroom was the most frequent home modification, reported by 19% of the paediatric-onset patients using assistive devices or home modification.

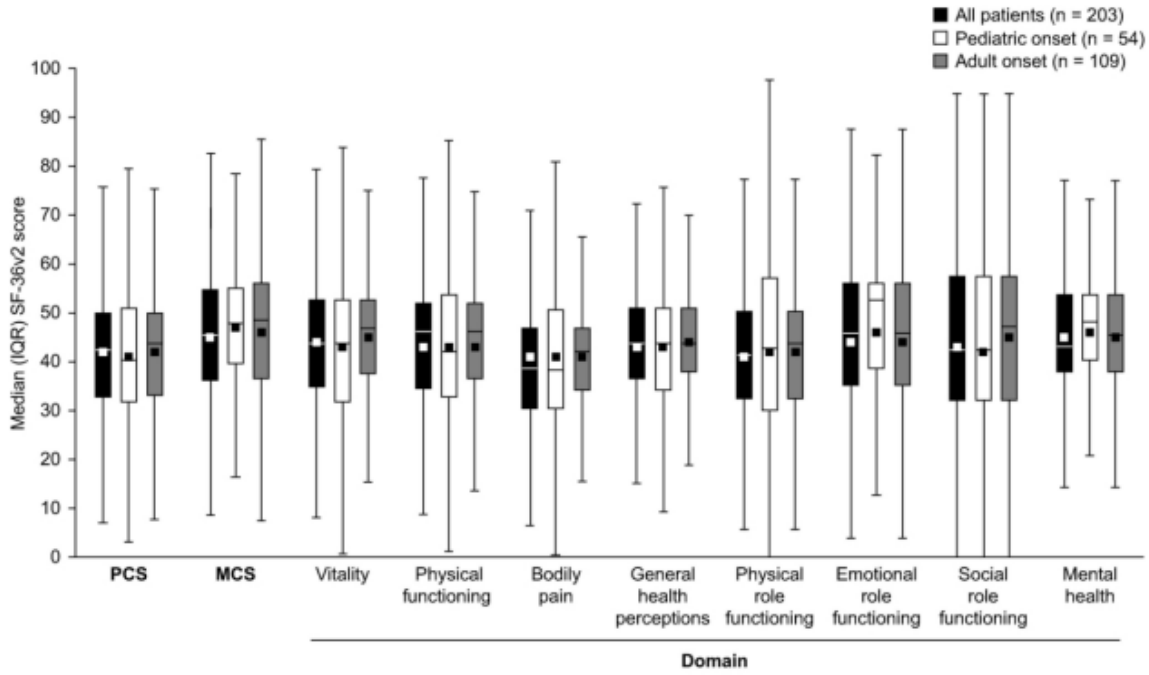
Figure 4: Proportion of study participants requiring assistive devices for disability and/or home modifications at the time of the Global HPP Registry



Key: AA, asfotase alfa; ERT, enzyme replacement therapy; HPP, hypophosphatasia.
Notes: Patients could report the use of more than 1 type of assistive device/home modification. Data are presented for assistive devices/home modifications used before registry enrolment. Patients who received ERT with AA before registry enrolment were excluded from this analysis. There was no statistical difference between the proportion of adults with paediatric- and adult-onset HPP requiring at least 1 assistive device for disability and/or home modification, as calculated using the chi-squared test ($p \geq 0.05$)
Source: Seefried et al. 2020.[15]

Of the 53 participants with available data, the mean self-reported disability score as assessed by the Health Assessment Questionnaire-Disability Index (HAQ-DI) was just over 0.5, which is higher (indicating more severe disability) than the general population mean of 0.25. In addition, more than half of patients with paediatric-onset HPP reported that their health negatively affected their physical and mental functioning, as measured by the 36-item Short-Form Health Survey version 2 (SF-36v2; Figure 5). All mean and median scores were lower (indicating worse QoL) than the general population mean of 50. Greater numbers of HPP manifestations experienced and body systems affected correlated significantly with poorer scores on the Brief Pain Inventory Short Form (BPI–SF), HAQ–DI and SF-36v2 (all $p < 0.05$).

Figure 5: Patient-reported impact of HPP on QoL using the SF-36v2



Key: HPP, hypophosphatasia; IQR, interquartile range; MCS, Mental Component Summary; PCS, Physical Component Summary; QoL, quality of life; SF-36v2, 36-item Short-Form Health Survey version 2.
Notes: PCS and MCS scores as assessed by the SF-36v2. Scale 0–100; higher scores indicate better QoL. There were no statistical differences between the mean SF-36v2 scores of adults with paediatric- and adult-onset HPP, as calculated using the t-test (all $p \geq 0.05$). The sample sizes shown are for PCS and MCS scores only; sample sizes for SF-36v2 domain scores for the overall study population, as well as patients with paediatric- and adult-onset HPP, ranged from 205 to 207, 54 to 55 and 109 to 110, respectively. Squares denote mean values.
Source: Seefried et al. 2020.[15]

In the most recent analysis of the Global HPP Registry of adult patients with paediatric-onset HPP ([redacted]), QoL assessment using the SF-36v2 showed that at baseline, adults with paediatric-onset HPP had [redacted] scores in all 8 domains (physical functioning; physical role limitations; bodily pain; general health perceptions; vitality; social functioning; emotional role limitations; and mental health) when compared with normative data from the US general population.[10]

B.1.3.3.3. Carer burden

There is currently a lack of data on caregiver burden for patients with HPP. Although patient- and caregiver-reported outcome surveys exist, the published findings focus on

patient burden.[18] While no published data report the impact on caregivers, the symptoms of HPP and necessary accommodations (including potential home modifications, frequent hospital visits, and breathing and feeding assistance in infantile-onset HPP) may be physically, emotionally and financially demanding on caregivers.[48-50]

Based on the lack of caregiver data in HPP, caregiver burden from other diseases with similar characteristics and impacts on patients could act as analogues for caregiver burden. Potential diseases that may serve as a comparison in the interim should reflect 1 or more of the following: chronic and progressive nature; genetic disorder; mobility challenges; increased need for healthcare treatment; and being potentially fatal in early presentations.

One potential disease analogue may be growth hormone deficiency or idiopathic short stature, as stature and mobility of patients may be broadly similar. In an observational study conducted in Europe, patients with these conditions and their parents completed self-reported measures of QoL.[49] Patients also completed a survey assessing psychological problems, and parents on caregiving stress. The study found that better psychosocial functioning among child patients was indirectly associated with better QoL for parents, as they reported less stress, regardless of diagnoses, treatment status and current height deviation. This study potentially provides insights into the relationship between disease severity and caregiver burden and QoL; as patient functioning improves, caregiver stress, burden and overall QoL improve too. Another potential disease analogue that may mirror some aspects of infantile- and juvenile-onset HPP is Duchenne muscular dystrophy (DMD), a rare paediatric neuromuscular disease associated with progressive muscle degeneration and extensive care needs. In a multinational, cross-sectional, observational study conducted in Germany, Italy, the UK and the US, caregiver health-related quality of life (HRQL) was assessed using the EQ-5D-3L and the SF-12.[53] Results were stratified by disease stage (early/late ambulatory/non-ambulatory) and caregivers' rating of patients' health and mental status. Half of all caregivers (383 out of 770) reported being moderately or extremely anxious or depressed, which was significantly higher than general population reference data for

individuals aged 40–49 years ($p < 0.001$ for all comparisons). Mean EQ-5D utility ranged between 0.85 (95% CI: 0.82–0.88) and 0.77 (0.74–0.80) across ambulatory classes, and 0.88 (0.85–0.90) and 0.57 (0.39–0.74) across caregivers' rating of patients' health and mental status. Compared with general population reference data for individuals aged 40–49 years, a significantly larger proportion of DMD caregivers reported having pain or discomfort (44% versus 33%, $p < 0.001$) and problems performing usual activities (18% versus 16 %, $p = 0.006$). The mean SF-12 MCS score was estimated at 44 (95% CI: 43–45), ranging between 44 (42–45) and 46 (45–48) across ambulatory classes, 48 (47–50) and 37 (35–40) across the caregivers' rating of their sons' current heath, and 46 (45–47) and 33 (26–40) across the caregivers' rating of their sons' current mental status. Mean PCS scores were within the normal range in all strata. The study showed that caring for a person with DMD was associated with impaired HRQL, suggesting that caregivers for patients with DMD should be screened for depression and emphasise the need for a holistic approach to family mental health in the context of chronic childhood disease.

B.1.3.4. Clinical guidelines

AA is the only approved treatment for HPP in the UK. It was recommended by NICE in August 2017 as an option for treating paediatric-onset HPP, only for use in people who meet the criteria for treatment within the context of the MAA.[7] Alexion is not aware of any other published NICE, National Health Service (NHS) England or other national/expert guidelines for the diagnosis, treatment or management of HPP in the UK.

One clinical practice guideline for HPP has been published based on recommendations from a Japanese task force.[54] These guidelines recommend alkaline phosphatase (ALP) enzyme replacement therapy (ERT) if patients have a definite HPP diagnosis and if they are expected to have a poor prognosis, including patients with perinatal severe (lethal) and infantile forms in which the outcomes are expected to be poor. In perinatal severe (lethal) and infantile HPP, the earliest possible initiation of ERT is recommended to improve the life prognosis. ALP ERT is also recommended to improve the motor

function of HPP patients. In addition, 1 paper containing input from 3 UK clinical experts provides monitoring guidance for patients with HPP treated with AA.[55] 2 papers highlight expert recommendations on frameworks for treatment in children and adult patient populations[56, 57], and 1 Canadian position paper provides recommendations for managing HPP based on current evidence.[58]

B.1.3.5. Clinical pathway of care

HPP is a rare, chronic, multi-systemic and heterogeneous genetic condition.[8] Because of the rarity of the condition and the variable nature of its clinical presentation, there is currently no typical pathway of care for the diagnosis, treatment, or management of patients with HPP. Consequently, the appropriate care pathway in the case of any individual patient is determined by their clinical presentation at diagnosis and the manner in which their condition progresses, which can vary between patients. NHS England have defined an interim service structure for the treatment of HPP patients in England, which includes 3 paediatric treatment centres (Sheffield, Manchester and Birmingham) and 8 adult treatment centres (Sheffield, Manchester, Birmingham, Stanmore [London], Oxford, Cambridge, Norfolk and Norwich).

B.1.3.5.1. Diagnosis

HPP can be diagnosed based on medical history, physical examination, laboratory studies and radiographic findings (Table 4). In some cases, HPP can be diagnosed through genetic testing, although not all patients with HPP will present with a detectable pathogenic or likely pathogenic variant in the *ALPL* gene.[11, 29]

As discussed in Section B.1.3.3, the variety of clinical manifestations and the rarity of HPP contribute to delays in diagnosing HPP, which often leads to initial misdiagnosis as well as underdiagnosis.[11, 22, 24, 25] Patients with paediatric-onset HPP are often misdiagnosed, with adults experiencing an average diagnostic delay of 24.5 years.[11] The delay in diagnosis leads to ineffective disease management that may exacerbate clinical manifestations, which highlights the importance of taking thorough medical histories to ensure timely diagnosis.

Table 4: Principles for diagnosis of HPP

Assessment	Observations
Medical history and clinical/physical examination	Premature loss of deciduous teeth in children and permanent teeth in adults, bone fragility, bone hypomineralisation, muscle weakness, pain, and non-traumatic and/or recurrent fractures
Radiographic findings	Osteopenia, poorly healing and non-healing stress fractures, pseudofractures, craniosynostosis in infants, and shortening, bowing and/or angulation of long bones
Laboratory tests	Total serum ALP activity adjusted for sex and age is persistently low in all forms of HPP. Other laboratory tests may be informative (PLP, PEA, PPi).
Genetic testing	Genetic testing for a variant in the *ALPL* gene may be used to confirm HPP, although testing positive for a mutation is not required for diagnosis.
Key: ALP, alkaline phosphatase; HPP, hypophosphatasia; PEA, phosphoethanolamine; PLP, pyridoxal 5'-phosphate; PPi, inorganic pyrophosphatase. **Notes**: Some observations presented here are observed across most HPP populations. All possible observations differ between age of assessment. **Source:** Rockman-Greenberg et al. 2013[34]; Bloch-Zupan et al. 2015[42]; Mornet et al. 2018.[29]	

B.1.3.5.2. Current management of HPP

Before AA was approved, the treatment approach for HPP focused on managing signs and symptoms, orthopaedic surgery and supportive care (Table 5).[22, 29, 34, 40] Different management techniques – surgical, therapeutic and dental – were used depending on the type and severity of symptoms. These supportive measures did not address the underlying cause of the disease and thus their impact on the outcomes of the patients are minimal/limited.

AA was the first and remains the only therapeutic option approved by NICE that targets the underlying cause of disease.[7] The MAA contained strict start and stop criteria, which are presented in full in Appendix M.1. Since NICE's initial recommendation of AA in the context of the MAA, no other treatments have been approved for use in HPP. Should NICE recommend routine commissioning of AA by NHS England following this re-appraisal process, no changes to the clinical pathway of care would be expected.

Table 5: Management options for signs and symptoms of HPP

Medical condition or disease symptom	Management option(s)
Seizures	Pyridoxine
Bone, muscle and joint pain and joint swelling	Opioids, NSAIDs and steroids
Ligamentous laxity	Orthotics
Prevent or alleviate GI reflux	Anti-ulcerative treatment
Pneumonia	Antibiotics, inhaled corticosteroids, bronchodilators
Infections	Antibiotics
Failure to thrive	Percutaneous enteral nutrition (G-tubes, GJ-tubes), parenteral nutrition
Respiratory compromise	Mechanical ventilation (invasive and non-invasive), supplemental oxygen
Respiratory support	Steroids
Renal insufficiency due to nephrocalcinosis	Steroids
Hypercalcaemia	Dietary calcium restriction; calcitonin; hydration; and diuretics
Hypercalciuria	Dietary calcium restriction; calciuretics; fluid hydration; phosphorous dietary management; urinary retention of phosphorous; diuretics; dietary calcium restrictions
Rickets and osteomalacia	Surgical procedures (e.g. osteotomy, fracture fixation) repair

Key: G-tube, gastrostomy tube; GI, gastrointestinal; GJ-tube, gastrostomy jejunostomy tube; NSAIDs, nonsteroidal anti-inflammatory drugs.
Source: Rockman-Greenberg et al. 2013[34]; Simmon et al. 2013[40]; Whyte a al. 2016[22]; Mornet et al. 2018.[29]

B.1.3.5.3. Treatment goals

Treatment goals for patients with HPP depend on the age of the patient and the severity of the disease presentation. In patients most severely affected by HPP (perinatal- and infantile-onset) and where disease is life threatening, the main goal of treatment is to keep patients alive.[56, 57] Due to the variety of possible signs and symptoms of HPP, goals of treatment in patients with less severe disease are individualised for the patient and are likely to include: improving bone mineralisation; minimising risk of seizures and

respiratory complications in infants; attaining growth and developmental milestones in children; reducing the number and frequency of fractures; reducing pain; improving ambulation; improving oral health; and improving patient and caregiver QoL.[55]

Alexion convened an expert panel of physicians experienced in treating HPP to discuss approaches to treatment. This group outlined treatment goals for patients with HPP treated with AA based on the traditional age-related disease presentation of HPP, and discussions and literature reviews. This is summarised in Table 6.[55]

Table 6: Treatment goals for patients with HPP treated with AA determined by an expert panel

Perinatal/infantile (in utero to < 6 months)	Juvenile (≥ 6 months to 18 years)	Adults (≥ 18 years)
• Survival • Improved respiratory status (ventilatory support) • Skeletal improvements • Metabolic control, prevention of renal failure • Improved growth and physical development (e.g. weight gain) • Meeting developmental milestones • Treating craniosynostosis • Seizure control • Hospital discharge • Pain reduction • Oral health • Improved QoL	• Improved mobility • Skeletal improvements • Radiographic improvements (reduced tongues of radiolucency) • Improved growth • Meeting developmental milestones • Nephrocalcinosis prevention • Pain reduction • Oral health • Improved QoL	• Patients with fractures: – Improved fracture healing – Reduced fracture frequency – Reduced number/prevention of pseudofractures and insufficiency fractures – Avoidance of treatments that could cause further clinical deterioration (e.g. bisphosphonates) • Patients with and without fractures[a]: – Improved functional status – Endurance – Strength – Gait/walking – Reduced fatigue – Reduced dislocations – Improved joint issues – Reduced joint pain – Improved bone quality – Pain reduction – Oral health – Improved QoL

Key: HPP, hypophosphatasia; QoL, quality of life
Note: [a] Patients may have residual complications owing to past fractures.

Perinatal/infantile (in utero to < 6 months)	Juvenile (≥ 6 months to 18 years)	Adults (≥ 18 years)
Source: Kishnani et al. 2017.[55]		

B.1.4. Equality considerations

There is currently inequity of access to effective treatments in the UK, for patients with rare diseases such as HPP when compared with patients who have more common diseases. The current eligibility criteria under the UK MAA excludes some patients with HPP (adults, with paediatric-onset) from accessing AA, impacting equity and access to AA. In addition, if AA receives a recommendation that differentiates between patients on the basis of their age, there may be potential equality considerations given that age is a protected characteristic under UK law.

B.2. Clinical effectiveness

B.2.1. Identification and selection of relevant studies

See Appendix D for full details of the process and methods used to identify and select the clinical evidence relevant to the technology being evaluated.

B.2.2. List of relevant clinical effectiveness evidence

After NICE approved AA in August 2017, Alexion initiated the UK MAA data collection that included all UK patients with HPP treated with AA. This data collection is ongoing, with the latest data cut-off completed in [redacted].[28] Alexion has also conducted 7 clinical trials that assessed the safety and efficacy of AA. These included 1 Phase I study, 4 Phase II studies and 2 extension studies in patients with HPP aged between 1 day to 66 years of age. The 4 Phase II studies and 2 extension studies are all completed and provide long-term outcomes data following up to 7 years of treatment with AA.

Patients included in the UK MAA also had the option to have their data included in the real-world Global HPP Registry (ALX-HPP-501), initiated in 2015.[59] This study is currently ongoing and includes both AA-treated (ever-treated) and non-AA-treated (never-treated) patients. is the Global HPP Registry is designed to collect data on HPP epidemiology, disease history, clinical course, symptoms and burden of disease from patients of all ages who have a diagnosis of HPP and to evaluate the safety and effectiveness in patients who have/are receiving treatment with AA. In 2018, Alexion also supported, as an internal collaboration study the real-world Evaluate and Monitor Physical Performance of Adults Treated With Asfotase Alfa for Hypophosphatasia (EmPATHY) study. This includes adult patients (≥ 18 years) diagnosed with paediatric-onset HPP who had received AA in routine clinical practice in Germany.[60] In addition, a prospective, longitudinal telephone-based survey that is currently unpublished, has been included in the submission.[61] It includes adults (≥ 18 years) with paediatric-onset HPP and is one of the first real-world studies to report improvements in physical functioning and QoL in patients with HPP over a 6-month period.

Summaries of the UK MAA data and the long-term safety and efficacy clinical trials are provided in Table 7 and Table 8, respectively. A summary of the Global HPP Registry, EmPATHY and the prospective, longitudinal telephone-based survey are provided in Table 9. Further details of the design of all studies are provided in Section B.2.3 and Appendix M.1.

Table 7: Clinical effectiveness evidence – UK MAA

Study	UK MAA
Study design	MAA database, data collection from patients treated with AA as per the terms of the MAA
Population	Patients with paediatric-onset HPP (regardless of current age)
Treatment duration and follow-up	Up to 4 years
Intervention	AA (n = [redacted])
Comparator	N/A
Indicate if study supports application for marketing authorisation	No
Indicate if study used in the economic model	Yes
Rationale if study not used in model	N/A
Reported outcomes specified in the decision problem	• Mortality • Pain • Respiratory function • Growth • Mobility and gross motor skills • Adverse effects of treatment • Health-related quality of life (for patients and carers)
All other reported outcomes	• Mobility assessments • Fractures
Key: AA, asfotase alfa; HPP, hypophosphatasia; MAA, managed access agreement; N/A, not applicable. **Sources:** Alexion MAA interim analysis report (ASF-MAA-001) 2022.[28]	

Table 8: Clinical effectiveness evidence – Clinical studies

Study	ENB-001-08 (NCT00739505)	ENB-002-08/ENB-003-08 (NCT00744042/ NCT01205152)	ENB-010-10 (NCT01176266)	ENB-006-09/ENB-008-10	ENB-009-10 (NCT01163149)
Study design	Phase I, multicentre, multinational, open-label, dose-escalation study	Phase II, 6-month, international, multicentre, open-label study, with open-label extension study	Phase II open-label, multicentre, multinational study	Phase II, randomised, international, multicentre, dose-ranging, open-label study, with open-label extension study	Phase II, multinational, multicentre, open-label, dose-ranging, randomised concurrent control study
Population	Patients aged 18 to 80 years of age with HPP	Patients ≤ 36 months of age with infantile-onset HPP (onset of symptoms prior to 6 months of age)	Patients with perinatal-/infantile-onset HPP (onset of HPP signs/symptoms prior to 6 months of age)	Patients aged ≥ 5 and ≤ 12 years of age with HPP	Adolescent and adult patients aged 13 to 65 years with HPP
Treatment duration and follow-up	8 weeks	Up to 7 years	Up to 6 years	Up to 7 years	Up to 5 years
Intervention	AA (n = 6)	AA (n = 11)	AA (n = 69)	AA (n = 13)	AA (n = 19)
Comparator	N/A	N/A	N/A	N/A	N/A
Indicate if study supports application for marketing authorisation	Yes	Yes	Yes	Yes	Yes

Study	ENB-001-08 (NCT00739505)	ENB-002-08/ENB-003-08 (NCT00744042/ NCT01205152)	ENB-010-10 (NCT01176266)	ENB-006-09/ENB-008-10	ENB-009-10 (NCT01163149)
Indicate if study used in the economic model	No	Yes	Yes	Yes	Yes
Rationale if study not used in model	This was a small dose-finding study. Other studies provided longer-term data	N/A	N/A	N/A	N/A
Reported outcomes specified in the decision problem	• Adverse effects of treatment	• Mortality • Radiographic response • Severity of rickets • Respiratory function • Cranio-synostosis and intracranial pressure • Growth • Tooth loss • Cognitive development and motor skills • Adverse effects of treatment	• Mortality • Radiographic response • Severity of rickets • Respiratory function • Cranio-synostosis and intracranial pressure • Growth • Tooth loss • Cognitive development and motor skills • Adverse effects of treatment	• Mortality • Radiographic response • Severity of rickets • Pain • Cranio-synostosis and intracranial pressure • Growth • Cognitive development and motor skills • Adverse effects of treatment • Health-related quality of life (for patients and carers)	• Mortality • Pain • Cranio-synostosis and intracranial pressure • Growth • Cognitive development and motor skills • Adverse effects of treatment

Study	ENB-001-08 (NCT00739505)	ENB-002-08/ENB-003-08 (NCT00744042/ NCT01205152)	ENB-010-10 (NCT01176266)	ENB-006-09/ENB-008-10	ENB-009-10 (NCT01163149)
All other reported outcomes	• PK of AA given SC and IV • Bioavailability of AA given SC	N/A	N/A	• Mobility assessments	• Mobility assessments • PPi and PLP levels over time

Key: AA, asfotase alfa; HPP, hypophosphatasia; IV, intravenous; N/A, not applicable; PK, pharmacokinetic; PLP, pyridoxal 5'-phosphate; PPi, inorganic pyrophosphate; SC, subcutaneous.
Sources: Whyte et al. 2018[6]; Hofmann et al. 2019[4]; Whyte et al. 2016[3]; Kishnani et al. 2018.[2]

Table 9: Clinical effectiveness evidence – Real-world evidence studies

Study	Global HPP Registry (ALX-HPP-501)	EmPATHY study	Dahir et al. 2022
Study design	Multinational, multicentre, observational, prospective, long-term registry	Observational, retrospective chart review and prospective data collection, conducted at a single centre in Germany	Prospective, longitudinal telephone-based survey
Population	Patients of all ages with a confirmed diagnosis of HPP	Adult patients with paediatric-onset HPP, aged 19–78 years	Adult patients with paediatric-onset HPP, aged ≥ 18 years
Treatment duration and follow-up	Up to 4 years	Up to 2 years	[redacted]
Intervention(s)	Ever-treated with AA (n = [redacted])	AA (n = 21)	AA (n = [redacted])
Comparator(s)	N/A	N/A	N/A
Indicate if study supports application for marketing authorisation	No	No	No
Indicate if study used in the economic model	Yes	No	No
Rationale if study not used in model	N/A	Small German real-world evidence study, the UK MAA and Global HPP Registry provide real-world evidence in a large number of patients more relevant to UK clinical practice	The UK MAA and Global HPP Registry provide real-world evidence in a large number of patients more relevant to UK clinical practice
Reported outcomes specified in the decision problem	• Mortality • Pain • Respiratory function • Craniosynostosis and intracranial pressure • Growth • Tooth loss • Cognitive	• Pain • Cognitive development and motor skills • Adverse effects of treatment • Health-related quality of life (for patients and carers)	• Health-related quality of life (for patients and carers)

Study	Global HPP Registry (ALX-HPP-501)	EmPATHY study	Dahir et al. 2022
	development and motor skills • Adverse effects of treatment • Health-related quality of life (for patients and carers)		
All other reported outcomes	• Mobility assessments • Fractures	• Mobility assessments	• N/A
Key: AA, asfotase alfa; HPP, hypophosphatasia; N/A, not applicable. **Sources:** ALX-HPP-501 study report 2021[59]; Genest et al. 2020;[60]; Dahir et al. 2022 (data on file).[61]			

EmPATHY and the prospective, longitudinal telephone-based survey were not used to populate the economic model but are included in Sections B.2.2 to B.2.6. The results of these studies provide real-world evidence for the use of AA, but were not included in the economic model because the UK MAA and Global HPP Registry provide real-world evidence in a large number of patients more relevant to UK clinical practice.

In addition, 3 natural history/non-interventional studies are relevant to the decision problem as they provide sources of epidemiology data for AA and of historical controls for some of the interventional studies. A summary of these studies is provided in Table 10, and further details of the study design are provided in Section B.2.3.

Table 10: Clinical effectiveness evidence – natural history studies

Study	ENB-011-10 (NCT01419028)	ALX-HPP-502 (NCT02104219)	ALX-HPP-502s (NCT02235493)
Study design	Multicentre, retrospective chart review study of the natural history of patients with perinatal-/infantile-onset HPP	Multicentre, multinational, retrospective, non-interventional medical records review study of the natural history of patients with juvenile-onset HPP	Single-centre, non-interventional sub-study of ALX-HPP-502
Population	Patients of any age	Patients with juvenile-	Patients with

Study	ENB-011-10 (NCT01419028)	ALX-HPP-502 (NCT02104219)	ALX-HPP-502s (NCT02235493)
	at inclusion, but with onset of disease < 6 months of age (n = 48)	onset HPP (n = 32)	juvenile-onset HPP (n = 6)
Intervention(s)	N/A	N/A	N/A
Comparator(s)	N/A	N/A	N/A
Indicate if study supports application for marketing authorisation	Yes	Yes	Yes
Indicate if study used in the economic model	Yes	No	No
Rationale if study not used in model	N/A	ENB-011-10 provided historical control data for a larger group of patients	ENB-011-10 provided historical control data for a larger group of patients
Reported outcomes specified in the decision problem	• Mortality • Respiratory function • Craniosynostosis and intracranial pressure • Tooth loss • Cognitive development and motor skills	• Mortality • Radiographic response • Severity of rickets • Pain • Respiratory function • Craniosynostosis and intracranial pressure • Growth • Tooth loss • Cognitive development and motor skills	N/A
All other reported outcomes	• Medication histories and hospitalisations	• Fractures • Mobility assessments • PPi and PLP levels	• Mobility assessments

Key: AA, asfotase alfa; HPP, hypophosphatasia; N/A, not applicable; PLP, pyridoxal 5'-phosphate; PPi, inorganic pyrophosphate.

Sources: Whyte et al. 2019.[51]

ALX-HPP-502 and ALX-HPP-502s were not used to populate the economic model but are included in Sections B.2.2 to B.2.6. These studies were not included in the economic model because ENB-011-10 provided historical control data for a larger group of patients. These data serve as the control group for comparative analyses to patients treated with AA in studies ENB-006-09/ENB-008-10.

B.2.3. Summary of methodology of the relevant clinical effectiveness evidence

As described in Section B.2.2, the UK MAA data collection that included paediatric-onset HPP patients treated with AA is ongoing, with the latest data-cut completed in January 2022.[28] Prior to this, Alexion initiated 4 original and 2 extension studies assessing the safety and efficacy of AA. These studies are now completed and provide the long-term outcomes data following up to 7 years of treatment with AA. In addition, real-world evidence for the use of AA are available from the Global HPP Registry[59] and the EmPATHY study.[60]

Given the high level of unmet medical need in HPP, the serious morbidity and mortality risk, the potential for irrevocable harm to affected organ systems, and the absence of any alternative disease-modifying treatments, no placebo or active comparator controls were used in the clinical studies of AA. All pivotal studies were open-label in their design. However, to provide control data to use for comparative analyses of selected endpoints in ENB-002-08/ENB-003-08, ENB-010-10, and ENB-006-09/ENB-008-10, 2 retrospective, non-interventional retrospective studies and 1 sub-study were also conducted. These natural history studies were conducted to describe the natural progression of the disease; collect individual patient data regarding demographics, baseline status, concomitant therapy, and disease-related outcomes (e.g. survival, skeletal structure, deficits in mobility); and to serve as historical control populations for patients with perinatal-/infantile-onset HPP (ENB-011-10) or juvenile-onset HPP (ALX-HPP-502 and sub-study ALX-HPP-502s).

The studies are presented below in order of relevance to the decision problem. Further information on the endpoints used in the studies is provided in Section B.2.6.

Unless otherwise stated, the methodology information, efficacy outcomes and safety data are derived from the most recent clinical study report (CSR; interim or final) for the following studies:

UK MAA

- UK MAA – April 2022[28]

Clinical trials

- ENB-002-08/ENB-003-08 – June 2017[62]
- ENB-010-10 – September 2017[63]
- ENB-006-09/ENB-008-10 – March 2017[64]
- ENB-009-10 – September 2017[63]

Other real-world evidence

- ALX-HPP-501 – August 2021[59]
- EmPATHY[60]
- Dahir et al. 2022[61]
- ENB-011-10 – January 2014[65]
- ALXN-HPP-502 – November 2014
- ALXN-HPP-502s – November 2014

Summaries of the methodology and details of the demographics and baseline characteristics of the studies described above are provided in Appendix M.1.

B.2.4. Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence

A summary of the different study populations and the statistical methods used in the UK MAA, the long term AA clinical trials, the Global HPP Registry, the real-world EmPATHY study and the natural history studies included in Section B.2.3 are presented in Appendix M.1.

B.2.4.1. Patient disposition

B.2.4.1.1. UK MAA

As of the most recent analysis cut-off date ([redacted]), [redacted] participants were enrolled and entered into the UK MAA Database.[28] Of these [redacted] participants, [redacted] had received at least 1 dose of AA (Safety Population) and [redacted] had a minimum exposure of 6 months on AA (Study Population).

As of the most recent analysis cut-off date, [redacted] paediatric participants (aged < 18 years at baseline) in the Study Population completed all visits through to the [redacted].[28] For this population, the median follow-up time was [redacted] and the most recent visit as of the analysis cut-off date was at [redacted], which [redacted] paediatric participants completed.

[redacted] paediatric participants (aged < 1 year at baseline) in the Study Population completed visits through the [redacted].[28] For this population, the median follow-up time was [redacted] and the most recent visit as of the analysis cut-off date was at [redacted] participants completed.

[redacted] adult participants (aged ≥ 18 years at baseline) in the Study Population completed all visits through to the [redacted].[28] For this population, the median follow-up time was [redacted] and the most recent visit was at [redacted], which [redacted] adult participants completed. Further details of patient disposition are provided in Appendix D.2.

B.2.4.1.2. Clinical trials

B.2.4.1.2.1. ENB-002-08 and ENB-003-08

A total of 11 patients were enrolled and treated with at least 1 dose of AA.[62] The median treatment duration among the 11 patients was 2,416 days (min, max: 1, 2,743 days). 9 of the 11 patients had received at least 72 months of treatment with AA. 1 patient was discontinued from study drug and discontinued from ENB-002-08 because of injection associated reactions (IARs) during the initial intravenous (IV) AA infusion. The remaining 10 patients all completed ENB-002-08 and continued participation into the extension study ENB-003-08. 1 patient died of sepsis during

participation in ENB-002-08. The remaining 9 patients completed participation in the extension study ENB-003-08. Further details of patient disposition are provided in Appendix D.2.

B.2.4.1.2.2. ENB-010-10

A total of 69 patients were enrolled and treated with AA.[63] 60 (87%) of the enrolled patients completed the study; 9 (13%) patients died after initiating treatment with AA. 1 additional patient was consented for enrolment but died before receiving any treatment with study drug. Further details of patient disposition are provided in Appendix D.2.

B.2.4.1.2.3. ENB-006-09 and ENB-008-10

13 patients were randomised to AA treatment in ENB-006-09 at a dose of either 2 mg/kg 3 times a week (n = 6) or 3 mg/kg 3 times a week (n = 7).[64] 16 historical control patients, selected from a natural history database of patients with HPP, were also included.

A total of 12 AA-treated patients completed the 24-week treatment period in ENB-006-09.[64] 1 patient randomised to the 3 mg/kg group prematurely withdrew after completion of Week 4 for a previously planned elective surgical repair of scoliosis. All 12 patients that completed ENB-006-09 subsequently enrolled in ENB-008-10 and completed that study. Further details of patient disposition are provided in Appendix D.2.

B.2.4.1.2.4. ENB-009-10

22 patients were screened, but 3 were screen failures and were not randomised.[66] 19 patients were randomised to receive treatment at and all 19 (100.0%) patients were included in the Safety set. During the primary treatment period (PTP), all patients received their randomised treatment (or were untreated controls) according to the randomisation schedule. In the extension treatment period (ETP), all patients received treatment with AA.

5 patients (26.3%) discontinued from the study.[66] 3 patients discontinued due to withdrawn consent. Although no adverse events (AEs) were listed as causes, the 3 patients had ongoing mild or moderate injection site reaction (ISR) events related to

study drug. 1 patient discontinued due to noncompliance (Week 264) and 1 patient was discontinued (Week 264) following 2 moderate serious AEs (SAEs).

All of the patients originally randomised to AA (n = 13) during the PTP received at least 96 weeks of exposure to AA.[66] Of the 6 patients originally assigned to the control group during the PTP, all received at least 96 weeks of exposure to AA during the ETP, 5 received at least 192 weeks of exposure to AA during the ETP (1 patient withdrew after 96 weeks of exposure), and 4 patients received 240 weeks of exposure (1 patient withdrawn due to noncompliance). Further details of patient disposition are provided in Appendix D.2.

B.2.4.1.3. Other real-world evidence

B.2.4.1.3.1. ALX-HPP-501

As of the most recent analysis cut-off date ([redacted]), [redacted] patients had been enrolled in the Global HPP Registry.[59] A total of [redacted] patients were excluded and [redacted] patients were included in the Study Population. Of these patients, [redacted] were < 18 years of age and [redacted] were ≥ 18 years of age at baseline. Overall, [redacted] patients were never-treated and [redacted]patients were ever-treated with AA. Of the ever-treated patients, [redacted] initiated treatment with AA prior to enrolment and [redacted] initiated AA on or after enrolment. Further details of patient disposition are provided in Appendix D.2.

B.2.4.1.3.2. Natural history studies

The patient disposition of the non-interventional natural history studies are provided in Appendix D.2.

B.2.5. Critical appraisal of the relevant clinical effectiveness evidence

All extracted data were verified against the original source paper by a second researcher. Included randomised controlled trials were subject to a quality appraisal using the standard NICE checklist[67], and all single-arm trials and observational studies were critically appraised using the Downs and Black checklist.[68] Historical-

control studies were assessed according to the 2009 Centre for Reviews and Dissemination (CRD) guidance.[69]

The AA clinical trials were considered to be good quality studies, being conducted in accordance with Good Clinical Practice guidelines. The rest of the studies were of good quality, with all studies assessed as low risk of bias in terms of randomisation, withdrawals, outcome selection and reporting and statistical analysis. There was a high risk of bias in terms of allocation concealment and blinding with all of the studies. In terms of baseline comparability between the treatment groups, the risk of bias was low in two-thirds of the studies.

Full details of the quality assessment for each study are presented in Appendix D.3.

B.2.6. Clinical effectiveness results of the relevant studies

In this section, the most recent efficacy outcome results are presented for the UK MAA data set (analysis cut-off date: [redacted])[28], followed by final long-term outcome results for the following completed clinical trials: ENB-002-08/ENB-003-08 (last patient visit: [redacted]; extension up to 7 years)[6, 62], ENB-010-10 (last patients visit: [redacted]; extension up to 6 years)[4, 63], ENB-006-9/ENB-008-10 (last patient visit: [redacted]; extension up to 7 years)[3, 5, 64], and ENB-009-10 (last patient visit: [redacted]; extension up to 5 years).[2, 66] In addition, interim efficacy outcome results are presented for the Global HPP Registry (analysis cut-off date: [redacted])[59] and the real-world EmPATHY study.[60] Results for the 3 natural history/non-interventional studies that provide a source of historical controls (ENB-011-10, ALX-HPP-502 and ALX-HPP-502s) are presented alongside the final long-term outcome results for the completed studies where relevant.

B.2.6.1. Overall clinical efficacy summary

- AA improved overall survival (OS) from 27% to 87% compared with historical controls in a pooled analysis of patients with perinatal- and infantile-onset HPP (ENB-002-08/ENB-003-08 and ENB-010-10) after 7 years of treatment[36]
- AA markedly increased the probability of invasive ventilator-free survival (VFS) in the same pooled analysis, with VFS rates of 81% after 7 years of AA treatment compared with 25% for untreated historical controls[36]

- AA enhances growth among paediatric and adolescent HPP populations relative to healthy peers, with weight and height improvements sustained for up to 5 years[2, 4-6, 23, 59, 62-64]
- AA offers significant improvements in ambulation and gait compared with age-matched healthy peers in patients with paediatric-onset HPP, as assessed by the six-minute walk test (6MWT)[2, 5, 28, 60, 64, 66]
- AA-treated patients with perinatal- and infantile-onset HPP acquired new motor and cognitive skills, reflecting sustained functional improvements versus profound developmental delays at baseline[2, 5, 6, 28, 62, 63]
- AA offers sustained improvements in strength, running speed and agility for up to 5 years versus age-matched healthy scores across patients with paediatric-onset HPP, irrespective of age, as assessed by the Bruininks-Oseretsky Test of Motor Proficiency, 2nd Edition (BOT-2)[2, 5, 6, 62, 63]
- Treatment with AA significantly reduces pain and improves functional disability in patients with paediatric-onset HPP, with sustained improvements over the long term, as assessed by the Brief Pain Inventory Short Form (BPI-SF), Child Health Assessment Questionnaire (CHAQ), Paediatric Outcomes Data Collection Instrument (PODCI) and the HAQ-DI[2, 5, 59, 64, 66]
- Treatment with AA increases HRQL in patients with paediatric-onset HPP, as assessed by the Paediatric Quality of Life Inventory, 36-item SF-36v2 and EQ-5D-3L[28, 59, 70]

B.2.6.2. UK MAA

B.2.6.2.1. Paediatric Population

B.2.6.2.1.1. Mortality endpoints

As of the most recent analysis cut-off date ([redacted]), [redacted] of the participants in the Paediatric Population had died (n = 18).[28] [redacted]) participants were classified as the most severely affected by HPP (perinatal- and infantile-onset), as they were < 1 year of age at AA treatment initiation. Therefore, these results demonstrate that AA is a lifesaving drug for babies born with HPP.

B.2.6.2.1.2. Respiratory support

As of the analysis cut-off date, [redacted] of the treatment-experienced ([redacted] with ≥ 6 months of exposure to AA before MAA enrolment) participants in the Paediatric Population required nasal oxygen support on or after enrolment into the MAA: [redacted] required brief (ended Month [redacted]) continuous positive airway pressure (CPAP), support and [redacted] required invasive ventilation support that ended by the Month 3 visit (Table 11).[28]

As of the analysis cut-off date, [redacted] treatment-naïve (< 6 months of exposure to AA before MAA enrolment) [redacted] required brief (ended by Month [redacted]) nasal oxygen support, [redacted] treatment naïve patients required brief (both ended by Month [redacted]) CPAP support and [redacted] treatment naïve patients required brief (both ended by Month [redacted]) invasive ventilation support (Table 11).[28]

Table 11: Respirator/ventilator use at baseline and follow-up – Paediatric Population (aged ≤ 4 years)

	Treatment experienced[a] (N = [redacted])	**Treatment naïve[b] (N = [redacted])**
Participants using supplemental nasal oxygen, n/N (%)		
Registry Enrolment Month 0	[redacted]	[redacted]
Follow-up Month 3	[redacted]	[redacted]
Follow-up Month 6	[redacted]	[redacted]
Follow-up Month 12	[redacted]	[redacted]
Follow-up Month 18	[redacted]	[redacted]
Follow-up Month 24	[redacted]	[redacted]
Participants using CPAP, n/N (%)		
Registry Enrolment Month 0	[redacted]	[redacted]
Follow-up Month 3	[redacted]	[redacted]
Follow-up Month 6	[redacted]	[redacted]
Follow-up Month 12	[redacted]	[redacted]
Follow-up Month 18	[redacted]	[redacted]
Follow-up Month 24	[redacted]	[redacted]

	Treatment experienced[a] (N = [redacted])	Treatment naïve[b] (N = [redacted])
Participants using BPAP, n/N (%)		
Registry Enrolment Month 0	[redacted]	[redacted]
Follow-up Month 3	[redacted]	[redacted]
Follow-up Month 6	[redacted]	[redacted]
Follow-up Month 12	[redacted]	[redacted]
Follow-up Month 18	[redacted]	[redacted]
Follow-up Month 24	[redacted]	[redacted]
Participants using invasive ventilation, n/N (%)		
Registry Enrolment Month 0	[redacted]	[redacted]
Follow-up Month 3	[redacted]	[redacted]
Follow-up Month 6	[redacted]	[redacted]
Follow-up Month 12	[redacted]	[redacted]
Follow-up Month 18	[redacted]	[redacted]
Follow-up Month 24	[redacted]	[redacted]

Key: BPAP, bilevel positive airway pressure; CPAP, continuous positive airway pressure; MAA, managed access agreement; N, number of participants; n, number of participants in a category.
Notes: Respirator/ventilator use is collected for participants 4 years old and younger in the MAA.
[a] Treatment-experienced is defined as at least 6 months of exposure to AA before MAA enrolment.
[b] Treatment-naïve is defined as < 6 months of exposure to AA before MAA enrolment.
Source: Alexion MAA interim analysis report (ASF-MAA-001) 2022.[28]

B.2.6.2.1.3. Growth

[redacted]) participants in the Paediatric Population demonstrated [redacted] (height [Figure 6] and weight [Figure 7]) [redacted].[28] [redacted]

At baseline and Month [redacted], participants in the Paediatric Population had a median height percentile of [redacted] (min, max: [redacted]) and [redacted] (min, max: [redacted]), respectively (Figure 6).[28] From baseline to Month [redacted], a median change of [redacted] (min,

max: [redacted]) percentiles was observed for height in the Paediatric Population.

Figure 6: Height percentiles – Paediatric Population (aged < 18 years)

Key: MAA, managed access agreement; Nobs, number of observations/participants.
Notes: Only participants with both baseline and at least 1 follow-up measurement were included. See Appendix M.2 for the figure legend.
Source: Alexion MAA interim analysis report (ASF-MAA-001) 2022.[28]

At baseline and Month [redacted], participants in the Paediatric Population had a median weight percentile of [redacted] (min, max: [redacted]) and [redacted] (min, max: [redacted]), respectively (Figure 7).[28] From baseline to Month [redacted], a median change of [redacted] (min, max: [redacted]) percentiles was observed for weight in the Paediatric Population.

Figure 7: Weight percentiles – Paediatric Population (aged < 18 years)

Key: MAA, managed access agreement; Nobs, number of observations/participants.
Notes: Only participants with both baseline and at least 1 follow-up measurements were included. See Appendix M.2 for the figure legend.
Source: Alexion MAA interim analysis report (ASF-MAA-001) 2022.[28]

B.2.6.2.1.4. Motor function/functional assessments

B.2.6.2.1.4.1. Brief Assessment of Motor Function

The Brief Assessment of Motor Function (BAMF) assessments were scheduled to be completed at baseline and each subsequent visit only in participants aged 1–4 years.[28] Participants aged ≥ 5 years completed the Bleck assessment to assess their mobility. All participants who completed the BAMF assessment were < 1 year of age at treatment initiation.

At baseline and Month [redacted], the Paediatric Population (aged 1–4 years) had a median Upper Extremity BAMF score of [redacted] (min, max: [redacted]) and [redacted] (min, max: [redacted]), respectively (Figure 8).[28] A median change of [redacted] (min, max: [redacted]) in Upper Extremity BAMF score was observed from baseline to Month [redacted], [redacted]

[redacted]

[redacted][28] [redacted]

[redacted]Figure 8[redacted]

Figure 8: Brief Assessment of Motor Function, Upper Extremity Scores – Paediatric Population (aged 1 to 4 years at time of annual baseline)

Key: BAMF, Brief Assessment of Motor Function; MAA, managed access agreement; Nobs, number of observations/participants.
Notes: See Appendix M.2 for the figure legend.
Source: Alexion MAA interim analysis report (ASF-MAA-001) 2022.[28]

At baseline and Month [redacted], the Paediatric Population (aged 1 to 4 years) had a median Lower Extremity BAMF score of [redacted] (min, max: [redacted]) and [redacted] (min, max: [redacted]), respectively (Figure 9).[28] A median change of [redacted] (min, max: [redacted]) in Lower Extremity BAMF score was observed from baseline to Month [redacted]

Figure 9: Brief Assessment of Motor Function, Lower Extremity Scores – Paediatric Population (aged 1 to 4 years at time of annual baseline)

Key: BAMF, Brief Assessment of Motor Function; MAA, managed access agreement; Nobs, number of observations/participants.
Notes: See Appendix M.2 for the figure legend.
Source: Alexion MAA interim analysis report (ASF-MAA-001) 2022.[28]

B.2.6.2.1.5. Mobility assessments

B.2.6.2.1.5.1. 6-Minute Walk Test

Overall, participants aged 5 to < 18 years showed a [redacted] propensity through Month [redacted] with regards to distance walked during the 6MWT (Figure 10).[28] At baseline and Month [redacted], participants in the Paediatric Population walked for a median of [redacted] metres (min, max: [redacted]) and [redacted] metres (min, max: [redacted]), respectively. A median change of [redacted] metres (min, max: [redacted] metres) was observed from baseline to Month [redacted] in this population, which is [redacted] than the minimum clinically important difference (MCID) of 25 metres specified in the MAA. Change from baseline to Month [redacted] was [redacted] than the MCID (median: [redacted] metres [min, max: [redacted] metres]), as only [redacted] participants with a baseline assessment completed this visit due to the COVID-19 pandemic. However, once assessments were able to continue to be completed, there was a continued [redacted] trend in distance walked during the 6MWT from Month [redacted] onwards.

Figure 10: 6-Minute Walk Test, distance walked – Paediatric Population (aged 5 to < 18 years)

Key: 6MWT, 6-Minute Walk Test; MAA, managed access agreement; Nobs, number of observations/participants.
Notes: Only participants with both baseline and at least 1 follow-up 6MWT distance with a minimum of 6 months' follow-up time were included. All available percent of predicted were populated for participants meeting the 6MWT distance criteria. See Appendix M.2 for the figure legend.
Source: Alexion MAA interim analysis report (ASF-MAA-001) 2022.[28]

Participants aged 5 to < 18 years also showed a [redacted] walking ability over treatment time in terms of percent of predicted for the 6MWT (Figure 11).[28] At baseline and Month [redacted], percent of predicted for the 6MWT for participants in the Paediatric Population was [redacted] (min, max: [redacted]) and [redacted] (min, max: [redacted]), respectively. A median change of [redacted] (min, max: [redacted]) was observed from baseline to Month [redacted]. Change from baseline to Month [redacted] was [redacted] than the MCID, as only [redacted] participants with a baseline assessment completed this visit due to the COVID-19 pandemic. However, once assessments were able to continue to be completed, there was a continued [redacted] trend in percent of predicted for the 6MWT from Month [redacted] onwards (Figure 11).

Percent of predicted in these participants was [redacted] normal (< 85%) at baseline (median = [redacted] [min, max: [redacted]]) relative to their healthy peers of similar age, sex and height.[71-73] However, as this was almost [redacted] as the median percent of predicted at baseline for the Adult Population ([redacted] [min, max: [redacted]

[redacted]; Section B.2.6.2.2.2), it indicates that the paediatric population had [redacted] walking ability at baseline. The majority ([redacted]) of participants in the Paediatric Population had previous exposure to AA treatment before MAA enrolment, with a median time on treatment of [redacted] (min, max: [redacted]) years prior to MAA enrolment. These participants may have had notable [redacted] before MAA enrolment and began to [redacted]

[redacted] participants aged 5 to < 18 years had a baseline 6MWT assessment and were included in the 6MWT analysis. [redacted] did not complete this assessment at enrolment but subsequently had data collected, which were used as the baseline and to calculate change from baseline.[28] [redacted]

[redacted][28] [redacted]

Figure 11: 6-Minute Walk Test, percent of predicted – Paediatric Population (aged 5 to < 18 years)

Key: 6MWT, 6-Minute Walk Test; MAA, managed access agreement; Nobs, number of observations/participants.

Notes: Only participants who had both baseline and at least 1 follow-up assessment were included. See Appendix M.2 for the figure legend. All available percent of predicted were populated for participants meeting the 6MWT distance criteria.
Source: Alexion MAA interim analysis report (ASF-MAA-001) 2022.[28]

B.2.6.2.1.5.2. Bleck score

For the purposes of the MAA, a decrease in Bleck score of more than 1 level was used to determine whether treatment with AA was benefitting participants in the Paediatric Population.[28] Overall, the Paediatric Population aged 5 to < 18 years showed a tendency towards remaining [redacted] the optimum Bleck score of 9 (Figure 12), indicating a [redacted] (Appendix M.2). At baseline and Month [redacted], participants in the Paediatric Population had a median Bleck score of [redacted] (min, max: [redacted]) and [redacted] (min, max: [redacted]), respectively. Therefore, median Bleck scored showed a change of [redacted] (min, max: [redacted]) from baseline to Month [redacted].

Median Bleck score may have been [redacted] at baseline because [redacted] of participants ([redacted]) in this population were enrolled in an AA clinical study and/or compassionate use programme before enrolment in the MAA; therefore, they may have already been benefitting from AA treatment.[28]

Of note, the Bleck score for [redacted] from a score of [redacted] at the baseline and Month [redacted] visits to a score of [redacted] at the Month [redacted] visit.[28] However, this was likely due to [redacted] Following this [redacted] this participants bleck score [redacted] to a score of [redacted] at Month [redacted]. This was likely due to [redacted].

Figure 12: Bleck scores – Paediatric Population (aged 5 to < 18 years)

Key: MAA, managed access agreement; Nobs, number of observations/participants.
Notes: Only participants with both baseline and at least 1 follow-up assessment were included. See Appendix M.2 for the figure legend.
Source: Alexion MAA interim analysis report (ASF-MAA-001) 2022.[28]

B.2.6.2.1.5.3. Use of mobility aids

Overall, [redacted] participants in the Paediatric Population required a mobility aid at baseline (Table 12).[28] As of the analysis cut-off date, [redacted] no longer required the use of a mobility aid, and [redacted] still required the use of a mobility aid at last follow-up. However, the [redacted] who still required the use of a mobility aid [redacted].

Of the [redacted] participants in the Paediatric Population who did not require a mobility aid at baseline, [redacted] still did not require the use of a mobility aid and [redacted] did require the use of a mobility aid as of the analysis cut-off date.[28] [redacted]

Table 12: Use of mobility aids at baseline and follow-up – Paediatric Population (aged < 18 years)

	Paediatric Population (N = [redacted])
Any mobility aid use[a] at first MAA assessment[b]	[redacted]
Any mobility aid use at last follow-up	[redacted]
No mobility aid use at last follow-up	[redacted]
No mobility aid use at first MAA assessment	[redacted]
Any mobility aid use at last follow-up	[redacted]
No mobility aid use at last follow-up	[redacted]

Key: MAA, managed access agreement.
Notes: [a] Mobility aids include crutches, a cane, walker, scooter, stairlift, and wheelchair. [b] Mobility aids are collected for participants 1 year of age and older.
Source: Alexion MAA interim analysis report (ASF-MAA-001) 2022.[28]

B.2.6.2.1.6. Pain assessments

B.2.6.2.1.6.1. Analgesic use

Overall, [redacted] participants in the Paediatric Population aged 1 to < 18 years were receiving [redacted] analgesic at enrolment in the MAA (Table 13).[28] The mean number of analgesics used at enrolment in these [redacted] participants was [redacted] (SD: [redacted]).

Throughout the MAA, [redacted] participants in the Paediatric Population received [redacted] analgesic (Table 13).[28] Of these [redacted] participants, [redacted] reported that they [redacted] taking any analgesic at their most recent follow-up and the other [redacted] reported [redacted] use. The mean number of analgesics used at last follow-up in this population was [redacted] (SD = [redacted]). [redacted][28]

Table 13: Analgesic use (Paediatric Population, 1 to < 18 years at baseline)

	Paediatric Population, 1 to < 18 years at baseline (N = [redacted])[a]
Status of analgesic use, n (%)[b]	
Participants with no record of analgesics	[redacted]
Participants ever on analgesics in MAA	[redacted]
On pain medications at enrolment[c]	[redacted]
Started pain medications after enrolment	[redacted]
Stopped all analgesics at last follow-up	[redacted]
Currently using analgesics at last follow-up	[redacted]
Number of pain medications used per patient among patients using pain medications at enrolment[d]	
n	[redacted]
Mean (SD)	[redacted]
Median (min, max)	[redacted]
Number of analgesics used per participant along participants currently using pain medications at last follow-up	
n	[redacted]
Mean (SD)	[redacted]
Median (min, max)	[redacted]
Class of analgesics used among participants currently using analgesics at last follow-up	
Opioid	[redacted]
Non-opioid	[redacted]
Duration of analgesic use among participants currently using analgesics at last follow-up	
N	[redacted]
Mean (SD)	[redacted]
Median (min, max)	[redacted]

Key: MAA, managed access agreement; max, maximum; min, minimum; N, number of participants; n, number of participants in a category; SD, standard deviation.
Notes: Baseline was considered the baseline/Enrolment visit. [a] Of paediatric participants, 5 were treatment-naïve and 12 were treatment-experienced at MAA enrolment. [b] Pain medication data are collected for participants at least 1 year of age at the visit. [c] There was 1 patient <18 years at AA treatment start with unknown pain medication start date(s). [d] Patients with missing treatment start date for 1 or more pain medications in the concomitant medication log are excluded.
Source: Alexion MAA interim analysis report (ASF-MAA-001) 2022.[28]

B.2.6.2.1.7. Health-related quality-of-life assessments

B.2.6.2.1.7.1. PedsQL

For the Paediatric Population (aged > 2 years to < 18 years), QoL was measured by Paediatric Quality of Life Inventory (PedsQL™), rated by participants and/or their parents.[28] This subset of the Paediatric Population demonstrated an [redacted] from baseline to Month [redacted] in PedsQL total scores followed by an overall stable propensity through the Month [redacted] visit, as shown in Figure 13 (paediatric-reported) and Figure 14 (parent-reported).

Researchers have suggested that a PedsQL psychosocial health summary score under 40 likely indicates a child with a high level of symptoms and low QoL, a score between 40 and 70 indicates a moderate level of symptoms and QoL, and a score over 70 indicates a low level of symptoms and high QoL.[74] In this MAA, participants aged > 2 years to < 18 years had a median total PedsQL score at baseline of [redacted] (min, max: [redacted]) for parent-reported and [redacted] (min, max: [redacted]) for child-reported, [redacted].[28] As previously mentioned, [redacted]. The median change from baseline to Month [redacted] in total score was [redacted] (min, max: [redacted]; Figure 13) for paediatric-reported PedsQL and [redacted] (min, max: [redacted]; Figure 14) for parent-reported PedsQL, demonstrating an [redacted]

Of note, [redacted] participants experienced an AE unrelated to treatment that affected their responses to PedsQL interviews after Month [redacted] and could therefore undermine AA treatment benefit.[28] [redacted]

[redacted]

[redacted]

[redacted].

Figure 13: PedsQL, total paediatric-reported scores – Paediatric Population (aged > 2 years to < 18 years)

Key: MAA, managed access agreement; Nobs, number of observations/participants; PedsQL, Paediatric Quality of Life Inventory.
Notes: See Appendix M.2 for the figure legend.
Source: Alexion MAA interim analysis report (ASF-MAA-001) 2022.[28]

Figure 14: PedsQL, total parent-reported scores – Paediatric Population (aged > 2 years to < 18 years)

Key: MAA, managed access agreement; Nobs, number of observations/participants; PedsQL, Paediatric Quality of Life Inventory.
Notes: See Appendix M.2 for the figure legend.
Source: Alexion MAA interim analysis report (ASF-MAA-001) 2022.[28]

B.2.6.2.2. Adult Population

B.2.6.2.2.1. Mortality

As of the most recent analysis cut-off date ( ), participants in the Adult Population (n = 17) who were treated with AA had died.[28] However, was reported, but had never received AA and therefore the was not related to treatment (narrative is provided in Section B.2.10.1).

B.2.6.2.2.2. Mobility assessments

B.2.6.2.2.2.1. 6-Minute Walk Test

Participants in the Adult Population showed walking ability according to distance walked during 6MWT assessments over time (Figure 15).[28] At baseline and Month , participants in the Adult Population walked for a median of metres (min, max: metres) and metres (min, max:

[redacted] metres), respectively. A median change of [redacted] metres (min, max: [redacted] metres) from baseline to Month [redacted] was observed in this population, which is [redacted] than the MCID of 25 metres specified in the MAA.

As shown in Figure 15, there was [redacted] in the distance walked in the 6MWT at Month [redacted].[28] At this timepoint, [redacted].

Figure 15: 6-Minute Walk Test, distance – Adult Population (aged ≥ 18 years)

Key: 6MWT, 6-Minute Walk Test; COVID-19, coronavirus disease 2019; MAA, managed access agreement; Nobs, number of observations/participants.
Notes: Only participants with both baseline and at least 1 follow-up 6MWT with a minimum of 6 months' follow-up time were included. Assessments do not need to be consecutive (the 7 participants at Month 6 are not the 8 participants at Month 12 because of missed visits due to COVID-19); all 11 participants with baseline data have at least 1 subsequent measurement included. All available percent of predicted were populated for participants meeting the 6MWT distance criteria. The 6MWT was not performed for participants aged ≥ 18 years at Month 3. See Appendix M.2 for the figure legend.
Source: Alexion MAA interim analysis report (ASF-MAA-001) 2022.[28]

Participants in the Adult Population also showed [redacted] walking ability in terms of 6MWT percent of predicted (Figure 16).[28] At baseline and Month [redacted], participants in the Adult Population had a percent of predicted for the 6MWT of [redacted] (min, max: [redacted]) and [redacted] (min, max: [redacted]), respectively. A median change of

[redacted] (min, max: [redacted]) from baseline to Month [redacted] was observed in this population, which is [redacted] than the MCID of 10% improvement specified in the MAA. Although median percent of predicted in these adult participants remained [redacted] normal (< 85%) relative to their healthy peers of similar age, sex, and height[71-73], this observed [redacted].

Of note, [redacted][28][redacted].

Figure 16: 6-Minute Walk Test, percent of predicted – Adult Population (aged ≥ 18 years)

[redacted]

Key: 6MWT, 6-Minute Walk Test; COVID-19, coronavirus disease 2019; MAA, managed access agreement; Nobs, number of observations/participants.
Notes: Only participants with both baseline and at least 1 follow-up 6MWT with a minimum of 6 months' follow-up time were included. Assessments do not need to be consecutive (the 7 participants at Month 6 are not the 8 participants at Month 12 because of missed visits due to COVID-19); all 10 participants with baseline data have at least 1 subsequent measurement included. The 6MWT was not performed for participants aged ≥ 18 years at Month 3. See Appendix M.2 for the figure legend.
Source: Alexion MAA interim analysis report (ASF-MAA-001) 2022.[28]

B.2.6.2.2.2.2. Bleck score

For the purposes of the MAA, a decrease in Bleck score of more than 1 level was used to determine whether treatment with AA was benefitting participants in the Adult Population.[28] [redacted] participants in the Adult Population showed a [redacted] in Bleck score from baseline, and Bleck scores over time [redacted] (Figure 17). At baseline and Month [redacted], participants in the Adult Population had a median Bleck score of [redacted] (min, max: [redacted]) and [redacted] (min, max: [redacted]), respectively. Therefore, a median [redacted] from baseline of [redacted] (min, max: [redacted]) in Bleck score was observed at Month [redacted].

Figure 17: Bleck score – Adult Population (aged ≥ 18 years)

[redacted]

Key: MAA, managed access agreement; Nobs, number of observations/participants.
Notes: Only participants with both baseline and at least 1 follow-up assessment were included. Bleck score was not collected at Month 3. See Appendix M.2 for the figure legend.
Source: Alexion MAA interim analysis report (ASF-MAA-001) 2022.[28]

B.2.6.2.2.2.3. Use of mobility aids

A total of [redacted] participants in the Adult Population required the use of a mobility aid at baseline (Table 14).[28] As of the analysis cut-off date, [redacted] out of [redacted] participants no longer required the use of a mobility aid, and [redacted] out of [redacted] participants still required the use of a mobility aid at last follow-up. Of the

participants who still required the use of a mobility aid at last follow-up, [redacted]. Of the [redacted] participants who did not require the use of a mobility aid at baseline, [redacted] participants still did not require the use of a mobility aid as of the analysis cut-off date.

Table 14: Use of mobility aids at baseline and follow-up – Adult Population (aged ≥ 18 years)

	Adult Population (N = [redacted])
Any mobility aid use[a] at first MAA assessment[b]	[redacted]
Any mobility aid use at last follow-up	[redacted]
No mobility aid use at last follow-up	[redacted]
No mobility aid use at first MAA assessment	[redacted]
Any mobility aid use at last follow-up	[redacted]
No mobility aid use at last follow-up	[redacted]

Key: MAA, managed access agreement.
Notes: Baseline was considered the baseline/Enrolment visit. [a] Mobility aids include crutches, a cane, walker, scooter, stairlift, and wheelchair. [b] Mobility aids are collected for participants 1 year of age and older.
Source: Alexion MAA interim analysis report (ASF-MAA-001) 2022.[28]

B.2.6.2.2.3. Pain assessments

B.2.6.2.2.3.1. BPI-SF

For the purposes of the MAA, an improvement of less than 2 points in the BPI-SF was used to determine whether treatment with AA was benefitting participants in the Adult Population.[28] Overall, there was a [redacted] in BPI-SF scores in the Adult Population, [redacted] (Figure 18). At baseline and Month [redacted], participants in the Adult Population had a median BPI-SF score of [redacted] (min, max: [redacted]) and [redacted] (min, max: [redacted]), respectively. Participants demonstrated a median [redacted] of [redacted] (min, max: [redacted]) in their BPI-SF score at Month [redacted] relative to baseline, [redacted].

Figure 18: Brief Pain Inventory Short Form scores – Adult Population (aged ≥ 18 years)

Key: BPI, Brief Pain Inventory; MAA, managed access agreement; Nobs, number of observations/participants.
Notes: Only participants with both baseline and at least 1 follow-up assessment were included. See Appendix M.2 for the figure legend.
Source: Alexion MAA interim analysis report (ASF-MAA-001) 2022.[28]

B.2.6.2.2.3.2. Analgesic use

Overall, [redacted] participants in the Adult Population were receiving [redacted] analgesic at enrolment in the MAA (Table 15).[28] The mean number of analgesics used at enrolment in this population was [redacted] (SD: [redacted]).

[redacted] participants in the Adult Population received [redacted] analgesic during the MAA (Table 15).[28] Of these participants, [redacted] were receiving [redacted] analgesic at the time of MAA enrolment, and [redacted] started receiving [redacted] after enrolment. Overall, [redacted] participants continued to receive [redacted] analgesic as of the analysis cut-off date. The mean number of analgesics used at last follow-up in this population was [redacted] (SD: [redacted]).

[redacted]

[redacted].[28]

Table 15: Analgesic use – Adult Population (aged ≥ 18 years at baseline)

	Adult Population, ≥ 18 years at baseline (N = [redacted])[a]
Status of analgesic use, n (%)	
Participants with no record of analgesics	[redacted]
Participants ever on analgesics in MAA	[redacted]
On pain medications at enrolment[b]	[redacted]
Started pain medications after enrolment	[redacted]
Stopped all analgesics	[redacted]
Currently using analgesics at last follow-up	[redacted]
Number of pain medications used per patient among patients using pain medications at enrolment[c]	
n	[redacted]
Mean (SD)	[redacted]
Median (min, max)	[redacted]
Number of analgesics used per participant along participants currently using pain medications at last follow-up	
n	[redacted]
Mean (SD)	[redacted]
Median (min, max)	[redacted]
Class of analgesics used among participants currently using analgesics at last follow-up	
Opioid	[redacted]
Non-opioid	[redacted]
Duration of analgesic use among participants currently using analgesics at last follow-up	
n	[redacted]
Mean (SD)	[redacted]
Median (Min, Max)	[redacted]

	Adult Population, ≥ 18 years at baseline (N = [redacted])[a]
Key: MAA, managed access agreement; max, maximum; min, minimum; N, number of participants; n, number of participants in a category; SD, standard deviation. **Notes:** Baseline was considered the baseline/Enrolment visit. [a] All adult participants started treatment with AA after enrolment. [b] There were 10 patients 18 years or older at AA treatment start with unknown pain medication start date(s). [c] Patients with missing treatment start date for 1 or more pain medications in the concomitant medication log are excluded. **Source:** Alexion MAA interim analysis report (ASF-MAA-001) 2022.[28]	

B.2.6.2.2.4. Fractures

[redacted] participants in the Adult Population had ongoing fractures at the time of MAA enrolment.[28] [redacted].

As of the analysis cut-off date, [redacted] new fractures occurred following enrolment in [redacted] participants in the Adult Population (Table 16).[28] Of these, [redacted]

Table 16: Fractures – Adult Population (aged ≥ 18 years)

	Adult Population (N = [redacted])
Any new fractures after enrolment, n (%) participants / n fractures	[redacted]
Before treatment initiation	[redacted]
< 6 months after treatment initiation	[redacted]
≥ 12 months after treatment start	[redacted]

	Adult Population (N = [redacted])
Number of new fractures per participant on/after treatment initiation	
n	[redacted]
Mean (SD)	[redacted]
Median (Min, Max)	[redacted]
Location of all new fractures[a]	
Other lower extremity	[redacted]
Vertebral	[redacted]
Other	[redacted]

Key: N, number of participants; n, number of participants in a category.
Notes: [a] Fractures can occur in multiple locations per participant; participants can also experience more than 1 fracture in the same location. Baseline was considered the baseline/Enrolment visit.
Source: Alexion MAA interim analysis report (ASF-MAA-001) 2022.[28]

B.2.6.2.2.5. Health-related quality-of-life assessments

B.2.6.2.2.5.1. EQ-5D-3L

The EQ-5D-5L was administered to the participants, and EQ-5D-3L utility scores were then mapped from results of the EQ-5D-5L. For the purposes of this MAA, an improvement of more than 0.15 in EQ-5D-3L utility score was used to determine whether treatment with AA was benefitting participants in the Paediatric Population.[28]

Overall, participants in the Adult Population demonstrated EQ-5D-3L scores that indicated [redacted] compared with baseline (Figure 19).[28] EQ-5D-3L scores increased from [redacted] (min, max: [redacted]) at baseline to [redacted] (min, max: [redacted]) at Month [redacted], corresponding to a median change from baseline of [redacted] (min, max: [redacted]), [redacted].

Overall, [redacted] participants [redacted] a more than 0.15 improvement specified in the MAA as of the analysis cut-off.[28] However, various non-HPP clinical events occurred in these participants that may have had the potential to undermine treatment benefit of AA. [redacted]

[redacted]

[redacted].

Figure 19: Total EQ-5D-3L scores – Adult Population (aged ≥ 18 years)

Key: MAA, managed access agreement; Nobs, number of observations/participants.
Notes: Only participants who had both baseline and at least 1 follow-up assessment were included. Utility index scores lie on a scale on which full health has a value of 1 and dead has a value of 0. See Appendix M.2 for the figure legend.
Source: Alexion MAA interim analysis report (ASF-MAA-001) 2022.[28]

B.2.6.3. Clinical trials

B.2.6.3.1. ENB-002-08/ENB-003-08

B.2.6.3.1.1. Mortality endpoints

B.2.6.3.1.1.1. Overall survival

By the end of the study, 1 (9.1%) of the 11 patients enrolled in the study had died; [redacted].[62] The patient died during study ENB-002-08 after 7.5 months of therapy, due to septic shock (assessed as unrelated to drug treatment).[6, 62] [redacted]

[redacted].[62]

OS data for this study were also included in a published analysis that pooled these data with those from ENB-010-10.[23, 36] The pooled analysis is discussed further in Section B.2.8 in comparison with patients with infantile-onset HPP in the natural history study (ENB-011-10).[51, 65]

B.2.6.3.1.1.2. Ventilator-free survival

Overall, [redacted] of the 11 enrolled patients were included in the analysis of VFS (including CPAP, BPAP, mechanical ventilation, and death), and 6 (55%) were included in the analysis of invasive VFS (including mechanical ventilation and death).[62] Patients on respiratory support at baseline were excluded from the analysis. [redacted].

VFS data for this study were also included in a published analysis that pooled these data with those from ENB-010-10.[23, 36] The pooled analysis is discussed further in Section B.2.8 in comparison with patients with infantile-onset HPP in the natural history study (ENB-011-10).[51, 65]

B.2.6.3.1.2. Respiratory support

At baseline, 5 (45%) of 11 patients required respiratory support, with 3 (27%) requiring mechanical ventilation, 1 (9%) receiving CPAP, and 1 (9%) receiving supplemental oxygen (Table 17).[6, 62]

By Year 2, 3 (33%) of 9 patients required respiratory support, with 1 (11%) requiring mechanical ventilation and 2 (22%) receiving just supplemental oxygen.[6, 62] From 4.5 years of treatment until study end, none of the 9 patients required respiratory support (including supplemental oxygen). This represents a long-term, clinically significant improvement for the patients who initially had severe respiratory compromise.

Table 17: ENB-002-08/ENB-003-08 shifts in respiratory support over 7 years of treatment

Respiratory support type, n (%)	Pre-study history (n = 11)	Baseline (n = 11)	Week 96 (n = 9)	Week 240 (n = 9)	Last overall (n = 9)[c]
No support	[redacted]	6 (54.5)[a]	6 (66.7)	9 (100.0)	9 (100.0)
Supplemental O_2	[redacted]	0 (0.0)	2 (22.2)	0 (0.0)	0 (0.0)
CPAP	[redacted]	1 (9.1)	0 (0.0)	0 (0.0)	0 (0.0)
Mechanical ventilation (invasive)	[redacted]	3 (27.3)	1 (11.1)	0 (0.0)	0 (0.0)
BPAP	[redacted]	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Other[b]	[redacted]	1 (9.1)	0 (0.0)	0 (0.0)	0 (0.0)

Key: BPAP, bilevel positive airway pressure; CPAP, continuous positive airway pressure.
Notes: [a] The category for 'No Support' at the baseline timepoint included patients with missing data at baseline. [b] Reported as continuous O_2 via nasal cannula. [c] 1 patient was discontinued from study drug and discontinued from Study ENB-002-08, and 1 patient died of sepsis during participation in Study ENB-003-08.
Source: ENB-002-08/ENB003-08 Final CSR. 2017[62]; Whyte et al. 2019.[6]

B.2.6.3.1.3. Growth

Table 18 presents median Z-scores and change from baseline for length/height and weight over 7 years of treatment. Long-term changes in head circumference, body mass index (BMI), arm span and chest circumference were also recorded (see ENB-002-08/003-08 final CSR section 11.4.1.2.3).[62] Z-scores reflect the number of SDs each value falls from the age-/sex-matched normal mean.

Median length or height was 56.5 cm (range: 39.0–83.0) at baseline (n = 11) and 112.5 cm (88.1–123.0) at Year 7 (n = 7).[6] The median length/height Z-score was higher than at baseline from Month 6 (median -3.6 [min, max: -8.2, -1.7]) until Year 7 (median -3.0 [min, max: -8.7, -0.6]), although this value remained more than 2 SDs below the mean for healthy age-matched and sex-matched peers at all timepoints. Overall, 4 (44.0%) of 9 patients had Z-scores within the normal range at last assessment. The mean increase from baseline in length or height Z-score was statistically significant at Year 3 (1.7 [SD = [redacted]]; p = 0.0385) and Year 4.5 (1.9 [SD = [redacted]]; p = 0.0346), but not at other timepoints.

Median weight was 4.1 kg (range 2.1–9.2) at baseline (n = 11) and 19.8 kg (range 15.1–31.4) at Year 7 (n = 7).[6] Median weight Z-scores increased to within 2 SDs of

the mean for healthy age-matched and sex-matched peers at most timepoints from Year 3 (median 1.2 [min, max: -5.1, 0.4]) to Year 7 (median -0.99 [min, max: -3.7, 0.5]). The mean increase from baseline in weight Z-score was statistically significant at Year 3 (2.4 [SD = [redacted]; p = 0.0096) and Year 4.5 (2.5 [SD = [redacted]; p = 0.0074), but not at other timepoints.

Table 18: ENB 002-08/ENB 003-08 Z-scores and change from baseline in growth over 7 years of treatment

Endpoint/ parameter	Baseline (n = 11)[b]	Month 6 (n = 10)	Year 1 (n = 9)	Year 2 (n = 9)	Year 3 (n = 8)	Year 4 (n = 6)	Year 5 (n = 9)	Year 6 (n = 9)	Year 7 (n = 7)	LA (n = 10)[c]
Length/height Z-scores										
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median (min, max)	-3.72 (-9.2, -0.7)	-3.62 (-8.2, -1.8)	-2.85 (-9.2, -1.2)	-2.67 (-8.4, -1.0)	-2.33 (-8.6, -0.4)*	-2.21 (-5.0, 0.3)	-2.71 (-9.0, 0.1)	-2.47 (-8.6, -0.5)	-3.02 (-8.7, -0.6)	-2.77 (-7.8, -0.2)
Mean change from baseline, (95% CI)	-	0.18 (-0.60, 0.97)	0.62 (-0.27 to 1.52)	1.00 (-0.43 to 2.42)	1.69 (0.12, 3.25)*	1.46 (-1.98, 4.90)	1.24 (-0.79, 3.26)	1.37 (-0.44, 3.18)	0.55 (-1.62, 2.73)	1.93 (-3.2, 4.6)
Weight Z-Scores										
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median (min, max)	-3.84 (-5.4, -0.5)	-4.35 (-6.4, -1.5)	-3.30 (-6.3, -1.7)	-2.44 (-4.8, -0.9)	-1.23 (-5.1, 0.4)*	-1.55 (-3.6, -0.8)	-1.21 (-5.0, 0.2)	-1.00 (-5.6, -0.1)	-0.99 (-3.7, 0.5)	-1.28 (-3.4, 0.2)
Mean change from baseline, (95% CI)	-	-0.53 (-1.36, 0.29)	0.32 (-0.98, 1.61)	1.03 (-0.63, 2.69)	2.43 (0.80, 4.06)*	1.27 (-1.17, 3.72)	1.85 (-0.17, 3.86)	2.02 (-0.10, 4.14)	2.40 (-0.31, 5.10)	2.43 (-2.9, 5.2)

Key: CI, confidence interval; max, maximum; min, minimum; SD, standard deviation.
Notes: [a] Z-scores for weight are based on CDC 2000 growth charts. The birth to 36 months chart was used for patients from birth to 36 months of age and the 2 to 20 years chart was used for patients greater than 36 months; [b] Baseline is defined as the last value on or prior to the date of first dose of study drug in Study ENB-002-08; [c] Last Overall assessment is defined as the latest post-baseline assessment. * $p < 0.05$ for comparison with baseline.
Source: Whyte et al. 2019.[6]

B.2.6.3.1.4. Motor function/functional assessments

In this study, the Bayley Scales of Infant and Toddler Development®, 3rd Edition (BSID-III) was used to assess motor and cognitive function in patients up to 42 months of age, although in some cases it may have been administered beyond this timepoint depending on developmental age.[6, 62] In addition, the Locomotion subtest of the Peabody Developmental Motor Scales, 2nd edition (PDMS-2) was used as an assessment of gross motor skills in patients aged 43–71 months who were considered to have evaluable functional abilities and the BOT-2 Running Speed and Agility and Strength subtest was used to assess motor skills in patients 72 months of age or older.

Results from the BSID-III, PDMS-2 and BOT-2 highlight the long-term benefit of AA on motor and cognitive development in patients with infantile-onset HPP over 7 years of treatment.[6, 62] Full results for these endpoints over 7 years of treatment are provided in Appendix M.3.

B.2.6.3.1.5. Additional endpoints

Results for RGI-C and Rickets Severity Score (RSS) over 7 years of treatment are presented in Appendix M.3. Long-term data for RGI-C demonstrate that treatment with AA results in sustainable and progressive improvements in skeletal manifestations over time.[6, 62] Long-term data for RSS scores are consistent with the improvements in RGI-C findings and suggest ongoing improvements in rickets for patients receiving long-term AA therapy.

B.2.6.3.2. ENB-010-10

B.2.6.3.2.1. Mortality endpoints

B.2.6.3.2.1.1. Overall survival

By the end of the study, 9 (13%) of the 69 patients enrolled in the study had died.[4, 63] Among all 69 patients, the Kaplan–Meier estimate of the OS rate at Year 6 was 80% (Figure 20).

Figure 20: ENB-010-10 Kaplan–Meier plot of overall survival – full analysis set

Notes: Patients on respiratory support at baseline are excluded from the analysis, and patients without events are censored at the latest ventilator status assessment.
Source: ENB-010-10 Final CSR. 2017.[63]

OS for this study was also included in a published analysis that pooled these data with those from ENB-002-08/ENB-003-08.[23, 36] The pooled analysis is discussed further in Section B.2.8 in comparison with infantile-onset HPP patients in the natural history study (ENB-011-10).[51, 65]

B.2.6.3.2.1.2. Ventilator-free survival

The VFS analysis assessed the occurrence of death, CPAP, BPAP and invasive mechanical ventilation via intubation or tracheostomy.[63] 38 of the 45 patients (84%) who were not receiving respiratory support at baseline remained ventilator-free.[4, 63] The Kaplan–Meier estimate of the VFS rate at Year 6 for these patients was 84% (Figure 21).

Figure 21: ENB-010-10 Kaplan–Meier plot of ventilator-free survival – full analysis set

Notes: Patients on respiratory support at baseline are excluded from the analysis and patients without events are censored at the latest ventilator status assessment.
Source: ENB-010-10 Final CSR. 2017.[63]

VFS data for this study were also included in a published analysis that pooled these data with those from ENB-002-08/ENB-003-08.[23, 36] The pooled analysis is discussed further in Section B.2.8 in comparison with patients with infantile-onset HPP in the natural history study (ENB-011-10).[51, 65]

The invasive VFS analysis assessed the occurrence of death or mechanical ventilation via intubation or tracheostomy using the patient's respiratory support data at the time of study visits.[63] Of the 45 patients who were not on respiratory support at baseline, [redacted] patients remained invasive ventilator-free (i.e. not on any invasive mechanical ventilation) until their last known ventilator support status. The Kaplan–Meier estimates of the invasive VFS rate at [redacted] and [redacted] for these patients were [redacted] and [redacted], respectively (Figure 22).

Figure 22: ENB-010-10 Kaplan–Meier plot of invasive ventilator-free survival – full analysis set

Notes: Patients on respiratory support at baseline are excluded from the analysis and patients without events are censored at the latest ventilator status assessment.
Source: ENB-010-10 Final CSR. 2017.[63]

B.2.6.3.2.2. Respiratory support

Overall, 24 out of 69 (35%) patients required respiratory support at baseline (including invasive mechanical ventilation, CPAP, or supplemental oxygen) (Table 19).[4] Of these patients, 11 (46%) no longer required respiratory support at last assessment. Of the 45 out of 69 (65%) patients who did not require respiratory support at baseline, 38 (84%) did not require respiratory support during the entire study period and 43 (96%) did not require respiratory support at the last assessment; 1 patient was receiving supplemental oxygen at Year 4, and 1 was receiving CPAP at Month 6. 3 patients developed the need for respiratory support after baseline but were weaned before last assessment (by Month 9, Year 1.5, and Year 2.5).

Table 19: ENB-010-10 shifts in respiratory support over 6 years of treatment

Respiratory support type, n (%)	Baseline[a] (n = 69)	Week 96 (n = [redacted])	Week 192 (n = [redacted])	Week 240 (n = [redacted])	Last overall (n = 69)
No support	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Supplemental O_2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CPAP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mechanical ventilation (invasive)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BPAP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Respiratory support type, n (%)	Baseline[a] (n = 69)	Week 96 (n = [redacted])	Week 192 (n = [redacted])	Week 240 (n = [redacted])	Last overall (n = 69)
Other	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Key: BPAP, bilevel positive airway pressure; CPAP, continuous positive airway pressure.
Notes: [a] Baseline is defined as the last value on or prior to the date of first dose of study drug.
Source: ENB-010-10 Final CSR. 2017.[63]

B.2.6.3.2.3. Growth

Table 20 presents median Z-scores and change from baseline for length/height and weight over 6 years of treatment. Long-term changes in head circumference, BMI, arm span and chest circumference were also recorded (see ENB-010-10 final CSR section 11.4.1.2.5).[63] Z-scores reflect the number of SDs each value falls from the age-/sex-matched normal mean.

Length/height and weight Z-score generally improved over 6 years of treatment, reflecting improvements in growth relative to healthy peers.[4, 63] Median changes from baseline in length/height Z-scores were positive from Month 6 ([redacted] [min, max: [redacted]]) to Year 6 ([redacted] [min, max: [redacted]]), although the median remained more than 2 SDs below the mean for healthy age-matched and sex-matched peers at all timepoints expect Year 4 and Year 5. Median changes from baseline in weight Z-scores were positive from Month 6 ([redacted] [min, max: [redacted]]) to Year 6 ([redacted] [min, max: [redacted]]), and Z-scores increased to within 2 SDs of the mean for healthy age-matched and sex-matched peers from Year 2 to Year 6. Median change from baseline at last assessment was significant for both the length/height (0.5 [min, max -4.0, 4.0]; p = 0.0025) and weight (1.0 [min, max -5.0, 6.0]; p = 0.0001) Z-scores.

Table 20: ENB 010-10 height and weight Z-scores and change from baseline over 6 years of treatment

Endpoint/ parameter	Baseline[a]	Month 6	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6	Last overall
Length/height Z-scores[b]									
n									
Mean (SD)									
Median (min, max)									
Length/height Z-scores: change from baseline									
n	-								66
Mean (SD)	-								
Median (min, max)	-								0.5 (-4.0, 4.0)
Weight Z-scores[b]									
n									
Mean (SD)									
Median (min, max)									
Weight Z-scores: change from baseline									
n	-								67
Mean (SD)	-								
Median (min, max)	-								1.0 (-5.0, 6.0)

Key: Max, maximum; Min, minimum; SD, standard deviation.

Notes: [a] Baseline is defined as the last value on or prior to the date of first dose of study drug. [b] Z-scores for length/height and weight were based on CDC 2000 growth charts. The birth to 36 months chart was used for patients from birth to 36 months of age and the 2 to 20 years chart was used for patients greater than 36 months. [c] $P < 0.05$ based on Wilcoxon signed-rank test comparing median change with zero.

Source: ENB-010-10 Final CSR. 2017[63]; Hofmann et al. 2019.[4]

B.2.6.3.2.4. Motor function/functional assessments

In this study, the BSID-III was used to assess motor and cognitive function in patients up to 42 months of age, the Locomotion subtest of the PDMS-2 was used as an assessment of gross motor skills in patients aged 43–71 months who were considered to have evaluable functional abilities and the BOT-2 Running Speed and Agility and Strength subtest was used to assess motor skills in patients 72 months of age or older.[4, 63]

Results from the BSID-III, PDMS-2 and BOT-2 highlight the long-term benefit of AA on motor and cognitive development in patients with infantile-onset HPP over 6 years of treatment.[4, 63] Full results for these endpoints over 6 years of treatment are provided in Appendix M.3.

B.2.6.3.2.5. Additional endpoints

Results for RGI-C and RSS scores over 6 years of treatment are presented in Appendix M.3. Long-term data for RGI-C demonstrate that treatment with AA results in sustainable and progressive improvements in skeletal manifestations over time.[4, 63] Long-term data for RSS scores are consistent with the improvements in RGI-C findings and suggest ongoing improvements in rickets for patients receiving long-term AA therapy.

B.2.6.3.3. ENB-006-09/ENB-008-10

B.2.6.3.3.1. Growth

Table 21 presents median Z-scores and change from baseline for length/height and weight over 7 years of treatment. Long-term changes in BMI, arm span and head circumference were also recorded (see ENB-006-09/ENB-008-10 final CSR section 11.4.1.2.7[64]). Median Z-scores for length/height and weight showed sustained improvements in growth in the treated patients from Month 6 until Year 7, although both remained more than 2 SDs below the mean for healthy age-matched and sex-matched peers at all timepoints.[5] The median increase from baseline in length/height Z-score was statistically significant ($p < 0.01$) at Year 2 (median -0.78 [min, max: -6.4, 0.0) and then from Year 4 (median -0.74 [min, max: -5.9, 0.2) through Year 7 (median -0.69 [min, max: -5.4, 0.4). The median increase from baseline in

weight Z-score was statistically significant ($p < 0.01$) from Month 6 (median -0.71 [min, max: -7.7, 1.8) until Year 7 (median -0.15 [min, max: -5.4, 2.7).

Table 21: ENB-006-09/ENB-008-10 Z-scores for growth over 7 years of treatment

Endpoint/ parameter	Baseline	Month 6	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6	Year 7
Length/height Z-scores									
n	13	12	12	12	8	11	12	12	12
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median (min, max)	-1.26 (-6.6, 0)	-1.11 (-6.9, -0.1)	-1.03 (-6.9, -0.2)	-0.78 (-6.5, 0)*	-0.75 (-6.1, 0.1)	-0.74 (-5.9, 0.2)*	-0.63 (-5.8, 0.4)*	-0.67 (-5.4, 0.4)*	-0.69 (-5.4, 0.4)*
Weight Z-scores									
n	13	12	12	12	8	11	12	12	12
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median (min, max)	-1.21 (-8.2, 2.3)	-0.71 (-7.7, 1.8)*	-0.59 (-7.8, 1.9)*	-0.48 (-6.6, 2.1)*	-0.29 (-5.9, 2.0)*	-0.26 (-5.9, 2.0)*	-0.32 (-5.4, 2.2)*	-0.39 (-5.3, 2.8)*	-0.15 (-5.4, 2.7)*

Key: Max, maximum; Min, minimum; SD, standard deviation.
Notes: * P < 0.01 versus baseline, based on within-group Wilcoxon signed-rank test assessing if median change differs from 0.
Source: ENB-006-09/ENB-008-10 Final CSR. 2017[64]; Whyte et al. 2017.[5]

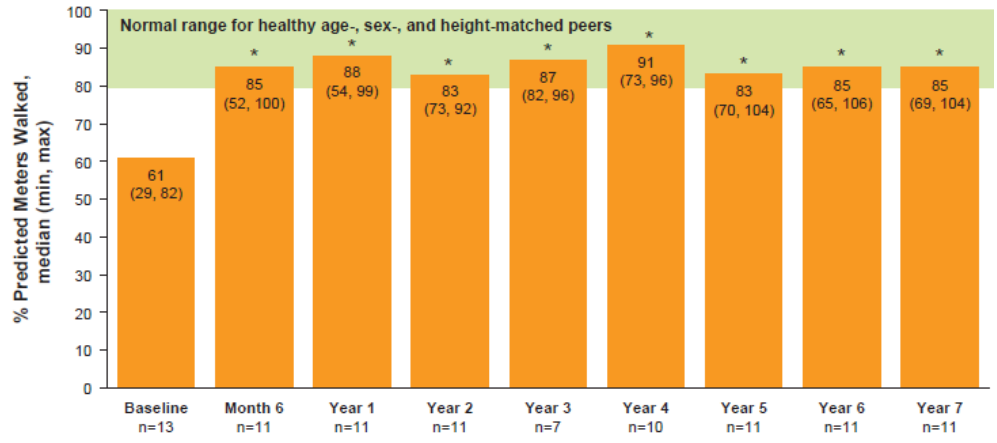
B.2.6.3.3.2. Mobility assessments

B.2.6.3.3.2.1. 6MWT

Figure 23 presents the results from baseline to Year 7 for percent of predicted for the 6MWT. The MCID for 6MWT distance walked is considered to be 25 metres and/or a 10% improvement in distance walked from baseline.[28]

All 13 patients attempted the 6MWT at baseline, and 11 patients completed the 6MWT at Year 7.[5] Improvements in ambulation were rapid and reflected significant increases in both absolute ($p < 0.0001$) and percent of predicted ($p \leq 0.001$). The median distance walked increased from [redacted] metres (min, max [redacted]) at baseline to [redacted] metres (min, max [redacted]) after 7 years of treatment, which is higher than the MCID of 25 metres. In addition, median percent of predicted increased significantly from 61% at baseline to 85% at Month 6 and was sustained at over 80% at all visits to Year 7, which is higher than the MCID of 10% improvement. These suggest a normalisation of ambulatory capacity independent of changes in age and height.

Figure 23: ENB-006-09/ENB-008-10 6MWT percent of predicted over 7 years of treatment



Key: 6MWT, 6-Minute Walk Test; Max, maximum, MCID, minimum clinically important difference; Min, minimum.
Notes: *P ≤ 0.001; P value testing whether the mean change from baseline at each visit is 0 based on a t-test. The MCID for 6MWT distance walked is considered 25 metres and/or a 10% improvement in distance walked from baseline.[28]
Source: Whyte et al. 2017.[5]

B.2.6.3.3.3. Motor function/functional assessments

The BOT-2 Running Speed and Agility and Strength subtest was used to assess motor skills in patients 72 months of age or older.[5]

As observed for the 6MWT, there was an early normalisation of mobility as assessed by the BOT-2 (6–12 months of treatment with AA) that was sustained over the 7 years of the study duration.[5] Results for this BOT-2 over 7 years of treatment are provided in Appendix M.3.

B.2.6.3.3.4. Pain and disability assessments

The CHAQ, PODCI and Paediatric Orthopaedic Society of North America (POSNA) were administered to assess post-treatment changes in parent-reported disability and pain.[64]

Results for these endpoints over 7 years of treatment are provided in Appendix M.3. These long-term data for suggests ongoing improvements in pain and disability with long-term AA therapy.[5, 64]

B.2.6.3.3.5. Additional endpoints

Results for RGI-C and RSS scores over 7 years of treatment are presented in Appendix M.3. Long-term data for RGI-C demonstrate that treatment with AA results in sustainable and progressive improvements in skeletal manifestations over time.[5, 64] Long-term data for RSS scores are consistent with the improvements in RGI-C findings and suggest ongoing improvements in rickets for patients receiving long-term AA therapy.

B.2.6.3.4. ENB-009-10

B.2.6.3.4.1. Growth

Growth was measured over time during the PTP and ETP for adolescent patients in the full analysis set. Markers for growth included measurements for length/height, weight and BMI and Z-scores were assigned to each growth marker for analysis.[66]

Table 22 presents median Z-scores and change from baseline for length/height and weight over 3 years of treatment. A total of [redacted] adolescent patients were evaluable for growth ([redacted] randomised to receive AA and [redacted] randomised to the untreated control group).[66] The adolescent patients in the AA combined group showed [redacted]. Patients originally randomised to the control group also showed [redacted]

Table 22: ENB 009-10 height and weight Z-scores and change from baseline over 3 years of treatment

Endpoint/ parameter	Baseline[a]	Month 6	Year 1	Year 2	Year 3	Last overall assessment
Length/height Z-scores						
n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median (min, max)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Length/height Z-score: change from baseline						
n	-	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	-	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median (min, max)	-	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weight Z-scores						
n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median (min, max)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weight Z-scores: change from baseline						
n	-	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	-	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median (min, max)	-	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Endpoint/ parameter	Baseline[a]	Month 6	Year 1	Year 2	Year 3	Last overall assessment
Key: AA, asfotase alfa; max, maximum; min, minimum; SD, standard deviation. **Notes:** [a] Baseline is defined as the last value on or prior to the date of first dose of AA. **Source:** ENB-009-10 Final CSR. 2017[66]; Kishnani et al. 2019.[2]						

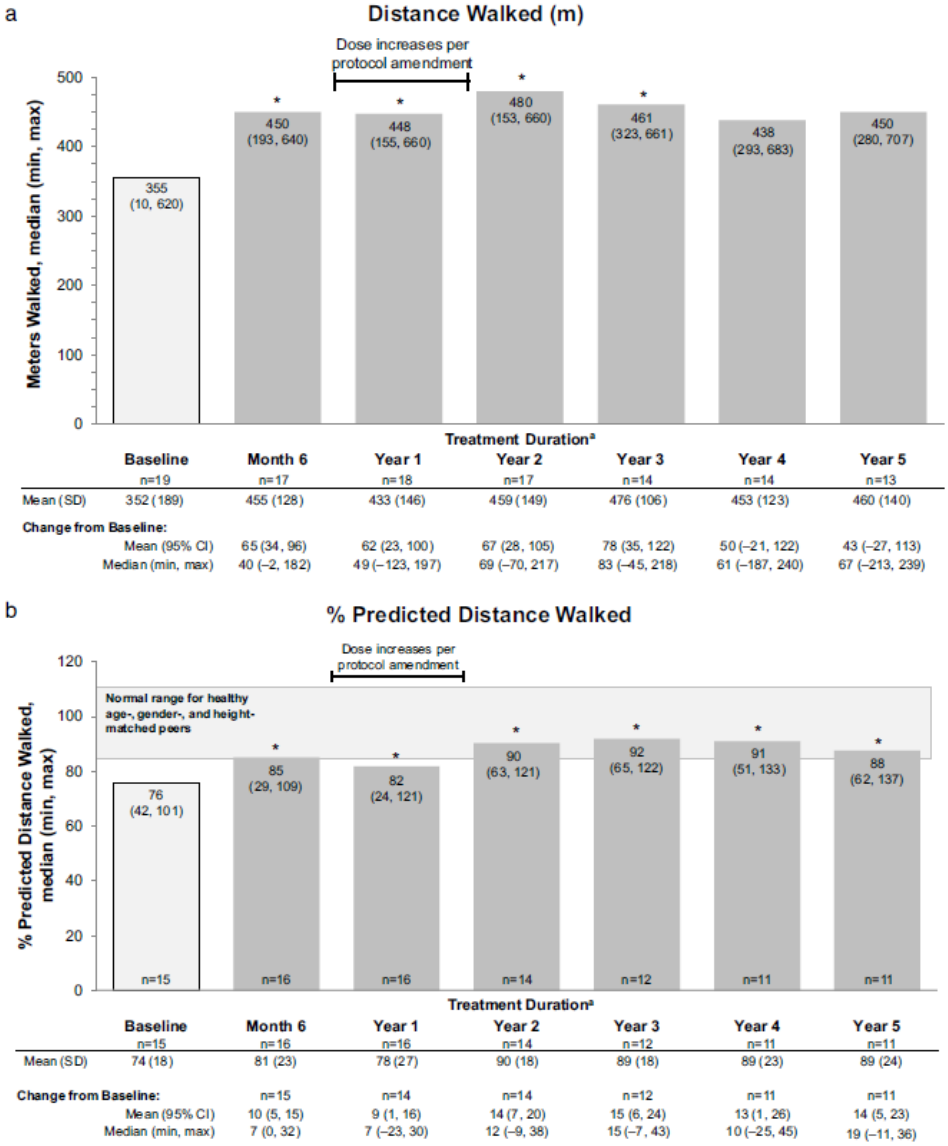
B.2.6.3.4.2. Mobility assessments

B.2.6.3.4.2.1. 6MWT

Figure 24 presents the results from baseline to Year 5 for distance walked and percent of predicted in the 6MWT. MCID for 6MWT distance walked is considered 25 metres and/or a 10% improvement in distance walked from baseline. All 19 patients attempted the 6MWT at baseline, and 13 patients completed the 6MWT at Year 5.[2] The median distance walked increased from 355 metres (min, max 10, 620; n = 19) at baseline to 450 metres (min, max 280, 707; n = 13) after 5 years of treatment, which is higher than the MCID of 25 metres. The increase from baseline was statistically significant at Month 6 and at Years 1, 2 and 3 ($p < 0.05$).

The median percent of predicted was below normal (< 84%) at baseline (76%; n = 15), but improved to within the normal range after 6 months of treatment (85%; n = 16) and was sustained at 88% (n = 11) after 5 years of treatment, which is higher than the MCID of 10% improvement.[2] The increase from baseline was statistically significant at Month 6 and Years 1, 2, 3, 4 and 5 ($p < 0.05$).

Figure 24: ENB-009-10 median distance walked and % predicted distance walked during the 6MWT over 5 years of treatment



Key: 6MWT, 6-Minute Walk Test; AA, asfotase alfa; CI, confidence interval; max, maximum; min, minimum; SD, standard deviation.
Notes: Data from primary treatment period and extension phase are combined. Of 18 AA dose increases, 14 occurred approximately at or after 1 year of treatment. The % predicted was calculated only if the patient walked the full 6 minutes. 3 patients initially assigned to the control group were not included in the % predicted analysis because they could not walk the full 6 minutes at baseline because of physical and/or cognitive impairment; 1 additional patient was not included because she was older (66 years old) than the cut-off for calculation (65 years). [a] Timepoints are from the start of treatment with AA. The control group began treatment 6 months after the treated group. Baseline for all analyses was the last assessment before the first dose of AA. * $P < 0.05$ (95% CI for mean change from baseline did not include 0).
Sources: Kishnani et al. 2019.[2]

B.2.6.3.4.2.2. Use of mobility aids

Use of assistive ambulatory devices was reported for 5 of the 19 patients who attempted the 6MWT at baseline (2 in the control group, 2 in the AA 0.3 mg/kg/day group and 1 in the AA 0.5 mg/kg/day group).[2] Following AA treatment, 1 patient initially in the control group was able to transition from a wheelchair to intermittent reliance on crutches at Year 1 and Year 1.5, but this patient was not able to perform the assessment at Year 4 because of pain. A second patient initially in the control group used a wheeled walker through Year 1.5 and with AA treatment; they did not require its use at both Year 2 and Year 2.5. However, compliance with study procedures was poor, and at both visits the assessment was not completed for the full duration. 3 patients maintained a reduction in reliance on assistive devices: 1 patient in the 0.3 mg/kg/day group used a cane for the first 2 years, and no further use was reported through Year 4.5; 1 patient in the 0.3 mg/kg/day group used a cane at baseline, and no further use of a cane was reported from Month 3 through Year 5.5; and 1 patient in the 0.5 mg/kg/day group improved from use of a wheeled walker to intermittent reliance on a cane from Year 2 through Year 6.

B.2.6.3.4.3. Motor function/Functional assessments

The BOT-2 Running Speed and Agility and Strength subtest was used to assess motor skills in patients 72 months of age or older and the Lower Extremity Functional Scale (LEFS) was used to assess lower extremity function.[2]

Results from the BOT-2 and LEFS highlight the long-term benefit of AA on motor skills and lower extremity function in patients with infantile-onset HPP over 5 years of treatment.[2] Results for these endpoints over 5 years of treatment are provided in Appendix M.3.

B.2.6.3.4.4. Pain assessments

B.2.6.3.4.4.1. BPI-SF

Table 23 presents the results for change from baseline to Year 5 for the BPI-SF. The BPI-SF consists of 11 items that use a numeric rating scale to assess pain severity (4

items) and pain interference (7 items) in the 24 hours prior to questionnaire administration. Lower pain scores are associated with less pain.[66]

At baseline, the median (min, max) BPI-SF total pain severity score was [redacted] (min, max: [redacted]) in all patients included in the ETP (n = 19).[2] BPI-SF scores improved over the ETP, with a median (min, max) decline from baseline of -1.0 (min, max: -21.0, 8.0) at Year 1 and -3.5 (min, max: -20.0, 5.0) up to 5 years of treatment.

Table 23: ENB-009-10 changes in BPI-SF over 5 years of treatment

Endpoint/ parameter	Baseline	6 months	Year 1	Year 2	Year 3	Year 4	Year 5
BPI-SF							
n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median (min, max)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BPI-SF: change from baseline							
n	-	[redacted]	19	[redacted]	[redacted]	[redacted]	16
Mean (SD)	-	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median (min, max)	-	[redacted]	-1.0 (-21.0, 8.0)	[redacted]	[redacted]	[redacted]	-3.5 (-20.0, 5.0)

Key: AA, asfotase alfa; BPI-SF; min, minimum, max, maximum. SD, standard deviation.
Notes: Baseline is defined as the last value on or prior to the date of first dose of AA. The BPI SF consists of 11 items that utilise a numeric rating scale to assess pain severity (4 items) and pain interference (7 items) in the 24 hours prior to questionnaire administration. Lower pain scores are associated with less pain.
Sources: ENB-009-10 Final CSR. 2017[66]; Kishnani et al. 2019.[2]

B.2.6.3.4.5. Additional endpoints

Changes in PPi and PLP levels from baseline through Year 5 of treatment exposure are presented in Appendix M.3. Significant ($p < 0.05$) reductions from baseline in PLP and plasma PPi concentrations were observed at 6 months of treatment and maintained through 5 years of treatment, highlighting the long term effects of AA on these substrates.[2]

B.2.6.4. Other real-world evidence

B.2.6.4.1. ALX-HPP-501

Analysis results for interim data collected in the Global HPP Registry from start date [redacted] through to the most recent data cut-off date of [redacted] are presented below.[59] As of the most recent analysis cut-off date, [redacted] patients had been enrolled in the Global HPP Registry and [redacted] patients were included in the study population. Of these patients, 402 were < 18 years at baseline and 518 were ≥ 18 years at baseline. Of the patients who were < 18 years, [redacted] had been treated with AA (ever-treated) and [redacted] patients had never received AA (never-treated). Of the patients who were ≥ 18 years, [redacted] were ever-treated and [redacted] patients were never-treated.

B.2.6.4.1.1. Respiratory support

Full details of the history of respirator/ventilator use are presented in Appendix M.3. Of the [redacted] patients aged < 18 years at baseline with data on respirator/ventilator use, [redacted] ever-treated patients and [redacted] never-treated patients had used respiratory support at any time during the study.[59] The most frequently reported respiratory support was invasive ventilation, which was reported in [redacted] ever-treated patients and [redacted] never-treated patients. Of the [redacted] ever-treated patients ever on invasive ventilation, [redacted] were currently using invasive ventilation as of the patient's last reported observation. The age reported at diagnosis was < 6 months for [redacted] patients and ≥ 6 months for [redacted]. This represents a clinically significant improvement for the patients who initially had severe respiratory compromise.

Of the [redacted] patients aged ≥ 18 years at baseline with data on respirator/ventilator use, [redacted] ever-treated patients and [redacted] never-treated patients had used respiratory support at any time during the study.[59] The most frequently reported respiratory support was CPAP/BPAP, which was reported in [redacted] ever-treated patients and [redacted] never-treated patients. Of the [redacted] ever-treated patients ever on CPAP/BPAP, [redacted] was currently using CPAP/BPAP as of the patient's last reported observation. Of the [redacted] never-treated patients ever on CPAP/BPAP, [redacted] were currently

using CPAP/BPAP as of the patient's last reported observation. As shown in Table 24, in the < 18 years and perinatal-/infantile-onset group, [redacted] ever-treated patients were ever on invasive ventilation.[59] At the last follow-up, [redacted] patients had ongoing invasive ventilation. The mean (SD) total duration of AA exposure for patients with ongoing invasive ventilation was [redacted]. A total of [redacted] patients stopped invasive ventilation after start of AA treatment; the median time on invasive ventilation after start of AA was [redacted] (min, max: [redacted]). Similar results were noted in the < 18 years at baseline group. This represents a clinically significant improvement for the patients who initially had severe respiratory compromise. [redacted] ≥ 18 years at baseline required invasive ventilation use.

Table 24: ALX-HPP-501 invasive ventilator use by duration of AA exposure in ever-treated patients (study population, global)

	< 18 years at baseline and perinatal-/infantile-onset (n = 105)	**< 18 years at baseline (n = 192)**	**≥ 18 years at baseline (n = 155)**
Patients ever on invasive ventilation at baseline, n (%)	[redacted]	[redacted]	[redacted]
Patients with ongoing invasive ventilation use at last follow-up, n (%)	[redacted]	[redacted]	[redacted]
Started prior to AA treatment start	[redacted]	[redacted]	[redacted]
Started on or after AA treatment start	[redacted]	[redacted]	[redacted]
Patients with ongoing invasive ventilation at last follow-up by respirator/ventilator follow-up time			
n	[redacted]	[redacted]	[redacted]
≥ 3 to < 6 months, n (%)	[redacted]	[redacted]	[redacted]
≥ 12 to 18 months, n (%)	[redacted]	[redacted]	[redacted]
≥ 24 months, n (%)	[redacted]	[redacted]	[redacted]
Total duration of invasive ventilation during follow-up starting at AA treatment start for patients with ongoing invasive ventilation (months)			
n	[redacted]	[redacted]	[redacted]

	< 18 years at baseline and perinatal-/infantile-onset (n = 105)	< 18 years at baseline (n = 192)	≥ 18 years at baseline (n = 155)
Mean (SD)	[redacted]	[redacted]	[redacted]
Median (min, max)	[redacted]	[redacted]	[redacted]
Total duration of invasive ventilation before AA treatment starts for patients with ongoing invasive ventilation (months)			
n	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]
Median (min, max)	[redacted]	[redacted]	[redacted]
Total duration of new invasive ventilation during follow-up (months) for patients with ongoing ventilation use			
n	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]
Median (min, max)	[redacted]	[redacted]	[redacted]
Total duration of invasive ventilation use including prior to and after AA treatment start for patients with ongoing invasive ventilation (months)			
n	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]
Median (min, max)	[redacted]	[redacted]	[redacted]
Total duration of AA exposure for patients with ongoing invasive ventilation (months)			
n	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]
Median (min, max)	[redacted]	[redacted]	[redacted]
Total duration of AA exposure in categories, n	[redacted]	[redacted]	[redacted]
≥ 3 to < 6 months, n (%)	[redacted]	[redacted]	[redacted]
≥ 6 to < 12 months, n (%)	[redacted]	[redacted]	[redacted]
≥ 18 to 24 months, n (%)	[redacted]	[redacted]	[redacted]
≥ 24 months, n (%)	[redacted]	[redacted]	[redacted]
Patients that stopped invasive ventilation after AA treatment	[redacted]	[redacted]	[redacted]

	< 18 years at baseline and perinatal-/infantile-onset (n = 105)	< 18 years at baseline (n = 192)	≥ 18 years at baseline (n = 155)
start, n (%)			
Started prior to AA treatment start, n (%)	[redacted]	[redacted]	[redacted]
Started on or after AA treatment start, n (%)	[redacted]	[redacted]	[redacted]
Total duration of invasive ventilation during follow-up (months) for patients who stopped			
n	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]
Median (min, max)	[redacted]	[redacted]	[redacted]
Total duration of AA exposure for patients who stopped invasive ventilation (months)			
n	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]
Median (min, max)	[redacted]	[redacted]	[redacted]
Patients that stopped invasive ventilation as of last follow-up by AA exposure time, n	[redacted]	[redacted]	[redacted]
< 3 months, n (%)	[redacted]	[redacted]	[redacted]
≥ 3 to < 6 months, n (%)	[redacted]	[redacted]	[redacted]
≥ 6 to < 12 months, n (%)	[redacted]	[redacted]	[redacted]
≥ 12 to 18 months, n (%)	[redacted]	[redacted]	[redacted]
≥ 24 months, n (%)	[redacted]	[redacted]	[redacted]

Key: AA, asfotase alfa; max, maximum; min, minimum; N/A, not applicable; SD, standard deviation.
Source: ALX-HPP-501 study report 2021.[59]

B.2.6.4.1.2. Growth

Growth measurements were only analysed for patients < 18 years of age at baseline.[59] Table 25 presents median Z-scores and change from baseline for length/height and weight over 4 years of treatment. Median change in height Z-score from baseline to the last assessment was [redacted] (min, max: [redacted]) for ever-treated patients and [redacted]

(min, max: [redacted]) for never-treated patients. Median change in weight Z-score from baseline to last assessment was [redacted] (min, max: [redacted]) for ever-treated patients and [redacted] (min, max: [redacted]) for never-treated patients.

The changes over 4 years reflect general improvements in growth relative to healthy, age-matched peers.[59] Height increased slightly over the course of the study for both never-treated patients and ever-treated patients. For ever-treated patients, weight decreased minimally over a period of 4 years, with a slight increase at the last assessment. Weight decreased minimally, with fluctuations over the duration of 4 years for never-treated patients (Table 25).

Table 25: ALX-HPP-501 change in growth measurements over 4 years of treatment (study population, global)

Endpoint/ parameter	< 18 years at baseline (n = 402)											
	Never-treated (n = 210)						Ever-treated (n = 192)					
	Baseline	Year 1	Year 2	Year 3	Year 4	LFU	Baseline	Year 1	Year 2	Year 3	Year 4	LFU
Height for age Z-score												
n	[redacted]											
Mean (SD)	[redacted]											
Median (min, max)	[redacted]											
Weight for age Z-score												
n	[redacted]											
Mean (SD)	[redacted]											
Median (min, max)	[redacted]											

Key: BMI, body mass index; LFU, last follow-up; max, maximum; min, minimum; SD, standard deviation.
Notes: Growth measurements were collected for patients < 18 years of age at baseline. Patients must have a baseline assessment plus at least 1 follow-up assessment ≥ 6 months after baseline assessment for inclusion in the table.
Source: ALX-HPP-501 study report 2021.[59]

B.2.6.4.1.3. Mobility assessments

B.2.6.4.1.3.1. 6MWT

Table 26 presents the results from baseline to last follow-up for distance walked and percent of predicted in the 6MWT. MCID for 6MWT distance walked is considered 25 metres and/or a 10% improvement in distance walked from baseline.

In patients aged < 18 years, the median distance walked at baseline by ever-treated patients was [redacted] metres (min, max: [redacted]), which increased by a median of [redacted] metres at last follow-up. This is higher than the 25 metre MCID, indicating [redacted] in the 6MWT.[59] The median distance walked by never-treated patients was [redacted] metres (min, max: [redacted]), which increased by a median of [redacted] metres at last follow-up. This is higher than the 25 metre MCID, suggesting improvement in the 6MWT. The distance walked and the percent of predicted improved from baseline to follow-up, at every 12-month interval over a period of 4 years, in both ever-treated and never-treated patients. The median change from baseline at last follow-up in percent of predicted was [redacted] (min, max: [redacted]) in ever-treated patients and [redacted] (min, max: [redacted]) in never-treated patients, which are both lower than the MCID of 10% improvement.

In patients aged ≥ 18 years, the median distance walked at baseline by ever-treated patients was [redacted] metres (min, max: [redacted]), which increased by a median of [redacted] metres at last follow-up. This is higher than the 25 metre MCID, indicating improvement in the 6MWT.[59] The median distance walked by never-treated patients was [redacted] metres (min, max: [redacted]), which decreased by a median of [redacted] metres at last follow-up, indicating a reduction in walking ability. The distance walked, and the percent of predicted of improved from baseline to follow-up, at every 12-month interval over a period of 4 years, in both ever-treated and never-treated patients. The median change from baseline at last follow-up in percent of predicted was [redacted] (min, max: [redacted]) in ever-treated patients and[redacted] (min, max: [redacted]) in never-treated patients. This is higher than the MCID 10% improvement, indicating improvement in the 6MWT.

The [redacted]([redacted]) of ever-treated patients initiated AA treatment before enrolling in the Global HPP Registry.[59] These patients may have had notable [redacted]

[redacted]before enrolment and may have begun to[redacted]
[redacted]Therefore, baseline data used for these patients are not true baseline levels, and the observed results may be [redacted]the effect of AA.

Table 26: ALX-HPP-501 change in distance walked and percent of predicted over 4 years of treatment (study population, global except Japan)

Period/measurement	< 18 years at baseline (n = [redacted])		≥ 18 years at baseline (n = [redacted])		Total (n = [redacted])	
	Never-treated (n = [redacted])	Ever-treated (n = [redacted])	Never-treated (n = [redacted])	Ever-treated (n = [redacted])	Never-treated (n = [redacted])	Ever-treated (n = [redacted])
Baseline						
Test performed, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Distance walked (metres)						
n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median (min, max)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Percent of predicted[a]						
n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median (min, max)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Year 1						
Test performed, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Distance walked (metres)						
n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median (min, max)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Period/measurement	< 18 years at baseline (n = [redacted])		≥ 18 years at baseline (n = [redacted])		Total (n = [redacted])	
	Never-treated (n = [redacted])	Ever-treated (n = [redacted])	Never-treated (n = [redacted])	Ever-treated (n = [redacted])	Never-treated (n = [redacted])	Ever-treated (n = [redacted])
Percent of predicted[a]						
n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median (min, max)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Change from baseline						
Distance walked (metres)						
n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median (min, max)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Percent of predicted[a]						
n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median (min, max)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Year 2						
Test performed, n (%)	**5 (2.5%)**	**3 (2.3%)**	**4 (1.1%)**	9 (6.2%)	9 (1.6%)	12 (4.4%)
Distance walked (metres)						
n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median (min, max)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Period/measurement	< 18 years at baseline (n = [redacted])		≥ 18 years at baseline (n = [redacted])		Total (n = [redacted])	
	Never-treated (n = [redacted])	Ever-treated (n = [redacted])	Never-treated (n = [redacted])	Ever-treated (n = [redacted])	Never-treated (n = [redacted])	Ever-treated (n = [redacted])
Percent of predicted[a]						
n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median (min, max)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Change from baseline						
Distance walked (metres)						
n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median (min, max)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Percent of predicted[a]						
n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median (min, max)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Year 3						
Test performed, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Distance walked (metres)						
n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median (min, max)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Period/measurement	< 18 years at baseline (n = [redacted])		≥ 18 years at baseline (n = [redacted])		Total (n = [redacted])	
	Never-treated (n = [redacted])	Ever-treated (n = [redacted])	Never-treated (n = [redacted])	Ever-treated (n = [redacted])	Never-treated (n = [redacted])	Ever-treated (n = [redacted])
Percent of predicted[a]						
n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median (min, max)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Change from baseline						
Distance walked (metres)						
n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median (min, max)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Percent of predicted[a]						
n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median (min, max)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Year 4						
Test performed, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Distance walked (metres)						
n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median (min, max)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Period/measurement	< 18 years at baseline (n = [redacted])		≥ 18 years at baseline (n = [redacted])		Total (n = [redacted])	
	Never-treated (n = [redacted])	Ever-treated (n = [redacted])	Never-treated (n = [redacted])	Ever-treated (n = [redacted])	Never-treated (n = [redacted])	Ever-treated (n = [redacted])
Percent of predicted[a]						
n						
Mean (SD)						
Median (min, max)						
Change from baseline						
Distance walked (metres)						
n						
Mean (SD)						
Median (min, max)						
Percent of predicted[a]						
n						
Mean (SD)						
Median (min, max)						
Last follow-up						
Test performed, n (%)						
Distance walked (metres)						
n						
Mean (SD)						
Median (Min, max)						

Period/measurement	< 18 years at baseline (n = [redacted])		≥ 18 years at baseline (n = [redacted])		Total (n = [redacted])	
	Never-treated (n = [redacted])	Ever-treated (n = [redacted])	Never-treated (n = [redacted])	Ever-treated (n = [redacted])	Never-treated (n = [redacted])	Ever-treated (n = [redacted])
Percent of predicted[a]						
n						
Mean (SD)						
Median (min, max)						
Change from baseline						
Distance walked (metres)						
n						
Mean (SD)						
Median (min, max)						
Percent of predicted[a]						
n						
Mean (SD)						
Median (min, max)						
Time from baseline to last follow-up, (years)						
n						
Mean (SD)						
Median (min, max)						

Key: 6MWT, 6-Minute Walk Test; max, maximum; min, minimum; N/A, not applicable; SD, standard deviation.
Notes: [a], Only patients with baseline plus at least 1 follow-up assessment ≥ 6 months after baseline assessment are included in the table.
Source: ALX-HPP-501 Report 2021.[59]

B.2.6.4.1.4. Pain assessments

B.2.6.4.1.4.1. BPI-SF

In patients aged ≥ 18 years, self-reported pain was measured by the BPI-SF.[59] BPI-SF results at baseline and last follow-up in patients ≥ 18 years are presented in Table 27. Data on pain severity from the BPI-SF were reported in [redacted] ever-treated patients and [redacted] never-treated patients at baseline and last follow-up. Pain severity is measured on a scale of 0 to 10, with a lower score indicating lesser pain. The median pain severity reported at baseline for ever-treated patients was [redacted] (min, max: [redacted]) and decreased by a median of [redacted] at last follow-up, indicating a small improvement in pain severity during the study. For never-treated patients, the median pain severity reported at baseline was [redacted] (min, max: [redacted]). Similar values were observed at last follow-up, indicating stable pain severity during the study.

Pain interference was also measured with the BPI-SF on a scale of 0 to 10, with a lower score indicating less interference.[59] For ever-treated patients, the median pain interference at baseline was [redacted] (min, max: [redacted]), which decreased by a median of [redacted] at last follow-up. This indicates an improvement in pain interference during the study. The median pain interference reported for never-treated patients at baseline was [redacted] (min, max: [redacted]). Similar values were observed at last follow-up, indicating stable pain interface during the study.

Table 27: ALX-HPP-501 change in BPI-SF from baseline to last follow-up in patients aged ≥ 18 years (study population, global)

	Total (n = [redacted])	
	Never-treated (n = [redacted])	**Ever-treated (n = [redacted])**
BPI-SF in patients ≥ 18 years		
Pain severity[a], n	[redacted]	[redacted]
Baseline		
Mean (SD)	[redacted]	[redacted]
Median (min, max)	[redacted]	[redacted]
Last follow-up		
Mean (SD)	[redacted]	[redacted]

	Total (n = [redacted])	
	Never-treated (n = [redacted])	**Ever-treated (n = [redacted])**
Median (min, max)	[redacted]	[redacted]
Change from baseline to last follow-up		
Mean (SD)	[redacted]	[redacted]
Median (min, max)	[redacted]	[redacted]
Time from baseline (years)		
Mean (SD)	[redacted]	[redacted]
Median (min, max)	[redacted]	[redacted]
Pain interference[b], n	[redacted]	[redacted]
Baseline		
Mean (SD)	[redacted]	[redacted]
Median (min, max)	[redacted]	[redacted]
Last follow-up		
Mean (SD)	[redacted]	[redacted]
Median (min, max)	[redacted]	[redacted]
Change from baseline to last follow-up		
Mean (SD)	[redacted]	[redacted]
Median (min, max)	[redacted]	[redacted]
Time from baseline (years)		
Mean (SD)	[redacted]	[redacted]
Median (min, max)	[redacted]	[redacted]

Key: BPI-SF, Brief Pain Inventory Short Form; max, maximum; min, minimum; SD, standard deviation.
Notes: BPI were collected for patients ≥ 18 years of age. Patients must have a baseline assessment plus at least 1 follow-up assessment ≥ 6 months after baseline assessment for inclusion in the table. [a] Scale 0–10. Lower scores mean lesser pain. [b] Scale 0–10. Lower scores mean lesser pain.
Source: ALX-HPP-501 Report 2021.[59]

B.2.6.4.1.5. Fractures

Table 28 presents a summary of the fractures in ever-treated and never-treated patients at baseline and follow-up. Of the [redacted] patients with data, [redacted] of ever-treated and [redacted] never-treated patients had a history of fractures/pseudofractures at baseline.[59] However, the types of fractures differed between the groups. For example, femoral fractures were twice as common in ever-treated patients ([redacted]) than in never-treated patients ([redacted]) at baseline.

The median number of fractures at baseline was higher in ever-treated patients than in never-treated patients ([redacted] and [redacted], respectively). After baseline, the proportion of patients with fractures decreased in both groups, with [redacted] ever-treated patients and [redacted] never-treated patients reported to have fractures/pseudofractures.

In patients aged < 18 years at baseline, [redacted] ever-treated patients and [redacted] never-treated patients had a history of fractures/pseudofractures at baseline.[59] However, at follow-up, the proportion of patients with fractures decreased, with [redacted] ever-treated patients and [redacted] never-treated patients reported to have fractures/pseudofractures.

In patients ≥ 18 years at baseline, [redacted] ever-treated patients and [redacted] never-treated patients had a history of fractures/pseudofractures at baseline.[59] However, at follow-up, the proportion of patients with fractures decreased, with only [redacted] ever-treated patients and [redacted] never-treated patients reported to have fractures/pseudofractures.

Table 28: ALX-HPP-501 fractures at baseline and follow-up (study population, global)

	< 18 years at baseline (n = [redacted])		≥ 18 years at baseline (n = [redacted])		Total (n = [redacted])	
	Never-treated (n = [redacted])	Ever-treated (n = [redacted])	Never-treated (n = [redacted])	Ever-treated (n = [redacted])	Never-treated (n = [redacted])	Ever-treated (n = [redacted])
Patients with data						
n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Patients with fractures/pseudofractures at baseline[a]						
Any fractures/pseudofractures, n (%) / E	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Location of fracture, n (%) (fractures/pseudofractures)						
Lower extremity						
Femur/hip	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Fibula/tibia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other lower extremity[b]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Upper extremity, n (%) (fractures/pseudofractures)						
Long bone upper extremity[c]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other upper extremity[d]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vertebral	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other[e]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of fractures/pseudofractures at baseline per patient with fractures/pseudofractures						
n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median (min, max)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of fractures/pseudofractures at baseline per patient with data						
n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	< 18 years at baseline (n = [redacted])		≥ 18 years at baseline (n = [redacted])		Total (n = [redacted])	
	Never-treated (n = [redacted])	Ever-treated (n = [redacted])	Never-treated (n = [redacted])	Ever-treated (n = [redacted])	Never-treated (n = [redacted])	Ever-treated (n = [redacted])
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median (min, max)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Average duration of fracture healing[f] at baseline (months)						
Fractures with onset and resolution dates, E	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median (min, max)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Patients with fractures/pseudofractures during follow-up[g] (patients/fractures), n (%) / E						
Any fractures/pseudofractures	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Location of fracture						
Lower extremity, n (%) (fractures/pseudofractures)						
Femur/hip	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Fibula/tibia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other lower extremity[b]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Upper extremity, n (%) (fractures/pseudofractures)						
Long bone upper extremity[c]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other upper extremity[d]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vertebral	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other[e]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of fractures/pseudofractures during follow-up per patient with fractures/pseudofractures						
n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	< 18 years at baseline (n = [redacted])		≥ 18 years at baseline (n = [redacted])		Total (n = [redacted])	
	Never-treated (n = [redacted])	Ever-treated (n = [redacted])	Never-treated (n = [redacted])	Ever-treated (n = [redacted])	Never-treated (n = [redacted])	Ever-treated (n = [redacted])
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median (min, max)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of fractures/pseudofractures during follow-up per patient with data						
n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median (min, max)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Average duration of fracture healing[f] during follow-up (months)[h]						
Fractures with onset and resolution dates, E	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median (min, max)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of patient-years of follow-up						
Years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Incidence of fracture / pseudofracture						
Events/100 person-years (95% CI)[i]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Key: CI, confidence interval; E, events; max, maximum; min, minimum; NA, not applicable; SD, standard deviation.
Notes: [a] Baseline includes all fracture/pseudofractures that occurred prior or on baseline date for ever-treated patients and prior or on baseline date + 30 days for never-treated patients. Patients may have more than 1 fracture per location reported. [b] Other lower extremity includes ankle/malleolus, foot other, patella and metatarsal. [c] Long bone upper extremity includes radius, humerus and ulna. [d] Other upper extremity includes elbow/olecranon, hand, radius/wrist and shoulder. [e] Other includes clavicle, craniofacial, pelvic bone, rib, scapula, skull and sternum. [f] Calculated as time from onset date to resolution date for patients with complete onset and resolution dates. [g] Follow-up includes all fractures or pseudofractures that occurred after baseline date and up to last treated follow-up date for ever-treated patients, and after baseline date + 30 days and up to last follow-up date for never-treated patients. [h] Average is calculated for all fractures regardless of whether they are experienced by the same patient. [i] Note that incidence is unadjusted and should not be directly compared between groups. Follow-up time is assessed starting at time of consent for never-treated patients and at time of treatment initiation for ever-treated patients. Approximately a third of fractures reported have no date available and are therefore excluded from this analysis.
Source: ALX-HPP-501 study report 2021.[59]

B.2.6.4.1.6. Health-related quality-of-life assessments

B.2.6.4.1.6.1. PedsQL

In patients aged > 2 to < 18 years, HRQL was measured by PedsQL.[59] PedsQL ranges from 0 to 100, with higher scores indicating better quality of life. Table 29 presents HRQL data at baseline and last follow-up for patients with data at baseline and at least 1 follow-up assessment (≥ 6 months).[59] PedsQL total score in patients aged 2 to < 18 years, was available for [redacted] ever-treated patients and [redacted] never-treated patients at both baseline and follow-up. The mean (SD) PedsQL total score reported for ever-treated patients at baseline was [redacted], which increased by [redacted] at last follow-up, indicating an improvement of functioning. The mean PedsQL score at last follow-up for ever-treated patients was [redacted], which was similar to the mean (SD) score of 81.34 (15.92) parent-proxy reported in a general paediatric health care population.[75] In never-treated patients, the mean (SD) score at baseline was [redacted], which decreased by [redacted] at last follow-up. This indicates a slight worsening of functioning in never-treated paediatric patients.

Table 29: ALX-HPP-501 change in PedsQL from baseline to last follow-up (study population, global)

	Never-treated (n = [redacted])	**Ever-treated (n = [redacted])**
Total score (PedsQL)[a]		
Patients with data, n	[redacted]	[redacted]
Baseline		
Mean (SD)	[redacted]	[redacted]
Median (min, max)	[redacted]	[redacted]
Last follow-up		
Mean (SD)	[redacted]	[redacted]
Median (min, max)	[redacted]	[redacted]
Change from baseline		
Mean (SD)	[redacted]	[redacted]
Median (min, max)	[redacted]	[redacted]

	Never-treated (n = [redacted])	**Ever-treated (n = [redacted])**
Time from baseline (years)		
Mean (SD)	[redacted]	[redacted]
Median (min, max)	[redacted]	[redacted]
Psychosocial functioning		
Patients with data, n	[redacted]	[redacted]
Baseline		
Mean (SD)	[redacted]	[redacted]
Median (min, max)	[redacted]	[redacted]
Last follow-up		
Mean (SD)	[redacted]	[redacted]
Median (min, max)	[redacted]	[redacted]
Change from baseline		
Mean (SD)	[redacted]	[redacted]
Median (min, max)	[redacted]	[redacted]
Time from baseline (years)		
Mean (SD)	[redacted]	[redacted]
Median (min, max)	[redacted]	[redacted]
Physical functioning		
Patients with data, n	[redacted]	[redacted]
Baseline		
Mean (SD)	[redacted]	[redacted]
Median (min, max)	[redacted]	[redacted]
Last follow-up		
Mean (SD)	[redacted]	[redacted]
Median (min, max)	[redacted]	[redacted]
Change from baseline		
Mean (SD)	[redacted]	[redacted]
Median (min, max)	[redacted]	[redacted]
Time from baseline (years)		
Mean (SD)	[redacted]	[redacted]
Median (min, max)	[redacted]	[redacted]

	Never-treated (n = [redacted])	Ever-treated (n = [redacted])
Emotional functioning		
Patients with data, n	[redacted]	[redacted]
Baseline		
Mean (SD)	[redacted]	[redacted]
Median (min, max)	[redacted]	[redacted]
Last follow-up		
Mean (SD)	[redacted]	[redacted]
Median (min, max)	[redacted]	[redacted]
Change from baseline		
Mean (SD)	[redacted]	[redacted]
Median (min, max)	[redacted]	[redacted]
Social functioning		
Patients with data, n	[redacted]	[redacted]
Baseline		
Mean (SD)	[redacted]	[redacted]
Median (min, max)	[redacted]	[redacted]
Last follow-up		
Mean (SD)	[redacted]	[redacted]
Median (min, max)	[redacted]	[redacted]
Change from baseline		
Mean (SD)	[redacted]	[redacted]
Median (min, max)	[redacted]	[redacted]
School functioning		
Patients with data, n	[redacted]	[redacted]
Baseline		
Mean (SD)	[redacted]	[redacted]
Median (min, max)	[redacted]	[redacted]
Last follow-up		
Mean (SD)	[redacted]	[redacted]
Median (min, max)	[redacted]	[redacted]
Change from baseline		

	Never-treated (n = [redacted])	Ever-treated (n = [redacted])
Mean (SD)	[redacted]	[redacted]
Median (min, max)	[redacted]	[redacted]

Key: HRQL, health-related quality of life; max, maximum; min, minimum; PedsQL, Paediatric Quality of Life Inventory; SD, standard deviation.
Notes: QoL data are collected for patients ≥ 2 years of age. PedsQL is administered to patients < 18 years. Patients must have a baseline assessment plus at least 1 follow-up assessment ≥ 6 months after baseline assessment for inclusion in the table. [a] The PedsQL scores range from 0 to 100, with higher scores indicating better HRQL.
Source: ALX-HPP-501 study report 2021.[59]

B.2.6.4.1.6.2. HAQ-DI

In patients aged ≥ 18 years, disability was measured by the HAQ-DI on a scale of 0 to 3, with a lower score indicating less disability.[59] HAQ-DI results at baseline and last follow-up in patients ≥ 18 years are presented in Table 30. For ever-treated patients, the median disability score at baseline was [redacted] (min, max: [redacted]), which decreased by a median of [redacted] at last follow-up. This indicates a small improvement in disability score during the study. The median disability score reported for never-treated patients at baseline was [redacted] (min, max: [redacted]). Similar values were observed at last follow-up, indicating stable disability score during the study.

Table 30: ALX-HPP-501 change in HAQ-DI from baseline to last follow-up (study population, global)

	Total (n = [redacted])	
	Never-treated (n = [redacted])	Ever-treated (n = [redacted])
HAQ-DI in patients ≥ 18 years		
Disability (HAQ-DI)[a], n	[redacted]	[redacted]
Baseline		
Mean (SD)	[redacted]	[redacted]
Median (min, max)	[redacted]	[redacted]
Last follow-up		
Mean (SD)	[redacted]	[redacted]
Median (min, max)	[redacted]	[redacted]
Change from baseline to last follow-up		

	Total (n = [redacted])	
	Never-treated (n = [redacted])	Ever-treated (n = [redacted])
Mean (SD)	[redacted]	[redacted]
Median (min, max)	[redacted]	[redacted]
Time from baseline (years)		
Mean (SD)	[redacted]	[redacted]
Median (min, max)	[redacted]	[redacted]

Key: HAQ-DI, Health Assessment Questionnaire-Disability Index; max, maximum; min, minimum; SD, standard deviation.
Notes: HAQ was collected for patients ≥ 18 years of age. Patients must have a baseline assessment plus at least 1 follow-up assessment ≥ 6 months after baseline assessment for inclusion in the table. [a] Scale 0–3; lower scores indicate reduced disability.
Source: ALX-HPP-501 Report 2021.[59]

B.2.6.4.1.6.3. SF-36v2

In patients aged ≥ 18 years, HRQL was measured by the SF-36v2.[59] The SF-36v2 ranges from a scale of 0 to 100, with higher scores indicating better quality of life.[76] In patients aged ≥ 18 years, the SF-36v2 PCS was reported in [redacted] ever-treated patients and [redacted] never-treated patients (Table 31).[59] The mean (SD) score reported for ever-treated patients at baseline was [redacted], which increased by [redacted], indicating a slight improvement in PCS. In never-treated patients, mean (SD) score reported at baseline was [redacted], which increased by [redacted] at last follow-up, indicating a slight improvement in PCS. At baseline and last follow-up, the mean SF-36v2 PCS was lower than the general population in both ever-treated and never-treated patients.[76]

In patients aged ≥ 18 years, the SF-36v2 MCS was reported in [redacted] ever-treated patients and [redacted] never-treated patients. The mean (SD) score reported for ever-treated patients at baseline was [redacted], which decreased by [redacted], indicating a slight worsening of MCS. Similarly, for never-treated patients the mean (SD) score reported at baseline was [redacted], which decreased by [redacted] at last follow-up – indicating a slight worsening of MCS. At baseline and last follow-up, the

average SF-36v2 MCS was lower than for the general population in both ever-treated and never-treated patients.[76]

Table 31: ALX-HPP-501 change in SF-36v2 from baseline to last follow-up (study population, global)

	Never-treated (n = [redacted])	Ever-treated (n = [redacted])
Patients with data, n	[redacted]	[redacted]
SF-36 v2[a] physical component score		
Baseline		
Mean (SD)	[redacted]	[redacted]
Median (min, max)	[redacted]	[redacted]
Last follow-up		
Mean (SD)	[redacted]	[redacted]
Median (min, max)	[redacted]	[redacted]
Change from baseline		
Mean (SD)	[redacted]	[redacted]
Median (min, max)	[redacted]	[redacted]
Time from baseline (years)		
Mean (SD)	[redacted]	[redacted]
Median (min, max)	[redacted]	[redacted]
SF-36 v2 mental component score		
Baseline		
Mean (SD)	[redacted]	[redacted]
Median (min, max)	[redacted]	[redacted]
Last follow-up		
Mean (SD)	[redacted]	[redacted]
Median (min, max)	[redacted]	[redacted]
Change from baseline		
Mean (SD)	[redacted]	[redacted]
Median (min, max)	[redacted]	[redacted]
Time from baseline (years)		
Mean (SD)	[redacted]	[redacted]
Median (min, max)	[redacted]	[redacted]

	Never-treated (n = [redacted])	Ever-treated (n = [redacted])
Vitality score		
Baseline		
Mean (SD)	[redacted]	[redacted]
Median (min, max)	[redacted]	[redacted]
Last follow-up		
Mean (SD)	[redacted]	[redacted]
Median (min, max)	[redacted]	[redacted]
Change from baseline		
Mean (SD)	[redacted]	[redacted]
Median (min, max)	[redacted]	[redacted]
Physical functioning score		
Baseline		
Mean (SD)	[redacted]	[redacted]
Median (min, max)	[redacted]	[redacted]
Last follow-up		
Mean (SD)	[redacted]	[redacted]
Median (min, max)	[redacted]	[redacted]
Change from baseline		
Mean (SD)	[redacted]	[redacted]
Median (min, max)	[redacted]	[redacted]
Bodily pain score		
Baseline		
Mean (SD)	[redacted]	[redacted]
Median (min, max)	[redacted]	[redacted]
Last follow-up		
Mean (SD)	[redacted]	[redacted]
Median (min, max)	[redacted]	[redacted]
Change from baseline		
Mean (SD)	[redacted]	[redacted]
Median (min, max)	[redacted]	[redacted]
General health perceptions score		

	Never-treated (n = [redacted])	Ever-treated (n = [redacted])
Baseline		
Mean (SD)	[redacted]	[redacted]
Median (min, max)	[redacted]	[redacted]
Last follow-up		
Mean (SD)	[redacted]	[redacted]
Median (min, max)	[redacted]	[redacted]
Change from baseline		
Mean (SD)	[redacted]	[redacted]
Median (min, max)	[redacted]	[redacted]
Physical role functioning score		
Baseline		
Mean (SD)	[redacted]	[redacted]
Median (min, max)	[redacted]	[redacted]
Last follow-up		
Mean (SD)	[redacted]	[redacted]
Median (min, max)	[redacted]	[redacted]
Change from baseline		
Mean (SD)	[redacted]	[redacted]
Median (min, max)	[redacted]	[redacted]
Emotional role functioning score		
Baseline		
Mean (SD)	[redacted]	[redacted]
Median (min, max)	[redacted]	[redacted]
Last follow-up		
Mean (SD)	[redacted]	[redacted]
Median (min, max)	[redacted]	[redacted]
Change from baseline		
Mean (SD)	[redacted]	[redacted]
Median (min, max)	[redacted]	[redacted]
Social role functioning score		
Baseline		

	Never-treated (n = [redacted])	Ever-treated (n = [redacted])
Mean (SD)	[redacted]	[redacted]
Median (min, max)	[redacted]	[redacted]
Last follow-up		
Mean (SD)	[redacted]	[redacted]
Median (min, max)	[redacted]	[redacted]
Change from baseline		
Mean (SD)	[redacted]	[redacted]
Median (min, max)	[redacted]	[redacted]
Mental health score		
Baseline		
Mean (SD)	[redacted]	[redacted]
Median (min, max)	[redacted]	[redacted]
Last follow-up		
Mean (SD)	[redacted]	[redacted]
Median (min, max)	[redacted]	[redacted]
Change from baseline		
Mean (SD)	[redacted]	[redacted]
Median (min, max)	[redacted]	[redacted]

Key: HRQL, health-related quality of life; max, maximum; min, minimum; QoL, quality of life; SF-36 v2, 36-item Short-Form Health Survey Version 2.
Notes: QoL data are collected for patients ≥ 2 years of age. SF-36v2 is administered to patients ≥ 18 years. Patients must have a baseline assessment plus at least 1 follow-up assessment ≥ 6 months after baseline assessment for inclusion in the table. [a] The SF-36v2 is scored on a scale of 0 to 100, with higher scores indicating better HRQL.
Source: ALX-HPP-501 study report 2021.[59]

B.2.6.4.1.7. Additional endpoints

A summary of the different skeletal manifestations at baseline and follow-up are provided in Appendix M.3.[59]

B.2.6.4.2. EmPATHY

B.2.6.4.2.1. Mobility assessments

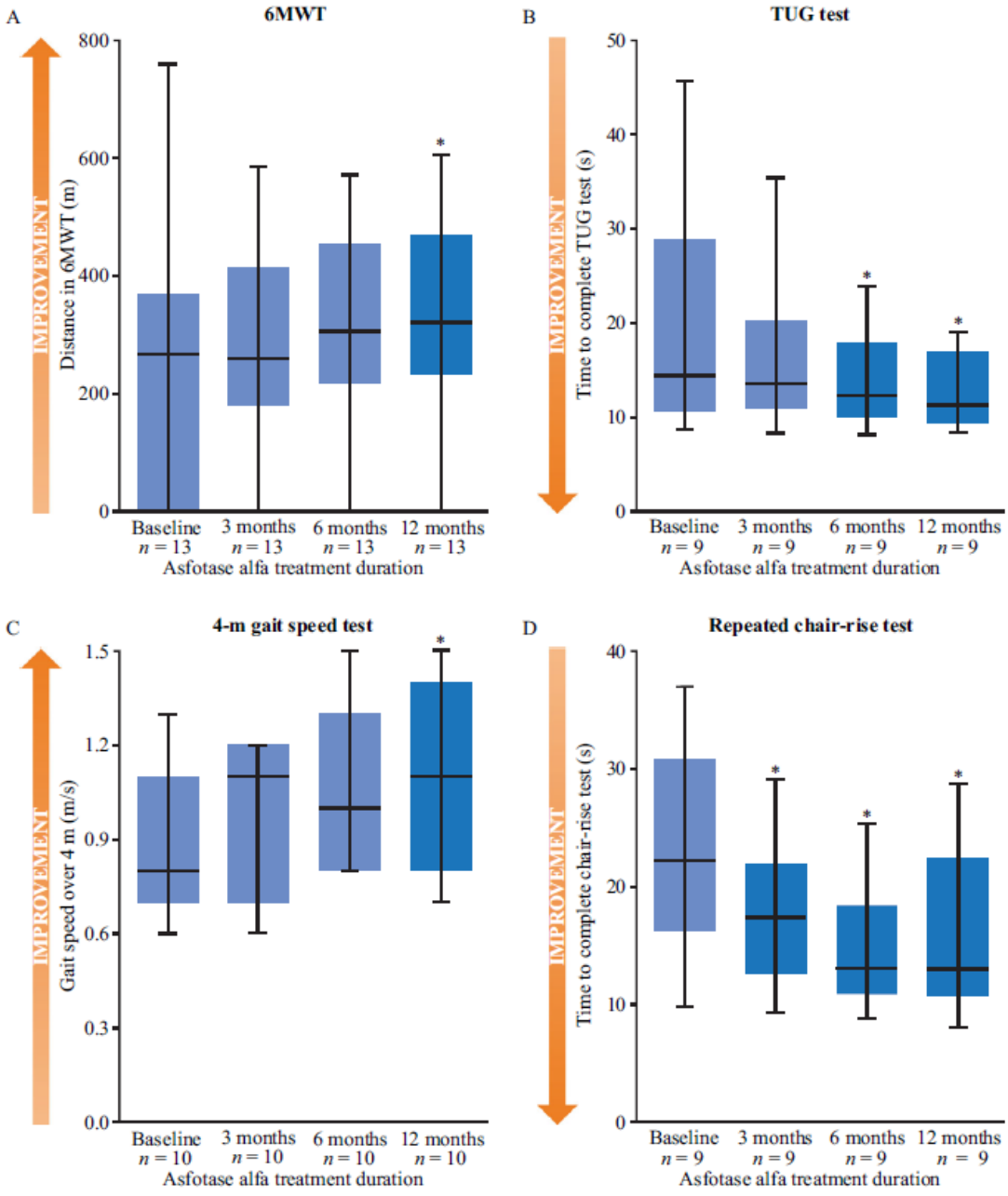
B.2.6.4.2.1.1. 6MWT

Figure 25A presents the results from baseline to 12 months for distance walked in the 6MWT. MCID for 6MWT distance walked is considered 25 metres and/or a 10% improvement in distance walked from baseline. Overall, 13 patients completed the 6MWT assessments at each timepoint. At baseline, the median distance walked was 267.0 metres (interquartile range [IQR]: 0, 368.0 metres), which increased to 320.0 metres (IQR: 234.0, 469.0) after 12 months of treatment.[60] The change from baseline to Month 12 in median distance walked was 53.0 metres (p = 0.023), corresponding to a 20% improvement. This is more than the MCID of 25 metres and/or a 10% improvement, indicating a significant improvement in the 6MWT.

B.2.6.4.2.1.2. Use of mobility aids

7 of the evaluable patients required assistive devices to complete the 6MWT at baseline (3 patients used crutches; 4 used a rolling walker).[60] 2 of these patients were able to complete the test unassisted later during the course of the study; 1 patient was able to complete the test unassisted from 3 months onwards, while 1 patient was able to complete the 12-month assessment without assistive devices. None of the patients who walked unassisted at baseline required assistance at any point during the study.

Figure 25: EmPATHY primary outcomes of physical function among adults treated with AA for paediatric-onset HPP



Key: 6MWT, 6-Minute Walk Test; HPP, hypophosphatasia; SPPB, Short Physical Performance Battery; TUG, Timed Up and Go.
Notes: (A) 6MWT distance, (B) TUG test time, (C) 4 m gait speed test, and (D) repeated chair-rise test at baseline, 3, 6, and 12 months of treatment. * $p < 0.05$ versus baseline. The lower and upper boundaries of blue boxes represent the 25th and 75th percentiles, respectively. Horizontal black lines represent the medians; whiskers represent the maximum and minimum values.
Source: Genest et al. 2020.[60]

Results of the Timed Up and Go (TUG), short physical performance battery and grip strength test are presented Figure 25B, Figure 25C and Figure 25D, respectively. These results are discussed in detail in in Appendix M.3.

B.2.6.4.2.2. Motor function/functional assessments

Results for the LEFS are presented Figure 26A and discussed in detail in Appendix M.3.

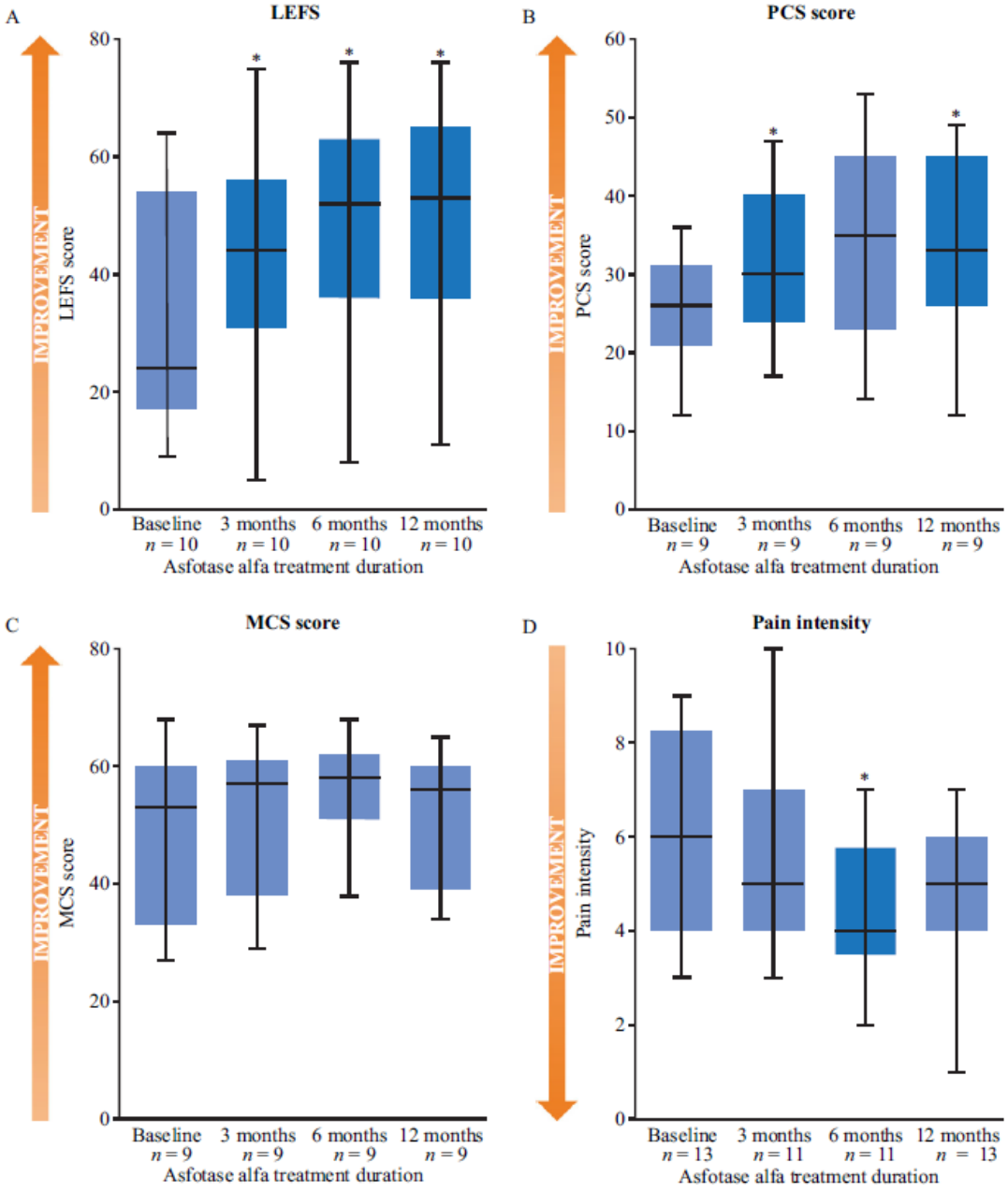
B.2.6.4.2.3. Pain assessments

B.2.6.4.2.3.1. Prevalence of pain

Information on categorical prevalence of pain (categorised as Never, Rarely, Sometimes, Frequently, or Persistently) was available for all 14 patients at baseline, for 12 patients at 3 months and 6 months, and for 13 patients at 12 months.[60] Expect for 1 patient at baseline, all patients reported that they were affected by pain at any given timepoint. At baseline, 9 out of 14 patients (64%) reported experiencing persistent or frequent pain. This decreased to 3 out of 12 patients (25%) at 6 months and 5 out of 13 patients (38%) at 12 months.

Data on pain intensity were available for 13 patients at baseline, for 11 patients at 3 months and 6 months, and for 13 patients at 12 months.[60] If pain was present, its intensity was quantitated using a 10-item Likert scale (1 = minimal pain; 10 = maximum possible pain). Median pain intensity at baseline was 6 (IQR: 4.0, 8.3) points, which decreased to 5 (IQR: 4.0, 6.0) points after 12 months of treatment (Figure 26D). The corresponds to a 17% improvement. After 3 months and 6 months of treatment, median pain intensity was 5 (IQR: 4.0, 7.0) points and 4 (IQR: 3.5, 5.8) points, respectively. A significant decrease in pain intensity compared with baseline was observed after 6 months of treatment ($p = 0.036$). However, changes in median pain intensity from baseline to Month 3 and Month 12 were not statistically significant.

Figure 26: EmPATHY secondary outcome measures of patient-reported physical function among adults treated with AA for paediatric-onset HPP



Key: HPP, hypophosphatasia; LEFS, Lower Extremity Functional Scale; MCS, Mental Component Summary; PCS, Physical Component Summary; SF-36v2, 36-Item Short-Form Health Survey version 2.
Notes: (A) LEFS, (B,C) SF-36v2, and (D) pain intensity questionnaire at baseline, 3, 6, and 12 months of treatment. * $p < 0.05$ versus baseline. The lower and upper boundaries of blue boxes represent the 25th and 75th percentiles, respectively. Horizontal black lines represent medians; whiskers represent the maximum and minimum values.
Source: Genest et al. 2020.[60]

B.2.6.4.2.3.2. Use of pain medication

12 patients had pain medication data available at baseline.[60] All of these patients were using pain medication before initiating AA treatment. 8 patients used pain medications daily, and 6 patients used a combination of pain medications. After 6 months of treatment, 2 patients were able to discontinue use of pain medication; 1 patient was not using pain medication at 12 months. Over the course of the study, 4 patients reduced their use of pain medication from daily use to an on-demand basis.

B.2.6.4.2.4. Health-related quality-of-life assessments

B.2.6.4.2.4.1. SF-36v2

9 patients completed the SF-36v2 at all 4 timepoints.[60] At baseline, the median PCS score was 26 (IQR: 21, 31), which increased to 33 (IQR: 26, 45) after 12 months of treatment (p = 0.010; Figure 26B). This corresponded to a 27% improvement. Changes were also significant between baseline and 3 months (p = 0.028). The median MCS score was 53 (IQR: 33, 60) at baseline and 56 (IQR: 39, 60) after 12 months of treatment (Figure 26C), corresponding to an improvement of 5%. No statistically significant changes were observed at any of the timepoints compared with baseline for the MCS score.

B.2.6.4.3. Dahir et al. 2022

[redacted] patients were enrolled in the study, of which [redacted] were evaluable at [redacted].[61] Patients' mean age at baseline was [redacted] years, and [redacted] were female. At [redacted], there was a statistically significant [redacted] from baseline across PROs: Patient Health Questionnaire-9 (PHQ-9) total score ([redacted]), Patient-Reported Outcomes Measurement Information System (PROMIS-29) domain scores (physical functioning: [redacted]; anxiety: [redacted]; depression: [redacted]; fatigue: [redacted]; sleep disturbance: [redacted]; social roles and activities: [redacted]; pain interference: [redacted]), and Routine Assessment of Patient Index Data 3 (RAPID3) domain scores

(functional status: [redacted]; pain tolerance: [redacted]; global health estimate: [redacted]). Additionally, the proportion of patients with high disease severity (RAPID3 weighted score: [redacted]) [redacted] at [redacted]. Based on the Work Productivity and Activity Impairment – Specific Health Problem (WPAI-SHP), there was no significant [redacted] in employment between baseline ([redacted]) and [redacted] ([redacted]). WPAI-SHP domains showed significant improvement at [redacted] in: absenteeism ([redacted]), presenteeism ([redacted]), activity impairment ([redacted]), and work productivity loss ([redacted]). A [redacted] of patients ([redacted]) continued on AA at [redacted].

This is one of the first real-world studies to report impact of AA treatment on symptoms and humanistic burden in patients with HPP over a [redacted] period.[61] These data illustrate the [redacted] of AA in [redacted] the patient burden and relevance of patient-reported outcomes (PROs) in clinical practice.

B.2.6.4.4. Natural history studies

The results of the non-interventional natural history studies were presented in the original submission, and are provided in Appendix M.3.

B.2.7. Subgroup analysis

B.2.7.1. UK MAA Paediatric Population

Subgroup analyses for the UK MAA Paediatric Population were conducted for participants < 1 year of age at treatment initiation and for treatment-naïve and treatment-experienced patients.[28] The assessed endpoints included growth and BAMF scores. Full details of the subgroup analyses are presented in Appendix E.

Participants who were < 1 year of age at treatment initiation

Overall, [redacted] were observed for growth for participants in the Paediatric Population who were < 1 year of age at treatment initiation compared to the overall

population. [redacted] participants who were < 1 year of age at treatment initiation demonstrated [redacted] (height and weight) within their centile line. 2 participants who were < 1 year of age at treatment initiation dropped more than 5% from their centile line.[28] [redacted].

[redacted]participants who completed the BAMF assessment were < 1 year of age at treatment initiation. Subgroup data for participants who were < 1 year of age at treatment initiation were therefore the same as the BAMF data presented in Section B.2.6.2.1.4. Overall, [redacted] from baseline to Month [redacted] were observed in both upper and lower BAMF scores, indicating [redacted] in participants who were < 1 year of age at treatment initiation.

Treatment-naïve and treatment-experienced participants

[redacted] treatment-naïve ([redacted] participants in the Paediatric Population demonstrated [redacted] (height and weight), and no participants [redacted].[28] [redacted] treatment-experienced ([redacted] participants in the Paediatric Population demonstrated stable growth (height and weight) [redacted]. However, unlike treatment-naïve participants, [redacted] treatment-experienced participants [redacted]. [redacted].

Treatment-naïve participants experienced [redacted] in both height and weight compared to treatment-experienced participants.[28] As described in Appendix E, in treatment-naïve participants, a median change of [redacted] (min, max: [redacted]) percentiles was observed for height and a median change of [redacted] (min, max: [redacted]) percentiles was observed for weight at Month [redacted]. In treatment-experienced participants, a median change of [redacted] (min, max: [redacted]) percentiles was observed for height and a median change of [redacted] (min, max: [redacted]) percentiles was observed for weight at Month [redacted]. [redacted]

[redacted]. Full details of the subgroup analyses are presented in Appendix E.

Both treatment-naïve and treatment-experienced participants showed improvements in both upper and lower BAMF scores, indicating improved mobility and gross motor skills.[28] Full details of the subgroup analyses are presented in Appendix E.

B.2.7.2. Clinical trials

4 sets of subgroup analyses of the long-term clinical trial data relevant to the decision problem have been undertaken. These are as follows:

- A pre-planned comparison of efficacy outcome data according to age of HPP symptom onset (infantile versus juvenile versus adolescent patients) was performed in ENB-006-09/ENB-008-10 (please see final ENB-006-09/ENB-008-10 CSR[64])
- A subgroup analysis of adolescent and adult patients in ENB-009-10. This was a pre-planned analysis (please see the final ENB-009-10 CSR[66])
- An analysis of 85 pooled patients with paediatric-onset HPP (comprising patients from ENB-002-08/ENB-003-08, ENB-010-10 and ENB-006-09/ENB-008-10).[36] This was a pre-planned analysis based on the long-term efficacy data for each trial
- An analysis of 112 pooled patients with paediatric-onset HPP (comprising patients from ENB-002-08/ENB-003-08, ENB-010-10 and ENB-006-09/ENB-008-10).[77] This was a pre-planned analysis based on the long-term data safety for each trial

The first 2 subgroup analyses are described briefly below and presented in full in Appendix E. The pooled analysis of 85 patients and the pooled analysis of 112 patients are presented in Section B.2.8 as integrated analyses.[36, 77]

B.2.7.2.1. ENB-006-09/ENB-008-10

Analyses were performed according to the following disease subgroups:[64]

- Infantile-onset HPP, defined here as onset of HPP signs/symptoms < 6 months of age (may include in utero onset)

- Juvenile-onset (or childhood-onset) HPP, defined as onset of HPP signs/symptoms ≥ 6 months to < 18 years
- Adolescent, defined as patients who turned age 13 to 17 years at any time during the trial

All efficacy analyses by subgroup were performed on the full analysis set, which consisted of all 13 AA-treated patients and all 16 historical control patients where applicable.[64] Long-term data are presented up to Year 7.

Overall, the subgroup data indicate that patients with infantile- and juvenile-onset HPP share a favourable long-term response to AA. This supports the efficacy of AA for the treatment of HPP, independent of age at symptom onset.[64] A favourable response was maintained in children who were older when treatment was initiated, i.e. patients who turned age 13 to 17 years during the trials. Full details of the subgroup analyses are presented in Appendix E.

B.2.7.2.2. ENB-009-10

The patient population was divided by age (patients ≥ 18 years versus < 18 years) to assess the effects of AA on adult (n = 13) and adolescent (n = 6) patients with HPP, respectively.

Results in the adolescent subgroup were difficult to interpret because of the small sample size, but they generally indicated improvement over time. The results in the adult subgroup were consistent with the overall results.[66] Adult patients in the combined treatment group also showed a trend toward greater improvements over time on the BOT-2 Running Speed and Agility Test and in lower extremity function (as measured by the LEFS) compared with the untreated control patients. Full details of the subgroup analyses are presented in Appendix E.

B.2.7.3. ALX-HPP-501 (Global HPP Registry)

An exploratory subgroup analysis was conducted using the Global HPP Registry data to characterise the effectiveness of AA in adults with paediatric-onset HPP, as measured by[70]:

- Change from baseline in HRQL as measured by the SF-36v2
- Change from baseline in self-reported pain and disability as measured by the BPI-SF and the HAQ-DI
- Change from baseline in functional status as measured by the 6MWT
- Occurrence of fractures/pseudofractures and fracture location after treatment with AA

As of the [redacted], [redacted] patients had been enrolled in the global HPP Registry.[70] Of these patients, [redacted] were ever-treated adults with paediatric-onset HPP and were included in the study population for this analysis. [redacted] patients initiated AA prior to enrolment, [redacted] initiated AA on or after enrolment and median treatment duration was [redacted] (min, max: [redacted]) years. The mean (SD) age at diagnosis was [redacted] years and [redacted] were female.

In summary, [redacted] in the change from baseline measures of HRQL, PROs, and 6MWT over time suggest a [redacted] of AA for adults with paediatric-onset HPP:[70]

- SF-36v2 change from baseline scores were consistently [redacted] for the PCS and the majority of its subscales (physical functioning, bodily pain, general health perception, physical role functioning) over time, suggesting [redacted] in physical HRQL while on AA; change values were consistently greater than the MCID of 2 for the PCS
- BPI-SF change from baseline scores were consistently [redacted], indicating [redacted] in pain over time while on AA
- Mean change from baseline in 6MWT distance walked was consistently [redacted] during follow-up, and [redacted] the MCID of 31 metres in many cases
- Mean changes were not consistently statistically significant due to small sample size and large variability

Full details of this subgroup analysis are provided in Appendix E.

B.2.8. Meta-analysis

2 pooled analyses were conducted to assess the long-term efficacy and safety of AA in patients with paediatric-onset HPP:

- An analysis of 85 pooled patients with paediatric-onset HPP (comprising patients from ENB-002-08/ENB-003-08, ENB-010-10 and ENB-006-09/ENB-008-10).[36] This was a pre-planned analysis based on the long-term efficacy data for each trial
- An analysis of 112 pooled patients with paediatric-onset HPP (comprising patients from ENB-002-08/ENB-003-08, ENB-010-10 and ENB-006-09/ENB-008-10).[77] This was a pre-planned analysis based on the long-term data safety for each trial

B.2.8.1. Pooled analysis to assess the long-term efficacy of AA

A pooled analysis was conducted to assess the long-term efficacy of AA in a pooled population of infants and children with HPP signs and symptoms that manifested before 6 months of age. This population was treated for 7 years (events after the studies ended were not included).[36] The pooled analysis efficacy set comprised 85 patients enrolled in ENB-002-08/ENB-003-08 (n = 11), ENB-010-10 (n = 69) and ENB-006-09/ENB-008-10 (n = 5). The following pooled efficacy endpoints for infants and children with paediatric-onset HPP are presented below:

- OS and VFS: data from ENB-002-08/ENB-003-08 and ENB-010-10 were compared with data from untreated historical controls of similar age and with similar HPP characteristics from a retrospective natural history study (ENB-011-10)[51]
- Growth: length/height and weight Z-scores were based on Centers for Disease Control and Prevention growth charts for age- and sex-matched healthy infants and children[78] (ENB-002-08/ENB-003-08, ENB-010-10, and ENB-006-09/ENB-008-10)
- Motor and cognitive function: assessed by BSID-III (ENB-002-08/ENB-003-08 and ENB-010-10)
- RGI-C scale score: 3 paediatric radiologists used the RGI-C independently to compare skeletal radiographs of the chest (ENB-002-08/ENB-003-08 and ENB-010-

10) and bilateral wrists and knees that were obtained before and after initiation of AA (ENB-002-08/ENB-003-08, ENB-010-10 and ENB-006-09/ENB-008-10)

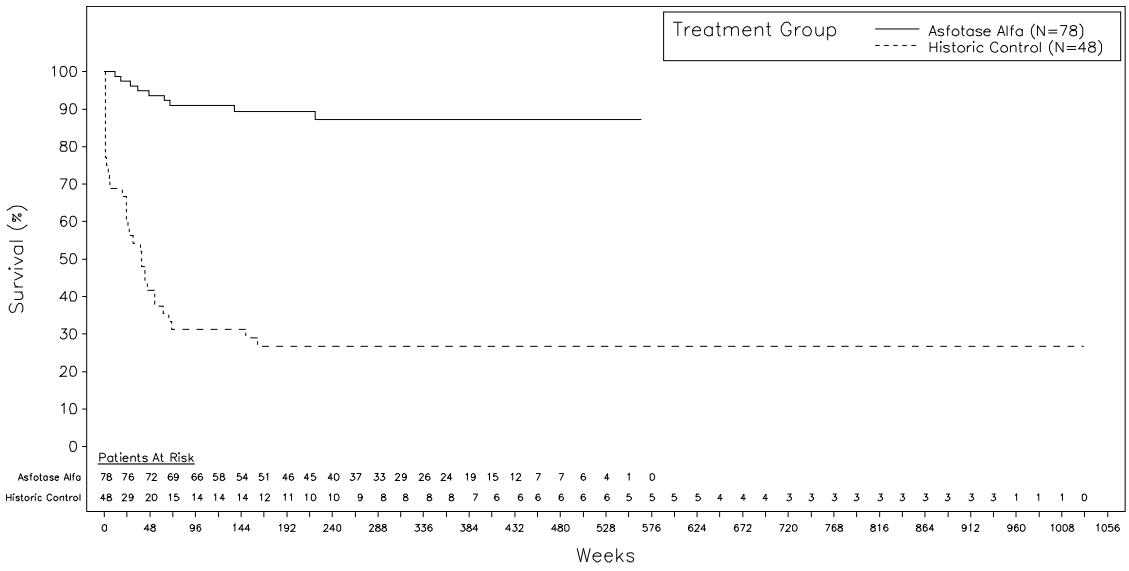
- RSS: radiographs of the wrists and knees used to determine RSS were read by a single independent radiologist (ENB-002-08/ENB-003-08, ENB-010-10 and ENB-006-09/ENB-008-10)

B.2.8.1.1. Mortality endpoints

In this pooled analysis, the effects of AA on OS and VFS were examined in infants and children with paediatric-onset HPP from ENB-002-08/ENB-003-08 and ENB-010-10. These patients were treated with AA, and their data were compared to data obtained from a group of comparable untreated historical control patients (ENB-011-10).[36, 51] The demographic, baseline and HPP-specific medical histories of the AA-treated patient cohort and the historical control group are presented in Appendix M.3, and indicate that the 2 groups are clinically similar.

The analysis showed that treatment with AA markedly improved OS in infants and children with paediatric-onset HPP, compared to the OS observed in untreated historical control patients. The probability (95% CI) of survival at 7 years for AA-treated patients was 87% (0.77, 0.93) compared to 27% (0.15, 0.40) for untreated historical controls (Figure 27).[36]

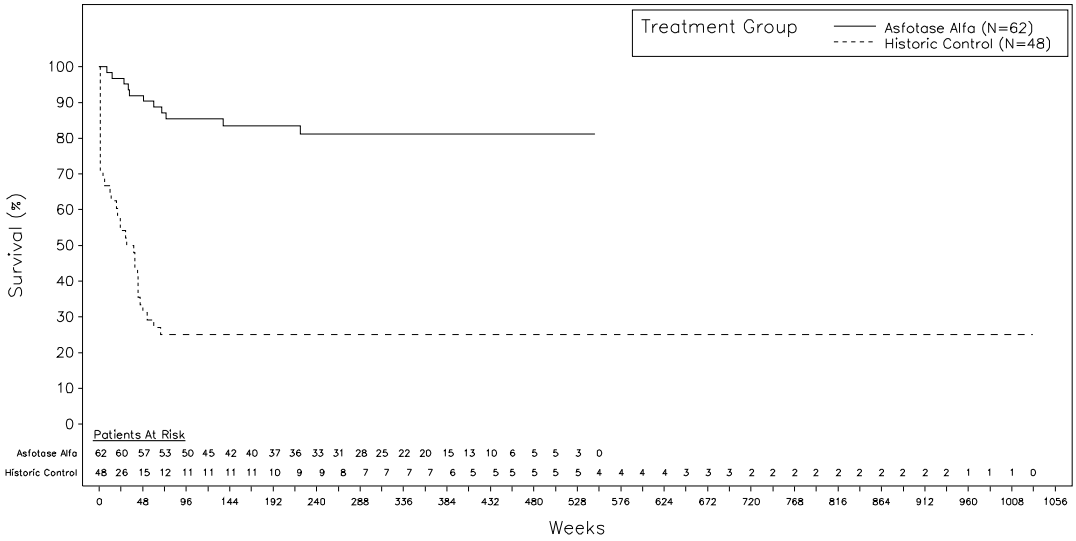
Figure 27: Pooled analysis – OS in infants and children with paediatric-onset HPP treated with AA versus historical control patients



Key: AA, asfotase alfa; HPP, hypophosphatasia; OS, overall survival.
Notes: *, A patient for whom survival time cannot be determined. Censoring was counted if patients withdrew from the study, or, in the case of historical controls, were lost to follow-up. Data were included for infants and children with paediatric-onset HPP from ENB-002-08/ENB-003-08 and ENB-010-10. These patients were treated with AA and their data were compared to data obtained from a group of comparable untreated historical control patients (ENB-011-10).
Source: Hogler et al. 2019.[36]

The analysis showed that treatment with AA markedly improved invasive VFS in infants and children with paediatric-onset HPP compared to that observed in untreated historical control patients. The probability (95% CI) of invasive VFS at 7 years for AA treated patients was 81% (0.68, 0.89) versus 25% (0.14, 0.38) for untreated historical controls (Figure 28).[36]

Figure 28: Pooled analysis – invasive VFS in perinatal-/infantile-onset HPP patients treated with AA versus historical-control patients



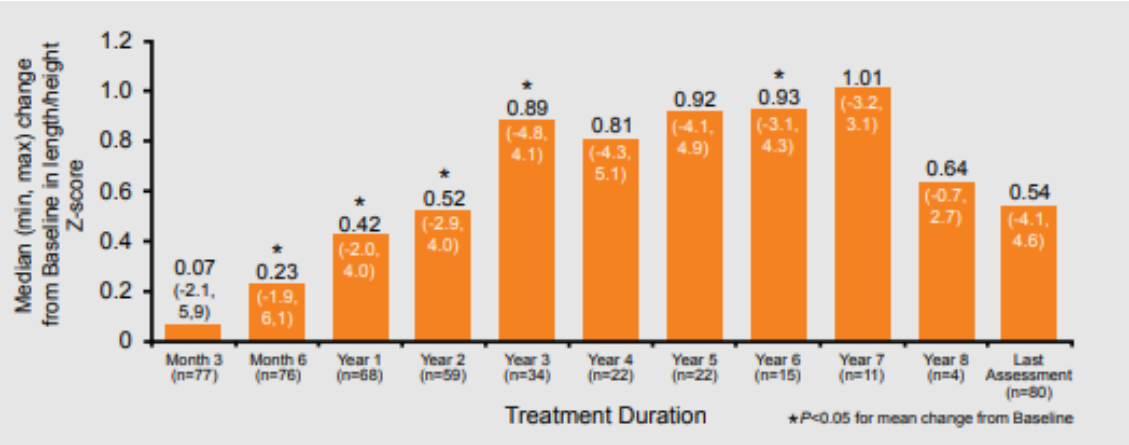
Key: AA, asfotase alfa; HPP, hypophosphatasia; VFS, ventilator-free survival.
Notes: *, A patient for whom survival time cannot be determined. Censoring was counted if patients withdrew from the study, or, in the case of historical controls, were lost to follow-up. Data were included for infants and children with paediatric-onset HPP from ENB-002-08/ENB-003-08 and ENB-010-10. These patients were treated with AA and their data were compared to data obtained from a group of comparable untreated historical control patients (ENB-011-10).
Source: Hogler et al. 2019.[36]

B.2.8.1.2. Growth

The pooled analysis for growth included AA-treated patients in ENB-002-08/ENB-003-08, ENB-010-10 and ENB-006-09/ENB-008-10.[36]

Figure 29 presents pooled median Z-score changes from baseline for length/height and weight over 8 years of treatment. The median length/height Z-scores were higher than at baseline from Month 3 (0.07 [min, max: -2.0, 5.9]) until Year 8 (0.64 [min, max: -0.7, 2.7]). The mean increase from baseline in length or height Z-score was statistically significant at Month 6, Year 1, Year 2, Year 3 and Year 6 ($p < 0.05$ for all), but not at other timepoints.

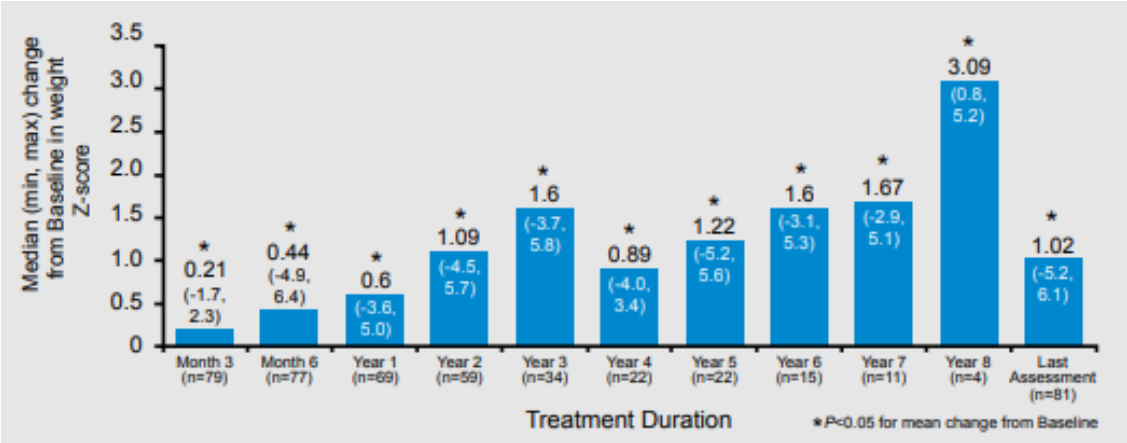
Figure 29: Pooled analysis – change from baseline in length/height Z-scores over time in infants and children with paediatric-onset HPP



Key: AA, asfotase alfa; HPP, hypophosphatasia; max, maximum; min, minimum.
Notes: Data were included for infants and children with paediatric-onset HPP from ENB-002-08/ENB-003-08, ENB-010-10 and ENB-006-09/ENB-008-10.
Source: Hogler et al. 2019.[36]

Figure 30 presents pooled median Z-score changes from baseline for length/height and weight over 8 years of treatment. The median weight Z-scores were higher than at baseline from Month 3 (0.21 [min, max: -1.7, 2.3]) until Year 8 (3.09 [min, max: 0.8, 5.2]). The median weight Z-score was significantly higher than at baseline from Month 3 until Year 7 ($p < 0.05$ for all).

Figure 30: Pooled analysis – change from baseline in weight Z-scores over 8 years of treatment in infants and children with paediatric-onset HPP

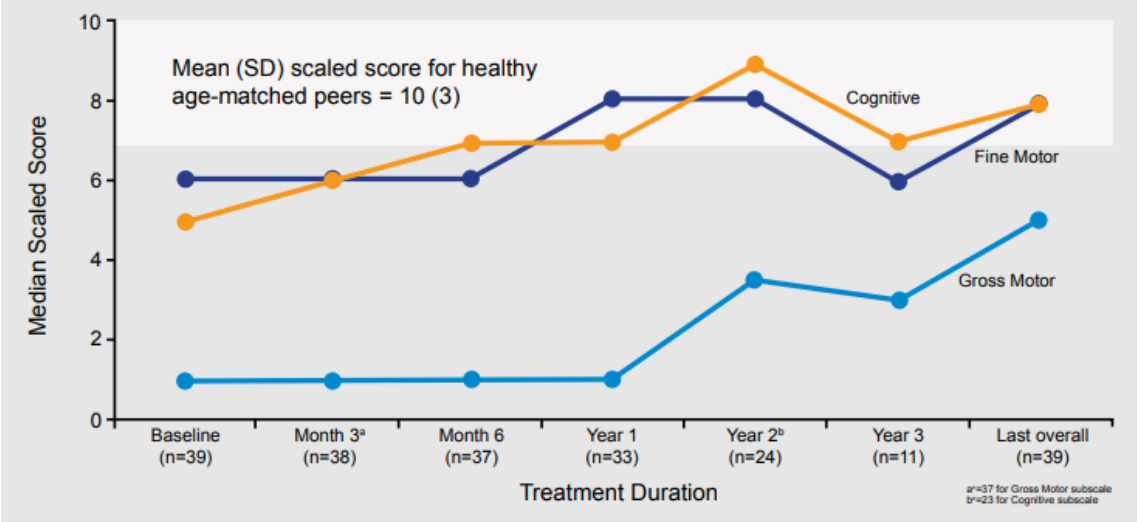


Key: AA, asfotase alfa; HPP, hypophosphatasia; min, minimum; max, maximum.
Notes: Data were included for infants and children with paediatric-onset HPP from ENB-002-08/ENB-003-08, ENB-010-10 and ENB-006-09/ENB-008-10.
Source: Hogler et al. 2019.[36]

B.2.8.1.3. BSID-III over time

Figure 31 presents median BSID-III scores over time. Improvements were observed in median BSID-III Gross Motor, Fine Motor, and Cognitive scaled scores over time in infants and toddlers (< 2 years) with paediatric-onset HPP treated with AA.[36]

Figure 31: Pooled analysis – median BSID-III Gross Motor, Fine Motor, and Cognitive scaled scores over time in infants and toddlers (< 2 years) with paediatric-onset HPP treated with AA



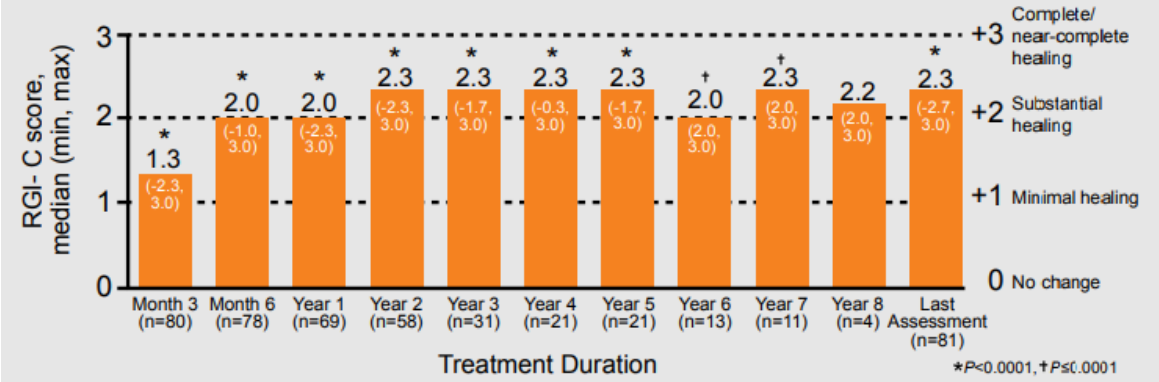
Key: AA, asfotase alfa; BSID-III, Bayley Scales of Infant Development, 3rd Edition; HPP, hypophosphatasia; SD, standard deviation.
Notes: Term newborn infants (age 0 to 27 days; n = 3) and children (age 2 to 11 years; n = 8) also generally showed improvements on the BSID-III after treatment with AA. However, results were variable because of the low number of patients with available data in each group. Data were included for infants and children with paediatric-onset HPP from ENB-002-08/ENB-003-08 and ENB-010-10. Scaled scores range from 1 to 19 with a normal mean (SD) of 10 (3), with higher scores meaning better motor and cognitive function.
Source: Hogler et al. 2019.[36]

B.2.8.1.4. RGI-C scores and RSS over time

The pooled analysis for changes in RGI-C scores and RSS included AA-treated patients in ENB-002-08/ENB-003-08, ENB-010-10 and ENB-006-09/ENB-008-10.[36]

As shown in Figure 32, median RGI-C scores documented improvements in HPP-related skeletal disease in infants and children with paediatric-onset HPP as early as Month 3 (median 1.3 [min, max: -2.3, 3.0]; $p < 0.0001$). These improvements were sustained over 8 years of treatment (median 2.2 [min, max: 2.0, 3.0]). Improvements were significant at all timepoints apart from Year 8.[36]

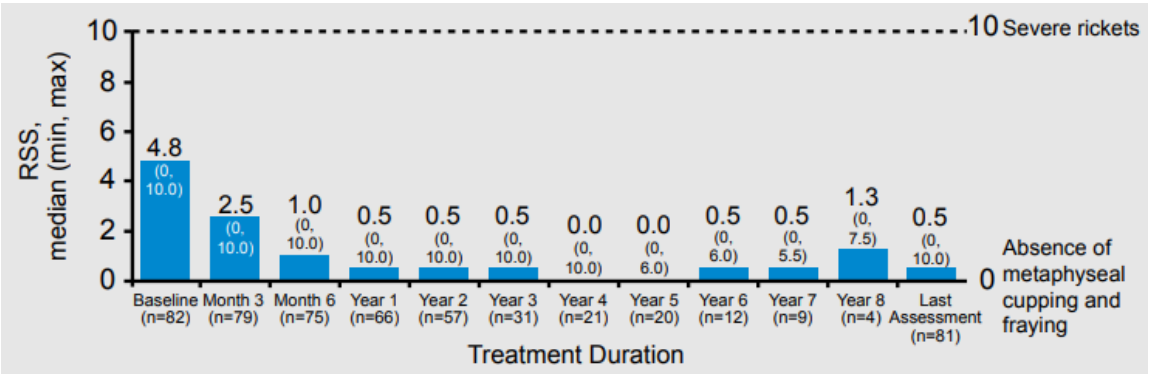
Figure 32: Pooled analysis – median RGI-C scores over 8 years of treatment in infants and children with paediatric-onset HPP



Key: AA, asfotase alfa; HPP, hypophosphatasia; min, minimum; max, maximum.
Notes: The RGI-C is a 7-point scale (–3 [severe worsening] to +3 [complete/near-complete healing]) used to assess radiographic changes from baseline in the most common skeletal characteristics of HPP. Data were included for infants and children with paediatric-onset HPP from ENB-002-08/ENB-003-08, ENB-010-10 and ENB-006-09/ENB-008-10.
Source: Hogler et al. 2019.[36]

As shown in Figure 33, median RSS indicated that the improvements documented as early as Month 3 (median 2.5 [min, max: 0.0, 10.0]) were sustained over 8 years of treatment (median 1.3 [min, max: 0.0, 7.5]).[36]

Figure 33: Pooled analysis – median RSS over 8 years of treatment in infants and children with paediatric-onset HPP



Key: AA, asfotase alfa; HPP, hypophosphatasia; min, minimum; max, maximum; RSS, Rickets Severity Score.
Notes: The RSS is a 10-point scale (0 = absence of metaphyseal cupping and fraying [both characteristic of rickets] to 10 = severe rickets; maximum of 4 points for the wrists and 6 points for the knees). It was originally developed to assess severity of nutritional rickets in the wrists and knees. Data were included for infants and children with paediatric-onset HPP from ENB-002-08/ENB-003-08, ENB-010-10 and ENB-006-09/ENB-008-10.
Source: Hogler et al. 2019.[36]

B.2.8.1.5. Summary

In this pooled analysis of data from the largest cohort of patients treated with AA to date, infants and children manifesting signs/symptoms of HPP before 6 months of age showed improvements in survival, radiographic skeletal manifestations of HPP and growth, indicating efficacy of AA.[36] In most patients, these improvements were observed early on and sustained over 7 years of treatment.

B.2.8.2. Pooled analysis to assess the long-term safety of AA

As of the final analysis cut-off dates for the completed interventional studies, safety data were pooled from 4 studies: in children aged ≤ 3 years (ENB-002-08/ENB-003-08; n = 11) and children aged ≤ 5 years (ENB-010-10; n = 69) with onset of HPP symptoms before the age of 6 months; and children aged 5–12 years (ENB-006-09/ENB-008-10; n = 13) and adolescents and adults aged 13–65 years with onset of HPP at any age (ENB-009-10; n = 19).[77] Patients included in the clinical studies and, therefore, in the Pooled Safety Set, represented a broad spectrum of patients with HPP as shown in the medical history and baseline characteristics, and according to both age of onset of first symptoms, age of first fracture and number of fractures.

At the final analysis cut-off dates for the integrated analyses, 112 patients (the Pooled Safety Set) had been exposed to AA, with a total of 95 patients completing the clinical studies. Of the 17 patients who discontinued, 8 discontinued due to AEs.[77] Safety data were available for up to 7 years from ENB-002-08/ENB-003-08, ENB-010-10 and ENB-006-09/ENB-008-10, and for up to 5 years from ENB-009-10.

B.2.8.2.1. Patient exposure

Overall, 83 (75%) patients received 2 mg/kg AA administered 3 times per week and 28 (25%) received 1 mg/kg AA administered 6 times per week.[77] Median (min, max) treatment duration was 2.7 years (1 day, 7.5 years) and the median average weekly total dose was 6.0 mg/kg, with a range of 2.1 to 11.9 mg/kg.

B.2.8.2.2. Summary of TEAEs

All patients experienced at least 1 treatment-emergent adverse event (TEAE).[77] In total, 1,466 TEAEs in 91 patients were considered treatment-related. Most treatment-related adverse events (TRAEs) (1310 [89.4%] in 82 patients) were ISRs, with the majority being mild (74%) or moderate (21%) in severity. The most common ISRs were erythema (54%), discoloration (24%) and pain (19%). ISRs occurred most frequently within the first 3 months of treatment (565 events in 53 patients), then generally decreased over time (207 events in 33 patients from 3 to 6 months; 178 events in 35 patients from 6 months to 1 year; 125 events in 32 patients from 1 to 2 years; and 247 events in 45 patients from 2 to 7 years). Meticulous rotation of injection sites may help prevent ISRs.

SAEs of special interest were craniosynostosis (28%; including 6 surgeries), IARs (6%; including 2 anaphylactoid reactions), ectopic calcifications (2%; including nephrolithiasis), and elevated transaminases or chronic hepatitis (2%; including chronic hepatitis and elevated liver enzymes).[77]

B.2.8.2.3. Deaths

10 deaths occurred, all of which occurred in patients with severe HPP (perinatal or infantile HPP).[77] 1 death was considered to be possibly related to AA treatment and was attributed to pneumonia, while the remaining 9 deaths were considered to be unrelated to treatment. 6 deaths were a result of the following complications: respiratory failure and cerebral death; HPP-related complications; severe respiratory failure; cardiopulmonary arrest; severe cardiopulmonary insufficiency; and transtentorial and cerebellar tonsillar herniation due to cerebral oedema. 3 deaths were due to pneumonia and/or sepsis.

B.2.8.2.4. Summary

Pooled analysis of data from mostly children (84%) who were given AA for up to 7 years showed that the most common TRAEs were ISRs, which occurred most frequently within the first 3 months of treatment, then somewhat less frequently after this point.[77]

Meticulous rotation of injection sites may help to prevent ISRs. It is unclear whether AA affects certain common HPP complications, such as craniosynostosis and ectopic calcifications. Asymptomatic conjunctival calcifications have been associated with AA treatment in adults with HPP.

B.2.9. Indirect and mixed treatment comparisons

Indirect treatment comparisons were not considered appropriate. However, 2 retrospective, non-interventional retrospective studies and 1 sub-study were conducted to provide control data to use in the comparative analyses of selected endpoints in ENB-002-08/ENB-003-08, ENB-010-10 and ENB-006-09/ENB-008-10. ENB-011-10 served as the historical control population for patients with perinatal-/infantile-onset HPP for long-term assessment of OS and VFS (ENB-002-08/ENB-003-08 and ENB-010-10). These comparisons are presented in Section B.2.8.1.

B.2.10. Adverse reactions

In this section, AE, tolerability and safety data are presented for the UK MAA data set (analysis cut-off date: [redacted])[28], followed by final long-term safety data for the following completed clinical trials: ENB-002-08/ENB-003-08 (last patient visit: [redacted]; extension up to 7 years)[6, 62]; ENB-010-10 (last patient visit: [redacted]; extension up to 6 years)[4, 63]; ENB-006-9/ENB-008-10 (last patient visit: [redacted]; extension up to 7 years)[3, 5, 64]; and ENB-009-10 (last patient visit: [redacted]; extension up to 5 years).[2, 66] In addition, interim safety data are presented for the ALX-HPP-501 Global HPP Registry (analysis cut-off date: [redacted])[59] and the real-world EmPATHY study.[60]

B.2.10.1. UK MAA

B.2.10.1.1. Paediatric Population

As of the analysis cut-off date for this report, [redacted] participants in this population had died or discontinued due to an AE.[28] In relation to data from other AA studies, including the Global HPP Registry, no new safety signals were identified.

Events of interest (EOIs) and SAEs were reported for participants in the Paediatric Safety Population, a summary table is presented in Appendix M.4.[28] A total of [redacted] SAEs in [redacted] participants were reported in the Paediatric Safety Population, [redacted] of which occurred during treatment or within 30 days of treatment discontinuation. [redacted] of the SAEs were assessed by the treating physician as definitely related to study treatment. The [redacted] of the SAEs were assessed as not related or unlikely to be related to study treatment.

As of the analysis cut-off date, [redacted] EOIs in [redacted] participants were reported, [redacted] of which occurred during study treatment or within 30 days of treatment discontinuation.[28] Of these [redacted], [redacted] events were assessed by the physician as related to study treatment and [redacted] events were assessed as not related to treatment. ISRs were the most frequently reported EOI in the Paediatric Safety Population. Overall, [redacted] ISRs in [redacted] participants were reported, all of which were considered mild or moderate in severity. All ISRs were assessed by the physician as related to study treatment and were not resolved as of the analysis cut-off date. However, data were consistent with what has been previously noted in the Global HPP Registry for this population. Additionally, [redacted] IARs were reported in [redacted] participants, which were assessed by the physician as related to study treatment.

Craniosynostosis was the [redacted] most frequently reported EOI in the Paediatric Safety Population.[28] It was reported in [redacted] participants, and [redacted] instances of this EOI occurred while patients were on study treatment or within 30 days of study treatment discontinuation. [redacted]craniosynostosis events were assessed by the treating physician as not related to AA treatment. These events were reported between 3 months after MAA enrolment to [redacted] months after enrolment.

B.2.10.1.2. Adult Population

As of the most recent data cut-off date ([redacted]), [redacted]was reported. [redacted]

[redacted].

SAEs and EOIs were reported for participants in the Adult Safety Population, a summary table is presented in Appendix M.4. [redacted] participants discontinued the study due to an SAE or EOI. In relation to data from other AA studies, no new safety signals were identified.

A total of [redacted] SAEs were reported in [redacted] adult participants, [redacted] of which occurred on treatment or within 30 days of treatment discontinuation. [redacted] of the SAEs were assessed by the treating physician as definitely related to study treatment. The treating physician assessed the [redacted] remaining SAEs as not related or unlikely to be related to study treatment.

A total of [redacted] EOIs were reported in [redacted] adult participants, [redacted] of which occurred on treatment or within 30 days of treatment discontinuation. Of these, [redacted] events were mild or moderate in severity, [redacted] events were assessed by the treating physician as related to study treatment and [redacted] events were assessed as not related to study treatment. ISRs were the most frequently reported EOI in the Adult Safety Population. Overall, [redacted] events were reported in [redacted] participants, all of which were considered mild or moderate in severity. [redacted] ISRs were assessed by the physician as possibly, probably or definitely related to study treatment and [redacted] were not resolved as of the analysis cut-off date. However, the data were consistent with what has been previously noted for this population. Additionally, [redacted] IARs were reported in [redacted] participants. Of these, [redacted] were assessed as related to study treatment.

B.2.10.2. ENB-002-08/ENB-003-08

11 patients received AA treatment.[6, 62] All 10 patients who completed the 6-month PTP entered the ETP; 9 patients received AA for at least 6 years and completed the study, with 4 of the 9 patients being treated for more than 7 years. The median duration of treatment for the 11 enrolled patients was 6.6 years (range: 1 day to 7.5 years). 2 patients ([redacted]) had [redacted] months of treatment with AA at the time of the final

analysis cut-off date, while the remaining [redacted] patients ([redacted]) were treated for [redacted] months.[62] The total patient years of exposure were [redacted] years.

An overview of TEAEs is provided in Appendix M.4. A total of 794 TEAEs were observed over 7 years of treatment with AA; all 11 patients had at least 1 TEAE.[6, 62] TEAEs were primarily mild (605 out of 794 [76%]) or moderate (151 out of 794 [19%]) in severity, and most were considered by investigators to be unrelated to the study drug (664 out of 794 [84%]). Events assessed by investigators as possibly, probably, or definitely related to AA in more than 2 patients were injection-site erythema (n = 4), irritability (n = 3), pyrexia (n = 3), and vomiting (n = 3). There were only 38 SAEs (in [redacted]).

4 patients had a total of 10 TEAEs that were considered by the investigators to possibly reflect hypersensitivity, and were therefore designated as IARs.[6, 62] Most TEAEs (8/10 [80%]) occurred on Day 1 in conjunction with the initial IV infusion. 7 (64%) patients had 78 ISRs, but most of them (47 out of 78 [60%]) occurred in 2 patients. No severe or serious ISRs were reported.

1 patient withdrew because of AEs during the initial IV infusion of AA and 1 patient died from sepsis at around age 8 months, after 7.5 months of therapy.[6, 62] No additional deaths or discontinuations occurred.

A summary of the TEAEs that occurred in more than 20% of patients over 7 years of treatment with AA is presented in Appendix M.4. The most common TEAEs were pyrexia (73%), upper respiratory tract infection (73%), craniosynostosis (64%), pneumonia (64%), constipation (55%), otitis media (55%) and vomiting (55%).[6, 62]

3 patients (3 out of 11; 27%) were reported to have a history of craniosynostosis before study entry.[6, 62] During the study, 7 patients (64%) experienced a total of 13 TEAEs of craniosynostosis. 4 patients (36.4%) had TEAEs of craniosynostosis that were considered severe by study investigators. 6 patients (54.5%) had TEAEs of craniosynostosis that were reported as SAEs. 1 SAE of severe craniosynostosis and conductive deafness was reported as possibly related to the study drug. Other reported TEAEs of special interest relevant to craniosynostosis included 2 patients who each had

SAEs of increased intracranial pressure and 1 patient who had an SAE of cerebrospinal fluid pressure.

B.2.10.3. ENB-010-10

69 patients were exposed to AA treatment for up to 5 years.[4, 63] The patients received the study drug for a median duration of 2.3 years, with a range from 0.02 to 5.8 years. Of the 69 patients treated with AA, 3 (4%) received treatment for < 3 months and 14 (20%) for ≥ 36 months. The total patient years of exposure was [redacted] years.[63]

An overview of TEAEs is provided in Appendix M.4. A total of 3,052 TEAEs was observed over 5 years of treatment with AA; all 69 patients had at least 1 TEAE.[4, 63] Most TEAEs were mild (2125 out of 3052 [70%]) or moderate (728/3052 [24%]) in severity. Most TEAEs were assessed by the investigator as unrelated to the study drug (2,409 out of 3,052 [79%]) and most related events were ISRs (593 out of 643 [92%]) and IARs (11 out of 643 [2%]), which occurred in 43 and 6 patients, respectively.

7 patients (10.1%) were reported to have a history of craniosynostosis, and 3 patients had pre-treatment SAEs of craniosynostosis before starting AA.[4, 63] Throughout the study, 28 patients (41%) experienced a total of 46 TEAEs relevant to craniosynostosis. 25 events were assessed as unlikely to be related or unrelated to study drug. 21 events were assessed as either mild or moderate in severity. 7 patients experienced craniosynostosis/craniosynostosis-related AEs that were assessed as severe and were considered SAEs. 1 patient who experienced an SAE of severe craniosynostosis subsequently died. With respect to other adverse events of special interest, 20%, 7%, and 19% of patients experienced ectopic calcifications, lipodystrophy and chronic hepatitis, respectively.

A total of 297 SAEs were reported in 50 (72%) patients. Of these, 286 (96%) were assessed by the investigator as unlikely to be related to or unrelated to the study drug.[4, 63] Of the 11 SAEs considered to be related to treatment, 7 were ISRs or IARs in 3 patients. The remaining 4 occurred in 3 patients: craniosynostosis (n = 1), pneumonia resulting in study drug withdrawal (n = 1) and Arnold-Chiari type 1 malformation and syringomyelia (n = 1).

9 (13%) patients died during the study.[4, 63] Causes of death included: pneumonia (n = 3); respiratory failure and cerebral death (n = 1); HPP-related complications (n = 1); severe respiratory failure (n = 1); cardiopulmonary arrest (n = 1); severe cardiopulmonary insufficiency (n = 1); and transtentorial and cerebellar tonsillar herniation as a result of cerebral oedema related to severe HPP (n = 1).

A summary of the most common TEAEs occurring in ≥ 10% of patients, regardless of the relationship to the study drug over 5 years of treatment with AA is provided in Appendix M.4. The most common TEAEs were pyrexia (68%), tooth loss (59%), injection-site erythema (48%) and vomiting (45%).[4, 63]

B.2.10.4. ENB-006-09/ENB-008-10

13 patients were exposed to AA treatment for up to 7 years.[5, 23, 64] The patients received the study drug for a median duration of [redacted] days, with a range from [redacted] days.[64] [redacted] patient ([redacted]) had [redacted] months of treatment with AA at the time of the final analysis cut-off date, while the remaining [redacted] patients ([redacted]) were treated for [redacted] months. The total patient years of exposure was [redacted] years.

Appendix M.4 provides an overview of TEAEs for the randomised treatment group (2 mg/kg and 3 mg/kg) and the combined dose group over 7 years of treatment with AA. No patients discontinued treatment because of an AE and no serious AEs or deaths were reported.[5, 23, 64] For the combined dose group, a total of [redacted] TEAEs were observed during the course of the study; all patients experienced at least 1 TEAE.[5, 64] TEAEs were almost all mild ([redacted]) or moderate ([redacted]) in severity; 2 events were severe. Approximately [redacted] of the events ([redacted]) were assessed as being related to the study drug. Most of the related events were ISRs (260 out of [redacted]) reported in 12 patients (92.3%). [redacted] patients ([redacted]) experienced an IAR, [redacted] patients ([redacted]) had ectopic calcification and [redacted] patients ([redacted]) had lipodystrophy.[64] There were [redacted] of craniosynostosis or chronic hepatitis.

3 patients (3 out of 13; 23%) had a history of craniosynostosis prior to treatment with AA.[5, 23, 64] No patients were reported to have craniosynostosis at baseline and no patients were reported to develop craniosynostosis during the study. Since cranial

sutures generally fuse by the age of 2–3 years, new craniosynostosis events would not be expected in patients from this age population.

A summary of the most common TEAEs occurring in ≥ 20% of patients, regardless of the relationship to the study drug over 7 years of treatment with AA is presented in Appendix M.4. The most common TEAEs were generally related to ISRs and included erythema (85%), macule (69%), hypertrophy (62%) and pruritus (54%).[5, 64] Other common TEAEs included upper respiratory tract infection ([redacted]), procedural pain ([redacted]) and arthralgia ([redacted]).[64]

B.2.10.5. ENB-009-10

An overview of TEAEs in the ETP is provided in Appendix M.4. All 19 patients experienced a TEAE and there were 1145 AEs during the study, the majority of which were mild (864 out of 1145, 75.4%) and not related to the study drug (731 out of 1145, 63.8%).[2, 66] The most common TEAEs were ISRs (385 out of 1145 [34%]), which occurred in all patients. 2 patients experienced TEAEs categorised as hypersensitivity IARs, 1 patients experienced oral hypoesthesia and chills in 1 patient had an anaphylactoid reaction; each was considered moderate in intensity. The patient who had the anaphylactoid reaction withdrew from the study; [redacted] [66] [redacted] 3 patients (3 out of 19; 16%) had a history of craniosynostosis prior to treatment with AA.[2, 66] [redacted]

No patients died during the study.[2, 66] Overall, 29 treatment-emergent SAEs were reported for 9 patients following cumulative exposure to the study drug; the majority of events were moderate in intensity [redacted]

A summary of the most common TEAEs occurring in ≥ 20% of patients is presented in Appendix M.4. The most common TEAEs were ISRs (385 out of 1145 [34%]), which occurred in all patients.[2, 66] The most common ISRs (≥ 5 patients) were erythema (13 [68%]), hematoma (10 [53%]), skin discoloration (9 [47%]), ISR not otherwise specified (7 [37%]), pain (6 [32%]), atrophy (5 [26%]), and pruritus (5 [26%]). Other common TEAEs included arthralgia (13 [68%]), pain in the extremity (12 [63%]) and back pain (10 [53%]).

B.2.10.6. ALX-HPP-501 (Global HPP Registry)

As of the most recent data cut off ([redacted]), [redacted] patients aged < 18 years and [redacted] patients aged ≥ 18 years had been exposed to AA treatment (ever-treated patients).[59] The median age at initiation of treatment for patients aged < 18 years was [redacted] (min, max: [redacted]), with a median of [redacted] (min, max: [redacted]) from diagnosis to initiation of AA treatment. The median age at initiation of treatment for patients aged ≥ 18 years was [redacted] (min, max: [redacted]), with a median of [redacted] (min, max: [redacted]) from diagnosis to initiation of AA treatment.

Across all age categories at baseline, [redacted] ever-treated patients with data were initiated with an AA dosage of 6 mg/kg/week with most ([redacted] patients) starting at 2 mg/kg 3 times per week.[59] Of the patients with dose and frequency data from treatment initiation to last follow-up, [redacted] patients had stable doses. Median duration of treatment with AA was 2.99 years (minimum, maximum: [redacted] years) with a total exposure of [redacted] person-years. A total of [redacted] ever-treated patients discontinued treatment and the most common reason for treatment discontinuation was physician decision ([redacted].

A summary of the targeted events and SAEs for ever-treated patients is presented in appendix M.4. As of the most recent analysis cut-off date ([redacted]), targeted events and SAEs were reported for [redacted] ever-treated patients aged < 18 years.[59] A total of [redacted] targeted events or SAEs were reported by [redacted] ever-treated patients.

[redacted] were the most frequently reported targeted events or SAEs ([redacted]) and a majority of these [redacted] were [redacted]. The targeted events observed were similar to the overall AA safety profile from clinical studies. A total of [redacted] SAEs were reported by [redacted] ever-treated patients. Most ([redacted] ever-treated patients) of all reported SAEs were considered to be not related to treatment with AA.

As of the most recent analysis cut-off date ([redacted]), targeted events and SAEs were reported for [redacted] ever-treated patients aged ≥ 18 years.[59] A total of [redacted] targeted events or SAEs were reported by [redacted] ever-treated patients. [redacted] were the most frequently reported targeted events or SAEs ([redacted]), and most of these [redacted] were [redacted]. The targeted events observed were similar to the overall AA safety profile from clinical studies. A total of [redacted] SAEs were reported by [redacted] ever-treated patients. Most ([redacted] ever-treated patients) of all reported SAEs were considered to be not related to treatment with AA.

Overall, a total of [redacted] were reported; [redacted] in patients < 18 years (ever-treated) and [redacted] in patients ≥ 18 years (never-treated).[59] However, only [redacted] had a confirmed date of death available; [redacted] < 18 years (ever-treated) and [redacted] ≥ 18 years (never-treated). [redacted].

B.2.10.7. EmPATHY

Retrospective assessment of available patient records and longitudinal photo documentation of injection sites and ISRs showed that 7 (50%) patients self-administered AA injections, and 7 (50%) had their partner or a friend administer the drug.[60] Although patients were advised to rotate their use of 4 subcutaneous injection sites (abdomen, thigh, upper arm and gluteal area), only 1 (7%) patient continually used all injection sites. 8 (57%) patients used 3 different sites, 3 (21%) patients used 2 sites and 2 (14%) patients tolerated injections only at a single injection site (one used the abdomen, 1 used the gluteal area).

The most common AEs were ISRs, with 11 (79%) patients noting reddening and/or tenderness at injection sites with variable intensity and duration sometime during the first 3 months of treatment.[60] This increased to 13 patients following 12 months of treatment. Affected injection sites were the abdomen (n = 12), thigh (n = 4), and upper arm (n = 3).

In addition to ISRs, 46 AEs were recorded in the patients being treated with AA for 12 months; all 14 patients experienced at least 1 AE.[60] Most of these events (n = 33) were not, or were unlikely to be, related to AA treatment. They were associated with underlying disease and/or comorbidities, such as degenerative disease of the spine, lower back pain/lumbago, knee osteoarthritis, myogelosis (muscle tension/stiffness), greater trochanteric pain syndrome and skin irritation. the 13 AEs reported as being possibly related to treatment with AA were: fatigue (n = 2); weight gain (n = 2): headache (n = 2); and back pain, increase in pain, performance loss in daily activities, insufficiency fracture, raised intraocular pressure, small bowel ileus and skin irritation (n = 1 each).

B.2.10.8. Safety summary

In summary, the following conclusions can be made regarding the safety and tolerability profile of AA when looking across all clinical trial data, real-world evidence and the pooled safety analysis presented in Section B.2.8.2:

- AA is well tolerated and suitable for long-term treatment across patients with paediatric-onset HPP, irrespective of age[28, 59, 60, 77]

- The majority of TEAEs were unrelated to AA treatment, while TRAEs were minimal, manageable and associated with low rates of discontinuation
- ISRs and IARs were the most frequently reported TEAEs. This was expected given the subcutaneous administration of the drug
  - Meticulous rotation of injection sites may help prevent ISRs
- Excluding ISRs and IARs, most TEAEs were consistent with the manifestations and management of HPP
- The overall safety profile for adult patients (≥ 18 years) with paediatric-onset HPP was similar to the overall paediatric-onset HPP population[28, 59]

B.2.11. Ongoing studies

The UK MAA and the Global HPP Registry are ongoing, and efficacy and safety data are being collected in both of them.

B.2.12. Interpretation of clinical effectiveness and safety evidence

B.2.12.1. Unmet medical need and innovation of AA

Before AA was approved, no other regulatory-approved treatment existed for HPP, and AA is the only approved treatment for paediatric-onset HPP in the UK.[7] AA directly targets the underlying cause of HPP, leading to increased bone mineralisation and reduced systemic complications associated with the disease. All other available treatments are supportive only, as they do not prevent or delay disease progression and most patients continue to experience significant morbidity and mortality in the most severe cases.[20-22, 34, 40, 55, 79] The limitations of current approaches to symptom management, coupled with their inability to address the underlying aetiology of HPP, indicate the need for an effective and targeted therapy that can change the course of disease in these patients.

The efficacy data presented in Section B.2.6 show that treatment with AA restores functional ALP activity, which is demonstrated by a rapid reduction in substrate concentration of PPi and PLP. This reduction leads to improved bone mineralisation, correction of rickets, improvement in growth and respiratory function, an increase in physical performance, increased HRQL, prolonged survival and an increase in daily

living activities.[2, 4-6, 10, 23, 36, 59, 62-64] The increased availability of a disease-modifying drug that addresses the fundamental biochemical abnormality leading to HPP, such as AA, will have a major impact on the disease morbidity and mortality and fulfil a clear unmet clinical need.

Overall, the efficacy and safety data presented in Sections B.2.6 and B.2.10 support the substantial benefit of AA for the treatment of patients of any age with paediatric-onset HPP. AA improves OS from 27% to 87% compared with historical controls in a pooled analysis of patients with perinatal- and infantile-onset HPP after 7 years of treatment.[36] AA also improves respiratory outcomes in patients with perinatal- and infantile-onset HPP, with VFS rates of 81% after 7 years of treatment. AA improves bone mineralisation compared with baseline, contributing to proper growth and development in patients with paediatric-onset HPP. It also promotes substantial healing of HPP-associated rickets in infants and children with paediatric-onset HPP by 24 weeks, with improvements sustained for up to 8 years.[2, 4-6, 23, 59, 62-64] The consistency and robustness of results across the continuum of inter-related endpoints across all paediatric-onset subgroups further strengthen the conclusion that AA is effective in the treatment of paediatric-onset HPP.

As the above data illustrate, AA has an innovative mode of action and represents a significant change in the management of patients with paediatric-onset HPP. AA offers a life-changing opportunity to patients diagnosed with HPP.

B.2.12.2. Principal findings from the evidence base

AA is the only approved therapy indicated for paediatric-onset HPP and has consistently demonstrated efficacy and safety across patients in a robust clinical programme. with data for up to 7 years of treatment follow-up. Prior to AA, only supportive care and symptoms management were available for HPP patients and their impact on the patients' outcomes are minimal/limited. Treatment with AA was associated with robust, long-term improvements across the continuum of endpoints, including TNSALP biochemical substrates (PPi and PLP), the skeletal system (bone mineralisation, structure and growth), and clinically meaningful improvements in survival, respiratory outcomes, assessments of physical function, ambulation, strength, disability and HRQL.[2, 4-6, 23, 36, 59, 62-64, 66]

In non-AA-treated patients most severely affected by HPP (perinatal- and infantile-onset), mortality ranges from 50% to 100% within 1 year.[20-23] AA improved OS from 27% to 87% compared with historical controls in a pooled analysis of patients with perinatal- and infantile-onset HPP (ENB-002-08/ENB-003-08 and ENB-010-10) after 7 years of treatment.[36] In addition, as of the most recent analysis cut-off date for the UK MAA, [redacted] participants in the Paediatric Population had died.[28] [redacted]) participants were classified as the most severely affected by HPP (perinatal- and infantile-onset), so these results demonstrate that AA is a lifesaving drug for babies born with HPP.

The primary cause of mortality in patients with infantile-onset HPP is respiratory failure.[20, 22, 23] Patients with respiratory failure are managed by the use of invasive and sometimes non-invasive mechanical ventilation, but historically, patients with HPP who are ventilated almost always die after prolonged periods of time because the underlying cause of the disease is not being addressed. AA is designed to treat the underlying cause of respiratory compromise in patients with HPP, improving respiratory function and survival. 36 of the 70 patients (51%) with infantile-onset HPP treated with AA in ENB-002-08/ENB-003-08 and ENB-010-10 required ventilator support.[4, 6, 62, 63] Of these, 29 patients were on ventilator support at baseline and 20 patients were successfully weaned from all ventilator support at last follow-up. In the Global HPP Registry, [redacted] ever-treated patients in the < 18 years and perinatal-/infantile-onset group were on invasive ventilation.[59] Of these patients, [redacted] patients stopped invasive ventilation following AA treatment. In addition, as of the most recent analysis cut-off date for the UK MAA, [redacted] patients in the Paediatric Population required respiratory support including invasive ventilation support, most ([redacted]) of whom were classified as the most severely affected by HPP (perinatal- and infantile-onset).[28] In the pooled analysis described above, treatment with AA markedly increased the probability of invasive VFS in patients with perinatal- and infantile-onset HPP (ENB-002-08/ENB-003-08 and ENB-010-10) compared with untreated historical patients, with VFS rates of 81% after 7 years of AA treatment compared with 25% for untreated historical controls.[36]

AA improves bone mineralisation compared with baseline, which contributes to proper growth and development in patients with paediatric-onset HPP.[2, 5, 64, 66] In

addition, AA promotes substantial healing of HPP-associated rickets in infants and children with paediatric-onset HPP by 24 weeks, with improvements sustained for up to 7 years.[2, 4-6, 23, 59, 62-64]

AA enhances growth among paediatric and adolescent HPP populations relative to healthy peers, with weight and height improvements sustained for up to 5 years.[2, 4-6, 23, 59, 62-64] As expected for children, mean and median height and weight increased over the course of the studies. However, mean and median changes from baseline in Z-scores for height and weight increased over time and with treatment, reflecting improvements in growth relative to healthy, same-aged peers. [redacted] results were observed in the UK MAA and the Global HPP Registry in patients < 18 years of age at baseline.[28, 59]

AA offers significant improvements in ambulation and gait compared with age-matched healthy peers in patients with paediatric-onset HPP, as assessed by the 6MWT.[2, 5, 28, 60, 64, 66] In the UK MAA, ENB-006-09/ENB-008-10, ENB-009-10 and patients < 18 years of age in the Global HPP Registry, the median distance walked increased more than the MCID of 25 metres after up to 7 years of treatment. This suggests that ambulatory capacity in paediatric patients becomes normalised, independent of changes in age and height.[2, 5, 28, 59] Similar results were observed for adult patients with paediatric-onset HPP in the UK MAA, the Global HPP Registry and in the real-world EmPATHY study. The median distance walked increased more than the MCID, indicating a significant improvement in the 6MWT in adult patients.[28, 59, 60]

AA-treated patients with perinatal- and infantile-onset HPP acquired new motor and cognitive skills, reflecting sustained functional improvements versus profound developmental delays at baseline.[2, 5, 6, 28, 62, 63] In the UK MAA, median [redacted] in upper and lower BAMF scores were observed in patients in the Paediatric Population (aged 1–4 years at time of annual baseline) from baseline to Month [redacted]. This [redacted].[28] In study ENB-002-08/ENB-003-08, all 9 patients showed improvements in age-equivalent BSID-III Gross Motor, Fine Motor, and Cognitive subscale scores over time, indicating motor skill improvement and reduced developmental delay.[6, 62] In addition, median Locomotion standard scores of the PDMS-2 improved from [redacted] at Week 72 to [redacted] at last overall

assessment. In ENB-010-10, most patients with ≥ 2 assessments showed [redacted] in age-equivalent scores on at least 1 of the BSID-III subscales. This indicated that patients acquired new gross motor, fine motor and cognitive skills while receiving treatment with AA.[63] Locomotion standard scores of the PDMS-2 [redacted] patients with scaled scores on 2 or more assessments. This suggests rapid skill acquisition, as patients acquired more skills in a given time frame than would generally be expected during locomotion development.

AA offers sustained improvements in strength, running speed and agility for up to 5 years versus age-matched healthy scores across patients with paediatric-onset HPP, irrespective of age.[2, 5, 6, 62, 63] In ENB-006-09/ENB-008-10, median composite standard scores for BOT-2 strength and agility significantly improved from 28 at baseline to 37 at Month 6. It then remained significantly improved at all timepoints ($p \leq 0.0002$) through 7 years of treatment. BOT-2 scores were sustained within the normal reference range for healthy peers at all visits from 1 through 7 years.

Treatment with AA significantly reduces pain in patients with paediatric-onset HPP, with sustained improvements over the long term.[2, 5, 64, 66] Patients in ENB-006-09/ENB-008-10 demonstrated improvements in pain as measured by the CHAQ. Significant decreases in the mean pain score were observed for patients in the combined group at most assessments up to 7 years of treatment.[64] For patients in ENB-009-10, BPI-SF scores improved over the ETP, with a median (min, max) decline from baseline of -1.0 at Year 1 and -3.5 up to 5 years of treatment, indicating a reduction in pain.[2, 66] In the UK MAA, adult participants demonstrated an overall [redacted] in pain (i.e. [redacted]).[28] In addition, in the Global HPP Registry, BPI-SF change from baseline scores were consistently less than 0 in adult patients with paediatric-onset HPP, indicating [redacted] in pain over time while on AA.[70] In the real-world EmPATHY study, median pain intensity decreased to 5 points after 12 months of treatment in adult patients, corresponding to a 17% improvement from baseline.[60] In addition, 8 adult patients used pain medication daily, and 6 patients used a combination of pain medications. After 6 months of

treatment, 2 patients were able to discontinue use of pain medication; 1 patient was not using pain medication at 12 months.

Treatment with AA provides significant improvements in functional disability with sustained improvements over the long term.[5, 59] Patients enrolled in ENB-006-09/ENB-008-10 demonstrated increases from baseline in CHAQ disability index (CHAQ-DI) (reflecting improvements in tasks involved in dressing and grooming, feeding, arising, and walking).[5, 64] The change in median CHAQ-DI score from baseline was statistically significant following AA treatment at every assessment from Month 1 to Year 7, with a median score of 0 (no disability detectable by CHAQ) at 2 years that was sustained through 7 years of treatment.[5] Consistent with CHAQ-DI scores, AA-treated children aged ≤ 10 years also demonstrated improvements in PODCI. In the Global HPP Registry, for ever-treated patients aged ≥ 18 years, the median HAQ-DI score [redacted] by a median of [redacted] from baseline to last follow-up, indicating an [redacted] in disability score following AA treatment.[59]

Treatment with AA increases HRQL in patients with paediatric-onset HPP. In the UK MAA and the Global HPP Registry, HRQL was measured by PedsQL for patients aged > 2 to < 18 years.[28, 59] In the UK MAA, the median change from baseline to Month [redacted] in PedsQL total score was [redacted] for paediatric-reported and [redacted] for parent-reported, demonstrating an [redacted] in QoL.[28] In the Global HPP Registry, the mean PedsQL total score reported for ever-treated patients < 18 years [redacted] by [redacted] from baseline to last follow-up, indicating an [redacted] in functioning. In ever-treated adult patients with paediatric-onset HPP, SF-36v2 change from baseline scores were consistently [redacted] for the PCS and the majority of its subscales (physical functioning, bodily pain, general health perception, physical role functioning) over time, suggesting [redacted] in physical HRQL while on AA.[70] In addition, change values were consistently over the MCID of 2 for the PCS. In the real-world EmPATHY study, the median PCS score of the SF-36v2 increased to 33 after 12 months of treatment ($p = 0.010$) in adult patients, corresponding to a 27% improvement.[60] In the real-world Dahir 2022 study, there was a statistically significant [redacted] from baseline to [redacted] across [redacted] PROs (PHQ-9 total, PROMIS-29 domain and RAPID3 domain scores).[61] Additionally, based on the WPAI-SHP, there was no significant [redacted] in employment between baseline and

Month 6, and there was a significant [redacted] at [redacted] in absenteeism, presenteeism, activity impairment and work productivity loss.

The observed efficacy improvements were sustained for up to 7 years of treatment. The consistency of results across the continuum of inter-related endpoints across all paediatric-onset subgroups further strengthens the conclusion that AA is effective in the treatment of paediatric-onset HPP.

AA is well tolerated and suitable for long-term treatment across patients with paediatric-onset HPP, irrespective of age.[28, 59, 60, 77] The majority of TEAEs were unrelated to AA treatment, and TRAEs were minimal, manageable, and associated with low rates of discontinuation. ISRs and IARs were the most frequently reported TEAEs across all studies, but this was expected given the subcutaneous administration of the drug. Meticulous rotation of injection sites may help prevent ISRs. A total of 10 deaths (all in patients with perinatal-/infantile-onset HPP) were reported in the long-term clinical trials, with only 1 death linked to AA treatment and attributed to pneumonia.[77] The overall safety profile for adult patients (≥ 18 years) with paediatric-onset HPP was similar to the overall paediatric-onset HPP population.[28, 59]

B.2.12.3. Strengths and limitations of the evidence base

The AA clinical trials were considered to be good quality studies, being conducted in accordance with Good Clinical Practice guidelines. The majority of studies were of good quality, with all of the studies assessed as low risk of bias in terms of randomisation, withdrawals, outcome selection and reporting, and statistical analysis.

AA has consistently demonstrated efficacy and safety across patients in a robust clinical programme with data for up to 7 years of treatment follow-up. AA is generally well tolerated, with a safety profile showing that it is suitable for long-term treatment of patients with paediatric-onset HPP. The data show that long-term clinically meaningful benefits from AA treatment in patients with paediatric-onset HPP were similarly observed across a continuum of efficacy endpoints. This started with a reduction of TNSALP substrate levels, followed by improvements in bone mineralisation, skeletal structure, physical function, HRQL, respiratory outcomes and

OS.[2, 4-6, 23, 36, 59, 62-64, 66] In addition, results from the UK MAA, the Global HPP Registry and the EmPATHY study have demonstrated real-world effectiveness and safety of AA.[28, 59, 60]

These results support the hypothesis that ERT with AA corrects the underlying biochemical cause of HPP, and that addressing the bone mineralisation deficiencies common to all patients with HPP can potentially prevent or reverse the severe and life-threatening systemic complications of this disease. The consistency of long-term results across all paediatric-onset subgroups, and the consistency across the inter-related endpoints that reflect the underlying pathophysiology of HPP, strengthens the conclusion that AA is effective in the treatment of paediatric-onset HPP.

Head-to head studies versus best supportive care were considered unethical given the high unmet medical need in HPP, the serious morbidity and mortality risk, the potential for irrevocable harm to affected organ systems and the absence of any alternative disease-modifying treatments (Section B.2.3). As such, single arm, long-term AA clinical trials (ENB-002-08/ENB-003-08, ENB-010-10 and ENB-006-09/ENB-008-10) were conducted as well as 2 non-interventional retrospective studies and 1 sub-study that to provided historical control data to use in comparative analyses of selected endpoints.

A strength of the UK MAA is that the efficacy of AA in the Adult Population was similar to the efficacy observed for adult patients in the ENB-009-10 clinical trial. Participants in the Adult Population typically showed improved QoL and walking ability (Bleck and 6MWT scores) with AA treatment over time. Additionally, adult participants demonstrated an overall reduction in the use of mobility aids and an overall reduction in pain (i.e. lower BPI-SF scores, no increase in analgesic usage and a reduction in opioid use as of the analysis cut-off date). Considering that all participants in the Adult Population started treatment with AA after enrolling in the MAA, these data are encouraging. It is possible that improved QoL scores in this population were largely due to increased mobility, reduced pain and lower fracture occurrence with AA treatment over time.

While the magnitude of effect observed in the UK MAA Paediatric Population may not seem as impressive as the data reported in the clinical trials, AA consistently demonstrated a positive effect on OS, respiratory support and physical functioning.[28]

In addition, there were [redacted] deaths in the Paediatric Population, and the level of respiratory support required was much [redacted] than what was reported in the AA registration studies. Furthermore, although the [redacted] of participants in the Paediatric Population treated in the MAA had already benefited from [redacted] years of AA treatment, and had therefore likely experienced most of the notable benefits of AA treatment before enrolling on the MAA, they continued to benefit throughout the MAA.

While the adolescent and adult populations patient numbers in the AA clinical trial programme were small (6 adolescents and 13 adults in ENB-009-10), this is unsurprising given HPP is an ultra-rare disease. Additional evidence captured in the UK MAA and Global HPP Registry supports the trial results and provides data for a large sample of [redacted] adult patients with paediatric-onset HPP treated with AA.[28, 59] In addition, data from the real-world EmPATHY study have demonstrated the real-world effectiveness of AA among adults with paediatric-onset HPP, particularly for the improvement of fracture healing, physical function and HRQL.[60]

No factors have been identified that might influence the external validity of the data provided. Real-world results from the UK MAA and ongoing experiences in the Global HPP Registry and the EmPATHY study demonstrate that the efficacy and tolerability of AA is reproduced in routine clinical practice.

Although the AA clinical trial programme included limited numbers of UK patients, the disease pathophysiology and clinical progression are common among all patients with HPP. As such, no differences are expected between UK patients and those in the trials. In addition, the AA clinical trials included a broad range of patients with HPP who had similar baseline characteristics to patients who were included in the UK MAA, so they are considered representative of the general population of patients in England (Appendix M.1) that can benefit from AA treatment.

B.3. Cost effectiveness

B.3.1. Published cost-effectiveness studies

A systematic search was conducted to identify existing cost-effectiveness studies in HPP. Full details of the search methods and results are presented in Appendix G. The search showed that there are no published cost-effectiveness analyses assessing treatment of paediatric-onset HPP.

Searching the NICE website identified one previous Highly Specialised Technology (HST) appraisal for HPP. This NICE submission from 2017 assessed the cost-effectiveness of AA treatment for patients with HPP.[7] The results of this submission are presented in Table 32. This submission is an updated submission of the same product and indication following completion of the MAA.

Table 32: Summary list of published cost-effectiveness studies

Study name	Model health states and definition	Modelling outcomes (base case)		
		QALYs/life years	Costs	ICERs
NICE HST6 (asfotase alfa) 2017[7]	The company's economic model had 6 states; there are 2 death health states and 4 alive health states. The 4 alive health states are according to the level of severity defined based on vignettes developed in collaboration with clinical experts with experience managing HPP • SLI (6MWT > 82.2% of predicted value) • SLII (82.2% ≥ 6MWT > 64.4% of predicted value) • SLIII (64.4% ≥ 6MWT > 46.6% of predicted value) • SLIV (46.6% ≥ 6MWT of predicted value) 2 death health states: • HPP death state • Background death state Invasive ventilator toll state: the invasive ventilator state is included as a toll state for patients < 5 years old, meaning that patients observed in the trials who required invasive ventilation received a health utility decrement and additional direct medical costs. All patients who experience invasive ventilation are assumed to transition to the SLIV state.	<u>Company's base case</u> Total QALYs (discounted): AA: 37.53 BSC: 12.48 Incremental (AA vs BSC): 25.04 Life years (discounted): AA: 44.85 BSC: 44.85 Incremental (AA vs BSC): 0 <u>Base case (revised analysis) 3.5% discount rate</u> Incremental (AA vs BSC) QALYs: Perinatal/infantile: 18.21 Age 0–4: 16.66 Age 5–11: 15.64 Age 12–17: 15.19 Age 18+: 13.47 <u>New base case (revised analysis) without annual per-</u>	<u>Company's base case</u> Total costs (discounted): AA: data redacted BSC: £336,447 Incremental (AA vs BSC): Data redacted <u>Company's model with ERG assumptions</u> Total costs (undiscounted): AA: data redacted BSC: £182,661 Incremental (AA vs BSC): Data redacted	N/R

Study name	Model health states and definition	Modelling outcomes (base case)		
		QALYs/life years	Costs	ICERs
		patient expenditure cap (1.5% discount rate) QALYs Incremental (AA vs BSC) QALYs: Base case: 25.04 Perinatal/infantile: 31.70 Age 0–4: 28.99 Age 5–11: 24.87 Age 12–17: 22.33 Age 18+: 5.07		
NICE HST6 (asfotase alfa) 2017 ERG[7]	The ERG considered that the company should have submitted separate models for people under 5 years old and for people 5 years or older, because the manifestations of hypophosphatasia and the effect of AA are different in these populations. The ERG exploratory analysis: • Estimated the transition probabilities using a single probit model for both AA and BSC, and controlled for treatment effect • Additional exploratory analysis for younger patients with paediatric-onset HPP: • ERG developed a new economic model structure with 2 health states: 'Alive' and 'Dead' • 'Alive' patients could also have invasive ventilation	ERG base case results using the company's model Discounted 1.5% results: Total QALY: AA: 36.55 BSC: 12.38 Incremental (AA vs BSC): 24.17 Total life years: AA: 43.85 BSC: 44.55 Incremental (AA vs BSC): -0.70	ERG base case results using the company's model Discounted 1.5% results: Total cost: AA: data redacted BSC: £331,843 Incremental (AA vs BSC): data redacted Discounted 3.5% results: Total cost: AA: data redacted BSC: £195,154 Incremental (AA vs BSC): data redacted	N/R

Study name	Model health states and definition	Modelling outcomes (base case)		
		QALYs/life years	Costs	ICERs
		Discounted 3.5% results: Total QALY: AA: 21.59 BSC: 7.46 Incremental (AA vs BSC): 14.13 Total life years: AA: 26.02 BSC: 26.41 Incremental (AA vs BSC): -0.39		

Key: 6MWT, 6-minute walk test; AA, asfotase alfa; BSC, best supportive care; ERG, Evidence Review Group; HPP, hypophosphatasia; HST, highly specialised technology; ICER, incremental cost-effectiveness ratio; NICE, National Institute for Health and Care Excellence; N/R, not reported; QALY, quality-adjusted life year; SL, severity level.

B.3.2. Economic analysis

There are no published cost-effectiveness analyses that assess treatment of paediatric-onset HPP. This finding is consistent with an SLR of studies of relevance to the economic evaluation, as described in Appendix G.

While no published cost-effectiveness analyses were identified, the SLR identified the initial HST NICE submission for AA for treating paediatric-onset HPP. The model that was submitted as part of the initial HST submission has been updated for the current analysis.

Additional cost-effectiveness analyses of AA for paediatric-onset HPP have been conducted as part of health technology assessment (HTA) in several countries, including Canada (CADTH[80] and INESSS[81]), Sweden[82], the Netherlands[83], France[84], and Australia.[85, 86] Feedback collected during the original NICE HST6 submission and from other HTA bodies have been incorporated into the updated model used in this submission.

B.3.2.1. Patient population

The base case population is patients with paediatric-onset HPP. The patient groups included in the cost-effectiveness analysis are:

- Patients diagnosed with perinatal-/infantile-onset HPP (onset before or at birth/onset at 0–6 months)
- Patients with juvenile-onset HPP (onset 6 months/1 year–17 years)

Patient groups were informed by published literature, which suggests patients may be severely affected regardless of the age of disease onset.[34, 40] However, mortality associated with HPP is predominantly experienced by patients with perinatal-/infantile-onset HPP, typically from respiratory complications.[20, 21, 23, 79]

The baseline age modelled for each patient group is presented in Table 33 below.

Table 33: Economic evaluation of patient groups

Patient group	Age (years) at baseline (SE)	Justification
Patients with perinatal-/infantile-onset HPP	0.0 (N/A)	The mean age of onset is 1 month old.[23] This rounds down to 0 months based on the model's 12-week cycle length. Efforts are made in clinical practice in England to ensure patients are diagnosed and treated as soon as possible. If skeletal defects are suspected during pregnancy or after birth, patients are referred to 1 of 3 UK specialist centres. Therefore, assuming patients start treatment at birth is deemed appropriate.
Patients with juvenile-onset HPP	5.0 (3.6)	All patients with juvenile-onset HPP are assumed to begin treatment at age of admission. According to Table 1 of Whyte et al. (2016)[3], among patients with 'severe childhood' HPP (N = 37), the mean age at first admission was 4.9 years (SD = 3.6 years), which is rounded to 5.0 years. Scenario analysis was conducted using the average age of patients receiving AA with juvenile-onset HPP at first admission from the MAA and clinical studies. 24 patients were included from the MAA and 27 from the clinical studies, with an average age of 26.5 years.
Key: AA, asfotase alfa, HPP; hypophosphatasia; MAA, managed access agreement; N/A, not applicable; PSA, probabilistic sensitivity analysis; SD, standard deviation; SE, standard error. **Note:** Age at baseline is the age at which patients start treatment in the model; age at onset is the age of HPP onset.		

The proportion of female patients (46.7%) was informed by the clinical studies ENB-002-08/ENB-003-08, ENB-010-10, ENB-006-09/ENB-008-10, ENB-009-10, ENB-011-10, and ALX-HPP-502.

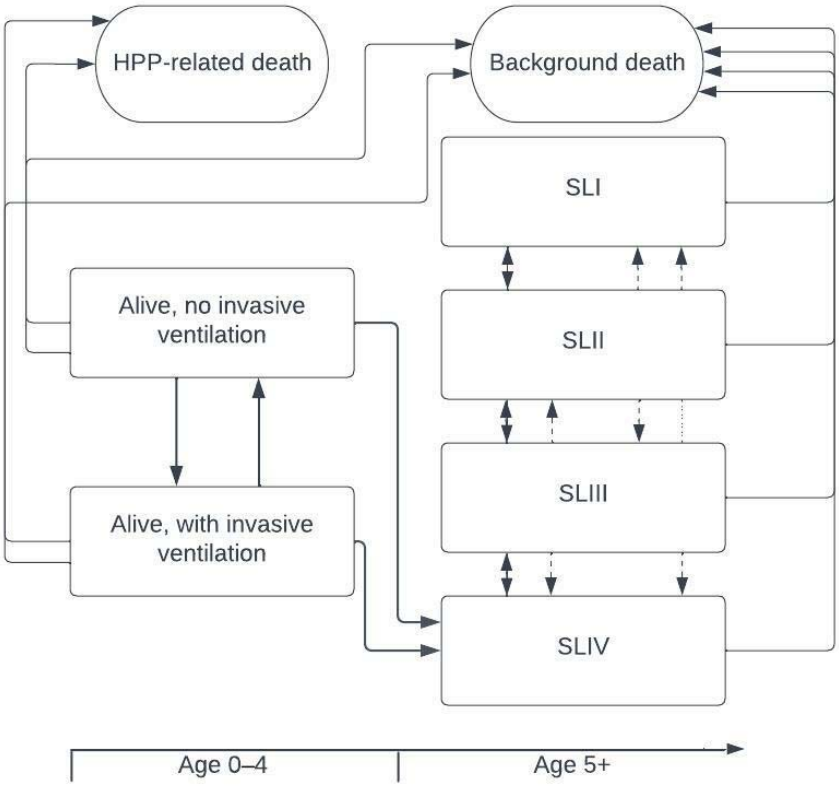
B.3.2.2. Model structure

The cost-effectiveness model is a cohort Markov model. The model structure is shown in Figure 34. The modelling approach is consistent with the economic model submitted and accepted in the original HST appraisal. A key difference in the updated model structure is that the health states included in the model depend on the age of the patients. Patients aged < 5 years are modelled according to their ventilation status, whereas patients aged 5+ years are modelled according to their severity of disease. This was implemented to account for the differences in HPP disease manifestations and effects of AA treatment for patients under 5 years old

and patients over 5 years old and addresses the Evidence Review Group's (ERG's) main structural concern with the original NICE submission.[87]

A more detailed comparison of the key differences between the current model and the model previously submitted to NICE is provided in Appendix N.

Figure 34: Model schematic



Key: HPP, hypophosphatasia; SL, severity level.

The model is split between patients who are under 5 years of age and patients who are over 5 years of age. This split reflects the difference in clinical manifestations between younger and older patients, as mortality and respiratory complications (ventilator use) are imminent risks for young patients with HPP, but much less so in older patients. For older patients, managing the severity of HPP symptoms is the focus of care, as there is a lack of evidence regarding excess mortality of HPP at ages greater than 5. However, clinical experts have stated patients with HPP are more likely to have increased comorbidities, which could impact mortality. Further

details on the clinical data and methods used to inform transitions are outlined in Section B.3.3.

Descriptions of the health states are given below:

Ages < 5 (i.e. 0–4) years:

- Alive, no invasive ventilation: patients aged 0–4 years are described as invasive ventilation-free or transitioning to the invasive ventilation state
- Alive, with invasive ventilation: patients transitioning to the invasive ventilation state receive a health utility decrement and additional direct medical costs. Rates of transition to the invasive ventilation state are based on the rates observed in the ENB-002-08/ENB-003-08 and ENB-010-10 (AA, N = 37) and ENB-011-10 (historical control N = 48) studies according to Whyte et al. (2016)[23]
- HPP-related death: the HPP-related death state is a terminal state based on mortality reported in trials for patients aged 0–4 years (also based on Whyte et al. [2016][23], as well as supplementary data for ENB-010-10). Data from the UK MAA were also included for the AA arm. An assumption was made that the risk of HPP-related death relates strictly to age, as per the trial observations. This means that there is no risk of HPP-related mortality for ages 5 and above, and mortality risk is applied in line with patient age

Ages 5+:

- Alive severity level (SL) states: these states reflect 4 levels of paediatric-onset HPP disability in patients aged 5+ years. They reflect clinical experts' characterisation of the clinical symptoms and complications that are likely to be associated with different levels of disease severity. The range of MCID in percent of predicted 6MWT, calculated for patients with paediatric-onset HPP, serves as a proxy for the levels of severity. These states are described in detail below
- Background death: the background death state is a terminal state based on mortality from all causes. Patients can transition to this state at any age during the model's horizon. Age-specific rates are based on life tables for England and Wales[88]

For patients aged 5+ years, conditional on being alive, patient progression through disease SLs was modelled using change in percent of predicted 6MWT as a proxy for severity. Given the complexity of HPP and the extent of clinical outcomes that are affected by living with HPP, it is likely that this economic model does not capture the full extent of living with HPP and therefore may underestimate the benefit of AA for patients with HPP. The 6MWT was used as a proxy to classify disease severity. Even though the 6MWT only assesses mobility, studies have shown that it correlates well with HRQL in a variety of disease areas, such as Type 2 diabetes, breast cancer, DMD, chronic obstructive pulmonary disease, and intermittent claudication.[89-93] Its value as a proxy for general disease severity has resulted in its use in HTAs for various diseases affecting the skeletal system, including ataluren for DMD (NICE HST3)[94], elosulfase alfa for treating mucopolysaccharidosis type IVa (NICE HST2)[95] and the previous AA submission to NICE (NICE HST6).[7]

At the previous Appraisal Committee meetings for AA, the Committee stated that although it would have preferred a model structure that captured all symptoms of HPP, it accepted that using 6MWT distance to define health states was reasonable due to the lack of evidence allowing for alternative structures. Although the 6MWT may not fully capture all the symptoms of HPP and in turn all the benefits of AA, correlations between 6MWT and other trial outcomes were noted. These include: QoL (as measured by the CHAQ); pain (as measured by CHAQ and the POSNA's PODCI); and various measures of physical and social functioning (as measured by the PODCI). This is shown in Table 34.

Table 34: 6MWT correlations with other trial endpoints (ENB-006-09 / ENB-008-10)

Correlation of 6MWT distance walked (m) with:	N[a]	r[b]	p-value[c]
CHAQ Disability Index	127	-0.57	< .001
CHAQ Pain Index	149	-0.28	0.0487
POSNA PODCI Global Functioning Scale Norm-Parent	127	0.76	< .001
POSNA PODCI Transfer and Basic Mobility Scale Norm-Parent	127	0.69	< .001
POSNA PODCI Sports/Physical Functioning Scale Norm-Parent	127	0.78	< .001

Correlation of 6MWT distance walked (m) with:	N[a]	r[b]	p-value[c]
POSNA PODCI Upper Extremity Scale Norm-Parent	127	0.52	< .0001
POSNA PODCI Pain/Comfort Scale Norm-Parent	127	0.41	0.0060
POSNA PODCI Happiness Scale Norm-Parent	127	0.37	0.0004

Key: 6MWT, 6-minute walk test; CHAQ, Childhood Health Assessment Questionnaire; PODCI, Pediatric Outcome Data Collection Instrument; POSNA, Pediatric Orthopaedic Society of North America
Notes: [a], number of paired patient values; [b], Pearson correlation coefficient; [c], 2-sided p-value from asymptotic test that H0: r = 0.
Source: Tomazos et al. 2016[96] ;Phillips et al. 2019[97]

In ENB-006-09/ENB-008-10, the 6MWT strongly correlated with the Rickets Severity Score (RSS; r = -0.7279). This shows that 6MWT is an appropriate proxy for the severity of musculoskeletal symptoms of HPP, in addition to the QoL, pain, and physical and social functioning correlations reported in Table 35. The strong correlation of 6MWT and RSS, in addition to the correlation between RSS, the RGI-C and bone biopsies of the amount of unmineralised bone matrix (osteoid volume and surface), further supports the relevance of the 6MWT as an indicator of the underlying disease process that affects patients with paediatric-onset HPP.

Table 35: 6MWT correlation between trial endpoints (ENB-006-09 / ENB-008-10)

Correlation between:		Pearson's correlation coefficient (p-value)
6MWT		
6MWT[a]	BOT-2[b]	-0.73654 (< 0.0001)
6MWT	Bone biopsy[c]	-0.21850 (0.3050)
6MWT	CHAQ[d]	-0.36931 (< 0.0001)
RSS		
RSS	6MWT	-0.72790 (< 0.0001)
RSS	RGI-C	-0.66441 (< 0.001)

Key: 6MWT, 6-Minute Walk Test; BOT-2, Bruininks-Oseretsky Test of Motor Proficiency, 2nd Edition; CHAQ, Childhood Health Assessment Questionnaire; RGI-C, Radiographic Global Impression of Change; RSS, Rickets Severity Score.
Notes: [a] Percent of predicted normal; [b] Shuttle run in seconds; [c] Osteoid thickness, percent healthy mean; [d] Measure of pain.
Source: Tomazos et al. 2016[96]; Whyte et al. 2015.[43]

Risks of transitioning between SLs were calculated with data from clinical studies in children, adolescents and adults. Ordered probit regressions were estimated with patient data to predict SL in the period that followed (i.e. at the following 12-week follow-up in the trials) as a function of SL at the previous visit and patient age. The estimated ordered probit regression was then used to predict a dynamic Markov model that varies by patient age. Specifications of the ordered probit models are described below.

The model's SL health states were stratified by the 6MWT as a percentage of predicted thresholds, using the MCID for paediatric-onset HPP of 8.8%.[96] A doubled estimate (17.6%) of MCID as a percentage of 6MWT distance at baseline was used to stratify health states. The doubling of MCID per state is based on the rationale that a patient could be in the middle of a health state and experience a severity increase or decrease up to, but not greater than, the MCID threshold, and still remain in the same severity state. In this case, a patient would not perceive a difference in health status, or the patient's doctor would not consider a change in patient management. This is aligned with the base case model submitted in the original NICE submission (NICE HST6).[7]

4 HPP severity health states were defined to cover the spectrum of patient presentations in the trial data, shown in Table 36 below.

Table 36: Health state definitions, based on the 6MWT as a percentage of predicted distance

Health state	6MWT as a percent (%) of predicted		
	Age 5–12 years	**Age 13–17 years**	**Age ≥ 18 years**
SLI (lowest impact on ambulation)	82.5–100	82.7–100	84.1–100
SLII	64.9–82.4	65.3–82.6	68.1–84.0
SLIII	47.3–64.8	47.9–65.2	52.1–68.0
SLIV (highest impact on ambulation)	≤ 47.2	≤ 47.8	≤ 52.0
Key: 6MWT, 6-minute walk test; SL, severity level.			

General model settings

In accordance with the NICE reference case, the base case cost-effectiveness analysis is conducted from an NHS and Personal Social Services (PSS) perspective. It considers the costs that are directly related to the medical treatment of HPP and the QoL of patients with HPP and their carers.

A lifetime horizon was selected (modelled until the age of 101 years). Due to the potential for differences between AA and BSC in mortality (for perinatal-/infantile-onset), lifelong morbidity, disutility, and costs in patients with paediatric-onset HPP, a lifetime horizon is appropriate.

The model cycle length is 12 weeks. This is the lowest common denominator in the time between visits in the trials used to inform the data. In ENB-006/ENB-008, mobility assessment visits occurred every 12 weeks until Week 72, then every 24 weeks thereafter. In ENB-009, the mobility assessment visits occurred every 12 weeks until Week 24 (2 visits), then every 24 weeks thereafter. Half-cycle correction was applied in the model.

In the base case, an annual discount rate of 3.5% is applied as per NICE recommendations. A lower annual discount rate of 1.5% for health effects is tested in scenario analysis, as the NICE methods state that a discount of 1.5% may be considered when benefits are likely to be sustained over a very long period.[98]

The general model settings and justifications are summarised in Table 37.

Table 37: Features of the economic analysis

Factor	**Current evaluation**	
	Chosen values	**Justification**
Perspective	• NHS and PSS perspective in the base case • Societal perspective considered in scenario analyses	As per NICE reference case.
Cycle length	• 12 weeks • Half-cycle correction applied	The time between 6MWT observations in the trials is 12 weeks.
Time horizon	• The model has a lifetime model horizon (age of 101 years)	NICE recommends that a lifetime horizon is required when there are differences in survival or benefits between alternative treatments that may persist for the remainder of a person's life. Due to the potential for

Factor	Current evaluation	
	Chosen values	**Justification**
	• Shorter time horizons tested in sensitivity analyses (10, 25, 50 years)	differences between AA and BSC in mortality, lifelong morbidity, disutility and costs for patients with paediatric-onset HPP, a lifetime horizon is appropriate.
Discounting of costs and benefits	• Discount of 3.5% annually for costs and benefits • Discount rates for costs and benefits of 0.0% and 1.5% are tested in sensitivity analyses	As per NICE reference case.
Source of utilities	Clinician-derived utilities are used for patient utilities. Carer disutility is based on values derived from published literature	The modelled health states represent a combination of multiple factors described in the vignettes that clinicians scored with the EQ-5D. This is in line with the values used for the original submission.
Source of costs	Costs related to the NHS and PSS were sourced from NHS Reference Costs and PSSRU unit costs. Other cost inputs were informed by literature	As per NICE reference case
Treatment waning effect	No	Treatment waning is not applied in the model as patients receive treatment for the entire duration of the model (lifetime).
Key: 6MWT, 6-Minute Walk Test; AA**,** asfotase alfa; BSC best supportive care; HPP, hypophosphatasia; MAA, managed access agreement; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; PSS, Personal Social Services; PSSRU, Personal Social Services Research Unit.		

B.3.2.3. Intervention technology and comparators

Intervention

AA is a bone-targeted enzyme replacement therapy designed to address the underlying cause of HPP. By replacing deficient activity of the TNSALP enzyme, AA prevents or reverses the mineralisation defects of the skeleton, which prevents systemic patient morbidity and premature death. AA is indicated by the European Commission (EC) for long-term enzyme replacement therapy in patients with paediatric-onset HPP to treat the bone manifestations of the disease.[1]

Recommended dosage consists of a regimen of 6 mg/kg of body weight administered subcutaneously each week.

Comparator

The relevant comparator to AA is BSC, as there are no other approved treatments for people with HPP. The BSC options currently available for HPP include:

- Medical management of symptoms and functional disorders such as seizures; chronic muscle and/or skeletal pain; respiratory complications; renal complications; and gastrointestinal complications
- Neurosurgical interventions for craniosynostosis
- Physical therapy to help improve muscle function, conditioning and strength, as well as mobility
- Orthopaedic management of fractures and pseudofractures
- Dental monitoring, including preventative care and dental hygiene aimed at avoiding a bacterial invasion

B.3.3. Clinical parameters and variables

B.3.3.1. Transition probabilities

The model structure is divided into 2 parts, with patients < 5 years of age being modelled differently to those aged 5+ years of age. The sections below outline the different clinical parameters used to model transitions between health states.

B.3.3.1.1. Mortality

Death is an absorbing health state in the model. For patients < 5 years of age, HPP-specific mortality and background mortality is applied in the model. For patients aged 5 years and over, an assumption was made that they have the same mortality risk as the general population. Although clinicians have indicated that the risk of mortality may be increased due to co-morbidities resulting from HPP, this conservative modelling approach is applied due to the lack of evidence regarding HPP-related mortality risk for patients above 5 years of age. General population mortality estimates were obtained from the Office for National Statistics (ONS) life tables for England and Wales and weighted by patient sex.[88]

B.3.3.1.1.1. HPP mortality

As with the previous NICE submission, HPP mortality is applied in the model to patients under 5 years of age. This is because patients with perinatal-/infantile-onset HPP have the highest risk of mortality. Data from the pivotal publication of the perinatal-/infantile-onset clinical trials were used, as reported by Whyte et al. 2016[23], with the addition of 43 treated patients from trial ENB-010-10 and [redacted] patients from the UK MAA. The total number of patients included was 48 for the BSC arm and [redacted] for the AA arm. All patients were required to have a documented diagnosis of perinatal-/infantile-onset HPP and to have presented symptoms before 6 months of age. Mortality risk was applied as a function of actual age. In the base case, HPP-related mortality was modelled as observed (i.e. based on Kaplan–Meier survival curves obtained from AA studies and historical control studies).

Table 38 and Table 39 demonstrate HPP death in the first 10 12-week time periods from birth for the AA- and BSC-treated patients, respectively. S(t) is the proportion of the original population alive at time t; f(t) is the proportion of the remaining population from the prior time period who died in the current time period. No parametric survival modelling was conducted in this analysis, as death occurs in the model as it is observed in the data for each age. The NICE Decision Support Unit (DSU) Technical Support Document (TSD) 14 states that extrapolation is required if clinical trial data are incomplete.[99] In this case, as HPP mortality was only applied for the first 5 years in the model and the trial data were mature for a greater duration than was required (i.e. a 7-year follow-up), extrapolation was not required. Figure 35 shows the Kaplan–Meier curves for both AA and BSC. For the BSC arm, the current base case aligns with the ERG's preferences to the original NICE submission, where patients who died on the first day were excluded from the analysis as it was considered likely that these patients would not be started on AA treatment.[87] This resulted in a total of 41 patients being included in the BSC arm, instead of 48.

Table 38: HPP death in the first 10 cycles (12 weeks) for AA-treated patients

Weeks	Age (years)	S(t)[a]	f(t)
0	0.00	[redacted]	[redacted]
12	0.23	[redacted]	[redacted]

24	0.46	[redacted]	[redacted]
36	0.69	[redacted]	[redacted]
48	0.92	[redacted]	[redacted]
60	1.15	[redacted]	[redacted]
72	1.38	[redacted]	[redacted]
84	1.61	[redacted]	[redacted]
96	1.84	[redacted]	[redacted]
108	2.07	[redacted]	[redacted]
120	2.30	[redacted]	[redacted]

Key: f(t), the proportion of the remaining population from the prior time period who died in the current time period; S(t), the proportion of the original population alive at time t.
Notes: [a] S(t) is calculated as 1-([number of deaths observed at time t]/N). An approximation of f(t) is calculated as 1-(S[t]/S[t-1]), where t is the current 12-week time interval, and t-1 is the prior 12-week time interval, indexed for a given age.
Source: ENB-002-08/ENB-003-08, ENB-010-10 and MAA UK study.

Table 39: HPP death in the first 10 cycles (12 weeks) for BSC-treated patients

Weeks	Age (years)	S(t)[a]	f(t)
0	0.00	1.000	0.195
12	0.23	0.805	0.152
24	0.46	0.683	0.107
36	0.69	0.610	0.280
48	0.92	0.439	0.000
60	1.15	0.439	0.167
72	1.38	0.366	0.000
84	1.61	0.366	0.000
96	1.84	0.366	0.000
108	2.07	0.366	0.000
120	2.30	0.366	0.000

Key: f(t), the proportion of the remaining population from the prior time period who died in the current time period; S(t), the proportion of the original population alive at time t.
Notes: [a] S(t) is calculated as 1-([number of deaths observed at time t]/N). An approximation of f(t) is calculated as 1-(S[t]/S[t-1]), where t is the current 12-week time interval, and t-1 is the prior 12-week time interval, indexed for a given age.
Source: ENB-011-10.

Figure 35: Overall survival Kaplan–Meier curves for AA and BSC

Key: AA, asfotase alfa; BSC, best supportive care.

To capture the uncertainty within the OS data, the Kaplan–Meier curves are varied in the probabilistic sensitivity analysis (PSA) by applying a hazard ratio (HR) to the Kaplan–Meier estimates. This HR is varied with a normal distribution, and the standard deviation is calculated through a calibration method using the Solver function in Microsoft Excel®. This method minimises the total sum of the squared differences between the minimum and maximum values obtained from the statistical Kaplan–Meier curve estimates, and those estimated with the calibrated standard deviation.

B.3.3.1.2. Transitions to invasive ventilation

AA is associated with a substantial improvement in patients' ability to discontinue invasive ventilation, with 75% of patients (12 out of 15) weaned from mechanical ventilatory support.[23]

Whyte et al. (2014) reported on clinical studies ENB-002-08/ENB-003-08, ENB-010-10, and ENB-011-10.[21] These included 37 AA and 48 BSC (historical-control) patients. The studies indicated that:

- For patients receiving BSC aged 0–5 years, 25% (12 out of 48) survived free of invasive ventilation

- For patients receiving AA aged 0–5 years, 84% (21 out of 25) survived free of invasive ventilation with a median follow-up time of 1.8 years

Invasive VFS was modelled based on the above rates as per Whyte et al. (2014).

It was assumed that a 25% rate of invasive VFS at 5 years among patients in the BSC arm, implied a 0.0638 rate of invasive ventilation per 12-week period (Equation 1). Similarly, it was assumed that an 84% rate of invasive VFS over 1.8 years implied a 0.0223 rate of invasive ventilation per 12-week period for AA (Equation 2). These rates were converted to probabilities and applied to all patients in each treatment arm from age 0 to 5. This resulted in a 12-week probability of receiving invasive ventilation of 0.0618 for BSC and 0.0220 for AA. No evidence of invasive ventilation after age 5 was collected in the clinical studies.

Equation 1: 12-week invasive ventilation-free survival rate; historical-control patients

$$\left(\frac{-1}{5 \times \left[\frac{365.25}{7 \times 12}\right]}\right) \times ln\left(\frac{12}{48}\right) = 0.0638$$

Equation 2: 12-week invasive ventilation-free survival rate; asfotase alfa patients

$$\left(\frac{-1}{1.8 \times \left[\frac{365.25}{7 \times 12}\right]}\right) \times ln\left(\frac{21}{25}\right) = 0.0223$$

In the UK MAA, [redacted] out of [redacted] treatment-naïve patients were on invasive ventilation at registry enrolment. However, [redacted] (see Section B.2.6.1). A scenario analysis is therefore conducted where [redacted] of patients in the AA arm are expected to be invasive ventilation-free ([redacted] probability of invasive ventilation).

B.3.3.1.3. Transitions between severity levels

Progression through disease SLs for patients aged 5+ years was modelled using 6MWT data. Severity was assessed based on the distance walked as a percentage

of predicted distance (i.e. observed 6MWT/predicted 6MWT). A value of 100% would indicate that the patient walked the expected distance based on age-, gender-, and height-adjusted normative data. Patients were assigned to SL states based on the distance walked as a percentage of the predicted threshold as described in Section B.3.2.2, Table 36. The threshold values of 6MWT as percent of predicted vary by age group due to the differences in MCID as calculated by age.[100]

Normative values for the 6MWT were calculated using the gender-specific formula presented by Geiger et al. (2007)[73]:

$$male\ 6MWT = 196.72 + (39.81 \times age) + (1.36 \times age^2) + (132.28 \times height); R^2 = 0.49, SEE = 66.72$$

$$female\ 6MWT = 188.61 + (51.50 \times age) + (1.86 \times age^2) + (86.10 \times height);\ R^2 = 0.50, SEE = 57.52$$

Key: SEE, standard error of the estimate.
Notes: Age is in years. Height is in metres.

A panel of patient visits with 6MWT data was used to estimate multivariate ordered probit models. This model was used to predict the current-period SL as a function of SL in the previous period and other covariates. The resulting coefficient estimates were used to generate standardised, age-specific transition probabilities to model patient progression in the model to patients assigned to AA and BSC, as described in Section B.3.2.2.

B.3.3.1.3.1. Baseline distribution

The baseline distribution of patients across SLs was informed by clinical studies and the MAA UK study, summarised in Table 40. SL distribution is not modelled in the perinatal-/infantile-onset patient group. For perinatal-/infantile-onset patients surviving to age 5, it was assumed that they would enter the model in health state SLIV. This was validated with a clinical expert who indicated that perinatal-/infantile-onset patients surviving to age 5 on BSC would likely be in a high-severity state. A scenario analysis is included where it is estimated that perinatal-/infantile-onset patients receiving AA have better outcomes. This scenario assumes no patients in the AA arm receive invasive ventilation (see Section B.3.3.1.2) and that 50% of perinatal-/infantile-onset patients receiving AA and surviving at age 5 enter the model in health state SLIII, with the remaining 50% entering health state SLIV.

In addition, in the scenario analysis where a higher baseline age is modelled for patients with juvenile-onset HPP, the baseline distribution for all patients ages 5+ from the clinical trials and MAA is used and shown in the table below.

Table 40: Patient group severity level distribution at baseline

Patient group	Baseline health state distribution				Justification
	SLI	SLII	SLIII	SLIV	
Perinatal-/infantile-onset HPP	N/A	N/A	N/A	N/A	N/A; SL is not modelled at age < 5 years
Patients with juvenile-onset HPP (base case)	10.53%	26.32%	42.11%	21.05%	SL distribution among the ENB-006-09 and ENB-009-10 and MAA UK study patients aged 5–17 years at baseline (n = 19)
Patients with juvenile-onset HPP (scenario analysis with baseline age 26.5 years)	10.87%	15.22%	30.43%	43.48%	SL distribution among the ENB-006-09 and ENB-009-10 and MAA UK study patients aged 5–17 years at baseline (n = 46)
Key: N/A, not applicable; SL, severity level					

B.3.3.1.3.2. Data for 6MWT model

As in the original submission, data on 6MWT performance were available for ENB-006-09 (a clinical trial of patients 5–12 years of age) and its extension trial ENB-008-10, as well as for ENB-009-10 (a clinical trial of patients 13–66 years of age). In addition, data on 6MWT performance from the UK MAA were included in the analysis.

At each visit, the distance walked in metres was assessed, and the percent of predicted was derived if the patient completed the 6MWT and was under the age of 65 (no normative data were available to calculate percent of predicted for patients over the age of 65). Patients who did not walk for the full 6 minutes were categorised as SLIV.

Patients were observed from pre-baseline visits to a maximum of 264 weeks post-baseline. Outcomes for AA patients were analysed using all visits where the patient was currently receiving treatment with AA (i.e. only post-baseline visits were

considered). Outcomes for BSC patients were analysed using screening/pre-baseline and baseline visits, as well as post-baseline visits for patients in ENB-009-10 treated with BSC. As such, screening and baseline visits for all patients were considered in the BSC analysis.

B.3.3.1.3.3. Sample in 6MWT model

Patients were included in the analysis if they had at least 2 6MWT assessments while on AA or BSC so that an SL transition could be observed. Visits where the patient completed the test but no distance walked percent of predicted was derived (e.g. if the patient was 65 years of age or older) were excluded from the analysis.

Table 41 below presents baseline characteristics for the AA and BSC patients used in this analysis. The AA and BSC cohorts included 51 and 26 patients, respectively. In the AA cohort, 24 patients were included from the MAA and 27 from the clinical studies. The BSC cohort included all clinical-studies patients from the AA cohort, except one.[*] The AA cohort had more visits and a much longer average follow-up, since most patients receiving BSC only had a screening and baseline visit.

Table 41: Baseline characteristics for 6-minute walk test analyses

Descriptor	AA	BSC
Sample size	51	26
Male (n, %)	25 (49.0%)	14 (53.8%)
White (n, %)	26 (96.3%)	25 (96.2%)
Visits		
Mean	9.5	2.2
Standard deviation	5.4	0.7
Min	2	2
Max	17	4
Follow-up length (months)		
Mean	44.2	2.6
Standard deviation	25.6	2.1
Min	3.0	0.7
Max	79.1	8.4
Age at first visit (years)		

[*] Subject ENB-006-09-01-04 required use of a walking device at their baseline visit but not at screening, such that they do not have 2 valid 6MWT assessments prior to treatment.

Descriptor	AA	BSC
Mean	26.5	28.0
Standard deviation	21.3	22.5
Min	5	6.0
Max	64	64
Age at onset (years)		
Mean	1.9	1.4
Standard deviation	2.8	1.2
Min	0	0
Max	14	4
Height (cm)		
Mean	138.3	142.3
Standard deviation	26.9	22.8
Min	89.0	89.0
Max	180.0	174.0
Weight (kg)		
Mean	47.8	51.2
Standard deviation	26.0	25.7
Min	11.4	11.4
Max	97.0	90.7

Key: AA, asfotase alfa; BSC, best supportive care; max, maximum; min, minimum.
Note: Values reported reflect patients with non-missing data (e.g. race was not reported for the MAA patients).

B.3.3.1.3.4. Descriptive analysis of changes in 6MWT performance

Table 42 below presents descriptive statistics on the changes seen in distance walked and the percent of predicted between visits (Observed 6MWT)/(Predicted 6MWT).

For patients meeting the inclusion criteria, there were 432 observed transitions for patients receiving AA and 32 observed transitions for patients receiving BSC. Patients receiving AA had a mean improvement between visits of 13.58 metres in distance walked, and 1.60 percentage points in the percent of predicted. Comparatively, patients receiving BSC had a mean decrease of -12.94 metres and -2.46 percentage points between visits. Note that in calculating these statistics,

a value of 0 was assigned for percent of predicted values where the patient did not complete the 6MWT.

Table 42: Descriptive statistics on the change in 6MWT between sequential visits

		Mean	SD
AA (N = 432 transitions)	Change in distance walked (metres)	13.58	68.55
	Percentage point change in percent of predicted	1.60	20.15
BSC (N = 32 transitions)	Change in distance walked (metres)	-12.94	49.01
	Percentage point change in percent of predicted	-2.46	7.72
Key: AA, asfotase alfa; BSC, best supportive care; SD, standard deviation.			

In Table 43 below, the same statistics are presented for the change between the first and last visit for each patient. The 51 patients receiving AA had an average improvement of 116.91 metres in distance walked and 13.53 percentage points in percent predicted over their observation period. Conversely, the 26 patients receiving BSC had an average decline of -15.92 metres in distance walked and -3.03 points in percent predicted.

Table 43: Descriptive statistics on the change in 6MWT between first and last visit

		Mean	SD
AA (N = 51 transitions)	Change in distance walked (metres)	116.91	144.91
	Percentage point change in percent of predicted	13.53	26.90
BSC (N = 26 transitions)	Change in distance walked (metres)	-15.92	33.38
	Percentage point change in percent of predicted	-3.03	5.47
Key: AA, asfotase alfa; BSC, best supportive care; SD, standard deviation.			

Table 44 and Table 45 present the observed frequency of transitions for AA and BSC, respectively. The table rows show the health state at the previous visit and the columns show the health state at the current visit, with the values representing how many times each transition was observed. Green shading indicates a transition to a less severe health state, and red shading indicates a transition to a more severe health state. For the BSC cohort, no transitions are observed from SLIV to another

health state, whereas 21 out of 64 transitions for AA patients in SLIV were to less severe states (SLI–III).

Table 44: Observed state transitions – AA

State at current visit / State at prior visit	SLI	SLII	SLIII	SLIV	*Row total*
SLI	152	23	2	2	*179*
SLII	33	64	15	6	*118*
SLIII	3	27	34	7	*71*
SLIV	2	6	13	43	*64*
Column total	*190*	*120*	*64*	*58*	*432*

Key: AA, asfotase alfa; SL, severity level.

Table 45: Observed state transitions – BSC

State at current visit / State at prior visit	SLI	SLII	SLIII	SLIV	*Row total*
SLI	5	3	0	0	*8*
SLII	2	5	3	0	*10*
SLIII	0	2	7	2	*11*
SLIV	0	0	0	3	*3*
Column total	*7*	*10*	*10*	*5*	*32*

Key: BSC, best supportive care; SL, severity level.

B.3.3.1.3.5. Multivariate ordered probit 6MWT prediction model

A multivariate ordered probit model was estimated to predict transitions from health states in the previous cycle to the current cycle, based on observed health state transitions, and controlling for patient age and the days elapsed between visits. This approach assumes that a latent continuous metric (e.g. disease severity) underlies the ordinal observations (e.g. SL). The resulting coefficient estimates can be used to generate predicted probabilities for a transition matrix, which provides the age-specific probability of being in a given health state, which is conditional on the prior health state. All estimations were conducted using STATA® software (StataCorp. 2013. Stata Statistical Software: Release 13. College Station, TX: StataCorp LP).

Multiple model specifications were tested in line with the previously tested specifications from the original NICE submission. In Specification 1, a model of the following form was estimated:

$$(1) \quad SeverityLevel_t = \alpha + \beta_1 SLI_{t-1} + \beta_2 SLII_{t-1} + \beta_3 SLIII_{t-1} + \beta_4 SLIV_{t-1} + \gamma Days_t + \varepsilon_t,$$

where *SLI–SLIV* are binary indicators of the patient's prior health state and *Days* is a continuous measure of the days elapsed between the prior and current visit. α is the intercept, or cut point 1. *Days* was included to control for variability in the frequency of observations so that predicted transition probabilities could be standardised to 84-day intervals. In estimating the model, $\beta_1 SLI_{t-1}$ is omitted so that all coefficient estimates are relative to being in the lowest SL at the previous visit.

In Specification 2, an additional covariate was included for the patient's age in years at the time of the current visit:

$$(2) \quad SeverityLevel_t = \alpha + \beta_1 SLI_{t-1} + \beta_2 SLII_{t-1} + \beta_3 SLIII_{t-1} + \beta_4 SLIV_{t-1} + \gamma Days_t + \varphi_1 Age_t + \varepsilon_t.$$

Specification 3 adds additional covariates to capture the interaction of age and prior SL:

$$(3) \quad SeverityLevel_t = \alpha + \beta_1 SLI_{t-1} + \beta_2 SLII_{t-1} + \beta_3 SLIII_{t-1} + \beta_4 SLIV_{t-1} + \gamma Days_t + \varphi_1 Age_t + \varphi_2 Age_t * SLII_{t-1} \quad \varphi_3 Age_t * SLIII_{t-1} + \varphi_4 Age_t * SLIV_{t-1} + \varepsilon_t.$$

Each specification was run separately for patients receiving BSC and patients receiving AA; this is identical to running one specification with treatment and treatment interactions with all other covariates.

Table 46 presents the resulting coefficient estimates and goodness-of-fit statistics for each specification. Specification 1 demonstrates that, as expected, higher SLs in the prior visit predict increased severity in the current visit. This relationship remains consistent in Specifications 2 and 3 when controlling for patient age and age interactions with prior SL. Cut points 1–3 represent the thresholds used to differentiate the SLs. The log likelihood values were used to test whether these models are statistically different from a model in which all coefficients are simultaneously zero, which each specification satisfied. The log likelihood values are

also used to calculate McFadden's pseudo R^2, another measure of fit. As with linear R^2 measures, higher scores indicate better explanatory power of the model. However, McFadden's pseudo R^2 tends to produce lower values.

Table 46: Coefficient estimates from ordered probit model of severity level at time t

	BSC			**AA**		
	Spec. 1	**Spec. 2**	**Spec. 3**	**Spec. 1**	**Spec. 2**	**Spec. 3**
Covariate	*Coefficient (p-value)*	*Coefficient (p-value)*	*Coefficient (p-value)*	*Coefficient (p-value)*	*Coefficient (p-value)*	*Coefficient (p-value)*
SLIIt-1	1.547 (p < 0.001)	1.647 (p = 0.002)	-0.743 (p = 0.510)	1.534 (p < 0.001)	1.546 (p < 0.001)	1.700 (p < 0.001)
SLIIIt-1	2.959 (p < 0.001)	2.957 (p < 0.001)	0.628 (p = 0.534)	2.463 (p < 0.001)	2.461 (p < 0.001)	2.392 (p < 0.001)
SLIVt-1	9.659 (p < 0.001)	9.956 (p < 0.001)	6.912 (p < 0.001)	3.632 (p < 0.001)	3.622 (p < 0.001)	3.045 (p < 0.001)
Days between visits	-0.017 (p = 0.033)	-0.012 (p = 0.075)	-0.009 (p = 0.221)	0.003 (p = 0.004)	0.003 (p = 0.007)	0.003 (p = 0.005)
Age at visit (years)	0.000	-0.012 (p = 0.193)	-0.181 (p = 0.032)	0.000	0.002 (p = 0.452)	0.000 (p = 0.974)
Age x LIIt-1	0.000	0.000	0.174 (p = 0.038)	0.000	0.000	-0.007 (p = 0.467)
Age x SLIIIt-1	0.000	0.000	0.178 (p = 0.039)	0.000	0.000	0.003 (p = 0.722)
Age x SLIVt-1	0.000	0.000	0.184 (p = 0.028)	0.000	0.000	0.020 (p = 0.130)
	Cut points	*Cut points*	*Cut points*	*Cut points*	*Cut points*	*Cut points*
Cut 1	-0.615	-0.703	-2.709	1.547	1.600	1.556
Cut 2	1.078	1.030	-0.888	2.897	2.951	2.913
Cut 3	3.106	3.054	1.067	3.845	3.902	3.885
	Sample N, fit	*Sample N, fit*	*Sample N, fit*	*Sample N, fit*	*Sample N, fit*	*Sample N, fit*
Sample size	32	32	32	432	432	432
Log likelihood	-24.11	-23.59	-22.02	-361.79	-361.42	-360.00
Pseudo R^2	0.4417	0.4538	0.4901	0.3403	0.3410	0.3491
Key: AA, asfotase alfa; BSC, best supportive care; SL, severity level; Spec., specification.						

B.3.3.1.3.6. Model specification selection, 6MWT model

To generate transition probabilities for the model, coefficient estimates from Specification 2 were used. The specifications that were tested produced comparable goodness-of-fit statistics, which are often differentiating factors used in justifying model selection.

Specification 2 was chosen for 2 reasons. First, the intention of the model is to produce age-specific transition probabilities, so a coefficient estimate for age is needed. This is important as the likelihood of being in different disease SLs could be expected to differ across age intervals, and the model must generate out-of-sample predictions for patients over the age of 65, as data were not available for these patients. Specification 1 was therefore deemed insufficient for the modelling purpose. Second, the number of covariates included in the estimation relative to the number of observations needs to be considered so that the model is not over-specified. The fewer covariates included, the more variation there is to accurately estimate the coefficients. As BSC especially had a limited number of observations available, it is understandable that adding interaction terms in Specification 3 resulted in coefficient estimates that did not statistically significantly differ from zero. In addition, Specification 2 was used as the base case in the original submission. During the ERG review, the ERG used Specification 2 as the base case and Specification 3 as a scenario analysis, so base case results were derived using Specification 2 and scenario analyses were carried out using Specification 3.

B.3.3.1.3.7. Sample age-specific transition probabilities

Using the coefficient estimates from Specification 2, transition probabilities can be predicted for each treatment and age, assuming 84 days between visits. In Table 47, the resulting transition probability matrices for AA for patients with juvenile-onset HPP (at age 5.0 years) is shown. The rows show the severity state at the previous visit and the columns show the severity state at the current visit, with the values indicating the expected percentage of patients in each state. As an example, among patients receiving AA at age 5.0 years who were in SLII at the previous visit, 40% are expected to now be in SLI, 46% in SLII, 11% in SLIII and 2% in SLIV.

Table 47: AA transition probability matrix at age 5.0 years

	SLI_t	$SLII_t$	$SLIII_t$	$SLIV_t$
SLI_{t-1}	90%	9%	0%	0%
$SLII_{t-1}$	40%	46%	11%	2%
$SLIII_{t-1}$	12%	45%	30%	13%
$SLIV_{t-1}$	1%	16%	33%	51%
Key: AA, asfotase alfa; SL, severity level.				

Table 48 presents the same probability matrices for patients receiving BSC. Among patients receiving BSC at age 5.0 who were in SLII at the previous visit, 10% are expected to now be in SLI, 58% in SLII, 31% in SLIII and 1% in SLIV. Patients receiving BSC in SLIV have a 100% probability of remaining in SLIV at both ages.

Table 48: BSC transition probability matrix at age 5.0

	SLI_t	$SLII_t$	$SLIII_t$	$SLIV_t$
SLI_{t-1}	65%	33%	2%	0%
$SLII_{t-1}$	10%	58%	31%	1%
$SLIII_{t-1}$	1%	20%	68%	12%
$SLIV_{t-1}$	0%	0%	0%	100%
Key: BSC, best supportive care; SL, severity level.				

B.3.3.1.4. Summary

Table 49 summarises the transition probabilities used in the cost-effectiveness analysis model.

Table 49: Summary of transition probabilities

Transition probability	Value	Reference in submission
Age 0–4: From any state to HPP-related death	Varies by age	See Section B.3.3.1.1.1
Age 0–4: From 'alive, no invasive ventilation' to 'alive, with invasive ventilation'	Constant probability by cycle	See Section B.3.3.1.2
Age 5+: From SLI, SLII, SLIII, or SLIV to SLI, SLII, SLIII, or SLIV	Varies by age	See Section B.3.3.1.3

All ages: From any state to background death	Varies by age	Based on life tables for England and Wales[88], see Section B.3.3.1.1.
Key: HPP, hypophosphatasia; SL, severity level.		

B.3.4. Measurement and valuation of health effects

B.3.4.1. Health-related quality-of-life data from clinical trials

Many QoL data sources were assessed for their inclusion in the cost-effectiveness model. Utility data were available from the MAA UK study and HPP Registry data, as well as the 2 clinician-derived utility studies conducted by Alexion; Lloyd et al. 2015[46]; which was presented in the previous NICE submission; and Lloyd et al. 2017.[47] Further information on each of the studies is provided in the following subsections.

B.3.4.1.1. Clinician elicitation of utilities from EQ-5D

A vignette study was designed to elicit utility estimates for the health states defined in the model using the EQ-5D-5L questionnaire.[46] There is no validated instrument (like the EQ-5D) that maps to health utility and covers the broad age range of the patients with paediatric-onset HPP. A proxy valuation of HPP-related health states was therefore undertaken with UK clinical experts.

Due to the complexity and variability of HPP symptoms, the health states were not easy to summarise in vignettes that were suitable for the general public to assess. The experience of clinical experts was therefore used to interpret the severity of the condition. This allowed for greater scope to include detailed clinical information.

Utilities were derived using standardised sets of preference weights. The EQ-5D-5L responses were mapped to 3L using van Hout et al. (2012)[101], then valued using Dolan (1997)[102], aligning with NICE's recommendation prior to the new 2022 guidance. The study elicited assessments of health states using the EQ-5D-5L rather than undertaking time trade-off interviews.

Utilities were elicited for health states defined by the need for invasive ventilation for patients under 5 years old and by SL for those age 5 and over. SLs were defined based on factors such as fractures, craniosynostosis, pain, mobility, psychological

wellbeing, independence, sleep, and limitations of social life, based on clinical experts' characterisation of these factors by percent of predicted 6MWT (100–82.2%, 82.2–64.4%, 64.4–46.6% and below 46.6%) for the SLI, SLII, SLIII, and SLIV states, respectively. This was consistent with the MCID for DMD from McDonald et al.[103] In early 2015 when this research was carried out, HPP-specific MCIDs had not been calculated, and DMD was used as an analogous disease.

Further details on how this study was conducted can be found in Appendix O.

The framework was tested with clinical experts in an advisory board held in February 2015. The values from this exercise were further verified with 2 clinicians in April 2022, to assess whether they were still considered plausible estimates. Both clinicians indicated that the utility values are still reflective of patients' QoL.

The health state utility values elicited from the 2015 vignette study are presented in Table 50.

Table 50: Health state utility values derived from clinical expert EQ-5D scoring, 2015

	EQ-5D-5L responses; mapped to 3L, valued using Dolan (1997)[102]		
Health state	**Mean**	**N**	**SE**
Under 5 - no ventilation	0.24	5	0.12
Under 5 - ventilation	0.00	5	0.17
5+ - SLI	0.86	9	0.04
5+ - SLII	0.67	9	0.03
5+ - SLIII	0.54	9	0.03
5+ - SLIV	0.23	9	0.08
Key: SE, standard error; SL, severity level.			

In 2016, Alexion conducted further research to estimate the MCID of the 6MWT in patients with HPP, as reflected in Section B.3.3.1.3, for 3 age groups: ages 5–12, ages 13–17, and age 18+.[96] Following this update, research into the QoL impacts associated with the new, age-varying SL ranges was undertaken in 2017.[47] The vignettes of the 2015 study were revised to describe patients in the 3 age groups: ages 5–12 (children), ages 13–17 (adolescents), and age 18+ (adults). Further details on how this study was validated are outlined in Appendix O. The age-group

and SL-specific vignettes are detailed in Appendix P. The revised vignettes were then reviewed in individual interviews with 4 clinical experts in HPP, including 3 paediatricians and 1 adult physician. 2 of the experts were based in the UK, 1 in Germany and 1 in the US. Following amendments to the vignettes after the interviews, the clinicians felt that the descriptions were a fair characterisation of a typical patient with paediatric-onset HPP at the different SLs and ages.

In the last phase of the study, a total of 12 clinical experts were asked to rate each of the vignettes using the EQ-5D-3L and EQ-5D-Y questionnaires.

The health state utility values elicited from the 2017 vignette study are presented in Table 51.

Table 51: Health state utility values derived from clinical expert EQ-5D scoring, 2017

	Lloyd et al. (2017), EQ-5D-3L and Y responses; valued using Dolan (1997)[102]								
	Age 5–12			**Age 13–17**			**Adults**		
Health state	**Mean**	**N**	**SE**	**Mean**	**N**	**SE**	**Mean**	**N**	**SE**
5+ - SLI	0.86	12	0.04	0.86	13	0.04	0.91	13	0.03
5+ - SLII	0.65	12	0.02	0.66	13	0.02	0.65	13	0.02
5+ - SLIII	-0.10	13	0.10	0.06	13	0.09	0.53	13	0.01
5+ - SLIV	-0.52	13	0.03	-0.52	13	0.04	-0.09	13	0.05
Key: SE, standard error; SL, severity level.									

The utility values derived from the 2017 vignette study were considered to be implausibly extreme. For example, SLIII is approximately equivalent to death for ages 5–17, and SLIV is worse than death in all age groups. Additionally, the 2017 vignette study used the EQ-5D-3L. This system has been found to underpredict utility and overpredict disutility for severe health states.[104] The utility values derived from the 2015 vignette study were therefore deemed more suitable to inform the economic model.

B.3.4.1.2. Managed access agreement data

The UK MAA collected data using the EQ-5D-5L questionnaire for adults and the PedsQL for paediatric patients. Data were collected at enrolment, 3 months, 6 months and every 6 months thereafter.

The EQ-5D questionnaire utility scores of patients matched to their 6MWT percent of predicted distance are presented in Table 52. Utility values increase as the 6MWT percent of predicted increases, except for the 82.2% group.

The EQ-5D utilities mapped from the PedsQL data by age and 6MWT percent of predicted are presented in Table 53. Utility in the 5–12 age group increases as patients' 6MWT percent of predicted increases, from [redacted] for the < 46.5% group to [redacted] for the > 82.24% group. Due to the lack of records in the 13–17 age group, increases across health states cannot be determined, as data are only available in the 64.4%–82.1% group and this group only contains information from [redacted] patient. Due to low patient numbers, the MAA-derived utilities are not suitable to inform the economic model. However, they validate the clinician-derived utility values; the data produced results similar to that of the clinician-derived utilities, which sufficiently reflect the clinicians' beliefs.

Table 52: EQ-5D utilities by 6MWT in MAA

	Overall		**Utility**	
Group	**Number of patients**	**Number of records**	**Mean (SD)**	**Median (range)**
Overall	[redacted]	[redacted]	[redacted]	[redacted]
Overall with matched 6MWTP test	[redacted]	[redacted]	[redacted]	[redacted]
SLIV: < 46.6%	[redacted]	[redacted]	[redacted]	[redacted]
SLIII: 46.6–64.4%	[redacted]	[redacted]	[redacted]	[redacted]
SLII: 64.4–82.1%	[redacted]	[redacted]	[redacted]	[redacted]
SLI: ≥ 82.2 %	[redacted]	[redacted]	[redacted]	[redacted]
Not matched to 6MWTP	[redacted]	[redacted]	[redacted]	[redacted]

Key: 6MWTP, 6-minute walk test percent of predicted; MAA, management access agreement; SD, standard deviation; SL, severity level.

Table 53: EQ-5D mapped utilities from PedsQL by 6MWT in MAA

Group	Number of patients	Number of records	Mean (SD)	Median (range)
Overall	[redacted]	[redacted]	[redacted]	[redacted]
By age				
< 5	[redacted]	[redacted]	[redacted]	[redacted]
5–12	[redacted]	[redacted]	[redacted]	[redacted]
SLIV: < 46.6%	[redacted]	[redacted]	[redacted]	[redacted]
SLIII: 46.6–64.4%	[redacted]	[redacted]	[redacted]	[redacted]
SLII: 64.4–82.2%	[redacted]	[redacted]	[redacted]	[redacted]
SLI: ≥ 82.2%	[redacted]	[redacted]	[redacted]	[redacted]
13–17	[redacted]	[redacted]	[redacted]	[redacted]
SLIV: < 46.6%	[redacted]	[redacted]	[redacted]	[redacted]
SLIII: 46.6–64.4%	[redacted]	[redacted]	[redacted]	[redacted]
SLII: 64.4–82.2%	[redacted]	[redacted]	[redacted]	[redacted]
SLI: ≥ 82.2%	[redacted]	[redacted]	[redacted]	[redacted]
18+	[redacted]	[redacted]	[redacted]	[redacted]

Key: 6MWT, 6-minute walk test; MAA, management access agreement; N/A, not applicable; PedsQL, Paediatric Quality of Life Inventory; SD, standard deviation.

B.3.4.1.3. Registry data

The HPP Registry contains data from January 2015 to July 2020. It includes patients in Australia, Asia, Europe and North America, although most patients were enrolled in Europe and the US. The HPP Registry collected data using the SF-36v2 for adults and PedsQL for paediatric patients. Data were collected at least every 3 months for the first year of enrolment, and at least every 6 months thereafter. Despite a large sample size, over 80% of records for adults were not matched to the 6MWT percent of predicted, limiting the validity of the data. The utility values in the Registry data showed an increase in utility as the 6MWT percent of predicted increases. This trend is as expected; however, the range in utility values across groups is significantly smaller than the MAA and clinician-derived utilities. The utility values tended to be densely populated towards 1, which was not deemed plausible by clinical experts. As a result, the Registry data are not suitable for modelling purposes as these data do not accurately capture the severity of HPP.

B.3.4.1.4. Consideration of available data

Exploring HRQL in this group of patients is difficult. The UK MAA aimed to establish HRQL in patients with HPP. Due to the model structure, this required matching patients' questionnaires with their 6MWT results. This meant that only observations containing values of 6MWT percent of predicted could be matched. The small sample sizes in the MAA UK study, coupled with the difficulties of conducting 6MWT observations during the COVID-19 pandemic (as patients were unable to attend the clinic to conduct 6MWT observations) resulted in a small number of observations.

Clinical expert validation was conducted to verify the utility values obtained from the UK MAA. Utilities stratified by 6MWT percent of predicted do not align with the definitions of the health states. The health states included in the model are inclusive of more symptoms and complications of HPP than mobility alone. 6MWT percent of predicted was deemed the best proxy by clinicians for transitions between the health state, but it is not the sole driver of utility/disutility in HPP.

Clinicians agreed that although the utility values derived for adults seemed reasonable, it was implausible that the SLI value was lower than the SLII value, as this is a preferential health state in all respects. This may be caused by the lower number of observations available for the lower severity groups. In addition, little variation was demonstrated between severity groups for patients aged 5–12, which again was deemed implausible by clinical experts. Data were only available for SLII in patients aged 13–17, and this was based on 1 participant. The paediatric clinician stated that the high utility value seen for SLIV in children may be due to the perception of patients and parents that once they have reached age 5 the severity of the disease in SLIV is better compared with the first few years of life. Despite the Registry data containing more observations, as mentioned above, the utility values were densely populated towards 1, which was not deemed plausible by clinical experts.

Given the limitations associated with the UK MAA and Registry study, clinicians agreed that the utilities derived during the expert elicitation exercise were more reflective of the QoL experienced by patients. In addition, the adult utilities from the UK MAA supported the overall trend of increasing utility for increasing 6MWT scores. As a result, the clinician-derived utilities were used in the base case. This was

consistent with the previous submission where the Committee agreed that the values were a good representation of the HRQL associated with HPP.

B.3.4.2. Mapping

MAA UK study

The QoL questionnaires collected in the MAA were EQ-5D-5L for adults and PedsQL for paediatric patients. As the EQ-5D-3L is NICE's preferred measure of utility, mapping was required for the PedsQL. The University of Oxford Health Economics Research Centre's mapping database was used to identify a suitable mapping algorithm. The PedsQL MAA data were mapped to EQ-5D-Y using the Khan et al. algorithm.[105]

Clinician-derived utilities

The clinician-derived utilities from Lloyd et al. 2015 (outlined in Section B.3.4.3) were collected using the EQ-5D-5L. Given NICE's preferred measure of utility is the EQ-5D-3L, the values were mapped to the EQ-5D-3L using the van Hout et al. 2012 algorithm.[101]

B.3.4.3. Health-related quality-of-life studies

An SLR was conducted to identify any published utility values related to HPP. Full information on the process, methods and findings are described in Appendix H. The final evidence base included 14 unique studies extracted from 20 publications. Aside from the previous NICE submission for AA, none of the other studies were sufficient for inclusion in the cost-effectiveness model as they did not report HRQL data according to the health states used in the model. Parthenaki et al. (2017) showed that overall QoL for adults with HPP was low, highlighting that QoL for patients living with HPP is poor.

Utility data were reported in 2 of the included studies. Details are provided in Table 54. The remaining studies reported HRQL data and can be found in Appendix H.

Table 54: Utility data reported in included SLR studies

Study name	Treatment/ comparator	Country Type of study	Cohort size Health states	Method of Elicitation Valuation	HPP form	Utility data
Parthenaki 2017[45]	N/R	• The UK, Germany, France and Switzerland • Population-based survey	• 27 • N/R	• EQ-5D • TTO and VAS	N/R	Mean overall EQ-5D: TTO: 0.36; (worst TTO score: -0.01) Mean overall EQ-5D: VAS: 0.43; (worst VAS score: 0.23)
NICE_HST6 [Asfotase alfa] 2017[7]	AA/BSC	• The UK • Economic evaluation (including models) not run alongside a trial	• N/R • SLI • SLII • SLIII • SLIV	• N/R • N/R	Paediatric-onset HPP	Utility values for each health state; mean (SE) SLI: 0.86 (0.11) SLII: 0.67 (0.09) SLIII: 0.54 (0.08) SLIV: 0.23 (0.25)
NICE_HST6 [Asfotase alfa] 2017_ERG[7]	AA/BSC	• The UK • Economic evaluation (including models) not run alongside a trial	• N/R • SLI • SLII • SLIII • SLIV	• N/R • N/R	Paediatric-onset HPP	Utility (EQ-5D) – 'Alive' health state: 0.575*

Key: AA, asfotase alfa; BSC, best supportive care; HPP, hypophosphatasia; N/R, not reported; SE, standard error; SL, severity level; TTO, time trade-off; VAS, visual analogue scale.
Note: * Average of the 4 health states included in the company's model.

B.3.4.4. Adverse reactions

AA is generally well tolerated. Adverse reactions were mostly mild to moderate in severity. The most commonly reported AEs from the trials were ISRs. The vast majority of ISRs were mild or moderate and self-limiting. Although almost all patients reported AEs in the HPP clinical studies, excluding ISRs, most AEs were not considered to be drug-related, but were related to the underlying HPP disease. Conversely, the BSC AEs have never been evaluated in similar research.

Since the AE profile is generally considered mild for AA, and there is no appropriate source for BSC, the model does not include any health or cost implications for TRAEs. This approach is consistent with that taken in the previous NICE HST6 submission.

B.3.4.5. Caregiver quality of life

Although data are not available that quantify the caregiver QoL burden caused by paediatric-onset HPP, this burden is likely to be substantial. While no published data report the impact on caregivers, the symptoms of HPP and necessary accommodations (including potential home modifications, frequent hospital visits, and breathing and feeding assistance in infantile-onset HPP) may be physically, emotionally and financially demanding on caregivers. Section B.1.3.3.3 highlights that research in similar disease areas shows that there is a relationship between disease severity and caregiver burden and QoL.

Landfeldt et al. 2016[53] conducted an observational study that reported the QoL of 770 carers of patients with DMD in Germany, Italy, the UK and the US. The study provides estimates of EQ-5D health utility decrements for caregivers associated with different levels of ambulatory, health and mental status for the patient. They found that caregiver QoL is reduced according to the gender- and age-matched general population. DMD is a neuromuscular disease characterised by progressive muscle weakening, diminishing functional ability and serious multisystem complications. It is similar to paediatric-onset HPP, and patients in the study had a mean age of 14 years old. From the results of Landfeldt et al. 2016, a utility decrement of -0.17 was used, based on the patient being in ‘fair/poor’ health.

In the base case, the caregiver is assumed to have no utility decrement if the patient is in SLI (ages 5+ years). A decrement of -0.17 is applied for 'fair/poor' health if their patient requires invasive ventilation (ages < 5 years) or is in SLIV (ages 5+ years). In states SLII and SLIII, the decrement is based on the proportion of the patient's disutility versus patient utility in SLI. For patients not requiring invasive ventilation (ages < 5 years), a utility decrement is applied equal to that applied for SLIII. These assumptions were validated with clinicians, and they stated that it was reasonable to capture caregiver QoL and that the assumptions made for each health state were plausible.

Finally, the utility decrement is assumed to be experienced by 1 caregiver of patients who survive in both treatment arms, until the patient turns 60 years old in the model. The model only applies caregiver decrements for patients surviving on both AA and BSC. It is acknowledged that this is not a precise estimate of caregiver disutility; however, it avoids a situation where there is more disutility associated with a carer if the patient survives.

Previous NICE submissions have modelled the impact of caregiver disutilities, especially where the condition begins in childhood and has an impact on the patient's ambulatory status.[94, 106]

B.3.4.5.1. Impact of infant death

Considering the significant mortality risk faced by patients with perinatal-/infantile-onset HPP, the model base case also considers the impact of infant mortality on their parents' QoL.

In the 2018 evaluation of Strimvelis® (NICE HST7)[107], the family disutility associated with an infant death was modelled based on Song et al. (2010), which examined the long-term effects of child death on bereaved parents' QoL.[108] The study showed that both mothers and fathers experience an ongoing utility decrement following an infant's death, as observed at 35+ years from the infant's death. The annual utility decrement, controlling for other factors, is estimated at 0.04.

The average age of parents at infant death, and the number of years until the average life expectancy, was used to calculate the number of years a parent is alive after infant death to apply the disutility. Song et al. (2010) presented the mean age of

parents at infant death as 25.7 for males and 28.1 for females. The ONS (2020) reports the average life expectancy is 79.61 years for males and 83.27 years for females.[88] This resulted in an average of 54.54 years from the infant's death until a parent dies. It is therefore assumed that 2 parents experience the 0.04 disutility from their infant's death, and that the disutility is experienced for 54.54 years from baseline age.

B.3.4.6. General population quality of life

Age-adjusted general population utilities for the UK were applied in the model for patients aged 18 years and over, based on Ara and Brazier (2010).[109] These were not applied for children as the general population utilities were obtained from the Health Survey for England, which is administered to adults only.

B.3.4.7. Health-related quality-of-life data used in the cost-effectiveness analysis

As per the discussion outlined above, Table 55 outlines the values used in the base case.

Table 55: Summary of utility values for cost-effectiveness analysis

State	Utility value: mean	SE	Reference in submission (section and page number)	Justification
Patients aged 0–4				
No invasive ventilation	0.24	0.12	Section B.3.4.1.1	Values from the clinician elicitation study were used as per the original submission and due to lack of other sources available
Invasive ventilation	0.00	0.17		
Patients aged 5+				
SLI	0.86	0.04		Values from the clinician elicitation study were used as per the original submission
SLII	0.67	0.03		
SLIII	0.54	0.03		
SLIV	0.23	0.08		
Carer disutility				
No invasive ventilation	-0.09	-0.009	Section B.3.4.5	The symptoms of HPP and necessary
Invasive ventilation	-0.17	-0.017		

State	Utility value: mean	SE	Reference in submission (section and page number)	Justification
SLI	N/A			accommodations are likely to have an impact on HRQL. Studies in similar disease areas have shown that disease severity can directly affect carers' QoL
SLII	-0.05	-0.005		
SLIII	-0.09	-0.009		
SLIV	-0.17	-0.017		
Infant death	-0.04	0.02	Section B.3.4.5.1	Song et al. 2010[108] showed that parents experience an ongoing utility decrement following an infant's death. This same decrement was applied and accepted by NICE in the 2018 evaluation of Strimvelis (NICE HST7)[107]
Key: HPP, hypophosphatasia; QoL, quality of life; SE, standard error; SL, severity level.				

B.3.5. Cost and healthcare resource use identification, measurement and valuation

There is no specific reference cost for patients with HPP. Given the broad range of symptoms associated with the disease, costing of the clinical management of the disease is complicated. To estimate the HPP management cost for the health states included in the cost-effectiveness analysis, a process was undertaken to evaluate the frequency of HPP symptoms by health state and the associated resource consumption. This process is described below.

B.3.5.1. Intervention and comparators' costs and resource use

B.3.5.1.1. Intervention costs

The list price of AA in England is £58.80 per mg. A simple patient access scheme (PAS) discount of 55.9% is considered in this submission, which gives a discounted cost of £25.93.

For each of the vial sizes of AA (i.e. 18 mg/0.45 ml, 28 mg/0.7 ml, 40 mg/1 ml and 80 mg/0.8 ml), prices modelled in the cost-effectiveness analysis are based on UK costs, obtained from the Monthly Index of Medical Specialities (MIMS).[110]

Modelled vial prices are presented in Table 56.

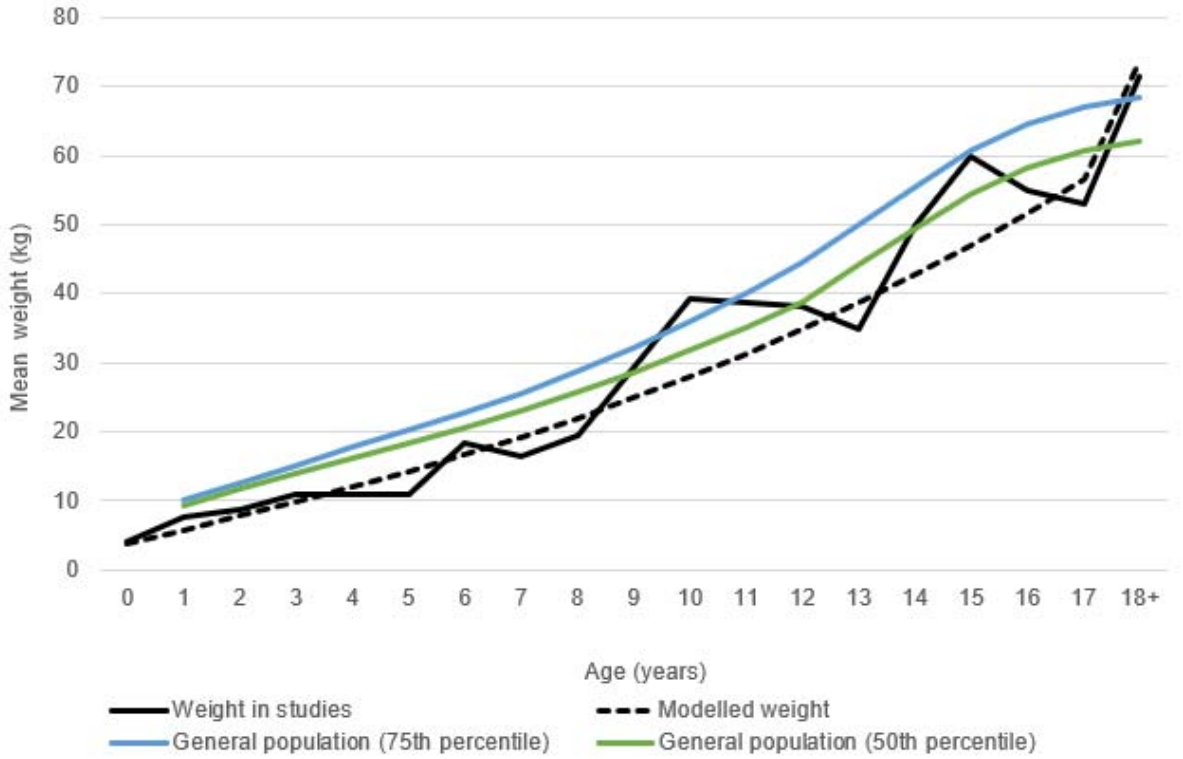
Table 56: Price of asfotase alfa in the UK (2021 GBP), by vial size

Strength	Price per 12-pack (GBP)	Price per vial (GBP)	Price per vial with PAS discount (GBP)
18 mg/0.45 ml	12,700.80	1,058.40	[redacted]
28 mg/0.7 ml	19,756.80	1,646.40	[redacted]
40 mg/1 ml	28,224.00	2,352.00	[redacted]
80 mg/0.8 ml	56,448.00	4,704.00	[redacted]

Annual costs of the technology consist of AA drug costs. The dosing schedule for AA varies by patient weight. The European Medicines Agency (EMA) summary of product characteristics recommends an AA dosage regimen of 2 mg/kg of body weight administered subcutaneously 3 times per week, or 1 mg/kg of body weight administered subcutaneously 6 times per week.[1]

The required AA dose was calculated using the average weight of patients from ENB-002-08/ENB-003-08, ENB-006-09/ENB-008-10, ENB-009-10, ENB-010-10 and the MAA UK study. Study data showed that, for some ages, the weight did not follow the trend of the general population (see Figure 36). As a result, smoothing was applied to the mean value curves using a 3rd-degree polynomial model.

Figure 36: Comparison of weight from studies, modelled prediction and general population



Sources: ENB-002-08/ENB-003-08, ENB-006-09/ENB-008-10, ENB-009-10, ENB-010-10 and the MAA UK study; General population weight based on UK-WHO growth charts.[111]

The age ranges and their respective average weights (kg) are presented in Table 57. The average weight for each age group is used to calculate the AA costs in the model.

Table 57: Average weight by age for patients with HPP

Age group	Average weight predicted by 3rd-degree polynomial model, kg
0–1 year	3.92
1 year	5.84
2 years	7.82
3 years	9.89
4 years	12.05
5 years	14.33
6 years	16.74
7 years	19.30
8 years	22.02

Age group	Average weight predicted by 3rd-degree polynomial model, kg
9 years	24.92
10 years	28.03
11 years	31.34
12 years	34.89
13 years	38.68
14 years	42.74
15 years	47.08
16 years	51.72
17 years	56.67
18+ years	73.58
Key: HPP, hypophosphatasia.	

Based on the weight assigned to the modelled cohort as they age, weekly purchased mg of AA are determined based on the weight-varying dosing schedules.

Combinations of vials by patient body weight are presented in Table 58. During validation interviews with 2 clinical experts, it was explained that in clinical practice, efforts are made to minimise unused drug – including rounding down of dose per administration to avoid drug wastage. As a result, rounding down was applied in the base case to reflect clinical practice. Clinicians stated that rounding down would only be done if the administered dose was not reduced by more than 3–4 mg per administration. Therefore, the model only allowed rounding down if the administered dose was 12 mg less than the required dose per week. Where rounding was not possible, wastage was assumed to occur (excess volumes of AA in partially used vials are not administered to the patient, but the costs of the excess AA are included in drug costs).

Table 58: Modelled weekly dosing of asfotase alfa by weight

Weight (kg)	Required dose per application (mg)	Purchased dosing (mg)	Dosing of asfotase alfa	
			Vials per administration	Administrations per week
1	6	54	1x 18 mg	3
2	12	54	1x 18 mg	3
3	18	54	1x 18 mg	3

Weight (kg)	Required dose per application (mg)	Purchased dosing (mg)	Dosing of asfotase alfa	
			Vials per administration	Administrations per week
4	24	54	1x 18 mg	3
5	30	54	1x 18 mg	3
6	36	54	1x 18 mg	3
7	42	54	1x 18 mg	3
8	48	54	1x 18 mg	3
9	54	54	1x 18 mg	3
10	60	54	1x 18 mg	3
11	66	54	1x 18 mg	3
12	72	84	1x 28 mg	3
13	78	84	1x 28 mg	3
14	84	84	1x 28 mg	3
15	90	84	1x 28 mg	3
16	96	84	1x 28 mg	3
17	102	108	2x 18 mg	3
18	108	108	2x 18 mg	3
19	114	108	2x 18 mg	3
20	120	120	1x 40 mg	3
21	126	120	1x 40 mg	3
22	132	120	1x 40 mg	3
23	138	138	1x 18 mg & 1x 28 mg	3
24	144	138	1x 18 mg & 1x 28 mg	3
25	150	138	1x 18 mg & 1x 28 mg	3
26	156	168	2x 28 mg	3
27	162	168	2x 28 mg	3
28	168	168	2x 28 mg	3
29	174	174	1x 18 mg & 1x 40 mg	3
30	180	174	1x 18 mg & 1x 40 mg	3
31	186	174	1x 18 mg & 1x 40 mg	3
32	192	204	1x 28 mg & 1x 40 mg	3
33	198	204	1x 28 mg & 1x 40 mg	3
34	204	204	1x 28 mg & 1x 40 mg	3
35	210	204	1x 28 mg & 1x 40 mg	3

Weight (kg)	Required dose per application (mg)	Purchased dosing (mg)	Dosing of asfotase alfa	
			Vials per administration	Administrations per week
36	216	240	1x 80 mg	3
37	222	240	1x 80 mg	3
38	228	240	1x 80 mg	3
39	234	240	1x 80 mg	3
40	240	240	1x 80 mg	3
41	246	240	1x 80 mg	3
42	252	240	1x 80 mg	3
43	258	294	1x 18 mg & 1x 80 mg	3
44	264	294	1x 18 mg & 1x 80 mg	3
45	270	294	1x 18 mg & 1x 80 mg	3
46	276	294	1x 18 mg & 1x 80 mg	3
47	282	294	1x 18 mg & 1x 80 mg	3
48	288	294	1x 18 mg & 1x 80 mg	3
49	294	294	1x 18 mg & 1x 80 mg	3
50	300	294	1x 18 mg & 1x 80 mg	3
51	306	294	1x 18 mg & 1x 80 mg	3
52	312	324	1x 28 mg & 1x 80 mg	3
53	318	324	1x 28 mg & 1x 80 mg	3
54	324	324	1x 28 mg & 1x 80 mg	3
55	330	324	1x 28 mg & 1x 80 mg	3
56	336	360	1x 40 mg & 1x 80 mg	3
57	342	360	1x 40 mg & 1x 80 mg	3
58	348	360	1x 40 mg & 1x 80 mg	3
59	354	360	1x 40 mg & 1x 80 mg	3
60	360	360	1x 40 mg & 1x 80 mg	3
61	366	360	1x 40 mg & 1x 80 mg	3
62	372	360	1x 40 mg & 1x 80 mg	3
63	378	480	2x 80 mg	3
64	384	480	2x 80 mg	3
65	390	480	2x 80 mg	3
66	396	480	2x 80 mg	3
67	402	480	2x 80 mg	3

Weight (kg)	Required dose per application (mg)	Purchased dosing (mg)	Dosing of asfotase alfa	
			Vials per administration	Administrations per week
68	408	480	2x 80 mg	3
69	414	480	2x 80 mg	3
70	420	480	2x 80 mg	3
71	426	480	2x 80 mg	3
72	432	480	2x 80 mg	3
73	438	480	2x 80 mg	3
74	444	480	2x 80 mg	3
75	450	480	2x 80 mg	3
76	456	480	2x 80 mg	3
77	462	480	2x 80 mg	3
78	468	480	2x 80 mg	3
79	474	480	2x 80 mg	3
80	480	480	2x 80 mg	3

Costs of AA per week, cycle (12 weeks) and year are presented by age in Table 59. These costs are calculated based on the modelled weight for the age of patients with paediatric-onset HPP, dosing by weight range, and price per vial of AA in the UK.

Table 59: Modelled annual drug costs of asfotase alfa (2022 GBP) by patient age

Age	Weekly purchased dose (mg)	Weekly drug cost (GBP)	12-week drug cost (GBP)	Annual drug costs (GBP)
0–1	54	[redacted]	[redacted]	[redacted]
1–2	84	[redacted]	[redacted]	[redacted]
2–3	108	[redacted]	[redacted]	[redacted]
3–4	120	[redacted]	[redacted]	[redacted]
4–5	138	[redacted]	[redacted]	[redacted]
5–6	168	[redacted]	[redacted]	[redacted]
6–7	174	[redacted]	[redacted]	[redacted]
7–8	204	[redacted]	[redacted]	[redacted]
8–9	216	[redacted]	[redacted]	[redacted]
9–10	240	[redacted]	[redacted]	[redacted]
10–11	294	[redacted]	[redacted]	[redacted]

Age	Weekly purchased dose (mg)	Weekly drug cost (GBP)	12-week drug cost (GBP)	Annual drug costs (GBP)
11–12	324	[redacted]	[redacted]	[redacted]
12–13	336	[redacted]	[redacted]	[redacted]
13–14	348	[redacted]	[redacted]	[redacted]
14–15	360	[redacted]	[redacted]	[redacted]
15–16	408	[redacted]	[redacted]	[redacted]
16–17	480	[redacted]	[redacted]	[redacted]
17–18	588	[redacted]	[redacted]	[redacted]
18+	648	[redacted]	[redacted]	[redacted]

Loss of exclusivity

The AA patent is due to expire in 2030. As AA costs are applied for the total duration of the model's time horizon, the model base case assumes that after 7 years from the start of the model, loss of data exclusivity leads to a 58.5% decrease in the AA list price.

Experience in Europe shows significant variance in price differentials between reference products and biosimilars. For example, recent reports of prices for biosimilar infliximab have suggested price reductions of 45–72% versus the originator product.[112] NICE has stated that 'biosimilars have the potential to offer the NHS considerable cost savings, especially as they are often used to treat long-term conditions'.[113] A loss of exclusivity discount of 58.5% was chosen as this is the mid-point reported. Therefore, scenario analyses are presented with a greater price reduction (72%) and lower price reduction (45%) following loss of exclusivity, in section B.3.10.3.

Stopping rule and discontinuation

Treatment discontinuation was applied in the model to account for patients who may withdraw from taking AA. The discontinuation rate was obtained from ENB-002-08/ENB-003-08, ENB-010-10, ENB-006-09/ENB-008-10 and the UK MAA. Data from the Global HPP Registry were also used to capture how patients may discontinue treatment in a real-world setting. Table 60 shows the discontinuation data from each study. These data excluded causes for discontinuation related to death. An annual

discontinuation rate of [redacted] was calculated from all sources. The rate was converted to a probability, and a 12-week discontinuation probability of [redacted] was applied to each cycle in the model.

Table 60: Summary of discontinuation data used in economic model

Trial	ENB-002-08/ ENB-003-08	ENB-010-10	ENB-006-09/ ENB-008-10	UK MAA	ALX-HPP-501 Global HPP Registry
Treated patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Exposure time (mean days)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of patients who discontinued treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Key: HPP, hypophosphatasia; MAA, managed access agreement.					

In addition, a scenario was explored where a treatment stopping rule was applied to patients entering SLIV after age 18, presented in section B.3.10.3.

Compliance

Treatment compliance is included in the model to account for patients that miss AA doses. In the MAA UK study, patients missed or interrupted doses for the following reasons:

- Patient forgot
- Patient ran out of the drug
- Patient was asked to skip doses by physician
- Patient decision
- AE

The model incorporates the combined treatment compliance rate of [redacted] for both adults and children from the MAA UK study.

B.3.5.1.2. Comparator costs

As BSC does not involve any specific treatment, there are no treatment costs applied in the BSC arm. All costs related to managing HPP are assumed to be covered by health state costs for patients with HPP.

B.3.5.2. Health state unit costs and resource use

Healthcare resource use costs for patients with HPP were derived for health states in the model. This was done by estimating the frequency of discrete clinical events expected in each health state, along with the background care levels in those states. Costs were assigned to each component of care to estimate the overall cost per health state in the model.

The resource use used in this analysis was informed by the estimates used in the previous cost-effectiveness model. During the previous NICE submission, estimates were agreed with NICE following the consultation process as part of the NICE submission, where the Committee suggested that the original model underestimated the costs associated with invasive ventilation use and the SL health states. Alexion consulted 5 UK HPP clinical experts to elicit standard treatment protocols for patients with varying severities of disease. The estimates from 3 physicians who provided the highest values were used. These estimates of resource use were validated with 2 clinical experts in April 2022. The clinical experts suggested that clinical practice has remained relatively unchanged since 2016, and therefore resource use estimates should still be reflective of current practice. However, some minor adjustments were made. This included adding additional pain management services, adding additional dietician visits and including mental health services, as patients with HPP may experience mental health difficulties due to the condition. Resource use estimates can be found in Table 61. The corresponding costs that were incorporated in the model can be found in Table 62. Costs that were available before 2020/21 were inflated using the NHS Cost Inflation Index from the 2021 Personal Social Services Research Unit.[114]

Table 61: Summary of annual resource use by health state

Resource item	Age < 5 – no invasive ventilation	Age < 5 – with invasive ventilation	Age ≥ 5 – SLI	Age ≥ 5 – SLII	Age ≥ 5 – SLIII	Age ≥ 5 – SLIV
Respiratory failure with ventilation, NICU (inpatient day)	0.00	15.00	0.00	0.00	0.00	0.00
Respiratory failure with ventilation, PICU (inpatient day)	0.00	134.00	0.00	0.00	0.00	0.00
LTV ward (inpatient day)	0.00	211.00	0.00	0.00	0.00	0.00
Community LTV (day)	0.00	55.25	0.00	0.00	0.00	0.00
Tracheostomy	0.05	0.20	0.00	0.00	0.00	0.00
Hickmann line	0.05	0.20	0.00	0.00	0.00	0.00
Gastrostomy	0.05	0.17	0.00	0.00	0.00	0.00
Respiratory complications, no ventilation ICU (inpatient days)	3.94	0.00	0.00	0.00	1.00	1.00
Respiratory complication, no ventilation, HDU (inpatient days)	39.43	0.00	0.00	0.11	1.00	1.00
Paediatric respiratory medicine (outpatient visit post-discharge)	0.00	1.31	0.00	0.12	0.59	1.00
Paediatric feeding difficulties or vomiting (inpatient stay)	0.09	0.09	0.00	0.07	0.06	0.06
Dietician (community visit)	4.00	6.00	0.00	0.00	0.00	0.00
Paediatric gastroenterology (outpatient visit)	0.96	0.96	0.00	0.16	0.20	0.10
Paediatric epilepsy/ paediatric febrile convulsions	0.02	0.02	0.00	0.06	0.02	0.02
Gait, abnormal posture (inpatient stay)	0.00	0.00	0.00	0.02	0.12	0.17

Resource item	Age < 5 – no invasive ventilation	Age < 5 – with invasive ventilation	Age ≥ 5 – SLI	Age ≥ 5 – SLII	Age ≥ 5 – SLIII	Age ≥ 5 – SLIV
Failure to thrive, nutrition disorders	0.05	0.05	0.00	0.00	0.00	0.00
Paediatric endocrinology follow-up (outpatient visit)	4.00	4.00	0.00	0.04	0.39	0.30
Craniosynostosis surgery (inpatient stay)	0.04	0.04	0.00	0.00	0.00	0.00
Intracranial pressure monitoring	0.22	0.22	0.00	0.00	0.00	0.00
Fractures (hip, lower limb, foot, hand, arm, multiple)	0.04	0.04	0.00	0.04	0.12	0.50
Paediatric rheumatologist (outpatient visit)	0.39	0.39	0.00	0.08	0.39	1.00
Orthopaedic surgery	0.20	0.20	0.00	0.00	0.00	1.00
Nephrology (outpatient visit)	0.51	0.51	0.00	0.08	0.05	0.33
Paediatric pain management (outpatient visit)	1.10	1.10				
Pain clinic	0.00	0.00	3.00	4.00	5.00	6.00
Group CBT	0.00	0.00	1.00	1.00	0.00	0.00
CBT (individual)	0.00	0.00	0.00	0.00	1.00	1.00
Audiometry or hearing assessment (visit)	0.01	0.01	0.00	0.00	0.00	0.00
Fitting of hearing aid (visit)	0.01	0.01	0.00	0.00	0.00	0.00
Follow-up, face to face (visit)	0.01	0.01	0.00	0.00	0.00	0.00
Aftercare (visit)	0.01	0.01	0.00	0.00	0.00	0.00
Dental problems (inpatient stay)	0.03	0.03	0.14	0.10	0.11	0.16
Paediatric dentistry (outpatient visit)	0.35	0.35	1.41	1.41	1.49	0.27
Paediatrician (outpatient visit)	1.10	1.10	4.00	4.00	4.00	12.00
GP (visits)	2.50	2.50	4.00	20.40	4.00	32.00

Resource item	Age < 5 – no invasive ventilation	Age < 5 – with invasive ventilation	Age ≥ 5 – SLI	Age ≥ 5 – SLII	Age ≥ 5 – SLIII	Age ≥ 5 – SLIV
Community physiotherapist (visit)	46.00	46.00	0.00	6.00	12.00	48.00
Community child specialist (portage) (visit)	1.10	1.10	0.00	0.00	0.00	0.00
Community nurse specialist (visit)	1.80	1.80	0.00	6.00	6.00	0.00

Key: CBT, cognitive behavioural therapy; GP, general practitioner; HDU, high dependency unit; ICU, intensive care unit; LTV, long-term ventilation; NICU, neonatal intensive care unit; PICU, paediatric intensive care unit; SL, severity level.

Table 62: Summary of resource use costs

Resource item	Cost	Source
Respiratory failure with ventilation, NICU (inpatient day)	£1,754	Neonatal intensive care (XA01Z). NHS reference costs 2019–20, inflated to 2020–21
Respiratory failure with ventilation, PICU (inpatient day)	£2,989	Paediatric Critical Care, Advanced Critical Care 1–5 (XB01-05Z). NHS reference costs 2019–20, inflated to 2020–21
LTV ward (inpatient day)	£1,074	Non-elective long stay. Non-invasive ventilation support assessment (DZ37B). NHS reference costs 2019–20, inflated to 2020–21
Community LTV (day)	£199	Community health services. Specialist Nursing, Asthma and Respiratory Nursing/Liaison, Child, Face to face (N08CF). NHS reference costs 2019–20, inflated to 2020–21
Tracheostomy	£4,048	Total HRGs. Code CA63Z - Tracheostomy. NHS reference costs 2019–20, inflated to 2020–21
Hickmann line	£2,973	Total HRGs. Code YR40C-D - Insertion of Non-Tunnelled Central Venous Catheter. NHS reference costs 2019–20, inflated to 2020–21
Gastrostomy	£2,640	Total HRGs. Code FE12B- Endoscopic Insertion of Gastrostomy Tube, 18 years and under. NHS reference costs 2019–20, inflated to 2020–21
Respiratory complications, no ventilation, ICU (inpatient days)	£2,104	Weighted average unit cost neonatal/paediatric critical care, total HRGs XA01Z, XB01Z-XB05Z5. NHS reference costs 2019–20, inflated to 2020–21
Respiratory complications, no	£1,247	Weighted average unit cost neonatal/paediatric critical care, total HRGs XA02Z, XB06Z-

Resource item	Cost	Source
ventilation, HDU (inpatient days)		XB07Z. NHS reference costs 2019–20, inflated to 2020–21
Paediatric respiratory medicine (outpatient visit post-discharge)	£244	Outpatient average unit cost (code 258). NHS reference costs 2019–20, inflated to 2020–21
Paediatric feeding difficulties or vomiting (inpatient stay)	£1,171	Total HRGs. Code PF28A-E - Feeding Difficulties and Vomiting with CC. NHS reference costs 2019–20, inflated to 2020–21
Dietician (community visit)	£95	Community visit (CHS - code A03). NHS reference costs 2019–20, inflated to 2020–21
Paediatric gastroenterology (outpatient visit)	£244	Outpatient average unit cost (code 251). NHS reference costs 2019–20, inflated to 2020–21
Paediatric epilepsy/paediatric febrile convulsions	£1,740	Total HRGs. PR02A-C - Paediatric Epilepsy Syndrome. NHS reference costs 2019–20, inflated to 2020–21
Gait, abnormal posture (inpatient stay)	£806	Total HRGs. Code AA26H- Muscular, Balance, Cranial or Peripheral Nerve Disorders; Epilepsy; Head Injury with CC 0-2. NHS reference costs 2019–20, inflated to 2020–21
Failure to thrive, nutrition disorders	£2,154	Total HRGs Code PX30A-B - Faltering Growth (Failure to Thrive) with CC and FD04A-E disorders of nutrition. NHS reference costs 2019–20, inflated to 2020–21
Paediatric endocrinology follow-up (outpatient visit)	£258	Outpatient visit consultant led (service code 252). NHS reference costs 2019–20, inflated to 2020–21
Craniosynostosis surgery (inpatient stay)	£6,392	Total HRGs. AA50A - AA57B - Intracranial procedures. NHS reference costs 2019–20, inflated to 2020–21
Intracranial pressure monitoring	£6,563	Cost data provided by Dr Raj Padidela at Royal Manchester Children's Hospital 2013–14, inflated to 2020–21
Fractures (hip, lower limb, foot, hand, arm, multiple)	£2,005	Weighted average unit cost Early Complications of Trauma or Injury of Non-Specific Joint Site Total HRGs HE83A-C. NHS reference costs 2019–20, inflated to 2020–21
Paediatric rheumatologist (outpatient visit)	£271	Total Outpatient attendance (code 262). NHS reference costs 2019–20, inflated to 2020–21
Orthopaedic surgery	£3,588	Total HRGs. HN12A-HN26C - NHS reference costs 2019–20, inflated to 2020–21
Nephrology (outpatient visit)	£354	Total Outpatient attendance (code 259). NHS reference costs 2019–20, inflated to 2020–21

Resource item	Cost	Source
Paediatric pain management (outpatient visit)	£293	Total Outpatient attendance (code 241). NHS reference costs 2019–20, inflated to 2020–21
Pain clinic	£485	Consultant led pain management (code 191). NHS reference costs 2019-20, inflated to 2020/21
Group CBT	£343	Taken from NICE guideline NG134; Depression in children and young people, 2019 evidence review. Inflated to 2020/21
CBT (individual)	£1,854	
Audiometry or hearing assessment (visit)	£114	Average unit cost of audiometry or hearing assessment, 4 years and under and 5–18 years (DAD - CA37B, CA37C). NHS reference costs 2019–20, inflated to 2020–21
Fitting of hearing aid (visit)	£175	Fitting of hearing aid, child, specialist audiology services (CHS - AS07). NHS reference costs 2019–20, inflated to 2020–21
Follow-up, face to face (visit)	£119	Follow-up, child, face to face (CHS - AS09). NHS reference costs 2019–20, inflated to 2020–21
Aftercare (visit)	£38	Aftercare (CHS - AS11). NHS reference costs 2019–20, inflated to 2020–21
Dental problems (inpatient stay)	£2,571	Elective inpatient. Dental procedures (code CD01A/B, CD02A/B, CD03A/B). NHS reference costs 2019–20, inflated to 2020–21
Paediatric dentistry (outpatient visit)	£159	Total Outpatient attendance (code 142). NHS reference costs 2019–20, inflated to 2020–21
Paediatrician (outpatient visit)	£192	Total Outpatient attendance (code 420). NHS reference costs 2019–20, inflated to 2020–21
GP (visits)	£39	GP visit lasting 9.22 minutes including direct staff care costs with qualifications. PSSRU 2021
Community physiotherapist (visit)	£54	Community-based Health Care Staff, Scientific and professional. Band 6. PSSRU 2021
Community child specialist (portage) (visit)	£106	Community visit specialist child nursing face to face (CHS - code N29CF). NHS reference costs 2019–20, inflated to 2020–21
Community nurse specialist (visit)	£75	Community-based Health Care Staff, Nurses. Band 8a. PSSRU 2021

Key: CBT, cognitive behavioural therapy; GP, general practitioner; HDU, high dependency unit; ICU, intensive care unit; LTV, long-term ventilation; NHS, National Health Service; NICU, neonatal intensive care unit; PICU, paediatric intensive care unit; PSSRU, Personal Social Services Research Unit.

The final costs associated with each of the health states are shown in Table 63.

Table 63: Costs by health state

Health state	Annual cost	Cost per cycle (12 weeks)
Age < 5 years		
No invasive ventilation	£66,162.18	£15,216.94
With invasive ventilation	£608,926.80	£140,040.66
Age ≥ 5 years		
SLI	£3,308.87	£760.97
SLII	£5,646.83	£1,298.66
SLIII	£11,027.83	£2,536.18
SLIV	£20,258.85	£4,659.12
Key: SL, severity level.		

B.3.5.3. Adverse reaction unit costs and resource use

AEs were not included in the cost-effectiveness analysis as per Section B.3.4.4.

B.3.5.4. Miscellaneous unit costs and resource use

Societal costs are included in the model as a scenario analysis to capture the financial burden faced by parents/caregivers and patients. To estimate productivity loss, weekly productivity was calculated as the average weekly earnings for the UK (£553)[115], multiplied by the employment rate for the UK, using the unemployment rate to estimate the employment rate; 95.2% (100% minus 4.8%). This resulted in weekly productivity cost of £527, which was converted to a 12-week productivity cost (due to the 12-week cycle length) of £6,323.

The potential annual productivity is assumed to be lost by 1 caregiver when patients are aged 1–17 years, and by the patient when they are aged 18–65 years. UK parental leave regulations meant that no productivity loss was modelled when patients are aged 0–1 years. It is assumed that when the patient is between ages 5–65 years, the probability of a patient or their caregiver (depending on age) being able to work corresponds to the ratio of their health state utility versus utility in SLI (i.e. that no productivity loss occurs in SLI). When a patient is between ages 1–4 years, it is assumed their caregiver can work normally if the patient does not require invasive ventilation, and a 50% productivity loss is assumed if the patient does require

invasive ventilation. Inputs for estimated proportion of patients and carers able to work are shown in Table 64.

Table 64: Inputs for estimated proportion of patients and carers able to work

Patient age	Health state	Proportion of patients able to work	Proportion of caregivers able to work
0–1 years	All	N/A	N/A
1–4 years	No ventilation	N/A	50%
	Invasive ventilation	N/A	0%
5–12 years	SLI	N/A	100%
	SLII	N/A	77%
	SLIII	N/A	62%
	SLIV	N/A	27%
13–17 years	SLI	N/A	100%
	SLII	N/A	77%
	SLIII	N/A	62%
	SLIV	N/A	27%
18–65 years	SLI	100%	N/A
	SLII	77%	N/A
	SLIII	62%	N/A
	SLIV	27%	N/A
Key: N/A, not applicable; SL, severity level			

B.3.6. Uncertainty

HPP is an ultra-rare lifelong condition, which poses difficulties to modelling and generating high-quality evidence. As HPP is an ultra-rare condition, studies often have low sample sizes, which makes it difficult to determine the effect of a treatment. One of the greatest limitations is the low number of patients in the BSC arm of the HPP trials. As all patients receiving BSC ended up switching to AA in the trials, there is limited follow-up time for these patients (and a low number of observations for estimating transition probabilities). The opportunity to compare AA with BSC is becoming more limited, as AA has received reimbursement in several countries, and therefore fewer patients are only receiving BSC.

The model includes trial data for AA, which means that patients present at a range of SLs and start treatment at different ages. With increased disease awareness, earlier diagnosis and intervention, and the establishment of specialist treatment services, it is anticipated that patients will receive AA treatment much earlier than some of the patients enrolled in the trial. Greater health gains are therefore more likely to occur in clinical practice.

Further limitations associated with the model are as follows:

- Aside from previous versions of this model, no other models of HPP have been published to date
- No similar BSC cohort of outcomes for patients with HPP have been published
- There are no established SLs (e.g. SLs I, II, III and IV) in HPP

Although uncertainty is present, the model has been developed using the best quality of evidence available and is supplemented with expert clinical opinion. A range of analyses exploring the uncertainty associated with the model have been conducted, as described in Section B.3.10.

B.3.7. Managed access proposal

Not applicable.

B.3.8. Summary of base-case analysis inputs and assumptions

B.3.8.1. Summary of base-case analysis inputs

A summary of variables applied in the economic model is provided in Appendix Q.

B.3.8.2. Assumptions

Table 65 summarises the assumptions made in the economic evaluation.

Table 65: Model assumptions

#	Assumption	Justification
1	Baseline age for juvenile-onset patients 5.0, as all patients as all patients with juvenile-onset HPP are assumed to begin treatment at age of first hospital admission	According to Table 1 of Whyte et al. 2016[3], among patients with 'severe childhood' HPP (N = 37), the mean age at first admission was 4.9 years (SD = 3.6 years), which is rounded to 5.0 years. As efforts are made in clinical practice in England to ensure patients are diagnosed and treated as soon as possible, the mean age of first admission was used in the model. This is also more reflective of how patients will be detected and treated in England
2	For patients aged 5+ years, progression in disease severity over time can be estimated using 6MWT as a proxy for disease severity	Correlation of measure to other trial endpoints (see Section B.3.2.2) and recommendation of clinical experts in the UK, France and Canada[100]
3	There is no excess risk of death for patients with HPP after age 5	This is a conservative modelling approach and is applied due to the lack of evidence regarding HPP-related mortality risk for patients above 5 years of age. However, clinicians have indicated that the risk of mortality may be increased due to co-morbidities resulting from HPP
4	Patients who were unable to complete the 6MWT at a visit were in the SLIV state	Evidence of attempt but failure to complete the test reflects severe disease
5	SL distribution is not modelled in the perinatal-/infantile-onset patient group. Perinatal-/infantile-onset patients who survived to age 5 would enter the model in health state SLIV	Validated with clinical experts. Scenario analysis was conducted for patients receiving AA in the perinatal-/infantile-onset group, where at age 5, 50% enter the model in health state SLIII, with the remaining 50% entering health state SLIV
6	The base case applied rounding down of a dose if the administered dose was 12 mg less than the required dose per week. Where rounding was not possible, wastage was assumed to occur	This was validated with clinical experts who stated that efforts are made in clinical practice to reduce drug wastage. 12 mg per week was deemed a plausible limit to apply within the model
7	Resource use is based on the assumptions made during the previous submission consultation	During the previous NICE submission, the Committee agreed that the original estimates of resource use were underestimating the costs associated with invasive ventilation and SLs. Alexion consulted 5 UK clinicians and updated the costs according to their estimates of resource use. These estimates were further validated with 2 UK clinicians in April 2022

#	Assumption	Justification
8	A single caregiver per patient will experience disutility, and this disutility is experienced until the patient reaches 60 years old	The number of caregivers is assumed to be 1 for paediatric patients. This is a conservative estimate as paediatric patients may have multiple caregivers. The number of caregivers remains 1 later in life, assuming adult patients would have a formal caregiver
9	The patient's caregiver experiences disutility associated with their patient's health or mental status, based on estimated disutilities from Landfeldt et al. (2016).[53] In SLI, there is no caregiver disutility, and in intermediate states (no invasive ventilation, SLII and III), the disutility of SLIV is scaled in proportion to the patient's utility compared with SLIV (and with invasive ventilation)	Clinicians stated that the disutility of caregiving for patients with DMD was deemed appropriate to use as a proxy for the disutility of caregiving for patients with paediatric-onset HPP Caregiver disutility increases proportionally with reduction in their patient's utility
10	2 parents experience disutility from their infant's death, and the disutility is experienced for 55 years from baseline age	According to Song et al. (2010), both mothers and fathers experience an ongoing utility decrement following the death of their infant.[108] The average age of parents at infant death and life expectancy is used to calculate the average number of years that parents will be alive, and therefore the duration over which the disutility is applied. The annual utility decrement, controlling for other factors, is estimated at -0.04
11	The AA patent is due to expire in 2030. Therefore, the model base case assumes that after 7 years from the start of the model, loss of data exclusivity leads to a 58.5% decrease in the AA list price	NICE has stated that 'biosimilars have the potential to offer the NHS considerable cost savings, especially as they are often used to treat long-term conditions'.[113] Recent reports of prices for biosimilar infliximab have suggested price reductions of 45–72% versus the originator product therefore the mid-point of a 58.5% price reduction is modelled[112]

Key: 6MWT, 6 Minute Walk Test; BSC, best supportive care; DMD, Duchenne muscular dystrophy HPP, hypophosphatasia; MAA, managed access agreement; NICE, National Institute for Health and Care Excellence; SL, severity level.

B.3.9. Base-case results

B.3.9.1. Base-case incremental cost-effectiveness analysis results

The base case analysis results with a 55.9% PAS discount applied are shown in Table 66. Discounted results show that AA is associated with 14.89 incremental life

years, 15.66 incremental QALYs, and incremental costs of £3,762,295 in the perinatal-/infantile-onset group versus BSC. The incremental cost-effectiveness ratio (ICER) is £240,279 per QALY gained. Discounted results for the juvenile-onset group show that AA is associated with 0.00 incremental life years, 16.32 incremental QALYs, and incremental costs of £4,824,341. The ICER is £295,536 per QALY gained.

Table 66 also shows undiscounted results, with AA associated with 44.86 incremental life years, 46.24 incremental QALYs, and incremental costs of £11,907,055 in the perinatal-/infantile-onset group versus BSC. The ICER is £257,521 per QALY gained. Undiscounted results for the juvenile-onset group show that AA is associated with 0.00 incremental life years, 43.91 incremental QALYs, and incremental costs of £13,215,139. The ICER is £300,932 per QALY gained. This shows that AA results in more than 30 unadjusted QALY gains in both populations. According to the NICE methods for HST[98], if the QALY gain is above 10, a 'QALY weight' between 1 and 3 can be applied. Given the undiscounted results show QALY gains greater than 30, a QALY weight of 3 was applied.

Table 67 shows the discounted results with the QALY weight applied. Costs and life years remain unchanged; the incremental QALY gain for the perinatal-/infantile-onset patients is 46.97 with an ICER of £80,093 per QALY gained. For the patients with juvenile-onset HPP, the results show 48.97 incremental QALYs and an ICER of £98,512 per QALY gained. This shows that both groups are below the £100,000 threshold. Appendix R presents the results at list price.

Table 66: Base case results (PAS price, without QALY weight)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
Population: Perinatal-/infantile-onset HPP							
Undiscounted							
BSC	[redacted]	[redacted]	[redacted]	-	-	-	-
AA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£257,521
Discounted							
BSC	[redacted]	[redacted]	[redacted]	-	-	-	-
AA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£240,279
Population: Patients with juvenile-onset HPP							
Undiscounted							
BSC	[redacted]	[redacted]	[redacted]	-	-	-	-
AA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£300,932
Discounted							
BSC	[redacted]	[redacted]	[redacted]	-	-	-	-
AA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£295,536

Key: AA, asfotase alfa; BSC, best supportive care; HPP, hypophosphatasia; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.

Table 67: Base case results (PAS price, with QALY weight applied)

Technologies	Total costs (£)	Total LYG	Total QALYs*	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
Population: Perinatal-/infantile-onset HPP							
Discounted							
BSC	[redacted]	[redacted]	[redacted]	-	-	-	-
AA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£80,093
Population: Patients with juvenile-onset HPP							
Discounted							
BSC	[redacted]	[redacted]	[redacted]	-	-	-	-
AA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£98,512

Key: AA, asfotase alfa; BSC, best supportive care; HPP, hypophosphatasia; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.
Note: * QALY weight of 3 is applied to both arms

Table 68: Net health benefit (discounted results, PAS price, with QALY weight)

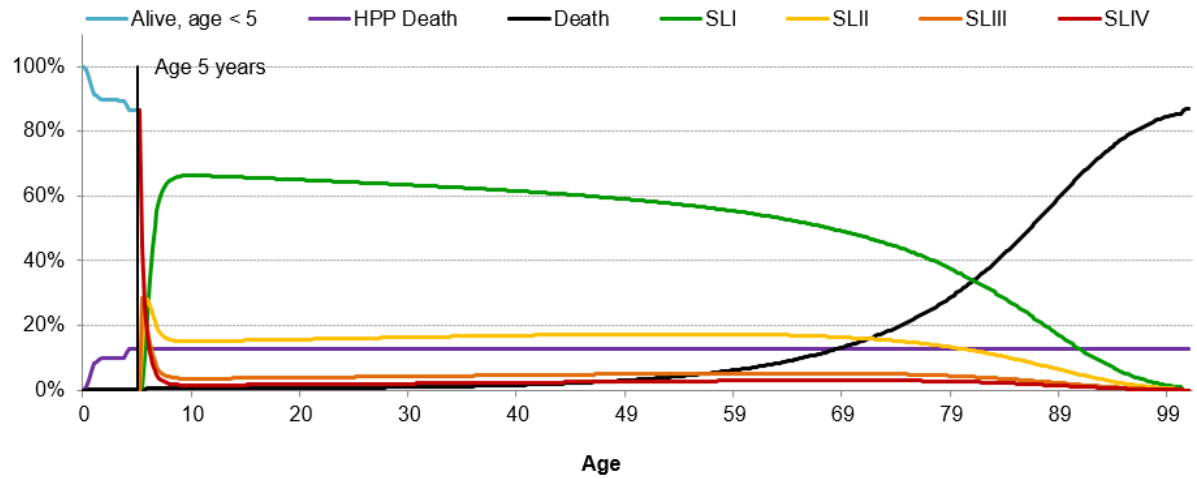
Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	NHB at £100,000
Population: Perinatal-/infantile-onset HPP					
BSC	[redacted]	[redacted]	-	-	-
AA	[redacted]	[redacted]	[redacted]	[redacted]	9.35
Population: Patients with juvenile-onset HPP					
BSC	[redacted]	[redacted]	-	-	-
AA	[redacted]	[redacted]	[redacted]	[redacted]	0.73

Key: AA, asfotase alfa; BSC, best supportive care; HPP, hypophosphatasia; ICER, incremental cost-effectiveness ratio; LYG, life years gained; NHB, net health benefit; QALYs, quality-adjusted life years.

Markov traces for the patients who were treated with AA and with BSC are provided for the base case analysis for the 2 patient populations: patients with perinatal-/infantile-onset HPP (Figure 37 and Figure 38) and patients with juvenile-onset HPP (Figure 39 and Figure 40). The traces reflect health state membership over time. They show that in the perinatal-/infantile-onset patients, a large proportion of patients in the BSC arm do not survive to age 5. For patients aged 5 years and over, both populations result in patients spending more time in SLI in the AA arm, whereas BSC results in patients spending most their time in the SLIV health state.

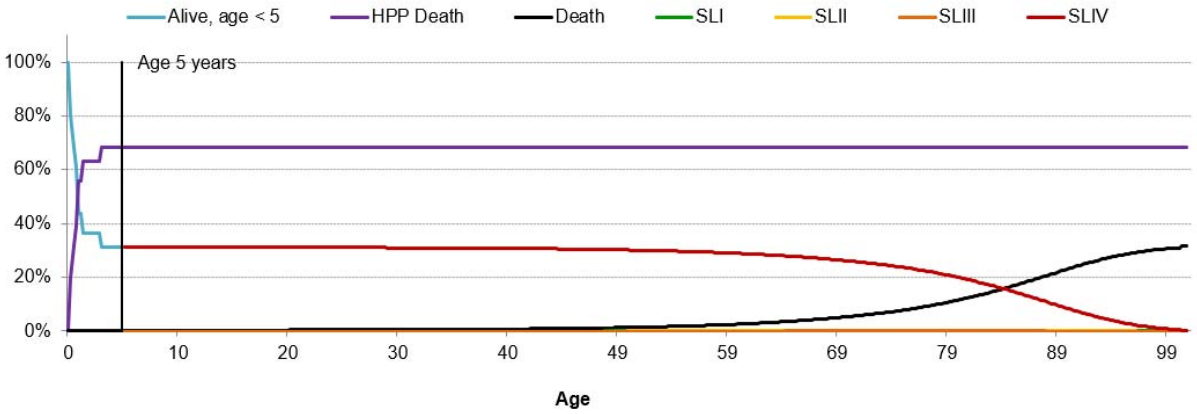
Perinatal-/infantile-onset HPP population

Figure 37: Base case Markov traces, asfotase alfa, perinatal-/infantile-onset HPP



Key: HPP, hypophosphatasia; SL, severity level.

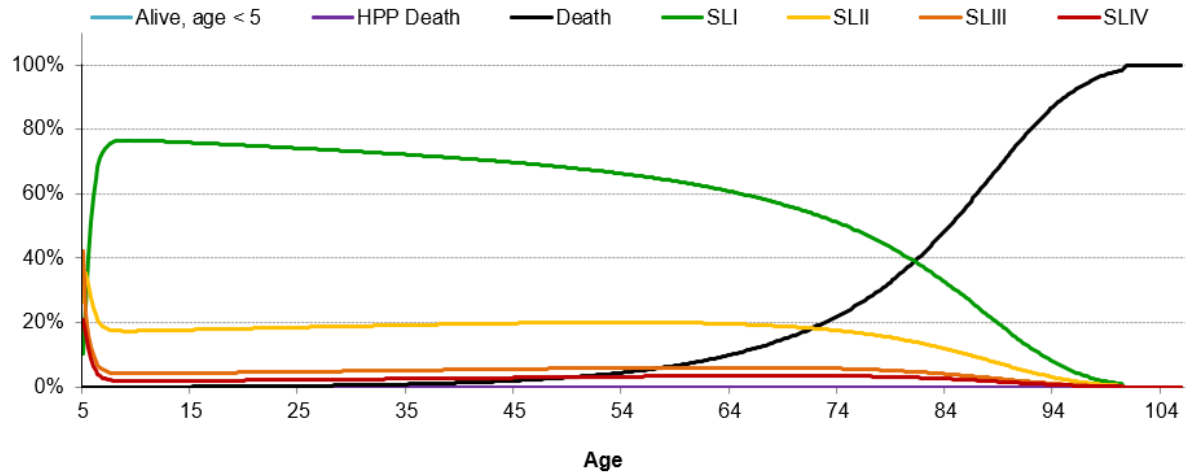
Figure 38: Base case Markov traces, BSC, perinatal-/infantile-onset HPP



Key: BSC, best supportive care; HPP, hypophosphatasia; SL, severity level.

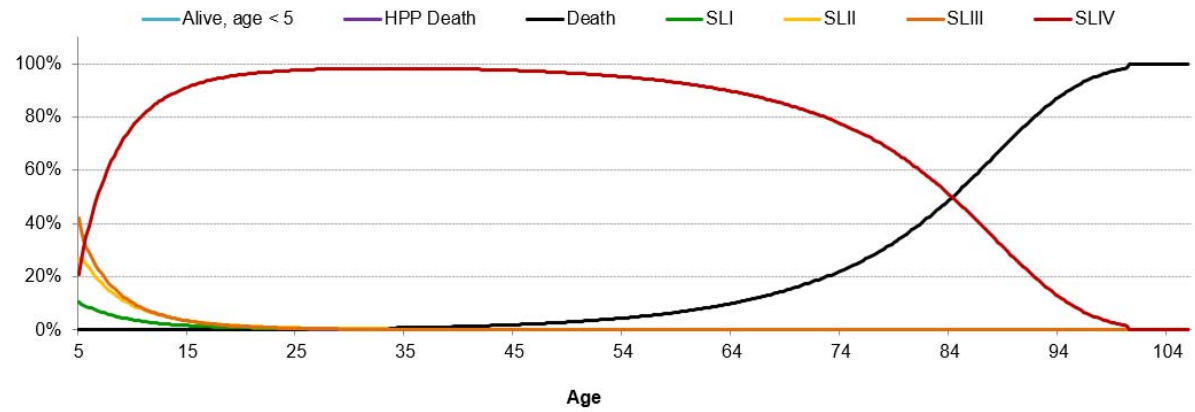
Patients with juvenile-onset HPP

Figure 39: Base case Markov traces, asfotase alfa, children with juvenile-onset HPP



Key: HPP, hypophosphatasia; SL, severity level.

Figure 40: Base case Markov traces, BSC, children with juvenile-onset HPP



Key: BSC, best supportive care; HPP, hypophosphatasia; SL, severity level.

B.3.10. Exploring uncertainty

Deterministic, probabilistic and scenario-based sensitivity analyses were undertaken. The variables used, and the range of variation (upper and lower values) and the methods used, are summarised in Sections B.3.10.1, B.3.10.2 and B.3.10.3. The following results are presented with QALY weighting applied. Appendix R presents the sensitivity analyses without QALY weighting being applied.

B.3.10.1. Probabilistic sensitivity analysis

A PSA was undertaken to explore the joint uncertainty of all model parameters based on their distributional information. Variables included in the PSA are summarised in Appendix Q. To ensure convergence, all inputs were varied simultaneously over 1,000 iterations; rolling average incremental costs, life years and QALYs were plotted on convergence graphs in the cost-effectiveness model and visually inspected. Appendix R shows the convergence plot for QALYs. Standard errors were assumed to be 10% of the base case value where unavailable.

All PSA iterations indicated that AA provides an incremental QALY benefit versus BSC at an increased total cost in both populations. When comparing average PSA results with deterministic results in the perinatal-/infantile-onset group (Table 69), results are very similar. For the patients with juvenile-onset HPP (Table 70), there is some variation in results, with the ICER being slightly higher due to higher QALYs in the BSC arm. Figure 41 and Figure 45 shows the scatter plot of the 1,000 PSA iterations for the perinatal-/infantile-onset and juvenile-onset patients, respectively. Due to the difference between the mean PSA and deterministic ICER (especially for patients with juvenile-onset HPP), the analysis was re-run, specifically without varying the transition probability parameters. This is because the difference in PSA ICER is partly due to the asymmetrical uncertainty distributions of regression analysis parameters resulting in non-normality in the sampled outcomes. There is more of a difference in the analysis for patients with juvenile-onset HPP because all patients remain alive in this analysis (i.e. there is no HPP death). For the perinatal-/infantile-onset group, a large proportion of patients in the BSC arm die before age 5 (where the transition probabilities that utilise the regression analysis is applied in the model). Appendix R shows the scatterplot when the regression parameters are not varied.

Table 69: Perinatal-/infantile-onset patients PSA results (PAS price, with QALY weight)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
PSA results							
BSC	[redacted]	[redacted]	[redacted]	-	-	-	-
AA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£80,661
Deterministic results							
BSC	[redacted]	[redacted]	[redacted]	-	-	-	-
AA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£80,093

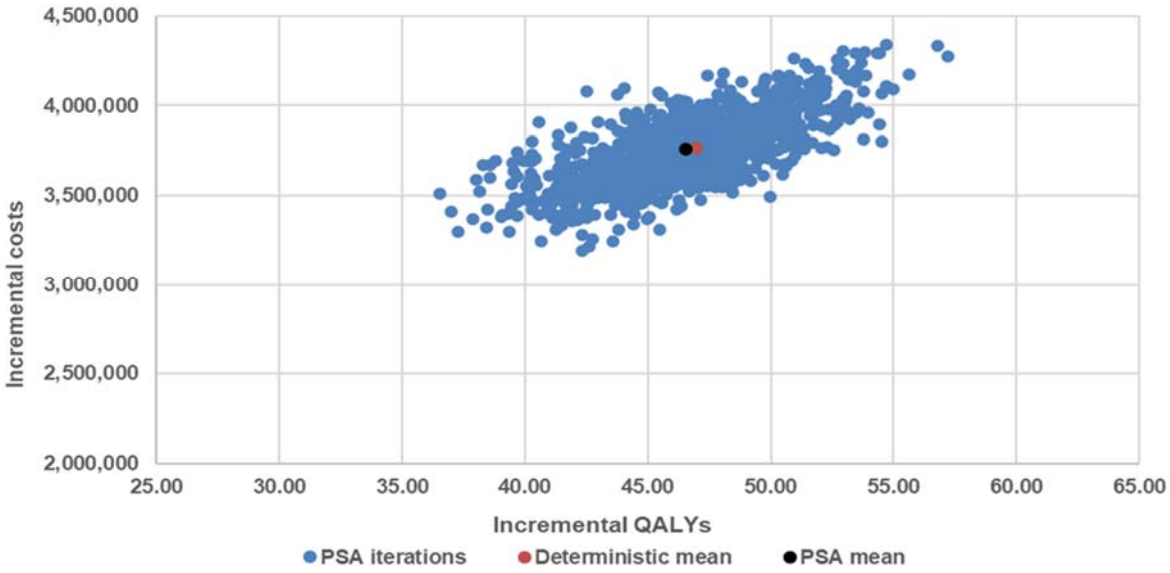
Key: AA, asfotase alfa; BSC, best supportive care; HPP, hypophosphatasia; ICER, incremental cost-effectiveness ratio; LYG, life years gained; PSA, probabilistic sensitivity analysis; QALYs, quality-adjusted life years.

Table 70: Patients with juvenile-onset HPP PSA results (PAS price, with QALY weight)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
PSA results							
BSC	[redacted]	[redacted]	[redacted]	-	-	-	-
AA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£106,799
Deterministic results							
BSC	[redacted]	[redacted]	[redacted]	-	-	-	-
AA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£98,512

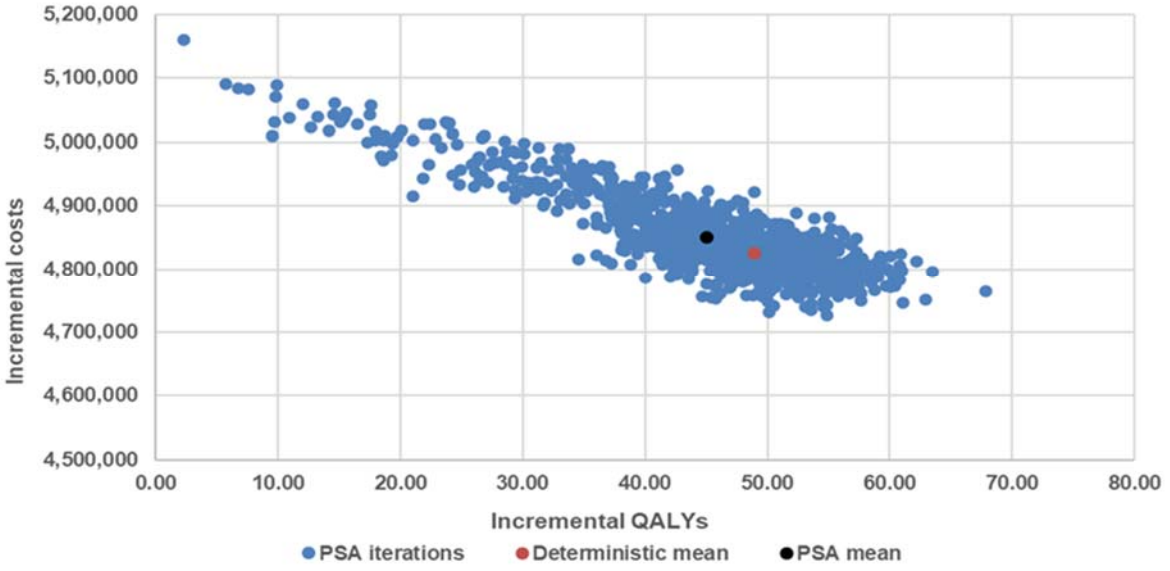
Key: AA, asfotase alfa; BSC, best supportive care; HPP, hypophosphatasia; ICER, incremental cost-effectiveness ratio; LYG, life years gained; PSA, probabilistic sensitivity analysis; QALYs, quality-adjusted life years.

Figure 41: PSA scatter plot – patients with perinatal-/infantile-onset HPP



Key: PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life year.

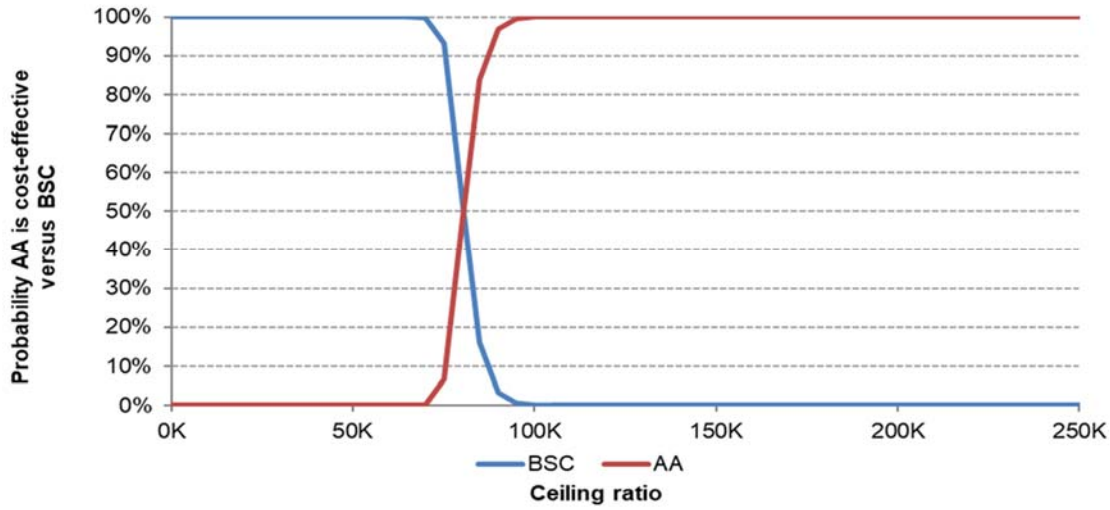
Figure 42: PSA scatter plot – patients with juvenile-onset HPP



Key: PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life year.

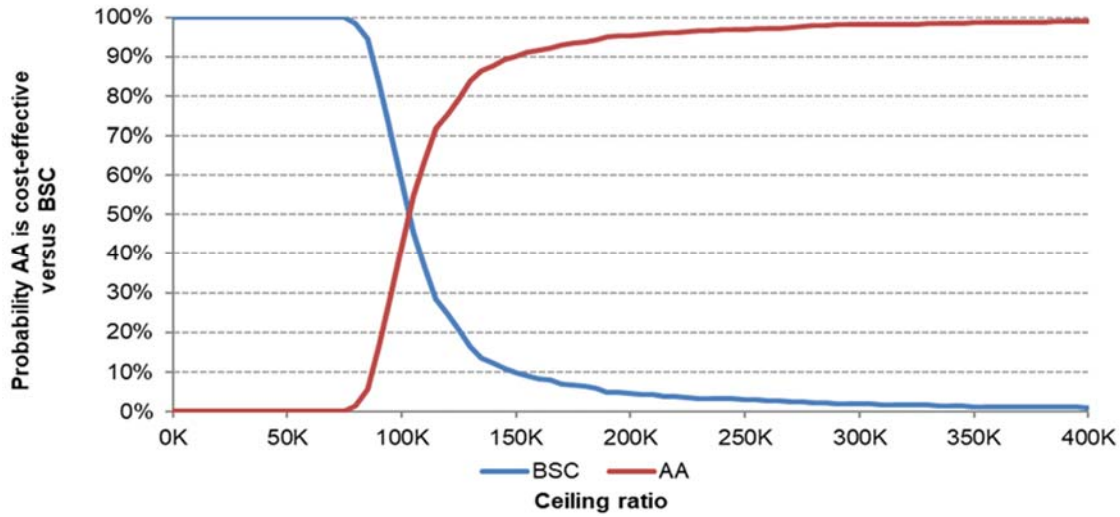
The cost-effectiveness acceptability curves are presented in Figure 43 and Figure 44 for perinatal-/infantile-onset and juvenile-onset patients, respectively.

Figure 43: Perinatal-/infantile-onset patients – Cost-effectiveness acceptability curve



Key: AA, asfotase alfa; BSC, best supportive care.

Figure 44: Patients with juvenile-onset – Cost-effectiveness acceptability curve



Key: AA, asfotase alfa; BSC, best supportive care.

B.3.10.2. Deterministic sensitivity analysis

A one-way sensitivity analysis was conducted to explore the impact that individual parameters have on the results, specifically the ICER. This analysis varies 1 parameter at a time, using plausible lower and upper bound values (e.g. the 95% CIs).

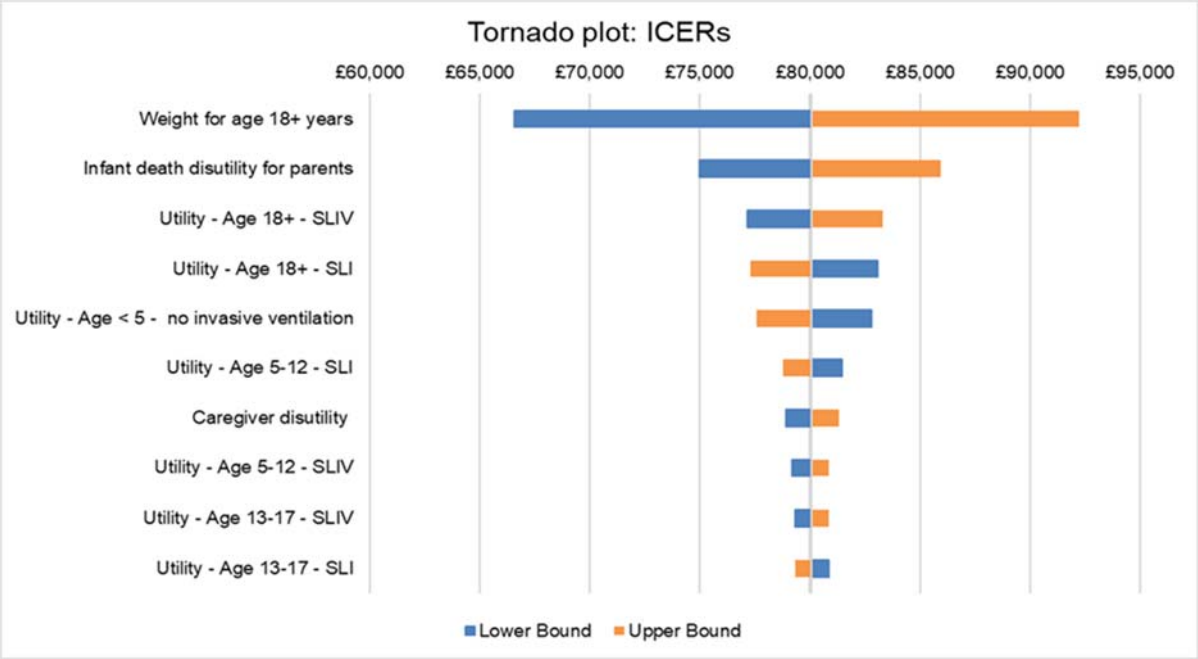
The parameters that are varied include: proportion of females; utility values associated with health states; disutilities; resource use estimates; healthcare costs; patient weight; and 12-week risk of invasive ventilation.

The 10 parameters that have the greatest impact on the ICER in order of descending sensitivity when their values were set to their upper and lower limits of the CIs are presented for the perinatal-/infantile-onset population in Figure 45 and Table 71, and for the juvenile-onset population in Figure 46 and Table 72.

The results demonstrate that the model is relatively insensitive to reasonable variation in most parameters. The parameters with the greatest impact on the ICER are the weight for patients aged 18 years and over, infant death disutility for parents and the utility values for the perinatal-/infantile-onset patients. For the juvenile-onset patients, the parameters with the greatest impact on the ICER are the weight for patients aged 18 years and over and utility values. Weight has a notable impact on results in both populations as the AA dose is determined by a patient's weight. As AA is administered over a lifetime, the weight for patients aged 18 and over is the most influential, as most AA costs are accrued after age 18.

Perinatal-/infantile-onset HPP population

Figure 45: Perinatal-/infantile-onset HPP tornado plot: ICERs



Key: ICER, incremental cost-effectiveness ratio; SL, severity level.

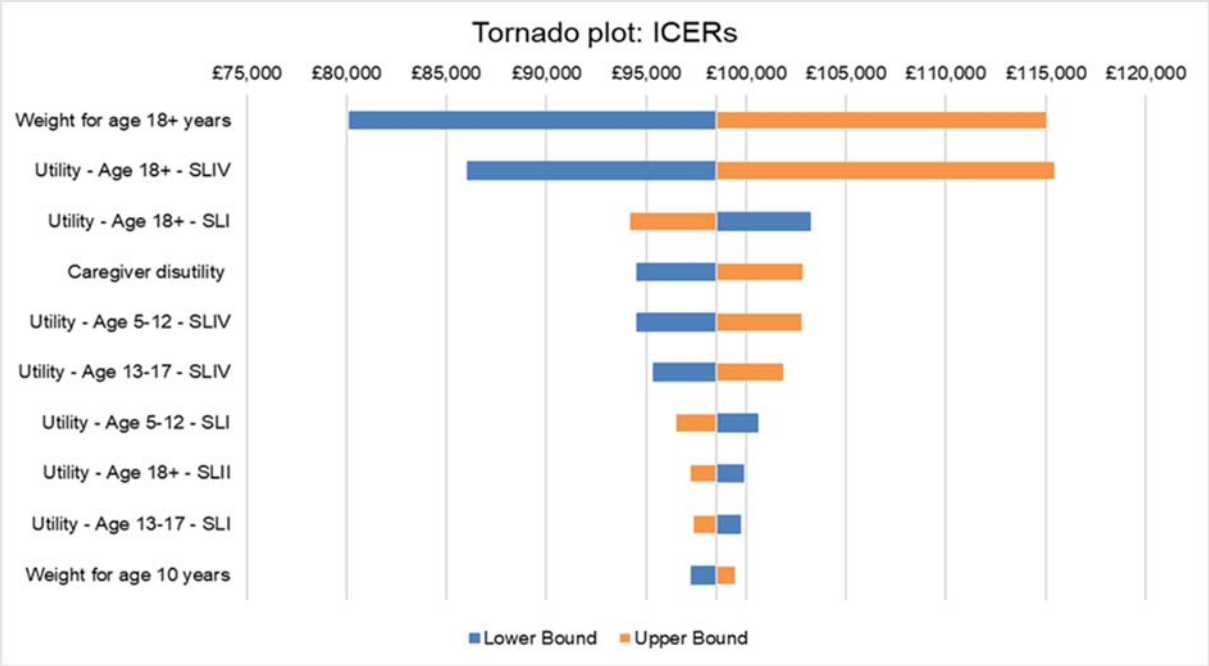
Table 71: Perinatal-/infantile-onset HPP one-way sensitivity analyses results

Rank of influence	Parameter	Input value			ICER	
		Base case	Lower bound	Upper bound	Lower bound	Upper bound
1	Weight for age 18 years	73.58	59.15	88.00	£66,593	£92,243
2	Infant death disutility for parents	-0.04	-0.08	-0.001	£74,992	£85,938
3	Utility – Age 18+ – SLIV	0.23	0.09	0.41	£77,151	£83,313
4	Utility – Age 18+ – SLI	0.86	0.78	0.93	£83,089	£77,292
5	Utility – Age < 5 – no invasive ventilation	0.24	0.06	0.49	£82,780	£77,575
6	Utility – Age 5–12 – SLI	0.86	0.78	0.93	£81,478	£78,775
7	Caregiver disutility	-0.17	-0.20	-0.14	£78,912	£81,310
8	Utility – Age 5–12 – SLIV	0.24	0.06	0.49	£79,186	£80,880
9	Utility – Age 13–17 – SLIV	0.24	0.06	0.49	£79,340	£80,870
10	Utility – Age 13–17 – SLI	0.86	0.78	0.93	£80,842	£79,355

Key: ICER, incremental cost-effectiveness ratio; SL, severity level.

Patients with juvenile-onset HPP population

Figure 46: Juvenile-onset HPP tornado plot: ICERs



Key: ICER, incremental cost-effectiveness ratio; SL, severity level.

Table 72: Juvenile-onset HPP one-way sensitivity analyses results

Rank of influence	Parameter	Input value			ICER	
		Base case	Lower bound	Upper bound	Lower bound	Upper bound
1	Weight for age 18 years	73.58	59.15	88.00	£80,172	£115,018
2	Utility – Age 18+ – SLIV	0.23	0.09	0.41	£86,055	£115,444
3	Utility – Age 18+ – SLI	0.86	0.78	0.93	£103,173	£94,193
4	Caregiver disutility	-0.17	-0.20	-0.14	£94,533	£102,841
5	Utility – Age 5-12 – SLIV	0.23	0.09	0.41	£94,559	£102,772
6	Utility – Age 13-17 – SLIV	0.23	0.09	0.41	£95,385	£101,880
7	Utility – Age 5-12 – SLI	0.86	0.78	0.93	£100,589	£96,521
8	Utility – Age 18+ – SLII	0.67	0.61	0.73	£99,834	£97,224

Rank of influence	Parameter	Input value			ICER	
		Base case	Lower bound	Upper bound	Lower bound	Upper bound
9	Utility – Age 13-17 – SLI	0.86	0.78	0.93	£99,676	£97,364
10	Weight for age 10 years	28.03	22.53	33.52	£97,284	£99,433
Key: ICER, incremental cost-effectiveness ratio; SL, severity level.						

B.3.10.3. Scenario analysis

Structural assumptions were explored in scenario analyses to determine the impact on the results. Each scenario analysis was varied probabilistically, with all inputs varied simultaneously over 1,000 iterations. QALY weighting was applied to each scenario only if the incremental QALY gain was between 10 and 30. Table 73 details the scenarios and the corresponding results. Results show that for the perinatal-/infantile-onset group, the scenarios that had the greatest impact were the 25-year time horizon, applying 1.5% discount rate to outcomes and applying a lower loss of exclusivity discount. The shorter time horizon resulted in a larger ICER as the QALY weighting was not applicable in this scenario, as a shorter time horizon resulted in lower QALY gains. The lower loss of exclusivity discount increased the ICER as AA costs have a large impact on incremental costs, and these were higher after 7 years compared with the base case.

For the patients with juvenile-onset HPP, the scenarios that had the greatest impact were the higher baseline age (26.5 years), the 25-year time horizon and applying a lower loss of exclusivity discount after 7 years. Increasing the baseline age resulted in the ICER increasing. This demonstrates that treating patients at onset is the most beneficial and cost-effective option.

Table 73: Scenario analyses results

Setting	Base case	Scenario	Incremental costs	Incremental QALYs	ICER	Change from base case
Perinatal-/infantile-onset HPP						
Base case			[redacted]	[redacted]	£80,093	-
Time horizon	Lifetime (until 101 years of age)	25 years	[redacted]	[redacted]	£144,947	£64,854
		50 years	[redacted]	[redacted]	£78,912	-£1,181
Discounting	3.5% for both health benefits and costs	1.5% for health benefits, 3.5% for costs	[redacted]	[redacted]	£46,612	-£33,481
Probability of invasive ventilation and distribution of patients entering SLs at age 5	Probability of invasive ventilation in AA arm = 0.022%; all alive patients enter SLIV at age 5 in AA arm	Probability of invasive ventilation in AA arm = 0.00%; 50:50 split of alive patients entering SLIII and SLIV at age 5 in AA arm	[redacted]	[redacted]	£78,535	-£1,558
Costs associated with productivity loss	Not included	Included	[redacted]	[redacted]	£74,689	-£5,404
Stopping rule	No stopping rule applied	Stopping rule applied after age 18	[redacted]	[redacted]	£79,895	-£198
Loss of exclusivity discount	58.5%	45%	[redacted]	[redacted]	£103,236	£23,143
		72%	[redacted]	[redacted]	£58,224	-£21,869

Setting	Base case	Scenario	Incremental costs	Incremental QALYs	ICER	Change from base case
Probit regression model	Model specification 2	Model specification 3	[redacted]	[redacted]	£79,965	-£128
Patients with juvenile-onset HPP						
Base case			[redacted]	[redacted]	£98,512	
Time horizon	Lifetime (until 101 years of age)	25 years	[redacted]	[redacted]	£219,990	£121,478
		50 years	[redacted]	[redacted]	£109,939	£11,427
Discounting	3.5% for both health benefits and costs	1.5% for health benefits, 3.5% for costs	[redacted]	[redacted]	£64,543	-£33,969
Costs associated with productivity loss	Not included	Included	[redacted]	[redacted]	£98,303	-£209
Stopping rule	No stopping rule applied	Stopping rule applied after age 18	[redacted]	[redacted]	£105,659	£7,147
Baseline age	5.0 years	26.5 years	[redacted]	[redacted]	£237,728	£139,216
Loss of exclusivity discount	58.5%	45%	[redacted]	[redacted]	£134,537	£36,025
		72%	[redacted]	[redacted]	£76,075	-£22,438
Probit regression model	Model specification 2	Model specification 3	[redacted]	[redacted]	£111,430	£12,918

Key: HPP, hypophosphatasia; ICER, incremental cost-effectiveness ratio; N/A, not applicable; QALY, quality-adjusted life year.

B.3.11. Subgroup analysis

No subgroup analysis has conducted as all patient groups are considered for the base case analysis.

B.3.12. Benefits not captured in the quality-adjusted life years calculation

There are a number of benefits that are not captured in the current QALY calculations. Although there are no data assessing mortality associated with HPP in patients aged 5 years and over, clinicians stated that being in a more severe health state may be associated with increased mortality for a variety of reasons. Firstly, as these patients may typically have mobility issues, they therefore have an increased risk of cardiovascular comorbidities. Also, two thirds of clinical expert's EQ-5D-5L responses had anxiety/depression scored as 3 (moderate) or higher in SLIV; depression is shown to have an increased risk of mortality.[116-118] As a result, the benefits associated with being in a less severe health state due to treatment with AA are therefore not fully captured, and incremental QALY benefits may be underestimated. The model outputs therefore could be considered conservative estimates of the cost-effectiveness of asfotase alfa.

B.3.13. Validation

B.3.13.1. Validation of cost-effectiveness analysis

Before submission, the cost-effectiveness model was quality-assured by the internal processes of the external economists who supported the economic modelling. In these processes, an economist who was not involved in building the model reviewed it for coding errors, inconsistencies and the plausibility of inputs. This was done using a thorough sheet-by-sheet check. The model was also reviewed against a checklist of known modelling errors and questioning of assumptions. The checklist followed was based on publicly available and peer-reviewed checklists.[119-121] Some of the basic validity checks included the following:

- Extreme-value testing

- Logical relationship testing (e.g. if the intervention drug acquisition costs increase, do the total intervention costs increase accordingly? Does the ICER increase accordingly?)
- Consistency checks (e.g. is an input parameter value in one cell consistently reflected elsewhere?)

A previous version of the model was submitted as part of the original NICE HST6 submission and was reviewed by the ERG. It was also submitted to other HTA bodies, where it was reviewed. The model has been updated to ensure that the feedback from the various HTA reviews was captured.

B.3.14. Interpretation and conclusions of economic evidence

In the base case PAS price results, AA was associated with incremental costs of £3,762,295, incremental LYs of 14.89 and an incremental QALY gain of 15.66 in patients with perinatal-/infantile-onset HPP. This resulted in an ICER of £240,279 per QALY. For patients with juvenile-onset HPP, AA was associated with incremental costs of £4,824,341, incremental LYs of 0.00 and an incremental QALY gain of 16.32. This resulted in an ICER of £295,536 per QALY. Undiscounted results showed that AA was associated with more than 30 incremental QALYs; therefore, QALY weighting was applied. This resulted in ICERs of £80,093 and £98,512 per QALY gained for the perinatal-/infantile-onset and juvenile-onset patients, respectively. Disaggregated results (presented in Appendix J) show that the biggest driver of results is the AA drug costs.

Sensitivity analyses showed that varying the weight of adults and utility values had the biggest impact on results. Scenario analyses showed that reducing the time horizon had the biggest impact on the ICER for patients with perinatal-/infantile-onset HPP, which is to be expected as fewer QALYs are accrued. For the patients with juvenile-onset HPP, increasing the baseline age that patients start treatment increased the ICER, as there are fewer QALYs accrued over a lifetime and the costs associated with AA are higher due to patients weighing more from the start of treatment. In addition, scenario analyses showed that changing the loss of exclusivity discount had a substantial impact on the ICER. There is uncertainty

regarding what price AA will be once it comes off patent in 2030; however, it is important to try and capture what the NHS will pay for treatment as accurately as possible over the time horizon of the model.

Scenario analyses showed that applying a 1.5% discount to health benefits reduced the ICER considerably. In the perinatal-/infantile-onset group the ICER reduced to £46,612, and in the juvenile-onset group the ICER reduced to £64,543. The NICE methods state that a discount rate of 1.5% may be applicable if the technology is for people who would otherwise die or have severely impaired life, if the benefits are likely to be sustained over a long period, and if the technology is likely to restore them to near-full health. In addition, the HM Treasury Green Book (2022) has a social time preference rate of 3.5%, but it states that where there is a risk to health and life values, a social time preference rate of 1.5% should be used.[122] HPP is a rare disease that can lead to premature death (in newborns and infants) and a range of health complications that have a substantial impact on quality of life. A risk to health and life values is evident; therefore, a discount of 1.5% for health benefits may be most suitable.

The economic analysis may underestimate the benefits associated with AA for several reasons. Firstly, mortality is not captured for patients 5 years and over. During a model validation exercise, clinicians stated that although there may not be HPP-related death for older patients, the condition is associated with increased comorbidities. For example, fractures and pseudofractures are common in patients with HPP and are associated with risks, especially as patients get older. In addition, mobility issues can lead to an increased chance of experiencing cardiovascular events, which have a greater mortality risk. It is likely that as AA can reduce symptoms associated with HPP, there may be survival benefits that are not captured in the model.

One of the greatest constraints with modelling HPP is the lack of data informing the BSC arm. As HPP is a rare condition, there are sparse data on BSC practices. Firstly, there are short follow-up times for BSC in the trials (all patients receiving BSC ended up switching to the active drug, AA, in the trial). In addition, AA is recommended in several countries and has been recommended in England under

the MAA agreement since 2017. This means that a large proportion of patients with HPP have been receiving AA, making it more difficult to draw comparisons with BSC.

Lastly, the economic model does not include outcomes that are of importance to patients, such as pain, history of surgical interventions, growth effects and renal complications. As HPP is a condition with many symptoms and complications, developing a cost-effectiveness model to capture all aspects of the condition would be difficult without making the model too complex. Due to the various limitations, it is possible that the current economic model underestimates the benefits of AA in HPP.

Despite the limitations, the economic analysis shows that BSC is associated with substantial mortality in patients with perinatal-/infantile-onset. In addition, BSC is associated with poor QoL in both perinatal-/infantile-onset patients and patients with juvenile onset. In contrast, patients treated with AA experience improved survival (perinatal-/infantile-onset patients) and improvements in QoL. When applying the QALY weighting and the PAS discount price, results show that AA is under the £100,000 threshold for both perinatal-/infantile-onset and juvenile-onset patients.

B.3.15. Cost to the NHS and Personal Social Services

B.3.15.1. Patient population

Due to the heterogeneity in the HPP prevalence and incidence estimates reported in the literature, data from the MAA up to the most recent data cut-off date of January 6th, 2022 were used to estimate the number of patients modelled in the budget impact analysis (BIA) in Year 1 and the following years over the time horizon of the model (Year 2 – Year 5). This approach is more pragmatic than relying on individual literature estimates and takes into account the various limiting steps (within and out of the scope of the MAA eligibility criteria) through which HPP patients pass in order to ultimately qualify for receiving AA (i.e. moving from being an undiagnosed HPP patient to being diagnosed and belonging to the subgroup of patients eligible to receive the treatment).

Since the start of the MAA and as of January 6th, 2022, a total of [redacted] patients received asfotase alfa treatment in England after having consented for their data to be collected during the entire treatment duration.

[redacted] out of these [redacted] patients discontinued treatment. Hence, the number of patients who are currently being treated within the MAA (i.e. active patients who were not lost to follow-up) is [redacted], distributed as per their age in 2022 and their disease onset as illustrated in Table 74 below. These numbers and distribution were used as such to model patients entering the BIA in Year 1. In other words, the current numbers of patients included in Year 1 in the BIA are as follows: [redacted] patients with perinatal- or infantile-onset and [redacted] patients with juvenile-onset HPP.

Table 74: Distribution of the patients currently treated (as of 6 January 2022) in the UK managed access agreement as per their age in 2022 and their disease onset

Age in 2022	Patients with perinatal- and infantile-onset HPP	Patients with juvenile-onset HPP
0	[redacted]	[redacted]
1	[redacted]	[redacted]
2	[redacted]	[redacted]
3	[redacted]	[redacted]
4	[redacted]	[redacted]
5	[redacted]	[redacted]
6	[redacted]	[redacted]
7	[redacted]	[redacted]
8	[redacted]	[redacted]
9	[redacted]	[redacted]
10	[redacted]	[redacted]
11	[redacted]	[redacted]
12	[redacted]	[redacted]
13	[redacted]	[redacted]
14	[redacted]	[redacted]
15	[redacted]	[redacted]
16	[redacted]	[redacted]
17	[redacted]	[redacted]
18+	[redacted]	[redacted]
Total	[redacted]	[redacted]

In order to calculate the average number of patients entering the BIA in Year 2 – Year 5, annual incidence rates for HPP patients newly starting AA treatment were

calculated after excluding [redacted] patients who were already receiving AA at the time of enrolment into the MAA (e.g., patients continuing treatment within the MAA after having initiated it in any of the clinical trials). This exclusion resulted in having [redacted] patients who were enrolled into the MAA over a period of 4 years (2018–2021), distributed as follows: [redacted] perinatal- or infantile-onset HPP patients and [redacted] juvenile-onset HPP patients. This led to annual AA initiation in approximately [redacted] and [redacted] patients, respectively. The average age at treatment start modelled for each patient subpopulation was aligned with the cost-effectiveness model and was 0 and 5 years, respectively.

B.3.15.2. Resources

Inputs relating to the dosing, patient weight and AA price are aligned with those used in the cost-effectiveness model and are described in Section B.3.5.1.

All other costs and inputs are outlined in Table 75 below.

Table 75: Budget impact model inputs

Parameter	Input	Source/justification
Cost of invasive ventilation for 12-week period	£140,041	Aligned with resource estimates in cost-effectiveness model (see Section B.3.5.4)
Average cost of treating HPP for patients age < 5 years (annual)		
AA cohort	£66,162	Aligned with resource estimates in cost-effectiveness model (see Section B.3.5.4)
BSC cohort	£66,162	
Average cost of treating HPP for patients age ≥ 5 years (annual)		
AA cohort	£3,309	It is assumed that BSC patients would remain in SLIV, and that AA patients would have the cost of patients in SLI.
BSC cohort	£20,259	
Percentage of each cohort requiring 12-week ventilation at age < 5 years		
AA cohort	9.69%	According to Whyte et al. (2016)
BSC cohort	27.73%	

Parameter	Input	Source/justification
Mortality rate for patients age < 5 years		
AA cohort	2.59%	ENB-002-08/ENB-003-08, ENB-010-10 and MAA UK study
BSC cohort	13.73%	ENB-011-10
Key: AA, asfotase alfa; BSC, best supportive care; HPP, hypophosphatasia; MAA, managed access agreement; SL, severity level.		

B.3.15.3. Uptake and market share

The BIA assumes that all newly diagnosed patients would receive AA treatment. A compliance rate of [redacted] and a discontinuation rate of [redacted] per year is applied in the analysis, in line with the cost-effectiveness model.

B.3.15.4. Estimated annual budget impact

Estimates of the eligible population and expected budget impact at list price are presented in Table 76.

Table 76: Expected budget impact

	Year 1	Year 2	Year 3	Year 4	Year 5
Eligible population for treatment with AA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
World without AA					
Invasive ventilation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other non-AA costs (<5 years)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other non-AA costs (≥5 years)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total cost of treatment pathway without AA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
World with AA					

Invasive ventilation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other non-AA costs (<5 years)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other non-AA costs (≥5 years)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
AA costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total cost of treatment pathway with AA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Net budget impact	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Key: AA: asfotase alfa; M, million.					

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B.4. Appendices

Appendix C: Summary of product characteristics (SmPC) and UK public assessment report

Appendix D: Identification, selection and synthesis of clinical evidence

Appendix E: Subgroup analysis

Appendix F: Adverse reactions

Appendix G: Published cost-effectiveness studies

Appendix H: Health-related quality-of-life studies

Appendix I: Cost and healthcare resource identification, measurement and valuation

Appendix J: Clinical outcomes and disaggregated results from the model

Appendix K: Price details of treatments included in the submission

Appendix L: Checklist of confidential information

Appendix M: Additional information for Section B.2

Appendix N: Comparison of original and current cost-effectiveness model

Appendix O: Clinician-elicited utilities

Appendix P: Health-state descriptions from Lloyd et al. (2017)

Appendix Q: Summary of variables applied in the economic model

Appendix R: Additional results from cost-effectiveness analysis

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

[ID3927]

Clarification questions

July 2022

File name	Version	Contains confidential information	Date
		Yes/no	

Notes for company

Highlighting in the template

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Section A: Clarification on effectiveness data

Decision problem

A 1. Priority question. The population stated in Table 1 is paediatric onset, which stated to include: *"patients with perinatal-, infantile- or juvenile-onset HPP*" (p. 16) However, to estimate comparative efficacy: *"A pooled analysis was conducted to assess the long-term efficacy of asfostase alfa (AA) in a pooled population of infants and children with hypophosphatasia (HPP) signs and symptoms that manifested before 6 months of age."* (p. 136) Using the definitions given in section 1.3.1 as those used in the Alexion clinical programme for AA, the pooled analysis of the long-term efficacy of AA was limited to patients with perinatal- or infantile-onset HPP (juvenile-onset, 6 months to 18 years) excluded).

a) Please explain the discrepancy between the population in the decision problem and the main source of efficacy data.

The totality of the clinical trial data presented in the submission, from the UK MAA, the long term follow up of the AA clinical trials (ENB-002-08/ENB-003-08, ENB-010-10, ENB-006-09/ENB-008-10 and ENB-009-10), the Global HPP Registry and the real-world EmPATHY study should be considered the main source of efficacy data

for the population in the decision problem, which includes patients with perinatal-, infantile- and juvenile-onset HPP. In addition to these data, the pooled analysis in the sub population of perinatal/infantile-onset patients from three AA clinical trials (ENB-002-08/ENB-003-08, ENB-010-10, ENB-006-09/ENB-008-10), has also been presented.

The pooled analysis was conducted to assess long-term survival in patients with perinatal/infantile-onset HPP, which is the only subgroup in which the disease can be life-threatening, with reported survival of 25% at 5 years. Therefore, assessing long-term survival and other outcomes following AA treatment was imperative when data were available for 85 patients treated in the AA clinical development program, with the most life threatening form of HPP.

The pooled analysis was conducted in 2019, prior to the decision problem being defined for this submission, and is therefore provided as a supplemental analysis from the AA clinical trials to inform long term survival in a sub population and should not be considered as the main source of efficacy data for AA in this appraisal process.

b) Should the population in the decision problem be qualified to only include perinatal or infantile onset?

No. As per the responses to A 1.a), the totality of the clinical trial data presented in the submission, including the UK MAA, long term follow up of the AA clinical trials, the Global HPP Registry and the real-world EmPATHY study should be considered the main source of efficacy data for the population in the decision problem, which includes patients with perinatal, infantile and juvenile-onset HPP. The pooled analysis was conducted in 2019, prior to the decision problem being defined for this submission, and is therefore provided as a supplemental analysis and should not be considered as the main source of efficacy data for AA in this appraisal process.

There are 27 patients with juvenile-onset HPP and severe disabilities, which impact quality of life in two of the AA clinical studies (ENB-006-09/ENB-008-10 and ENB-009-10). In addition, a high number of juvenile-onset HPP patients were included in the UK MAA and in the post-marketing phase IV studies (EmPATHY, Global HPP Registry), and these outcomes are presented in this submission dossier.

c) If the population is as in the decision problem then please conduct a comparative analysis that includes patients with age of onset that reflects the whole population including the juvenile onset.

As per the responses to A 1.a) and A 1.b), the evidence in the submission does cover the population in the decision problem. The current submission includes AA treated patients with perinatal/infantile and juvenile onset HPP from the following sources: the UK MAA, AA clinical trials, the Global HPP Registry and the real-world EmPATHY study. All of these studies' inclusion criteria and ESAP were based on patients age at enrolment, therefore the data were not analysed based on age of symptoms onset. Currently, no further pooled analyses are available and it would not be feasible to conduct a pooled analysis across all populations due to the limited availability of historical control data across all populations and all endpoints, and such an analysis would require re-designing the ESAP for all studies and would require several months to complete.

d) Please include all study data relevant to the decision problem population, as reported in Table 1 or excluding juvenile if amended in response to question (b).

As per the responses to A 1.a), the totality of the clinical trial data presented in the submission from the UK MAA and long term follow up of the AA clinical trials provides all study data relevant to the decision problem population, which includes data for patients with perinatal-, infantile- and juvenile-onset HPP.

e) Please present all data and conduct subgroup analyses for all outcomes comparing AA to best supportive care (BSC) according to age of onset category i.e. perinatal-, infantile- and juvenile-onset HPP, using the most appropriated evidence from all studies.

The focus of Alexion's clinical program was primarily based on the age of study enrolment, and patients were therefore, not stratified according to age of disease onset, except for perinatal/infantile-onset patients as these represent the group with the life-threatening disease and were studied for survival. Disease onset age can be a proxy for disease severity, however, as HPP is multisystemic heterogenous disease, it can affect patients to different extents throughout their lifetime.

As per Table 8 in the submission dossier, the Phase II/III clinical program included patients of all age groups with paediatric-onset HPP, but patients were not split out into age at onset categories, instead the AA clinical studies stratified patients by age and enrolment: < 3 years, < 5 years, 5-12 years ≥13 years. The UK MAA was designed differently to the studies that formed the AA clinical development program. The UK MAA focuses on the age of the patient and their symptoms at presentation in one of the designated treatment centres. Within the UK MAA, there are 4 distinct groups of patients based on current age: < 12months, between 1-4 years, between 5-18 years and >18 years. All of these patients have paediatric-onset HPP. In addition, some of the endpoints included in the UK MAA (e.g. BAMF scale, PedsQL, Bleck score) were not included in the AA clinical trials. Therefore, efficacy data split by age disease onset are not available for all studies and all endpoints, so summary tables would be non-informative and have not been provided.

Regarding the comparison with BSC, it would be challenging to find (from natural history studies) a matching BSC population of HPP patients for each population, and the three available natural history studies do not contain data for all relevant endpoints, so a comparison for all endpoints would not be possible. In addition, such an analysis would require re-designing the ESAP for all studies and would require several months to complete. Where possible, the Alexion clinical trials have included a comparison with BSC for the primary endpoint and a pooled analysis of perinatal/infantile AA treated patients compared with BSC historical controls is included in the submission.[1]

A 2. Priority question. Please provide a complete list of changes since the original appraisal in terms of scope and evidence.

[Company: please enter your answer to this question here]

A 3. Table 1, in the company submission (CS), indicates that the outcomes craniosynostosis and intracranial pressure have been excluded from the company's definition of the decion problem, because these outcomes were "not measured in the AA clinical trials" and because "these outcomes are related to the underlying disease and not with a causality association with AA". However, Table 8, in the CS, indicates these outcomes were reported in four of the five included clinical effectiveness studies (ENB-002-08/ENB-003-

08, ENB-010-10, ENB-006-09/ENB-008-10 and ENB-009-10). Although outcomes craniosynostosis and intracranial pressure are sometimes reported as adverse events (AEs), as noted by the company, these outcomes are related to the underlying disease; all disease-related outcomes are of potential interest and those specified in the NICE scope should be reported, where available.

a) Please explain this discrepancy

Craniosynostosis a manifestation of HPP, is documented in published literature and occurred in 61% of patients between birth and 5 years of age in a natural history study of untreated infantile-onset HPP patients.[2] The exact mechanism of craniosynostosis in relation to the disease's pathophysiology (ALP function) is not well understood. Therefore, it was never studied as an outcome of AA treatment but it has been reported as a safety event in the AA studies. In the AA clinical studies, adverse events of craniosynostosis (associated with increased intracranial pressure), including worsening of pre-existing craniosynostosis and occurrence of Arnold-Chiari malformation, have been reported in HPP patients < 5 years of age. There are insufficient data to establish a causal relationship between exposure to AA and progression of craniosynostosis. Periodic monitoring and prompt intervention for increased intracranial pressure is recommended in HPP patients below 5 years of age.

b) Please provide data for the outcomes craniosynostosis and intracranial pressure from all studies where these outcomes were measured.

Craniosynostosis and intracranial pressure were not measured as an outcome in any of the AA clinical studies, but were only reported as a part of the safety data analysis. Data on craniosynostosis and intracranial pressure are provided in Table 8 and Table 11 in the response to A19.

Systematic review

A 4. Concerning the eligibility criteria outlined in Table 9 of Appendix D, the list of eligible outcomes includes, 'skeletal system changes'. Please provide more information on what skeletal mineralisation complications were targeted.

The systematic literature review (SLR) for clinical outcomes aimed to assess the number of patients with reported skeletal system changes after being treated with interventions included in the review.

The search strategy for the clinical SLR was not restricted by the outcomes listed in the PICOS criteria. The search strategies were restricted to hypophosphatasia as a broad disease, but the data extraction grid was designed in a way to extract any skeletal system changes reported across the studies.

The SLR did not identify much evidence regarding such changes. Only a limited number (three) of included studies reported the number of patients with new fractures in patients treated with commonly used interventions. More details of these are provided in the Table 1.

Table 1: Studies identified in the SLR that reported the number of patients with new fractures in patients treated with commonly used interventions

Study Name (Trial name/NCT)	Intervention/ comparator	Overall/ Subgroup	Time point	N	n (%)	Comments
Camacho 2018	Teriparatide	Overall	Study endpoint (follow up)	8	1 (12.5)	One patient developed new bilateral femur pseudofractures 8 months after discontinuation of the drug. This was a conference abstract with limited information available.
Lefever 2020	Bisphosphonates/ Bisphosphonates + Denosumab	Overall	Endpoint	2	2 (100)	Atypical femoral fracture (one sided). Limited information available in the study.
Moss 2021	Asfotase Alfa	Overall	104.2 weeks	12	0 (0)	For patients with >7 days of asfotase alfa treatment, no new fracture occurred over a 2-year period.

A 5. Please provide details of the selection process for cost-effectiveness and health-related quality-of-life studies in the systematic literature review (SLR).

The study selection process for the cost-effectiveness and HRQoL studies in the SLR are given in Appendices G and H respectively.

Please see below details of the primary screening/ secondary screening/ data extraction. Please note that this was the same for both the economic and the HRQoL studies.

Primary screening

All retrieved studies were assessed against the eligibility criteria listed in **Error! Reference source not found.**. Primary (Level 1) screening was performed by two independent reviewers to ensure everything was quality-checked to HTA standard. The reviewers considered each reference (title and abstract) identified in the literature search, applied basic study selection criteria (population, intervention and study design) and decided whether to include or exclude the study reference at that stage. Any uncertainty was checked by a third reviewer.

Secondary screening

Full articles were obtained for secondary (Level 2) screening of potentially relevant materials. These were reviewed by two independent reviewers against each eligibility criterion; any uncertainty regarding the inclusion of a study was checked by a third reviewer.

Data extraction

Data were extracted into pre-designed Microsoft Excel® tables for all included studies and were extracted with the expected needs of global HTA submission templates in mind.

The key information captured in the extraction grid is presented below (a non-exhaustive list):

- Study characteristics (location, setting, study design, study methods, etc.)
- Patient characteristics (inclusion/exclusion criteria, baseline characteristics, etc.)
- Model summary (including perspective, time horizon and discounting) and structure

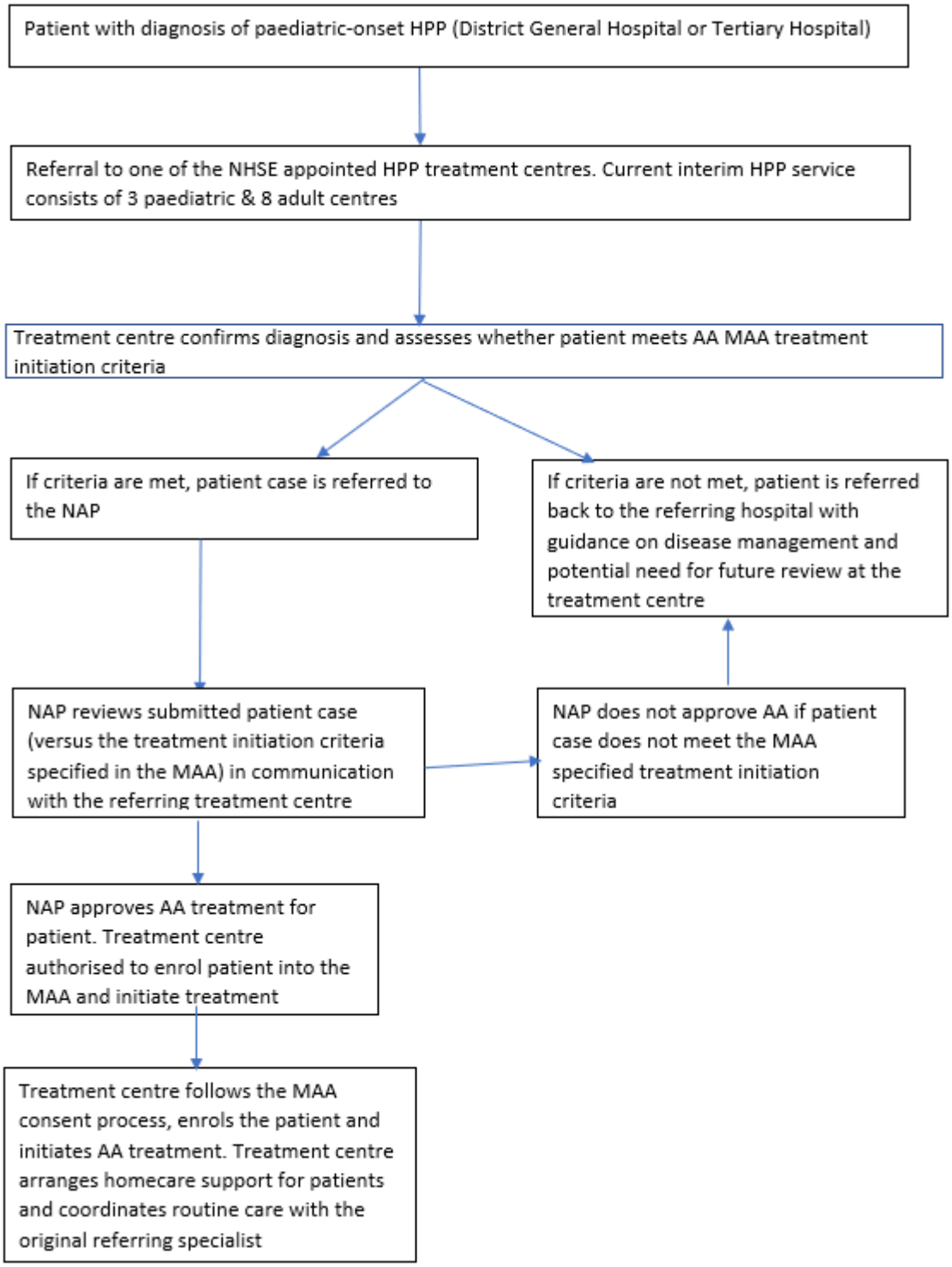
- Assumptions underpinning model structures
- Sources of clinical, cost and quality of life (QoL) inputs
- Description of health states/utilities (along with details of instrument used)
- Summary health outcomes (e.g. quality-adjusted life years and life years gained)
- Direct, indirect and total costs, and incremental cost-effectiveness analysis
- Resource consumption

Clinical pathway of care

A 6. Section B.1.3.5 of the submission discusses the current clinical management and treatment goals for HPP. Please provide a figure showing the current clinical pathway for the treatment of patients with paediatric-onset hypophosphotasia in England and Wales (not limited to the context of the managed access agreement), and another figure showing the proposed place for asfotase alfa. Please provide supporting references.

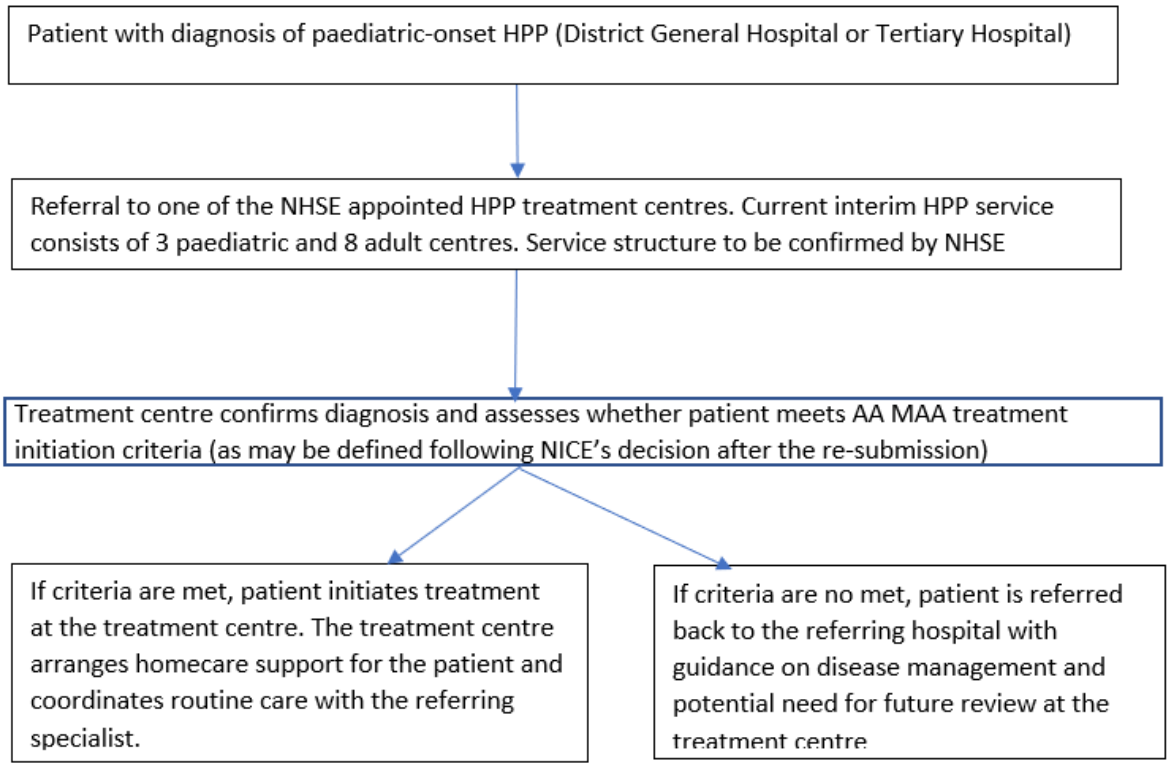
Figure 1 presents the current clinical pathway for the treatment of patients with paediatric-onset HPP in England and Wales. The proposed clinical pathway for the treatment of patients with paediatric-onset HPP in England and Wales including the proposed positioning of AA is presented in Figure 2.

Figure 1: Current clinical pathway for the treatment of patients with paediatric-onset HPP in England and Wales



Key: AA, asfotase alfa; HPP, hypophosphatasia; MAA, Managed Access Agreement; NAP, National Authorisation Panel; NHSE, National Health Service England.

Figure 2: Proposed clinical pathway for the treatment of patients with paediatric-onset HPP in England and Wales



Key: AA, asfotase alfa; HPP, hypophosphatasia; MAA, Managed Access Agreement; NAP, National Authorisation Panel; NHSE, National Health Service England.

Clinical effectiveness evidence

A 7. Priority question. The managed access agreement (MAA) states in Section 5.14 that the global HPP registry should be used to collect data for BSC too. "The company highlighted that this registry was set up as part of its regulatory commitments, and so was separate from the managed access arrangement, and that it would provide evidence from hundreds of people with hypophosphatasia worldwide, including those not treated with asfotase alfa".

a) Please explain why data from the global HPP registry (ALX-HPP-501) were not used to provide control data for patients not treated with AA.

The Global HPP registry (ALX-HPP-501) is an observational, non-interventional study that includes HPP patients irrespective of whether they are on AA treatment or not. Enrolment in the Global HPP Registry is voluntary and assessments are not mandatory. During the study, clinic visits are scheduled by the clinicians in accordance with their usual clinical practice. Frequency of visits may vary depending

upon several factors, including the age of the patient and severity of disease. Patients are monitored per the clinicians standard of care, which does not include the RGI-C (a research tool) or the 6MWT. In cases where these assessments have been conducted, they were not conducted uniformly over time (i.e. every 6 months) or in a standard fashion between sites (no training). In addition, as presented in Table 66 of Appendix M, the non-AA treated patients in the Global HPP Registry are usually patients with milder symptoms that are not comparable with the patients that are treated with AA. The AA clinical studies and the UK MAA include patients that are severely affected by the disease, therefore, it is highly unlikely that such patients in the Global HPP Registry would not be treated with AA. Moreover, the UK MAA mandated a schedule of certain clinical assessments that are not all captured within the Global HPP Registry (e.g., Bleck score, BAMF scale) and the patients that are enrolled in the Global HPP Registry are not mandated to any schedule of clinical assessments.

All the above would make the comparison of AA treated patients versus non-treated Global HPP Registry patients considerably biased. As such, data from the Global HPP Registry are limited and are not comparable with the AA clinical trials and have not been used as a source of data for patients not treated with AA.

b) Please revise and expand Table 10 from the CS to include all potential sources of data for patients not treated with AA (including ALX-HPP-501).

All potential sources of data for patients not treated with AA are already provided in Table 10 in document B.

A 8. Priority question. Tables 7 (UK MAA), 8, 9 and 10 provide some information on type of HPP (by age of onset category). There are further details in Appendix M. However, it is unclear how many patients in each study fall into each age of onset category.

a) Please provide the numbers of patients in each of perinatal, infantile, juvenile and adult-onset categories for all studies including the ALX-HPP-501, as referred to in question A8.

b) Please provide baseline age data (minimum, maximum, mean and median) for each study and for each age of onset category

UK MAA

All patients included in the UK MAA had a diagnosis of paediatric-onset HPP (in line with AA licensed indication), therefore no patients with adult-onset HPP have been approved for treatment with AA. Table 2 provides an overview of the number of patients in the perinatal/infantile-onset and juvenile-onset categories and the age and age group at enrolment in in the paediatric (<18 years at baseline) and adult (≥ 18 years) populations in the UK MAA. In the MAA, the population that was defined to have the life-threatening form of the disease was patients aged < 12 months without differentiating between perinatal and infantile onset.[3] Therefore, as per the statistical analysis plan, clinical data for the UK MAA were not split out into perinatal, infantile and juvenile-onset categories. Nevertheless, all patients included in the MAA have paediatric onset HPP (perinatal/infantile or juvenile).

Table 2: UK MAA Study Population

	Study Population (N = [redacted])	**Paediatric Population < 18 years at baseline (N = [redacted])**	**Adult Population ≥ 18 years at baseline (N = [redacted])**
Population	Patients with paediatric-onset HPP (regardless of current age)		
Age at enrolment (years)			
Mean (SD)	[redacted]	[redacted]	[redacted]
Median (min, max)	[redacted]	[redacted]	[redacted]
Age group at enrolment, n (%)			
< 1 year	[redacted]	[redacted]	[redacted]
1 to < 5 years	[redacted]	[redacted]	[redacted]
5 to < 18 years	[redacted]	[redacted]	[redacted]
≥ 18 years	[redacted]	[redacted]	[redacted]
HPP onset category, n (%)			
Perinatal/infantile onset HPP (<6 months)	[redacted]	[redacted]	[redacted]

Table 2: UK MAA Study Population

	Study Population (N = [redacted])	**Paediatric Population < 18 years at baseline (N = [redacted])**	**Adult Population ≥ 18 years at baseline (N = [redacted])**
Juvenile onset (≥ 6 months to < 18 years)	[redacted]	[redacted]	[redacted]
Age at enrolment by HPP onset category			
Perinatal/infantile-onset			
n	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted] months [redacted]	[redacted] months [redacted]	[redacted] months [redacted]
Median (min, max)	[redacted] months [redacted]	[redacted] months [redacted]	[redacted] months [redacted]
Juvenile onset			
n	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted] months [redacted]	[redacted] months [redacted]	[redacted] months [redacted]
Median (min, max)	[redacted] months [redacted]	[redacted] months [redacted]	[redacted] months [redacted]

Key: HPP, hypophosphatasia; max, maximum; min, minimum; N, number of participants; n, number of participants in a category; N/A, not applicable; SD, standard deviation.
Notes: Baseline was considered the baseline/enrolment visit.
Source: Alexion MAA interim analysis report (ASF-MAA-001) 2022.[3]

Clinical trials

Table 3 provides an overview of the number of patients in the perinatal/infantile, juvenile and adult-onset categories and the age and age group at enrolment for patients who were included in the AA clinical trials. Perinatal/infantile onset have been grouped together, as both forms are life-threatening, it is sometimes difficult to know whether an infant born with symptoms had signs of the disease in utero, and the inclusion criteria for the ENB-002-08, ENB-010-10 studies was symptoms of disease onset <6 months of age, which covers both forms. In addition, in the previous NICE/NHSE negotiation and the agreed MAA, the population that was

defined to have the life-threatening form of the disease was patients aged < 12 months without differentiating between perinatal and infantile onset.

Table 3: Clinical effectiveness evidence – Clinical studies

	ENB-002-08/ENB-003-08 (n = 13)	ENB-010-10 (n = 69)	ENB-006-09/ENB-008-10 (n = 13)	ENB-009-10 (n = 19)
Population	Patients ≤ 36 months of age with infantile-onset HPP (onset of symptoms prior to 6 months of age)	Patients with perinatal-/infantile-onset HPP (onset of HPP signs/symptoms prior to 6 months of age)	Patients aged ≥ 5 and ≤ 12 years of age with HPP	Adolescent and adult patients aged 13 to 65 years with HPP
Age at enrolment				
Mean (SD)	[redacted]	[redacted]	8.8 years (2.2)	[redacted]
Median (min, max)	[redacted]	[redacted]	8.6 years (6.0, 12.0)	53 years (13.0, 66.0)
Age at first at first signs of HPP/symptom onset				
Mean (SD)	Not available	[redacted]months ([redacted])	10.5 ± 7.0	[redacted]
Median (min, max)	Not available	[redacted]months ([redacted])	12.0 (1, 22)	2.0 years (0.0, 36.0)
HPP onset category, n (%)				
Perinatal/infantile onset HPP (<6 months)	13 (100.0)	69 (100.0)	5 (38.0)	[redacted]
Juvenile onset (≥ 6 months to < 18 years)	0	0	8 (62.0)	[redacted]
Adult onset (≥ 18 years)	0	0	0	[redacted]
Age at enrolment by HPP onset category				

	ENB-002-08/ENB-003-08 (n = 13)	ENB-010-10 (n = 69)	ENB-006-09/ENB-008-10 (n = 13)	ENB-009-10 (n = 19)
Mean (SD)	N/A	N/A	**Infantile-Onset:** 3.0 months (2.0) **Juvenile onset:** 15.3 months (4.03)	Not available
Median (min, max)	N/A	N/A	**Infantile-Onset:** 3.0 months (1.0, 5.0) **Juvenile onset:** 13.5 months (12.0 22.0)	Not available

Key: AA, asfotase alfa; HPP, hypophosphatasia; IV, intravenous; N/A, not applicable; PK, pharmacokinetic; PLP, pyridoxal 5'-phosphate; PPi, inorganic pyrophosphate; SC, subcutaneous.
Sources: ENB-002-08/ENB-003-08 Final CSR. 2017[4]; Whyte at al. 2018[5]; ENB-010-10 Final CSR. 2017[6]; Hofmann et al. 2019[7]; ENB-006-09/ENB-008-10 Final CSR. 2017[8]; Whyte et al. 2017[9]; ENB-009-10 Final CSR. 2017[10]; Kishnani et al. 2019.[11]

Other real-world evidence

Table 4 provides an overview of the number of patients in the perinatal, infantile, juvenile and adult-onset categories and the age and age group at enrolment for patients who were included in the Global HPP Registry. As per the statistical analysis plan, clinical data for the global HPP Registry were not split out into perinatal, infantile, juvenile and adult-onset categories.

Table 4: ALX-HPP-501 (Global HPP Registry) baseline characteristics

	Overall population			**< 18 years old**			**≥ 18 years old**		
	Total (n = [redacted])	**Never treated (n = [redacted])**	**Ever treated (n = [redacted])**	**Total (n = [redacted])**	**Never treated (n = [redacted])**	**Ever treated (n = [redacted])**	**Total (n = [redacted])**	**Never treated (n = [redacted])**	**Ever treated (n = [redacted])**
Population	Patients of all ages with a confirmed diagnosis of HPP								
Age at enrolment (years)									
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median (min, max)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HPP onset, n (%)									
n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Perinatal/infantile onset HPP (<6 months)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Juvenile onset (≥ 6 months to < 18 years)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adult onset (≥ 18 years)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Age at enrolment by HPP onset category									
Perinatal/									

	Overall population			< 18 years old			≥ 18 years old		
	Total (n = [redacted])	**Never treated (n = [redacted])**	**Ever treated (n = [redacted])**	**Total (n = [redacted])**	**Never treated (n = [redacted])**	**Ever treated (n = [redacted])**	**Total (n = [redacted])**	**Never treated (n = [redacted])**	**Ever treated (n = [redacted])**
infantile onset									
n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median (min, max)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Juvenile onset									
n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median (min, max)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adult onset									
n	[redacted]	[redacted]	[redacted]	N/A	N/A	N/A	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	N/A	N/A	N/A	[redacted]	[redacted]	[redacted]

	Overall population			< 18 years old			≥ 18 years old		
	Total (n = [redacted])	**Never treated (n = [redacted])**	**Ever treated (n = [redacted])**	**Total (n = [redacted])**	**Never treated (n = [redacted])**	**Ever treated (n = [redacted])**	**Total (n = [redacted])**	**Never treated (n = [redacted])**	**Ever treated (n = [redacted])**
Median (min, max)	[redacted]	[redacted]	[redacted]	N/A	N/A	N/A	[redacted]	[redacted]	[redacted]

Key: HPP, hypophosphatasia; max, maximum; min, minimum; SD, standard deviation.
Source: ALX-HPP-501 study report 2021.[12]

No data are available relating to the number of patients in the perinatal, infantile and juvenile onset categories in for the real-world EmPATHY study and the longitudinal telephone-based survey, but both studies include patients with paediatric-onset HPP.[13, 14]

Table 5 provides an overview of the number of the age at onset and age at diagnosis of HPP of patients included in the natural history studies. All patients in ENB-011-10 had perinatal/infantile-onset HPP and [redacted] patients in ALX-HPP-502 and ALX-HPP-502s had juvenile-onset HPP (> 6 months of age at the time of first signs/symptoms of HPP).

Table 5: Clinical effectiveness evidence – natural history studies

	ENB-011-10 (n = 48)	**ALX-HPP-502 (n = [redacted])**	**ALX-HPP-502s (n = 6)**
Age at onset of HPP (months)			
Mean (SD)	5.2 (9.3)	[redacted]	[redacted]
Median (min, max)	2.0 (0, 179)	[redacted]	[redacted]
Age at HPP diagnosis (months)			
Mean (SD)	5.2 (9.3)	[redacted]	[redacted]
Median (min, max)	2.0 (0, 40.9)	[redacted]	[redacted]
HPP onset category, n (%)		[redacted]	[redacted]
Perinatal/infantile onset HPP (<6 months)	48 (100.0)	[redacted]	[redacted]
Juvenile onset (≥ 6 months to < 18 years)	0	[redacted]	[redacted]

Key: AA, asfotase alfa; HPP, hypophosphatasia; N/A, not applicable; PLP, pyridoxal 5'-phosphate; PPi, inorganic pyrophosphate.
Sources: Whyte et al. 2019[2]; ALX-HPP-502 Final CSR. 2014[15]; ALX-HPP-502s final CSR. 2014.[16]

A 9. Priority question. Section B.2.4.1.1 of the CS describes participants in the UKMAA as paediatric or adult, based on their age at baseline, but does not report age at onset of HPP. Please confirm that all particpants met the terms of the UKMAA, specifically point 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."

All patients included in the MAA have a diagnosis of paediatric-onset HPP (in line with AA licensed indication), therefore no patients with adult-onset HPP have been approved for treatment with AA. As agreed in the MAA, the NHSE designated treatment centres must refer any HPP patient that meet the specified treatment eligibility criteria to the National Authorisation Panel (NAP). After reviewing each patient case against the treatment initiation criteria (part of which is the documentation for the paediatric-onset of HPP), the NAP makes the final decision on whether the referred patient is eligible for treatment initiation at the treatment centre. The NAP consists of representatives from the following stakeholders: One paediatric clinical expert, one adult clinical expert, one pain specialist, NHSE, NICE. Therefore, all participants included in the UK MAA data set had a diagnosis of paediatric-onset HPP (regardless of current age) confirmed by one of the national HPP expert centres, according to national guidelines, and therefore, met the terms of the MAA. Table 6 provides a summary of the age at onset of HPP for participants included in the paediatric (< 18 years) and adult (≥ 18 years age) populations of the UK MAA.

Table 6: Age at onset of HPP – UK MAA

	Paediatric Population < 18 (n = [redacted])	**Adult Population ≥ 18 years age (n = [redacted])**
Age at onset		
Mean (SD)	[redacted]	[redacted]
Median (min, max)	[redacted]	[redacted]

Key: MAA, managed access agreement; min, minimum; max, maximum; SD, standard deviation.
Source: Alexion MAA interim analysis report (ASF-MAA-001) 2022.[3]

A 10. Priority question. Section B.2.6.2 of the CS reports clinical effectiveness data from the UKMAA. These data are reported for the adult population (section B.2.6.2.2) and the paediatric population (section B.2.6.2.1), with results in section B.2.6.2.1 being variously presented for the whole paediatric population(<18 years), paediatric population aged 5 to <18 years, and paediatric population aged 1 to 4 years. Section B.2.6.3 describes the clinical effectiveness results for the included clinical trials of AA in a way that makes comparison between studies difficult. Please provide results tables,

comparing results across all AA studies including the MAA, for each outcome measure (as listed in Tables 7 and 8); results should be grouped by age of onset category (perinatal-, infantile-, and juvenile-onset HPP).

The UK MAA was designed differently to the studies that formed the AA clinical development program. The AA clinical studies stratified patients differently by age and enrolment: < 3 years, < 5 years, 5-12 years ≥13 years. The UK MAA focuses on the age of the patient and their symptoms at presentation in one of the designated treatment centres. Within the UK MAA, there are 4 distinct groups of patients based on current age: < 12months, between 1-4 years, between 5-18 years and >18 years. All of these patients have paediatric-onset HPP. In addition, some of the endpoints included in the UK MAA (e.g. BAMF scale, PedsQL, Bleck score) were not included in the AA clinical trials.

Therefore, efficacy data split by age disease onset are not available for all studies and the differences discussed above would make a comparison between the studies non-informative so summary tables have not been provided.

A 11. Priority question. Section B.2.6.4.4 of the CS states that "The results of the non-interventional natural history studies were presented in the original submission, and are provided in Appendix M.3." As for the clinical trials of AA, please provide results tables, comparing results across all non-interventional natural history studies, including ALX-HPP-501, for each outcome measure; results should be grouped by age of onset category (perinatal-, infantile-, and juvenile-onset HPP).

The Global HPP Registry was designed differently to the three natural history studies. The three natural history studies were designed to specifically assess the outcomes of patients with perinatal/infantile onset (ENB-011-10) and juvenile-onset HPP (ALX-HPP-502 and ALX-HPP-502s), whereas the Global HPP Registry focuses on the age of the patient and their symptoms at presentation. Within the Global HPP Registry, there are 2 distinct groups of patients based on current age < 18 years and ≥ 18 years.

In addition, some of the endpoints included in the Global HPP Registry (e.g. 6MWT, BPI-SF, PedsQL, SF-36v2) were not included in the natural history studies.

Therefore, efficacy data split by age disease onset are not available for all studies and the differences discussed above would make a comparison between the studies non-informative so summary tables have not been provided.

A 12. Priority question. Section B.2.2 of the CS (Table 10) lists three "natural history/non-interventional studies" that are described as "relevant to the decision problem as they provide sources of epidemiology data for AA and of historical controls for some of the interventional studies."

Please explain how these three studies were identified and selected for inclusion, given that they are not included in the list of 18 studies identified by the SLR described in Appendix D of the CS.

The clinical SLR conducted focused on studies that demonstrate the clinical and economic outcomes of HPP treatments. Hence, it selected studies with interventions or treatments and "no treatment" was an exclusion criterion. Therefore, these three natural history studies were not picked up by the SLR. However, these Alexion sponsored studies were included to provide control data to use for comparative analyses of selected endpoints in ENB-002-08/ENB-003-08, ENB-010-10, and ENB-006-09/ENB-008-10.

A 13. Priority question. The pooled analysis (described in section B.2.8.1 of the CS), to assess the long-term efficacy of AA, included only two AA studies (ENB-002-08/ENB-003-08 and ENB-010-10) and one natural history study (ENB-011-10), all of which included only patients with perinatal- and/or infantile onset HPP (Table 8 and Table 10) and hence represent only a subset of the population defined in the decision problem (see question A1).

> **a) Please explain why patients from study ENB-006-09/ENB-008-10, which appears to have included a mixed population of patients with paediatric-onset HPP "Patients aged ≥ 5 and ≤ 12 years of age with HPP" (Table 8) were not included in the pooled efficacy analysis.**

As per the response to A 1.a), the pooled analysis was conducted to assess long-term survival in patients with perinatal/infantile-onset HPP, which is the only subgroup in which the disease can be lethal, with reported survival of 25% at 5

years. Therefore, patients with juvenile-onset HPP from study ENB-006-09/ENB-008-10 were not included in this analysis.

b) Study ENB-009-10 is described as including "Adolescent and adult patients aged 13 to 65 years with HPP" (Table 8). If any of the participants in this study met the criteria for paediatric-onset HPP, please explain why these patients were not included in the pooled efficacy analysis.

As per the response to A 1.a) and A 13.a), the pooled analysis was conducted to assess long-term survival in patients with perinatal/infantile-onset HPP only, which is the only subgroup in which the disease can be lethal. Therefore, patients with juvenile-onset HPP from study ENB-009-10 were not included in this analysis.

c) Please explain why data from the UKMAA were not included in the pooled efficacy analysis.

As per the response to A 1.a), the pooled analysis was conducted in 2019, prior to the decision problem being defined for this submission and prior to the UK MAA data presented in the submission being available. Therefore, patients with perinatal/infantile-onset HPP from the UK MAA were not included in this analysis.

d) Please explain why ALX-HPP-501 and ALX-HPP-502 were omitted from the pooled efficacy analysis.

As per the response to A 1.a) and A 13.a), the pooled analysis was conducted to assess long-term survival in patients with perinatal/infantile-onset HPP only, which is the only subgroup in which the disease can be lethal. Therefore, patients with juvenile-onset HPP from ALX-HPP-501 and ALX-HPP-502 were not included in this analysis.

e) Please repeat the pooled efficacy analysis, including all relevant patients, i.e. those with paediatric-onset (perinatal-, infantile- or juvenile-onset) HPP from all relevant studies including ENB-006-09/ENB-008-10, study ENB-009-10, the UKMAA and AA-treated patients from the wider Global HPP Registry (ALX-HPP-501), ENB-011-10, ALX-HPP-501 and ALX-HPP-502.

As per the responses to A 1.c), no further pooled analyses are available and it would not be feasible to conduct a pooled analysis across all populations due to the limited availability of historical control data across all populations and all endpoints, and such an analysis would require re-designing the ESAP for all studies and would require several months to complete.

f) Please conduct subgroup pooled analyses using all relevant data from all studies for each of perinatal-, infantile- or juvenile-onset HPP.

As per the responses to A 1.e), the focus of Alexion's clinical program was primarily based on the age of study enrolment, and patients were therefore, not stratified according to age of disease onset, except for perinatal/infantile-onset patients as these represent the group with the life-threatening disease and were studied for survival. In addition, the UK MAA was designed differently to the studies that formed the AA clinical development program. The UK MAA focuses on the age of the patient and their symptoms at presentation in one of the designated treatment centres. Therefore, efficacy data split by age disease onset are not available for all studies and all endpoints.

Furthermore, as per the responses to A 1.c) and A 13.e), no further pooled analyses are available and it would not be feasible to conduct a pooled analysis across the subgroups due to the lack of subgroup efficacy data, the limited availability of historical control data across all populations and all endpoints, and such an analysis would require re-designing the ESAP for all studies and would require several months to complete.

A 14. Section B.2.2. of the CS states that, "Patients included in the UK MAA also had the option to have their data included in the real-world Global HPP Registry (ALX-HPP-501)…" This registry study appears to have included a large number of AA-treated patients (in addition to those from the UKMAA)

a) Please provide the number of patients in the UK MAA who consented to have their data included in ALX-HPP-501.

31 patients from the [redacted] data cut off, had consented to have their data included in the Global HPP Registry.

b) Please explain why AA-treated patients, with paediatric-onset HPP, from this registry study were not included in the pooled efficacy analysis.

The pooled efficacy analysis focused on patients with perinatal/infantile onset disease from the AA clinical trials. The global HPP Registry is an observational, non-interventional study and therefore the participating patients do not follow any specific treatment monitoring protocol or specific AA eligibility criteria. This fundamental difference would result in a very heterogenous population in terms of baseline characteristics and treatment monitoring making any conclusions less comprehensive. In addition, at the time when the pooled analysis was conducted (2018), ever-treated patients in the Global HPP Registry mostly came from the clinical trials. Hence, there would be a minor added benefit from using the Global HPP Registry as a source of more patients.

A 15. Please discuss how the COVID-19 pandemic may have affected the UK MAA in terms of:

a) Treatment administration

b) Follow up

c) Efficacy and safety assessment

COVID-19 affected [redacted]MAA sites and caused challenges in collecting data. Overall, [redacted] paediatric and [redacted]adult participants missed at least 1 6MWT assessment due to restrictions in attending hospital appointments, as this assessment could not be conducted remotely. Patients had to have remote consultations with the treatment centres due to restricted access of face to face appointments in the hospitals. Whilst most of the MAA assessments could be performed remotely, the 6MWT and appropriate weight/length measurements for small children could not be collected. Eligibility assessment delays for some participants and site team resourcing issues (e.g. research staff were unavailable to input study data as many were front-line COVID-19 responders) have also resulted from COVID-19. After the lockdowns had ended, patients were also reluctant to travel to hospitals for face to face visits as they were considered vulnerable. As of the analysis cut-off date, [redacted]sites had overcome

their staff resource shortfall with the addition/replacement of research nurses delegated to the MAA; however, other sites remained affected.

The MAA for AA was originally due to expire in [redacted], but as a result of all the above, Alexion agreed a 6-month extension to the MAA and the data collection period with NICE and NHSE, to ensure that AA treatment impact is appropriately captured and the data set is as complete as possible.

A 16. Please clarify if any patient (paediatric or adult) was discontinued from AA in the UK MAA due to treatment-related adverse events or non-response.

[redacted] participants in the UK MAA discontinued AA due to a TEAE or non-response.

Adverse events

A 17. Priority question. The pooled analysis (described in section B.2.8.2 of the CS), to assess the long-term safety of AA, included ENB-002-08/ENB-003-08, ENB-010-10, ENB-006-09/ENB-008-10, and ENB-009-10. Also, it appears that no comparative analysis was conducted using natural history data.

a) Please explain the discrepancy between the studies included in the pooled analyses for efficacy and for safety.

Alexion conducted the efficacy pooled analysis including all patients from the three paediatric AA clinical trials (ENB-002-08/ENB-003-08, ENB-010-10, ENB-006-09/ENB-008-10) that had patients with perinatal/infantile onset disease. This is a patient population that had the most severe form of the disease with survival rate of 25% at 5 years and there was an unmet need to produce a comprehensive data set for this population. The pooled safety analysis, included patients from all 4 studies (patients with perinatal/infantile & juvenile onset HPP) evaluating the most frequent treatment-related adverse events (TRAEs) and the timing of their occurrence after beginning AA therapy. The onset of the disease is not expected to affect the safety profile of AA, thus the inclusion of 4 studies in the pooled safety analysis.

b) Please clarify whether any patients with adult-onset HPP were included in the pooled analysis for safety.

No patients with adult-onset HPP were included in the pooled analysis for safety.

c) Please repeat the pooled safety analysis excluding any adult patients and including data from the UKMAA, if available.

As per the response to A 17.b), no patients with adult-onset HPP were included in the pooled analysis for safety. No further pooled safety analyses including the UK MAA are available.

d) Please make a comparison with no AA via including natural history safety data.

It is not be feasible to conduct a comparison to the natural history safety data due to the limited availability of historical control data across all populations and all safety outcomes, and such an analysis would require re-designing the ESAP for all studies and would require several months to complete.

A 18. In the Asfotase Alfa Metabolic Support case study reports included in the submission, both the adult patient and parent carer of child with HPP reported injection site reactions and skin discolouration as being distressing adverse events experienced. Table 93 and 94 of Appendix M also show that injection site reactions were the most reported AEs in the UK MAA safety population. Please provide details of all injection site reactions across all data sets.

In the UK MAA, Injection site reactions (ISRs) were the most frequently reported event of interest in both the paediatric and adult safety populations.[3] Overall, [redacted] ISRs were reported in [redacted] paediatric participants and [redacted] ISRs were reported in [redacted] adult participants. [redacted] ISRs were considered [redacted] or [redacted] in severity. Paediatric participants reported soreness and muscle wastage at the injection site, and one participant reported that they occasionally developed small red lumps at the injection site and the area became slightly bruised. Adult participants reported soreness, bruising, redness, tingling/stinging and red lumps at their injection sites. Participants also reported suffering from nausea and headaches, which resolve within around 1 hour and some patients were diagnosed with lipoatrophy at abdominal injections sites.

In the AA clinical trials, most TRAEs (1,310 [89.4%] events in 82 patients) were ISRs, with the majority being mild (74%) or moderate (21%) in severity.[17] The most commonly reported ISRs was injection site erythema (53.6%), discolouration

(24.1%), pain (18.8%) and pruritus (17.0%). New onset ISRs occurred most frequently within the first 3 months of treatment (565 events in 53 patients), then generally decreased over time (207 events in 33 patients from 3 to 6 months; 178 events in 35 patients from 6 months to 1 year; 125 events in 32 patients from 1 to 2 years; and 247 events in 45 patients from 2 to 7 years). One patient withdrew from the trial due to injection site hypersensitivity.

In the Global HPP Registry, ISRs were the most frequently reported even of interest in ever-treated patients aged < 18 years at baseline and ever-treated patients aged ≥ 18 years at baseline.[12] Overall, [redacted] ISRs were reported in [redacted] ever-treated patients aged < 18 years, [redacted] SRs were reported in [redacted] ever-treated patients aged ≥ 18 years and most of these [redacted] were [redacted]

In the real-world EmPATHY study, the most common AEs were ISRs, with 11 (79%) patients noting reddening and/or tenderness at injection sites with variable intensity and duration sometime during the first 3 months of treatment.[14] This increased to 13 patients following 12 months of treatment. Affected injection sites were the abdomen (n = 12), thigh (n = 4), and upper arm (n = 3). Comparing available photographs over the course of the study revealed that 5 patients exhibited faint initial signs of soft tissue distension during the first 3 months of treatment, including bulging of subcutaneous fat tissue suggesting lipohypertrophy; upon palpation, no bulky fat masses were identified, but rather sagging of the skin suggesting dystrophy of the subcutaneous fat tissue, providing insufficient suspension for overlying skin. Of the 11 women included in this study, such alterations were visible at the abdomen in 9 of these patients at 12 months of treatment; all of these patients had extensive abdominal fat tissue before treatment. None of these soft tissue distensions receded over time; nevertheless, these findings did not lead to treatment interruption or termination. No tissue distension was observed at any injection site of the two women who were not obese (one of whom did not inject in the abdomen). No relevant tissue distension was seen in men, even though two of them had extensive abdominal fat tissue.

A19. Section B.2.10 of the CS provides a narrative summary of safety data, by study.

For clarity, please provide safety results tables, comparing the results of all relevant studies, for:

a) Serious treatment emergent adverse events (TEAEs), using MedDRA preferred terms, occurring in ≥2% of patients

Table 7 provides an overview of the serious AE occurring in > 2% of patients in the UK MAA.

Table 7: Summary of SAEs occurring in > 2% of patients in the UK MAA

	Paediatric safety Population (N =)			Adult safety Population (N =)		
	All reported events			All reported events		
	Any	Related	Not related	Any	Related	Not related
	n (%) E	n (%) E	n (%) E	n (%) E	n (%) E	n (%) E
Serious adverse events, n (%)						
Craniosynostosis						
Infectious mononucleosis						
Pneumonia						
Data pending						
Injection site atrophy						
Scoliosis						
Respiratory distress						
Injection site reaction						
Musculoskeletal and connective tissue disorders						
Flank pain						
Nervous system disorders						

	Paediatric safety Population (N = [redacted])			Adult safety Population (N = [redacted])		
	All reported events			All reported events		
	Any	Related	Not related	Any	Related	Not related
	n (%) E	n (%) E	n (%) E	n (%) E	n (%) E	n (%) E

Key: E, number of events; N, number of participants; n, number of participants in a category; SAE, serious adverse event.
Notes: All events occurred after enrolment in the MAA while the participant was on AA treatment or within 30 days of treatment discontinuation. Related events included those that were possibly [a] The coded system organ call and preferred term were not available at data cut-off. Participant 0915-M01 had orthopaedic surgery for the insertion and removal of hamiepiphysiodesis at the time the SAE was reported. [b] The coded system organ call and preferred term were not available at data cut-off. Participant 0826-M02 had post-operative urinary retention and had surgery on their right femur at the time the SAE was reported.
Source: Alexion MAA interim analysis report (ASF-MAA-001) 2022.[3]

Table 8 provides a summary of the all serious TEAEs occurring in > 2% of patients across the AA clinical trials.

Table 8: Summary of all serious TEAEs occurring in > 2% of patients across studies AA clinical trials

	ENB-002-08/ENB-003-08 (n = 11)		ENB-010-10 (n = 69)		ENB-006-09/ENB-008-10 (n = 13)		ENB-009-10 (n = 19)	
	Events, n	Patients, n (%)	Events, n	Patients, n (%)	Events, n	Patients, n (%)	Events, n	Patients, n (%)
Patients with serious TEAEs		10 (90.9)	297	50 (72.5)	0	0 (0.0)	29	9 (47.1)
Craniosynostosis		6 (54.5)			0	0 (0.0)		
Pneumonia		4 (36.4)			0	0 (0.0)		
Respiratory distress		2 (18.2)			0	0 (0.0)		
Respiratory syncytial virus bronchiolitis		2 (18.2)			0	0 (0.0)		
Restrictive pulmonary disease		2 (18.2)			0	0 (0.0)		
Hypoxia		2 (18.2)			0	0 (0.0)		
Convulsion		2 (18.2)			0	0 (0.0)		
Intracranial pressure increased		2 (18.2)			0	0 (0.0)		
Tracheostomy tube removal		2 (18.2)			0	0 (0.0)		
Medical device complication		2 (18.2)			0	0 (0.0)		
Pain in extremity		0 (0.0)			0	0 (0.0)		
Femur fracture		1 (9.1)			0	0 (0.0)		
Scoliosis		1 (9.1)			0	0 (0.0)		
Cyanosis		1 (9.1)			0	0 (0.0)		
Congenital bowing of long bones		1 (9.1)			0	0 (0.0)		

	ENB-002-08/ENB-003-08 (n = 11)		ENB-010-10 (n = 69)		ENB-006-09/ENB-008-10 (n = 13)		ENB-009-10 (n = 19)	
	Events, n	Patients, n (%)	Events, n	Patients, n (%)	Events, n	Patients, n (%)	Events, n	Patients, n (%)
Talipes	[redacted]	1 (9.1)	[redacted]	[redacted]	0	0 (0.0)	[redacted]	[redacted]
Conductive deafness	[redacted]	1 (9.1)	[redacted]	[redacted]	0	0 (0.0)	[redacted]	[redacted]
Papilloedema	[redacted]	1 (9.1)	[redacted]	[redacted]	0	0 (0.0)	[redacted]	[redacted]
Immediate post-injection reaction	[redacted]	1 (9.1)	[redacted]	[redacted]	0	0 (0.0)	[redacted]	[redacted]
Chronic hepatitis	[redacted]	1 (9.1)	[redacted]	[redacted]	0	0 (0.0)	[redacted]	[redacted]
Bacterial tracheitis	[redacted]	1 (9.1)	[redacted]	[redacted]	0	0 (0.0)	[redacted]	[redacted]
Croup infectious	[redacted]	1 (9.1)	[redacted]	[redacted]	0	0 (0.0)	[redacted]	[redacted]
Gastroenteritis salmonella	[redacted]	1 (9.1)	[redacted]	[redacted]	0	0 (0.0)	[redacted]	[redacted]
H1N1 influenza	[redacted]	1 (9.1)	[redacted]	[redacted]	0	0 (0.0)	[redacted]	[redacted]
Lower respiratory tract infection	[redacted]	1 (9.1)	[redacted]	[redacted]	0	0 (0.0)	[redacted]	[redacted]
Lower respiratory tract infection viral	[redacted]	1 (9.1)	[redacted]	[redacted]	0	0 (0.0)	[redacted]	[redacted]
Pneumonia respiratory syncytial viral	[redacted]	1 (9.1)	[redacted]	[redacted]	0	0 (0.0)	[redacted]	[redacted]
Sepsis	[redacted]	1 (9.1)	[redacted]	[redacted]	0	0 (0.0)	[redacted]	[redacted]
Septic shock	[redacted]	1 (9.1)	[redacted]	[redacted]	0	0 (0.0)	[redacted]	[redacted]
Tracheitis	[redacted]	1 (9.1)	[redacted]	[redacted]	0	0 (0.0)	[redacted]	[redacted]
Upper respiratory tract infection	[redacted]	1 (9.1)	[redacted]	[redacted]	0	0 (0.0)	[redacted]	[redacted]

	ENB-002-08/ENB-003-08 (n = 11)		ENB-010-10 (n = 69)		ENB-006-09/ENB-008-10 (n = 13)		ENB-009-10 (n = 19)	
	Events, n	Patients, n (%)	Events, n	Patients, n (%)	Events, n	Patients, n (%)	Events, n	Patients, n (%)
Collapse of lung	[redacted]	1 (9.1)	[redacted]	[redacted]	0	0 (0.0)	[redacted]	[redacted]
Stress fracture	[redacted]	1 (9.1)	[redacted]	[redacted]	0	0 (0.0)	[redacted]	[redacted]
Blood urea increased	[redacted]	1 (9.1)	[redacted]	[redacted]	0	0 (0.0)	[redacted]	[redacted]
CSF pressure	[redacted]	1 (9.1)	[redacted]	[redacted]	0	0 (0.0)	[redacted]	[redacted]
Investigation	[redacted]	1 (9.1)	[redacted]	[redacted]	0	0 (0.0)	[redacted]	[redacted]
Oxygen saturation decreased	[redacted]	1 (9.1)	[redacted]	[redacted]	0	0 (0.0)	[redacted]	[redacted]
Feeding disorder	[redacted]	1 (9.1)	[redacted]	[redacted]	0	0 (0.0)	[redacted]	[redacted]
Weight gain poor	[redacted]	1 (9.1)	[redacted]	[redacted]	0	0 (0.0)	[redacted]	[redacted]
Nephrolithiasis	[redacted]	1 (9.1)	[redacted]	[redacted]	0	0 (0.0)	[redacted]	[redacted]
Urinary tract obstruction	[redacted]	1 (9.1)	[redacted]	[redacted]	0	0 (0.0)	[redacted]	[redacted]
Adenoidal disorder	[redacted]	1 (9.1)	[redacted]	[redacted]	0	0 (0.0)	[redacted]	[redacted]
Apnoeic attack	[redacted]	1 (9.1)	[redacted]	[redacted]	0	0 (0.0)	[redacted]	[redacted]
Asthma	[redacted]	1 (9.1)	[redacted]	[redacted]	0	0 (0.0)	[redacted]	[redacted]
Obstructive airways disorder	[redacted]	1 (9.1)	[redacted]	[redacted]	0	0 (0.0)	[redacted]	[redacted]
Respiratory depression	[redacted]	1 (9.1)	[redacted]	[redacted]	0	0 (0.0)	[redacted]	[redacted]
Respiratory failure	[redacted]	1 (9.1)	[redacted]	[redacted]	0	0 (0.0)	[redacted]	[redacted]
Sleep apnoea syndrome	[redacted]	1 (9.1)	[redacted]	[redacted]	0	0 (0.0)	[redacted]	[redacted]
Tonsillar disorder	[redacted]	1 (9.1)	[redacted]	[redacted]	0	0 (0.0)	[redacted]	[redacted]
Urticaria	[redacted]	1 (9.1)	[redacted]	[redacted]	0	0 (0.0)	[redacted]	[redacted]
Central venous catheter	[redacted]	1 (9.1)	[redacted]	[redacted]	0	0 (0.0)	[redacted]	[redacted]

	ENB-002-08/ENB-003-08 (n = 11)		ENB-010-10 (n = 69)		ENB-006-09/ENB-008-10 (n = 13)		ENB-009-10 (n = 19)	
	Events, n	**Patients, n (%)**	**Events, n**	**Patients, n (%)**	**Events, n**	**Patients, n (%)**	**Events, n**	**Patients, n (%)**
removal								
Tracheal fistula repair	[redacted]	1 (9.1)	[redacted]	[redacted]	0	0 (0.0)	[redacted]	[redacted]
Deep vein thrombosis	[redacted]	1 (9.1)	[redacted]	[redacted]	0	0 (0.0)	[redacted]	[redacted]
Pyrexia	0	0 (0.0)	[redacted]	[redacted]	0	0 (0.0)	[redacted]	[redacted]
Decreased oxygen saturation	0	0 (0.0)	[redacted]	[redacted]	0	0 (0.0)	[redacted]	[redacted]
Respiratory disorder	0	0 (0.0)	[redacted]	[redacted]	0	0 (0.0)	[redacted]	[redacted]
Food intolerance	0	0 (0.0)	[redacted]	[redacted]	0	0 (0.0)	[redacted]	[redacted]
Back pain	0	0 (0.0)	[redacted]	[redacted]	0	0 (0.0)	[redacted]	[redacted]
Muscular weakness	0	0 (0.0)	[redacted]	[redacted]	0	0 (0.0)	[redacted]	[redacted]
Osteoarthritis	0	0 (0.0)	[redacted]	[redacted]	0	0 (0.0)	[redacted]	[redacted]
Chills	0	0 (0.0)	[redacted]	[redacted]	0	0 (0.0)	[redacted]	[redacted]
Hypoesthesia oral	0	0 (0.0)	[redacted]	[redacted]	0	0 (0.0)	[redacted]	[redacted]
Abscess	0	0 (0.0)	[redacted]	[redacted]	0	0 (0.0)	[redacted]	[redacted]
Cellulitis	0	0 (0.0)	[redacted]	[redacted]	0	0 (0.0)	[redacted]	[redacted]
Endocarditis	0	0 (0.0)	[redacted]	[redacted]	0	0 (0.0)	[redacted]	[redacted]
Enterovirus infection	0	0 (0.0)	[redacted]	[redacted]	0	0 (0.0)	[redacted]	[redacted]
Staphylococcal abscess	0	0 (0.0)	[redacted]	[redacted]	0	0 (0.0)	[redacted]	[redacted]
Staphylococcal infection	0	0 (0.0)	[redacted]	[redacted]	0	0 (0.0)	[redacted]	[redacted]
Tympanic membrane perforation	0	0 (0.0)	[redacted]	[redacted]	0	0 (0.0)	[redacted]	[redacted]

	ENB-002-08/ENB-003-08 (n = 11)		ENB-010-10 (n = 69)		ENB-006-09/ENB-008-10 (n = 13)		ENB-009-10 (n = 19)	
	Events, n	Patients, n (%)	Events, n	Patients, n (%)	Events, n	Patients, n (%)	Events, n	Patients, n (%)
Anaphylactoid reaction	0	0 (0.0)	[redacted]	[redacted]	0	0 (0.0)	[redacted]	[redacted]
Adrenal adenoma	0	0 (0.0)	[redacted]	[redacted]	0	0 (0.0)	[redacted]	[redacted]
Bradycardia	0	0 (0.0)	[redacted]	[redacted]	0	0 (0.0)	[redacted]	[redacted]
Arnold-chiari malformation	0	0 (0.0)	[redacted]	[redacted]	0	0 (0.0)	[redacted]	[redacted]
Cardiac arrest	0	0 (0.0)	[redacted]	[redacted]	0	0 (0.0)	[redacted]	[redacted]
Vomiting	0	0 (0.0)	[redacted]	[redacted]	0	0 (0.0)	[redacted]	[redacted]
Hydrocephalus	0	0 (0.0)	[redacted]	[redacted]	0	0 (0.0)	[redacted]	[redacted]
Syringomyelia	0	0 (0.0)	[redacted]	[redacted]	0	0 (0.0)	[redacted]	[redacted]
Dyspnoea	0	0 (0.0)	[redacted]	[redacted]	0	0 (0.0)	[redacted]	[redacted]
Feeding tube complication	0	0 (0.0)	[redacted]	[redacted]	0	0 (0.0)	[redacted]	[redacted]
Device related infection	0	0 (0.0)	[redacted]	[redacted]	0	0 (0.0)	[redacted]	[redacted]
Cardio-respiratory arrest	0	0 (0.0)	[redacted]	[redacted]	0	0 (0.0)	[redacted]	[redacted]
Failure to thrive	0	0 (0.0)	[redacted]	[redacted]	0	0 (0.0)	[redacted]	[redacted]
Rhinovirus infection	0	0 (0.0)	[redacted]	[redacted]	0	0 (0.0)	[redacted]	[redacted]
Acute respiratory failure	0	0 (0.0)	[redacted]	[redacted]	0	0 (0.0)	[redacted]	[redacted]
Osteopenia	0	0 (0.0)	[redacted]	[redacted]	0	0 (0.0)	[redacted]	[redacted]
Headache	0	0 (0.0)	[redacted]	[redacted]	0	0 (0.0)	[redacted]	[redacted]
Irritability	0	0 (0.0)	[redacted]	[redacted]	0	0 (0.0)	[redacted]	[redacted]
Viral infection	0	0 (0.0)	[redacted]	[redacted]	0	0 (0.0)	[redacted]	[redacted]
Gastroenteritis	0	0 (0.0)	[redacted]	[redacted]	0	0 (0.0)	[redacted]	[redacted]

	ENB-002-08/ENB-003-08 (n = 11)		ENB-010-10 (n = 69)		ENB-006-09/ENB-008-10 (n = 13)		ENB-009-10 (n = 19)	
	Events, n	Patients, n (%)	Events, n	Patients, n (%)	Events, n	Patients, n (%)	Events, n	Patients, n (%)
Gastroenteritis rotavirus	0	0 (0.0)	[redacted]	[redacted]	0	0 (0.0)	[redacted]	[redacted]
Hyponatraemia	0	0 (0.0)	[redacted]	[redacted]	0	0 (0.0)	[redacted]	[redacted]
Viral upper respiratory tract infection	0	0 (0.0)	[redacted]	[redacted]	0	0 (0.0)	[redacted]	[redacted]
Atelectasis	0	0 (0.0)	[redacted]	[redacted]	0	0 (0.0)	[redacted]	[redacted]
Pneumonia aspiration	0	0 (0.0)	[redacted]	[redacted]	0	0 (0.0)	[redacted]	[redacted]
Drug hypersensitivity	0	0 (0.0)	[redacted]	[redacted]	0	0 (0.0)	[redacted]	[redacted]

Key: AA, asfotase alfa; TEAE, treatment-emergent adverse event.
Source: ENB-002-08/ENB-003-08 Final CSR. 2017[4]; Whyte at al. 2018[5]; ENB-010-10 Final CSR. 2017[6]; Hofmann et al. 2019[7]; ENB-006-09/ENB-008-10 Final CSR. 2017[8]; Whyte et al. 2017[9]; ENB-009-10 Final CSR. 2017[10]; Kishnani et al. 2019.[11]

Table 9 provides an overview of the serious AE occurring in > 2% of patients in the Global HPP Registry.

Table 9: Summary of SAEs occurring in > 2% of patients in the Global HPP Registry

	Total (n = 364)		< 18 years at baseline (n = 199)		≥ 18 years at baseline (n = 165)	
	n (%)	Events, n	n (%)	Events, n	n (%)	Events, n
Targeted events or SAEs reported	[redacted]					
Injection site reaction	[redacted]					
SAEs	[redacted]					
Pneumonia	[redacted]					
Febrile convulsion	[redacted]					

Key: AA, asfotase alfa; AE, adverse event; ALP, alkaline phosphatase; CSF, cerebrospinal fluid; HPP, hypophosphatasia; SAE, serious adverse event.
Note: This table includes 19 patients without confirmation of HPP from genetic testing or ALP levels. Patients with a missing treatment start date are excluded from the table as it cannot be determined if the event occurred before or after treatment start. Adverse events that occurred before the start of treatment are excluded from the analysis.
[a], n patients includes 2 patients without confirmation of HPP from genetic testing or ALP levels.
Source: ALX-HPP-501 study report 2021.[12]

No additional data are available for the real-world EmPATHY study or the longitudinal telephone-based survey than what are presented in the submission dossier.[13, 14]

b) TEAE of any grade, using MedDRA preferred terms, occurring in ≥10% of patients

Table 10 provides an overview of the events of interest occurring in > 10% of patients in the UK MAA.

Table 10: Summary of EOIs occurring in > 10% of patients in UK MAA

	Paediatric safety Population (N = [redacted])			Adult safety Population (N = [redacted])		
	All reported events			All reported events		
	Any	Related	Not related	Any	Related	Not related
	n (%) E	n (%) E	n (%) E	n (%) E	n (%) E	n (%) E
Events of interest						
Lack of efficacy/drug effect						
Craniosynostosis						
Injection-associated reaction						
Injection site reaction						

Key: E, number of events; N, number of participants; n, number of participants in a category; SAE, serious adverse event.
Notes: All events occurred after enrolment in the MAA while the participant was on AA treatment or within 30 days of treatment discontinuation. Related events included those that were possibly.
Source: Alexion MAA interim analysis report (ASF-MAA-001) 2022.[3]

Table 11 provides a summary of the all TEAEs occurring in > 10% of patients across the AA clinical trials.

Table 11: Summary of all TEAEs occurring in > 10% of patients across studies AA clinical trials

	ENB-002-08/ENB-003-08 (n = 11)		ENB-010-10 (n = 69)		ENB-006-09/ENB-008-10 (n = 13)		ENB-009-10 (n = 19)	
	Events, n	Patients, n (%)	Events, n	Patients, n (%)	Events, n	Patients, n (%)	Events, n	Patients, n (%)
Patients with TEAEs	794	11 (100.0)	3,052	69 (100.0)	626	13 (100.0)	1,145	19 (100.0)
Injection site erythema	[redacted]	5 (45.5)	[redacted]	33 (47.8)	73	11 (85.0)	[redacted]	13 (68.4)
Upper respiratory tract infection	[redacted]	8 (72.7)	[redacted]	19 (27.5)	[redacted]	[redacted]	[redacted]	7 (36.8)
Pyrexia	[redacted]	8 (72.7)	[redacted]	47 (68.1)	[redacted]	[redacted]	[redacted]	[redacted]
Injection site macule	[redacted]	[redacted]	[redacted]	[redacted]	66	9 (69.2)	[redacted]	[redacted]
Arthralgia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	13 (68.4)
Pneumonia	[redacted]	7 (63.6)	[redacted]	14 (20.3)	[redacted]	[redacted]	[redacted]	[redacted]
Craniosynostosis	13	7 (63.6)	[redacted]	19 (27.5)	[redacted]	[redacted]	[redacted]	[redacted]
Pain in extremity	[redacted]	4 (36.4)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	12 (63.2)
Headache	[redacted]	5 (45.5)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	6 (31.6)
Injection site hypertrophy	[redacted]	[redacted]	[redacted]	[redacted]	27	8 (61.5)	[redacted]	4 (21.1)
Tooth loss	[redacted]	4 (36.4)	[redacted]	41 (59.4)	[redacted]	[redacted]	[redacted]	[redacted]
Otitis media	[redacted]	6 (54.5)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vomiting	[redacted]	6 (54.5)	[redacted]	31 (44.9)	[redacted]	[redacted]	[redacted]	[redacted]
Constipation	[redacted]	6 (54.5)	[redacted]	16 (23.2)	[redacted]	[redacted]	[redacted]	[redacted]
Injection site pruritus	[redacted]	[redacted]	[redacted]	[redacted]	23	7 (53.8)	[redacted]	5 (26.3)
Procedural pain	[redacted]	3 (27.3)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	5 (26.3)
Injection site haematoma	[redacted]	3 (27.3)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	10 (52.6)
Back pain	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	10 (52.6)

	ENB-002-08/ENB-003-08 (n = 11)		ENB-010-10 (n = 69)		ENB-006-09/ENB-008-10 (n = 13)		ENB-009-10 (n = 19)	
	Events, n	Patients, n (%)	Events, n	Patients, n (%)	Events, n	Patients, n (%)	Events, n	Patients, n (%)
Bone pain	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	9 (47.4)
Injection site discolouration	[redacted]	[redacted]	[redacted]	[redacted]	17	5 (35.8)	[redacted]	9 (47.4)
Injection site pain	[redacted]	[redacted]	[redacted]	[redacted]	18	6 (46.2)	[redacted]	6 (31.6)
Injection site atrophy	[redacted]	[redacted]	[redacted]	[redacted]	18	6 (46.2)	[redacted]	5 (26.3)
Conjunctival deposit	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Musculoskeletal pain	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	8 (42.1)
Oedema peripheral	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	8 (42.1)
Gastroenteritis	[redacted]	3 (27.3)	[redacted]	17 (24.6)	[redacted]	[redacted]	[redacted]	[redacted]
Foot fracture	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	7 (36.8)
Dizziness	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	7 (36.8)
Deposit eye	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	7 (36.8)
Joint swelling	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	7 (36.8)
Injection site reaction	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	7 (36.8)
Decreased haemoglobin	[redacted]	4 (36.4)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Diarrhoea	[redacted]	4 (36.4)	[redacted]	20 (29.0)	[redacted]	[redacted]	[redacted]	[redacted]
Irritability	[redacted]	4 (36.4)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nasopharyngitis	[redacted]	4 (36.4)	[redacted]	18 (26.1)	[redacted]	[redacted]	[redacted]	6 (31.6)
Dental caries	[redacted]	4 (36.4)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pain	[redacted]	4 (36.4)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Rash	[redacted]	4 (36.4)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	ENB-002-08/ENB-003-08 (n = 11)		ENB-010-10 (n = 69)		ENB-006-09/ENB-008-10 (n = 13)		ENB-009-10 (n = 19)	
	Events, n	Patients, n (%)	Events, n	Patients, n (%)	Events, n	Patients, n (%)	Events, n	Patients, n (%)
Viral infection	[redacted]	4 (36.4)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Myalgia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Sinusitis	[redacted]	3 (27.3)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	5 (26.3)
Pharyngitis	[redacted]	3 (27.3)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Influenza	[redacted]	3 (27.3)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Tracheitis	[redacted]	3 (27.3)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Respiratory distress	[redacted]	3 (27.3)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Wheezing	[redacted]	3 (27.3)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Acute sinusitis	[redacted]	3 (27.3)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Allergic rhinitis	[redacted]	3 (27.3)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Decreased oxygen saturation	[redacted]	3 (27.3)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Increased urine calcium:creatinine ratio	[redacted]	3 (27.3)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Drug dependence	[redacted]	3 (27.3)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nausea	[redacted]	3 (27.3)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	4 (21.1)
Papilloedema	[redacted]	3 (27.3)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Sleep apnoea syndrome	[redacted]	3 (27.3)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cough	[redacted]	[redacted]	[redacted]	17 (24.6)	[redacted]	[redacted]	[redacted]	5 (26.3)
Respiratory tract infections	[redacted]	[redacted]	[redacted]	16 (23.2)	[redacted]	[redacted]	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	4 (21.1)

	ENB-002-08/ENB-003-08 (n = 11)		ENB-010-10 (n = 69)		ENB-006-09/ENB-008-10 (n = 13)		ENB-009-10 (n = 19)	
	Events, n	Patients, n (%)	Events, n	Patients, n (%)	Events, n	Patients, n (%)	Events, n	Patients, n (%)
Gait disturbance	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Joint sprain	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Limb injury	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Epistaxis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nasal congestion	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Oropharyngeal pain	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	4 (21.1)
Seasonal allergy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Skin papilloma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Fall	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	5 (26.3)
Contusion	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Injection site swelling	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	4 (21.1)
Osteoarthritis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	4 (21.1)
Post-traumatic pain	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	4 (21.1)
Parathesia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	4 (21.1)
Ear infection	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nephrolithiasis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scoliosis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Visual impairment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Conjunctivitis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Procedural site reaction	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	ENB-002-08/ENB-003-08 (n = 11)		ENB-010-10 (n = 69)		ENB-006-09/ENB-008-10 (n = 13)		ENB-009-10 (n = 19)	
	Events, n	Patients, n (%)	Events, n	Patients, n (%)	Events, n	Patients, n (%)	Events, n	Patients, n (%)
Agitation	[redacted]							
Hydronephrosis	[redacted]							
Anaemia	[redacted]							
Hand fracture	[redacted]							
Rib fracture	[redacted]							
Skin laceration	[redacted]							
Tibia fracture	[redacted]							
Excessive granulation tissue	[redacted]							
Urticaria	[redacted]							
Skin irritation	[redacted]							
Flatulence	[redacted]							
Gingivitis	[redacted]							
Impaired gastric emptying	[redacted]							
Stomatitis	[redacted]							
Hypoxia	[redacted]							
Restrictive pulmonary disease	[redacted]							
Congenital bowing of long bones	[redacted]							
Convulsion	[redacted]							
Intracranial pressure increased	[redacted]							
Speech disorder developmental	[redacted]							

	ENB-002-08/ENB-003-08 (n = 11)		ENB-010-10 (n = 69)		ENB-006-09/ENB-008-10 (n = 13)		ENB-009-10 (n = 19)	
	Events, n	Patients, n (%)	Events, n	Patients, n (%)	Events, n	Patients, n (%)	Events, n	Patients, n (%)
Hypocalcaemia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Tachycardia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nephrocalcinosis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Central venous catheter removal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Tracheostomy tube removal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Drug hypersensitivity	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Catheter site rash	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Injection site nodule	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Medical device complication	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lower respiratory tract infection	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Respiratory syncytial virus bronchiolitis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Tonsillitis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Tooth abscess	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Varicella	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Viral upper respiratory infection	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Injection site induration	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Injection site warmth	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Bursitis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Metatarsalgia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	ENB-002-08/ENB-003-08 (n = 11)		ENB-010-10 (n = 69)		ENB-006-09/ENB-008-10 (n = 13)		ENB-009-10 (n = 19)	
	Events, n	Patients, n (%)	Events, n	Patients, n (%)	Events, n	Patients, n (%)	Events, n	Patients, n (%)
Muscle spasms	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Tendonitis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dyspepsia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hypoaesthesia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vitreous detachment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gastroenteritis viral	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Arthropod bite	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Excoriation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Muscular weakness	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Neck pain	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Oral pain	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Toothache	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Rhinorrhoea	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Acne	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ingrowing nail	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anxiety	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dermatitis diaper	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Blood 25-hydroxycholecalciferol decreased	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Bronchitis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	ENB-002-08/ENB-003-08 (n = 11)		ENB-010-10 (n = 69)		ENB-006-09/ENB-008-10 (n = 13)		ENB-009-10 (n = 19)	
	Events, n	Patients, n (%)	Events, n	Patients, n (%)	Events, n	Patients, n (%)	Events, n	Patients, n (%)
Gastroesophageal reflux disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Eczema	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dyspnoea	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dry skin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Urinary tract infection	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Medical device pain	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Arthritis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Chondrocalcinosis pyrophosphate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Joint range of motion decreased	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Musculoskeletal chest pain	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Musculoskeletal stiffness	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nodule on extremity	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ankle fracture	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Tooth fracture	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Post procedural swelling	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Abdominal pain upper	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Loose tooth	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Tooth infection	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Migraine	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dermal cyst	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	ENB-002-08/ENB-003-08 (n = 11)		ENB-010-10 (n = 69)		ENB-006-09/ENB-008-10 (n = 13)		ENB-009-10 (n = 19)	
	Events, n	Patients, n (%)	Events, n	Patients, n (%)	Events, n	Patients, n (%)	Events, n	Patients, n (%)
Skin lesion	[redacted]							
Lacrimation increased	[redacted]							
Optic atrophy	[redacted]							
Alanine aminotransferase increased	[redacted]							
Aspartate aminotransferase increased	[redacted]							
Blood parathyroid hormone increased	[redacted]							
Blood pressure increased	[redacted]							
Initial insomnia	[redacted]							
Breast calcifications	[redacted]							
Breast mass	[redacted]							
Dysmenorrhoea	[redacted]							
Ear discomfort	[redacted]							
Use of accessory respiratory muscles	[redacted]							
Atelectasis	[redacted]							
Abdominal pain	[redacted]							

Key: AA, asfotase alfa; TEAE, treatment-emergent adverse event.
Source: ENB-002-08/ENB-003-08 Final CSR. 2017[4]; Whyte at al. 2018[5]; ENB-010-10 Final CSR. 2017[6]; Hofmann et al. 2019[7]; ENB-006-09/ENB-008-10 Final CSR. 2017[8]; Whyte et al. 2017[9]; ENB-009-10 Final CSR. 2017[10]; Kishnani et al. 2019.[11]

Table 12 provides an overview of the targeted events occurring in > 2% of patients in the Global HPP Registry.

Table 12: Summary of targeted event in Global HPP Registry – >10%

	Total (n = 364)		< 18 years at baseline (n = 199)		≥ 18 years at baseline (n = 165)	
	n (%)	Events, n	n (%)	Events, n	n (%)	Events, n
Targeted events or SAEs reported	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Injection site reaction	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Key: AA, asfotase alfa; AE, adverse event; ALP, alkaline phosphatase; CSF, cerebrospinal fluid; HPP, hypophosphatasia; SAE, serious adverse event.
Note: This table includes 19 patients without confirmation of HPP from genetic testing or ALP levels. Patients with a missing treatment start date are excluded from the table as it cannot be determined if the event occurred before or after treatment start. Adverse events that occurred before the start of treatment are excluded from the analysis. [a], n patients includes 2 patients without confirmation of HPP from genetic testing or ALP levels.
Source: ALX-HPP-501 study report 2021.[12]

No additional data are available for the real-world EmPATHY study or the longitudinal telephone-based survey than what are presented in the submission dossier.[13, 14]

c) Number of TEAE leading to discontinuation

[redacted] participants in the UK MAA discontinued AA due to a TEAE.[3]

Table 14 provides a summary of the TEAEs leading to discontinuations in the AA clinical trials.

Table 13: TEAEs leading to discontinuations across studies AA clinical trials

	ENB-002-08/ENB-003-08 (n = 11)		ENB-010-10 (n = 69)		ENB-006-09/ENB-008-10 (n = 13)		ENB-009-10 (n = 19)	
	Events, n	Patients, n (%)	Events, n	Patients, n (%)	Events, n	Patients, n (%)	Events, n	Patients, n (%)
TEAEs leading to discontinuation	[redacted]	[redacted]	[redacted]	[redacted]	0	0 (0.0)	[redacted]	[redacted]

	ENB-002-08/ENB-003-08 (n = 11)		ENB-010-10 (n = 69)		ENB-006-09/ENB-008-10 (n = 13)		ENB-009-10 (n = 19)	
	Events, n	**Patients, n (%)**	**Events, n**	**Patients, n (%)**	**Events, n**	**Patients, n (%)**	**Events, n**	**Patients, n (%)**
Serious TEAEs leading to discontinuation	2	2 (18.2)	[redacted]	[redacted]	0	0 (0.0)	[redacted]	[redacted]

Key: AA, asfotase alfa; TEAE, treatment-emergent adverse event.
Source: ENB-002-08/ENB-003-08 Final CSR. 2017[4]; Whyte at al. 2018[5]; ENB-010-10 Final CSR. 2017[6]; Hofmann et al. 2019[7]; ENB-006-09/ENB-008-10 Final CSR. 2017[8]; Whyte et al. 2017[9]; ENB-009-10 Final CSR. 2017[10]; Kishnani et al. 2019.[11]

[redacted] participants in the global HPP Registry discontinued AA due to a TEAE.[12]

No additional data are available for the real-world EmPATHY study or the longitudinal telephone-based survey than what are presented in the submission dossier.[13, 14]

d) Number of TEAE leading to death

[redacted] participants in the UK MAA died due to a TEAE.[3]

Table 14 provides a summary of the TEAEs leading to death in the studies AA clinical trials.

Table 14: TEAEs leading to death across studies AA clinical trials

	ENB-002-08/ENB-003-08 (n = 11)	ENB-010-10 (n = 69)	ENB-006-09/ENB-008-10 (n = 13)	ENB-009-10 (n = 19)
Number of TEAEs leading to death, n (%)	1 (9.1)	9 (13.0)	0 (0.0)	[redacted]

Key: AA, asfotase alfa; TEAE, treatment-emergent adverse event.
Source: ENB-002-08/ENB-003-08 Final CSR. 2017[4]; Whyte at al. 2018[5]; ENB-010-10 Final CSR. 2017[6]; Hofmann et al. 2019[7]; ENB-006-09/ENB-008-10 Final CSR. 2017[8]; Whyte et al. 2017[9]; ENB-009-10 Final CSR. 2017[10]; Kishnani et al. 2019.[11]

A total of [redacted] deaths were reported in ever-treated patients < 18 years in the Global HPP Registry.[12] However, only [redacted] deaths had a confirmed date of death available, all [redacted] patients died due to TEAEs.

No additional data are available for the real-world EmPATHY study or the longitudinal telephone-based survey than what are presented in the submission dossier.[13, 14]

Indirect treatment comparison (ITC)

A 20. Priority question. In Section B.2.8.1, for the pooled efficacy analysis, the only mention of a comparative analysis relates to overall survival (OS) and event-free survival (EFS).

> **a) Please conduct analyses comparing AA with BSC (using natural history control data) for all outcomes mentioned in the scope, including adverse effects. Please include all study data relevant to the decision problem population, as reported in Table 1 or excluding juvenile-onset HPP if amended in response to question 3b. Please ensure that these analyses include data from the UK MAA and from the wider Global HPP Registry (ALX-HPP-501), as well as all other relevant AA treated and natural history data sources.**
>
> **b) Please conduct all of these analyses using appropriate methods for adjusting for potential confounders according to the methods described in NICE TSD 17 (National Institute for Health and Care Excellence. Decision Support Unit. Utilities TSD series. Available from: http://nicedsu.org.uk/technical-support-documents/utilities-tsd-series).**
>
> **c) Please conduct subgroup analyses for all outcomes comparing AA to BSC according to age of onset category i.e. at least to match the subgroups in the cost effectiveness section i.e. perinatal/infantile and juvenile, using the most appropriate evidence from all studies for each subgroup.**

RESPONSE to parts a to c:

Disease onset age can be a proxy for disease severity, however, as HPP is multisystemic heterogenous disease, it can affect patients to different extents

throughout their lifetime. The age of onset of symptoms is a predictor of disease severity, but HPP is multisystemic heterogenous disease that can affect patients to different extents throughout their lifetime. Therefore, grouping patients by age of disease onset, would result in highly variable groups in terms of symptoms severity and affected QoL. As such, the age of the patient at the point of treatment initiation is more important (with the exception of perinatal/infantile-onset cases with high mortality risk), as it reflects the current state of the disease and can result in a group of patients with similar baseline characteristics that make assessment of efficacy and safety of AA more reliable and less biased. This rationale was applied when the AA clinical trials were designed.

Regarding the comparison with BSC, it would be challenging to find (from natural history studies) a matching BSC population of HPP patients, as severely affected patients have been included in the AA clinical trials and the UK MAA, and it would be challenging to find similar patients who are untreated. Where possible, the Alexion clinical trials have included a comparison with BSC for the primary endpoint and a pooled analysis of perinatal/infantile AA treated patients compared with BSC historical controls is included in the submission.[1] Furthermore, the available natural history studies do not contain data for all relevant endpoints, so a comparison on all endpoints would not be possible.

Moreover, even if it were possible to find matching BSC patients, this would require re-writing the ESAP for our AA clinical trials and the UK MAA which, would need at least 6-12 months-worth of delay to materialise; this is not feasible in the time available.

Section B: Clarification on cost-effectiveness data

Model structure

B1. Priority question: Please answer the following questions about the structure of the economic model.

> **Please explain exactly how the model that was submitted as part of the initial highly specialised technology (HST) submission has been updated for the current analysis.**

The differences between the original HST6 submission to NICE and the current model are highlighted in Appendix N (Table 104). This table is provided again below, with further clarifications.

Table 7: Cost-effectiveness model updates since HST6 submission to NICE

Setting/input	Original NICE HST submission	Current model	Rationale
Type of economic evaluation	Cost–consequence analysis	Cost–utility analysis	This is in line with the latest NICE highly specialised technology guidance, which states that results should be expressed as an incremental cost per QALY gained.
Base case population	Average age of all trial patients (age 5.8)	The current model presents results for the 2 populations (perinatal-/infantile-onset and juvenile-onset HPP) separately.	This change allows for more accurate modelling of costs and outcomes in the 2 patient populations.
Discount rate	Discount rate of 1.5% applied to both costs and outcomes.	Discount rate of 3.5% applied to both costs and outcomes.	In line with NICE reference case, 1.5% was explored in a scenario analysis.
Estimation of transition probabilities between severity levels	Transition probabilities were estimated using 2 separate probit regression models; 1 for BSC and 1 for AA. This was based on the ENB-006-09, ENB-008-10, ENB-009-10 and ENB-009-10 trials.	The same probit regression models were used, but were updated to include 6MWT data from the UK MAA.	Incorporating new data available from the UK MAA makes the model more tailored to the UK population.
Costs associated with AA	No discontinuation applied.	Discontinuation is applied in the model to account for patients that may stop treatment.	Data from the clinical trials, UK MAA and global registry showed that some patients discontinue treatment.
	No efforts to reduce wastage were considered in the model.	Rounding down of doses was considered in the model (at a cap of 12 mg per week) to reflect efforts to reduce wastage in clinical practice.	Clinicians stated that they would reduce the dose by a low amount (approximately no more than 3–4 mg per administration) to avoid another vial being opened.
	Compliance was not modelled and therefore assumed to be 100%.	Compliance was incorporated in the model to account for patients skipping doses.	The UK MAA showed that in some instances, patients would skip a dose, and clinicians stated that the compliance rate used in the model was reflective of clinical practice.

Setting/input	Original NICE HST submission	Current model	Rationale
	Combinations of vials were not considered when calculating the dosing regimen.	Different vial combinations were used to achieve recommended weekly dosing.	To achieve the recommended weekly dose, clinicians said that combinations of vials may be administered to avoid high drug wastage.
Sampling of parameters	Probit regression parameters were sampled independently in the PSA (using the normal distribution).	Probit regression parameters were sampled using the multivariate normal distribution.	This ensured that the relationship between the coefficients was maintained in every iteration of the PSA.
	Overall survival data was not varied in the PSA.	Hazard ratios were applied using a calibration method to vary the Kaplan–Meier estimates in the PSA.	This ensured that the uncertainty associated with survival was captured.
Further clarifications in response to B1:			
Model structure	All patients are modelled according to severity level (I, II, III, or IV) of disease, requiring extrapolation of pp6MWT to ages <5. Invasive ventilator was included as a toll state.	Patients aged < 5 years are modelled according to their ventilation status, whereas patients aged 5+ years are modelled according to severity level of disease.	To account for the differences in HPP disease manifestations and effects of AA treatment for patients under 5 years old and patients over 5 years old. This addresses the ERG's main structural concern with the original NICE submission.
Background mortality	ONS life tables for the UK (2010-2012 dataset).	ONS life tables for the UK and weighted by patient sex (2018-2020 dataset).	Updated using most recently available data.
HPP mortality	AA: Kaplan–Meier curves were estimated using the ENB-002-08 and ENB-010-10 trials.	AA: Kaplan–Meier curves were estimated using the ENB-002-08, ENB-010-10, and ENB-011-10 studies, as well as the UK MAA.	Including new data available from the UK MAA increases the sample size for the AA arm and makes the model more tailored to the UK population.

Setting/input	Original NICE HST submission	Current model	Rationale
	BSC: patients who died on the first day were included in the analysis.	BSC: patients who died on the first day were excluded from the analysis as it was considered likely that these patients would not be started on AA treatment.	Aligns with ERG preferences in the original NICE submission.
	Predicted HPP mortality sensitivity analysis in the AA arm using a Weibull distribution.	No parametric survival modelling was conducted for HPP mortality, as death occurs in the model as it is observed in the data for each age.	The NICE Decision Support Unit (DSU) Technical Support Document (TSD) 14 states that extrapolation is required if clinical trial data are incomplete.[18] HPP mortality was only applied for the first 5 years in the model and the trial data were mature for a greater duration than was required (i.e. a 7-year follow-up), therefore extrapolation was not required.
Transitions to invasive ventilation	The age- and cycle-specific likelihood of invasive ventilation used Kaplan-Meier data for historical control patients in ENB-011-10, and comparable AA patients from ENB-002-08/ENB-003-08 and ENB-010-10 meeting the inclusion criteria for ENB-011-10.	Whyte et al. (2014) [19] reported on clinical studies ENB-002-08/ENB-003-08, ENB-010-10, and ENB-011-10. Invasive VFS was modelled using rates per Whyte et al. (2014) converted for 12-week cycles. The rates were converted to probabilities and applied to all patients in each treatment arm from age 0 to 5.	Given the need for invasive ventilation is not consistent over time and patients may start and stop, a constant rate (converted to a probability) has been used and applied to each cycle to allow patients to start and stop receiving invasive ventilation. No evidence of invasive ventilation after age 5 was collected in the clinical studies.
General population quality of life	No adjustments were applied to utilities based on the general population.	Age-adjusted general population utilities for the UK were applied in the model for patients aged 18 years and over.	To ensure utility decreases in line (relatively) with general population utility.

Setting/input	Original NICE HST submission	Current model	Rationale
Caregiver quality of life	Caregiver QoL burden associated with each health state is not included in the model.	Per cycle utility decrements associated with caregiver quality of life are applied for patients in the invasive ventilation and without invasive ventilation (age <5 years) and SII-SLIV health states.	The symptoms of HPP and necessary accommodations are likely to have an impact on HRQL. Studies in similar disease areas have shown that disease severity can directly affect carers' QoL. Clinicians agreed HPP impacts carer QoL.
	Impact of infant death on caregiver QoL is not included in the model.	Per cycle utility decrements are applied for 2 caregivers from their infant's death for 54.54 years from baseline age.	Song et al. 2010[20] showed that parents experience an ongoing utility decrement following an infant's death. This same decrement was applied and accepted by NICE in the 2018 evaluation of Strimvelis (NICE HST7).[21]
Costs associated with AA	Assume that 10 years from the start of the model, loss of data exclusivity leads to a 30% decrease in asfotase alfa's list price.	The AA patent is due to expire in 2030. Therefore, the model base case assumes that after 7 years from the start of the model, loss of data exclusivity leads to a 58.5% decrease in the AA list price.	NICE has stated that 'biosimilars have the potential to offer the NHS considerable cost savings, especially as they are often used to treat long-term conditions'.[22] Recent reports of prices for biosimilar infliximab have suggested price reductions of 45–72% versus the originator product therefore the mid-point of a 58.5% price reduction is modelled.
	The required AA dose was calculated using the average weight of patients from the clinical trials (ENB-002-08/ENB-003-08, ENB-006-09/ENB-008-10, ENB-009-10, ENB-010-10).	The required AA dose was calculated using the average weight of patients from ENB-002-08/ENB-003-08, ENB-006-09/ENB-008-10, ENB-009-10, ENB-010-10 and the MAA UK study.	Including new data available from the UK MAA increases the sample size and makes the model more tailored to the UK population.

Setting/input	Original NICE HST submission	Current model	Rationale
Health state resource use	Resource use was elicited from clinical experts by Alexion in 2015.	Original estimates were further validated by 2 clinicians in 2022. Addition of mental health services, additional pain management and dietician services, as well as minor changes to frequencies recommended by the clinicians.	The clinical experts suggested that clinical practice has remained relatively unchanged since 2016, and therefore resource use estimates should still be reflective of current practice.
	Costs from 2013-2014 price year.	Most recently available costs (2019-2020) were used and were inflated using the NHS Cost Inflation Index from the 2021 Personal Social Services Research Unit.	To most accurately reflect the cost of resource use.
Societal costs	Societal costs were not considered in the model.	Societal costs are included in the model as a scenario analysis. Productivity loss is estimated for 1 caregiver when patients are aged 1–17 years, and for the patient when they are aged 18–65 years.	To capture the financial burden faced by parents/caregivers and patients.

Key: AA, asfotase alfa; BSC, best supportive care; ERG, Evidence Review Group; HRQL, health-related quality of life; HPP, hypophosphatasia; HST, highly specialised technology; MAA, managed access agreement; NICE, National Institute for Health and Care Excellence; ONS, Office for National Statistics; PSA, probabilistic sensitivity analysis; QALYs, quality-adjusted life years; QoL, quality of life; SL, severity level; VFS, ventilation-free survival.

b) Please explain how the feedback collected during the original NICE HST6 submission and from other health technology assement (HTA) bodies have been incorporated into the updated model used in this submission.

The feedback collected during the original NICE HST6 submission was incorporated throughout the model. Please refer to B1a for details of these changes.

c) Please clarify how many parameters are age-dependent.

As the model structure is dependent on age of the patients, a large number of parameters are age-dependent. The parameters dependent on age are provided in the Table 8 below.

Some parameters are listed in aggregate, such as ‘resource use’ due to the extensive number of inputs. These inputs are referenced from the CS. Where parameters are extendedly dependent on age, this is noted in the second column. For example, ‘Disutility of caregiver - Age 5-12 – SLII’ is calculated using utilities, which are dependent upon age.

Table 8: Model parameters dependent on age

Parameter	Dependent on
Baseline distribution across health states	Baseline age
Utility - Age < 5 - no invasive ventilation	Age
Utility - Age < 5 - with invasive ventilation	Age
Utility - Age 5-12 – SLI	Age
Utility - Age 5-12 – SLII	Age
Utility - Age 5-12 – SLIII	Age
Utility - Age 5-12 – SLIV	Age
Utility - Age 13-17 – SLI	Age
Utility - Age 13-17 – SLII	Age
Utility - Age 13-17 – SLIII	Age
Utility - Age 13-17 – SLIV	Age
Utility - Age 18+ - SLI	Age
Utility - Age 18+ - SLII	Age
Utility - Age 18+ - SLIII	Age
Utility - Age 18+ - SLIV	Age
Disutility of caregiver – Age < 5 years – no invasive ventilation	Utility, Age
Disutility of caregiver – Age < 5 years – invasive ventilation	Utility, Age
Disutility of caregiver - Age 5-12 – SLI	Utility, Age
Disutility of caregiver - Age 5-12 – SLII	Utility, Age
Disutility of caregiver - Age 5-12 – SLIII	Utility, Age
Disutility of caregiver - Age 5-12 – SLIV	Utility, Age
Disutility of caregiver - Age 13-17 – SLI	Utility, Age
Disutility of caregiver - Age 13-17 – SLII	Utility, Age
Disutility of caregiver - Age 13-17 – SLIII	Utility, Age
Disutility of caregiver - Age 13-17 – SLIV	Utility, Age
Disutility of caregiver - Age 18+ - SLI	Utility, Age
Disutility of caregiver - Age 18+ - SLII	Utility, Age
Disutility of caregiver - Age 18+ - SLIII	Utility, Age
Disutility of caregiver - Age 18+ - SLIV	Utility, Age
Duration of caregiver burden from infant death	Baseline age
Age adjusted utility decrement	Age
Weight (for ages 0-4)	Age
Weight (for ages 5-18+)	Age
Resource use (CS Table 61)	Age
Drug costs	Age, Weight

Productivity loss – Age 2-17 – Caregiver	Utility, Age
Productivity loss – Age 18+ – Patient (age<=65)	Utility, Age
AA – ordinal probit coefficient – visit_age	Age
AA – ordinal probit coefficient - AgeXSLII_lag	Age
AA – ordinal probit coefficient - AgeXSLIII_lag	Age
AA – ordinal probit coefficient - AgeXSLIIV_lag	Age
BSC – ordinal probit coefficient – visit_age	Age
BSC – ordinal probit coefficient - AgeXSLII_lag	Age
BSC – ordinal probit coefficient - AgeXSLIII_lag	Age
BSC – ordinal probit coefficient - AgeXSLIIV_lag	Age
Key: AA, asfotase alfa; BSC, best supportive care; CS, company submission; SL, severity level.	

d) Please explain the rationale behind the assumption that all alive patients move to SLIV health state even when they were not on invasive ventilation.

In the base case, all patients move to SLIV health state when they reach 5 years of age to reflect the severity of disease associated with perinatal-/infantile-onset HPP. As described in the CS Section B.1.3.3, perinatal-/infantile-onset HPP is the most severe form of HPP. Life with perinatal- or infantile-onset HPP is generally characterised by symptoms that lead to frequent and prolonged hospitalisation in intensive care units (ICUs).

Clinical experts were consulted during submission development to discuss the plausibility and face validity of the modelling assumptions. A UK paediatric clinician, drawing on their own experience, explained that a patient with perinatal-onset HPP could be on invasive ventilation within one to two years, and subsequently go to SLIV at the age of 5 years old. Infantile-onset patients may be in either invasive ventilation health and would also enter SLIV at the age of 5 years old. Therefore, the assumption that patients in the perinatal-/infantile-onset population enter SLIV at age 5 is clinically valid.

B2. Priority question: Please answer the following questions regarding the data sources used to inform the economic model.

a) **Please clarify (e.g., in a table format) what data sources were used to inform what type of parameters (and why). For example, as explained Section A, it was expected that data from the UK MAA and AA-treated patients from the wider Global HPP Registry (ALX-HPP-501) would be used for all parameters in the model whenever possible, but these data were not used for example to estimate invasive ventilation probabilities.**

Table 9 outlines the parameters and data sources that were used in the model. As explained in the response to question A7a, the Global HPP Registry was not used to inform the BSC arm as data from the Global HPP Registry are limited and are not comparable with the AA clinical trials. In addition, the Global HPP Registry is an observational study and patients that are enrolled in the Global HPP Registry are not mandated to any schedule of clinical assessments, therefore it was not included in the clinical effectiveness data feeding into the model. The input relating to discontinuation utilised the Global HPP Registry as this data is easily collected and reported within observational studies.

Table 9: Summary of sources to inform key parameters and rationale

Variable	Data source	Rationale
Age at baseline (patients with perinatal-/infantile-onset HPP)	Whyte et al. 2016[1]	Includes relevant clinical data and was considered reasonable by clinicians
Age at baseline (patients with juvenile-onset HPP)	Whyte et a. 2016[23]	
Baseline severity distribution	SL distribution among the ENB-006-09 and ENB-009-10 and MAA UK study (ages 5-17)	From clinical trial data that included baseline severity according to 6MWT. In addition, incorporating new data available from the UK MAA makes the model more tailored to the UK population
Utility values	Lloyd et al. 2015[24]	Given the limitations associated with the UK MAA and Registry study (CS Sections B.3.4.1.1 and B.3.4.1.2), clinicians agreed that the utilities derived during the expert elicitation exercise were more reflective of the QoL experienced by patients and were used in the base-case analysis.
Infant death disutility	Song et al. 2010[20]	Precedence set by 2018 evaluation of Strimvelis® (NICE HST7)[21]
Caregiver disutility	Landfeldt et al. 2016[25]	Given the lack of available data in HPP, DMD was used as a proxy and was considered reasonable by clinicians
General population utility regression	Ara and Brazier 2010[26]	Based on NICE guidance on adjusting utilities for age
Weight	ENB-002-08/ENB-003-08, ENB-006-09/ENB-008-10, ENB-009-10, ENB-010-10 and the MAA UK study.	Use of relevant AA studies, in order to reflect demographics of patients that would be receiving AA
Resource use (frequency)	Elicited from UK clinicians that treat patients with HPP	Due to lack of available data in HPP, clinical expert opinion was used

Discontinuation	ENB-010-10, ENB-006-09, ENB-008-10, MAA UK study and Global Registry	Taken from studies that reported discontinuations and number of exposure days. The Global Registry was included given that the other studies had low number of patients and therefore low rates of discontinuation. The discontinuation rate was validated with clinicians and they stated it was reflective of real world practice
Compliance rate	UK MAA data	Only available source of compliance data. Specific to UK population
12-week risk of ventilation (for ages 0–4, inclusive)	Whyte et al. (2014) - reported on clinical studies ENB-002-08/ENB-003-08, ENB-010-10, and ENB-011-10.	Use of interventional clinical studies for AA and historical control study for BSC, that reported on invasive ventilation. UK MAA data was used in scenario.
Ordinal probit coefficients	ENB-006-09, ENB-008-10, ENB-009-10 and ENB-009-10 trials and UK MAA data.	Use of existing trials that has data available on 6MWT performance. Incorporating new data available from the UK MAA makes the model more tailored to the UK population
Overall survival for BSC	ENB-002-08, ENB-010-10, and ENB-011-10 studies and UK MAA.	Use of studies reporting overall survival for patients receiving AA. Including new data available from the UK MAA increases the sample size for the AA arm and makes the model more tailored to the UK population.
Overall survival for BSC	ENB-011-10 study	Historical control study that reports overall survival for BSC, in line with patients that would be expected to receive AA.
Background mortality	UK life tables from ONS	Best source of available data for general population mortality
Key: AA, asfotase alfa; BSC, best supportive care; DMD, Duchenne muscular dystrophy; HPP, hypophosphatasia; MAA, Managed access agreement; ONS, Office for National Statistics.		

b) In the CS (page 45) it is stated that the Global HPP registry (ALX-HPP-502) was not used in the economic model because the ENB-011-10 provided historical control data for a larger group of patients (n=48). A major limitation of this analysis, as also recognised by the company in Section B.3.6., is the low number of patients in the BSC arm of the HPP trials. As also explained in priority question A7, the MAA states that the global HPP registry should be used to collect data for BSC too. It is not clear to the evidence assessment group (EAG) why the patients from the Global HPP registry are not used to inform inputs in the BSC arm of the model. Please use the Global HPP registry dataset to inform inputs for the BSC arm.

Data from the Global HPP Registry are limited and are not comparable with the AA clinical trials and have not been used as a source of data for the BSC arm. Reasoning has been provided in the response to question A7a.

Population and subgroups

B3. Priority question: Please explain whether the patient characteristics included in the model are representative for the UK patient population.

UK MAA and clinical trial data was used to inform the patient characteristics in the model for the perinatal-/infantile-onset and juvenile-onset patient groups. It is acknowledged that the AA clinical trial programme included limited numbers of UK patients. However, the disease pathophysiology and clinical progression are common among all patients with HPP. Therefore, patient characteristics between UK patients and those in the trials are expected to be consistent. This assumption is further validated as the AA clinical trials included a broad range of patients with HPP who had similar baseline characteristics to patients who were included in the UK MAA. Therefore, the AA clinical trials are considered representative of the general population of patients in England (see Appendix M.1) that can benefit from AA treatment.

Mortality

B4. Priority question: Please provide details of:

How mortality data for AA were pooled.

As described in the company submission, HPP-related mortality is modelled for ages < 5 years. For AA, data were sourced for the N=37 patients from the pivotal publication of the perinatal-/infantile-onset clinical trials (see Whyte et al. 2016). Further, data for N=43 AA-treated patients from trial ENB-010-10 and 11 patients from the UK MAA were added, yielding a total sample of N=91 AA-treated patients.

The source for mortality data for BSC.

For BSC, data were sourced from the N=48 historical-control population included in the pivotal publication of the perinatal-/infantile-onset clinical trials (see Whyte et al. 2016). To align with the ERG's preferences from the original NICE submission, in the base case patients who died on the first day were excluded from the analysis as it was considered likely that these patients would not be started on AA treatment. This resulted in a total of 41 patients being included in the BSC arm, instead of 48.

Any pooling of mortality data for BSC.

No pooling was performed for the BSC mortality data.

Table 38, 39 and Figure 35. Please show complete tables and numbers at risk for the OS curves. The curves seem quite flat since well before 5 years; please discuss this.

As reflected in the figure requested (see below), both curves reflect greatest hazard in the early stages, before beginning to plateau between 50-100 weeks of age. At 75 weeks of age, [redacted]) of AA patients remain at risk, while only ~35% (15 / 41) BSC patients remain at risk. This suggests that the plateauing of the curves is driven more by stability of the survival estimate (vs. limited at-risk sample) for the AA vs. BSC curve.

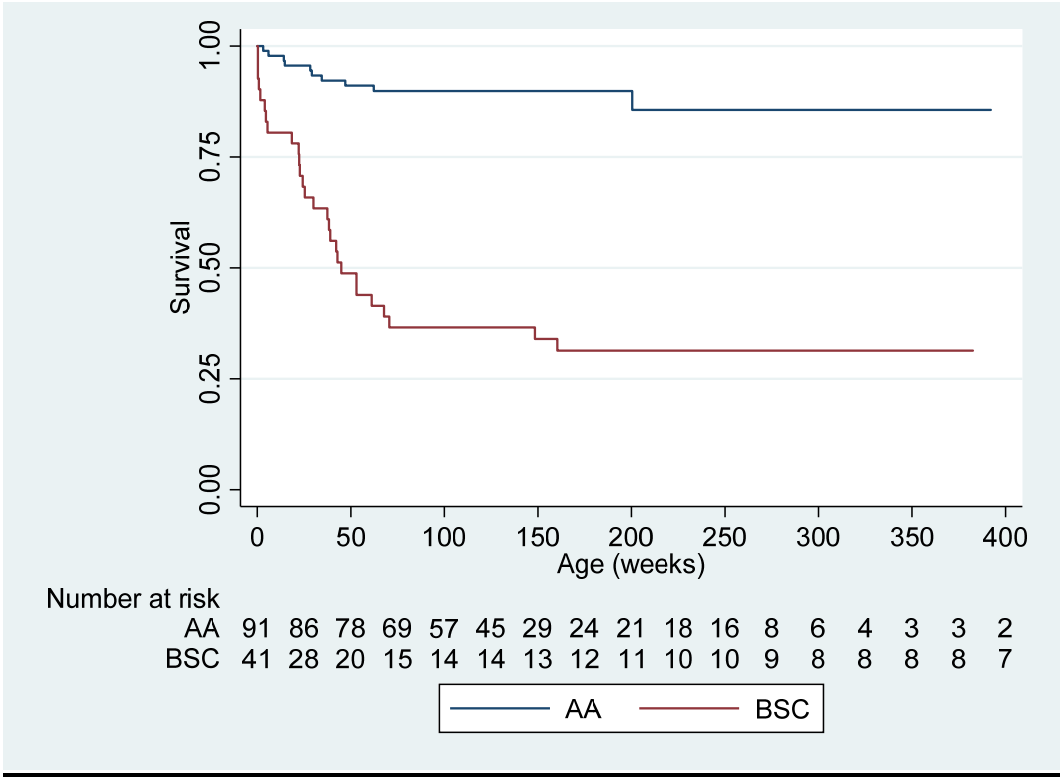


Table 38 (Section B.3.3.1.1.1 in the CS) provides data on HPP mortality risk for AA-treated patients as a function of actual age. To be able to distinguish the impact of AA treatment, please provide the HPP mortality (as provided in Table 38) for AA from treatment initiation instead of from birth.

The model incorporates overall survival from age 0, which allows for a comparison of AA and BSC mortality from the same timepoint. The index timepoint must be aligned across treatments to make a reasonable comparison, given AA and BSC are not directly compared in a randomised control study and BSC patients by definition do not have a treatment initiation time, it is not possible to make this comparison plausibly using time from treatment initiation. Comparing AA from treatment initiation to BSC from birth would result in bias since inevitably AA patients begin treatment at an age greater than 0. Nonetheless, the onset of HPP symptoms was close to birth for all patients, with the average age of HPP onset for patients included from the ENB-010-10 trial and Whyte et al. 2016 publication at 1 month, and for the MAA the median age of onset was 0 years. On average, patients started treatment at approximately 1 year of age across all studies. Given the above presenting data from treatment initiation was considered inappropriate.

Please confirm that the most recent background mortality for the UK was used in the model.

We can confirm that the most recent background mortality data for the UK was used the model, this was taken from the Office for National Statistics and the data for 2018-2020 was used[27].

B5. Priority question: On page 181 of the CS it is stated that to capture the uncertainty within the OS data, the Kaplan–Meier (KM) curves are varied in the probabilistic sensitivity analysis (PSA) by applying a hazard ratio (HR) to the Kaplan–Meier estimates. Please provide further details on:

a) Whether there is one or two HR's and to what curve(s) it is applied.

Two separate HRs were applied, one for the AA OS curve and one for the BSC OS curve. These are named OS_HR_AA and OS_HR_BSC within the model. Please note that the HRs are only applied in order to allow the model to vary the OS data in the probabilistic sensitivity analysis. A value of 1 is applied for both HRs in the deterministic analysis (applying no variation to the curves).

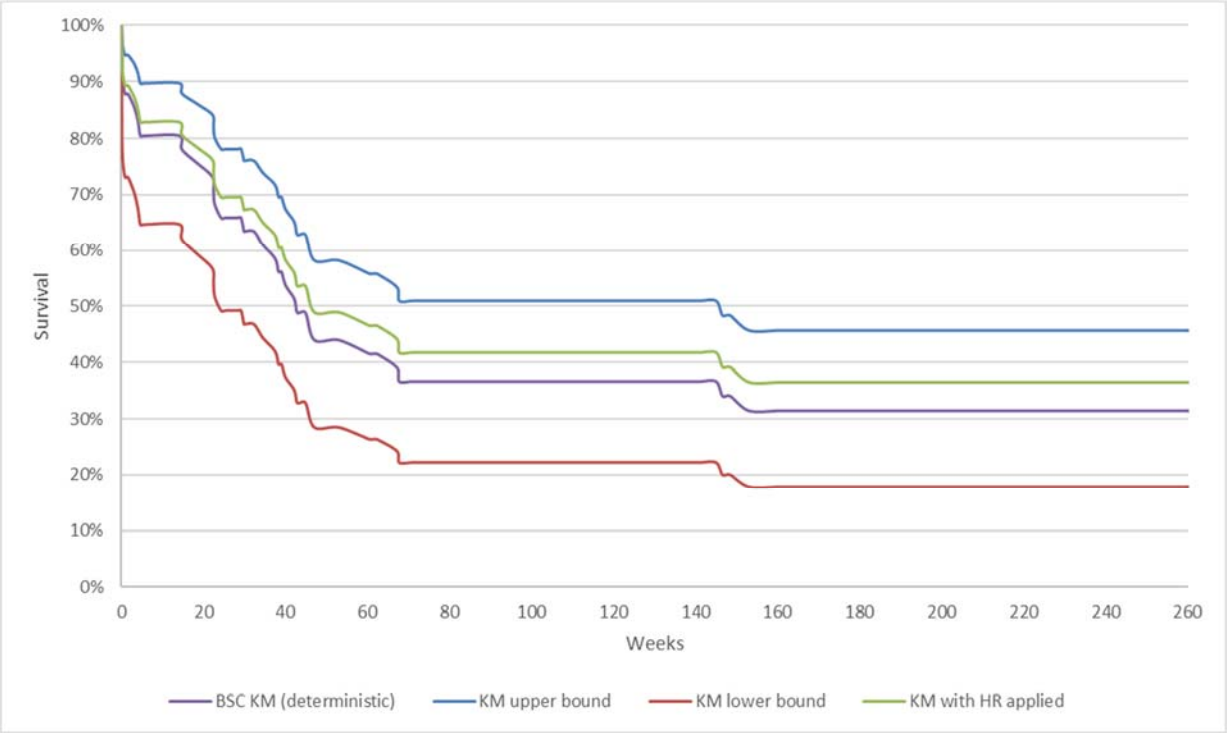
b) The methods used to estimate the HR's.

In the deterministic model both HRs are set to 1, applying no variation to either curve. The HRs are only varied during probabilistic sensitivity analysis according to the observed uncertainty around the Kaplan-Meier (KM) curves. This approach allows for exploration of plausible uncertainty around KM curves, without affecting the deterministic analysis.

In order to estimate the plausible distribution of HRs to apply within the probabilistic sensitivity analysis, the standard deviation of the KM curves was estimated using a calibration method using the Solver function in Microsoft Excel®. This method minimised the total sum of the squared differences between the upper and lower 95% CI values obtained from the statistical KM curve estimates, and those estimated with the calibrated standard deviation when applying a normal distribution centred around a value of 1 to the observed KM curve. I.e. the method sought to match the observed 95% CIs with those that would be created during probabilistic sensitivity analysis. It is acknowledged that the uncertainty around the KM is unlikely to be strictly normal, however this method gave a close approximation to the observed

95% CIs. The HRs are then varied in the probabilistic sensitivity analysis by applying this normal distribution with the calibrated standard deviation. The graph below shows the Kaplan-Meier curves for BSC, with the deterministic curve, upper and lower bounds according to the 95% CIs and an example of when the HR is applied during one of the PSA iterations.

Figure 3: BSC Kaplan-Meier curve with upper and lower bound and HR applied



Key: BSC, best supportive care; HR, hazard ratio; KM, Kaplan-Meier.

While there are different methods that can be employed to capture uncertainty around KM data in a probabilistic sensitivity analysis, this method allows uncertainty to be explored without creating implausible scenarios (as the entire curve is varied according to the HR) and without making the model excessively complex or slow.

c) The magnitude of the HR's.

The magnitude of the hazard ratios are presented in the table below.

Table 10: Magnitude of OS hazard ratios

Arm	Deterministic HR	Calibrated SD	95% CI LB HR	95% CI UB HR
BSC	1.00	0.190	0.627005	1.372995
AA	1.00	0.355	0.303296	1.696704
Key: AA, asfotase alfa, BSC, best supportive care; HR, hazard ratio; LB, lower bound; SD, standard deviation; UB, upper bound.				

d) How exactly the OS HR's were implemented in the PSA.

The HRs were implemented in the PSA by sampling a normal distribution centered around 1 using the calibrated standard deviation values for each curve. The sampled HRs were then applied to the instantaneous hazard from the deterministic S(t) at each cycle and then used to estimate the resulting sampled S(t).

e) In case of two HR's, please explain how these are correlated.

The two HRs are not correlated as they are estimated for the AA and BSC curves separately. It is acknowledged that there is likely to be a degree of correlation in the uncertainty of the AA and BSC curves, however this not being captured is not expected to affect the resulting mean values, the only expected impact is that the total uncertainty of the analysis is likely to be overestimated.

f) Please provide the 95% confidence intervals for the HRs.

The 95% confidence intervals for the HRs are presented in Table above.

B6. Priority question: On page 179 of the CS it is stated that as HPP mortality was only applied for the first 5 years in the model and that the trial data were mature for a greater duration than was required (i.e. a 7-year follow-up), extrapolation was not required. Please clarify if this applies to both AA and BSC arms, considering the multiple sources were used to inform HPP mortality for the AA treatment arm. Please indicate also if and how HPP mortality for the first 5 years in the model was included in the PSA (e.g., using the 95% confidence bands for the KM curves). If they are not, please include them in the PSA.

This was relevant for both AA and BSC. A maximum follow-up time of 7-years is available for the AA arm and for BSC the maximum follow-up time is 19 years.

The KM curves are included in the PSA, further details on how they are included is provided in the response to question B5.

Invasive ventilation health states

B7. Priority question: Please anwer the following questions regarding invasive ventilation.

a) Information about AA improvement in patients' ability to discontinue treatment from invasive ventilation does not seem to be consistent: in section B.3.3.1.2 of the CS it is mentioned that "75% of patients (12 out of 15) weaned from mechanical ventilatory support" and also that "for patients receiving AA aged 0–5 years, 84% (21 out of 25) survived free of invasive ventilation". Both estimates seem to be from Whyte et al., please clarify this discrepancy.

b) Please clarify what the baseline distribution of patients in IV health states is and the rationale for that assumption.

c) Invasive ventilator-free survival (IVFS) was modelled using the rates at 5 years for BSC and 1.8 years for AA as provided in Whyte et al. (2014) (Page 182 of the CS). As already discussed in question A.14, it is not clear why MAA data were not used to inform IVFS in both arms. Please clarify.

d) Furthermore, the company assumed constant rates (exponential distribution) for IVFS. Please explain why other distributions to fit IVFS data were not explored.

e) Please clarify what is assumed to happen in the AA arm after 1.8 years. For instance, is it assumed to apply the same rate up to year 5 or is it a rate equal to 0 asumed.

f) Please use patient level data to inform the time to event analysis for invasive ventilator (IV) use for both arms by each age of onset category and

incorporate this in the model. If necessary make use of parametric models for IVFS.

g) Please provide the KM curves including the at risk table for invasive ventilator-free survival for AA and BSC patients.

[Company: please enter your answer to this question here]

Severity health states

B8. Please discuss the clinical validity of the scenario which assumes no patients in the AA arm receive invasive ventilation (see Section B.3.3.1.2) and that 50% of perinatal-/infantile-onset patients receiving AA and surviving at age 5 enter the model in health state SLIII, with the remaining 50% entering health state SLIV. Also, for the scenario where a higher baseline age is modelled for patients with juvenile-onset HPP, the baseline distribution for all patients ages 5+ from the clinical trials and MAA is used. In this later scenario, please clarify whether or not a different subgroup is assessed. Please also explain what other parameters were changed besides age.

As mentioned in Section B.3.3.1.2, in the UK MAA [redacted] (see Section **Error! Reference source not found.**). A scenario analysis was therefore conducted where [redacted] of patients in the AA arm are expected to be invasive ventilation-free ([redacted] probability of invasive ventilation). As a consequence of [redacted] of patients being invasive-ventilation free, it was assumed that 50% of perinatal-/infantile-onset patients receiving AA and surviving at age 5 enter the model in health state SLIII, with the remaining 50% entering health state SLIV. This reflects the lower severity of disease associated with patients not requiring invasive ventilation. The assumption that 50% of perinatal-/infantile-onset AA patients enter SLIII and 50% enter SLIV was validated as a plausible scenario by a paediatric HPP clinician. In addition, this assumption was the base-case scenario in the original submission.

In the scenario where a higher baseline age is modelled for patients with juvenile-onset HPP, the baseline distribution for all patients ages 5+ from the clinical trials

and MAA is used, whereas the base case analysis used patients aged 5-17 years at baseline. The only parameters directly changed were baseline age and baseline health state distribution. The table below shows the difference between these two baseline distributions. Baseline age impacts various parameters throughout the model as discussed in question B1c.

Table 11: Patient group severity level distribution at baseline

Analysis	Age of patients used in analysis	Baseline health state distribution				
		SLI	SLII	SLIII	SLIV	Total
Base case (baseline age = 5.0)	5–17 years at baseline (n = 19)	2	5	8	4	19
		10.53%	26.32%	42.11%	21.05%	100.00%
Scenario analysis (baseline age = 26.5 years)	5+ years at baseline (n = 46)	5	7	14	20	46
		10.87%	15.22%	30.43%	43.48%	100.00%
Key: SL, severity level						

B9. Please provide the coefficients, standard errors (SEs) and P-values of two new multivariate ordered probit models including a treatment duration as covariate for AA/BSC (as shown in Table 46).

[Company: please enter your answer to this question here]

6MWT

B10. Please provide new versions of Tables 42 to 45 stratified per age group. To

[Company: please enter your answer to this question here]

B11. Please explain the impact of assuming "a value of 0 was assigned for percent of predicted values where the patient did not complete the 6MWT". Please clarify why these observations were not excluded from the analysis.

The impact of assigning a percent-of-predicted value of 0 to patients who could not complete the 6MWT is that their health state was considered to be SLIV at

assessments when they could not complete the 6MWT. This is due to the fact that 0% is lower than the SLIV percent-of-predicted threshold for all ages in the analysis (≤ 47.2% at ages 5–12 years, ≤ 47.8% at ages 13–17, and ≤ 52.0% at ages ≥ 18 years). Of note, this approach is consistent with the original analysis submitted to NICE, in which the ERG noted "Patients who could not complete the 6MWT were assumed to be in the most severe health state (i.e. SLIV)", and critiques of this approach were not made.

These observations were not excluded from the analysis as context for observations when the 6MWT was not completed supported that patients were unable to complete the assessment due to severity of their condition. Values of 0 were assigned for [redacted] patients from the clinical trials (ENB-006-09-01-02, ENB-009-10-01-06, ENB-009-10-01-09) and [redacted] patients from the UK MAA (0826-M10, 0940-M01). Available notes in the data supported modelled severity in these patients; for example:

ENB-009-10-01-06	"SEVERE PAIN IN HIPS, RIGHT SIDE WORSE THAN LEFT. LIMPING DURING WALK" "PAIN IN BOTH HIPS" "HIP JOINTS HAVE SIGNIFICANT PAIN, 'SEIZING UP'" "HIPS SEIZING WITH 2:41 LEFT, PACE SLOWED THEN STOPPED AT 2:08"
ENB-009-10-01-09	"AMBULATED LESS THAN 1 METER, SEE VIDEO TAPE. DOES NOT AMBULATE FUNCTIONALLY. SOMETIMES USES WALKER BUT DID NOT HAVE IT HERE WITH HIM." "WHEELED WALKER." "SAT DOWN ON FLOOR DUE TO FATIGUE AT 5:33 SECONDS. PAIN IN RIGHT SHIN, TIRED." "TIRED, PAIN TO INSIDE OF RIGHT ANKLE."
0826-M10	"Patient unwell, unable to walk"
0940-M01	"Patient was unsafe to walk"

B12. Priority question: Table 45 shows that the number of observed transitions for BSC is very limited. Table 44 for AA shows for example that all transitions are possible, which was not observed in BSC. Please include registriy data to re-estimate transition probabilities and add this option to the economic model (the user should be able to choose between different options). If some

transitions remain unobserved, please add +1 to all states and recalculate the transition probabilities. Please add this as an option in the model (again, the user should be able to choose between different options).

Limited 6MWT data were collected in the Global Registry, as described in response to question B16. Patients were monitored per clinicians standard of care, and this rarely included the 6MWT as it is a research based tool. Use of 6MWT data from the Global Registry was therefore not possible to supplement this analysis.

The tables referred to in this question are replicated below, for reference.

Table 44: Observed state transitions – AA

State at current visit State at prior visit	SLI	SLII	SLIII	SLIV	*Row total*
SLI	152	23	2	2	*179*
SLII	33	64	15	6	*118*
SLIII	3	27	34	7	*71*
SLIV	2	6	13	43	*64*
Column total	*190*	*120*	*64*	*58*	*432*

Key: AA, asfotase alfa; SL, severity level.

Table 45: Observed state transitions – BSC

State at current visit State at prior visit	SLI	SLII	SLIII	SLIV	*Row total*
SLI	5	3	0	0	*8*
SLII	2	5	3	0	*10*
SLIII	0	2	7	2	*11*
SLIV	0	0	0	3	*3*
Column total	*7*	*10*	*10*	*5*	*32*

Key: BSC, best supportive care; SL, severity level.

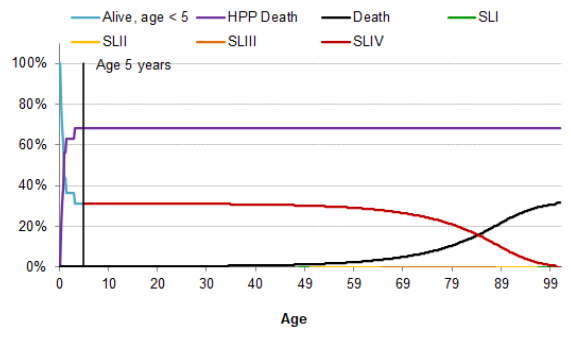
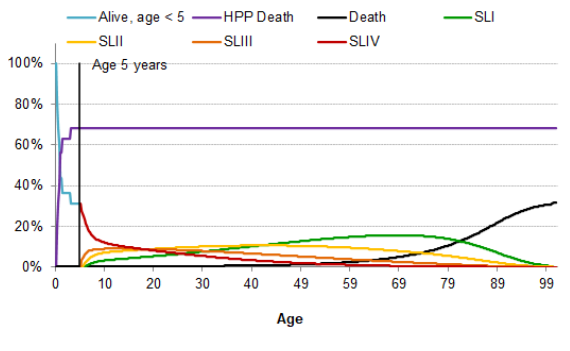
Without the addition of more data points, the recommendation to add +1 observations to all transitions that were unobserved is problematic due to the small sample size. For instance, only 3 observations were made for transitions from SLIV, all to SLIV in the following period. Addition of +1 observations to the SLIV->SLI,

SLIV->SLII, and SLIV->SLIII transitions would therefore equate to fabricating as many data points as were actually observed, and may introduce considerable bias. Whereas the observed data indicate no patient on BSC improved from SLIV to a less severe state, the recommended approach would indicate the probability of improvement from SLIV to a less severe state is equal to that of remaining in the state while on BSC.

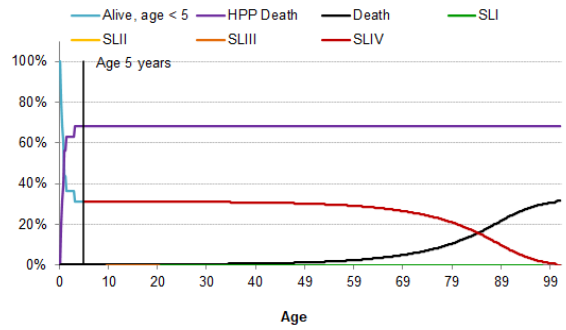
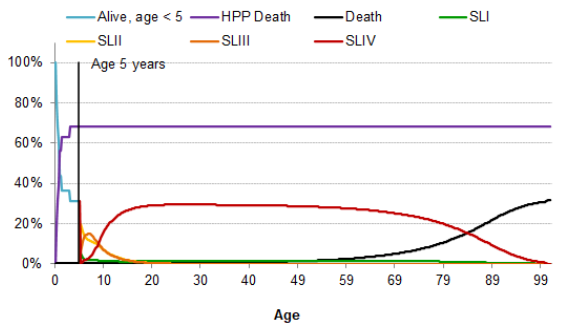
To explore this recommendation while avoiding the bias referenced above, we added +1 observations to all transitions that were unobserved, and frequency weighted transitions that were actually observed by a factor of 13, to approximate the number of transitions observed for AA (i.e., 432 / 32 = 13.5). In particular, this required addition of transitions from SLI-SLIII, SLI->SLIV, SLIV->SLI, SLIV->SLII, and SLIV->SLIII. As the regressions require patient age and time between visits, the mean age of BSC patients at first visit (5 years, per the baseline age of juvenile-onset patients) and 12 weeks (the model's cycle length, and time between 6MWT assessments in the clinical studies) were specified. Resulting ordered-probit results for model specifications MS2 and MS3 for BSC are presented below, alongside the original results modelled in the CUA.

Below, base-case Markov traces are compared between the original analysis (left) and this scenario analysis (right).

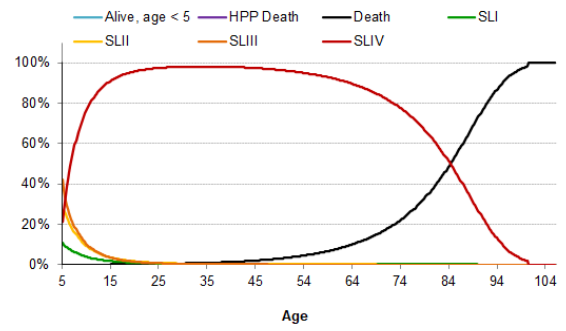
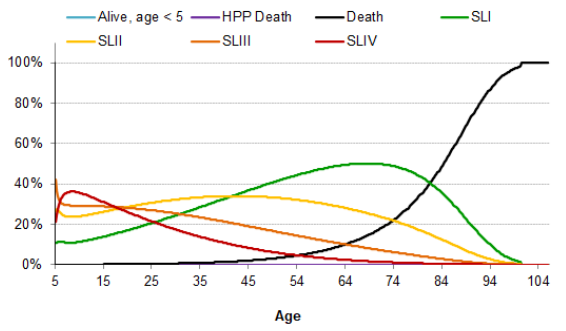
Perinatal/infantile onset population, MS2

Original results	Scenario results
	

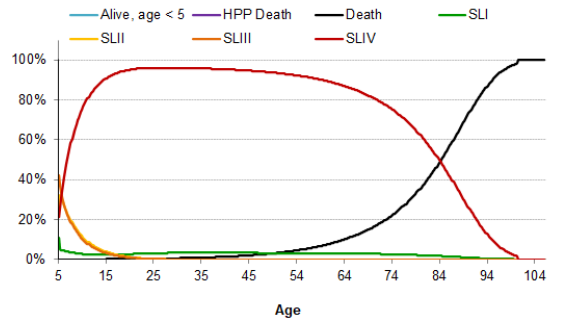
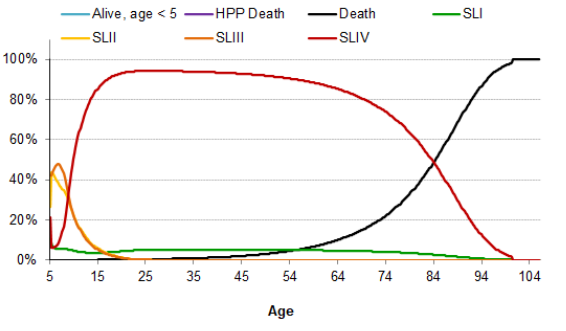
Perinatal/infantile onset population, MS3

Original results	Scenario results
	

Juvenile onset population, MS2

Original results	Scenario results
	

Juvenile onset population, MS3

Original results	Scenario results
	

Results using these analyses are shown in the table below. The ICERs remain close to the base case apart from the scenario in the juvenile-onset population with the updated regression using MS2. However, the updates made to MS2 does not

produce clinically plausible scenarios, as it can be seen from the traces that the historical controls move out of SLIV over time and into the less severe health states.

Table 14: Scenario results using updated BSC regression estimates (PAS price, with QALY weight applied)

Technologies	Total costs (£)	Total LYG	Total QALYs *	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
Scenario results using adjusted regression models for BSC – MS2							
Population: Perinatal-/infantile-onset HPP							
Discounted							
BSC	[redacted]	[redacted]	[redacted]	-	-	-	-
AA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£99,348
Population: Patients with juvenile-onset HPP							
Discounted							
BSC	[redacted]	[redacted]	[redacted]	-	-	-	-
AA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£671,393
Scenario results using adjusted regression models for BSC – MS3							
Population: Perinatal-/infantile-onset HPP							
Discounted							
BSC	[redacted]	[redacted]	[redacted]	-	-	-	-
AA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£83,843
Population: Patients with juvenile-onset HPP							
Discounted							
BSC	[redacted]	[redacted]	[redacted]	-	-	-	-
AA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£108,320

Key: AA, asfotase alfa; BSC, best supportive care; HPP, hypophosphatasia; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.
Note: * QALY weight of 3 is applied to both arms

B13. Priority question: Please clarify the following regarding the multivariate ordered probit 6MWT prediction model.

Please clarify the sentence on page 189: "In estimating the model, β1SLIt-1 is omitted so that all coefficient estimates are relative to being in the lowest severity levela (SL) at the previous visit." Provide a numerical example.

As with other regression models, multicollinearity will prevent estimating the ordered-probit model if multiple covariates are sufficiently correlated (in the most extreme case, if a covariate is a function of others). To avoid multicollinearity, if covariates included in a regression represent mutually-exclusive classifications of an observation, one classification must be "omitted" / considered the "referent" classification, as it will be perfectly determined by the covariates for the other classifications (and therefore perfectly collinear). The estimated coefficient for a classification covariate will therefore indicate difference associated with the particular classification vs. the referent.

In the ordered-probit regression model, inclusion of covariates for lags of all four severity states would yield multicollinearity, as a patient must by definition have been in one of the health states in the lagged period. As such, one severity state must be selected as the referent, relative to which coefficients for lags of the other severity states will be calculated. Any severity state could be selected as the referent, and predicted probabilities of the ordered-probit model would not change (coefficients would change, but cutpoints for calculating predicted probabilities estimated for the model would change accordingly).

For example, in Table 46 of the company submission, the coefficient of 9.956 for the SLIVt-1 covariate in the BSC Spec. 2 ordered-probit model indicates that if a patient was in SLIV rather than SLI (the referent) in the previous period, the value of their continuous latent variable to which the estimated cutpoints would apply (see next question) would be 9.956 higher. Considering that cutpoint 3 (the threshold for SLIV) is 3.054, this indicates that the estimated regression model predicts that a BSC-treated patient will remain in SLIV if in SLIV in the previous period (i.e., as 9.956 > 3.054).

Cut points 1–3 represent the thresholds used to differentiate the SLs. Please explain how the threshold values were determined.

The cutpoints were estimated as ancillary parameters to the ordered-probit model. The ordered-probit model assumes that a latent continuous metric (e.g., disease severity) underlies the ordinal observations (e.g., severity level). The resulting coefficient estimates can be used to generate predicted probabilities across the different ordered levels of the dependent variable, by applying estimated coefficients from the model to covariate values (as a linear function) to derive a value for the latent continuous metric of the dependent variable, then comparing the value to the cutpoints estimated for the model.

For further detail on estimation of the ordered-probit model, please see the manual from StataCorp[28], for example.

Table 46: Please provide a numerical example of how the equation is used in practice. If there is an intercept, please include this in the table. Please discuss whether the signs of the coefficients are approapiate, according to prior expectations and how to interpret them. For example, the coefficient for days between visits is negative for BSC but positive for AA.

As an example, please consider a BSC-treated patient, according to Spec. 2. In this case, coefficients are 1.647 for the lag of SLII, 2.957 for the lag of SLIII, 9.956 for the lag of SLIV, -0.012 for days between visits, and -0.012 for years of age at the visit. Cutpoints 1-3 are estimated at -0.703, 1.030, and 3.054, respectively.

Consider a 5-year old, who was in SLIII at their previous visit 12 weeks (84 days) prior. This patient has 0 values for the lags of SLII and SLIV (as they were in SLIII at the previous visit). Thus:

(1 x 2.957) + (84 x -0.012) + (5 x -0.012) = 1.889

The probability, for example, that this patient will remain in SLIII in the current period is calculated as:

Φ(cutpoint 3 – 1.889) - Φ(cutpoint 2 – 1.889) = 68.2%

(where Φ represents the cumulative distribution function (CDF) of the standard normal distribution)

See alignment with the corresponding cell in the BSC table in the response to the next question (note that the predicted probability 68.172% is rounded to 68.2% in this example, as the model coefficients and cutpoints were rounded).

Please note that in Table 47 and 48 the sum of the rows is not 100%.

Thank you for this note. These discrepancies were due to rounding. Table 15 and Table 16 have been provided below with transition probabilities to 3 decimal places such that each row sums to 100%.

Table 15: AA transition probability matrix at age 5.0 years

	SLI_t	**$SLII_t$**	**$SLIII_t$**	**$SLIV_t$**
SLI_{t-1}	90.407%	9.198%	0.379%	0.015%
$SLII_{t-1}$	40.464%	46.185%	11.385%	1.967%
$SLIII_{t-1}$	12.388%	45.360%	29.667%	12.585%
$SLIV_{t-1}$	1.026%	15.689%	32.698%	50.587%
Key: AA, asfotase alfa; SL, severity level.				

Table 16: BSC transition probability matrix at age 5.0

	SLI_t	**$SLII_t$**	**$SLIII_t$**	**$SLIV_t$**
SLI_{t-1}	64.824%	33.446%	1.728%	0.002%
$SLII_{t-1}$	10.272%	57.681%	31.410%	0.637%
$SLIII_{t-1}$	0.499%	19.435%	68.172%	11.893%
$SLIV_{t-1}$	0.000%	0.000%	0.000%	100.000%
Key: BSC, best supportive care; SL, severity level.				

Table 44 shows that transitions to stages SLIII and SLIV are possible too. Please explain at what ages these transitions are possible in the model.

Table 44 reflects that of 179 transitions observed for AA-treated patients who were in SLI at their previous visit, 2 were to SLIII and 2 were to SLIV. Accordingly, the ordered-probit model predicts small probabilities that transitions from SLI to SLIII and SLIV would occur. For example, at age 5, per the table above, the probability of transition from SLI to SLIII is 0.379%, and from SLI to SLIV is 0.015%. Note that these probabilities will vary with age in model specifications that include age as a covariate (i.e., specifications 2 and 3).

Health related Quality of Life

B14. Priority question: Table 55 on page 203 of the CS shows the utility values for each health state in the cost-effectiveness model.

Please clarify the source of the uncertainty (i.e., standard errors) shown in Table 55, as it does not seem to be presented in the referenced sources.

Standard deviations were calculated from the mapped EQ-5D-3L utilities elicited from experts by Lloyd et al. 2015[24]. Standard errors were calculated using the standard formula (SD/sqrt[N]).

In the absence of published confidence intervals, caregiver disutility (0.17) standard error was assumed to be 10 percent of the parameter (0.017), which is consistent with the approach taken in all other model parameters where no published confidence intervals are available. Separate standard errors are not applicable for carer disutilities for no invasive ventilation, SLII and SLIII since during probabilistic analysis they are calculated using the sampled caregiver disutility of 0.17 and sampled utilities for SLI, SLII and SLIII. Therefore, uncertainty is captured by varying these parameters. A new version of CS Table 55 is provided in C3.

Please discuss whether the included parameter uncertainty is an appropriate representation of the parameter uncertainty for these input parameters. The evidence review group (ERG) noted on the original appraisal that the vignette method did not capture the expected heterogeneity in experienced quality of life within one health state. Were

other values for parameter uncertainty considered? If so, what was the rationale for using the parameter uncertainty as it is in the model?

During the previous submission the ERG stated that the vignettes used to elicit utility values considered all aspects of the disease as strongly correlated, which may not be the case in real practice. The vignettes that were used in the elicitation exercise were developed with clinical experts, therefore it is deemed that they are reflective of the different health states for HPP. In addition, these were further verified with a clinical expert during a validation exercise in April 2022 and were considered relevant and reflective of HPP.

The table below presents the utility values for each health state, their standard deviation, standard error and the range of values from highest value to lowest value from the vignette study. In addition, the median values have been provided which show that the data is not skewed. To the best of our knowledge the best available data has been used to estimate the uncertainty associated with the utilities (standard errors).

Table 17: Utility values and range

State	Mean	Median	SD	SE	Range
SLI	0.86	0.84	0.11	0.04	1.00 to 0.71
SLII	0.67	0.65	0.09	0.03	0.84 to 0.56
SLIII	0.54	0.53	0.08	0.03	0.64 to 0.38
SLIV	0.23	0.27	0.25	0.08	0.57 to -0.27

Key: SD, standard deviation; SE, standard error; SL, severity level.

Utility values were varied in the one-way sensitivity analysis according to the estimated 95% confidence intervals from a normal distribution which is derived from the standard errors. They are also varied in the probabilistic sensitivity analysis using a normal distribution, incorporating the standard errors derived from the elicitation study.[24] While no standard parameter distribution can perfectly match the

observed distribution of values in any data source the applied approach was considered a reasonable approximation enabling exploration of the impact of uncertainty without overcomplicating the model.

B15. Priority question: Please answer the following question regarding caregiver disutility.

a) **Regarding the impact on caregiver quality of life, on page 202 of the CS it is stated that: 'In states SLII and SLIII, the decrement is based on the proportion of the patient's disutility versus patient utility in SLI.' Please clarify this statement, preferably with a worked example of how the caregiver decrements for the health states SLII and SLIII are obtained.**

Caregiver disutility associated with invasive ventilation (-0.17) is the greatest disutility applied for any health state. Caregiver disutility in SLII and SLIII is calculated by weighting the disutility associated with invasive ventilation by the difference in utility between SLII (or SLIII) and SLI, relative to the difference in utility between SLI and SLIV. This ensures the disutility is lower than the disutility associated with invasive ventilation and allows the utility decrement to increase with the severity level.

A worked example is provided for SLII below. Table presents the multiplier and resultant carer disutility for each health state.

$$SLII\ caregiver\ disutility$$

$$= invasive\ ventilation\ disutility * \frac{SLI\ utility - SLII\ utility}{SLI\ utility - SLIV\ utility}$$

$$= -0.17 * \frac{(0.863 - 0.668)}{(0.863 - 0.233)}$$

$$= -0.17 * \frac{0.195}{0.630}$$

$$= -0.17 * 0.310$$

$$= -0.05$$

Table 12: Carer disutility by health state

State	Multiplier	Utility value: mean	SE	Reference in submission (section and page number)
No invasive ventilation	0.52	-0.09	N/A	Section **Error! Reference source not found.**
Invasive ventilation	N/A	-0.17	0.017	
SLI	N/A	N/A	N/A	
SLII	0.31	-0.05	N/A	
SLIII	0.52	-0.09	N/A	
SLIV	1.00	-0.17	0.017	
Key: SE, standard error; SL, severity level.				

b) **On page 201 it is stated that based on the "results of Landfeldt et al. 2016, a utility decrement of -0.17 was used, based on the patient being in 'fair/poor' health". Please explain how the utility decrement for the caregiver was exactly estimated from the results of Landfeldt et al. 2016.**

Landfeldt et al. 2016[25] conducted an observational study that reported the QoL of carers of patients with DMD. They found carers of patients in "Excellent" health, highest health category, had a mean EQ-5D utility of 0.88. Carers of patients in "fair/poor" health, the lowest health category, had a mean EQ-5D utility of 0.71. This is shown in Figure 2 of Landfeldt et al. 2016.

The utility decrement was calculated as the difference in utility between these observations (0.71-0.88= -0.17).

c) **Furthermore, the 0.17 disutility seems quite high compared to values used in other HST's. Please provide an overview of values used in previous appraisals and whether these could be applicable to the current HST.**

In the CS, the disutility of 0.17 is applied per year (0.0391 per model cycle) to the most severe health states (invasive ventilation for age < 5 years and SLIV) for one

carer. It should be noted that the disutility of 0.17 was not applied to all health states. As discussed in B15a, the 0.17 decrement is weighted according to severity of disease for SLII-SLIII. The rationale for the disutility applied to the invasive-ventilation free state is provided in B13e.

Given time restrictions, a full review of previous appraisals could not be independently conducted, however, a recent review of carer health-related quality of life in NICE appraisals was conducted by Pennington 2020[29] and has been used to draw comparisons to previous HSTs. This review included the size of the carer disutility by patient's disease severity or ambulatory status in 3 HSTs. A summary of these results are provided the table below.

Table 1318: HST caregiver disutilities

HST	Indication	Size of carer disutility	Population to whom carer disutility applied
HST2	Mucopolysaccharidosis type IVa	0.00 – 0.14	1 carer
HST3	Duchenne muscular dystrophy	0.11	Company original submission: 1 carer. Company revised model: 3 carers. ERG analysis: 2 carers
HST8	X-linked hypophosphataemia	0.08	1 carer

Key: HST, highly specialized technology; QALY, quality-adjusted life year; TA, technology appraisal.
Source: Pennington 2020[29]

HST2 applied disutilities ranging from 0.00 to 0.14 for 1 carer. HST8 applied a disutility of 0.08 for 1 carer. HST3 applied a disutility of 0.11 for 1 carer and 0.33 for 3 carers for the original and revised models, respectively. The ERG analysis applied the disutilities for 2 carers (a 0.22 disutility overall), which is greater than the maximum value applied in this submission.

The maximum disutility applied in this submission (applied to the invasive ventilation and SLIV health states) of 0.17 lies within the range of previous HST total caregiver utility decrements (greater than HST2 and HST8, but less than HST3 after ERG review). The remaining decrements used in the model for no invasive ventilation and

SLIII (0.09) are similar to HST8 and the decrement used for SLII (0.05) is lower than those presented.

In addition, the source of utility decrement was clinically validated during submission. Clinicians stated that the disutility of caregiving for patients with DMD was deemed appropriate to use as a proxy for the disutility of caregiving for patients with paediatric-onset HPP. Given the information provided above, Alexion believe that the decrements used in the model are not overestimating the caregiver disutility and do not deviate from the previous HST submissions reviewed by Pennington 2020.

d) Please explain whether the utility decrements are applied per model cycle or per year.

The caregiver utility decrements (Table 55 of the CS) are the decrement per year. These decrements are converted to 12-week decrements and applied per model cycle.

For example, the caregiver utility decrement associated with invasive ventilation (-0.17) is converted to a decrement of -0.0391 per model cycle. Please see the numerical example below.

$$= -0.17 * \frac{12}{\left(\frac{365.25}{7}\right)}$$

$$= -0.0391$$

e) For patients not requiring invasive ventilation (ages < 5 years), a utility decrement is applied equal to that applied for SLIII. Please explain the rationale for this assumption.

Clinical experts were consulted during submission development to discuss the plausibility and face validity of the modelling assumptions. A paediatric HPP clinician stated it was essential that the model should capture caregiver burden for perinatal-

/infantile-onset patients even without invasive ventilation. The clinician suggested the disutility should be similar to that of SLIII or SLIV due to the high burden of illness associated with perinatal-/infantile-onset HPP as discussed in Section B.1.3.3 of the CS. The clinician emphasised their real-world experience of the devastating impact of perinatal-/infantile-onset HPP on parents.

Taking into account the clinician's suggestion, a caregiver utility decrement of -0.09 was applied for patients not requiring invasive ventilation (ages <5 years), equal to the caregiver utility decrement for SLIII. This is considered a conservative approach, given the clinician recommended a decrement similar to SLIII or SLIV.

f) According to the CS, the utility decrement is assumed to be experienced by 1 caregiver. This is not clear in the model as "Inputs – AA76" specifies 2 caregivers, although in the model it seems to be specific for the disutility associated to the child's death. Please clarify whether the same parameter applies to both disutilities or not. If not, please clarify why 1 caregiver is assumed to receive the "health state disutility" and 2 caregivers the disutility for death.

Within the model two parents experience the disutility associated with infant death (inputs sheet, cell AA76), however only one caregiver experiences the disutility associated with being a carer whilst the patient is alive.

The caregiver disutility is applied to one caregiver only, as it usually expected that patients only require one caregiver to help them with their daily activities. A recent review into the inclusion of carer health-related quality of life in NICE appraisals highlighted that the majority of technology appraisals and HST appraisals applied carer HRQL to one carer only.[29] Therefore, it is deemed appropriate that one carer is captured in the caregiver disutilities, but we acknowledge this might also be a conservative assumption.

For the disutility relating to bereavement, this is in relation to the grief that parents would experience due to their child prematurely dying. Although only one caregiver

may be required to help the patient with daily activities, a death would be expected affect both parents in the same way, therefore it is appropriate to capture the impact of infant death on two parents.

g) Please clarify to what extent the study by Song et al. is applicable to the UK.

The data from Song et al. 2010 is taken from The Wisconsin Longitudinal Study which is a long-term study of a random sample of 10,317 women and men who graduated from Wisconsin high schools in the United States. [20] The paper does not report detailed data on patient demographics, therefore we are unable to make a thorough comparison to the UK population. The only reported demographic information is that the 'majority of the respondents were White'. This is a limitation of the paper as it does not capture quality of life of other ethnic groups.

Alexion maintain that this study is broadly generalisable, given the similarities between the UK and USA populations (for example, the USA is an OECD country and has similarities to the UK with regards to economic and social development).

Given the paucity of data investigating the impact of infant death on parent's quality of life, Alexion believe this is the most suitable study to inform the utility decrement being used in the model.

h) Please explain why caregiver disutility is applied until patients turn 60 years old in the model.

The model applies caregiver disutility until patients turn 60, to reflect that as patients age they may be less likely to receive care from a family member/caregiver and that they may start to receive care from government funded social services. However, we acknowledge that this is a conservative assumption. Exploring a scenario where the caregiver disutility is applied for the duration of the time horizon has been provided in the table below, and shows that compared to the company base case there is a

minimal impact on the results. This is due to fewer patients being alive in the model beyond 60 years.

Table 14: Scenario versus company base case results (PAS price, with QALY weight applied)

Technologies	Total costs (£)	Total LYG	Total QALYs *	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
Scenario results using total time horizon for caregiver disutility							
Population: Perinatal-/infantile-onset HPP							
Discounted							
BSC	[redacted]	[redacted]	[redacted]	-	-	-	-
AA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£79,690
Population: Patients with juvenile-onset HPP							
Discounted							
BSC	[redacted]	[redacted]	[redacted]	-	-	-	-
AA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£97,253
Company base case							
Population: Perinatal-/infantile-onset HPP							
Discounted	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
AA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£80,093
Population: Patients with juvenile-onset HPP							
Discounted	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
AA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£98,512

Key: AA, asfotase alfa; BSC, best supportive care; HPP, hypophosphatasia; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.
Note: * QALY weight of 3 is applied to both arms

i) **Please explain these sentences, especially the last one: "The model only applies caregiver decrements for patients surviving on both AA and BSC. It is acknowledged that this is not a precise estimate of caregiver disutility; however, it avoids a situation where**

there is more disutility associated with a carer if the patient survives."

If there are differences in the number of patients alive in each arm of the model, applying caregiver disutility will negatively impact the arm that has more patients alive (e.g. asfotase alfa arm). This would not be a reasonable representation of how quality of life would be impacted in the real world; it would be unreasonable, and unethical, to suggest that parents would prefer the death of their child versus providing care for them.

In order to avoid penalising a treatment averting mortality, an adjustment is made where caregiver disutility is applied to those surviving in both treatment arms. It is acknowledged that this is an imperfect solution, however there does not currently exist guidance or approved methods for solving this issue.

j) Please explain how all these assumptions were validated with clinicians and how were deemed plausible.

Clinical experts were consulted independently on various inputs relating to health-related quality of life. With regards to caregiver disutilities, clinicians were asked to comment on the plausibility of capturing caregiver burden through quality of life and the estimates used. Given the lack of data available for caregiver quality of life burden in HPP, clinicians stated that using the Landfeldt et al. 2016 study in DMD was reasonable. In addition, the different utility decrements for each health state were verified with clinicians, and they stated that it was reasonable to assume that worst health states required a greater caregiver decrement. They believed that SLIV and invasive ventilation should result in the worst decrement, followed by SLIII and no invasive ventilation. In addition, they stated that it was reasonable that patients in SLI would not result in caregiver's experiencing a decrement in quality of life.

B16. Please provide more details on this sentence (Section B.3.4.1.3): ”Despite a large sample size, over 80% of records for adults were not matched to the 6MWT percent of predicted, limiting the validity of the data” when referring to the HPP registry data. Please explain how matching was performed and provide potential explanations why the registry data did not match well with the severity levels of HPP included in the model.

The analysis datasets were derived from matching patients' questionnaires with their corresponding 6MWT, this was achieved using R Version 4.1.1 software[30], under the following assumptions:

- Observations that were not complete were removed (i.e. the patient did not answer all questions in the questionnaire); no data was imputed
- Only observations containing values of 6MWT percent predicted were matched (i.e. observations with a raw value and no percent predicted were not included)
- The closest 6MWTP observation to utility observation was matched regardless of the time difference.

Exploratory analyses were first performed to determine the number of patients and records of utility that matched up to each of the health states, and the range of time between the two records. The derived utility values were then summarized using descriptive statistics (i.e. mean, standard deviation, median, range) overall and categorized by severity levels of the disease based on the 6MWTP and age (for paediatric patients only). Overall, there were 1,874 observations from 534 patients who answered the SF-36 questionnaire, 42 observations from 37 patients were removed as they contained at least 1 missing question. Subsequently, 338 observations from 81 patients were matched to a 6MWT.

The registry data did not match well with the severity levels of HPP as there was limited 6MWT data collected in the Global Registry. Patients were monitored per clinicians standard of care, and this rarely included the 6MWT as it is a research based tool.

Costs

B17. On page 217 of the CS, it is stated that the model only allowed rounding down if the administered dose was 12 mg less than the required dose per week and when rounding is not possible, wastage is assumed to occur. The model currently includes three options of "rounding" (up, down with 12 mg cap, and closest) and apart from the rounding down option, the other two are not currently explained in the CS. Please explain the differences in these options and reflect on the impact of using each of the options in annual costs of AA treatment. Please also confirm that or include an option not to account for rounding in the model.

The option of 'rounding up' is the same as assuming wastage is applied (costing the total vials required to purchase the required mg). The table below highlights an example of how the 'rounding up' and 'rounding down' functions are applicable. For example, if a patient requires 180mg of asfotase alfa, 204mg will be purchased if assuming 'rounding up' as there is no vial combination to accommodate the exact amount of 180mg. However, if selecting the 'rounding down with a 12mg cap' option, the patient can receive 174mg of asfotase alfa per week. The 'closest' option in the model will simply select which out of the 'rounding down with 12mg cap' or 'rounding up' is closest to the required dose (in this case it is the 'rounding down with 12mg cap' option).

Table 15: Example of purchased vials

Costing option	Required mg per week	Purchased mg per week	Purchased vials
Rounding up	180	204	1x 18mg & 1x 40mg, 3 per week
Rounding down (with 12mg cap)		174	1x 28mg & 1x 40mg, 3 per week
Key: mg, milligram.			

As the 'rounding up' function assumes that wastage occurs in every case, this results in the costs associated with asfotase alfa increasing. Despite there being a 'rounding

down' function, this only rounds down if the purchased mg is within the plausible limit (12mg per week), therefore in quite a lot of instances within the model, wastage is still occurring. This approach was built into the model following consultation with two clinicians who treat patients with HPP, and they stated that efforts are made in clinical practice to avoid excessive wastage and that where possible, patients may receive a lower dose as long as it does not exceed 12mg per week. Therefore, the 'rounding down with 12mg cap' is the most reflective of clinical practice, as this allows some rounding down to occur, but also allows wastage to occur if rounding down is not possible due to more than 12mg being missed per week.

Please note that a new option has not been added to the model as the 'rounding up' option is already included which assumes wastage occurs.

B18. The company reported that AA patent is due to expire in 2030 and that as AA costs are applied for the total duration of the model's time horizon, the model base case assumes that after 7 years from the start of the model, loss of data exclusivity would lead to a 58.5% decrease in the AA list price. The 58.5% decrease was based on recent reports of prices for biosimilar infliximab suggesting price reductions of 45–72% versus the originator product. Please specify why it is expected that biosimilars for HST would lead to similar price reductions.

We appreciate there is uncertainty in the price reduction expected for AA due to the loss of data exclusivity. As there is a paucity of data for price reduction in rare diseases due to the introduction of biosimilars, we used the example of infliximab as there was data available for this. Due to the uncertainty associated with this, we tested both the upper and lower bounds in scenario analyses.

B19. Priority question. The company estimated an annual AA treatment discontinuation rate of [redacted] combining data from the ENB-002-08/ENB-003-08, ENB-010-10, ENB-006-09/ENB-008-10 clinical trials and the UK MAA (Table

60 of the CS). As also indicated in clarification questions 0and 0it is unclear how these data were used. Please specify how where these data were used to estimate the AA annual treatment discontinuation rate for each study and for each age of onset category (question 0).

Data from the studies mentioned was combined to allow a calculation of discontinuation. The table below shows the number of discontinuations per study and reason for discontinuation. In order to avoid double counting, patients who died in any of the studies were excluded from the data, as modelling would already count for patients not receiving AA due to death. As shown below, data from ENB-002-08/ENB-003-08 was not included in the final calculation as there was no information available on the mean number of exposure days. Responses in A19 show discontinuations due to TEAEs, whereas the estimates used in the model include discontinuation for any reason (other than death). Data was combined across all studies and all age of onset categories, to calculate a single discontinuation rate and was validated with two clinicians who stated it was reflective of real world practice. The calculation of the discontinuation rate has been added to the model.

Table 19: Data used to calculate discontinuation rate in the model

Study	N	Discont.	Exposure days	Reason for discontinuation
ENB-002-08/ENB-003-08	11	[redacted]	[redacted]	[redacted]
ENB-010-10	69	[redacted]	[redacted]	[redacted]
ENB-006-09 and ENB-008-10	13	[redacted]	[redacted]	[redacted]
MAA UK study	18	[redacted]	[redacted]	[redacted]
Global registry	347	[redacted]	[redacted]	[redacted]

Key: AE, adverse event; Discont, discontinuation; TEAE, treatment-emergent adverse event.

Validation

B20. Priority question. Please compare the results in the original submission with the new results (cross-validation). Explain what has changed, what has not and what causes the differences between results. Please compare the new results with those submitted as part of HTA in Canada (Canadian Agency for Drugs and Technologies in Health [CADTH] and Institut national d'excellence en santé et en services sociaux [INESSS]), Sweden, the Netherlands, France, and Australia. Explain what causes the differences between results.

A comparison of the original submission and current submission is provided below. A comparison against the results for the HTA submissions in Canada, Sweden, Netherlands, France and Australia has not been conducted as their HTA requirements differ from the UK and is therefore not deemed applicable to the current submission.

The original submission conducted a cost-consequence analysis. A summary of discounted incremental costs and QALYs for AA- and BSC-treated patients are presented in Table 20 for two scenarios conducted: patient baseline age 0, patient baseline age 6.7. The results for these scenarios most closely align with the approach in the current submission. The approach differs in the current submission as the model populations are aligned with the decision problem, whereas the original submission presented one base-case result. The ICERs have been calculated for the purpose of comparison to the current submission. The current submission base case results are provided without QALY weighting in Table 21.

The changes made to the model since the original submission are detailed in B1a. The results are therefore different for a number of reasons. The most influential changes on the results include:

- PAS price. Results without PAS price are provided in Appendix R2.
- Updated probit regressions to include UK MAA data
- Greater discount rates, per the NICE reference case, in the current submission
- Increased price reduction due to loss of exclusivity
- Inclusion of caregiver QoL in the current submission

- Use of vial combinations to help reduce wastage associated with asfotase alfa
- Rounding down of a dose where plausible, to reduce wastage associated with asfotase alfa

Table 20: Original submission HST6 results

Scenario	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
Scenario 1: Age 0 patient							
BSC	[redacted]	15.21	3.56				
AA	[redacted]	42.48	35.28	[redacted]	27.27	31.72	[redacted]
Scenario 3: Trials age 5-11 (Patient age 6.7)							
BSC	[redacted]	44.56	12.39				
AA	[redacted]	44.56	37.26	[redacted]	0.00	24.87	[redacted]

Key: AA, asfotase alfa; BSC, best supportive care; HPP, hypophosphatasia; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.

Table 21: Current submission base case results (PAS price, without QALY weight)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
Population: Perinatal-/infantile-onset HPP							
Discounted							
BSC	[redacted]	[redacted]	[redacted]	-	-	-	-
AA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£240,279
Population: Patients with juvenile-onset HPP							
Discounted							
BSC	[redacted]	[redacted]	[redacted]	-	-	-	-
AA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£295,536

Key: AA, asfotase alfa; BSC, best supportive care; HPP, hypophosphatasia; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.

Section C: Textual clarification and additional points

C1. Please explain how to interpret results in Table 34 and 35 and whether these are in line with prior expectations.

Alexion has conducted correlation studies for 6mWT with the various endpoints that were used to assess mobility, disability, pain, physical and social functions. These correlation studies were necessary as 6mWT is the proxy that is used to define health states for patients over the age of 5 years in the original model as agreed with the Committee. Although the 6MWT may not fully capture all the symptoms of HPP and in turn all the benefits of AA, correlations between 6MWT and other trial outcomes were noted. These include: QoL (as measured by the CHAQ); pain (as measured by CHAQ and the POSNA's PODCI), various measures of physical and social functioning (as measured by the PODCI), the Rickets Severity Score (RSS) & RGIC score. These correlations show that 6MWT is an appropriate proxy for the severity of musculoskeletal symptoms of HPP, the QoL, pain, and physical and social functioning. Moreover, the correlations support the relevance of the 6MWT as an indicator of the underlying disease process that affects patients with paediatric-onset HPP

C2. Page 183: A panel of patient visits with 6MWT data was used to estimate multivariate ordered probit models. This model was used to predict the current-period SL as a function of SL in the previous period and other covariates. Please specify and justify what were the covariates included.

As noted in the company submission, the three model specifications tested align with the specifications included in the original NICE submission. The rationale / justification for these specifications, as reported in the original submission, is included below:

"The specifications tested produced comparable goodness-of-fit statistics; which are often differentiating factors used in justifying model selection. Specification 2 was chosen primarily for two reasons. First, the intention of the model is to produce age-specific transition probabilities, so a coefficient estimate for age is needed. This is important as the likelihood of being in different disease severity levels could be expected to differ across age intervals, and the model must generate out-of-sample predictions for patients under age of 5 and over age 65, as data were not available for these patients. Thus, Specification 1 was deemed insufficient for the modeling purpose. Second, consideration should be given to the number of covariates included in the estimation relative to the number of observations so that the model is not over-specified. In general, the fewer the number of covariates, the more variation remains for accurately estimating the coefficients. Given the limited number of observations available for BSC especially, it is not surprising that the addition of interaction terms in Specification 3 resulted in coefficient estimates that did not statistically significantly differ from zero. While base case results are derived using Specification 2, sensitivity analyses were also done using Specifications 1 and 3."

C3. Table 55 reports negative standard errors for some variables. Please provide a new version of Table 55 with the corrected standard errors and these changed in the model if needed.

An updated version of the table has been provided below. The standard errors for carer disutilities for no invasive ventilation, SLII and SLIII are N/A as they are calculated using the caregiver disutility of 0.17 and utilities for SLI, SLII and SLIII. Therefore, uncertainty is captured by varying these parameters.

Table 22: Summary of utility values for cost-effectiveness analysis

State	Utility value: mean	SE	Reference in submission (section and page number)	Justification
Patients aged 0–4				
No invasive ventilation	0.24	0.12	Section **Error! Reference source not found.**	Values from the clinician elicitation study were used as per the original submission and due to lack of other sources available
Invasive ventilation	0.00	0.17		
Patients aged 5+				
SLI	0.86	0.04		Values from the clinician elicitation study were used as per the original submission
SLII	0.67	0.03		
SLIII	0.54	0.03		
SLIV	0.23	0.08		
Carer disutility				
No invasive ventilation	-0.09	N/A	Section **Error! Reference source not found.**	The symptoms of HPP and necessary accommodations are likely to have an impact on HRQL. Studies in similar disease areas have shown that disease severity can directly affect carers' QoL
Invasive ventilation	-0.17	0.017		
SLI	N/A	N/A		
SLII	-0.05	N/A		
SLIII	-0.09	N/A		
SLIV	-0.17	0.017		
Infant death	-0.04	0.02	Section **Error! Reference source not found.**	Song et al. 2010[20] showed that parents experience an ongoing utility decrement following an infant's death. This same decrement was applied and accepted by NICE in the 2018 evaluation of Strimvelis (NICE HST7)[21]
Key: HPP, hypophosphatasia; HRQL, health-related quality of life; N/A, not applicable; SE, standard error; SL, severity level.				

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Decision problem

A 2. Priority question. Please provide a complete list of changes since the original appraisal in terms of scope and evidence.

Table 1 presents a list of changes since the original appraisal in terms of scope.

Table 1: Changes since the original appraisal in terms of scope

	Original NICE HST submission	NICE HST resubmission	Rationale
Population	Patients with paediatric-onset hypophosphatasia	Patients with paediatric-onset hypophosphatasia	The population aligns with the final NICE scope in the original submission and the resubmission
Intervention	AA	AA	The intervention aligns with the final NICE scope in the original submission and the resubmission
Comparator(s)	Best supportive care	Best supportive care	The comparator aligns with the final NICE scope in the original submission and the resubmission
Outcomes	• Mortality • Radiographic response • Bone mineralisation • Severity rickets • Pain • Respiratory function • Growth • Tooth loss • Cognitive development and motor skills • Adverse effects of treatment • Health-related quality of life (for patients and carers)	• Mortality • Radiographic response • Bone mineralisation • Severity of rickets • Pain • Respiratory function • Growth • Tooth loss • Cognitive development and motor skills • Adverse effects of treatment • Health-related quality of life (for patients and carers)	Bone mineralisation was added to the outcomes in the original submission and the resubmission, as although this outcome was not included in the NICE final scope document, it was included in the AA clinical trials (i.e. bone biopsy and DEXA). Craniosynostosis and intracranial pressure were removed from the list of outcomes in the original submission and the resubmission because these outcomes are related to the underlying disease and are unlikely to be affected by use of AA. These outcomes were not measured as an outcome in any of the AA clinical studies, but were reported as a part of the safety data analysis. See response to A.3 for more details.
Key: AA, asfotase alfa; DEXA, dual energy X-ray absorptiometry; N/A, not applicable; NICE, National Institute for Health and Care Excellence.			

Table 2 presents a list of changes since the original appraisal in terms of evidence.

Table 2: Changes since the original appraisal in terms of evidence

		Original NICE HST submission	NICE HST resubmission	Rationale
Included studies	**UK MAA**	N/A	UK MAA (n = [redacted])	
	AA clinical trials	ENB-001-08 (n = 6) ENB-002-08/ENB-003-08 (n = 11) ENB-010-10 (n = 59) ENB-006-09/ENB-008-10 (n = 13) ENB-009-10 (n = 13)	ENB-001-08 (n = 6) ENB-002-08/ENB-003-08 (n = 11) ENB-010-10 (n = 69) ENB-006-09/ENB-008-10 (n = 13) ENB-009-10 (n = 19)	After NICE approved AA in August 2017, Alexion initiated the UK MAA data collection that included all UK patients with HPP treated with AA. This data collection is ongoing, with the latest data cut-off completed in [redacted] and these data are presented first in the resubmission.[1] All new and relevant studies have been presented within the NICE HST resubmission. The totality of the clinical data presented in the submission, from the UK MAA, the long term follow up of the AA clinical trials (ENB-002-08/ENB-003-08, ENB-010-10, ENB-006-09/ENB-008-10 and ENB-009-10), the Global HPP Registry and the real-world EmPATHY study should be considered the main source of efficacy data for the population in the decision problem, which includes patients with perinatal-, infantile- and juvenile-onset HPP.
	Real-world evidence studies	N/A	Global HPP Registry (n = [redacted]) EmPATHY (n = 21) Dahir et al. 2022 (n = [redacted])	
	Natural history studies	ENB-011-10 (n = 48) ALX-HPP-502 (n = 32) ALX-HPP-502s (n = 6)	ENB-011-10 (n =48) ALX-HPP-502 (n = 32) ALX-HPP-502s (n = 6)	
Outcomes presented for AA clinical trials included in	**ENB-002-08/ ENB-003-08**	OS, VFS, respiratory support, growth (length/height and weight), BSID-III, RGI-C, RSS, PPi, PLP, safety	OS, VFS, respiratory support, growth (length/height and weight), BSID-III, the PDMS- 2, BOT- 2, RGI-C, RSS, safety	The final analyses for the AA clinical trials were presented in the NICE HST resubmission, for all key endpoints with long term follow up data.
	ENB-010-10	OS, VFS, respiratory support, growth	OS, VFS, respiratory support, growth	

both submissions		(length/height and weight), BSID-III, the PDMS- 2, BOT- 2, RGI-C, RSS, safety	(length/height and weight), BSID-III, the PDMS- 2, BOT- 2, RGI-C, RSS, safety	
	ENB-006-09/ ENB-008-10	Growth (length/height and weight), 6MWT, BOT-2, PODCI, CHAQ, RGI-C, RSS, bone mineralisation, safety	Growth (length/height and weight), 6MWT, BOT-2, PODCI, CHAQ, RGI-C, RSS, safety	
	ENB-009-10	6MWT, BOT-2, LEFS, BPI-SF, PPi, PLP, bone mineralisation, handheld dynamometry, safety	Growth, 6MWT, BOT-2, LEFS, BPI-SF, PPi, PLP, safety	
Length of follow up for AA clinical trials included in both submissions	**ENB-002-08/ ENB-003-08**	5 years	7 years	The final analyses for the AA clinical trials with longer follow up were presented in the NICE HST resubmission.
	ENB-010-10	3.5 years	6 years	
	ENB-006-09/ ENB-008-10	5 years	7 years	
	ENB-009-10	3 years	5 years	
Pooled survival analysis	**Population**	Patients with perinatal/infantile HPP (n = 37)	Patients with perinatal/infantile HPP (n = 78)	An updated pooled survival analysis was included in the NICE HST resubmission with more patients and longer follow up.
	AA clinical trials	ENB-002-08/ENB-003-08 (n = 11) ENB-010-10 (n = 26)	ENB-002-08/ENB-003-08 (n = 11) ENB-010-10 (n = 69)	
	Historical control study	ENB-011-10 (n = 48)	ENB-011-10 (n = 48)	
	Outcomes	OS and VFS	OS and VFS	
	Follow up	5 years[2]	7 years[3]	
Pooled efficacy analyses for other outcomes	**Population**	Patients with paediatric-onset HPP (n = [redacted])	**Population:** Patients with perinatal/infantile HPP (n = 85)	As per the response to A 1., an updated pooled efficacy analysis in patients with perinatal/infantile-onset HPP was included in the NICE HST resubmission as assessing long-term outcomes
	AA clinical trials	ENB-002-08/ENB-003-08 and ENB-010-10 (n = [redacted]) ENB-006-09/ENB-008-10 (n = [redacted])	ENB-002-08/ENB-003-08 (n = 11) ENB-010-10 (n = 69) ENB-006-09/ENB-008-10 (n = 5)	

	Outcomes	PPi, PLP, RGI-C, RSS, bone mineralisation, growth (length/height and weight), 6MWT, functional outcomes including BSID-III, BOT-2, PODCI and CHAQ	RGI-C, RSS, growth (length/height and weight), functional outcomes including BSID-III, BOT-2, PODCI and CHAQ	following AA treatment was imperative when data were available for 85 patients treated in the AA clinical development program, with the most life threatening form of HPP.
	Follow up	5 years	7 years[3]	
Pooled safety analyses	**Population**	All patients included in the AA clinical trials (n = [redacted])	All patients included in the AA clinical trials (n = 112)	An updated pooled safety analysis was included in the NICE HST resubmission with more patients and longer follow up.
	AA clinical trials	ENB-002-08/ENB-003-08 (n = [redacted]) ENB-010-10 (n = [redacted]) ENB-006-09/ENB-008-10 (n = [redacted]) ENB-009-10 (n = [redacted])	ENB-002-08/ENB-003-08 (n = 11) ENB-010-10 (n = 69) ENB-006-09/ENB-008-10 (n = 13) ENB-009-10 (n = 19)	
	Follow up	5 years	7 years[4]	

Key: AA, asfotase alfa; BOT-2; Bruininks-Oseretsky Test of Motor Proficiency, 2nd Edition; BPI-SF, Brief Pain Inventory Short Form; BSID-III, Bayley Scales of Infant and Toddler Development®, 3rd Edition; HPP, CHAQ, Child Health Assessment Questionnaire; hypophosphatasia; HST, highly specialised technology; MAA, managed access agreement; N/A, not applicable; NICE, National Institute for Health and Care Excellence; PDMS-2, Peabody Developmental Motor Scales, 2nd edition; RGI-C, Radiographic Global Impression of Change; RSS, Rickets Severity Score; 6MWT, six-minute walk test.

Invasive ventilation health states

B7. Priority question: Please anwer the following questions regarding invasive ventilation.

a) **Information about AA improvement in patients' ability to discontinue treatment from invasive ventilation does not seem to be consistent: in section B.3.3.1.2 of the CS it is mentioned that "75% of patients (12 out of 15) weaned from mechanical ventilatory support" and also that "for patients receiving AA aged 0–5 years, 84% (21 out of 25) survived free of invasive ventilation". Both estimates seem to be from Whyte et al., please clarify this discrepancy.**

For AA, the 75% of patients that were weaned from mechanical ventilatory support refers to the patients that were on ventilatory support at baseline (start of AA treatment). The 84% refers to all patients who received AA aged 0-5 years, and what percentage of them survived free of invasive ventilation.

b) **Please clarify what the baseline distribution of patients in IV health states is and the rationale for that assumption.**

At each cycle there is a constant risk of a patient being on invasive ventilation. Therefore, the baseline distribution is aligned with this risk. At t=0, the proportion of patients on invasive ventilation is equal to the risk of invasive ventilation at each cycle. For AA there are 2.2% of patients on invasive ventilation. For BSC, 6.2% are on invasive ventilation.

Although in reality more patients may start on invasive ventilation and then be weaned off support, applying a constant probability of receiving invasive ventilation across the first 5 years instead of using Kaplan-Meier data is done to try to capture the fact that patients may be on invasive ventilation more than once within the 5 years.

c) **Invasive ventilator-free survival (IVFS) was modelled using the rates at 5 years for BSC and 1.8 years for AA as provided in Whyte et al. (2014) (Page 182 of the CS). As already discussed in question A.14, it is not**

clear why MAA data were not used to inform IVFS in both arms. Please clarify.

MAA data could not be used to inform the BSC arm as the MAA only collected data for patients receiving AA.

For the AA arm, given the number of patients that had data relating to invasive ventilation was lower than that reported by Whyte et al. 2014 ([redacted] treatment experienced and [redacted] treatment naïve in the MAA) a decision was made to keep the Whyte et al. 2014 source as the base case, and include MAA data as a scenario analysis. As shown in the CS, the use of the MAA estimate for invasive ventilation did not have a substantial impact on results.

d) Furthermore, the company assumed constant rates (exponential distribution) for IVFS. Please explain why other distributions to fit IVFS data were not explored.

There is uncertainty around the rate of invasive ventilation being constant, especially for the AA arm, as one might expect the risk of receiving invasive ventilation to fall with treatment exposure. However, given that patients do not permanently move to invasive ventilation, a constant probability was applied in the model to allow patients to enter invasive ventilation more than once throughout the model, rather than modelling parametric survival models of invasive-ventilation free survival. Additionally, as noted above, sensitivity analysis shows that invasive ventilation does not drive results of the CUA model. It was therefore deemed that incorporating parametric models of invasive ventilation into the model, and allowing patients to transition out of the failure state, would add unwarranted complexity to the model compared to modelling a constant rate.

e) Please clarify what is assumed to happen in the AA arm after 1.8 years. For instance, is it assumed to apply the same rate up to year 5 or is it a rate equal to 0 asumed.

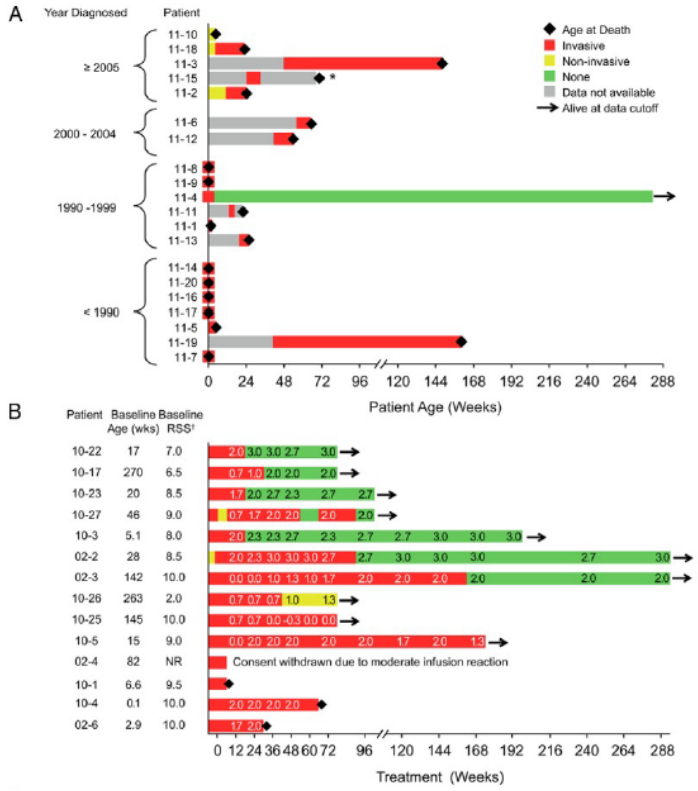
For the AA arm, although the 84% rate of invasive ventilation free survival was estimated from 1.8 years, this rate was applied up to 5 years in the model.

f) Please use patient level data to inform the time to event analysis for invasive ventilator (IV) use for both arms by each age of onset category

and incorporate this in the model. If necessary make use of parametric models for IVFS.

The incorporation of time-to-event data in the model would either result in patients permanently transitioning to invasive ventilation or applying the hazard for invasive ventilation free survival at a given cycle. The former would not be accurate as patients do not remain in the invasive ventilation state permanently. In addition, applying the hazard for invasive ventilation free survival in a given cycle would not account for patients who may receive respiratory support more than once. Although time to event data has been used to model mortality, it is appropriate in this case as patients permanently move to the death health state/cannot move to the death health state more than once. However, for invasive ventilation, patients may require invasive ventilation support more than once, which is shown in the Whyte et al. 2016 study (see Figure 2 of the publication, replicated in part below)[2]. As a result, time-to-event data may not be fully representative of this.

Figure 1: Whyte et al. 2016 on invasive ventilation



Ventilatory support and patient outcomes in asfotase alfa–treated and historical control patients. (A) Ventilatory status and patient outcome for the 20 historical control patients (study ENB-011-10) who required ventilatory support in the first 5 years of life. (B) Ventilatory support status improved with bone mineralization for asfotase alfa–treated patients who required ventilatory support at baseline (n = 14) or (C) did not require ventilatory support at baseline but required support later in the study (n = 7). Initiation and discontinuation of ventilatory support are shown as colored bars. Death is indicated by black diamonds. Patient number, age at enrollment in studies ENB-002-08/ENB-003-08 (patients numbered according to Whyte et al (1)) and ENB-010-10, and baseline Rickets Severity Score (RSS); 0 = no rickets, 10 = severe rickets (21)) are shown on the left. Numbers within the colored bars represent the Radiographic Global Impression of Change (RGI-C) scale score. NR, not recorded.

Source: White et al. 2016.[2]

Given the need for invasive ventilation is not consistent over time and patients may start and stop receiving invasive ventilation, a constant rate (converted to a probability) has been used and applied to each cycle to allow patients to start and stop receiving invasive ventilation.

g) Please provide the KM curves including the at risk table for invasive ventilator-free survival for AA and BSC patients.

As described above, the including the time-to-event data would not be representative of how patients may receive invasive ventilation.

Severity health states

B.9 Please provide the coefficients, standard errors (SEs) and P-values of two new multivariate ordered probit models including a treatment duration as covariate for AA/BSC (as shown in Table 46).

Upon request for clarification of the desired specification for these models, the EAG stated:

"It seems there was a typo in this question, please refer to this one: Please provide the coefficients, SE and P value of single probit models for specifications 1-3 (as shown in Table 46), including a treatment effect for BSC and asfotase alfa simultaneously, instead of separate probit models for the two treatment arms."

In the submission, the rationale for including separate ordered probit models for AA and BSC was noted, stating that each ordered-probit model specification "was run separately for patients receiving BSC and patients receiving AA; this is identical to running one specification with treatment and treatment interactions with all other covariates." As described, estimating a joint model with a treatment-indicator covariate would require interaction terms of the treatment indicator multiplied by each covariate, in order to achieve the same flexibility as the separate models. The inclusion of so many covariates would result in very high variance of the estimated model parameters, and in some cases the models may not converge due to data limitations vs. the number of parameters estimated.

Given these challenges, in order to provide the order-probit results requested, but to maintain adequate flexibility in the modelling of the AA treatment effect, we included in the model specifications (1) a treatment indicator and (2) interactions of the treatment indicator with the lag of severity level (i.e., the severity level the patient was in during the previous period). This flexibility was deemed necessary to allow for variability in the treatment effect on transitions between different health states (e.g., the effect on the probability of a patient treated on AA transitioning from SLIV to SLI in a 12-week period may be different vs. the effect on the probability of transitioning from SLII to SLI). Per the results included below, there appears to be significant variation in estimated treatment effects by lagged health state, emphasizing the importance of this dimension of the specification.

Table 3: Coefficient estimates from ordered probit model of severity level at time t

	BSC			AA			Joint model		
	Spec. 1	**Spec. 2**	**Spec. 1**	**Spec. 1**	**Spec. 2**	**Spec. 3**	**Spec. 1**	**Spec. 2**	**Spec. 3**
Covariate, coefficient (p-value)									
SLIIt-1	1.547 (<0.001)	1.647 (0.002)	-0.743 (0.510)	1.534 (<0.001)	1.546 (<0.001)	1.700 (<0.001)	1.138 (0.012)	1.131 (0.015)	1.354 (0.013)
SLIIIt-1	2.959 (<0.001)	2.957 (<0.001)	0.628 (0.534)	2.463 (<0.001)	2.461 (<0.001)	2.392 (<0.001)	2.319 (<0.001)	2.325 (<0.001)	2.194 (<0.001)
SLIVt-1	9.659 (<0.001)	9.956 (<0.001)	6.912 (<0.001)	3.632 (<0.001)	3.622 (<0.001)	3.045 (<0.001)	7.585 (<0.001)	7.591 (<0.001)	7.219 (<0.001)
Days between visits	-0.017 (0.033)	-0.012 (0.075)	-0.009 (0.221)	0.003 (0.004)	0.003 (0.007)	0.003 (0.005)	0.003 (0.008)	0.003 (0.009)	0.003 (0.010)
Age at visit (years)	N/A	-0.012 (0.193)	-0.181 (0.032)	N/A	0.002 (0.452)	0.000 (0.974)	N/A	0.001 (0.759)	-0.003 (0.697)
Age x LIIt-1	N/A	N/A	0.174 (0.038)	N/A	N/A	-0.007 (0.467)	N/A	N/A	-0.005 (0.594)
Age x SLIIIt-1	N/A	N/A	0.178 (0.039)	N/A	N/A	0.003 (0.722)	N/A	N/A	0.005 (0.530)
Age x SLIVt-1	N/A	N/A	0.184 (0.028)	N/A	N/A	0.020 (0.130)	N/A	N/A	0.023 (0.086)
Treatment (with AA)	N/A	N/A	N/A	N/A	N/A	N/A	-0.914 (0.053)	-0.907 (0.053)	-0.933 (0.041)
Treatment x	N/A	N/A	N/A	N/A	N/A	N/A	0.401	0.413	0.289

	BSC			AA			Joint model		
	Spec. 1	**Spec. 2**	**Spec. 1**	**Spec. 1**	**Spec. 2**	**Spec. 3**	**Spec. 1**	**Spec. 2**	**Spec. 3**
SLIIt-1							(0.419)	(0.417)	(0.584)
Treatment x SLIIIt-1	N/A	N/A	N/A	N/A	N/A	N/A	0.163 (0.755)	0.155 (0.764)	0.156 (0.757)
Treatment x SLIVt-1	N/A	N/A	N/A	N/A	N/A	N/A	-3.903 (<0.001)	-3.915 (<0.001)	-4.212 (<0.001)
Cut points									
Cut 1	-0.615	-0.703	-2.709	1.547	1.600	1.556	0.627	0.527	0.627
Cut 2	1.078	1.030	-0.888	2.897	2.951	2.913	1.985	1.892	1.985
Cut 3	3.106	3.054	1.067	3.845	3.902	3.885	2.998	2.927	2.998
Sample N, fit									
Sample size	32	32	32	432	432	432	464	464	464
Log likelihood	-24.11	-23.59	-22.02	-361.79	-361.42	-360.00	-390.99	-390.93	-385.75
Pseudo R2	0.4417	0.4538	0.4901	0.3403	0.3410	0.3491	0.3438	0.3439	0.3526

Key: AA, asfotase alfa; BSC, best supportive care; SL, severity level; Spec., specification.
Note: p values for covariate estimates statistically significant at the $p < 0.05$ level are reflected in green font.

6MWT

B10. Please provide new versions of Tables 42 to 45 stratified per age group.

Considering the scoping of the evaluation, which distinguishes patient populations with perinatal/infantile vs. juvenile onset, this request was inferred to reference this stratification based around age of onset. Stratification by other thresholds of patient age were considered to be beyond the scope specified by NICE, and therefore arbitrary/biased in selection of a single stratification threshold. Tables 42 to 45 from the original submission, stratifying by perinatal/infantile onset (i.e., age of onset < 1 year) and juvenile onset (i.e., age of onset ≥ 1 year), are provided below. As reflected in these results, magnitudes and patterns of treatment effects of AA and BSC are maintained across the age-of-onset strata.

Table 4: Descriptive statistics on the change in 6MWT between sequential visits

		Perinatal/ infantile onset		**Juvenile onset**	
		Mean	SD	Mean	SD
AA (N = 432 transitions)	Change in distance walked (metres)	12.37	79.32	14.46	59.71
	Percentage point change in percent of predicted	1.60	23.37	1.60	17.39
BSC (N = 32 transitions)	Change in distance walked (metres)	-14.30	80.36	-12.32	27.87
	Percentage point change in percent of predicted	-2.16	11.93	-2.60	5.19
Key: AA, asfotase alfa; BSC, best supportive care; SD, standard deviation.					

Table 5: Descriptive statistics on the change in 6MWT between first and last visit

		Perinatal/ infantile onset		Juvenile onset	
		Mean	SD	Mean	SD
AA (N = 51 transitions)	Change in distance walked (metres)	101.74	160.43	128.83	133.26
	Percentage point change in percent of predicted	13.15	25.23	13.81	28.54
BSC (N = 26 transitions)	Change in distance walked (metres)	-17.88	48.48	-15.10	25.84
	Percentage point change in percent of predicted	-2.70	7.58	-3.17	4.50
Key: AA, asfotase alfa; BSC, best supportive care; SD, standard deviation.					

Table 6: Observed state transitions – AA

Perinatal/infantile onset

	State at current visit				
State at prior visit	**SLI**	**SLII**	**SLIII**	**SLIV**	***Row total***
SLI	47	8	1	0	*56*
SLII	9	21	11	5	*46*
SLIII	2	16	23	6	*47*
SLIV	1	3	11	17	*32*
Column total	*59*	*48*	*46*	*28*	*181*
Key: BSC, best supportive care; SL, severity level					

Juvenile onset

	State at current visit				
State at prior visit	**SLI**	**SLII**	**SLIII**	**SLIV**	***Row total***
SLI	105	15	1	2	*123*
SLII	24	43	4	1	*72*
SLIII	1	11	11	1	*24*
SLIV	1	3	2	26	*32*
Column total	*131*	*72*	*18*	*30*	*251*
Key: BSC, best supportive care; SL, severity level					

Table 7: Observed state transitions – BSC

Perinatal/infantile onset

	State at current visit				
State at prior visit	**SLI**	**SLII**	**SLIII**	**SLIV**	***Row total***
SLI	1	1	0	0	*2*
SLII	1	0	1	0	*2*
SLIII	0	2	3	1	*6*
SLIV	0	0	0	0	*0*
Column total	*2*	*3*	*4*	*1*	*10*
Key: BSC, best supportive care; SL, severity level					

Juvenile onset

	State at current visit				
State at prior visit	**SLI**	**SLII**	**SLIII**	**SLIV**	***Row total***
SLI	4	2	0	0	*6*
SLII	1	5	2	0	*8*
SLIII	0	0	4	1	*5*
SLIV	0	0	0	3	*3*
Column total	*5*	*7*	*6*	*4*	*22*
Key: BSC, best supportive care; SL, severity level					

References

1. Alexion. Interim Analysis Report ASF-MAA-001 STRENSIQ® UK Managed Access Agreement (MAA) (ASF-MAA-001) 4 March 2022. Data on file.

2. Whyte MP, Rockman-Greenberg C, Ozono K, et al. Asfotase Alfa Treatment Improves Survival for Perinatal and Infantile Hypophosphatasia. *J Clin Endocrinol Metab*. 2016; 101(1):334-42.

3. Hogler W, Rockman-Greenberg C, Petryk A and et al. Long-Term Efficacy Profile of Asfotase Alfa in the Treatment of Patients with Hypophosphatasia: A Pooled Analysis. 9th Biennial International Conference on Children's Bone Health (ICCBH). Salzburg, Austria 22–25 June 2019. Poster P77.

4. Whyte MP, Bishop N, Hasan J and et al. Safety Profile of Asfotase Alfa Treatment of Patients with Hypophosphatasia: A Pooled Analysis. 9th Biennial International Conference on Children's Bone Health (ICCBH). Salzburg, Austria 22–25 June 2019. Poster P76.

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Understanding Patient & Carers Experiences with Hypophosphatasia & Strensiq

February 2022



berry INSIGHT

Objectives

OVERALL OBJECTIVE:

To gain deeper understanding of the experiences and challenges of people living with Hypophosphatasia and the benefits and challenges of Strensiq.

BY EXPLORING THE FOLLOWING:

1. What it's like for patients and carers to live with HPP? What are the key symptoms and impact on Patients and Carers lives

2. Experiences with current treatments and practices – specifically the benefits and challenges of Strensiq

Patient and carer insight will be used within the MSUK final Managed Access Agreement submission to NICE.

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Who we spoke to

Berry Insight conducted six in-depth, one on one virtual discussions (over zoom) with HPP patients and carers

5 x Adult patients of HPP

1 x Carer of a child with HPP

Strensiq: 5 out of 6 the patients/ carers were being treated with Strensiq

More detailed information on the patients and carers we spoke to can be found in the case studies in the appendix.

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LIVING WITH HPP

Symptoms

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Patient’s experiences with HPP are unique

- Symptoms vary in type and severity depending on:
  - Stage of the condition
  - Patient’s age
  - Treatment and length of time on treatment

- In addition, symptoms tend to change over time
  - Periods of time where symptoms are more/ less severe
  - Change with age - for most, symptoms have increased in type or severity over time, alongside the natural ageing process

A lot of uncertainty for patients - how they will feel from one day to the next and how things will be for them in the future

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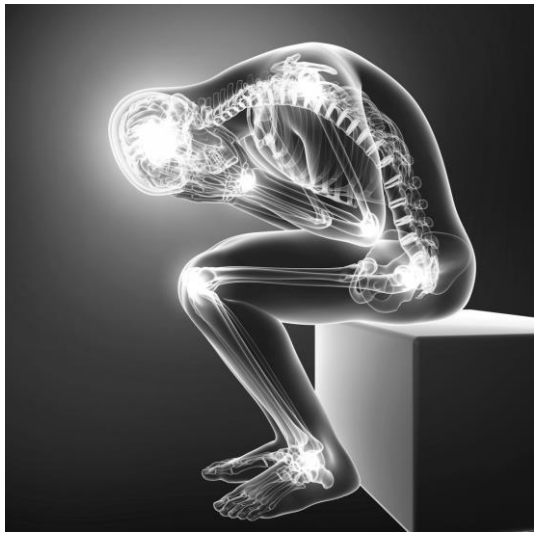
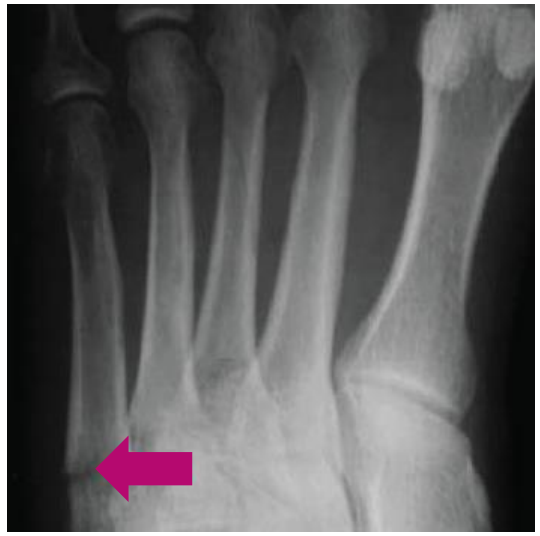
Despite unique experiences, there are some common shared symptoms across the patients we spoke to

Stiffness & Tightness	Pain	Fatigue	Weak bones
			

Strensiq users experienced all of these symptoms to some degree. However, the non-user had not broken bones and had better mobility than those using Strensiq

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Patients experience a lot of stiffness & tightness across their bodies

Stiffness and aching, especially in their back and joints

Makes movement or standing for any length of time challenging and uncomfortable

Tightness in ligaments, particularly affecting hands and feet

Makes it challenging to open things, do up buttons, hold onto things and walk easily

> *I feel very stiff all over and can find it quite hard to move. Especially when I wake up in the morning – everything feels very solid.*

> *I get what I've always called, since a child, this 'pull tight' feeling in my hands and feet, which I now know to be to do with my tendons and ligaments.*

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All patients were suffering from regular discomfort and pain

Neuropathic pain	Tingling and sensitivity, feel very sore to the touch
Aching and discomfort	From stiff, sore muscles, back and joints
Headaches	Can be regular, severe and debilitating
Bone Pain	'Gnawing', 'burning' pain inside of the bone. Comes in surges and moves around the body. For most it's regular and the pain levels severe and sometimes unbearable

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HPP patients suffer from physical and mental fatigue

- **Physically:** Body is easily exhausted from any physical exertion, or standing for too long
- **Mentally:** Patients regularly feel foggy headed and find it hard to concentrate, or hold a conversation
- Fatigue tends to be worse if patients have been busy or pushed themselves too much
    - Going out socially, undertaking tasks in the home or doing a day's work can leave patients feeling totally 'wiped out'
- Experiencing regular pain and discomfort can be mentally and physically exhausting for patients

> *I get so tired as the day goes on; I often feel so fatigued I need to lie down.*

> *I get really foggy headed – it can be really hard to concentrate on anything or hold a conversation without losing your thread.*

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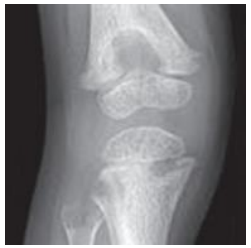
HPP Patients are prone to breaking and fracturing bones

- Patients describe breaking and fracturing bones easily, from minor, everyday events i.e.
    - Breaking ribs from sneezing, turning over in bed or using the banister to help pull themselves up the stairs
    - Fracturing or breaking feet, heels or legs by putting too much weight on them
- Many have lived with fractures for some time without knowing
- Regular visits to hospital for x-rays, having bones pinned or put in plaster or joints replaced

> *When I was younger my shoulder used to dislocate a lot. I'd sneeze or turn over in bed and dislocate it. I'd crack ribs all the time just by sneezing, it was agony.*

> *When we got her (daughter) diagnosed, they looked and we found out that she had multiple fractures which is why she was struggling so much.*



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LIVING WITH HPP

Impact on Patient and Carers' Lives

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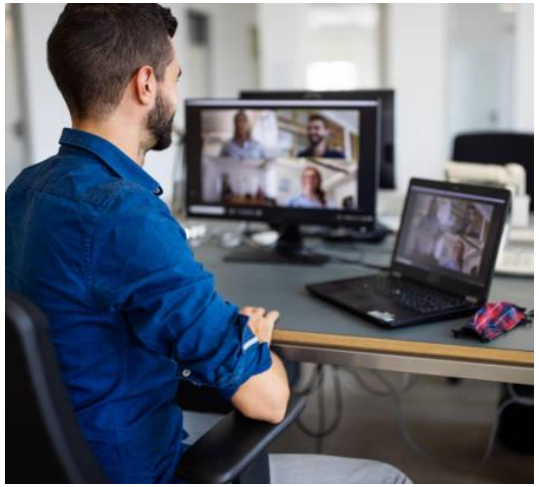
HPP impacts patients lives physically, socially & emotionally

Mobility	Work	Leisure	Mental Health
			

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One of the greatest challenges for patients with HPP is the impact the condition has on their mobility

- Patients are unable to walk very far
    - Nearly all used walking aids to assist them both inside and outside of the home, i.e. crutches and/ or mobility scooters
- Unable to stand for any length of time
- Pushing, pulling, lifting and bending is difficult and painful

> *I really miss walking… I could deal with the pain if I only could have my mobility back. Dealing with both is just awful.*

Poor mobility makes everyday activities and independent living difficult

Self care

- **Getting washed** - Hard to stand up for long in the shower or get in and out of the bath
- **Dressing themselves** - Bending and lifting to put clothes on, doing up and undoing buttons is hard

Housework and shopping

- **Physically exerting** - a lot of walking, pushing and lifting involved – pushing a trolly/ vacuum or carrying a basket is difficult and painful

All reliant on others to some extent to help them with these activities. Many have adapted their homes to help with their mobility i.e. rails and stools.

Working with HPP can be very challenging

- Physical limitations to what and where you can work – any form of physical exertion is difficult
- Mentally challenging – patients often feel fatigued, foggy headed and struggle with their concentration
- A lot of time off required for appointments and sickness
- Reliant on understanding and goodwill of your employer – many don't recognize or understand the condition – hard to understand and empathize
- Many had either stopped or changed the way they work e.g. retiring early, reducing hours, changing jobs or working for themselves – easier to manage workload and symptoms

> *I've had to leave several jobs because I just haven't been able to cope. I'm now self employed which is much better - I can manage my hours and have a lie down and rest when I need to.*

> *I was a truck driver but I'm now on reduced hours and working in the office there. It's still difficult to get through the day, but I need to work to pay my mortgage.*

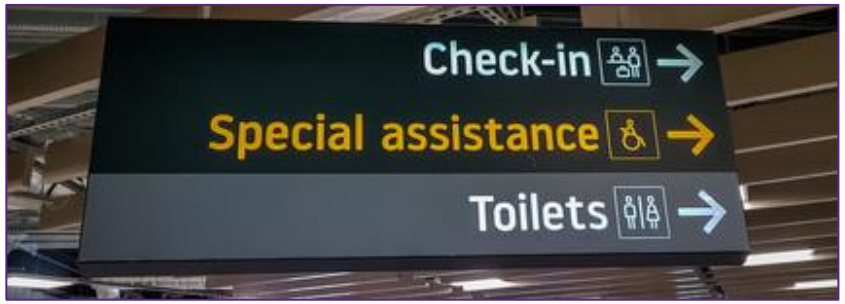
Having HPP makes it hard to live a normal, enjoyable life

- Hard to plan and commit – never know how you will feel and anxious about how you might feel afterwards
- Mobility issues affect many leisure activities – involve walking or sitting for long periods (often on uncomfortable chairs)
- Travel & holidays – often involve long drives and pulling/ carrying bags. Most patients need to travel with someone to help them
- Patients often don't feel like going out or being around people
  - Don't have the will or the energy when feeling tired or experiencing pain and discomfort
  - Low self-esteem– some feel self conscious about their condition and having to use walking aids, feel different

HPP has a negative impact on patient's quality of life

> *"It's hard when you're with friends and they want to do things. I can't walk very far or sit for long. They're really understanding and supportive, but it does make it hard.*

> *"I'd love to be able to go on holiday. I'd only go with my husband though because I need help with everything – carrying my bags, getting on and off the plane, getting myself dressed. It's exhausting just thinking about it.*



Living with the physical symptoms of HPP has an impact on patients' mental health

- All patients we spoke to had struggled at some point with their mental health
- For some this is believed to be due to a physical symptom of the condition - low vitamin D impacts their mood
- But for many the impact the condition has on their life also has an impact on their mental health and mood
  - Living in constant pain and discomfort is very tough
  - Not being able to enjoy day to day life as they used to is very tough – makes it hard to remain positive

> *"I've found it really hard the past few years to accept that this is it for me now and I need to just try and get on with it – what choice do I have?*

Emotional impact of the condition starts before diagnosis

- Most of the patients we spoke to had experienced symptoms for a significant part of their life, without knowing why
  - Years spent fighting for answers – from GP and different hospital departments
  - Continuous disappointment and frustration of no answers whilst living in constant pain and discomfort
  - Tried to push themselves to get on with life as normal, despite experiencing incredible pain and discomfort - further exacerbating symptoms

The fight for diagnosis is frustrating and distressing and can have a long-term impact on patient's mental health

> *"Over the years I'd been told I had mental health problems and it was all in my head. I've been suffering with my mental health for years. Every time you go to see a specialist you get buoyed up and then I'd just end up leaving in tears with no answers.*

Diagnosis comes with mixed emotions

- **Shock/overwhelmed**– At hearing you have a rare condition
- **Relief –** Finally having an answer
- **Worry & Guilt** – for the children/ grandchildren who have, or may have HPP and for those caring for them
- **Anxious and fearful** - about the future for them and their children/ grandchildren who may have HPP
- **Helplessness** Nothing to help them and their situation is unlikely to improve
- **Lonely** - having a rare condition can be a lonely place

Although diagnosis gives some peace and understanding, it's hard for many patients to come to terms with having the condition

> *Diagnosis is bittersweet. It was a relief to know I wasn't making it up but in some ways it was easier when I didn't know – ignorance is bliss in a way!*

> *This condition doesn't just impact me, it impacts my whole family. I look at my children who are following in my footsteps and I wonder what the future holds for them – will they end up like me?*

HPP also has a big impact on **Carers** lives

Practical Impact - Time and Energy

- As with patients, carers have had to fight hard and spend a lot of time and energy to get a diagnosis
- A lot of time spent in hospital while patient has been unwell – i.e. for fractured and broken bones, difficulty breathing etc.
- Very little time for themselves, partner, family or work

Physical Impact

- Can be physically demanding looking after someone with HPP – helping them with everyday activities, i.e. self care.
- Small children/ infants with HPP need a lot of physical support from parents for longer – delays to physical development

> *"Me and my husband live quite separate lives. In the pandemic there was only one person allowed in the hospital, so we've been passing ships in the night. We hope in the future my in-laws will be able to move closer and can help more – it would give us a new lease of life!*

NB: This learning is based on speaking with one Carer; a parent of a 2-year old child

HPP also has a big impact on **Carers** lives

Emotional impact

Carers experience many of the same emotions as patients when it comes to living with HPP

- **Fear & Anxiety:** For the patient's future i.e. symptoms getting worse, not being able to enjoy a normal life
- **Guilt:** For patents that they passed the condition on and/ or that they hadn't been aware of the level of pain or damage
- **Helplessness:** Watching someone you love in pain and discomfort and being unable to make it stop
- **Loneliness**: Few others really understand what it's like. Not much support (esp. during COVID).

A lot of pressure and dependance on Carers, especially during the pandemic – onus on one person

> *She (daughter) had fractures since birth we didn't even know about. I do feel guilty – she must have been in agony, and we didn't know why.*

> *No one really understands the daily struggles and the things that happen behind closed doors, it can be a very difficult and lonely place.*

NB: This learning is based on speaking with one Carer; a parent of a 2-year old child

LIVING WITH HPP

Information & Support

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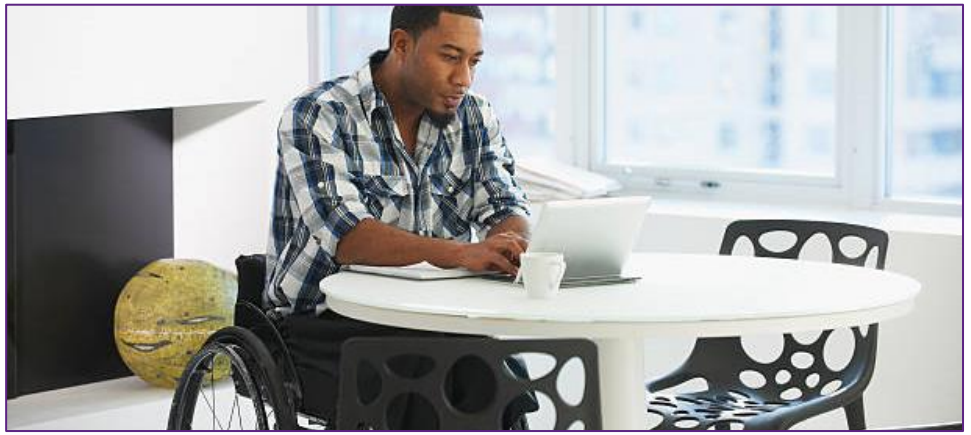
Information at diagnosis tends to focus on what the condition is, rather than the implications for patients

- Very little information and support from the medical community at the point of diagnosis
- Information provided is very clinical - describing what the condition is
- Very little about the implications for the patient i.e. the symptoms they might experience, how this may impact and where they can get support
- Onus is on patients and carers to do their own research and fight for their own support

> *“There’s lots of useful information out there but none of it was from the people treating me – I had to go and look for it.*

> *“I was told what I had and what it was and then I was just sort of left to it to do some googling. There’s lots of medical information out there, telling me what the condition is, but not much how it was going to affect me and my life.*



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Some valuable resources supporting patients and carers

Charities and support groups - Soft Bones US & UK & MSUK

- Facebook and support groups
- Provide lots of information on the condition, the latest research and treatment
- Opportunity to meet and talk to other patients and Carers who share the same experiences and understand

Other Patients & Carers

- Usually met through the above channels
- One consultant set up a WhatsApp group of other patients on Strensiq to allow them to share experiences & support each other

> *I joined the Soft Bones group and met a lady in America who has a little girl who's a similar age. She understands. When you feel like friends and family don't understand I can turn to her and we have a good chat about it.*

> *US Soft Bones group sent information which was very helpful. The people in that group are very knowledgeable.*

A desire for greater awareness, information and support in two areas

Within the Medical Community

- More information and support at the point of diagnosis
- Better communication across NHS
  - Patients and Carers must repeatedly explain the condition to doctors which can be time consuming, tiring and stressful

> *Within the NHS it would be good to have multi-disciplinary teams like they do with children. I have to be the go-between, no one understands. It's such a big stress to always be the one sharing the information. You shouldn't have to do that when you're really ill.*

For Employers

- Information for employers on what the condition is and how it affects patients, to help them understand and better support employees with HPP in the workplace
- Information for patients (and carers) to access support and benefits i.e. income support and employment rights

> *It would be great to have more information available explaining what HPP does to patients. That would really help my employer understand why I struggle. At the moment he can read what the condition is, but it doesn't mean much really – he has soft bones, so what?*

Living With HPP

HPP TREATMENT

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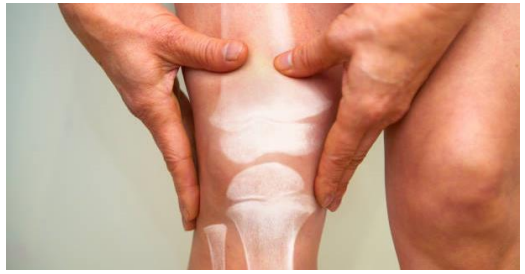
Our common fight.

Historically, medical treatment has focused on alleviating the symptoms of HPP

Pain		Prescribed painkillers – paracetamol, co-codamol, and for more severe bone pain – tramadol & morphine
Stiffness		Anti-inflammatories & cortisone injections
Broken/ Fractured Bones		Bones plastered and pinned, replacement joints i.e. hip/ knee/ shoulder

Treatments offer some temporary relief, but don't address the root cause

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Alternative Therapy is often used by patients in conjunction with medical treatment, to help alleviate symptoms

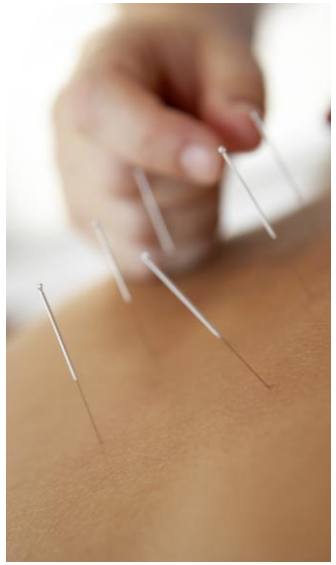
For stiffness, aches, discomfort and pain

Soft Tissue Massage

Hydrotherapy

Heat Pads

Acupuncture



For anxiety & depression

CBT

This is something that is SELF FUNDED by the patients and not a long-term solution

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Patients develop their own coping strategies to get on with life as best as they can

Knowing their limits

- Not pushing themselves and resting when they need it
- Managing expectations of what they are able to do

Distraction techniques

- Keeping busy
- Focusing on something enjoyable and positive i.e. hobbies

Asking for help

- Getting friends/ loved ones to help them do things i.e. shopping, lifting, housework etc.

Patients have learnt to live with the condition, despite continuous suffering

> *Over time you do just learn what you can and can't do and develop coping mechanisms. I try and distract myself and focus on something positive, like my art. It keeps me busy, and the heat of the wax helps my hands. If I didn't do that it would really get me down - it can be a very dilapidating condition.*

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HPP TREATMENT

Strensiq

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Strensiq offers a ray of hope for patients

- Until now there has been no long-term solution for treating HPP – patients have had little hope of improving their situation
- Strensiq offers a chance for a better, more normal life and a brighter future for them and their families
- But a long and difficult journey for most to receive treatment
  - Most heard about it through FB support groups and asked or were approached by their consultant to apply for the treatment (one heard about it from the Rudy study panel)
  - Tough application process – consultants often fight hard to make the case
  - A long wait for treatment to start – over a year for many
  - Frustrating & distressing – keen and apprehensive to start, while waiting many were deteriorating further

> *“There’s nothing anyone has been able to do. It was a bit of a hopeless situation before. But you just had to get on with life, what other choice did we have?*

> *“Strensiq gives us a bit of hope – it’s the only thing out there. Before there was absolutely nothing, no hope, just a future of deterioration*

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HPP TREATMENT

Strensiq - Benefits

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All patients have experienced some improvements to their symptoms since starting the treatment

- Patients had been using Strensiq from just 6 months up to 3 years
- Across patients there were improvements to all the key symptoms
- The extent of improvement varies from person to person depending on type and severity of symptoms, age of patient/ stage of condition and how long been using the treatment
- Greatest improvements were seen in the youngest patient with the severest symptoms and for those who had been using it the longest (over 12 months)
- For those patients who had not been on the treatment as long, or had deteriorated significantly pre-treatment, improvements were more subtle and gradual but a hope they would continue to improve

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The greatest improvements have been to patient's bone strength & levels of stiffness and tightness

Bone strength

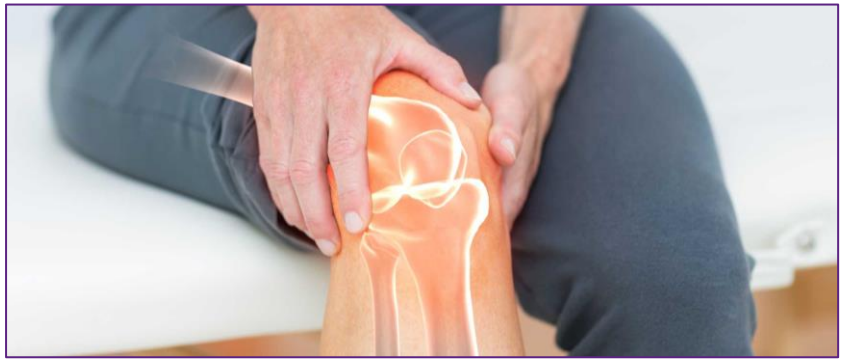
- Patients who were regularly breaking bones are not any more
- Existing breakages and fractures are healing better and much faster
- Bones look stronger on x rays – patients and doctors can see the difference – clearer outline of the bone, bones are re-forming

Stiffness and Tightness

- Patients feel stronger in their muscles and joints
- Less stiffness and aching when standing and moving
- Movement overall is easier and smoother

All patients we spoke to had seen some level of improvement to these symptoms

> *"I broke my femur before starting the treatment and when I went back to the hospital for an x-ray it had completely healed! That shows what it can do – that would have taken a long time to heal before!*



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Most patients have also seen an increase in their energy levels since starting the treatment

- Energy levels have increased, fatigue levels greatly reduced
- Improvements have been quite dramatic for some after beginning the treatment and after each dose – some describe a ‘surge of energy’
- This makes patients feel able to do more
  - **Physically** – feel more motivated to do more and challenge themselves to do more
  - **Mentally** – feel more alert, positive and stronger mentally to cope with the condition
- Improved energy also makes patients able to deal with other symptoms better i.e. pain and discomfort

> *“She’s like a completely different child on Strensiq. She has more eye contact, she smiles. About 10 minutes later she runs around and has a bit of a ‘hyper hour’.*

> *“I’ve got so much more energy now. I feel like I can challenge myself now to do a bit more.*

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Although there has been an improvement to patient's overall discomfort, Strensiq has had less impact on bone pain

- Stronger bones and less stiffness has meant less aching and discomfort for patients
- One patient had felt a difference to her bone pain (been on Strensiq for over 2 years)
- But not much difference to bone and other related pain for others, especially in the first 6-12 months
- Bone pain can get temporarily worse after taking Strensiq
- However, progress in other symptoms have improved patient's situation overall and helps patients feel able to manage their pain better

> *Unfortunately, it hasn't made much difference to my pain levels, but, overall I feel stronger and more able to manage that*

> *Initially I get a bit more pain in my bones but I think that's because it's starting to work and do what it needs to do*

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Improvement to symptoms have had a positive impact on patient's mobility

All patients have seen improvement to their mobility levels since starting the treatment

- Patients can walk further without their crutches, sticks or scooter
- Can stand for longer periods of time
- Are able to push/ pull more easily i.e. pull themselves self up from bath/ toilet
- One infant patient was hitting key physical milestones each time medication increased, i.e. sitting up, crawling and now walking

> *My friends have noticed it the most. I'll turn up now and they'll comment that I haven't got my crutches and can keep up with them. So that keeps me going that they are noticing the difference in me and are really happy about it!*

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And on patients and carer's quality of life

Patients

- Feel physically and mentally able to get involved in life and do more
- Greater independence – able to do more things for themselves, less reliance on family, friends and carers
- Enabled them to get a bit of normality back to their lives
- Less need medical care – less time in hospital and GP appointments for their symptoms
- Levels of anxiety and depression have decreased for many

Carers

- Carers can see the positive difference Strensiq is making and enjoy seeing patients in less discomfort and able to enjoy life more
- Less reliance on them for physical, emotional and practical support
- Less anxious and more hopeful for the future of their loved one

> *"It's just nice to be able to get around the house and do things without going from room to room reliant on my crutches. Small things really, but they make a big difference to me.*

> *"It's massively changed her life, but ours too. I used to be in floods of tears that she couldn't join in and do things. It's so lovely to watch her get involved and play!*

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HPP TREATMENT

Strensiq - Challenges

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Two main challenges of Strensiq

Administration

Cost/ Access

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Administration of Strensiq is very tough for patients

- All were Injecting the treatment 6 days a week, with one day off. Usually into thighs or stomach
- The process of injecting the medication is extremely tough
  - Very painful – especially as treatment is going in. Some increased bone pain afterwards
  - Large needle and slow to inject – liquid is cold and thick
- Some side effects from the injections
  - Reactions around the injection site (red, sore and itchy)
  - Lasting damage to skin – scarred, uneven surface
  - Rotate where to inject - becomes hard to find space
  - Some put on weight which can exacerbate symptoms

Despite being grateful for treatment, the administration adds some additional discomfort and stress for patients

> *It's a painful thing to have to do and afterwards my skin was really red and blotchy, with nowhere else to go to inject.*

> *It makes me quite stressed out when I have to do it. I dread doing it – I just get home from work and get really stressed out by the whole process.*

For carers, administering Strensiq to a child is really challenging

- Seeing your child in pain and discomfort while you give the treatment is stressful and upsetting

- Trying to encourage a child to let you administer the treatment, **and** stay still long enough to do the injection is very difficult
  - Parents having to trial multiple different strategies to overcome this, i.e. negotiation and role play
  - Requires a great deal of patience and physical and emotional strength

A very tough experience for Carers to have, on top of pressures they are already experiencing

> *The injections are really tough. She will cry a painful cry when the medication is going in which is horrible. Me and my husband have both been in tears, but we have to keep telling ourselves that this is saving her life.*

ADMINISTRATION

The first six months are the most difficult

- Apprehension about trialing a new treatment
- Side effects are worse initially while patient's bodies get used to the treatment
- Improvements to symptoms are often gradual - initially the challenges can outweigh, or mask the benefits
- Many experience feelings of stress and dread around the process, and some struggle to do all the injections prescribed
- After six months things settles down
    - Body gets used to it – side effects settle down/ go away
    - Patients get used to the process and find solutions
    - Experiencing benefits helps them cope with the injections

Opportunity for those who've been on Strensiq longer to mentor and support patients during first 6 months, by sharing their advice and experiences

> *"The first 6 months are quite difficult. There are so many changes in your body. I felt very odd. But after that things start to settle down and you start to get better. It's been a bit of a rollercoaster!*

> *"People online kept telling me to keep going and that it would get easier, and it has.*

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COST/ACCESS

Patients and carers are concerned that the cost of the treatment will mean it will be stopped or restricted

- Patients are hugely grateful for the treatment and believe the benefits outweigh the challenges – even for those early on in treatment struggling the most
- Concern that high cost of treatment will mean it won't be approved and their progress would stop
- Worry for others, i.e. family members who are beginning to follow their path – don't want them to suffer as they have
- Although patients understand the high costs of the treatment, a belief that it is saving costs elsewhere
    - GP & hospital appointments, operations & medication
    - Giving the treatment to patients earlier, will stop people deteriorating and thus save costs

A request that the cost savings of Strensiq are fully investigated, as well as the costs of treatment

> *"I know it's an expensive drug but I look at my daughter and I see her following my path. If she had treatment earlier she would save the NHS a fortune. She wouldn't have to have all the operations I've had, all of the x-rays, the painkillers and GP appointments. It's a false economy really.*

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Strensiq – Non-Users

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Non Strensiq users understand why access is limited, but hope that this is reviewed and re-considered in the future

- The non-user we spoke to was aware of Strensiq
- Although discussing this with doctors, their symptoms were not severe enough to apply for and access the treatment – no bone fractures and more mobile (able to walk unaided)
- An understanding of high costs associated and acceptance that treatment should be prioritized for those who need it most
- But disappointment that diagnosis and treatment is not happening earlier, before symptoms get severe vs waiting to get very bad before getting help – feels a bit counterintuitive
- Aware from others in HPP community about the challenges with administration and side effects – some small sense of relief

Hope that access for (improved) treatment will be possible, if not for them, for their children and grandchildren

> *It's fair enough that those people with severe symptoms should be prioritized, I just hope that for the sake of my children and grandchildren that they find a way of funding this in the future for more patients, so they don't end up like me.*

> *I've heard it is very tough and can make you feel a lot worse before you get better, so for now I'm okay to just carry on with life as I know it.*

NB: This learning is based on speaking with one patient not receiving Strensiq and anecdotal learnings from Strensiq users about family members unable to access the treatment

HPP TREATMENT

HPP TREATMENT

Hopes for the Future

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Hopes for the future surround improved access and administration

Continued and widened Access

- The biggest hope for patients and carers is that their treatment can continue, and they will carry on improving
- Patients (esp. older) are not expecting dramatic results, but hope they will continue to feel stronger and be able to lead a more normal life
- A hope that criteria is broadened so patients without severe symptoms can access treatment earlier, before they deteriorate

Improved method of administration

- A hope that the administration method can be improved
    - Current injections don't feel like a long-term solution
    - In the long-term patients would love a more traditional means of administration, i.e. a tablet
    - In the short-term, less regular injections – perhaps a stronger dose administered in hospital once a month

> *"I don't expect to suddenly be able to walk or run a marathon but just to be able to do normal things like walk around the shops in town or go on a nice holiday would make a world of difference to us.*

> *"I feel life would improve significantly if there was a different way to administer it. Live an IV once a month or gene therapy, just a different way than this.*

Patients and carers biggest fear is the impact of treatment being taken away

- It would be extremely tough for patients if Strensiq was stopped
  - For those who have experienced improvements - progress would stop and a return to deterioration
  - For those very early on in the treatment - haven't had the opportunity to experience the benefits
- Taking away the chance for a normal life (or in some severe cases, taking away a chance of life)
- Patients fear for the future of their children and grandchildren – can see them following in their path and don't want their future to be like theirs has been

The stakes are high – all patients said they were willing to fight hard for continued access to the treatment

> *I don't know what I'll do if they take the treatment away. There will be no hope for me. I would fight for it as hard as I can for the chance to keep going!*

> *I already see the signs in some of my grandchildren, they have lost teeth and are breaking bones. I don't want them to end up like me. They still have a chance, please don't take it away!*

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HOPES & FEARS FOR THE FUTURE

APPENDIX

Patient Case Studies

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UCD PATIENT CASE STUDY

NAME:	Jake
AGE:	28
CONDITION:	Recently Diagnosed with HPP (in mid 20s)
CARER:	Girlfriend helps with shopping, housework and getting dressed

Key Symptoms & Impact

Key symptoms:
- Severe bone pain & fractures, stiffness and fatigue

Impact
- Poor mobility – uses crutches and a mobility scooter
- Struggles with work – used to drive trucks but changed to an office role. Better but still finds it very tiring.
- Low self-esteem: Embarrassed to be around people - feels different & that people are looking at him.

Current treatment

- Morphine for his pain – helps sleep but less with pain
- Anti-inflammatories for stiffness
- Occasional soft tissue massage to help with stiffness
- Using Strensiq for 18 months

Experiences with Strensiq

Challenges: Struggles to cope with the injections - extremely painful, time consuming and uncomfortable. Damages the skin – finds it hard to find space to inject. Has reduced his injections to 3 x a week instead.
Benefits: Stronger bones in x-rays & slight improvement to mobility – can stand for longer and movement is easier

> ***I really miss doing normal things but I'm so knackered and in so much pain because work has taken it out of me that I don't feel I can be around people. People look at me and it feels demoralizing. I feel like I shouldn't be in this situation.***

UCD PATIENT CASE STUDY

NAME:	Mel
AGE:	62
CONDITION:	Diagnosed with HPP at 51 after years of symptoms
CARER:	Husband helps support her

Key Symptoms & Impact

Key symptoms:
- Severe bone and joint pain, stiffness, tightness and fatigue

Impact
- Poor mobility – feels very weak
- Struggled with mental health most of her adult life – driven by lack of diagnosis/ mis- diagnosis and constant pain and dis-comfort

Current treatment

- Cortisone injections & anti-inflammatories for stiffness
- Back operation and shoulder replacement
- Heat pads and art that uses warm wax
- On Strensiq for 2 years – advised as part of Rudy panel

Experiences with Strensiq

Challenges: Struggled with severe allergic reactions to injection sites during first six months
Benefits: Significant improvement to energy levels which have helped her cope with pain. Improved bone pain and mobility levels. As a result, mental health has improved.

> ***Throughout my life I've tried to hide it and get on with things. I'd put up and shut up and be in agony later. It's very difficult when you can't fit in with people. Since the diagnosis it's become obvious that I can't hide it anymore, so I've trained myself to tell people.***

UCD PATIENT CASE STUDY

NAME:	Jill
AGE:	57
CONDITION:	Diagnosed with HPP recently (in her 50s)
CARER:	Husband and children help and support her

Key Symptoms & Impact

Key symptoms:

- Weak bones (been very easily breaking and fracturing bones all her life), neuropathic pain, fatigue, severe anxiety and low mood

Impact

- Poor mobility – feels like her legs can't hold her up
- Work - had to retire early as too unwell to continue
- Social life – hard to plan or enjoy the good things in life

Current treatment

- Acupuncture and hydrotherapy to manage pain
- Both femurs have been pinned and plastered
- On Strensiq for 1 year

Experiences with Strensiq

Challenges: Found first 6 months very challenging. Some nausea, increased anxiety, bone pain and weight initially

Benefits: Anxiety has decreased significantly, fracture in her leg has healed completely and she has improved mobility – able to walk further without crutches and has removed the rail from her bathroom

> ***You have to completely re-think how you live your life (after diagnosis). It's taken me a good 3-4 years to get my head around it. There are lots of implications because it's not just about me, it's a family issue.***

UCD PATIENT CASE STUDY

NAME:	Emily
AGE:	Daughter Eden is 2
CONDITION:	Full Time Carer for Eden who was diagnosed at 6 months old with severe HPP (has two gene mutations)

Key Symptoms & Impact

Key symptoms:

- Short stature/ Dwarfism, weak bones and skull, poor mobility – unable to lift head, sit up, crawl or walk until later in infancy

Impact of being a full-time carer

- Work - had to leave work to become a full-time carer
- Has little time with her husband and family and little support from others due to COVID hospital rules
- Her and her husband have suffered with poor mental health during Eden's illness and diagnosis

Current treatment

- Been on Strensiq since diagnosis (past 18 months)

Experiences with Strensiq

Challenges: Injections are very tough – Eden finds them painful and struggles to comply

Benefits: Mobility and energy levels have improved significantly. She has hit key mobility milestones and is now walking and running. Also had a big social impact as she is able to join in and play with other children

> ***Strensiq is amazing medication. It's saved her life and helped her in so many ways. Every time they've increased her dose she's hit another milestone, it's incredible! The thought of them taking it away is just mind blowing, I can't bring myself to think about it.***

UCD PATIENT CASE STUDY

NAME:	Tarin
AGE:	54
CONDITION:	Diagnosed at 3 months old
CARER:	Friends help and support her

Key Symptoms & Impact

Key symptoms:

- Fatigue, short stature, curved spine, bowlegs, regularly breaking ribs and bones, aching, stiffness & headaches

Impact

- Poor mobility – struggles to walk - uses crutches, finds movement difficult which impacts her social life
- Feels exhausted after a day at work or any physical exertion

Current treatment

- Vitamin D tablets
- Paroxetine for headaches
- Strensiq for 3 years

Experiences with Strensiq

Challenges: Struggles with painful injection process and suffered **i**nitial side effects – reactions at injection sites
Benefits: Existing bone breakages and fractures have healed quickly, increased energy levels and improved mobility – able to walk further without crutches

> ***I had broken my arm shortly before starting the treatment. It healed very quickly – just a few months, whereas normally that would have taken at least a couple of years! I used to break a lot of bones but since I've been on Strensiq I haven't broken any!***

UCD PATIENT CASE STUDY

NAME:	Anita
AGE:	58
CONDITION:	Diagnosed with infantile HPP after her son, 3 years ago
CARER:	N/A Family have formed a support unit since their diagnosis

Key Symptoms & Impact

Key symptoms:

- Muscle stiffness and weakness, hip and back pain and fatigue, restless legs

Impact

- Struggles with mobility – can't walk far or do anything strenuous without feeling discomfort, pain and fatigue
- Work – moved jobs to become self-employed as fatigue and discomfort meant she was struggling to keep jobs

Current treatment

- Paracetamol for pain
- Heat pads and hot water bottles for stiffness and pain

Experiences with Strensiq

- Unable to receive Strensiq as symptoms are not severe enough – no broken bones or fractures
- Hopes that diagnosis and treatment for HPP can happen earlier, before symptoms progress, so her children have a brighter future ahead

> ***I felt so horrendous when I was diagnosed, knowing that I had passed this onto my children. And that there is no treatment for us or anything they can do. We may as well not have been diagnosed – ignorance is bliss in a way.***

NICE National Institute for Health and Care Excellence

HIGHLY SPECIALISED TECHNOLOGIES (HST)

Guidance review following a period of managed access - Patient organisation submission

Asfotase alfa for treating paediatric-onset hypophosphatasia (review of HST6) [ID3927]

Thank you for agreeing to give us your organisation's views on this treatment following a period of managed access. You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

PLEASE NOTE: You do not have to answer every question. Your organisations involvement in the managed access agreement for this treatment is likely to determine which questions you can answer.

To help you give your views, please use this questionnaire with **NICE's guide for patient organisations "completing an organisation submission following a period of Managed Access for Technology Appraisals or Highly Specialised Technologies".** Please contact pip@nice.org.uk if you have not received a copy with your invitation to participate.

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 20 pages.

NICE National Institute for Health and Care Excellence

This form has 8 sections

NICE National Institute for Health and Care Excellence

Section 1. About you

Table 1 Name, job, organisation

1. Your name	[redacted]
2. Name of organisation	Metabolic Support UK
3. Job title or position	[redacted]
4a. Provide a brief description of the organisation. How many members does it have?	Metabolic Support UK is a non-profit patient umbrella organisation, supporting patients and families worldwide living with Inherited Metabolic Disorders through helplines, online resources, social media, peer support programmes, newsletters, and events. Metabolic Support UK delivers a wide range of support and advocacy services to address unmet needs. Using qualitative and quantitative data generated via various methodologies, our small, dedicated team works to proactively identify priority needs and develop evidence-based outputs and programmes to ensure the maximum impact for individual patients, collective patient communities and the wider IMD community. Metabolic Support UK receives it's funding from corporation, community fundraising and grants, trusts and giving. Metabolic Support UK supports over 20,000 members worldwide.
4b. Has the organisation received any funding from the company/companies of the treatment and/or comparator products in the last 12 months? [Relevant companies are listed in the appraisal stakeholder list which was provided to you when the appraisal started]	Metabolic Support UK have received a total of £10,887.50 sponsorship from Alexion Pharmaceuticals in the last 12 months. Alexion Pharmaceutical provided sponsorship towards the Metabolic Support UK 2021 annual conference (£10,000) and reimbursed Metabolic Support UK employees for their participation in two patient-facing workshops and for the recruitment of patient experts to these workshops to a total value of £887.50.

If so, please state the name of company, amount, and purpose of funding.	
4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
5. How did you gather information about the experiences of patients and carers to include in your submission?	The information contained within this submission has been obtained through long-term discussion with patients and families, through surveys, interviews, focus groups, and case studies.

Section 2 Living with the condition and current treatment

Table 2 What it's like for patients, carers and families to live with the condition and current NHS treatment

6. What is it like to live with the condition? Consider the experience of living with the condition and the impact on daily life (physical and emotional health, ability to work, adaptations to your home, financial impact, relationships, and social life). For children, consider their ability to go to school, develop emotionally, form friendships and participate in school and	In all age-ranges, although symptoms vary, paediatric-onset Hypophosphatasia is a debilitating condition. From our most recent survey the most common symptoms of HPP described as being moderate to severe included growth delays short stature (64%), delayed walking (55%), fatigue (55%), tooth loss with roots / premature tooth loss (55%), skeletal deformities (45%), painful or swollen joints (45%), fractures (36%), bone pain (36%), and weak limbs (36%). Additional symptoms included feeding difficulties, breathing difficulties, calcium build-up / crystal deposit, difficulties gaining weight, vomiting, seizures, kidney problems, and regular headaches. Many of the more severe symptoms contribute significantly towards mobility problems, with many adults and children requiring the use of aids to walk or have been required adaptions to their home. Sitting for long periods in one position is also uncomfortable so there is fine balance between needing to move regularly but to also balance fatigue levels and manage pain levels. From the adults we have spoken with, bone pain and fatigue are described as going hand-in-hand, with one exacerbating the other. A clear point

social life. Is there any impact on their siblings?	that has been raised by adults is that there is constant requirement to prepare and plan for any events or activity which often means that there is little opportunity for spontaneity in their lives, as fatigue means they often require up to a day of rest before and after, regular rest breaks during, and ensuring they carefully regulate their energy levels (both physical and mental) throughout any day out. One patient described this to us "*I have to plan my days in order to be able to have a social life. i.e., if I am going out for the evening I have to be very careful about what I do all day*". One adult told us "*I have continual constant pain throughout my body which can roam about and flare severely at different or multiple sites. I cannot remember not being in pain*" Many patients describe this pain as a radiating pain or a deep gnawing pain which causes anxiety from not knowing how severe it will be from one day to the next. Care also needs to be taken when performing daily tasks. Even simple movements like stepping off a curb or sneezing can cause fractures. In others it causes inflammation, one patient told us "*I find everyday tasks difficult because of my pain and weakness. I always have great difficulty and am often left exhausted and in agony if I shop with a trolley or carry bags, drive any distance, sit for long periods, or make any repetitive movements as it seems to cause inflammation which in turn causes pain. I have difficulty much of the time with dressing and undressing, chopping food and lifting pans, getting out of a chair, and I always struggle to walk initially but things improve as I take more steps*". Respiratory difficulties, bone malformations, and failure to grow or gain weight were more commonly reported amongst the paediatric patients. One parent told us *"(my child's) chest was sunken in and so he was put on opti-flow to help the pressure, so he didn't have to make as much effort when breathing for the first weeks of his life*". Another told us *"(my child) still has a peg feed, he never got on with feeding from day one, this is one of our biggest struggles in trying to get him to eat*". Others described bowing of the legs and arms, severe reflux, curvature of the spine, tooth loss, and a delay in motor skills *"(he is) behind in his motor skills, but gradually progressing, he is one and he cannot yet sit up unsupported*". Adults reflecting back on their challenges also recount similar memories from growing up. One adult told us "*as a 6-month baby I was very floppy and would be unable to sit unless propped*". These early symptoms described by adults were often followed by a long period of living without a diagnosis, with multiple appointments, surgeries, treatments, and diagnoses with consultants trying to manage individual symptoms but struggling to put together an overall confirmed diagnosis. 65% of those who participated in our survey told us that HPP had impacted their finances and 83% of those who participated told us that HPP had affected their ability to work or study. These statistics include both adult patients and parents/carers.

Employment

Patients with the condition often struggle to find a balance with employment. 50% of the patients we surveyed are currently in full time employment. However, worsening of symptoms means that mobility issues and intensity of pain become troublesome and result in individuals consequently being unable to fulfil their original role. One patient told us "*I was unable to continue with my job as it was a stressful and demanding job*". Fatigue affects people both physically and mentally and so those with HPP often struggle to focus or think clearly. We are currently supporting a further patient through a discrimination complaints procedure to help ensure they are able to access their rights to employment support, reasonable adjustments and a referral to occupational health after the patient had been signed off for stress, anxiety and declining health. However, many do not see this route as an option, and it can be particularly draining especially when already suffering with debilitating fatigue. The remaining 50% of patients from our survey have given up work and retired. However, from discussions we also know some have moved to self-employed positions. One patient told us "*I have never been able to hold down a full-time job for long therefore I have tended to work from home or be on part time contracts. I am now self-employed so that I can tailor my days according to my pain levels. I have bought specialist equipment so I can be as comfortable as possible*". In our experience of supporting families, we know that many have struggled with the financial burden of HPP, the impact of either giving up work or moving to part time hours means that they are reliant on benefits and/or support from other family members. Some simply cannot find this balance and need to explore supportive measures from work to allow them to pay their bills. One person told us *"I have HPP, but I also have a mortgage to pay so I can't just quit my job*".

Education

57% of children surveyed were in full time education, with an equal distribution of those receiving minimal classroom support to those on an EHCP plan. The remaining 43% of children were too young to be in education. Although being able to participate in classroom-based lessons such as literacy and maths is largely unaffected, sitting for long periods of time and participating in physical activities exacerbated pain and mobility problems made physical education lessons unachievable. One parent told us "*It was very difficult for (my child) starting primary school not being able to walk properly and finding it difficult to participate in sports etc"*. Adults reflecting on their school life also agreed with this and recalled sitting at desks as being painful. One told us "*I was often needing to lie down at school, but no-one understood*". From our survey, on average, the children in school attend one appointment every two-three months, with

	one parent telling us their child had "too many to recollect". This in itself has an impact on a child's attainment due to days off to attend, which may be extended if overnight stays are required due to distance to the family's nearest treatment centre. **Mental Health** 73% of respondents to our survey described a negative impact on their mental health due to their HPP. Many patients link this with high degrees of pain with one telling us "*I suffer with depression as a result of the pain. My GP is very understanding and has prescribed antidepressants*" and a second. "*When there are multiple sites the pain is extremely debilitating and can make you very miserable*". In addition to emotional support sought through patient groups and peer opportunities patients often seek mental health support via their GP. One patient told us "*my emotional wellbeing is once again looked after by my GP through me asking for support. I book in to see the physiotherapist if I am suffering terribly but this can take some weeks to organise which makes life extremely difficult to manage emotionally. I take anti-depressants to help me cope emotionally. I am tearful sometimes. I have paid for courses to learn 'mindfulness techniques' to try and distract myself*". **Relationships** The impact of HPP on relationships varies, largely depending on the period of time in which patients have been together with partners or spouses. Relationships where the spouse or partner has witnessed a worsening of symptoms over time generally tend to be more supportive and understanding. One patient told us "*my husband is very understanding and helps me as much as he can. He insists I rest when feeling unwell*". Often spouses and partners are required to adjust to a caring role to support patients with HPP and assist with tasks, manage care needs, and accessing support. As a patient organisation we often speak to partners/spouses who are trying to manage appointments or medications on behalf of those they are caring for. When we speak to patients themselves, partners and spouses are very often in the background with supporting information and have a high degree of involvement in the patients care. One patient told us "*my husband and I met at school, so he has always known my difficulties and we have grown up together. He has always helped me with everyday tasks and supported me through the difficult years of misdiagnosis and no diagnosis*". 55% of those who participated in our survey told us that their relationships with immediate and wider networks had been negatively impacted. One of the main contributors to this is a lack of understanding about the impact of HPP and the degree of pain or the requirement to manage fatigue particularly with friends or family. One patient told us "*I have some friends*

	who find it difficult to accept that I cannot do the things that they are capable of doing" and another seconded this stating *"I have friends who don't understand that I can't just get better!"* **Social Life** Due to pain, fatigue and mobility issues, socialising and hobbies are two key areas that are impacted by hypophosphatasia. It is imperative that patient's plan events accordingly and manage their own, and other's expectations about what is and isn't achievable. One patient told us " *My life has changed completely since I was diagnosed with HPP*". Discussions with families revealed the following "*my social life has been severely curtailed. I am unable to walk my dog. I have to ensure that if I am going out for a meal that I have a comfortable chair*" A second agreed "*I am always considering the seating arrangements etc., when I go out whether it be to friend's houses, pubs or the cinema*". For those who enjoy creative hobbies, there is a constant need to adapt and change depending on worsening of symptoms, particularly pain or inflammation in the joints. "*I have to take up new hobbies when I am no longer able to do the things I used to be able to do"*. This often means moving away from circles of friends where they are members of groups where interests are shared, contributing to a sense of isolation. **More information about the impact of living with HPP can be found in our report "Understanding Patient & Carers Experiences with Hypophosphatasia & Strensiq".**
7. What do carers experience when caring for someone with the condition?	Parents and carers of children with this condition experience a huge impact on their ability to work with 57% of those we surveyed describing themselves as full-time carers. 29% are in part time employment and 14% are self-employed managing their own hours. One parent told us "*I am unable to work more than one day as at the moment it would be unsafe for (my child) to attend a nursery, so his dad takes a day off work a week so I can work*". Another parent shared their experiences of how the HPP affected the whole family. "*I've had to leave my job….. (my child's) dad has to go out and work every hour he can to keep a roof over our family's head. We never saw the green side of our bank statements since we have had only one wage coming in, however you just get on with it. When (my child) is unwell it effects myself and (my child's) dad mentally we become stressed and take it out on each other. When (my child) goes off to nursery and is settled I hope to be able to return to work where I would be able to take some of the financial strain from (my child's) dad. We would also be able to take (my child) to every theme park, zoo and any attraction we can find as he more than deserves it. (My child's) health comes first, we hope that everything falls into*

	place as he gets older and stronger (with treatment) we can then return to a normal routine. There are also no plans for no more children at present as (our child) is our main focus". Parents and carers also have to manage their child's care and hospital appointments. Parents reported needing to attend on average 2 appointments per month with an average of 7 healthcare professionals involved in the management of their child's HPP. For the younger children this increases as high as 8 appointments per month with increased number of healthcare professionals. "*We see one particular professor for bones however we have around 10-15 other professionals that look after us*". There is a high degree of burden when it comes to travelling to appointments, many are based in treatment centres that are some distance from home. This requires a lot of negotiation, particularly when it comes to other children being involved. During our discussions, one parent told us "*Whenever we have to attend, I have to take time off work, take my child out of school for 2 days, as it requires an overnight stay, book accommodation, and then organise childcare for my other child*". Due to the rarity of the condition, there is often very little information or advice provided. When asked if this impacts wellbeing, one parent told us "*it has in that being a mother of a child with HPP, and with it being so rare it is difficult to know what his quality of life will be, whether he will eventually eat, whether he will be able to weight bear etc also that people find it hard to understand all of the difficulties (my child) has just for having a bone disorder, it is difficult to explain at times*". Having a child diagnosed with any rare disorder is often very stressful, however particularly in young children this can be especially traumatic and frightening. We have supported HPP families who have struggled to find a diagnosis for their child, who have been told that the prognosis is extremely poor, as well as having to witness life-saving treatments *"(my child's) ribs were not strong enough to support his tiny chest. When (he) caught a chest infection he was immediately rushed into intensive care. After a month of intensive care and two failed decans (he) received an emergency tracheostomy…. Two months later we returned home bringing with us a fully ventilated, oxygenated baby with a tracheotomy*". We know from our experiences that many parents suffer long term mental health problems from such traumas. As well as trying to navigate their own feelings and emotions parents are also left to try and support the wellbeing of their children as they grow up with the condition and the fallout from surgeries and not being able to participate in activities with peers. One parent told us "*our older daughter was very hard to manage at times as a child. We don't know if that was part influenced by her frustrations as a child and what had been 'done to her' but I suspect it had. I asked for professional help on more than one occasion but got none. I did find parenting books helped and a parenting course and a couple of telephone chats with a telephone helpline".*

	Many families have to adapt their hobbies and social lives around their child's HPP. One parent told us "*we are a very 'outdoor' family who love hillwalking, cycling etc. We could not participate in even child versions of such activities with our friends who had kids the same age. We did eventually find a partial solution though in tandem cycling and had years of great outings as a family with other families*". Parent's often also reach out to family members to support them and provide respite in caring for their child. "*We still try to have a reasonable social life, when (my child) was in hospital away from home this became pretty much impossible, but since being at home we do go out on occasions as a couple and my parents will look after (my child), they have been trained and can care for him, so this is nice as it gives us a break*".
8. What do patients and carers think of current treatments and care available on the NHS Please state how they help and what the limitations are.	The current management of HPP is symptomatic and supportive. There is no standard therapy that is given and so any therapy or management option offered is solely based on the individual and their symptoms. One patient told us "*nothing was offered, all pain relief did not work but there is nothing out there to actually heal/help the effects of HPP*". For babies and young children with the condition, the condition is life-limiting and often terminal. One parent told us they were informed their child "*was lucky to make it past six months*". Existing treatments being accessed by the HPP patient community include physiotherapy, ventilation, and medications including reflux medications, vitamin D, multivitamins, Keppra, pyridoxine, dihydracodeine, naproxen, ventolin inhaler, senna (laxative), esomeprazole, calpol. One patient described trying multiple pain relievers, "*only morphine takes the edge off the pain slightly, but I cannot function when on Morphine*". No patients reported any side effects from the above treatment, but all felt that they did not resolve the effects of HPP.
9. Considering all treatments available to patients are there any unmet needs for patients with this condition? If yes please state what these are	This group of patients have a high unmet need. There are no current treatments for HPP patients. This view is also supported by 100% of the respondents in our survey. One parent described the current offer as "conservative treatment and management of breathing issues and seizures. I think it was more managing the condition than any effective treatments". The final sentence in this statement is reflective of the existing symptomatic and supportive approach offered to those with HPP of all ages. Babies and children with the condition have no treatment for the condition and many adult patients are not offered any solution other than painkillers and physiotherapy providing little to no resolution for patients.

	Adult patients with this condition have described fatigue, pain, and fractures to be the 3 main symptoms of HPP that they would like to see resolved by treatments. Although painkillers and pain management programmes can be used they do not resolve the pain experienced in HPP. The remaining two symptoms cannot be controlled by existing treatments.

Section 3 Experience during the managed access agreement (MAA)

Table 3 Experience, advantages and disadvantages during the MAA

10. What are patients' and carers' experience of accessing and having the treatment? • Please refer to the MAA re-evaluation patient submission guide	Access to treatment centres has not been raised as a key issue through our experience of supporting families, through discussions, or interviews. In our survey results 82% of respondents stated that there had been no change to the number of appointments they were required to attend since starting treatment. The start of the MAA was somewhat problematic for some with one parent telling us *"I find the hospital appointments chaotic having 2 children with HPP and trying to fit in questionnaires, blood tests and appointments with other health care professionals in the space of a small period of time*". However, this has since resolved with time. Early challenges around phone calls and delivery of treatment were also quickly resolved. There were some grievances around the length of time taken from being approved for treatment to starting treatment. This was felt to be extensive for some. "*I am pleased with how the managed access agreement is being run once prescribed the medication. It took over 12 months from being told I was eligible for the vaccine to actual receipt of the drug. When this is a managed access agreement of a limited time this was extremely valuable time lost to me as a patient*." However, we must acknowledge the impact of the coronavirus pandemic on the NHS and appointments and believe this may be the cause of some delays. Although not pleasant, particularly with small children, it was felt that injections were relatively straightforward. One patient told us "*it's something that just becomes part of my routine, and I am in control of taking this medication*". All patients we spoke to would have preferred the treatment to be delivered by an alternative method (i.e., orally) due to reactions at the injection sites. Some patients said they would prefer fewer injections; one suggested a higher dose with less frequency. Treatment is administered at home. 100% of our survey respondents confirmed this and all patients and parents/carers welcomed this

	as it meant they could fit it in around their schedule in the comfort of their own home and reduced the need for hospital visits and associated costs. One patient stated, "*at home is the easiest way to fit around life, Hospital would make it difficult to hold down a job*". A parent stated, "*it is a bit more relaxed for her at home and she does not have to miss out on school to go get it (the treatment) there are no disadvantages*". However, another felt that it was a burden on them as parents to deliver the medication to their child "*Advantages would be that we're in our own home comforts, disadvantage is that Mummy and Daddy have to give it.*"
11. What do patients and carers think are the advantages of the treatment? Please refer to the MAA re-evaluation patient submission guide	83.3% see fewer medical professionals since starting Strensiq. Due to the assessments as part of the managed access agreement, the number of hospital appointments have remained the same. However, some patients and parents anticipate this to decrease should Strensiq be approved. Since starting treatment, parents have reported children being slowly weaned off reflux medications, anti-seizure medications, and pain relief. Some adults who are taking pain medications and antidepressants have also started to reduce the dosage and reported a reduced need to access GP services. 100% of respondents to our survey said they saw improvements in mobility and 73% saw in improvements in the number of daily activities they were able to carry out. **Children:** Parents and carers have seen a significant improvement in their child's health as a result of treatment with Strensiq. They have reported that the biggest changes are the ability to breathe independently and regaining control of symptoms or becoming seizure-free. One parent told us *"(my child) was on a ventilator and having poorly controlled seizures prior to commencing on Strensiq. He is still small, but his weight is improving. He is becoming more mobile*". Their child is now "*not requiring ventilation and seizures are mostly controlled. He has only had one seizure since starting Strensiq due to viral illness*". A family stated that they felt "Strensiq has given us our baby back. Without it, it is likely he would have been unable to breathe without a ventilator or his seizures would have been uncontrolled". A further parent agreed "*my baby had a low respiratory drive and shallow breathing requiring oxygen however this has resolved*". One parent told us the most significant changes were in "*breathing and b6 dependant seizures. His breathing is great and no longer needs oxygen even at night and he has not had any seizures since he commenced on the treatment*". Since starting treatment, children have also been described as being more comfortable and happier and more alert. In discussions, one parent stated "*it gives her quality of life to enable her to join in activities other children are doing, reduces pain element and is a very happy little lady*" another told us that her son was now a "Happy, healthy toddler. Always wakes with a big smile". One parent stated that they felt unprepared for the significant improvement in her child's condition saying "*we were certainly not ready*

	for the outcome. "(My child's) bones from the first x-ray were blurred, no outline and his ribs were shockingly thin. the x-rays taken a day earlier, an outline was visible, there was bone where it wasn't before, and his ribs were becoming thicker. We returned home from the visit on cloud nine". Children are also reported to be significantly more independent and mobile, learning motor skills and reaching developmental milestones. Bones are becoming stronger and there is a reduction of pain and fractures since being on Strensiq. Reflecting on their child's health prior to starting Strensiq and comparing to now, one parent told us "*my little one was struggling with feeding, dropping from the 95th centile to the 5th, she had fractures and was unable to hold her own head...Since starting Strensiq she is doing incredible, She is not the same little girl, she has gone from lying flat and unable to hold her own head to sitting unaided, crawling and now standing up all within 6 months. I genuinely dread to think how she would have been without the medication.*" Another parent supported this stating that their child "learnt to walk independently at the age of 3. No fractures since being on treatment". Some parents acknowledged that reaching milestones takes time and that improvements are not seen overnight. One parent told us that despite seeing some improvements "*my child still had some problems with breath holding/ sleep apnoea and has had a seizure recently, so it is creating an issue with childcare and working. We also have to manage his diet very carefully*" Another parent explained that their child "*still needs to catch up with development, weight gain and deal with reflux/ tummy issues but he is happy and overall seems healthy. He has dramatically improvement since commencing Strensiq and it has not only saved his life but gave him a brilliant quality of life*." The development of mobility and independence also means there is more freedom for parents too to be able to work and regain a social life, feeling more confident in leaving their child in nursery, school, or with friends and family. "*I feel like the Strensiq has given us the best chance of my child being able to attend nursery and school so I can return to work. I can also see a more positive future for our family. We have also been saved from our child dying which would have had a massive impact on our whole family*". Another parent commented *"(My child's) activity level increased significantly, the burden of taking care of (my child's) daily life has been reduced/ The time for outdoor activities with (my child) has increased*" One parent told us that their child's sleep had improved significantly " 100% of parents have seen an increase in attainment/performance in school, 100% have seen an increase of participation in physical activities in school, 75% have seen improvements in school attendance and 75% have seen improvements in socialising with peers.

	Adults: Adults have reported their biggest changes to be increased mobility, a reduction in fractures, a reduction in fatigue and feeling as though their quality of life had significantly improved. The ability to be more physically active provides increased independence and a sense of freedom for many. One adult highlighted their main change as "*being able to walk very short distances without crutches again as my muscles became so weak. This makes such a difference to my quality of life*." Others agree that their overall health has improved, and they are getting out more and getting more exercise: *"Being able to walk, more understanding of this condition, not as weak, no broken bones*" Another told us: *"I have not broken any bones thankfully since being on Strensiq. That has had a great impact on my life*". Since taking Strensiq patients experiencing these improvements have grown or are growing in confidence as they start to become more active, and the risk of painful fractures reduces. Mental health has also improved in many, some requiring less medication. One told us *"(my) anxiety was very severe and has reduced considerably since starting Strensiq"*. The degree of improvement varies between individuals, some seeing a higher improvement than others. In our survey this equated to 50% seeing significant improvement in mobility and 50% seeing some improvement in mobility. One patient told us their biggest change was "*being able to live a normal life without being in discomfort*" and another described themselves as being "pain free", in comparison others told us "*I require crutches to walk, I can painfully hobble 20metres, but this is around the home rather than out and about. I find I can potter about in my home a bit better but outside of the home my mobility still requires crutches*". The reduction of fatigue in some has not only led to adults feeling able to do more but has also reduced the accompanying brain fog and inability to focus, 50% of patients described feeling as though they had a "clearer head" since taking Strensiq.
12. What do patients or carers think are the disadvantages of the treatment? Please refer to the MAA re-evaluation patient submission guide	The most commonly described disadvantage of this treatment is the reactions at injection sites. These are problematic for many. For some the injection sites cause lipodystrophy. One patient told us "*preparing the injections is fine, but the injections are not easy, it ruins the skin/fat, leaving less and less places to inject. the injections are very painful, adding to the pain of HPP itself. I do keep in mind long term my HPP will improve so try to keep thinking of that*". Injections are described as feeling like a "bee sting". Injection site reactions when first starting treatment in one patient was a 12cm round area surrounding the site which was itchy, this reduced down to 2.5cm over 2 years. Guidance from medical teams and the development of an app has helped patients to rotate injection sites and manage this better. However, the size of injection site reactions and the length of time they appear (one reported this being over a week) means patients in particular sometimes find it difficult to find new sites to inject. One patient told us it "*interferes with life as it can be stressful and time consuming due to the issues trying to inject and the pain*". 82% of patients agreed that despite the injection site reactions and challenges, the benefits of treatment and hopes for the

	future outweighed the disadvantages of administering it. "*In the scheme of things, all the difficulties are worth struggling with, as this is the only option to help my condition and hopefully give me some quality of lifelong term*". Parents have also described that injecting babies and children is stressful, one told us the treatment was "*easy to give in theory but never completely nice or easy to inject a young baby*", a second agreed saying it is "easy to do the Injection but my child is not a bit fan of getting it as it hurts her". A parent of an older child told us "*it can be extremely upsetting giving our little one the injections especially more so now she is older, she gets extremely upset but thankfully it only lasts a couple of seconds, and we can take her mind off it*". Despite these parents did agree that these disadvantages were worth it given the impact of treatment. One parent told us "*regular injections are not ideal for a baby but a small price to pay. Sites can bruise quite easily, and good site rotation is needed*". 18% of patients we surveyed told us their peripheral neuropathy and fatigue had worsened somewhat since starting Strensiq. One patient told us told us "*I feel very tired, my joints feel much freer, but my mobility has not improved*". This same patient struggled with the injections, finding them painful and experiencing injection site reactions. This patient has now made the decision to stop treatment as they felt that the disadvantages of administering the treatment outweighed the minimal benefits they experienced. There have also been mixed views on storage of the medication. In our survey, 91% felt that there were no disadvantages to managing treatment at home and noted that storage in the refrigerator was easy. Discussions with patients and parents/carers revealed that travelling for long periods of time caused some difficulties when travelling with the medication. One parent told us "*when taking (my child) on long-time travel, I have to plan the storage and carrying of the injection drugs*". Some patients have sought temperature-regulated cool bags and purchased these online.
13. What place do you think this treatment has in future NHS treatment and care for the condition? Consider how this treatment has impacted patients and how	There have been no reported issues around administering and managing the treatment at home. With training and guidance patients and parents are confident to do this and feel that they are able to manage their time better. From discussions with patients and families, there are positive relationships with leading consultants and other healthcare professionals involved in their care. The treatment is life-saving in babies and life-changing in other age groups. Some adult patients describe varying levels of success and so we anticipate that should this treatment be approved; these patients will continue to access secondary services to assist with mobility problems and support wider ranges of movements through physiotherapy.

it fits alongside other treatments and care pathway.	One patient has suggested that a rheumatologist be involved as part of their care pathway going forward as they feel it more relevant to their symptoms.

Section 4 Patients views on assessments used during the MAA

Table 4 Measurements, tests and assessments

14. Results from tests and assessments are used to help reduce uncertainty about the effectiveness of treatment. **How well do you think these tests and assessments worked in measuring the effectiveness of the treatment?**	Feedback from patients and families has been largely positive. The provision of questionnaires and assessments were accepted by patients. Questionnaires were preferred when done over the phone. One patient felt that the 6-minute walk test was not the most appropriate measure as it was dependent on how much activity was required by the patients beforehand to get to the appointment and so there were some uncertainties about the measure of fatigue in these instances. There is an understanding that there is a lot of data collected that patients that they do not necessarily see. We received no complaints or issues around the support offered by the treatment centres and patients were pleased with the degree of communication from the clinicians and teams.
15. Were there any tests or assessments that were difficult or unhelpful from a patient's or carer's perspective?	None reported.
16. Do patients and carers consider that their experiences (clinical, physical, emotional and psychological) were captured adequately in the MAA tests and assessments?	Overall, yes. One patient felt that the questionnaire was restrictive with no room to expand on their answers. They felt able to tick boxes on where they felt pain but were unable to provide information on the severity of this. However, there is also a widespread trust in clinicians and that there is reasoning behind the data collection methods used and that perhaps this data is captured elsewhere.

If not please explain what was missing.	
17. What outcomes do you think have not been assessed or captured in the MAA data? Please tell us why	We believe all reasonable outcomes have been assessed or considered.

Section 5 Patient population

Table 5 Groups who may benefit and those who declined treatment

18. Are there any groups of patients who might benefit more or less from the treatment than others? If so, please describe them and explain why.	

19. Were there people who met the MAA eligibility criteria who decided not to start treatment? Please state if known the proportion of eligible patients who did not start the treatment and any reasons for this.	None reported to us.

Section 6 Equality

20. Are there any potential equality issues that that should be taken into account when considering this condition and the treatment? See NICE's equality scheme for more details. None

Section 7 Other issues & Topic Specific Questions

21. Are there any other issues that you would like the committee to consider? N/A

Commented [MT1]: Committee teams please check with technical teams if there are any topic specific questions and if so add them under question 21.
If no topic specific questions please remove text highlighted in yellow before sending with ITP.

Section 8 Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- Treatment with Asfotase alfa (Strensiq) for babies and children is both life-saving and life-changing with babies going from requiring ventilation and little to no hope of survival to growing into alert, active children who have reached or are reaching developmental milestones and interacting with their peers.
- Treatment with Asfotase alfa (Strensiq) for the majority of adults with paediatric-onset HPP is similarly life-changing providing increased mobility, reduced pain, reduced fatigue, and a reduction in fractures thus covering all key symptoms this group stated they wished could be improved prior to treatment.
- It is imperative to understand that there is no existing treatment for this condition for any age group with all management solely being symptomatic and supportive with minimal impact.
- We acknowledge there are issues around injection sites, and this presents difficulties for both parents/carers and patients however we fully support the vast majority of patients and parents/carers views that the benefits of treatment massively outweigh the disadvantages of administering the treatment and there are hopes that with time easier methods of administering the treatment will become available.
- Asfotase alfa (Strensiq) in the treatment of patients of paediatric-onset hypophosphatasia brings significantly improved quality of life and hope for the future in all age groups.

Thank you for your time.

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METABOLIC SUPPORT UK

Your rare condition.
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Patient Case Study 1

Status: Patient with Childhood onset Hypophosphatasia

Age of diagnosis: 51

Written by the patient:

"Living with Hypophosphatasia is incredibly difficult as it is - a life with constant pain with regular bouts of severe to excruciating pain. Once diagnosed you realise that this is a progressive condition and that the future is pretty bleak with limited mobility, fractures, joint and tendon issues and operations for the foreseeable future. Mentally this is incredibly difficult to deal with as you often feel a burden to your family, friends and the workplace. You are unable to be reliable in that you never know how you are going to be physically and mentally from day to day. Constant pain is exhausting, and it is hugely difficult to have the energy and enthusiasm for anything. Pacing yourself is essential and so it limits your ability to be spontaneous and this is difficult for people in general to understand. Consequently, as a sufferer you put up with a lot of discomfort to try and fit in as best you can. Finding an employer is extremely difficult. I have been lucky enough to have enough 'evidence' to prove I had childhood onset, have limited walking ability and have had a fracture so I qualified for the MAA.

Strensiq for me has totally change my life. It has unexpectedly given me a huge amount of energy. It has reduced the severe bouts of gnawing surging pain that used to happen every few minutes. The pain is still there but it is now manageable. I am now 61 years of age and unfortunately the condition has caused a lot of damage to my body over time, and this cannot be undone by the drug so my mobility is still limited but I now have the hope that I will not deteriorate to the state where I cannot walk at all and will be able to manage my self-care. I am so thankful for that hope as I am proud and would wish to be independent in the future. Friends and family comment that I look better - not so drawn/exhausted. My husband no longer has to massage pain relief ointments or creams for me. At times I have been in so much agony in the past this has been the only help. I already feel that my husband's role as carer is not so intensive for him, which really helps me not to feel guilty about not being able to do things for myself. My husband took early retirement to help look after me. It is a joy to be able to undertake journeys on my own in my car without the fear of being too exhausted to cope. I am now able to exercise on my specialist battery adapted trike - it's such a joy to get out into the fresh air and access the countryside again. I have a special smile when I ride my trike!

Prior to Strensiq I would visit my GP regularly for referrals for degenerative tendon related symptoms which involved hugely painful cortisone injections deep into joints. As the years passed I needed stronger and stronger painkillers to be able to have any quality of life at all. I have spent a lot of my life propped on cushions, with my joints wrapped in ice or heat or with my arms supported to be able to deal with the excruciating pain in my shoulders and arms. I had a spinal operation at 14, elbow operation, two arthroscopic shoulder operations and eventually a shoulder replacement. I am awaiting ankle surgery for both feet and possibly another operation on my spine.

When you have lived your whole life in constant pain it is difficult to understand what 'normal' life feels like. Having Strensiq has given me a taste of freedom. Sometimes I can be spontaneous and meet up with friends of an evening without staying in bed in the afternoon. It's given me the opportunity to be able to do my self-employed work and then be able to visit my grandchildren instead of being in bed by 20.00. It's enabled me to reduce my alcohol consumption - prior to Strensiq I needed to drink with my pills to be able to tolerate the pain. I haven't visited my GP for anything related to HPP since starting on Strensiq which is unbelievable. I have reduced Escitalopram for mental health and pain from 20mg to 5mg, haven't needed any cortisone injections and have only had one repeat prescription for Co-Codamol and Co-Dydramol over the last 8 months!

With my inside knowledge as a forever sufferer of HPP I can tell you that this condition does become more severe over time. The lack of the Alkaline Phosphatase Enzyme causes your body to create crystals which in turn wears away your joints, causes soft bones, kidney problems and tendon issues. It causes us to have weak muscles which over time eats away at your ability to keep mobile or even have the ability to try. Your mental health is challenged each time you meet a new surgeon who doesn't know about the condition, and you have to fight to be heard. The thought of another operation when you have suffered so much already is extremely hard to contemplate. The problem is that you don't just have one joint with a problem (i.e., normally someone has an injury to need an operation) so you have to consider how you will cope if you have to have your foot operated on if you don't have the strength to manage with crutches, or in my case are not allowed to lift or put weight on my replaced shoulder. Add to this the pain and the future doesn't hold much hope and you survive.

There is a further burden when you have a daughter and a sister also with the condition who cannot access the treatment and yet you can see they are following in your path. It's torture to see unnecessary suffering. I am trying to explain here that I feel that the criteria for accessing Strensiq really do need to be looked at again so that more people can benefit. Many people with HPP do not break bones, many can walk at a fair pace when they are young but …… if they could access Strensiq the Alkaline Phosphatase Enzyme would save their bodies from degeneration. They would be able to have careers of their choice, be self-sufficient and have less pain and have hope that they can live a near to normal life. That is priceless. The only treatment options available if you are not allowed Strensiq are pain relief drugs, steroid injections and operations to help with degenerative joints.

There is agony whilst waiting for usually over 12 months to see a specialist to get started on the route to treatment. It is hell mentally, physically and is a trauma for the whole family and often you are unable to work! You have little hope for the future as it looks very bleak. Having spent all my life looking for a diagnosis, collecting my own evidence and battling to be heard I am extremely concerned about the future if I am not able to access 'Strensiq'. I feel that life will be even harder than it was before the medication as I have tasted freedom. I am frightened that I will deteriorate rapidly, be in excruciating pain once again and become more of a burden to my family over time. If Strensiq is stopped there will need to be a team in place to help us re-adjust to the pain and mental stress. Strensiq as a medication was challenging initially due to injection site reactions. They set in on the 4th day of injecting and initially were huge red patches 10cm x 15cm , extremely itchy and painful. The itching was intense and would keep you awake at night. I inject 6 days a week and it was difficult to find a place to inject that wasn't covered in a reaction. This was a troubling time, and it was very hard

mentally to inject knowing that you were going to cause yourself more trauma. I received support during this time from the 'HPP Soft Bones' Websites both in the UK and America. It was good to be able to ask questions to the community who had been through the process. The injection site reactions were severe for the first 8 months and then have gradually diminished. I still sometimes get an itching reaction, but it is 'WORTH IT'.

There is no question - I now have quality of life and I thank you sincerely for this opportunity to share my insights in the hope that future generations can benefit".

Case Study 2

Status: Parent/caregiver of child with HPP

Age of patient at submission of case study: 18 Months

Written by the parent/caregiver:

Life with HPP

[name redacted] was diagnosed with HPP back in June 2020, life was challenging at this time due to [redacted] being extremely unwell with the following symptom's:

- Respiratory reserve
- Failure to thrive, losing excessive amounts of weight
- Excessive vomiting (Every bottle feed)
- Fractures
- Low muscle tone
- Poor bone growth, short statue, short limbs and underdeveloped ribcage
- Hypercalcemia
- craniostynosis
- Neutropenia
- Pain on a regular basis (She would cry for long periods of time)

[redacted] respiratory reserve was extremely poor to which she needed oxygen on a regular basis, her ribcage was not big enough to allow her lungs to expand correctly. We were admitted to hospital on numerous occasions and spent the majority of [redacted] first year or her life in hospital, 5 different hospitals before we got [redacted] diagnosis. Prior to strensiq we knew the outcome for [redacted] was not great as we were advised without the treatment [redacted] would not survive. As new parents the emotional side of hearing that type of information was unbearable and heart wrenching.

[redacted] did not hold her own head up until she was 10 months old, she could only lie flat as this was the only comfortable position for her. As parents we could only pick [redacted] up one way and she would only be comfortable resting on my shoulder, I could not feed [redacted] in my arms she would have to lie on a flat surface, this would open her lungs up and allow her to breath sufficiently while feeding. Prior to her diagnosis we never understood why we couldn't feed her in our arms. [redacted] would projectile vomit every feed to which would result in her losing drastic amounts of weight going from the 98th centile to the 5th in weight. At this stage we stopped leaving the house due to the excessive amounts of vomit and [redacted] being too uncomfortable in her car seat.

If [redacted] was to stop with her medication (Strensiq) now I am unsure what the outcome would be for her or her life span, as prior to strensiq she was extremely sick. When [redacted] is due her injection she is usually in discomfort that day prior to receiving her medication, That tells me that her body is requiring and expecting the medication as the following day she is back to her happy self again. To

imagine [redacted] life without strensiq is upsetting and I would be distraught to see [redacted] go back over from how far she has come. I believe her quality of life would be affected so much and after coming so far from starting with strensiq that seems unfair for it to be taken away and her more severe symptoms to return.

[redacted] has now been on Strensiq for one year and the results have been phenomenal she can now sit, stand, crawl and even more so recently she has taken her first steps! [redacted] is now a happy and content little lady with such a big personality, unfortunately due to her being so unwell prior to strensiq we never saw this side of her. We have had less hospital admissions also which has helped [redacted] massively. We are delighted in the progress she has made; she can now join in activities with her friends which she loves. We are now able to attend baby classes and small soft play for [redacted] to interact with other children too.

Life with Hpp for myself and [redacted]'s Dad is tough, Extremely tough at times however what I do know is how much [redacted]'s life has changed since starting the medication so at present life seems a lot better that previously. The medication to us was and still is a blessing in disguise as we have seen the impact it has had on [redacted].

Having to inject [redacted] 3 x per week is so difficult, As she becomes more aware it is becoming more distressing but thankfully for us [redacted] is distracted very easily which means she forgets about it very quickly, We have things in place that help [redacted] and I do genuinely believe she now knows that it helps as she claps afterwards. As parents it really does break our heart having to give her the medication however this medication is saving her life, so we are eternally grateful for that and having that constant reminder of that helps.

Emotionally and physically for me and my husband it has been a rollercoaster the different symptoms, reactions to things and the unknown of a lot of things is mentally draining but we are extremely positive people and things are improving every day for [redacted] which keeps us going as a family.

Views on Current treatment

I think a lot of the above covers on how much Strensiq has impacted [redacted]s life and what the treatment means for her. My expectation of the treatment would be to carry on with the process we are currently doing with [redacted], To continue to see the big improvements she is making daily.

Due to the impact of Strensiq [redacted] is now able to walk which she has developed more recently, This has built her confidence as she recently developed a phobia of Hospitals which was so distressing however since being able to walk her last two visits have been great, She has gone from screaming, holding her breath being genuinely frightened something bad was going to happen to walking into her consultation room and showing off her moves, smiling and showing professor what she is made off.

Our coordination of care since [redacted]'s diagnosis has been excellent! I could not explain the exceptional people we have around in [redacted]'s care plan, they exceed all of our expectations and

if not more. If we need something it's there, they are all very easy to communicate with and give both, parents & [redacted] support in all areas.

The financial impact has certainly been a strain as for myself & husband as I am no longer able to return to work due to [redacted] requiring full time care at the moment therefore we have no longer two salaries coming into the household. We don't have a lot of family close by to support us in [redacted]s care and due to the severe symptoms of [redacted]'s condition we are unable to place [redacted] in a nursery environment just yet. Travelling to hospitals for numerous appointments per month sometimes can cost us over £200 and if we attend two of the further a field Hospitals [redacted] is under this can range from £100 - £200 per visit (For E.G One particular hospital charges £26 per day parking and we were there 3 weeks) this can add up to a substantial amount of money. We were attending hospital weekly however more recently [redacted]'s appointments have slowed down due to her increased progress she is making.

The treatment itself I find personally easy to use however administrating it to [redacted] is sometimes distressing, As the dose increases it seems to be becoming slightly more difficult to hold [redacted] in the correct place for me to administrate more easily. If the actual volume could be smaller but a bigger strength that would impact the process massively or If they could make strensiq in a tablet form that would be amazing and help us parents with young children.

Views on Strensiq

There is one view I have on this medication and its exceptional! The impact it has had on [redacted] is unbelievable. Its extremely difficult to put into words how much this has changed [redacted]s life and what I find more amazing is that every time the volume/ strength has been increased for [redacted] she has hit a milestone, I have the dates of each increase and the following date of when she has hit her milestone which I find unbelievable. I expect for the therapy to continue to improve [redacted]'s quality of life as she grows up into a toddler, young lady & an adult.

The biggest disadvantage of the therapy for me is how its administered, more so for parents with young children, It can be tough. As previously stated, the actual dose too, if it could be a smaller volume with the same strength that would make the process slightly easier as it would be over quicker. As the drug is administered, I do believe that there may be a sore reaction as [redacted] tends to be more upset when the medication is going in rather that the actual needle itself, This is hard to tell as she is unable to talk right now but I do believe something is happening at that stage as she does tend to scratch the area straight after as if the area is itchy. The site reactions have not been too severe for [redacted], More so recently she does have discoloration on her thighs which does seem to bother her now but may affect her later on in life. We carry out [redacted]'s injections at home in our living room, It's a lovely calm safe place that [redacted] loves. We make this our absolute priority to be at home as I do believe the environment helps massively.

As parents we would not want to go through the heart ache 3 x per week injecting [redacted] if we didn't think the medication wasn't giving her exceptional results, so that needs to count for something.

NICE National Institute for Health and Care Excellence

HIGHLY SPECIALISED TECHNOLOGIES (HST)

Guidance review following a period of managed access

NHS commissioning expert statement

Asfotase alfa for treating paediatric-onset hypophosphatasia (review of HST6) [ID3927]

Thank you for agreeing to give us your views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type. Your response should not be longer than 10 pages.

Information on completing this expert statement

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you	
1. Your name	**Ayesha Ali**

2. Name of organisation	**NHS England**
3. Job title or position	**Medical Advisor Highly Specialised Services**
4. Are you (please tick all that apply):	☐ commissioning services for a CCG or NHS England in general? ☐ **x** commissioning services for a CCG or NHS England for the condition for which NICE is considering this technology? ☐ responsible for quality of service delivery in a CCG (for example, medical director, public health director, director of nursing)? ☐ an expert in treating the condition for which NICE is considering this technology? ☐ an expert in the clinical evidence base supporting the technology (for example, an investigator in clinical trials for the technology)? ☐ other (please specify):
Current treatment of the condition in the NHS (outside of the managed access agreement [MAA])	
5. Are any clinical guidelines used in the treatment of the condition, and if so, which?	**There are no NHS England clinical commissioning policies for this condition**
6. Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across	**There are a number of centres with a specialist interest in this condition but this is not a specifically commissioned highly specialised service.**

the NHS? (Please state if your experience is from outside England.)	
Experience of the technology during the managed access agreement [MAA]	
7. Have there been advantages of the technology and managed access agreement? What are they?	**The MAA has allowed access to a wide group of patients who have met the starting criteria.**
8. Have there been disadvantages of the technology and managed access agreement? What are they?	
The use of the technology (after the managed access agreement [MAA])	
9. To what extent and in which population(s) will the	**If approved by NICE NHS England would commission the drug as per recommendations.**

technology be used in your local health economy?	
10. Would you expect any changes to the pathway of care compared to what has been established as part of the managed access agreement?	**There may be formal designation of expert centres who can prescribe the drug if approved. This will map onto those who prescribed during the MAA but may include additional centres to ensure geographical access.**
11. Would you expect any changes if the technology became part of routinely commissioned care?	
• How does healthcare resource use differ between the technology and routinely commissioned care?	**The treatment represents a step change compared to currently commissioned care which is largely supportive**
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	**The decision to treat should be made by specialised centres with expertise in the condition**

• What investment is needed to introduce the technology into routine practice? (For example, for facilities, equipment, or training.) • Will further centres need to be commissioned?	**No additional investment. See previous comment re : additional centres**
• If there are any rules (informal or formal) for starting and stopping treatment with the technology, would these apply if the technology is routinely commissioned? • If not, how would starting and stopping criteria be adapted?	**The current starting and stopping criteria relate to the MAA. It is not envisaged these would continue unless included in any NICE recommendations.**
12. What is the outcome of any evaluations or audits of the use of the technology?	**No audits or evaluations have been undertaken by NHS England**
Equality	

13a. Are there any potential equality issues that should be taken into account when considering this treatment?	
13b. Consider whether these issues are different from issues with current care and why.	

Thank you for your time.

Please log in to your NICE Docs account to upload your completed statement, declaration of interest form and consent form.

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NICE National Institute for Health and Care Excellence

Highly Specialised Technologies (HST)

Guidance review following a period of managed access

Patient expert statement

Asfotase alfa for treating paediatric-onset hypophosphatasia (review of HST6) [ID3927]

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- Your response should not be longer than 10 pages.

About you	
1.Your name	**Melanie Deborah Williams**
2. Are you (please tick all that apply):	✓ a patient with the condition? ✓ a carer of a patient with the condition? other (please specify):
3. Did your nominating organisation submit a submission?	✓ yes, they did no, they didn't I don't know
4. How did you gather the information included in your statement? (please tick all that apply)	✓ I have personal experience of the condition ✓ I have personal experience of the technology being appraised I have other relevant personal experience. Please specify what other experience: I am drawing on others' experiences. Please specify how this information was gathered:

Living with the condition

5. What is it like to live with the condition? Consider • the experience of living with the condition and the impact on daily life (physical and emotional health, ability to work, adaptations to your home, financial impact, relationships and social life). • if you are the parent of an affected child, include their ability to go to school, develop emotionally, form friends and participate in school and social life. What is	My earliest memory is of crying with pain in my knees and feet when I was just 3 years old. During early childhood I had problems with pain in my feet and aches and pains in my joints and would complain and cry. Being forced to take part in PE at school and hurting my neck - not being listened to. I had an operation on my spine at 13 due to severe pain. Extreme stiffness and pain in my teenage years. Struggling to walk around the playground and being carried by mates when the pain was too bad. Lying on the floor at school between lessons as the desks and seats were so uncomfortable. Not being able to keep up with others in sports lessons. Noticing more and more stiffness in my late teens and struggling with severe back pain and pain in my joints which would be extreme at times. Since being an adult my experience of living with HPP is one of complete exhaustion and fatigue because of the constant pain, interspersed with worse pain, which never completely goes away. This pain can be joint specific or in multiple joints. When immobile even for short periods I feel as if I am seizing up and have difficulty moving. In addition there is a gnawing, vicious pain which creeps and surges in the long bones. This pain has worsened over time. Over the last 40 years I have developed additional pain from stress fractures, pseudo gout, chrondocalcinosis, tendinothapy, degenerative tendons, arthritis, degenerative disks, calcium deposits in joints, muscles, tendons and muscle weakness which all add to the already debilitating daily pain. As the day goes on I find that I develop a sickening pain in my ribs at the back which forces me to lie down. I have profound muscle weakness. I have had long episodes of severe vertigo. Making journeys unsupported is difficult both driving and mentally. I find the process of cooking and preparing exhausting. Gripping, lifting or chopping causes severe shooting pains. I am unable to get out of our bath due to muscle weakness and pain so we have put in a large shower with a stool and grab rail. Having HPP doesn't take away your wish to work and be a valued part of society. My experience has been that because I didn't have a diagnosis it was very difficult to declare my limitations and receive the adaptations or adjustments required to do the job. Eventually I gave up trying and became self employed so that I could pace myself and buy the equipment I needed to do the work. It is very difficult to be spontaneous when you are in constant pain and even more difficult to be sociable. Each day you make choices and prioritise so that you can achieve your goal. Very often people don't understand your reluctance to take part in activities even though you try to explain time and again. You still wish to be part of your circle of friends and do 'stuff 'but not make them feel guilty for excluding you or making adjustments. My daughter (now 39) was never able to be as adventurous as her sister. Always hurting herself and struggling with sporting activities. She always complained of sharp stabbing pains in her feet. She had pain and stiffness

the effect on any siblings? • what carers experience when caring for someone with the condition	in her arms, neck and shoulders. She tore ligaments in her neck doing PE at school. She began suffering with pseudo gout in her hands at 14. By now this affects her fingers, palms, elbows and toes. With flare ups lasting a few weeks. She now has severe pain throughout her body. She is a full time teacher and mother of a child with HPP. She is struggling to cope at work and also with the driving. She is exhausted and in pain when she arrives home and is not able to have a social life at all. She is depressed and anxious and has daily debilitating headaches. As a parent carer also with HPP you know the condition can cause extreme disability and pain so you are faced with trauma, anxiety, extreme sadness and helplessness and sometimes guilt. It is difficult watching your child suffer when you know the exact pain they are in. It is hard to be optimistic and encouraging when you know the challenges they will face to overcome difficulties at school or in the workplace. It is hard to strike a balance when encouraging them to undertake activities you know will cause pain. You try to teach them pain management strategies as there is nothing apart from pain killers to offer. There are problems getting teachers to understand the exhaustion and pain faced by the child when they look OK. It is difficult to see their career choices decided by their capability to do the job. My husband as a carer has always been a much needed support at appointments when dealing with the aftermath of a good or bad consultation. He helps with personal grooming without being too obvious. He guides, moves things, lift things, helps me to get up or out of a chair etc., He can't be spontaneous as he has to plan according to my needs. He has guilt about being able to do more than me. He worries about long term effects of the condition. He feels low when I am in terrible pain and he can't do anything just observe. He is always supporting when I am doing activities - needing to be there in case of difficulty. He helps with medication - applying creams, injections etc., It is difficult trying to be positive and encouraging all the time. It is very hard to find a work/life balance. He retired early to support me.

6. Did you have any difficulty or delays in receiving a diagnosis; appropriate treatment or helpful information about the condition? What was the impact of this on you and your family?	I had a long and arduous route to diagnosis that took until I was 51 even though I had symptoms since birth. Throughout my life I have visited specialists trying to get answers. As a baby I was put into traction and my parents were taught how to stretch my body in the hope this would help me to sit up. At 13 I went through a traumatic exploratory operation as possible cancer was misdiagnosed. Throughout my journey to diagnosis I have been misdiagnosed with Polymyalgia, Mental Health issues and Fibromyalgia. I eventually collated my own evidence in table format noting all specialists seen, results of tests, operations, symptoms and diagnosis over 50 years. I presented this evidence to my GP who then referred me to a metabolic specialist. Within 12 months I received my diagnosis of HPP. I was told there was no treatment and at this point in time there was no information about the condition available in the UK. My initial relief of diagnosis soon changed to feeling abandoned and just left to get on with it using my GP for support. Since travelling to Sheffield I have had much more support. I have never received any information about the condition and have had to do my own research. My experience of treatment for HPP has been organised through my GP as metabolic specialists are not trained in pain management. The standard treatments for HPP have been NSAIDs, amitriptyline, co-codamol, co-dydramol, tramadol, cortisone injections and surgery. These treatments don't relieve the symptoms and give a limited amount of pain relief. The medications also add to the fatigue and brain fog. There is much suffering whilst waiting for surgery and then many months of recovery. There is a lot of trauma, pain, anxiety and depression whilst on long waiting lists to see specialists which is extremely difficult to live through both for patients, carers and the wider family. When waiting for treatments there is no quality of life and you get to the point when you really can't face further surgical interventions.

Current treatment of the condition in the NHS (outside of the managed access agreement [MAA])	
7. What do you think of current treatments (if they exist) and care available on the NHS (outside of the managed access agreement)? What are the things they do not do well enough?	There are no specific current treatments for Hypophosphatasia only management of symptoms through medication, surgery or cortisone injections. The pain relief medications do not adequately reduce the pain they just take the edge off. The surgery adds to the trauma and pain. Cortisone injections are not only harmful to joints over time they are extremely painful to endure and do not always relieve the symptoms. Medications for depression and anxiety cause severe brain fog and exhaustion and even restrict your functionality for driving, working etc., You can be referred to physio if new symptoms appear or following surgery but unfortunately all this comes to an end. This condition is degenerative and lifelong and therefore we constantly battle to maintain function and mobility and ongoing physio is much needed but unavailable. We see our metabolic specialists once a year for routine tests but apart from this there is no support available to us.
8. Is there an unmet need for patients with this condition?	Many patients living with HPP have not been able to access AA because of the strict criteria set out in the MAA. This includes my daughter who is the main breadwinner, teacher and mother. She is struggling to keep working and cannot function when she gets home because of the pain and exhaustion. I believe that Health Care Professionals do not fully understand the impact of this disease (we are still educating them) and you can be easily labelled as a mild case as an adult if you have not presented with fractures. You could say I was 'lucky' as I have a healed hairline fracture in my femur which gave me access to AA. In my experience of lifelong visits to different specialists trying to help me deal with the impact of calcium build up as spurs, chrondocalcinosis, severe bursitis, tendinothapy and degenerative tendons I would never call my symptoms 'mild'. For me watching my daughter and others with HPP who have no evidence of fractures just tolerating their severe symptoms causing pain, depression and mobility issues is extremely upsetting. Many people have the gene proving childhood onset or they have shown symptoms since childhood. The condition is progressive and has a huge impact not only on our bones and bodies but our expectations for life. We constantly have to make difficult choices in order to make the best of every day.
What was the experience of the technology during the managed access agreement [MAA]?	

9. What has been the experience of having access to the technology during the period of managed access?	I was disappointed and frustrated at the amount of time it took from approval for treatment to actually receiving the medication. It took 12 months. I feel that Strensiq has halted the progress of the disease over the two and a half years I have been on the drug. It hasn't removed all pain as it can't repair years of damage done prior to the medication but I have hope for the future and feel better able to cope. Having access to this treatment has been life changing for me and my whole family. People comment that I look better too. The hospital appointments needed for the MAA were organised along with my routine appointments and therefore I didn't have any extra travel. During Covid the appointments were taken over the phone and I kept my consultant informed with my progress.
10. How has the technology fitted in with other treatment and care for the condition?	Since beginning on Asfotase Alfa I have not needed to have any other treatment and care for my condition. I have been able to reduce my reliance on painkillers significantly and have been able to cut down on my medication for mental health issues because I am less anxious and depressed. There is no other treatment available for this condition apart from symptomatic pain relief.
11. Describe how receiving the technology has impacted everyday life. Has it had an impact on what carers experience? How?	I am not so reliant on my husband or family. I am enjoying the fact that I have more energy and stamina and reduced pain. The severe gnawing pain which moved around my body is diminished greatly. I no longer have to endure excruciating cortisone injections. I have more clarity of mind due to less medication and pain. I don't feel to be such a burden on my family and friends as I can be more sociable. I can undertake journeys in my car independently. I am able to do more every day tasks and even have the stamina to do some exercise. For my husband as a carer he is not so in demand all the time. He has more time to do exercise and hobbies. He is able to leave me unattended and doesn't feel so guilty about doing so as I am able to do other things nowadays. He doesn't have to drive me everywhere. He no longer has to undertake all household tasks. He is less anxious about my care and the long term effects of the condition.

12. How easy or difficult is it to take/have the treatment? How does this impact you and your family (for example, travel or how the treatment is received?	The medication is delivered to my home and can be administered by myself or my partner if needed. The medication is not difficult to prepare for injection although it takes a bit of time to prime the syringe to inject. You are able to choose the timing of your injections yourself. Injecting itself isn't difficult but the pain of the injection is sometimes difficult to tolerate. The injection site reactions are troublesome but the advantages make the discomfort 'worth it'. Travelling with the medication is not easy as it has to be kept refrigerated between 4 and 8 degrees. This isn't too difficult for short journeys but for a longer holiday I have needed to buy a portable fridge in order to ensure my medication is safe and secure.
13. What place do you think the technology has in future treatment and care?	I think the medication is essential for treatment of HPP as there is no alternative treatment available. I feel the burden of care on the NHS will reduce significantly if patients can access this treatment.

Advantages of the technology (treatment) (including those experienced through the managed access agreement [MAA])	
14. What do you think are the advantages of the treatment? Consider the impact on everyday life and anything you described in the 'living with the condition' section.	Once trained adults are able to manage their own injections at home. I live in a rural area 30 miles from the nearest hospital. The medication can be easily stored in fridge at home. Parent carers are able to administer the injections at home. I can inject in my own time and fit it in around my schedule. I don't need regular hospital visits for my treatment which has been amazing for me considering how often I used to have to visit different specialists. Today sees my 860th injection of Asfotase Alfa (7/7/22) through the MAA. The severe gnawing pain which radiated around my body is diminished greatly. My pain medication is reduced significantly which means I have more clarity of mind. I am less anxious and depressed and am being weaned off my medication for mental health. I have a lot more energy which helps me deal much better with the pain I still have because I am not so exhausted. I have more mobility and am able to do more at home. I am able to do some exercise. I am not as anxious about my condition and the deterioration over time as I feel the medication has stabilised my condition. I have more spontaneity in my life as I don't have to sleep so much. I am able to socialise more easily. Since being on Asfotase Alfa I have not had to visit my GP for my Hypophosphatasia over the period of two years and 9 months. This gives me hope for the future.
Disadvantages of the technology (treatment) (including those experienced through the managed access agreement [MAA])	
15. What do you think are the disadvantages of the technology? Consider the impact on everyday life and anything you described in the	My injection site reactions have been extremely severe leaving me with no places left to inject that are not affected by large red raised patches. It was challenging to inject over the first 6 months knowing I was going to suffer with reactions. The sites felt like severe mosquito bites each lasting in severity for up to a week. Compounded by injections 6 days a week it was difficult to persevere. Injecting the medication is painful also feeling like a bee sting the whole time you are pushing in the liquid. Injecting the medication into babies and young children is heartbreaking for adult carers. Having to securely hold them down is not easy to manage and it is stressful. It is fairly time consuming preparing the medication for injecting. It isn't easy to travel as the medication has to be kept between 4 and 8 degrees.

'living with the condition' section.	
16. Are there any side effects? What are they, how many are there, are they long term or short term and what impact do they have? Are there any aspects of the condition that the treatment does not help with or might make worse?	I have injection site reactions always. The first 6 months were very difficult to manage both physically and mentally. The pain of injecting feels like a bee sting and this can last following the injection for a few minutes. The injection site reactions initially were severe with large wheels extending 12.5cm round. These were red with bruises in the centre. The itching begins within a few hours and the redness extends over a few days. The itching feels like mosquito bites. This is compounded by the fact that dosage is decided upon weight so as an adult I am injecting 6 days a week. It was difficult to find a place to inject without impacting on a previous injection site. By now my injection site reactions are 2.5cm across and the itching is much less severe. The injections make the skin loose and pitted. The marks can cause embarrassment if exposed. It is extremely stressful for carers and especially parent carers to inject their young children as they have to pin them down to inject them. During the initial two weeks on AA I was exhausted and had more pain until my body became adjusted to receiving the enzyme and my body began to heal and process calcium for the first time. By now I feel there are no aspects of treatment that makes the symptoms worse. I feel the benefits of treatment by far outweigh the injection site reactions.
What was measured during the managed access agreement [MAA]?	

17. Thinking about the things that got measured during the period of the managed access agreement (MAA), do you think that all the things that were important were measured? Please list what they were and why they were important (or unimportant)	As an adult with childhood onset accessing the MAA I believe that the following measures were used to note efficacy: Quality of life questionnaires - mobility, self-care, usual activities, pain/discomfort and anxiety/depression, 6 minute walk test and Pain scale. Fractures and pain medications. The phone call questionnaires were very limited and it was sometimes difficult to answer the questions as the context wasn't always clear. I think more information could have been captured. The 6 minute walk test may have been a useful indication of improvement for some patients but I believe not all. As I have explained over time the condition is progressive and therefore for someone of my age there is a lot of damage already done. I don't believe that the walk test was necessarily the best way of getting a true indication of the efficacy. Also if you had to walk a long distance from parking or are exhausted from the journey to hospital this also adds to the mobility issue. I travel 112 miles to hospital and it takes over 3 hours. I believe that the pain scale is difficult for HPP. Because we have pain throughout our body it isn't easy to answer the questions simply. The scoring of quality of life I believe will show improvement over time.

18. Were there things that were not measured but are important to you? If there were, please list what they were and why they were important.	I think that a phone call discussion that captured more information would have been more useful. Scoring from 1 - 10 on a pain scale is difficult when you have pain in more than one place! I don't think the questions asked over the phone calls captured all positive outcomes of Strensiq adequately due to the phrasing of questions. We could had been asked to add positive or negative outcomes. I believe that a strength test would have been useful to monitor as we suffer with muscle weakness. Sleep Questionnaire - I have gone from sleeping in the day to staying up late The effect on quality of life of carers could be considered and monitored because without them and without the medication we cannot manage on our own.

Patient population (including experience during the managed access agreement [MAA])	
19. Are there any groups of patients who might benefit more or less from the treatment than others? If so, please describe them and explain why.	As I note with my granddaughter age 5. Some young children with HPP may not initially show severe signs of disease although they may complain of pain. Guidance is needed from HPP specialists to decide if treatment with AA is essential to establish normal bone mineralisation and avoid associated complications. The trauma of injecting and injection site reactions may be unreasonable at this stage. We are at this stage with my granddaughter awaiting an appointment with the specialist to decide the next steps. Having said the above, in my experience, over a lifetime the symptoms of HPP do progressively worsen causing a high burden of illness as symptoms develop over time. Untreated HPP can result in the constant management of symptoms and can impact quality of life regardless of age at onset with issues such as fatigue, fractures, bursitis, tendonitis, bone spurs, headaches, depression, seizures and mobility limitations. If unmanaged, pain from HPP is debilitating, make it difficult to perform daily activities, get around at home or work, and stay alert throughout the day.
Equality	
20. Are there any potential equality issues that should be taken into account when considering this condition and the treatment?	In my opinion all patients, regardless of age of onset of symptoms should be able to benefit from this technology.

Other issues	
21. Are there any other issues that you would like the committee to consider?	If Asfotase Alfa is not recommended I feel my body will begin to deteriorate once again. I will be back to waiting to see different consultants over many months. I will have no alternative to interventions to manage my condition such as operations and cortisone injections. I will be in debilitating pain for the rest of my life. I feel that the NHS will ultimately save money by giving patients access to this treatment. Over my lifetime my medical file is huge and I have had 8 surgeries (so far). My visits to specialists has been exhausting and pretty hopeless to be honest as specialists have no alternatives to offer apart from surgery and pain killers. It is a vicious cycle that never ends and there is no real quality of life. As stated previously I have not had to visit any health care professional for my HPP since being on Strensiq. I have had monitoring visits to my metabolic specialist as part of the MAA. There are no other drugs that can equal the efficacy of Strensiq at the present time. I would like the committee to consider re-evaluating the criteria for accessing AA to include all those living with HPP regardless of age of onset. I should like the committee to widen the criteria used to access AA. There are many other associated symptoms that need to be recognised as debilitating and we as patients are still educating our health care professionals. I feel that the impact on carers could also be measured. There is only symptomatic and supportive treatment available at the present time. Untreated HPP can result in the constant management of symptoms and can impact quality of life regardless of age at onset with issues such as fatigue, fractures, bursitis, tendonitis, bone spurs, headaches, depression, seizures and mobility limitations. HPP can also cause problems in the brain, muscles, joints, lungs, and kidneys. If unmanaged, pain from HPP can become debilitating, make it difficult to perform daily activities, get around at home or work/school, and stay alert throughout the day. The advantages of AA are that the medication has a huge impact greatly improving my quality of life, that of my family and wider social circle. I have not had to visit my GP over the period of 2 years and 9 months since being on Asfotase Alfa.

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Asfotase alfa for treating paediatric-onset hypophosphatasia (review of HST6) [ID3927]

Produced by Kleijnen Systematic Reviews (KSR) Ltd., in collaboration with Erasmus University, Rotterdam (EUR)

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Commercial in Confidence (CiC) data are highlighted in blue throughout the report.

Academic in Confidence (AiC) data are highlighted in yellow throughout the report.

Rider on responsibility for report

The views expressed in this report are those of the authors and not necessarily those of the NIHR Evidence Synthesis Programme. Any errors are the responsibility of the authors.

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Contributions of authors

Marie Westwood acted as project lead and systematic reviewer on this assessment, critiqued the clinical effectiveness methods and evidence and contributed to the writing of the report. Isaac Corro Ramus acted as health economic project lead, critiqued the company's economic evaluation and contributed to the writing of the report. Gimon de Graaf, Venetia Qendri and Nigel Armstrong acted as health economists on this assessment, critiqued the company's economic evaluation and contributed to the writing of the report. Charlotte Ahmadu acted as systematic reviewer, critiqued the clinical effectiveness methods and evidence and contributed to the writing of the report. Steven Duffy critiqued the search methods in the submission and contributed to the writing of the report. Maiwenn Al acted as health economist on this assessment, critiqued the company's economic evaluation, contributed to the writing of the report and provided general guidance.

Abbreviations

6MWT	6-minute walk test
AA	Asfotase alfa
AiC	Academic in Confidence
AE	Adverse events
ALP	Alkaline phosphatase
ALPL	Alkaline phosphatase gene
BAMF	Brief Assessment of Motor Function
BIA	Budget impact analysis
BMI	Body mass index
BOT-2	Bruininks-Oseretsky Test of Motor Proficiency, 2nd Edition
BPAP	Bilevel or biphasic positive airway pressure
BPI-SF	Brief Pain Inventory - Short Form
BSC	Best supportive care
BSID-III	Bayley Scales of Infant and Toddler Development®, 3rd Edition
CADTH	Canadian Agency for Drugs and technologies in Health
CDC	Centres for Disease Control
CDSR	Cochrane Database of Systematic Reviews
CE	Cost effectiveness
CEA	Cost effectiveness analysis
CEAC	Cost effectiveness acceptability curve
CENTRAL	Cochrane Central Register of Controlled Trials
CHAQ	Childhood Health Assessment Questionnaire
CHAQ-DI	Childhood Health Assessment Questionnaire – Disability Index
CiC	Commercial in Confidence
CI	Confidence interval
CPAP	Continuous positive airway pressure
CRD	Centre for Reviews and Dissemination
CS	Company submission
CSR	Clinical Study Report
DARE	Database of Abstracts of Reviews of Effects
DEXA	Dual energy X-ray absorptiometry
DMD	Duchenne's muscular dystrophy
DP	Decision problem
DSA	Deterministic sensitivity analysis
DSU	Decision Support Unit
EAG	External Assessment Group
EMA	European Medicines Agency
EOI	Events of interest
EQ-5D	European Quality of Life-5 Dimensions
ERT	Enzyme replacement therapy
ESHPM	Erasmus School of Health Policy and Management
ETP	Extension treatment period
EUR	Erasmus University, Rotterdam
GB	Great Britain
GJ-tube	Gastrostomy jejunostomy tube
HAQ-DI	Health Assessment Questionnaire-Disability Index
HOST	Hypophosphatasia Outcomes Study Telephone
HPP	Hypophosphatasia
HR	Hazard ratio
HRQoL	Health-related quality of life
HST	Highly Specialised Technologies
HTA	Health Technology Assessment
IAR	Injection-associated reaction

ICER	Incremental cost-effectiveness ratio
ICU	Intensive Care Unit
iMTA	Institute for Medical Technology Assessment
IQR	interquartile range
ISR	Injection-site reaction
ITT	Intention to treat
IV	Intravenous
KM	Kaplan-Meier
KSR	Kleijnen Systematic Reviews Ltd
LEFS	Lower Extremity Functional Scale
LY	Life year
LYG	Life year gained
MAA	Managed Access Agreement
max	Maximum
MCS	Mental Component Summary
MCID	Minimal clinically important difference
min	Minimum
mITT	Modified intention to treat
Mmol/L	Millimoles per litre
MPOMA-G	Modified Performance-Oriented Mobility Assessment, Gait Subtest
NAP	National Authorisation Panel
N/A	Not applicable
Ng/MI	Nanograms per millilitre
NHS	National Health Service
NHS EED	National Health Service Economic Evaluation Database
NHSE	National Health Service England
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
NR	Not reported
NSAIDs	Non-steroidal anti-inflammatory drugs
ONS	Office for National Statistics
OS	Overall survival
PAS	Patient Access Scheme
PCS	Physical component summary
PDMS-2	Peabody Developmental Motor Scales, 2nd edition
PEA	Phosphoethanolamine
PedsQL	Paediatric Quality of Life Inventory
PFS	Progression-free survival
PHQ-9	Patient Health Questionnaire-9
PICO	Population, intervention, comparators, outcomes
PLP	Pyridoxal 5’ -phosphate
PODCI	Paediatric Outcome Data Collection Instrument
POSNA	Pediatric Orthopaedic Society of North America
PPi	Inorganic pyrophosphate
PRESS	Peer Review of Electronic Search Strategies
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PRO	Patient-reported outcome
PROMIS-29	Patient-Reported Outcomes Measurement Information System
PSA	Probabilistic sensitivity analyses
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
PTP	Primary treatment period
QALY(s)	Quality-adjusted life year(s)
QoL	Quality of life
RAPID3	Routine Assessment of Patient Index Data 3

RCT	Randomised controlled trial
RGI-C	Radiographic Global Impression of Change
RSS	Rickets Severity Scale
SAE	Serious adverse events
SD	Standard deviation
SF-36v2	36-Item Short Form Health Survey (Version 2)
SLR	Systematic literature review
SmPC	Summary of product characteristics
SPPB	Short physical performance battery
STA	Single Technology Appraisal
TA	Technology Appraisal
TEAEs	Treatment-emergent adverse events
TNSALP	Tissue non-specific alkaline phosphatase
TRAEs	Treatment-related adverse events
TSD	Technical Support Document
TUG	Timed Up and Go
UK	United Kingdom
US	United States
VFS	Ventilator-free survival
WPAI-SHP	Work Productivity and Activity Impairment – Specific Health Problem

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1 SUMMARY

1.1 Background

Hypophosphatasia (HPP) is a rare, chronic, metabolic disease characterised by insufficient bone mineralisation, which can lead to premature death (in new-borns and infants) and a range of skeletal and systemic complications.

In the musculoskeletal system, skeletal deformities, premature tooth loss, fractures, impaired bone healing, muscle weakness, unusual gait and chronic debilitating pain can occur. These symptoms can lead to gross motor and cognitive developmental delays, reduced physical function, impaired mobility, the need for ambulatory assistance and the need for respiratory support. Additionally, patients can experience a variety of systematic complications including fatigue, failure to thrive, impaired renal function, craniosynostosis, seizures and respiratory failure in patients with infantile-onset HPP.

The first clinical manifestation of HPP can occur as early as in utero or as late as in adult life, and age at onset often determines which clinical manifestations patients may experience (e.g., rickets-like features are only present in children; see Section 2.2 for further details).

Asfotase alfa (AA) is a human recombinant tissue non-specific alkaline phosphate (TNSALP)-Fc-deca-aspartate fusion protein enzyme replacement therapy (ERT). It is a soluble glycoprotein comprised of two identical polypeptide chains, each with a length of 726 amino acids made from the catalytic domain of human TNSALP, the human immunoglobulin G1 Fc domain and a deca-aspartate peptide domain used for bone targeting.

Asfotase alfa targets the underlying causes of HPP, a deficiency of TNSALP activity, by replacing the defective enzyme and reducing the accumulation of extracellular substrates, thereby preventing or reversing bone mineralisation defects.

Asfotase alfa received marketing authorisation from the European Medicines Agency (EMA) on 28 August 2015, which was converted to a national Great Britain (GB) license on 1 January 2021. It is the only approved treatment for HPP and is indicated for long-term ERT in patients with paediatric-onset HPP to treat the bone manifestations of the disease.

Two pharmaceutical formulations of AA have been approved: 40 mg/ml solution for injection: containing 18 mg (0.45 ml), 28 mg (0.7 ml) and 40 mg (1.0 ml), and 100 mg/ml solution for injection: containing 80 mg (0.8 ml).

After the National Institute for Health and Care Excellence (NICE) approved AA, within the context of Managed Access Agreement (MAA),[1] in August 2017, Alexion initiated the United Kingdom (UK) MAA data collection that included all UK patients with HPP treated with AA. As of [redacted], a total of [redacted] patients had been enrolled into the UK MAA database and [redacted] patients had received AA treatment. Of these patients, [redacted] patients received AA treatment in England.

1.2 Critique of the decision problem in the company's submission

Some components of the decision problem (DP) addressed by the company were broadly in line with the NICE scope (population and intervention), with some discrepancies between in the data reported, whilst the External Assessment Group (EAG) noted more substantial discrepancies with others (comparators, outcomes and subgroups).

Population: People with paediatric-onset HPP – It should be noted that all of the evidence about the comparative efficacy of AA, in relation to best supportive care (BSC; historical controls) was for patients with perinatal-/infantile-onset HPP (symptoms manifested before 6 months of age).

Intervention: AA (Strensiq®) administered subcutaneously in a dosing regimen of 2 mg/kg of body weight 3 times per week, or a 1 mg/kg of body weight 6 times per week – It should be noted that not all of the included clinical trials used AA at this dose in all treated participants.

Comparators: BSC without AA – The historical control data are unlikely to be representative of current BSC, and there is a potential issue with immortal time bias in the comparative survival analyses.

Outcomes: Analyses of the comparative efficacy of AA were only conducted for survival outcomes (overall survival (OS) and ventilator-free survival (VFS)); no comparative efficacy data were presented in the clinical effectiveness section of the submission, for any functional outcomes.

Subgroups: Data were not consistently presented using the accepted categories of paediatric-onset HPP (perinatal-, infantile- and juvenile-onset) which are also the subgroups specified in the decision problem.

1.3 Summary of clinical effectiveness evidence submitted by the company

The company presented clinical efficacy results from five clinical trials of AA (ENB-001-08 (NCT00739505), ENB-002-08/ENB-003-08 (NCT00744042/NCT01205152), ENB-010-10 (NCT01176266), ENB-006-09/ENB-008-10, ENB-009-10 (NCT01163149)), together with additional data from the UK MAA, and real world evidence from the Global HPP Registry (ALX-HPP-501) and EmPATHY studies and a telephone survey conducted to assess health-related quality of life (HRQoL) for patients and carers. These studies are described in Section 4.2.

1.4 Summary of the EAG's critique of clinical effectiveness evidence submitted

The detailed EAG's summary and critique of the clinical effectiveness evidence submitted by the company can be found in Section 4 of this report. The key issues highlighted in the EAG's critique are summarised in Tables 1.1 to 1.5.

Table 1.1: Key issue 1: Discrepancy between the population in decision problem and the main source of efficacy data

Report Sections	**3.3.1, 4.2.1 and 4.3**
Description of issue and why the EAG has identified it as important	Lack of evidence about the efficacy and relative efficacy of asfotase alpha (AA) for patients with juvenile-onset (symptom onset between 6 months and 18 years of age) hypophosphatasia (HPP). All of the evidence about the comparative efficacy of AA, in relation to best supportive care (BSC) (historical controls) was for patients with perinatal-/infantile-onset HPP (symptoms manifested before 6 months of age).
What alternative approach has the EAG suggested?	Use all of the available data, including data from study ENB-006-09/ENB-008-10, adolescent subgroup data from study ENB-009-10 and data from the Managed Access Agreement (MAA), to provide estimates of the efficacy of AA for the whole of the specified population (paediatric-onset HPP, including perinatal-, infantile- and juvenile-onset) and use data from the Global HPP

Report Sections	3.3.1, 4.2.1 and 4.3
	Registry (ALX-HPP-502) to inform estimates of comparative efficacy. Conduct subgroup analyses for perinatal-/infantile onset HPP and juvenile onset HPP.
What is the expected effect on the cost effectiveness estimates?	It is not possible to predict the impact of increasing the evidence base on the point estimate of the incremental cost-effectiveness ratio (ICER). However, it is likely to reduce uncertainty and provide more accurate estimates for the cost effectiveness of AA for patients perinatal-/infantile onset HPP and juvenile onset HPP.
What additional evidence or analyses might help to resolve this key issue?	As per priority clarification question A13: Please repeat the pooled efficacy analysis, including all relevant patients, i.e., those with paediatric-onset (perinatal-, infantile- or juvenile-onset) HPP from all relevant studies including ENB-006-09/ENB-008-10, study ENB-009-10, the United Kingdom (UK) MAA and AA-treated patients from the wider Global HPP Registry (ALX-HPP-501), ENB-011-10, ALX-HPP-501 and ALX-HPP-502. Please conduct subgroup pooled analyses using all relevant data from all studies for each of perinatal-, infantile- or juvenile-onset HPP.
AA = asfotase alfa; BSC = best supportive care; EAG = External Assessment Group; HPP = hypophosphatasia; ICER = incremental cost-effectiveness ratio; MAA = Managed Access Agreement; UK = United Kingdom	

Table 1.2: Key issue 2: Non-standard subgrouping of study participants

Report Section	4.2.1
Description of issue and why the EAG has identified it as important	The results of the Managed Access Agreement (MAA) and study ENB-009-10 were not presented using the accepted categories of paediatric-onset hypophosphatasia (HPP) (perinatal-, infantile- and juvenile-onset) which are also the subgroups specified in the decision problem but were instead presented by age at study entry (<18 years and ≥18 years).
What alternative approach has the EAG suggested?	Present results and conduct subgroup analyses for perinatal-/infantile onset HPP and juvenile onset HPP, for all studies where these data are available.
What is the expected effect on the cost effectiveness estimates?	The effect on the cost effectiveness estimates is unclear.
What additional evidence or analyses might help to resolve this key issue?	As per priority clarification question A10: Please provide results tables, comparing results across all AA studies including the MAA, for each outcome measure, with results grouped by age of onset category (perinatal-, infantile-, and juvenile-onset HPP).
AA = asfotase alfa; EAG = External Assessment Group; HPP = hypophosphatasia; MAA = Managed Access Agreement	

Table 1.3: Key issue 3: Use of historical controls in comparative survival analyses

Report Sections	3.3.3, 4.3 and 4.5.2
Description of issue and why the EAG has identified it as important	Analyses of the comparative survival (overall survival (OS) and ventilator-free survival (VFS)) for asfotase alpha (AA) versus best supportive care (BSC) utilised historical control data which may not be representative of current BSC. Exploratory analysis of survival data by year, reported in the clinical study report (CSR) for ENB-011-10,[2] showed the probability of survival to 3 months of age [redacted] There is also a potential issue with immortal time bias in the survival analysis.[3] Immortal time bias can occur, in observational studies, where there is a delay to the start of treatment; this wait period is considered immortal because individuals who enter the treatment group have survived (be alive and event free) until the treatment definition is met.[3] Bias, which necessarily favours the treatment under study, is introduced when the immortal period is either misclassified with respect to treatment status or is excluded from the analysis.[3] The External Assessment Group (EAG) report for the previous assessment notes that, with respect to ENB-011-10, [redacted] These data were redacted from the publicly available version of the ERG report and were not included in the current submission. Given that the median age at baseline, for patients AA-treated patients (ENB-002-08/ENB-003-08), was [redacted]
What alternative approach has the EAG suggested?	Comparative analyses should be conducted, using all available data for AA-treated patients, including data from the Managed Access Agreement (MAA) and the Global HPP Registry (ALX-HPP-502) should be used to provide comparator data for patients not treated with AA.
What is the expected effect on the cost effectiveness estimates?	Given that the bias is likely to make AA appear to be more effective, the incremental cost-effectiveness ratio (ICER) will almost certainly increase if the immortal time bias is addressed appropriately.
What additional evidence or analyses might help to resolve this key issue?	In order to reduce the risk of immortal time bias, natural history data should be selected to be as comparable as possible to the AA data, particularly in terms of excluding patients who die earlier than might be possible to receive AA. As per priority clarification question A20: Please conduct analyses comparing AA with BSC (using natural history control data) for all outcomes mentioned in the scope, including adverse effects. Please include all study data relevant to the decision problem population, as reported in Table 1 or excluding juvenile-onset HPP if amended in response to question 3b. Please ensure that these analyses include data from the United Kingdom (UK) MAA and from the wider Global HPP Registry (ALX-HPP-501), as well as all other relevant AA treated and natural history data sources. Please conduct all of these analyses using appropriate methods for adjusting for potential confounders according to the methods described in NICE TSD 17 (National Institute for Health and Care Excellence. Decision Support Unit. Utilities TSD series. Available from: http://nicedsu.org.uk/technical-support-documents/utilities-tsd-series). Please conduct subgroup analyses for all outcomes comparing AA to BSC according to age of onset category i.e., at least to match the subgroups in the cost effectiveness section i.e., perinatal/infantile and juvenile, using the most appropriate evidence from all studies for each subgroup.

Report Sections	3.3.3, 4.3 and 4.5.2
AA = asfotase alfa; BSC = best supportive care; CSR = clinical study report; EAG = External Assessment Group; HPP = hypophosphatasia; ICER = incremental cost-effectiveness ratio; MAA = Managed Access Agreement; NICE = National Institute for Health and Care Excellence; OS = overall survival; TSD = Technical Support Document; UK = United Kingdom; VFS = ventilator-free survival;	

Table 1.4: Key issue 4: Inclusion of selected outcomes for the comparative efficacy analyses and weak comparator data

Report Sections	4.2.1 and 4.3
Description of issue and why the EAG has identified it as important	Analyses of the comparative efficacy of asfotase alpha (AA) were only conducted for survival outcomes (overall survival (OS) and ventilator-free survival (VFS)), using AA studies that included only participants with perinatal-/infantile-onset hypophosphatasia (HPP) and comparator data from historic controls which may not be representative of current best supportive care (BSC).
What alternative approach has the EAG suggested?	Comparative analyses should be conducted for all specified outcomes, using all available data for AA-treated patients, including data from the Managed Access Agreement (MAA) and the Global HPP Registry (ALX-HPP-502) should be used to provide comparator data for patients not treated with AA.
What is the expected effect on the cost effectiveness estimates?	The effect on the cost effectiveness estimates is unclear.
What additional evidence or analyses might help to resolve this key issue?	As per priority clarification question A20: Please conduct analyses comparing AA with BSC (using natural history control data) for all outcomes mentioned in the scope, including adverse effects. Please include all study data relevant to the decision problem population, as reported in Table 1 or excluding juvenile-onset HPP if amended in response to question 3b. Please ensure that these analyses include data from the United Kingdom (UK) MAA and from the wider Global HPP Registry (ALX-HPP-501), as well as all other relevant AA treated and natural history data sources. Please conduct all of these analyses using appropriate methods for adjusting for potential confounders according to the methods described in NICE TSD 17 (National Institute for Health and Care Excellence. Decision Support Unit. Utilities TSD series. Available from: http://nicedsu.org.uk/technical-support-documents/utilities-tsd-series). Please conduct subgroup analyses for all outcomes comparing AA to BSC according to age of onset category i.e., at least to match the subgroups in the cost effectiveness section i.e., perinatal/infantile and juvenile, using the most appropriate evidence from all studies for each subgroup.
AA = asfotase alfa; BSC = best supportive care; EAG = External Assessment Group; HPP = hypophosphatasia; MAA = Managed Access Agreement; NICE = National Institute for Health and Care Excellence; OS = overall survival; PFS = progression-free survival; TSD = Technical Support Document; UK = United Kingdom	

Table 1.5: Key issue 5: Inappropriate methods used to calculate estimates of comparative efficacy

Report Section	4.2.1
Description of issue and why the EAG has identified it as important	No matching of patients of attempt to adjust for confounders.
What alternative approach has the EAG suggested?	Analyses should be conducted, comparing asfotase alpha (AA) with best supportive care (BSC) (using natural history control data, including data from the Global HPP Registry) for all outcomes mentioned in the scope, including adverse effects. All study data relevant to the decision problem population, paediatric-onset hypophosphatasia (HPP), should be included. These analyses should include data from the United Kingdom (UK) Managed Access Agreement (MAA) and from the wider Global HPP Registry (ALX-HPP-501), as well as all other relevant AA treated and natural history data sources. Analyses should be conducted using appropriate methods for adjusting for potential confounders according to the methods described in NICE TSD 17 (National Institute for Health and Care Excellence. Decision Support Unit. Utilities TSD series. Available from: http://nicedsu.org.uk/technical-support-documents/utilities-tsd-series). Subgroup analyses should be conducted for all outcomes comparing AA to BSC according to age of onset category i.e., at least to match the subgroups in the cost effectiveness section i.e., perinatal/infantile and juvenile, using the most appropriate evidence from all studies for each subgroup.
What is the expected effect on the cost effectiveness estimates?	The effect on the cost effectiveness estimates is unclear, though it is reasonable to expect that these estimates will become less biased.
What additional evidence or analyses might help to resolve this key issue?	Please see Table 1.3.
AA = asfotase alfa; BSC = best supportive care; EAG = External Assessment Group; HPP = hypophosphatasia; MAA = Managed Access Agreement; NICE = National Institute for Health and Care Excellence; TSD = Technical Support Document; UK = United Kingdom	

1.5 Summary of the evidence submitted to support the value for money of the treatment and cost to the NHS and PSS

The searches reported for the systematic literature review (SLR) were clearly structured and documented. Searches were carried out on a broad range of resources, including supplementary searches of conference proceedings and other relevant resources such as a trials database, company records and the checking of references lists to identify additional studies not retrieved by the main searches.

The company submission (CS) presents a model-based cost-effectiveness analysis for AA versus BSC for the treatment of patients with HPP from the perspective of the National Health Service (NHS) in England. To a large extent, this model is the same as in the original submission.[4] A major difference in the current submission is that the model is structured differently for patients aged <5 years old at HPP onset than for patients aged 5+ years at HPP onset. For patients aged <5 years, the model simulates the

disease severity by ventilation status and accounts for HPP-related mortality, whereas for patients aged 5+ years, disease progression is simulated by using the 6-minute walk test (6MWT) as a surrogate for disease severity and HPP-related mortality is not considered, in patients receiving either AA or BSC. That is because younger patients face elevated risks of HPP-related mortality and respiratory complications requiring invasive ventilation compared to older patients. Disease impact in the submitted cost effectiveness model is estimated in terms of costs, HRQoL for patients and caregivers, and, for patients aged <5 years only, also in terms of HPP-related survival.

Costs and health outcomes are discounted at a rate of 3.5%.

For patients receiving AA, treatment dosage is assumed to be dependent on bodyweight, with a maximum recommended dose of 6 mg/kg/week. Upon starting treatment with AA, it is assumed that patients will remain on AA for the rest of their lives. No drug costs for BSC were included to the model; however, the components of BSC were incorporated as background healthcare resource use.

The transition probabilities for HPP-related mortality in the model were based on the survival data from the ENB-002-08/ENB-003-08 (11 patients) and ENB-010-10 (26 patients) trials as reported by Whyte et al. 2016,[5] with the addition of 43 treated patients from the ENB-010-10 trial,[6] and [redacted] patients from the UK MAA for AA patients.[7] For BSC patients, the respective transition probabilities were based a historical control group, consisting of 48 patients from the ENB-011-10 trial. Seven patients were excluded, as they died on the first day after birth. Mortality rates based on unadjusted survival from birth data for both treatment arms were compared. The difference in survival from birth between AA treated patients and historical controls were assumed to reflect a treatment effect.

Transition probabilities for invasive ventilation were estimated using the same trials mentioned above for HPP-related mortality. Nonetheless, transition probabilities for invasive ventilation were modelled independent of age but separate for AA and BSC.

For the model for 5+ years, transition probabilities between the four health states were derived based on patients with at least two 6MWT assessments on AA or BSC, so that a transition between severity levels could be observed. In total, the AA and BSC arms included respectively 51 and 26 patients. In the AA arm, 27 patients were included from the clinical studies and 24 from the UK MAA. Multivariate ordered probit models were fitted separately to both AA and BSC arms, based on the observed health state transitions and controlling for patient age and the days elapsed between visits. The results of the probit model were used to generate predicted probabilities for the transition matrices, which provides the age-specific probability of being in a given health state conditional on prior health state.

Age-specific background death risks are estimated from UK life tables.

Health utility estimated were based on a vignette study using input from HPP clinical experts in the UK. Data from the UK MAA and the Global HPP Registry were available but considered to be of inferior quality. The model included caregiver disutilities for caregiver burden as well as for bereavement related to the death of a child due to HPP.

AA treatment costs were estimated based on the average weight observed in different age ranges of patients from the various clinical trials and the UK MAA study. Treatment compliance, and annual discontinuation rate, were incorporated to account for reduced AA treatment costs. Resource use costs associated with the different HPP health states were primarily based on the previous NICE submission of 2017.[4] HPP natural history studies (ENB-011-10 and ALX-HPP-502), the European patient survey, UK patient case studies and clinical expert opinion served as sources of information to derive estimates of healthcare resource use for each health state. Resource use of discrete clinical events remained

relatively aligned with the NICE submission of 2017,[4] following clinical experts' confirmation that clinical practice for HPP treatment has remained relatively unchanged since 2016. Small adjustments included addition of pain management services, addition of dietician visits and inclusion of mental health services. Unit costs for resource use associated with HPP health states were updated accordingly and inflated to 2020-21 if values were prior to 2021 using the NHS Cost Inflation Index from the 2021 Personal Social Services Research Unit (PSSRU).[8]

The discounted company base-case results using a Patient Access Scheme (PAS) discount of [redacted] for AA showed that, compared to BSC, AA is associated with [redacted] incremental quality-adjusted life years (QALYs) at an additional cost of [redacted] in the perinatal-/infantile-onset group. In the juvenile-onset group, AA is associated with [redacted] incremental QALYs at an additional cost of [redacted] versus BSC. These correspond to incremental cost-effectiveness ratios (ICERs) of £240,279 per QALY gained in the perinatal-/infantile-onset group and £295,536 per QALY gained in the juvenile-onset group.

The undiscounted gain in QALYs with AA was [redacted] in the perinatal-/infantile-onset HPP patients and [redacted] in the juvenile-onset HPP patients compared to BSC, indicating that a weighting of [redacted] can be used to calculate a weighted threshold (of [redacted]).

The company explored various scenarios. From the scenarios explored in both the perinatal-/infantile-onset and the juvenile-onset HPP patients, the use of a 25-year time horizon (instead of lifetime in base-case) has a very large impact on the ICER, leading to a substantial increase. Using a 1.5% discount rate for health outcomes (instead of 3.5% in base-case) or applying a higher price discount in AA costs following the loss of patent exclusivity (72% instead of 58.5% in the base-case), decreased the ICERs in both patient populations. On the other side, applying a lower price discount for AA costs following the loss of patent exclusivity (45% instead of 58.5% in the base-case) substantially increased the ICERs in both patient populations. In the juvenile-onset HPP patients, the scenario that had the greatest impact was the use of a higher baseline age at 26.5 years (instead of 5.0 in the base-case), leading to a higher ICER.

1.6 Summary of the EAG's critique of the value for money evidence submitted

The EAG's summary and detailed critique of the value for money evidence submitted by the company can be found in Section 5 of this report. The key issues in the value for money evidence are summarised in Tables 1.6 to 1.8.

Table 1.6: Key issue 6: Uncertainty in transition probabilities

Report Section	**5.3.3.3**
Description of issue and why the EAG has identified it as important	• The number of patients in the best supportive care (BSC) arm in the current submission is the same as in the original National Institute for Health and Care Excellence (NICE) submission of 2017, no new data were added.[4] To model the impact of treatment on hypophosphatasia (HPP)-related mortality for patients aged <5 years receiving asfotase alpha (AA) versus BSC, mortality rates based on unadjusted survival from birth were compared as in the original submission of 2017. This approach is subject to several potential biases as survival curves may erroneously indicate that AA patients were treated from birth, whereas they were treated only after the study enrolment (see Key issue 3 on immortal time bias). As also criticised in the original submission of 2017, other biases exist related to the company's decision to not matching AA patients with BSC patients for an adjusted comparison. For instance, in the BSC group only 21 patients were diagnosed after 2000 compared

Report Section	5.3.3.3
	with AA patients being diagnosed after 2005, whilst in the 2017 report it was shown that survival had improved in younger cohorts of BSC patients. The committee in the original appraisal found comparing only the BSC patients diagnosed after 2000 to AA patients more appropriate when comparing overall survival (OS) data for AA with BSC.[4] Furthermore, a matched analysis was requested by the External Assessment Group (EAG) in the original appraisal, not only because risk factors between the two groups would need to be comparable, but also because matched patients in the BSC arm had to be alive when 'their' AA patient started treatment, considering that AA patients start treatment at approximately 1 year. A matched comparison provided by the company in the original appraisal showed that the survival benefit in the matched analysis was lower than the unmatched analysis. • Risks for invasive ventilation in the patient population aged <5 years are assumed to be age independent. If many patients require repeated ventilation support, then a time to event analysis would not be the most appropriate approach as argued by the company in response to EAG's request to use time to event analysis instead of a constant ventilation risk. However, the company did not provide any additional evidence to show the number of patients requiring repeated ventilation support. If the number of patients with repeated ventilation support is low, then a time to event analysis would still be more informative than a constant risk. • The number of patients in the BSC arm used to estimate transition probabilities between disease severity levels in the current submission is the same as in the original NICE submission of 2017, whereas for the AA arm the United Kingdom (UK) Managed Access Agreement (MAA) data were added.[4] Therefore, the number of observations used to estimate transition probabilities between the severity health states in the BSC arm is small, implying a large uncertainty associated to these input parameters which is not resolved when compared with the original appraisal. In response to clarification question B16,[9] the company indicated that limited 6-minute walk test (6MWT) data were collected in the Global HPP Registry. However, these data were not used in the model to estimate transition probabilities for 6MWT-defined health states. The company provided three probit regression models developed separately for the AA and BSC arms to estimate transition probabilities between the severity levels. Considering the uncertainty around model predictions due to the limited number of observations, especially for BSC, the EAG agrees with the company's preferred model and considers the 2nd specification more appropriate for the base-case analysis. Nonetheless, as the EAG has several concerns around the fit of these model specifications, considers the alternative specifications appropriate for inclusion in the scenario analyses. In the company submission (CS), the scenario analyses only explored the impact of using the third instead of the second specification, completely neglecting the most parsimonious the 1st specification.
What alternative approach has the EAG suggested?	To address biases related to estimates of HPP-related mortality for patients aged <5 years, a matched analysis would be a better approach. The company would need to provide the number of patients requiring repeated ventilation support. If the number of patients with repeated ventilation support is low, then a time to event analysis would be more informative than a constant risk of invasive ventilation support, as it includes the timing of the ventilation.

Report Section	5.3.3.3
	Alternative model specifications as per the EAG's request could address some of the EAG's concerns on the stability of the results due to the small number of observations for BSC. Using data from the Global HPP Registry on the 6MWT could help in resolving this uncertainty around model predictions.
What is the expected effect on the cost effectiveness estimates?	Because of a lack of patient level data, the EAG is unable to assess the impact of the above biases. The EAG could only explore the impact of using alternative model specifications for estimating transition probabilities between the different severity levels. In the 2017 EAG report, it was shown that a matched analysis for mortality led to a smaller survival effect and thus larger incremental cost-effectiveness ratios (ICERs). For perinatal/infantile onset HPP patients, using alternative model specifications for transitions between health states had a minor impact on results. For juvenile-onset HPP patients, the most parsimonious 1st specification substantially increased the EAG's base-case ICER from £739,120 per quality-adjusted life year (QALY) gain to £945,924 per QALY gain, whereas the impact on the ICER was slightly lower for the 3rd specification at £744,319 per QALY gain. Please see Table 6.4.
What additional evidence or analyses might help to resolve this key issue?	To reflect AA treatment effect on HPP-related mortality for patients aged <5 years, a matched analysis between AA and BSC patients is necessary. In the absence, of patient-level data such analysis can only be performed by the company. To appropriately measure the risk for invasive ventilation, the company would need to provide the number of patients requiring repeated ventilation support from the ENB-002-08/ENB-003-08, ENB-010-10, and ENB-011-10 trials. To address uncertainty in transition probabilities between severity levels due to the small number of observations for BSC, alternative model specifications based also on Global HPP Registry data would be required.
AA = asfotase alfa; BSC = best supportive care; CS = company submission; EAG = External Assessment Group; HPP = hypophosphatasia; ICER = incremental cost-effectiveness ratio; MAA = Managed Access Agreement; NICE = National Institute for Health and Care Excellence; OS = overall survival; QALY = quality-adjusted life year; UK = United Kingdom; 6MWT = 6-minute walk test	

Table 1.7: Key issue 7: Uncertainty in utility values and carer disutilities

Report Section	5.3.3.5
Description of issue and why the EAG has identified it as important	The utility values used in the cost effectiveness model were estimated using a vignette study in which clinical experts scored representations of different severity states (vignettes) on the European Quality of Life-5 Dimensions (EQ-5D). No patient reported data were used. In the probabilistic sensitivity analysis (PSA) parameter uncertainty for these utility values was based on the standard deviation (SD) calculated from the elicited utilities, which is not an appropriate representation of parameter uncertainty in this case. Parameter uncertainty likely is much larger than represented in the PSA, and the univariate sensitivity analysis shows that the model outcomes are sensitive to changes in the utility values.

Report Section	5.3.3.5
	The model included a parental disutility for infant death. The size of this disutility and the duration for which it is experienced is uncertain due to limited evidence and it is not clear to what extend it applies to a United Kingdom (UK) population. The univariate sensitivity analysis indicated that model results are highly sensitive to the assumptions and parameter input values on this part.
What alternative approach has the EAG suggested?	The health-related quality of life (HRQoL) reported by patients should be used in the model. Parental disutility for infant death should be evaluated in a scenario rather than the base-case until more robust evidence is available.
What is the expected effect on the cost effectiveness estimates?	The impact of uncertainty in the patient utility values is unknown since these were obtained from a vignette study done with HPP clinical experts in the UK and not from patients. No alternative utilities were available to quantify this uncertainty and assess its impact on the model outcomes. Excluding the parental disutility due to infant death increased the incremental cost-effectiveness ratio (ICER) of the company's base-case analysis from £240,279 per quality-adjusted life year (QALY) gained to £258,200 per QALY gained for the perinatal/infantile-onset hypophosphatasia (HPP) patient population (without QALY weighting).
What additional evidence or analyses might help to resolve this key issue?	The HRQoL data collected as part of the United Kingdom (UK) Managed Access Agreement (MAA) and/or Global HPP Registry should be used as model input.
EAG = External Assessment Group; EQ-5D = European Quality of Life-5 Dimensions; HPP = hypophosphatasia; HRQoL = health-related quality of life; ICER = incremental cost-effectiveness ratio; MAA = Managed Access Agreement; PSA = probabilistic sensitivity analysis; QALY = quality-adjusted life year; SD = standard deviation; UK = United Kingdom	

Table 1.8: Key issue 8: Price reduction due to patent expiry

Report Section	5.3.3.8
Description of issue and why the EAG has identified it as important	The model includes a price reduction of 58.5% in asfotase alpha (AA) treatment costs to account for patent expiration in 7 years from now, an assumption that is only based on expectations and not on evidence. The number of existing biosimilars for orphan diseases is very limited, likely attributed to the economically unattractiveness of producing biosimilars for orphan diseases targeting small populations. The committee in the original appraisal of 2017, acknowledged that there was no robust basis for assuming a price reduction due to future patent expiry and stated that it had not previously considered price reductions resulting from the potential introduction of generics or biosimilars because this is speculative, and the impact of their introduction is unknown.
What alternative approach has the EAG suggested?	Omit price reduction due to future patent expiry of AA treatment from the base-case analysis.
What is the expected effect on the cost	Excluding the AA price reduction due to patent expiry increased the incremental cost-effectiveness ratios (ICERs) of the company base-case analysis from £240,279 per quality-adjusted life year (QALY) gain to £529,032 for the perinatal/infantile-onset hypophosphatasia (HPP)

Report Section	5.3.3.8
effectiveness estimates?	patient population and from £295,536 per QALY gain to £658,265 for the juvenile-onset HPP patient population, without QALY weighting. Please see Table 6.2.
What additional evidence or analyses might help to resolve this key issue?	No additional evidence is needed.
AA = asfotase alfa; EAG = External Assessment Group; HPP = hypophosphatasia; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life year	

Table 1.9: Key issue 9: Resource use and costs

Report Sections	5.3.3.8 and 6.4.3
Description of issue and why the EAG has identified it as important	To estimate asfotase alfa (AA) treatment costs the company used mean weight value curves using a 3rd-degree polynomial model fitted to data from AA clinical trials and the United Kingdom (UK) Managed Access Agreement (MAA) study. The modelled patient's weight based on the polynomial model is much lower than the weight of the general population as shown in Figure 36 of the company submission (CS). The company did not provide any information on the goodness-of-fit for the polynomial model and on other smoothing curves that they have potentially explored. The External Assessment Group (EAG) also noted that for the higher age range (i.e., above the age of 13), the difference between the smoothed curve and the curves from the general population are larger than for the respective differences in the younger age range. Also, the company's deterministic sensitivity analysis (DSA) showed the weight of patients aged 18+ had a substantial impact in the cost effectiveness outcomes of AA versus best supportive care (BSC).
What alternative approach has the EAG suggested?	The EAG's sensitivity analysis considered a scenario in which the patients' weight followed the median values of the general population. As data from the Royal College of Paediatrics and Child Health cover people up to the age of 17, the weight from the smoothed curve and the lower bound of the differences between the 50th percentile weight curve and the smoothed curve was used to estimate the weight for people aged 18+ (i.e., 1.15 times the weight estimated from the smoothed curve) in the EAG scenario analysis.
What is the expected effect on the cost effectiveness estimates?	When the patient weight was assumed to follow the pattern of the weight in the general population, the incremental cost-effectiveness ratio (ICER) of the EAG's base-case analysis increased from £621,370 per quality-adjusted life year (QALY) gained to £770,947 per QALY gained for the perinatal/infantile-onset hypophosphatasia (HPP) patients, whereas the ICER of the juvenile-onset HPP patients increased from £739,120 per QALY gained to £917,000 per QALY gained.
What additional evidence or analyses might help to resolve this key issue?	The company could provide additional information on the goodness-of-fit for the polynomial model and on other smoothing curves that have been potentially explored.

Report Sections	5.3.3.8 and 6.4.3
AA = asfotase alfa; BSC = best supportive care; CS = company submission; DSA = deterministic sensitivity analysis; EAG = External Assessment Group; HPP = hypophosphatasia; ICER = incremental cost-effectiveness ratio; MAA = Managed Access Agreement; QALY = quality-adjusted life year; UK = United Kingdom	

1.7 Summary of the evidence submitted on the impact of the technology beyond direct health benefits and on the provision of specialised services

The impact of AA on the productivity of caregivers and patients were included in a scenario analysis of the CS.[10] The impact of HPP on productivity was linked to the health states, with patients and caregivers being able to work less in the more severe health states. The extent to which patients or caregivers were able to work in each health state was based on assumptions and was assumed the same under AA and BSC treatment. Productivity was valued using the average value of a person's productivity in the UK.

In the CS the company explains that HPP is associated with other costs borne by patients, such as modifications to homes and frequent travel for hospital visits. These costs were not quantified in the current submission.[10]

1.8 Summary of the EAG's critique on the evidence submitted on the impact of the technology on non-health-related benefits

The impact of HPP on the productivity of patients and caregivers was based on assumptions, whereas in the original submission data from the European HPP survey were used.[4] In addition, the previous submission explicitly took other societal costs into account, such as the costs for special schooling, out of pocket expenditures for transportation, costs for the adaptation of cars and homes, and the value of informal care. These costs are only mentioned but not taken into account in the current submission.

1.9 Summary of the EAG preferred base-case and exploratory sensitivity analyses undertaken by the EAG

The EAG's preferences regarding alternative assumptions led to the following changes to the company base-case analysis:

- The utility decrement in caregivers of patients under 5 years of age that required invasive ventilation, as well as patients 5 years and older in the most severe health state (SLIV) was assumed to be 0.17. The EAG prefers to assume that the caregiver disutility of 0.11 is a more suitable value.
- The assumption made by the company that caregiver disutility is only applied to those surviving in both treatment arms is changed. Caregiver disutility is considered appropriate to be applied to those surviving in each of the treatment arms.
- The effect of infant death on the HRQoL of parents was not included in the EAG's preferred base-case due to the limited evidence around this modelling assumption.
- The price reduction for AA of 58.5% after 7 years was excluded.
- Full wastage is assumed for AA treatment costs to align dosing strategy with the recommended dosage in summary of product characteristics (SmPC) of AA for all patients.

The results from the EAG deterministic base-case are shown below in Table 1.10. The five changes together have a very large impact on the ICER (Table 1.11). Applying a 3.5% discount rate for both costs and effects, the EAG base-case results showed that compared with BSC, AA is associated with [redacted] incremental QALYs, and [redacted] incremental costs in the perinatal-/infantile-onset group. In the juvenile-onset group AA is associated with [redacted] incremental QALYs and [redacted] incremental costs

versus BSC. The ICER is £621,370 per QALY gained in the perinatal-/infantile-onset group and £739,120 per QALY gained in the juvenile-onset group, without QALY weighting. When a discount rate of 0% is applied, the EAG's base-case estimates show that perinatal-/infantile-onset patients treated with AA gain [redacted] undiscounted QALYs compared to BSC, and for juvenile-onset HPP patients, the respective gain is [redacted] undiscounted QALYs, indicating that a weighting of [redacted] can be used to calculate a weighted threshold.

Table 1.10: EAG discounted base-case results without QALY weight

Technologies	Total costs (£)	Total LYG	Total QALYs	Inc. costs (£)	Inc. LYG	Inc. QALYs	ICER (£)
Population: Perinatal-/infantile-onset HPP							
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	621,370
AA	[redacted]	[redacted]	[redacted]				
Population: Patients with juvenile-onset HPP							
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	739,120
AA	[redacted]	[redacted]	[redacted]				

Based on Table 69 and Table 70 of the CS.[10]
AA = asfotase alfa; BSC = best supportive care; CS = company submission; EAG = External Assessment Group; HPP = hypophosphatasia; ICER = incremental cost-effectiveness ratio; Inc. = incremental; LYG = life-years gained; QALY = quality-adjusted life year

Table 1.11: Isolated impact of the EAG's preferred model assumptions without QALY weight

Preferred assumption	Section in EAG Report	Inc. Costs (£)	Inc. QALYs	ICER (£/QALY)
Population: Perinatal-/infantile-onset HPP				
Company base-case	**5.4.1**	[redacted]	[redacted]	**£240,279**
Company base-case after error correction on the invasive ventilation risk at t=0	6.2.1.1	[redacted]	[redacted]	240,473
Company base-case after error correction on rounding down of age	5.3.3.8	[redacted]	[redacted]	241,839
EAG change 1 – Caregiver disutility 0.11	5.3.3.5	[redacted]	[redacted]	246,933
EAG change 2 – Caregiver disutility applied survivors in each of the treatment arms	5.3.3.5	[redacted]	[redacted]	248,179
EAG change 3 - Parental disutility due to infant death not included	5.3.3.5	[redacted]	[redacted]	258,200

Preferred assumption	Section in EAG Report	Inc. Costs (£)	Inc. QALYs	ICER (£/QALY)
EAG change 4 - Exclude price reduction for asfotase alfa (AA) after 7 years	5.3.3.8	[redacted]	[redacted]	529,032
EAG change 5 - Consider full wastage of AA	5.3.3.8	[redacted]	[redacted]	245,067
EAG base-case – all 5 changes combined	**-**	[redacted]	[redacted]	**621,370**
Population: Patients with juvenile-onset HPP				
Company base-case	**5.4.1**	[redacted]	[redacted]	**£295,536**
Company base-case after error correction on the invasive ventilation risk at t=0	6.2.1.1	[redacted]	[redacted]	295,536
Company base-case after error correction on rounding down of age	5.3.3.8	[redacted]	[redacted]	299,737
EAG change 1 – Caregiver disutility 0.11	5.3.3.5	[redacted]	[redacted]	319,773
EAG change 2 – Caregiver disutility applied survivors in each of the treatment arms	5.3.3.5	[redacted]	[redacted]	295,537
EAG change 3 - Parental disutility due to infant death not included	5.3.3.5	[redacted]	[redacted]	295,536
EAG change 4 - Exclude price reduction for AA after 7 years	5.3.3.8	[redacted]	[redacted]	658,265
EAG change 5 - Consider full wastage of AA	5.3.3.8	[redacted]	[redacted]	305,114
EAG base-case – all 5 changes combined	**-**	[redacted]	[redacted]	**739,120**

AA = asfotase alfa; EAG = External Assessment Group; HPP = hypophosphatasia; ICER = incremental cost effectiveness ratio; Ínc. = incremental; QALY = quality-adjusted life year

The EAG scenarios that had the largest impact on results of the perinatal/infantile-onset HPP patients were assumptions around the parental disutility due to infant death, the weight of the patient population, and the compliance and discontinuation rates (Table 1.12). The EAG scenarios that had the largest impact on results of the juvenile-onset HPP patients were assumptions around the model specification used to estimate transition probabilities between severity levels, the weight of the patient population, the caregiver disutility, and the compliance and discontinuation rates.

Table 1.12: EAG scenario analyses results, without QALY weight

Scenario	Assumptions	Inc. costs (£)	Inc. QALYs	ICER (£)
Population: Perinatal-/infantile-onset HPP				
EAG base-case		[redacted]	[redacted]	**621,370**
Transition probabilities for SLs	1st model specification	[redacted]	[redacted]	620,130
	3rd model specification	[redacted]	[redacted]	613,194
Caregiver disutility	0.08	[redacted]	[redacted]	626,948
	0.17	[redacted]	[redacted]	610,506
Number of carers to which disutility is applied	2	[redacted]	[redacted]	601,738
Disutility bereavement	0.04 for 15 years	[redacted]	[redacted]	598,612
	0.04 for 30 years	[redacted]	[redacted]	586,150
	0.04 for lifetime	[redacted]	[redacted]	576,087
Weight function	Weight of the general population	[redacted]	[redacted]	770,947
Drug wastage	'Round down' option	[redacted]	[redacted]	609,600
	'Closest' option	[redacted]	[redacted]	613,185
Discontinuation and Compliance	0% discontinuation rate	[redacted]	[redacted]	745,730
	100% compliance rate	[redacted]	[redacted]	630,744
	0% discontinuation and 100% compliance rate	[redacted]	[redacted]	756,998
Population: Patients with juvenile-onset HPP				
EAG base-case		[redacted]	[redacted]	**739,120**
Transition probabilities for SLs	First model specification	[redacted]	[redacted]	945,924
	Third model specification	[redacted]	[redacted]	744,319
Caregiver disutility	0.08	[redacted]	[redacted]	770,722
	0.17	[redacted]	[redacted]	683,102
Number of carers to which disutility is applied	2	[redacted]	[redacted]	642,520
Disutility bereavement	0.04 for 15 years	[redacted]	[redacted]	739,120
	0.04 for 30 years	[redacted]	[redacted]	739,120
	0.04 for lifetime	[redacted]	[redacted]	739,120
Weight function	Weight of the general population	[redacted]	[redacted]	917,000

Scenario	Assumptions	Inc. costs (£)	Inc. QALYs	ICER (£)
Drug wastage	'Round down' option	[redacted]	[redacted]	724,158
	'Closest' option	[redacted]	[redacted]	728,643
Discontinuation and Compliance	0% discontinuation rate	[redacted]	[redacted]	872,668
	100% compliance rate	[redacted]	[redacted]	750,762
	0% discontinuation and 100% compliance rate	[redacted]	[redacted]	886,344

EAG = External Assessment Group; HPP = hypophosphatasia; ICER = incremental cost effectiveness ratio; Inc. = incremental; QALY = quality-adjusted life year

1.10 EAG commentary on the robustness of evidence submitted including strengths, weaknesses and areas of uncertainty

Strengths: The EAG is confident that all relevant studies (published and unpublished) of AA were included in the CS. The CS includes additional data from trials completed the previous assessment of AA, in this indication, in 2015/2016, as well as reporting a substantial amount of data from the UK MAA, which was initiated following that assessment to allow collection of further data. The CS also includes a substantial amount of real world data including data, for both AA-treated and untreated patients from the Global HPP Registry (ALX-HPP-501).

Weaknesses: Despite the relative completeness of the CS with respect to included studies, the EAG considers that the results were not provided in a way which allowed for ready comparison across studies and for interpretation against the decision problem specified in the scope. In particular, results were not consistently presented by age of onset category (perinatal/infantile- and juvenile-onset) and the company have declined to provide results by age of onset category, even though the provision of baseline data for age of onset category appears to indicate that sufficient data are available to support this.

Although the CS includes results from the UK MAA, the EAG does not consider that these results have been appropriately used in the analyses of clinical effectiveness presented. No data from the UK MAA were included in any of the pooled analyses of efficacy or comparative efficacy presented in the clinical effectiveness sections of the CS. There was a lack of consistency between the data presented in the clinical effectiveness sections of the CS and the company's approach to providing inputs for their cost effectiveness modelling, where some data from the UK MAA were included.

The only comparative effectiveness data, for AA versus BSC, presented in the clinical effectiveness section of the CS, were for survival outcomes (OS and VFS). The clinical effectiveness sections of the CS did not include any information about the comparative efficacy of AA versus BSC, with respect to growth or functional outcomes, either for babies born with HPP who survive, following treatment with AA, or for those with juvenile-onset HPP (less severe disease).

With respect to control data used in the reported comparative survival analyses, the same historical control data were used as in the submission for the previous assessment and, as such, the previously issues with the control data remain. The EAG considers that historical control data used may not be representative of current BSC in that 27% of the included patients were diagnosed before 1990. No attempt was reported to explore the potential use of 'never treated' patients from the Global HPP

Registry to improve the comparator data set. The EAG does not consider that all potential sources of comparator data have been adequately explored. In addition, no attempt appears to have been made to match AA-treated patients and untreated controls, with respect to key demographic and clinical characteristics, or to adjust for potential confounders. The EAG, therefore, considers these analyses to be fundamentally flawed.

These weaknesses carry over to the cost effectiveness analyses, rendering the results of it highly uncertain.

2 BACKGROUND

2.1 Introduction

This chapter presents an overview of hypophosphatasia (HPP) and its management. The content of this chapter is based on relevant literature, clinical information obtained by the External Assessment Group (EAG) and information presented in the background sections of the company submission (CS).[10] For additional information on the aetiology, epidemiology, health impact, prognosis, and management of PH1, please see Section B.1.3 of the CS.[10]

2.2 Description of health problem

2.2.1 Disease overview

Hypophosphatasia (HPP) is a rare, chronic, metabolic disease characterised by insufficient bone mineralisation, which can lead to premature death (in new-borns and infants) and a range of skeletal and systemic complications.[10, 11] In the musculoskeletal system, skeletal deformities, premature tooth loss, fractures, impaired bone healing, muscle weakness, unusual gait and chronic debilitating pain can occur.[10] These symptoms can lead to gross motor and cognitive developmental delays, reduced physical function, impaired mobility, the need for ambulatory assistance and the need for respiratory support.[10]

In those most severely affected by HPP (perinatal- and infantile-onset), mortality ranges from 50–100% within 1 year and survival beyond 1 year of age comes with significant co-morbidities with impact on patients' quality of life (QoL).[10, 12-14]

The traditional clinical description of HPP is based on categorising the disease by age of onset:

- Perinatal-onset (onset in utero or at birth)
- Infantile-onset (onset between 0–6 months of age)
- Juvenile-onset (also referred as childhood onset; onset between 6 months to 18 years of age)
- Adult-onset (onset ≥18 years of age)
- Odonto-HPP (only dental clinical symptoms)

The traditional clinical description does not consider that diagnosis is often delayed, which leads to underdiagnosis and creates confusion when it comes to classification.[10] For example, adults may not have been diagnosed until adulthood despite having symptoms during childhood, which means that they have paediatric-onset HPP, whereas others may have true adult-onset HPP.[10] Nonetheless, due to its standardised use in literature, the Alexion clinical programme for asfotase alfa (AA) also used this to describe patients.

EAG comment: The National Institute for Health and Care Excellence (NICE) final scope recognises that there are six clinical forms of HPP: perinatal (lethal), perinatal (non-lethal), infantile, childhood, adult, and odontohypophosphatasia, with the most severe form being those that occur before birth and in early infancy.

2.2.2 Epidemiology

Paediatric-onset HPP is a rare disease that presents before the age of 18 years and includes patients with perinatal-, infantile- or juvenile-onset HPP. Due the rarity of the disease, estimates of the prevalence and incidence for paediatric-onset HPP in England are limited. A 10-year study of 20 European countries reported an estimated birth prevalence of perinatal-/infantile-onset HPP of 1 in 300,000 live

births.[15] Another study estimated an incidence of HPP of 0.8 per 1,000,000 for children under age 18 and 2.8 per 1,000,000 for children under age 1 using a survey method in 2003.[16]

EAG comment: The NICE final scope defined the population of interest as 'patients with paediatric-onset HPP' classification of HPP which in the CS has been classified to include traditional classifications of those with perinatal-, infantile- or juvenile-onset HPP. See Section 3.3.1 for further information.

2.2.3 Aetiology

The underlying cause of HPP is missing or deficient tissue non-specific alkaline phosphatase (TNSALP), encoded by the *ALPL* gene.[11] Since the initial characterisation of the *ALPL* gene in 1988, over 400 mutations have been identified, resulting in a range of TNSALP activity, with more mutations likely to be identified. These are predominantly missense mutations, which indicates a strong allelic heterogeneity in the disease.[17, 18] In the Global HPP Registry sponsored by Alexion, *ALPL* pathogenic variant analysis was performed on 172 participants.[19] Among these patients, 218 variants were reported, the majority of which were missense variants (73.9%), which confirms findings from previous publications.[19]

EAG comment: No comments on this Section.

2.2.4 Pathogenesis

In patients with HPP, loss-of-function mutations in *ALPL* cause a deficiency in TNSALP enzymatic activity, which leads to accumulation of its known substrates: inorganic pyrophosphate (PPi), pyridoxal 5'-phosphate (PLP) and phosphoethanolamine (PEA). These results in deficient bone mineralisation, leading to the skeletal defects and systemic complications that are characteristic of HPP.[19, 20] High extracellular levels of PPi inhibit bone mineralisation by blocking hydroxyapatite crystal formation.[21-23] Consequently, calcium and PPi accumulate in the bloodstream, causing disturbances in calcium/phosphate homeostasis.[24] This can disrupt bone formation and skeletal mineralisation, with secondary effects on respiratory function and muscular/rheumatologic symptoms.

Dysregulation of PLP, the principal form of circulating vitamin B_6, in the central nervous system has been associated with pyridoxine-responsive seizures in the most severely affected patients. The clinical consequences of PEA accumulation are not currently known, but the biomarker has been used as a diagnostic marker for HPP.[25]

EAG comment: No comments on this Section.

2.2.5 Clinical features

The loss or reduced functionality of *ALPL* associated with HPP has the potential to affect multiple organ systems. As such, the clinical manifestations of HPP can vary considerably between individuals and may include skeletal abnormalities, muscle weakness, ambulatory difficulties, respiratory insufficiencies such as asthma, pain, neurological, articular, renal and dental manifestations.[11, 26] The exact manifestations exhibited will vary by patient and may change as the patient ages, depending on whether the disease manifested itself before or after 6 months of age, and on disease progression over a patient's lifetime.[10]

Clinical manifestations can be severe across all populations and result in high mortality among patients with perinatal- and infantile-onset disease.[10] This is primarily a result of respiratory insufficiency but is

also due to B_6-responsive seizures when the condition is left untreated.[10] Table 2.1 provides an overview of the potential clinical manifestations according to the traditional clinical description of HPP.

EAG comment: The clinical features of HPP are heterogeneous, multi-systemic, and are characterised by large variations in severity. It can be understood that for some patients, the signs and symptoms detailed in Table 2.1 may not be obvious, leading to subsequent misdiagnosis in those with later onset or less severe manifestations, and potential worsening of disease.

Table 2.1: Overview of potential clinical manifestations by the traditional clinical description

Clinical form by time of onset	Bone signs and symptoms	Physical signs and symptoms	Dental signs
Perinatal HPP (in utero and at birth), usually lethal	Hypo mineralisation Osteochondral spurs Marked shortening of long bones Rachitic chest deformities	Respiratory complications Hypoplastic lungs Apnoea Seizures	Not relevant to developmental stage
Prenatal benign HPP (in utero)	Bowed, shortened long bones Benign post-natal Spontaneous improvement of skeletal defects	Not reported	Not relevant to developmental stage
Infantile (<6 months of age)	Craniosynostosis Hypo mineralisation Rachitic ribs Hypercalciuria Presence of open fontanelles Non-traumatic fractures Deformities of long bones Short stature in adulthood	May appear normal Respiratory insufficiencies Increased cranial pressure Seizures (vitamin B_6-responsive) Muscle weakness/hypotonia Hypercalcaemia (irritability, poor feeding, anorexia, vomiting, hypotonia, polydipsia, hypercalciuria) Organ calcification (e.g. nephrocalcinosis)	Premature loss of deciduous teeth
Juvenile (≥6 months–18 years of age)	Hypo mineralisation Short stature Skeletal deformity Bone pain/fractures Rickets Focal bone defects in long bones Spontaneous remission of bone symptoms has been reported	Chronic muscle pain Waddling gait Delayed walking Intracranial hypertension Failure to thrive Secondary metabolic inflammation Hyperprostaglandinism	Premature loss of deciduous teeth Premature loss of permanent teeth (in older aged children)

Clinical form by time of onset	Bone signs and symptoms	Physical signs and symptoms	Dental signs
Adult (≥18 years of age)	Stress fractures (e.g., metatarsal, tibia) Chronic bone pain Osteomalacia Osteoarthritis Recurring/pseudo fractures of femur Chondrocalcinosis	Chronic muscle and joint pain Muscle weakness Arthropathy with or without chondrocalcinosis Enthesopathy Impaired ambulation Foot pain Thigh pain	Dental history may reveal premature loss of deciduous teeth Severe caries Premature loss of permanent teeth
Odonto-HPP (any age)	Loss of alveolar bone	Biochemical markers similar to those with mild HPP	Exfoliation (incisors) Reduced dentin thickness Enlarged tooth pulp chambers Dental caries

Adapted from Table 3 of CS[10]
CS = company submission; HPP = hypophosphatasia

2.2.6 Diagnosis

The variety of clinical manifestations and the rarity of HPP contribute to delays in diagnosing HPP, which often leads to initial misdiagnosis as well as underdiagnosis. Patients with paediatric-onset HPP are often misdiagnosed, with adults experiencing an average diagnostic delay of 24.5 years.[19, 24, 27] This leads to ineffective disease management that may exacerbate clinical manifestations. HPP can be diagnosed based on medical history, physical examination, laboratory studies and radiographic findings.[19] In some cases, HPP can be diagnosed through genetic testing, although not all patients with HPP will present with a detectable pathogenic or likely pathogenic variant in the *ALPL* gene.[17, 19] Table 2.2 summarises the principles for diagnosis of HPP.

Table 2.2: Principles for diagnosis of HPP

Assessment	Observations
Medical history and clinical/physical examination	Premature loss of deciduous teeth in children and permanent teeth in adults, bone fragility, bone hypo mineralisation, muscle weakness, pain, and non-traumatic and/or recurrent fractures
Radiographic findings	Osteopenia, poorly healing and non-healing stress fractures, pseudo fractures, craniosynostosis in infants, and shortening, bowing and/or angulation of long bones
Laboratory tests	Total serum alkaline phosphatase (ALP) activity adjusted for sex and age is persistently low in all forms of hypophosphatasia (HPP). Other laboratory tests may be informative (pyridoxal 5'-phosphate (PLP), phosphoethanolamine (PEA), inorganic pyrophosphatase (PPi)).
Genetic testing	Genetic testing for a variant in the *ALPL* gene may be used to confirm HPP, although testing positive for a mutation is not required for diagnosis.

Adapted from Table 4 of CS[10]
ALP = alkaline phosphatase; CS = company submission; HPP = hypophosphatasia; PEA = phosphoethanolamine; PLP = pyridoxal 5'-phosphate; PPi = inorganic pyrophosphatase
Notes: Some observations presented here are observed across most HPP populations. All possible observations differ between age of assessment.

EAG comment: A clinical practice guideline for HPP published based on recommendations from a Japanese task force also recommended early diagnosis of HPP by foetal ultrasound.[28]

2.2.7 Current clinical management

The CS identified one clinical practice guideline for HPP has been published based on recommendations from a Japanese task force.[28] These guidelines recommend alkaline phosphatase (ALP) enzyme replacement therapy (ERT) if patients have a definite HPP diagnosis and if they are expected to have a poor prognosis, including patients with perinatal severe (lethal) and infantile forms in which the outcomes are expected to be poor. In perinatal severe (lethal) and infantile HPP, the earliest possible initiation of ERT is recommended to improve the life prognosis. ALP ERT is also recommended to improve the motor function of HPP patients.

In the United Kingdom (UK), before the NICE recommendation of AA within the scope of the Managed Access Agreement (MAA), no treatment had been approved for use in the management of HPP.[10] The treatment approach for HPP without AA focussed on the management of signs and symptoms, orthopaedic surgery and supportive care. Different management techniques – surgical, therapeutic and dental – were used depending on the type and severity of symptoms. See Section 2.3 for further information.

EAG comment: There is currently no treatment for HPP with the medical management of symptoms being the current standard of care. The Japanese clinical practice guideline for HPP[28] also recommended that, *"Forms of the disease with a relatively favorable life prognosis are also relative indications for enzyme replacement therapy if symptoms based on HPP, such as bone symptoms and muscle weakness, are present because they are expected to be improved by the therapy."*

2.2.8 Impact on patients' health-related quality of life (HRQoL)

Given the heterogeneity of clinical manifestations and disease severity, the impact of HPP on QoL will differ from patient to patient. Overall, patients with HPP report poor QoL, as disease presentation consists of varying levels of functional and mobility impairment, fatigue and pain, as well as impact on emotional status, employment, school attendance and daily living, which are aspects that are usually captured by various QoL measures.[10]

EAG comment: No comments on this Section.

2.2.8.1 Paediatric patient HRQoL

Life with perinatal- or infantile-onset HPP is generally characterised by symptoms that lead to frequent and prolonged hospitalisation in intensive care units (ICUs).[10] Hospitalisations are required to support and enable vital functions in patients, such as feeding, breathing and corrective surgeries (i.e. for craniosynostosis) to allow brain development and/or address skeletal deformities to allow for ambulation.[29] Additionally, a recent study that used patient- or caregiver-reported surveys to assess patients with juvenile-onset HPP revealed common experiences of prevalent pain (86%), muscle weakness (71%), delayed walking (59%), bowing of legs or knock knees (57%) and fractures (36%).[30] Just over half (51%) of the children required an assistive device at some point, including a wheelchair (34%) or in-shoe orthotics (27%).[30] These invasive procedures are usually associated with QoL decrements as seen in Figure 2 of the CS.[10]

2.2.8.2 Adult patients with paediatric-onset HRQoL

The HIPS and the Hypophosphatasia Outcomes Study Telephone (HOST) survey (n=84) illustrated that 86% of adult patients with paediatric-onset HPP reported difficulty with walking and 67% reported difficulty standing from a sitting position.[31] These patients commonly required wheelchairs (36%) and crutches (32%), as well as home modifications (30%) such as alterations to the kitchen, bathroom, bedroom and/or entrance ways.[31]

In the Global HPP Registry of adult patients with paediatric-onset HPP (n=68), 24% of patients needed an assistive device for disability and/or home modifications.[32] Of the 53 participants with available data, the mean self-reported disability score as assessed by the Health Assessment Questionnaire-Disability Index (HAQ-DI) was just over 0.5, which is higher (indicating more severe disability) than the general population mean of 0.25.[32] In the most recent analysis of the Global HPP Registry of adult patients with paediatric-onset HPP ([redacted]), QoL assessment using the short form-36 (SF-36) version 2 showed that at baseline, adults with paediatric-onset HPP had [redacted] scores in all eight domains (physical functioning; physical role limitations; bodily pain; general health perceptions; vitality; social functioning; emotional role limitations; and mental health) when compared with normative data from the United States (US) general population.[33]

2.2.9.3 Family and Carer HRQoL

There is currently a lack of data on caregiver burden for patients with HPP. Although patient- and caregiver-reported outcome surveys exist, the published findings focus on patient burden.[31] While no

published data report the impact on caregivers, the symptoms of HPP and necessary accommodations (including potential home modifications, frequent hospital visits, and breathing and feeding assistance in infantile-onset HPP) may be physically, emotionally and financially demanding on caregivers.[34-36]

2.3 Current service provision

Different management techniques – surgical, therapeutic and dental – depending on the type and severity of symptoms, have been used for the management of HPP signs and symptoms.[10] These have been summarised in Table 2.3.

Treatment goals for patients with HPP depend on the age of the patient and the severity of the disease presentation.[37, 38] In patients most severely affected by HPP (perinatal- and infantile-onset) and where disease is life threatening, the main goal of treatment is to keep patients alive. In patients with less severe disease, treatment goals are likely to include: improving bone mineralisation; minimising risk of seizures and respiratory complications in infants; attaining growth and developmental milestones in children; reducing the number and frequency of fractures; reducing pain; improving ambulation; improving oral health; and improving patient and caregiver QoL.[39]

In August 2017, AA was recommended by NICE as an option for treating paediatric-onset HPP, only for use in people who meet the criteria for treatment within the context of the MAA, and it is currently the only recommended treatment for HPP in the UK.[4] Treatment goals for patients on AA according to traditional classifications of HPP have been summarised in Table 2.4.

Table 2.3: Management options for signs and symptoms of HPP without AA

Medical condition or disease symptom	Management option(s)
Seizures	Pyridoxine
Bone, muscle and joint pain and joint swelling	Opioids, NSAIDs and steroids
Ligamentous laxity	Orthotics
Prevent or alleviate GI reflux	Anti-ulcerative treatment
Pneumonia	Antibiotics, inhaled corticosteroids, bronchodilators
Infections	Antibiotics
Failure to thrive	Percutaneous enteral nutrition (G-tubes, GJ-tubes), parenteral nutrition
Respiratory compromise	Mechanical ventilation (invasive and non-invasive), supplemental oxygen
Respiratory support	Steroids
Renal insufficiency due to nephrocalcinosis	Steroids
Hypercalcaemia	Dietary calcium restriction; calcitonin; hydration; and diuretics
Hypercalciuria	Dietary calcium restriction; calciuretics; fluid hydration; phosphorous dietary management; urinary retention of phosphorous; diuretics; dietary calcium restrictions
Rickets and osteomalacia	Surgical procedures (e.g., osteotomy, fracture fixation) repair

Based on Table 5 of CS[10]
AA = asfotase alfa; CS = company submission; G-tube = gastrostomy tube; GI = gastrointestinal; GJ-tube = gastrostomy jejunostomy tube; HPP = hypophosphatasia; NSAIDs = nonsteroidal anti-inflammatory drugs

Table 2.4: Treatment goals for patients with AA (determined by Alexion panel of physicians)

Perinatal/infantile (in utero to <6 months)	Juvenile (≥6 months to 18 years)	Adults (≥18 years)
Survival Improved respiratory status (ventilatory support) Skeletal improvements Metabolic control, prevention of renal failure Improved growth and physical development (e.g., weight gain) Meeting developmental milestones Treating craniosynostosis Seizure control Hospital discharge Pain reduction Oral health Improved quality of life (QoL)	Improved mobility Skeletal improvements Radiographic improvements (reduced tongues of radiolucency) Improved growth Meeting developmental milestones Nephrocalcinosis prevention Pain reduction Oral health Improved QoL	Patients with fractures: Improved fracture healing Reduced fracture frequency Reduced number/prevention of pseudo fractures and insufficiency fractures Avoidance of treatments that could cause further clinical deterioration (e.g., bisphosphonates) Patients with and without fractures[a]: Improved functional status Endurance Strength Gait/walking Reduced fatigue Reduced dislocations Improved joint issues Reduced joint pain Improved bone quality Pain reduction Oral health Improved QoL

Based on Table 6 of the CS[10]
AA = asfotase alfa; QoL = quality of life
Note: [a] Patients may have residual complications owing to past fractures.

EAG comment: The company were asked to provide a figure showing the current clinical pathway for the treatment of patients with paediatric-onset HPP in England and Wales (not limited to the context of the MAA), and another figure showing the proposed place for AA, along with supporting references.[40] The following figures were provided, without supporting references:

Figure 2.1: Current clinical pathway for the treatment of patients with paediatric-onset HPP in England and Wales

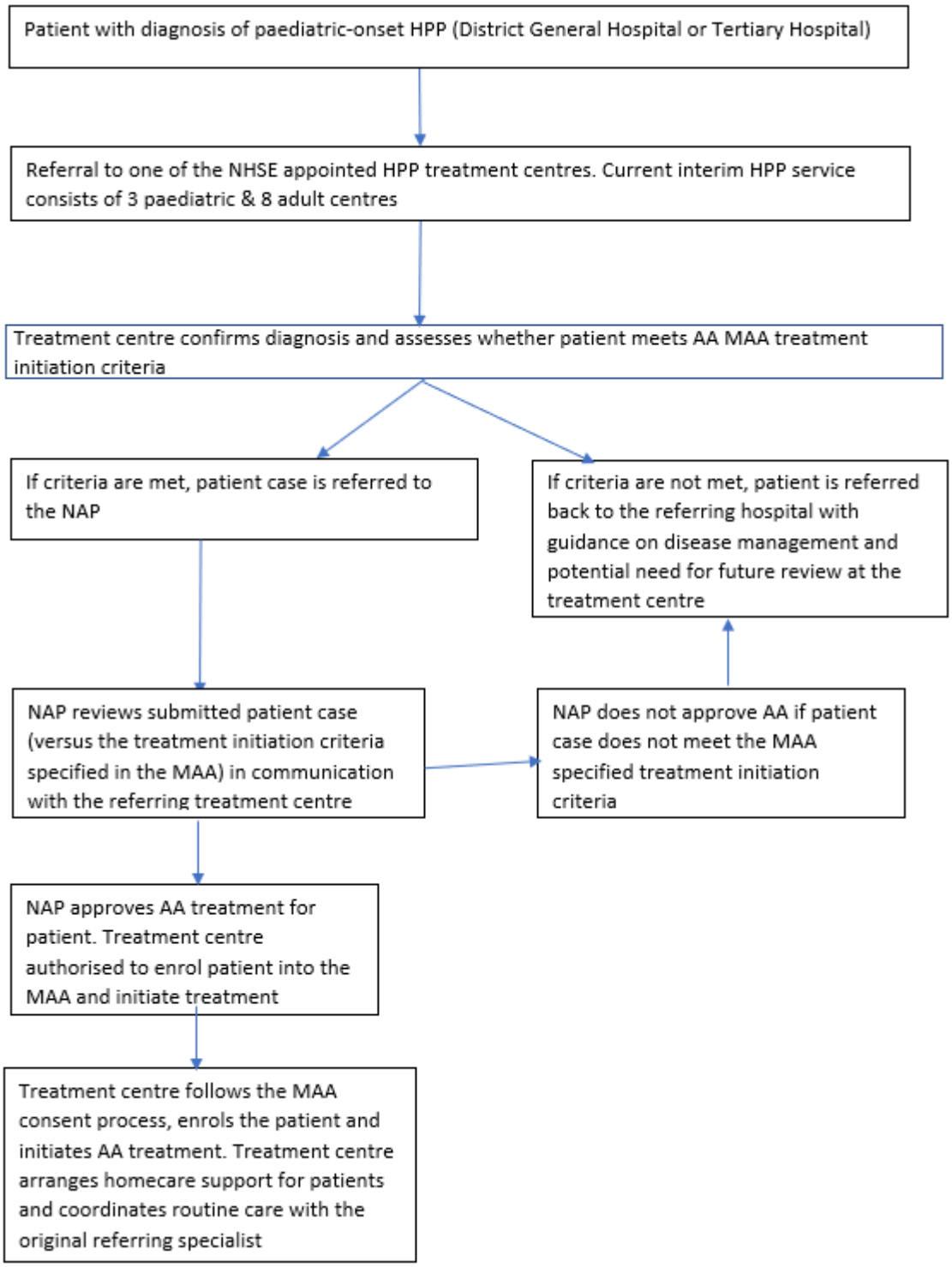


Figure 1 in the response to clarification questions[9]
AA = asfotase alfa; HPP = hypophosphatasia; MAA = Managed Access Agreement; NAP = National Authorisation Panel; NHSE = National Health Service England

Figure 2.2: Proposed clinical pathway for the treatment of patients with paediatric-onset HPP in England and Wales

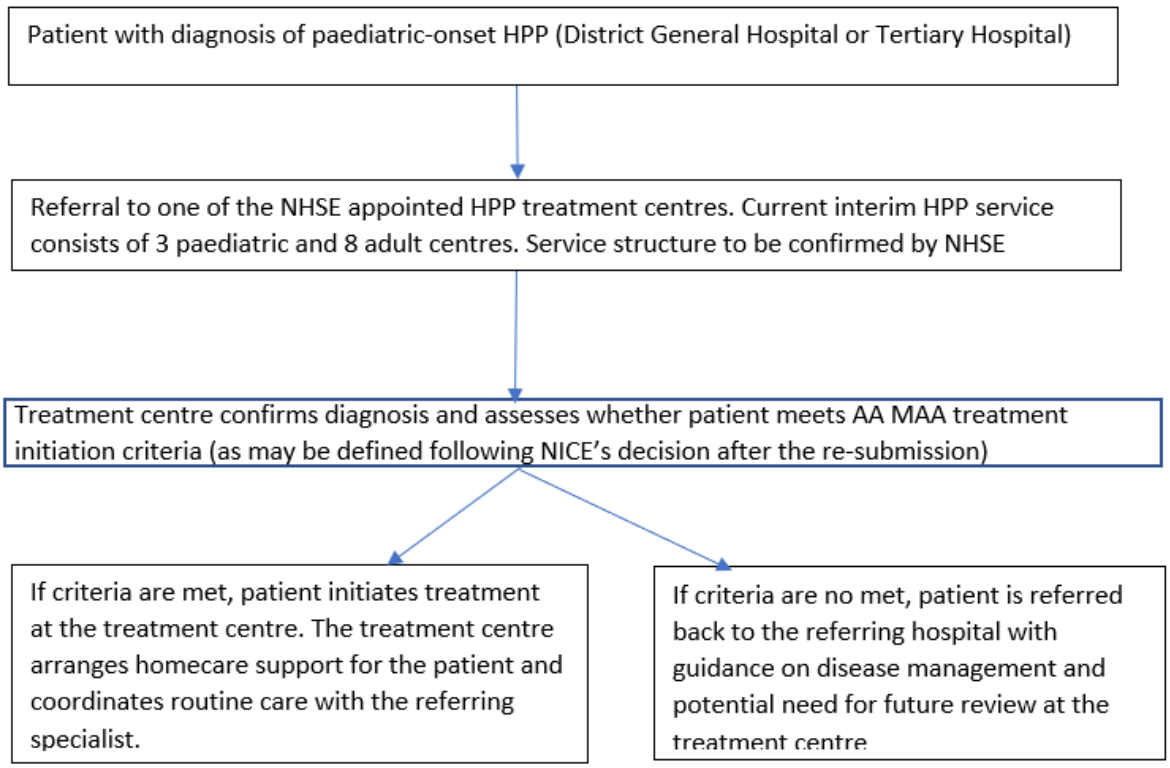


Figure 2 in the response to clarification questions[9]
AA = asfotase alfa; HPP = hypophosphatasia; MAA = Managed Access Agreement; NHSE = National Health Service England

2.4 Description of treatment under assessment

Asfotase alfa (Strensiq®, Alexion Pharma UK) is a recombinant fusion protein that includes the catalytic domain of human TNSALP and a peptide that targets the enzyme to bone.[41] It is a targeted ERT designed to restore the regulation of metabolic processes in the bones and teeth and reduce complications of dysregulated bone mineral metabolism. It is administered by subcutaneous injection.[41]

Asfotase alfa has a marketing authorisation in the UK under exceptional circumstances for long-term ERT in people with paediatric-onset HPP to treat the bone manifestations of the disease.[41] The marketing authorisation states that treatment with AA should be started by a physician experienced in the management of metabolic or bone disorders.[41] Table 2.5 summarises the product characteristics of AA.

Table 2.5: Asfotase alfa: description of technology

UK approved name and brand name	**▼Asfotase alfa (AA; Strensiq®)**
Mechanism of action	Asfotase alfa (AA) is a human recombinant tissue non-specific alkaline phosphatase (TNSALP)-Fc-deca-aspartate fusion protein enzyme replacement therapy (ERT). It is a soluble glycoprotein comprised of two identical polypeptide chains, each with a length of 726 amino acids made from the catalytic domain of human TNSALP, the human immunoglobulin G1

	Fc domain and a deca-aspartate peptide domain used for bone targeting. AA targets the underlying causes of HPP, a deficiency of TNSALP activity, by replacing the defective enzyme and reducing the accumulation of extracellular substrates, thereby preventing or reversing bone mineralisation defects. It reverses the pathophysiological mechanism of HPP by normalising values of inorganic pyrophosphate (PPi) and pyridoxal 5' - phosphate (PLP), restoring phosphate homeostasis and removing PPi, the inhibitor of bone mineralisation. Restoring normal TNSALP substrate activity leads to renewed bone development and improvements in rickets and growth.
Marketing authorisation/CE mark status	AA received marketing authorisation from the European Medicines Agency (EMA) on 28 August 2015, which has been converted to a national Great Britain (GB) license on 1 January 2021. It is the only approved treatment for HPP and is indicated for long-term ERT in patients with paediatric-onset HPP to treat the bone manifestations of the disease. A black triangle warning features in the summary of product characteristics (SmPC). AA is subject to additional monitoring, which will allow quick identification of new safety information.
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	The indication under appraisal is: for long-term ERT in patients with paediatric-onset HPP to treat the bone manifestations of the disease.
Method of administration and dosage	Two pharmaceutical formulations of AA are approved: 1. 40 mg/ml solution for injection: containing 18 mg (0.45 ml), 28 mg (0.7 ml) and 40 mg (1.0 ml) 2. 100 mg/ml solution for injection: containing 80 mg (0.8 ml) Both strengths are a clear, slightly opalescent, or opalescent, colourless to slightly yellow, aqueous solution; pH 7.4. A few small translucent or white particles may be present. The recommended dosage regimen is 2 mg/kg of body weight administered subcutaneously 3 times per week, or a dosage regimen of 1 mg/kg of body weight administered subcutaneously 6 times per week. The maximum volume of medicinal product per injection should not exceed 1 ml. If more than 1 ml is required, multiple injections may be administered at the same time.
Additional tests or investigations	No additional tests will be needed for selecting or monitoring patients over and above what is currently used.
List price and average cost of a course of treatment	1. 18 mg/0.45 ml = £12,700.80 per 12 pack 2. 28 mg/0.7 ml = £19,756.80 per 12 pack 3. 40 mg/1 ml = £28,224.00 per 12 pack 4. 80 mg/0.8 ml = £56,448.00 per 12 pack Average cost of treatment varies by patient age and weight. The model currently assumes an average cost of treatment per year (at list price) ranging from [redacted].
Patient access scheme (if applicable)	A simple discount Patient Access Scheme (PAS) has been proposed to National Health Service England (NHSE)

	(pending approval) offering AA at a price equating to a [redacted] discount on the approved list price. At the proposed PAS price, AA pack costs are as follows: 1. 18 mg/0.45 ml = £5,600.88 per 12 pack 2. 28 mg/0.7 ml = £8,712.48 per 12 pack 3. 40 mg/1 ml = £12,446.40 per 12 pack 4. 80 mg/0.8 ml = £24,892.80 per 12 pack Average cost of treatment by patient age and weight (at PAS price) as per the model ranges from [redacted].
Table 2 of CS[10] AA = asfotase alfa; CS = company submission; EMA = European Medicines Agency; ERT = enzyme replacement therapy; GB = Great Britain; HPP = hypophosphatasia; PAS = Patient Access Scheme; PLP = pyridoxal 5'-phosphate; PPi = inorganic pyrophosphate; SmPC = summary of product characteristics; TNSALP = tissue non-specific alkaline phosphatase; UK = United Kingdom	

3 CRITIQUE OF COMPANY'S INTERPRETATION OF THE DECISION PROBLEM

3.1 Introduction

The remit of this appraisal, as defined in the final agreed NICE scope is to evaluate the benefits and costs of AA within its licensed indication for long-term ERT in patients with paediatric-onset HPP to treat the bone manifestations of the disease. Asfotase alfa received marketing authorisation from the EMA on 28 August 2015, which was converted to a national GB license on 1 January 2021.

Asfotase alpha was previously assessed, in this indication, in 2015/2016,[42] and guidance was issued by NICE in 2017,[4] which approved the use of AA within the context of a MAA.[1] This appraisal is a re-assessment of the clinical effectiveness and cost effectiveness of AA, following the collection of data in the UK MAA.

The final NICE scope outlines the agreed population, intervention, comparators and outcomes for the appraisal. The NICE scope also sets out wider considerations relating to the impact of the technology beyond direct health benefits and on the delivery of the specialised service, the nature of the condition, costs to the National Health Service (NHS) and Personal Social Services (PSS) and value for money.

EAG comment: The company were asked to please provide a complete list of changes since the original appraisal in terms of scope and evidence;[40] the following tables were provided, in response:[9]

Table 3.1: Changes since the original appraisal in terms of scope

	Original NICE HST submission	NICE HST resubmission	Rationale
Population	Patients with paediatric-onset hypophosphatasia	Patients with paediatric-onset hypophosphatasia	The population aligns with the final National Institute for Health and Care Excellence (NICE) scope in the original submission and the resubmission
Intervention	Asfotase alfa (AA)	AA	The intervention aligns with the final NICE scope in the original submission and the resubmission
Comparator(s)	Best supportive care (BSC)	BSC	The comparator aligns with the final NICE scope in the original submission and the resubmission
Outcomes	Mortality Radiographic response Bone mineralisation Severity rickets Pain Respiratory function Growth Tooth loss Cognitive development and motor skills	Mortality Radiographic response Bone mineralisation Severity of rickets Pain Respiratory function Growth Tooth loss Cognitive development and motor skills Adverse effects of treatment	Bone mineralisation was added to the outcomes in the original submission and the resubmission, as although this outcome was not included in the NICE final scope document, it was included in the AA clinical trials (i.e., bone biopsy and dual energy x-ray absorptiometry (DEXA)). Craniosynostosis and intracranial pressure were

	Adverse effects of treatment Health-related quality of life (HRQoL) (for patients and carers)	HRQoL (for patients and carers)	removed from the list of outcomes in the original submission and the resubmission because these outcomes are related to the underlying disease and are unlikely to be affected by use of AA. These outcomes were not measured as an outcome in any of the AA clinical studies but were reported as a part of the safety data analysis. See response to A.3 for more details.

Based on Table 1 in the response to clarification questions[9]
AA = asfotase alfa; BSC = best supportive care; DEXA = dual energy X-ray absorptiometry; HRQoL = health-related quality of life; HST = highly specialised technologies; NICE = National Institute for Health and Care Excellence

Table 3.2: Changes since the original appraisal in terms of evidence

		Original NICE HST submission	NICE HST resubmission	Rationale
Included studies	**UK MAA**	N/A	UK MAA (n=[redacted])	
	AA clinical trials	ENB-001-08 (n=6) ENB-002-08/ENB-003-08 (n=11) ENB-010-10 (n=59) ENB-006-09/ENB-008-10 (n=13) ENB-009-10 (n=13)	ENB-001-08 (n=6) ENB-002-08/ENB-003-08 (n=11) ENB-010-10 (n=69) ENB-006-09/ENB-008-10 (n=13) ENB-009-10 (n=19)	After the National Institute for Health and Care Excellence (NICE) approved asfotase alfa (AA) in August 2017, Alexion initiated the United Kingdom (UK) Managed Access Agreement (MAA) data collection that included all UK patients with hypophosphatasia (HPP) treated with AA. This data collection is ongoing, with the latest data cut-off completed in [redacted] and these data are presented first in the resubmission.[10] All new and relevant studies have been presented within the NICE Highly Specialised Technology (HST) resubmission. The totality of the clinical data presented in the submission, from the UK MAA, the long term follow-up of the AA clinical trials (ENB-002-08/ENB-003-08, ENB-010-10, ENB-006-09/ENB-008-10 and ENB-009-10), the Global HPP Registry and the real-world EmPATHY study should be considered the main source of efficacy data for the population in the decision problem, which includes patients
	Real-world evidence studies	N/A	Global HPP Registry (n=[redacted]) EmPATHY (n=21) Dahir et al. 2022 (n=[redacted])	
	Natural history studies	ENB-011-10 (n=48) ALX-HPP-502 (n=32) ALX-HPP-502s (n=6)	ENB-011-10 (n=48) ALX-HPP-502 (n=32) ALX-HPP-502s (n=6)	

				with perinatal-, infantile- and juvenile-onset HPP.
Outcomes presented for AA clinical trials included in both submissions	**ENB-002-08/ ENB-003-08**	OS, VFS, respiratory support, growth (length/height and weight), BSID-III, RGI-C, RSS, PPi, PLP, safety	OS, VFS, respiratory support, growth (length/height and weight), BSID-III, the PDMS- 2, BOT- 2, RGI-C, RSS, safety	The final analyses for the AA clinical trials were presented in the NICE HST resubmission, for all key endpoints with long term follow-up data.
	ENB-010-10	OS, VFS, respiratory support, growth (length/height and weight), BSID-III, the PDMS- 2, BOT- 2, RGI-C, RSS, safety	OS, VFS, respiratory support, growth (length/height and weight), BSID-III, the PDMS- 2, BOT- 2, RGI-C, RSS, safety	
	ENB-006-09/ ENB-008-10	Growth (length/height and weight), 6MWT, BOT-2, PODCI, CHAQ, RGI-C, RSS, bone mineralisation, safety	Growth (length/height and weight), 6MWT, BOT-2, PODCI, CHAQ, RGI-C, RSS, safety	
	ENB-009-10	6MWT, BOT-2, LEFS, BPI-SF, PPi, PLP, bone mineralisation, handheld dynamometry, safety	Growth, 6MWT, BOT-2, LEFS, BPI-SF, PPi, PLP, safety	
Length of follow-up for AA clinical trials included in both submissions	**ENB-002-08/ ENB-003-08**	5 years	7 years	The final analyses for the AA clinical trials with longer follow-up were presented in the NICE HST resubmission.
	ENB-010-10	3.5 years	6 years	
	ENB-006-09/ ENB-008-10	5 years	7 years	
	ENB-009-10	3 years	5 years	
Pooled survival analysis	**Population**	Patients with perinatal/infantile HPP (n=37)	Patients with perinatal/infantile HPP (n=78)	An updated pooled survival analysis was included in the NICE HST resubmission with more patients and longer follow-up.
	AA clinical trials	ENB-002-08/ENB-003-08 (n=11) ENB-010-10 (n=26)	ENB-002-08/ENB-003-08 (n=11) ENB-010-10 (n=69)	
	Historical control study	ENB-011-10 (n=48)	ENB-011-10 (n=48)	
	Outcomes	OS and VFS	OS and VFS	

	Follow-up	5 years[5]	7 years[43]	
Pooled efficacy analyses for other outcomes	**Population**	Patients with paediatric-onset HPP (n= [redacted])	**Population:** Patients with perinatal/infantile HPP (n = 85)	As per the response to A 1., an updated pooled efficacy analysis in patients with perinatal/infantile-onset HPP was included in the NICE HST resubmission as assessing long-term outcomes following AA treatment was imperative when data were available for 85 patients treated in the AA clinical development program, with the most life threatening form of HPP.
	AA clinical trials	ENB-002-08/ENB-003-08 and ENB-010-10 (n= [redacted]) ENB-006-09/ENB-008-10 (n= [redacted])	ENB-002-08/ENB-003-08 (n = 11) ENB-010-10 (n = 69) ENB-006-09/ENB-008-10 (n = 5)	
	Outcomes	PPi, PLP, RGI-C, RSS, bone mineralisation, growth (length/height and weight), 6MWT, functional outcomes including BSID-III, BOT-2, PODCI and CHAQ	RGI-C, RSS, growth (length/height and weight), functional outcomes including BSID-III, BOT-2, PODCI and CHAQ	
	Follow-up	5 years	7 years[43]	
Pooled safety analyses	**Population**	All patients included in the AA clinical trials (n= [redacted])	All patients included in the AA clinical trials (n = 112)	An updated pooled safety analysis was included in the NICE HST resubmission with more patients and longer follow-up.
	AA clinical trials	ENB-002-08/ENB-003-08 (n= [redacted]) ENB-010-10 (n= [redacted]) ENB-006-09/ENB-008-10 (n= [redacted]) ENB-009-10 (n= [redacted])	ENB-002-08/ENB-003-08 (n=11) ENB-010-10 (n=69) ENB-006-09/ENB-008-10 (n=13) ENB-009-10 (n=19)	
	Follow-up	5 years	7 years[44]	

Based on Table 2 in the response to clarification questions[9]

AA = asfotase alfa; BOT-2 = Bruininks-Oseretsky Test of Motor Proficiency, 2nd Edition; BPI-SF = Brief Pain Inventory Short Form; BSID-III = Bayley Scales of Infant and Toddler Development®, 3rd Edition; HPP = hypophosphatasia; CHAQ = Child Health Assessment Questionnaire; HPP = hypophosphatasia; HST = Highly Specialised Technology; MAA = Managed Access Agreement; N/A = not applicable; NICE = National Institute for Health and Care Excellence; OS = overall survival; PDMS-2 = Peabody Developmental Motor Scales, 2nd edition; PPi = inorganic pyrophosphate; PLP = pyridoxal 5' -phosphate; RGI-C = Radiographic Global Impression of Change; RSS = Rickets Severity Score; UK = United Kingdom; 6MWT = 6-minute walk test

3.2 Adherence to the decision problem

Table 3.3 presents a summary of the decision problem (DP) as set out in the NICE scope[41] and the company's adherence to this (based on information presented in Table 1 of the CS).[10]

Table 3.3: Statement of the decision problem (as presented by the company)

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
Population	Patients with paediatric-onset hypophosphatasia (HPP)	Patients with paediatric-onset HPP	Not applicable (N/A)	The External Assessment Group (EAG) notes that, although the submission included data for both patients with perinatal/infantile-onset HPP and juvenile-onset-HPP, the only pooled analysis and the main source of long-term efficacy data were limited to patients with perinatal/infantile-onset HPP. In addition, the results of individual studies were not consistently presented, so as to allow their interpretation against age of onset categories of HPP.
Intervention	Asfotase alfa (AA)	AA	N/A	None
Comparator(s)	Best supportive care (BSC)	BSC	N/A	The EAG notes that, although the company submission (CS) specifies BSC as the comparator, the extent to which the historical control data utilised can be considered representative of current BSC is questionable. The EAG considers that potential sources of comparator data were not fully explored.

Outcomes	• Mortality • Radiographic response • Severity of rickets • Pain • Respiratory function • Craniosynostosis and intracranial pressure • Growth • Tooth loss • Cognitive development and motor skills • Adverse effects of treatment • Health-related quality of life (HRQoL) (for patients and carers)	• Mortality • Radiographic response • Bone mineralisation • Severity of rickets • Pain • Respiratory function • Growth • Tooth loss • Cognitive development and motor skills • Adverse effects of treatment • HRQoL (for patients and carers)	<u>Bone mineralisation added</u>: Outcome not included in the NICE final scope document but was included in the AA clinical trials (i.e., bone biopsy and dual energy x-ray absorptiometry (DEXA)). <u>Craniosynostosis and intracranial pressure removed</u>: Outcome included in the NICE final scope document, but not measured in the AA clinical trials. This was because these outcomes are related to the underlying disease and not with a causality association with AA.	None
Subgroups to be considered	Patients with infantile-onset HPP Patients with childhood-onset HPP	Patients with infantile-onset HPP Patients with childhood-onset HPP	N/A	The EAG notes that the results of individual studies were not consistently presented, so as to allow their interpretation against age of onset categories of HPP (clinically relevant subgroups).
Cost to the NHS and PSS, and Value for Money	• Cost effectiveness using incremental cost per quality-adjusted life year (QALY) • Patient Access Schemes (PAS) and other commercial agreements			

	• The nature and extent of the resources needed to enable the new technology to be used			
Impact of the technology beyond direct health benefits, and on the delivery of the specialised service	• Whether there are significant benefits other than health. • Whether a substantial proportion of the costs (savings) or benefits are incurred outside of the National Health Service (NHS) and Personal Social Services (PSS). • The potential for long-term benefits to the NHS of research and innovation. • The impact of the technology on the overall delivery of the specialised service. • Staffing and infrastructure requirements, including training and planning for expertise.			

Based on Table 1 in CS[10] and NICE final scope[41]

AA = asfotase alfa; BSC = best supportive care; CS = company submission; DEXA = dual energy X-ray absorptiometry; EAG = External Assessment Group; HPP = hypophosphatasia; HRQoL = health-related quality of life; N/A = not applicable; NHS = National Health Service; NICE = National Institute for Health and Care Excellence; PAS = Patient Access Scheme; PSS = Personal Social Services; QALY = quality-adjusted life year

3.3 EAG critique of the company's adherence to the decision problem as set out in the NICE scope

3.3.1 Population

The population included in the clinical sections of the submission relates to people with paediatric-onset HPP.

The current clinical description of HPP is based upon categorising disease by age of onset:

a) Perinatal-onset (onset *in utero* or at birth)
b) Infantile-onset (onset between 0-6 months of age)
c) Juvenile or Childhood-onset (onset between 6 months to 18 years of age)
d) Adult-onset (onset ≥18 years of age)
e) Odonto-hypophosphatasia (only dental clinical symptoms)

Although it is noted that this method of categorisation does not account for the progression of the disease as patients age, overlap in symptoms across age groups, or the possibility of delayed diagnosis,[10, 14, 19, 24, 27] it remains the method used in both the NICE scope[41] and in the Alexion clinical trials programme for AA.[10]

For this assessment there are two relevant populations:

a) Perinatal-onset and Infantile-onset (onset before 6 months of age)
b) Juvenile or Childhood-onset (onset between 6 months to 18 years of age)

The company have stated that the population, in the DP addressed by their submission, is patients with paediatric-onset HPP (see Table 1, Section B.1.1 of the CS).[10]

EAG comment: The EAG notes that the pooled analysis of efficacy data for AA, provided in the CS (Section B.2.8.1),[10] included data from patients with perinatal- and infantile-onset HPP only. The company were asked to a) explain the discrepancy between the population in the DP and the main source of efficacy data, b) state whether the population in the DP be qualified to only include perinatal or infantile onset HPP and c) if the population is as in the DP, please conduct a comparative analysis that includes patients with age of onset that reflects the whole population including the juvenile onset.[40] The company provided the following responses:

A) *'The totality of the clinical trial data presented in the submission, from the UK MAA, the long term follow up of the AA clinical trials (ENB-002-08/ENB-003-08, ENB-010-10, ENB-006-09/ENB-008-10 and ENB-009-10), the Global HPP Registry and the real-world EmPATHY study should be considered the main source of efficacy data for the population in the decision problem, which includes patients with perinatal-, infantile- and juvenile-onset HPP. In addition to these data, the pooled analysis in the sub population of perinatal/infantile-onset patients from three AA clinical trials (ENB-002-08/ENB-003-08, ENB-010-10, ENB-006-09/ENB-008-10), has also been presented.*

The pooled analysis was conducted to assess long-term survival in patients with perinatal/infantile-onset HPP, which is the only subgroup in which the disease can be life-threatening, with reported survival of 25% at 5 years. Therefore, assessing long-term survival and other outcomes following AA treatment was imperative when data were available for 85 patients treated in the AA clinical development program, with the most life threatening form of HPP.

The pooled analysis was conducted in 2019, prior to the decision problem being defined for this submission, and is therefore provided as a supplemental analysis from the AA clinical trials to inform long term survival in a sub population and should not be considered as the main source of efficacy data for AA in this appraisal process.'[9]

B) *'No. As per the responses to A 1.a), the totality of the clinical trial data presented in the submission, including the UK MAA, long term follow up of the AA clinical trials, the Global HPP Registry and the real-world EmPATHY study should be considered the main source of efficacy data for the population in the decision problem, which includes patients with perinatal, infantile and juvenile-onset HPP. The pooled analysis was conducted in 2019, prior to the decision problem being defined for this submission, and is therefore provided as a supplemental analysis and should not be considered as the main source of efficacy data for AA in this appraisal process.*

There are 27 patients with juvenile-onset HPP and severe disabilities, which impact quality of life in two of the AA clinical studies (ENB-006-09/ENB-008-10 and ENB-009-10). In addition, a high number of juvenile-onset HPP patients were included in the UK MAA and in the post-marketing phase IV studies (EmPATHY, Global HPP Registry), and these outcomes are presented in this submission dossier.'[9]

C) '*As per the responses to A 1.a) and A 1.b), the evidence in the submission does cover the population in the decision problem. The current submission includes AA treated patients with perinatal/infantile and juvenile onset HPP from the following sources: the UK MAA, AA clinical trials, the Global HPP Registry and the real-world EmPATHY study. All of these studies' inclusion criteria and ESAP were based on patients age at enrolment, therefore the data were not analysed based on age of symptoms onset. Currently, no further pooled analyses are available and it would not be feasible to conduct a pooled analysis across all populations due to the limited availability of historical control data across all populations and all endpoints, and such an analysis would require re-designing the ESAP for all studies and would require several months to complete.'*

The EAG does not consider that these responses adequately address the issues raised because data from the UK MAA, which is the source for the majority of the new data about AA-treated patients, included in this resubmission, have not been used to inform pooled analyses, and were presented separately from the results of clinical trials in a way which does not support ready comparison with the trial data or assessment of the UK MAA data against the population defined in the DP (UK MAA data were not reported by age of onset category). Further, the age of onset subgroups of interest has been clear since the definition of the scope for the original submission, inclusion criteria based on age at enrolment do not *per se* rule out the possibility of analyses based on age at symptom onset and the limited availability of historical control data could have been addressed by making appropriate use of the Global HPP Registry data.

The EAG further notes that, for some of the sources of efficacy data presented in the CS (Sections B.2.6.2 to B.2.6.4),[10] the age of onset categories of study participants were not clear. The company were asked to provide the numbers of patients in each age of onset category, as well as baseline age data, for all data sources included in their submission.[40] The company provided the following tables, in their response to clarification questions:[9]

Table 3.4: Age at onset and age at enrolment data for the UK MAA population

	Study Population (N=[redacted])	**Paediatric Population <18 years at baseline (N=[redacted])**	**Adult Population ≥18 years at baseline (N=[redacted])**
Population	Patients with paediatric-onset HPP (regardless of current age)		
Age at enrolment (years)			
Mean (SD)	[redacted]	[redacted]	[redacted]
Median (min, max)	[redacted]	[redacted]	[redacted]
Age group at enrolment, n (%)			
<1 year	[redacted]	[redacted]	[redacted]
1 to <5 years	[redacted]	[redacted]	[redacted]
5 to <18 years	[redacted]	[redacted]	[redacted]
≥18 years	[redacted]	[redacted]	[redacted]
HPP onset category, n (%)			
Perinatal/infantile onset HPP (<6 months)	[redacted]	[redacted]	[redacted]
Juvenile onset (≥6 months to <18 years)	[redacted]	[redacted]	[redacted]
Age at enrolment by HPP onset category			
Perinatal/infantile-onset			
N	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]
Median (min, max)	[redacted]	[redacted]	[redacted]
Juvenile onset			
n	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]
Median (min, max)	[redacted]	[redacted]	[redacted]

Based on Table 2 in the response to clarification questions[9]
HPP = hypophosphatasia; MAA = Managed Access Agreement; max = maximum; min = minimum; N = number of participants; n = number of participants in a category; N/A = not applicable; SD = standard deviation; UK = United Kingdom

Table 3.5: Age at onset and age at enrolment data for patients in the clinical effectiveness studies

	ENB-002-08/ENB-003-08 (n=13)	**ENB-010-10 (n=69)**	**ENB-006-09/ENB-008-10 (n=13)**	**ENB-009-10 (n=19)**
Population	Patients ≤36 months of age with infantile-onset hypophosphatasia (HPP) (onset of symptoms prior to 6 months of age)	Patients with perinatal-/infantile-onset HPP (onset of HPP signs/symptoms prior to 6 months of age)	Patients aged ≥5 and ≤12 years of age with HPP	Adolescent and adult patients aged 13 to 65 years with HPP
Age at enrolment				
Mean (SD)	[redacted]	[redacted]	8.8 years (2.2)	[redacted]
Median (min, max)	[redacted]	[redacted]	8.6 years (6.0, 12.0)	53 years (13.0, 66.0)
Age at first signs of HPP/symptom onset				
Mean (SD)	Not available	[redacted]	10.5 ± 7.0	[redacted]
Median (min, max)	Not available	[redacted]	12.0 (1, 22)	2.0 years (0.0, 36.0)
HPP onset category, n (%)				
Perinatal/infantile onset HPP (<6 months)	13 (100.0)	69 (100.0)	5 (38.0)	[redacted]
Juvenile onset (≥6 months to <18 years)	0	0	8 (62.0)	[redacted]
Adult onset (≥18 years)	0	0	0	[redacted]
Age at enrolment by HPP onset category				
Mean (SD)	Not applicable (N/A)	N/A	**Infantile-Onset:** 3.0 months (2.0) **Juvenile onset:** 15.3 months (4.03)	Not available

	ENB-002-08/ENB-003-08 (n=13)	ENB-010-10 (n=69)	ENB-006-09/ENB-008-10 (n=13)	ENB-009-10 (n=19)
Median (min, max)	N/A	N/A	**Infantile-Onset:** 3.0 months (1.0, 5.0) **Juvenile onset:** 13.5 months (12.0 22.0)	Not available
Based on Table 3 in the response to clarification questions[9] HPP = hypophosphatasia; N/A = not applicable; max = maximum; min = minimum; SD = standard deviation				

Table 3.6: Age at onset and age at enrolment data for the ALX-HPP-501 (Global HPP Registry) population

	Overall population			< 18 years old			≥18 years old		
	Total (n=[redacted])	Never treated (n=[redacted])	Ever treated (n=[redacted])	Total (n=[redacted])	Never treated (n=[redacted])	Ever treated (n=[redacted])	Total (n=[redacted])	Never treated (n=[redacted])	Ever treated (n=[redacted])
Population	Patients of all ages with a confirmed diagnosis of HPP								
Age at enrolment (years)									
Mean (SD)	[redacted]								
Median (min, max)	[redacted]								
HPP onset, n (%)									
N	[redacted]								
Perinatal/infantile onset HPP (<6 months)	[redacted]								
Juvenile onset (≥6 months to <18	[redacted]								

	Overall population			< 18 years old			≥18 years old		
	Total (n=[redacted])	**Never treated (n=[redacted])**	**Ever treated (n=[redacted])**	**Total (n=[redacted])**	**Never treated (n=[redacted])**	**Ever treated (n=[redacted])**	**Total (n=[redacted])**	**Never treated (n=[redacted])**	**Ever treated (n=[redacted])**
years)									
Adult onset (≥18 years)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Age at enrolment by HPP onset category									
Perinatal/ infantile onset									
N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median (min, max)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Juvenile onset									
n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median (min, max)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adult onset									
n	[redacted]	[redacted]	[redacted]	N/A	N/A	N/A	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	N/A	N/A	N/A	[redacted]	[redacted]	[redacted]
Median (min,	[redacted]	[redacted]	[redacted]	N/A	N/A	N/A	[redacted]	[redacted]	[redacted]

	Overall population			< 18 years old			≥18 years old		
	Total (n=[redacted])	**Never treated (n=[redacted])**	**Ever treated (n=[redacted])**	**Total (n=[redacted])**	**Never treated (n=[redacted])**	**Ever treated (n=[redacted])**	**Total (n=[redacted])**	**Never treated (n=[redacted])**	**Ever treated (n=[redacted])**
max)									

Based on Table 4 in the response to clarification questions[9]
HPP = hypophosphatasia; max = maximum; min = minimum; N/A = not applicable; SD = standard deviation

Table 3.7: Age at onset and age at enrolment data for patients in the natural history studies

	ENB-011-10 (n=48)	ALX-HPP-502 (n=[redacted])	ALX-HPP-502s (n=6)
Age at onset of HPP (months)			
Mean (SD)	5.2 (9.3)	[redacted]	[redacted]
Median (min, max)	2.0 (0, 179)	[redacted]	[redacted]
Age at HPP diagnosis (months)			
Mean (SD)	5.2 (9.3)	[redacted]	[redacted]
Median (min, max)	2.0 (0, 40.9)	[redacted]	[redacted]
HPP onset category, n (%)		[redacted]	[redacted]
Perinatal/infantile onset HPP (<6 months)	48 (100.0)	[redacted]	[redacted]
Juvenile onset (≥6 months to <18 years)	0	[redacted]	[redacted]

Based on Table 5 in the response to clarification questions[9]
HPP = hypophosphatasia; max = maximum; min = minimum; SD = standard deviation

The company's response to clarification questions stated that *'No data are available relating to the number of patients in the perinatal, infantile and juvenile onset categories in for the real-world EmPATHY study and the longitudinal telephone-based survey.'*[9]

3.3.2 Intervention

The intervention (asfotase alpha) is in line with the scope.

Asfotase alpha received marketing authorisation from the EMA on 28 August 2015, which was converted to a national GB license on 1 January 2021.[45] It is being appraised under its license indication *'for long-term ERT in patients with paediatric-onset HPP to treat the bone manifestations of the disease.'*[10, 45]

Two formulations of AA have been approved:[4, 10]

40 mg/ml solution for injection: containing 18 mg (0.45 ml), 28 mg (0.7 ml) and 40 mg (1.0 ml)
100 mg/ml solution for injection: containing 80 mg (0.8 ml)

The recommended dosage regimen is 2 mg/kg of body weight administered subcutaneously 3 times per week, or a dosage regimen of 1 mg/kg of body weight administered subcutaneously 6 times per week.[4, 10] The maximum volume of medicinal product per injection should not exceed 1 ml. If more than 1 ml is required, multiple injections may be administered at the same time.[4, 10]

EAG comment: The EAG notes that the dose of AA, evaluated in the included trials, varied and was not always consistent with the recommended dose:

ENB-002-08/ENB-003-08 - The starting dose was reported as 1 mg/kg, 3 times per week, increasing to a maximum of 3 mg/kg, 3 times per week.[46]

ENB-006-09/ENB-008-10 – For the first 24 weeks, six participants received the recommended dose of 2 mg/kg, 3 times per week, and seven participants received 3 mg/kg, 3 times per week.[47] Information provided by the company, in their Factual Accuracy Check, stated that: *'Following amendment 4 of Protocol ENB-008-10 (01 February 2011), all patients in the extension study received 6 mg/kg/week (the recommended dose), which was administered as 2 mg/kg, 3 times weekly, or as 1 mg/kg, 6 times weekly, at the discretion of the Investigator.'*

ENB-009-10 - Patients in this study were initially randomised to receive AA 0.3 mg/kg/day (n=7), AA 0.5 mg/kg/day (n=6) or no AA (n=6) for 24 weeks. During the 72 week extension phase, all participants (including previously un-treated controls) received 0.5 mg/kg/day for approximately 24 to 48 weeks and the dose was then increased to 1 mg/kg, 6 times per week (the recommended dose).[48]

ENB-010-10 - All participants received the recommended dose, either 1 mg/kg, 6 times per week, or 2 mg/kg, 3 times per week, at the investigators' discretion.[6]

Global HPP Registry (ALX-HPP-501) 17/182 (9.3%) paediatric (age <18 years at baseline) participants and 28/144 (19.4%) adult (age ≥18 years at baseline), were reported to have received a dose of <6 mg/kg per week (lower than the recommended dose, and 10/182 (5.5%) paediatric (age <18 years at baseline) participants and 9/144 (6.3%) adult (age ≥18 years at baseline), were reported to have received a dose of >6 mg/kg per week (higher than the recommended dose).[49]

UK MAA 3/21 (14.3%) paediatric (age <18 years at baseline) participants and 2/20 (10.0%) adult (age ≥18 years at baseline), were reported to have received a dose of <6 mg/kg per week (lower than the recommended dose), and 6/20 (30%) adults (age ≥18 years at baseline), were reported to have received a dose of >6 mg/kg per week (higher than the recommended dose).[7]

The EAG further notes that Section B.2 of the CS[10] did not report the clinical efficacy and safety results in relation to the actual dose of AA received by study participants.

3.3.3 Comparators

The comparator is described in the CS as BSC. Data for the comparator were taken from two natural history studies including 48 patients with infantile-onset (before 6 months of age) HPP (study ENB-011-10) and 32 patients with juvenile-onset (onset between 6 months and 18 years) HPP (study ALX-HPP-502). In addition, a sub-study of study ALX-HPP-502 was presented in the CS including six patients from one of the centres participating in that study. As noted in the CS (Section B.2.6.4.4),[10] these were the same studies used in the original submission.

The nature of BSC was outlined in Section B (see Section 5.2.4) and more precisely specified in terms of health state costs based on clinical expert opinion elicited for the original 2017 NICE appraisal with some 'small adjustments' (see Section 5.3.3.8).

EAG comment: There is a substantial problem with the data presented in the CS for the comparator, as most of the data from control patients are from patients diagnosed and treated before 2000. In contrast, all patients in intervention studies were diagnosed and treated after 2005. Even without AA treatment, treatment outcome for intervention patients would be expected to be considerably better than treatment for control patients. Therefore, data from control studies are not suitable for a reliable comparison with data from AA studies. This is a major weakness of the CS which limits the interpretation of the available evidence.

The EAG question why data from the Global HPP Registry (ALX-HPP-501) were not used to provide control data for patients not treated with AA. The company were asked to explain why data from the Global HPP Registry (ALX-HPP-501) were not used to provide control data for patients not treated with AA[40] and the following response was provided:

'The Global HPP registry (ALX-HPP-501) is an observational, non-interventional study that includes HPP patients irrespective of whether they are on AA treatment or not. Enrolment in the Global HPP Registry is voluntary and assessments are not mandatory. During the study, clinic visits are scheduled by the clinicians in accordance with their usual clinical practice. Frequency of visits may vary depending upon several factors, including the age of the patient and severity of disease. Patients are monitored per the clinicians standard of care, which does not include the RGI-C (a research tool) or the 6MWT. In cases where these assessments have been conducted, they were not conducted uniformly over time (i.e., every 6 months) or in a standard fashion between sites (no training). In addition, as presented in Table 66 of Appendix M, the non-AA treated patients in the Global HPP Registry are usually patients with milder symptoms that are not comparable with the patients that are treated with AA. The AA clinical studies and the UK MAA include patients that are severely affected by the disease, therefore, it is highly unlikely that such patients in the Global HPP Registry would not be treated with AA. Moreover, the UK MAA mandated a schedule of certain clinical assessments that are not all captured within the Global HPP Registry (e.g., Bleck score, BAMF scale) and the patients that are enrolled in the Global HPP Registry are not mandated to any schedule of clinical assessments.

All the above would make the comparison of AA treated patients versus non-treated Global HPP Registry patients considerably biased. As such, data from the Global HPP Registry are limited and are not comparable with the AA clinical trials and have not been used as a source of data for patients not treated with AA.'

The EAG acknowledges the limitations of the Global HPP Registry data, but notes that the natural history studies also have substantial limitations as sources of data for comparable non-AA treated patients. The EAG therefore considers that it would be preferrable to present analyses based on both potential sources of control data; use of all available data, with appropriate consideration of limitations/risk of bias, could inform considerations of the uncertainty in estimates of relative efficacy. The discrepancy between current and historical clinical practice is also highlighted by the lack of evidence on resource use from the natural history data with instead a reliance on expert opinion.

3.3.4 Outcomes

The range of outcomes reported within the CS differs for AA and the comparator.[10] In addition, the reporting of efficacy outcomes, for AA clinical trials, and for the UK MAA and AA-treated patients from the Global HPP Registry (ALX-HPP-501), was inconsistent, with some outcomes being reported only in Section B of the CS[10] and some reported only in an Appendix,[50] in a manner that was not consistent across studies.

EAG comment: The company were asked to provide results tables, comparing results across all AA studies including the UK MAA, for each outcome measure listed in Tables 7 and 8 of the CS, with results grouped by age of onset category (perinatal-, infantile-, and juvenile-onset HPP).[40] The company did not provide the requested tables, or any further results stratified by age of onset of HPP. The following response was provided:[9]

'The UK MAA was designed differently to the studies that formed the AA clinical development program. The AA clinical studies stratified patients differently by age and enrolment: < 3 years, < 5 years, 5-12

years ≥13 years. The UK MAA focuses on the age of the patient and their symptoms at presentation in one of the designated treatment centres. Within the UK MAA, there are 4 distinct groups of patients based on current age: < 12 months, between 1-4 years, between 5-18 years and >18 years. All of these patients have paediatric-onset HPP. In addition, some of the endpoints included in the UK MAA (e.g. BAMF scale, PedsQL, Bleck score) were not included in the AA clinical trials.

Therefore, efficacy data split by age disease onset are not available for all studies and the differences discussed above would make a comparison between the studies non-informative so summary tables have not been provided.'

The EAG does not agree that the use of consistent patient categorisation would be *'non-informative'* and notes that the information about numbers of patients in each age of onset category, provided in response to clarification questions,[9] (see Tables 3.4 to 3.7, above) would appear to indicate that sufficient patient information was available to permit presentation of results by age of onset category.

For the natural history study (ENB-011-10), used to provide data for control patients with infantile-onset (before 6 months of age) HPP, the CS reported overall survival (OS) and invasive ventilator-free survival (VFS)[50] In addition, tertiary endpoints included survival time to first respiratory support, defined as the time during which the patient was alive and not on any respiratory support, invasive or non-invasive, and the proportion of patients requiring respiratory assistance.[50] These outcomes are not fully representative of those specified in the NICE scope and listed, in Table 10 of the CS,[10] as measured in ENB-011010; craniosynostosis and intracranial pressure, growth, tooth loss and cognitive development and motor skills were included in the NICE scope and listed as measured outcomes, but no results were reported for these outcomes.[50]

For the natural history study (ALX-HPP-502), used to provide data for control patients with juvenile-onset (between 6 months and 18 years) HPP, the following outcomes were reported: radiographic change in skeletal manifestations of HPP, growth, OS. Again, outcomes are not fully representative of those specified in the NICE scope and listed, in Table 10 of the CS,[10] as measured in ALX-HPP-502; respiratory function, craniosynostosis and intracranial pressure, growth, tooth loss and cognitive development and motor skills, and pain were included in the NICE scope and listed as measured outcomes, but no results were reported for these outcomes.[50]

EAG comment: The company were asked to provide results tables, comparing results across all non-interventional natural history studies, including ALX-HPP-501, for each outcome measure; results should be grouped by age of onset category (perinatal-, infantile-, and juvenile-onset HPP).[40] The company did not provide the requested tables, or any further results stratified by age of onset of HPP. The following response was provided:[9]

'The Global HPP Registry was designed differently to the three natural history studies. The three natural history studies were designed to specifically assess the outcomes of patients with perinatal/infantile onset (ENB-011-10) and juvenile-onset HPP (ALX-HPP-502 and ALX-HPP-502s), whereas the Global HPP Registry focuses on the age of the patient and their symptoms at presentation. Within the Global HPP Registry, there are 2 distinct groups of patients based on current age < 18 years and ≥ 18 years.

In addition, some of the endpoints included in the Global HPP Registry (e.g., 6MWT, BPI-SF, PedsQL, SF-36v2) were not included in the natural history studies.

Therefore, efficacy data split by age disease onset are not available for all studies and the differences discussed above would make a comparison between the studies non-informative so summary tables have not been provided.'

The EAG does not agree that the use of consistent patient categorisation would be *'non-informative'* and notes that the information about numbers of patients in each age of onset category, provided in response to clarification questions,[9] (see tables 3.4 to 3.7, above) would appear to indicate that sufficient patient information was available to permit presentation of results by age of onset category.

Craniosynostosis and intracranial pressure, listed as outcomes in the NICE scope, have been excluded from the company's definition of the DP, because these outcomes were "not measured in the AA clinical trials" and because "these outcomes are related to the underlying disease and not with a causality association with AA" (see Table 1, Section B.1.1 of the CS).[10] However, Table 8 in the CS, indicates these outcomes were reported in four of the five included clinical effectiveness studies (ENB-002-08/ENB-003-08, ENB-010-10, ENB-006-09/ENB-008-10 and ENB-009-10).

EAG comment: The company were asked to explain this discrepancy[40] and the following response was provided:[9]

'Craniosynostosis a manifestation of HPP, is documented in published literature and occurred in 61% of patients between birth and 5 years of age in a natural history study of untreated infantile-onset HPP patients.[29] The exact mechanism of craniosynostosis in relation to the disease's pathophysiology (ALP function) is not well understood. Therefore, it was never studied as an outcome of AA treatment, but it has been reported as a safety event in the AA studies. In the AA clinical studies, adverse events of craniosynostosis (associated with increased intracranial pressure), including worsening of pre-existing craniosynostosis and occurrence of Arnold-Chiari malformation, have been reported in HPP patients < 5 years of age. There are insufficient data to establish a causal relationship between exposure to AA and progression of craniosynostosis. Periodic monitoring and prompt intervention for increased intracranial pressure is recommended in HPP patients below 5 years of age.'

Although outcomes craniosynostosis and intracranial pressure are sometimes reported as adverse events (AEs) as noted by the company, these outcomes are related to the underlying disease. The EAG considers that all disease-related outcomes are of potential interest and those specified in the NICE scope should be reported, where available. The company were asked to provide data for the outcomes craniosynostosis and intracranial pressure from all studies where these outcomes were measured.[40] The following response was provided:[9]

'Craniosynostosis and intracranial pressure were not measured as an outcome in any of the AA clinical studies but were only reported as a part of the safety data analysis.'

3.3.5 Cost to the NHS and PSS, and value for money

The CS includes cost effectiveness analyses (CEAs) of which the results are presented in the form of incremental costs per QALYs over a lifetime time horizon, with the impact of treatment on the HRQoL of patients and caregivers included in the analysis. Costs are calculated according to the NHS and PSS perspective. Costs and QALYs discounted at 3.5%. In general, the NICE scope and reference case were followed when assessing the costs of AA to the NHS and the value for money it provides.

4 IMPACT OF THE NEW TECHNOLOGY – CLINICAL EFFECTIVENESS

4.1 Critique of the methods of review(s)

A systematic literature search was conducted to identify relevant clinical evidence. Full details of the search strategy, study selection process and results were reported in Appendix D.[50]

4.1.1 Searches

The following Section contains a summary and critique of literature searches related to clinical effectiveness presented in the CS.[10, 50] The Canadian Agency for Drugs and Technologies in Health (CADTH) evidence-based checklist for the Peer Review of Electronic Search Strategies (PRESS), was used to inform this critique.[51, 52] The CS was checked against the Single Technology Appraisal (STA) and Highly Specialised Technologies (HST) evaluation specification for company/sponsor submission of evidence.[53]

Appendix D of the CS provided details of the literature searches conducted for the SLR of clinical efficacy and safety.[50] The searches were conducted in July 2021, then updated in February 2022. A summary of the resources searched is provided in Table 4.1.

Table 4.1: Resources searched for the clinical effectiveness systematic review (as reported in the company submission).

Resource	Host/Source	Date Ranges	Dates searched
Electronic databases			
MEDLINE In-Process	PubMed	Not applicable Not applicable	07/07/21 07/02/22
Embase and MEDLINE	embase.com	Not reported Not reported	07/07/21 07/02/22
Health Technology Assessment (HTA) Database	Centre for Reviews and Dissemination (CRD) interface	Not reported Not reported	07/07/21 07/02/22
National Health Service Economic Evaluation Database (NHS EED)	CRD interface	Not reported Not reported	07/07/21 07/02/22
Cochrane Central Register of Controlled Trials (CENTRAL)	Cochrane Library	Not reported Not reported	07/07/21 07/02/22
Cochrane Database of Systematic Reviews (CDSR)	Cochrane Library	Not reported Not reported	07/07/21 07/02/22
Conference proceedings			
Annual Meeting of the American Society for Bone and Mineral Research	Not reported	2019-2022 2019-2022	July 2021 February 2022
Annual Meeting of the Endocrine Society	Not reported	2019-2022 2019-2022	July 2021 February 2022
European Society for Paediatric Endocrinology	Not reported	2019-2022 2019-2022	July 2021 February 2022
International Conference on Children's Bone Health	Not reported	2019-2022 2019-2022	July 2021 February 2022

Resource	Host/Source	Date Ranges	Dates searched
Bibliographies of key systematic review and meta-analysis articles were also screened to ensure that the initial searches captured all relevant clinical studies.			

EAG comment:

- The CS provided full details of the literature searches for the EAG to appraise.[10, 50]
- A good range of databases and relevant conference proceedings were searched.
- Full details of the database search strategies, including the database name, host platform, and date searched, were provided. The database date ranges were not reported.
- Details of the conference proceedings searched were provided, including the date range. The search terms used, URL links, specific date of searches, and results, were not reported.
- Despite reporting that the systematic review was conducted to identify existing and upcoming studies about treatments for HPP, the company did not search any clinical trials registries, such as ClinicalTrials.com or the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) to identify completed and ongoing clinical trials.
- The database search strategies were well structured, transparent and reproducible. They included truncation, proximity operators, synonyms, and subject headings (MeSH and EMTREE in embase.com, and MeSH in the Cochrane Library and Centre for Reviews and Dissemination (CRD) databases). There were no language or date limits.
- MEDLINE was searched using embase.com on the understanding that Embase contains all MEDLINE content. This approach is not recommended as MEDLINE records are indexed differently in Embase; MeSH terms are replaced with EMTREE subject headings.[54] To fully utilise MeSH indexing it is preferable to search MEDLINE separately.
- It would have been preferable for the database search strategies to be presented exactly as run, rather than copied into a tabular format, as Item 8 of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)-S reporting checklist recommends.[55] The Cochrane Handbook also recommends that *"...bibliographic database search strategies should be copied and pasted into an appendix exactly as run and in full, together with the search set numbers and the total number of records retrieved by each search strategy. The search strategies should not be re-typed, because this can introduce errors"*.[54]
- Study design search filters for randomised controlled trials (RCTs), observational and real-world evidence studies were included in the search strategies. The search filters used were not cited, as current practice recommends.[55]
- The facet of study design filters used in embase.com was run as a one-line search, making it very difficult to read, decipher what the search was designed to identify, and to spot any errors. A more transparent, easier to read approach would have been to structure the search strategy using multiple search lines.
- The search strategies were designed to combine the population (HPP) with study design search filters (RCT, observational and real world evidence). As the population of interest (HPP) has a relatively small literature, it might have been beneficial to conduct the searches without the facet of study design search filters. This sensitive approach would have ensured that relevant studies were not missed.
- There was a spelling mistake in the population facet: (phosphatase NEAR/3 (**defecien** * OR disorder*)):ab,ti,kw. This error was repeated in the Cochrane and PubMed searches, and the update searches.

- The CS reported that MEDLINE In-Process was searched using PubMed. This is inaccurate, as the search limit used in PubMed identifies recently added records, not In-Process records: (publisher[sb] NOT pubstatusnihms NOT pubstatuspmcsd NOT pmcbook) OR (pubstatusaheadofprint). The correct subset to use is 'inprocess[sb]'. MEDLINE In-process records were excluded from the company's PubMed search.
- The CS reported searching the National Health Service Economic Evaluation Database (NHS EED) and HTA databases via the CRD interface, but the search strategy suggested that the Database of Abstracts of Reviews of Effects (DARE) was also searched, and the results from all three database searches were retrieved.
- There was no reason to search the CRD databases for the update (February 2022), as NHS EED and DARE have not been updated since March 2015 and the HTA database has not been updated since October 2018. A better approach would have been to search the International HTA Database which has superseded the CRD HTA database.
- The Cochrane search strategy did not report the database issue numbers or differentiate the results for Cochrane Central Register of Controlled Trials (CENTRAL) from CDSR.
- The final line from the original July 2021 Cochrane search strategy was missing. This was likely to be a reporting error rather than a searching error.
- Separate searches for safety outcomes were not conducted. It is unlikely that efficacy searches that include study design filters for RCTs and observational studies will be sensitive enough to identify safety data. Ideally, searches for AEs should be carried out alongside the efficacy searches.[56]

4.1.2 Inclusion criteria

The eligibility criteria used in the search strategy for RCTs and non-RCTs are presented in Table 4.2.

Table 4.2: Eligibility criteria

	Inclusion criteria	Exclusion criteria
Population	All patients with perinatal-, infantile-, juvenile- and adult-onset hypophosphatasia (HPP).	Healthy volunteers
Interventions	All pharmacological therapies, such as asfotase alfa (AA) (Strensiq®), bone marrow transplantation, stem cell transplantation, diuretics, glucocorticoids.	None
Comparators	Placebo. Best supportive care (BSC) (author-defined). Any other pharmacological intervention. No comparator limit for single arm trials.	None
Outcomes	Tissue non-specific alkaline phosphatase (TNSALP) substrates. Skeletal system changes. Survival. Health-related quality of life (HRQoL). Incidence of adverse events. Study/treatment discontinuation. Subgroup extractions: age	Studies assessing only pharmacodynamics. Studies assessing outcomes not relevant to the review.

	Inclusion criteria	Exclusion criteria
Study design	Randomised controlled trials (RCTs). Non-RCTs. Real world evidence studies. Single-arm trials. Systematic literature reviews (SLRs) meeting the defined population, intervention, comparators, outcomes (PICOS) criteria for the clinical studies.*	Non-systematic reviews, letters, comments, and editorials. Case studies or case reports.
Language restrictions	English language only[a]	Non-English
Time limits	Original SLR: no time limits. Update SLR: July 2021–February 2022.	

Based on Table 9 of Appendix D[50]
*Relevant SLRs will be included for the bibliography only.
[a]Non-English citations relevant to the SLR were flagged and discussed with Alexion to decide on the inclusion of non-English studies into the SLR.
AA = asfotase alfa; BSC = best supportive care; HPP = hypophosphatasia; HRQoL = health-related quality of life; PICOS = population, intervention, comparison, outcomes and study; RCTs = randomised controlled trials; SLR = systematic literature review; TNSALP = tissue non-specific alkaline phosphatase

EAG comment: Title and abstract, and full text screening were reported to have been performed by two independent reviewers against the eligibility criteria detailed in Table 4.2, with uncertainties regarding the inclusion of a study being resolved by a third reviewer. The EAG is reasonably satisfied that the study selection process is up to standard.

Language restriction - The EAG notes that the eligibility criteria restricted relevant studies to those published in the English language only, with the option of including non-English articles if they were found to be relevant by the company. The EAG does not consider this a standard approach that complies with best practice, as potentially relevant studies may have been missed.

Outcomes **-** In its clarification letter, the EAG asked the company to provide more information on what skeletal mineralisation complications were targeted under the umbrella of 'skeletal system changes' outcomes when conducting the SLR.[40] The company in their response[9] stated:

'The search strategy for the clinical SLR was not restricted by the outcomes listed in the PICOS criteria. The search strategies were restricted to hypophosphatasia as a broad disease, but the data extraction grid was designed in a way to extract any skeletal system changes reported across the studies.'

The company also provided the following table, detailing the three included studies that reported the number of patients with new fractures in patients treated with commonly used interventions (references for these studies were not provided).

Table 4.3: Studies identified in the SLR that reported the number of patients with new fractures in patients treated with commonly used interventions

Study Name (Trial name/NCT)	Intervention/ comparator	Overall/Subgroup	Time point	N	n (%)	Comments
Camacho 2018	Teriparatide	Overall	Study endpoint (follow-up)	8	1 (12.5)	One patient developed new bilateral femur pseudo fractures 8 months after discontinuation of the drug. This was a conference abstract with limited information available.
Lefever 2020	Bisphosphonates/ Bisphosphonates + Denosumab	Overall	Endpoint	2	2 (100)	Atypical femoral fracture (one sided). Limited information available in the study.
Moss 2021	Asfotase Alfa	Overall	104.2 weeks	12	0 (0)	For patients with >7 days of asfotase alfa treatment, no new fracture occurred over a 2-year period.

4.1.3 Critique of data extraction

The CS[10] states that *"all extracted data were verified against the original source paper by a second researcher."*

EAG comment: Double data extraction by two independent reviewers with a third reviewer being involved to resolve disagreements on discrepancies that may arise, is largely recommended to reduce bias, and avoid error.[57] Therefore, there is greater uncertainty on the veracity of the extracted data.

4.1.4 Quality assessment

In the SLR, included RCTs were subject to a quality appraisal using the standard NICE checklist,[58] single-arm and observational studies were appraised using the Downs and Black checklist,[59] and historical-control studies were assessed according to the 2009 CRD guidance.[57] Quality assessment of included studies appear to have been conducted by one reviewer and checked by a second reviewer. The results of these assessments will be discussed in Section 4.2.2 of this report.

EAG comment: The EAG is reasonably satisfied that the methodological quality appraisal tools employed were appropriate and covered all relevant domains for the included study designs. Although not followed, independent quality assessment of included studies by two reviewers is the recommended best practice for SLRs.[57] Additionally, the approach to resolving disagreements was not stated.

4.1.5 Evidence synthesis

The CS[10] states that two pooled analyses were conducted to assess the long-term efficacy and safety of AA in patients with paediatric-onset HPP. As these are in truth naïve comparisons, they will be discussed further in Section 4.3 of this report.

4.2 Critique of trials of the technology of interest, their analysis and interpretation (and any standard meta-analyses of these)

4.2.1 Studies of AA-treated patients included in the submission

As reported in Section B.2 of the CS,[10] Table 4.4 provides a summary of the clinical trials included in the CS. Data from the UK MAA are presented separately (Section 4.2.1.1) and the results of included clinical trials are presented separately, by trial, in the subsequent sections.

EAG comment: For clarity and consistency, to allow comparison of data from the UK MAA with trial data and to facilitate the interpretation of data from the UK MAA against the DP specified in the scope, the company were asked to provide results tables, comparing results across all AA studies including the UK MAA, for each outcome measure with results grouped by age of onset category (perinatal-, infantile-, and juvenile-onset HPP).[40] These tables were not provided and the company stated:

'The UK MAA was designed differently to the studies that formed the AA clinical development program. The AA clinical studies stratified patients differently by age and enrolment: < 3 years, < 5 years, 5-12 years ≥13 years. The UK MAA focuses on the age of the patient and their symptoms at presentation in one of the designated treatment centres. Within the UK MAA, there are 4 distinct groups of patients based on current age: < 12 months, between 1-4 years, between 5-18 years and >18 years. All of these patients have paediatric-onset HPP. In addition, some of the endpoints included in the UK MAA (e.g., BAMF scale, PedsQL, Bleck score) were not included in the AA clinical trials.

Therefore, efficacy data split by age disease onset are not available for all studies and the differences discussed above would make a comparison between the studies non-informative so summary tables have not been provided.'[9]

The EAG does not consider that this response provides sufficient justification for the inconsistent presentation of results. Where common outcomes were measured across the AA clinical trials and the UK MAA, the EAG considers that the data could and should have been presented in a way which would facilitate meaningful comparison; information about the age of onset categories of patients in the UK MAA was available and was provided by the company in their response to clarification questions (Table 3.4).[9]

Table 4.4: Summary of clinical effectiveness evidence - clinical trials

Study	ENB-001-08 (NCT00739505)	ENB-002-08/ENB-003-08 (NCT00744042/ NCT01205152)	ENB-010-10 (NCT01176266)	ENB-006-09/ENB-008-10	ENB-009-10 (NCT01163149)
Study design	Phase I, multicentre, multinational, open-label, dose-escalation study	Phase II, 6-month, international, multicentre, open-label study, with open-label extension study	Phase II open-label, multicentre, multinational study	Phase II, randomised, international, multicentre, dose-ranging, open-label study, with open-label extension study	Phase II, multinational, multicentre, open-label, dose-ranging, randomised concurrent control study
Population	Patients aged 18 to 80 years of age with hypophosphatasia (HPP)	Patients ≤ 36 months of age with infantile-onset HPP (onset of symptoms prior to 6 months of age)	Patients with perinatal-/infantile-onset HPP (onset of HPP signs/symptoms prior to 6 months of age)	Patients aged ≥5 and ≤12 years of age with HPP	Adolescent and adult patients aged 13 to 65 years with HPP
Treatment duration and follow-up	8 weeks	Up to 7 years	Up to 6 years	Up to 7 years	Up to 5 years
Intervention	Asfotase alfa (AA) (n=6)	AA (n=11)	AA (n=69)	AA (n=13)	AA (n=19)
Comparator	Not applicable (N/A)	N/A	N/A	N/A	N/A
Indicate if study supports application for marketing authorisation	Yes	Yes	Yes	Yes	Yes
Indicate if study used in the economic model	No	Yes	Yes	Yes	Yes
Rationale if study not used in model	This was a small dose-finding study. Other studies provided longer-term data	N/A	N/A	N/A	N/A

Study	ENB-001-08 (NCT00739505)	ENB-002-08/ENB-003-08 (NCT00744042/ NCT01205152)	ENB-010-10 (NCT01176266)	ENB-006-09/ENB-008-10	ENB-009-10 (NCT01163149)
Reported outcomes specified in the decision problem	Adverse effects of treatment	Mortality Radiographic response Severity of rickets Respiratory function Cranio-synostosis and intracranial pressure Growth Tooth loss Cognitive development and motor skills Adverse effects of treatment	Mortality Radiographic response Severity of rickets Respiratory function Cranio-synostosis and intracranial pressure Growth Tooth loss Cognitive development and motor skills Adverse effects of treatment	Mortality Radiographic response Severity of rickets Pain Cranio-synostosis and intracranial pressure Growth Cognitive development and motor skills Adverse effects of treatment Health-related quality of life (HRQoL) (for patients and carers)	Mortality Pain Cranio-synostosis and intracranial pressure Growth Cognitive development and motor skills Adverse effects of treatment
All other reported outcomes	Pharmacokinetic (PK) of AA given subcutaneous (SC) and intravenous (IV) Bioavailability of AA given SC	N/A	N/A	Mobility assessments	Mobility assessments Inorganic pyrophosphate (PPi) and pyridoxal 5'-phosphate (PLP) levels over time

Table 8 of CS[10]
AA = asfotase alfa; CS= company submission; HPP = hypophosphatasia; HRQoL = health-related quality of life; IV = intravenous; N/A = not applicable; PK = pharmacokinetic; PLP = pyridoxal 5'-phosphate; PPi = inorganic pyrophosphate; SC = subcutaneous

4.2.1.1 UK MAA

4.2.1.1.1 Study details

As of the most recent analysis cut-off date ([redacted]), [redacted] participants were enrolled and entered into the UK MAA database. Of these [redacted] participants, [redacted] had received at least one dose of AA (safety population) and [redacted] had a minimum exposure of 6 months on AA (study population). Table 47 of Appendix M[50] summarised the UK MAA study methodology.

As of the most recent analysis cut-off date, all ([redacted]) paediatric participants (aged <18 years at baseline) in the study population completed all visits through to the Month 12 visit. For this population, the median follow-up time was [redacted] years (min, max: [redacted]) and the most recent visit as of the analysis cut-off date was at Month 48, which seven ([redacted] paediatric participants completed.

All ([redacted] adult participants (aged ≥18 years at baseline) in the study population completed all visits through to the Month 12 visit. For this population, the median follow-up time was [redacted] years (min, max[redacted]) and the most recent visit was at Month 36, which [redacted] adult participants completed.

4.2.1.1.2 Patient characteristics

Patient demographics and baseline characteristics have been summarised in Table 4.5. Participants were classified into two categories based on age at enrolment. Of the 35 participants in the study population as of the analysis cut-off date[redacted] were aged <18 years (paediatric population) and [redacted] were aged ≥18 years (adult population) at the time of enrolment.

Overall, [redacted] of the [redacted] participants in the paediatric population were receiving AA treatment at the time of enrolment into the UK MAA as they were part of an Alexion clinical trial and/or compassionate use programme. However, no [redacted] in the adult population was [redacted] with AA. Of the [redacted] participants in the paediatric population, [redacted] participant was initiated with an AA dosage of <6 mg/kg per week, [redacted] were initiated with an AA dosage of 2 mg/kg 3 times per week (6 mg/kg per week total), and [redacted] were initiated with a AA dosage of >6 mg/kg per week. Overall, [redacted] patients had a [redacted] and remained on the same dose from treatment initiation to last follow-up. In this population, [redacted] participants had missed or interrupted AA dosing, with a median of [redacted] missed doses (min, max: [redacted]).

Table 4.5: UK MAA Participant demographics (study population)

	Study Population (N=[redacted])	**Paediatric Population <18 years at baseline (N=[redacted])**	**Adult Population ≥18 years at baseline (N=[redacted])**
Age at enrolment (years)			
Mean (SD)	[redacted]	[redacted]	[redacted]
Median (min, max)	[redacted]	[redacted]	[redacted]
Age group at enrolment, n (%)			
<1 year	[redacted]	[redacted]	[redacted]
1 to <5 years	[redacted]	[redacted]	[redacted]
5 to <18 years	[redacted]	[redacted]	[redacted]
≥18 years	[redacted]	[redacted]	[redacted]

	Study Population (N=[redacted])	Paediatric Population <18 years at baseline (N=[redacted])	Adult Population ≥18 years at baseline (N=[redacted])
Age group at last follow-up, n (%)			
<1 year	[redacted]	[redacted]	[redacted]
1 to <5 years	[redacted]	[redacted]	[redacted]
5 to <18 years	[redacted]	[redacted]	[redacted]
≥18 years	[redacted]	[redacted]	[redacted]
Age at HPP symptom onset (years)			
n	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]
Median (min, max)	[redacted]	[redacted]	[redacted]

Table 48 of Appendix M[50]
HPP = hypophosphatasia; MAA = Managed Access Agreement; max = maximum; min = minimum; N = number of participants; n = number of participants in a category; N/A = not applicable; SD = standard deviation; UK = United Kingdom
Note: Baseline was considered the baseline/enrolment visit.

EAG comment: The EAG notes that participants have not been grouped using age of symptom onset (perinatal, infantile, juvenile and adult-onset) categories, as defined for the population in the NICE scope and used in the Alexion clinical trials programme. This makes it difficult to assess data from the UK MAA against the DP, as defined in the NICE scope, and to compare the results obtained from the UK MAA with those of the Alexion clinical trials. The company were asked to provide the numbers of patients in each of perinatal-, infantile-, juvenile- and adult-onset categories for all studies including the UK MAA and the Global HPP Registry (ALX-HPP-501);[40] these data were provided (see Section 3.3.1 of this report). The company were also asked to provide results grouped by these categories;[40] results, by age of onset category, were not provided (see Section 3.3.4 of this report).

The EAG notes that the terms of the UK MAA, specifically point 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 AA must only be initiated by the expert centre." The company were asked to confirm that all participants in the UK MAA met this criterion[40] and the following response was provided:

'All patients included in the MAA have a diagnosis of paediatric-onset HPP (in line with AA licensed indication), therefore no patients with adult-onset HPP have been approved for treatment with AA. As agreed in the MAA, the NHSE designated treatment centres must refer any HPP patient that meet the specified treatment eligibility criteria to the National Authorisation Panel (NAP). After reviewing each patient case against the treatment initiation criteria (part of which is the documentation for the paediatric-onset of HPP), the NAP makes the final decision on whether the referred patient is eligible for treatment initiation at the treatment centre. The NAP consists of representatives from the following stakeholders: One paediatric clinical expert, one adult clinical expert, one pain specialist, NHSE, NICE. Therefore, all participants included in the UK MAA data set had a diagnosis of paediatric-onset

HPP (regardless of current age) confirmed by one of the national HPP expert centres, according to national guidelines, and therefore, met the terms of the MAA.'

The EAG further notes that [redacted] paediatric (age <18 years at baseline) participants and [redacted] adult (age ≥18 years at baseline), were reported to have received a dose of <6 mg/kg per week (lower than the recommended dose, and [redacted] adult (age ≥18 years at baseline), were reported to have received a dose of >6 mg/kg per week (higher than the recommended dose,[7] and that clinical efficacy and safety results were not reported in relation to the actual dose of AA received by study participants.[10]

4.2.1.1.3 Efficacy results

The most recent efficacy outcome results are presented for the UK MAA data set (analysis cut-off date: [redacted]).

Paediatric population

Mortality endpoints - As of the most recent analysis cut-off date [redacted]), [redacted] of the participants in the paediatric population had died [redacted]). [redacted] participants were classified as the most severely affected by HPP (perinatal- and infantile-onset), as they were <1 year of age at AA treatment initiation. Therefore, these results demonstrate that AA is a lifesaving drug for babies born with HPP.

Respiratory support - As of the analysis cut-off date, [redacted] of the treatment-experienced ([redacted] with ≥6 months of exposure to AA before UK MAA enrolment) participants in the paediatric population required nasal oxygen support on or after enrolment into the UK MAA: [redacted] required brief (ended Month [redacted]) continuous positive airway pressure (CPAP), support and [redacted] required invasive ventilation support that ended by the Month 3 visit; , [redacted] treatment-naïve (<6 months of exposure to AA before UK MAA enrolment) [redacted] required brief (ended by Month [redacted]) nasal oxygen support, [redacted] treatment naïve patients required brief (both ended by Month [redacted] CPAP support and [redacted] treatment naïve patients required brief (both ended by Month [redacted]) invasive ventilation support. See Table 11 (Section B.2.6.2.1.2.) in the CS[10] for results on respiratory/ventilator use results in the paediatric population.

Growth - [redacted] participants in the paediatric population demonstrated [redacted]

At baseline and Month [redacted], participants in the paediatric population had a median height percentile of [redacted] (min, max: [redacted]) and [redacted] (min, max: [redacted]), respectively. From baseline to Month [redacted], a median change of [redacted] (min, max: [redacted]) percentiles was observed for height in the paediatric population (see Figure 6 of CS).[10]

At baseline and Month [redacted], participants in the paediatric population had a median weight percentile of [redacted] (min, max: [redacted]) and [redacted] (min, max: [redacted]), respectively. From baseline to Month [redacted], a median change of [redacted] (min, max: [redacted]) percentiles was observed for weight in the paediatric population (see Figure 7 of CS).[10]

Motor function/functional assessments - In the paediatric population (aged 1–4 years), a median change of [redacted] (min, max: [redacted]) in Upper Extremity Brief Assessment of Motor Function (BAMF) score was observed from baseline to Month [redacted], [redacted] A median change of [redacted] (min, max: [redacted]) in Lower Extremity BAMF score was also observed from baseline to Month 30, also [redacted]. See Figures 8 and 9 in (Section B.2.6.2.1.4.1.) the CS[10] for BAMF assessment results at 6, 12, 18, 24, 30, 36, 42, and 48 months.

Mobility assessments - Sections B.2.6.2.1.5.1 to B.2.6.2.5.3 of the CS[10] report mobility assessment results in UK MAA paediatric patients using the 6MWT, Bleck score, and use of mobility aids. For participants in the paediatric population (aged 5 to <18 years), a median change of [redacted] metres (min, max: [redacted] metres) was observed from baseline to Month [redacted] during the 6MWT, which is [redacted] than the minimum clinically important difference (MCID) of 25 metres specified in the UK MAA. Change from baseline to Month [redacted] was [redacted] than the MCID (median[redacted] metres [min, max: [redacted] metres]), as only [redacted] participants with a baseline assessment completed this visit due to the COVID-19 pandemic. However, once assessments were able to continue to be completed, there was a continued [redacted] trend in distance walked during the 6MWT from Month [redacted] onwards.

For the purposes of the UK MAA, a decrease in Bleck score of more than 1 level was used to determine whether treatment with AA was benefitting participants in the paediatric population. At baseline and Month [redacted] participants in the paediatric population (aged 5 to <18 years) had a median Bleck score of [redacted] (min, max: [redacted]) and [redacted] (min, max: [redacted]), respectively. Therefore, median Bleck scored showed a change of [redacted] (min, max[redacted]) from baseline to Month [redacted]. Median Bleck score may have been [redacted] at baseline because [redacted] of participants ([redacted] in this population were enrolled in an AA clinical study and/or compassionate use programme before enrolment in the UK MAA; therefore, they may have already been benefitting from AA treatment.

Overall, [redacted] participants in the paediatric population required a mobility aid at baseline. As of the analysis cut-off date, [redacted] no longer required the use of a mobility aid, and [redacted] still required the use of a mobility aid at last follow-up. However, the [redacted] who still required the use of a mobility aid [redacted]. Of the [redacted] participants in the paediatric population who did not require a mobility aid at baseline, [redacted] still did not require the use of a mobility aid and [redacted] did require the use of a mobility aid as of the analysis cut-off date. [redacted].

Pain assessments - Overall, [redacted] participants in the paediatric population aged 1 to <18 years were receiving [redacted] analgesic at enrolment in the UK MAA. Throughout the UK MAA, [redacted] participants in the paediatric population received [redacted] analgesic. Of these [redacted] participants, [redacted] reported that they [redacted] taking any analgesic at their most recent follow-up and the other [redacted] reported [redacted] use. The mean number of analgesics used at last follow-up in this population was [redacted] (SD = [redacted]).

Health-related quality of life (HRQoL) - For the paediatric population (aged >2 years to <18 years), QoL was measured by Paediatric Quality of Life Inventory (PedsQL™), rated by participants and/or their parents. Participants aged >2 years to <18 years had a median total PedsQL score at baseline of [redacted] (min, max: [redacted]) for parent-reported and [redacted] (min, max: [redacted]) for child-reported, indicating moderate QoL.

The median change from baseline to Month [redacted] in total score was [redacted] (min, max: [redacted]) for paediatric-reported PedsQL and [redacted] (min, max: [redacted]) for parent-reported PedsQL, demonstrating an [redacted].

Adult population

Mortality endpoints - As of the most recent analysis cut-off date ([redacted]), [redacted] participants in the adult population (n=17) who were treated with AA had died. However, [redacted] was reported, but [redacted] had never received AA and therefore the [redacted] was not related to treatment (see Section 4.2.1.1.5 - adult population).

Mobility assessments - Sections B.2.6.2.2.2.1 to B.2.6.2.2.2.3 of the CS[10] report mobility assessment results in the UK MAA adult patients for 6MWT, Bleck score, and use of mobility aids.

A median change of [redacted] metres (min, max: [redacted] metres) from baseline to Month [redacted] in 6MWT was observed in the adult population, which is [redacted] than the MCID of 25 metres specified in the MAA. There was [redacted] in the distance walked in the 6MWT at Month [redacted] because [redacted]

[redacted] participants in the adult population showed a [redacted] in Bleck score from baseline, and Bleck scores over time [redacted]. Additionally, a median [redacted] from baseline of [redacted] (min, max: [redacted]) in Bleck score was observed at Month [redacted].

A total of [redacted] participants in the adult population required the use of a mobility aid at baseline. As of the analysis cut-off date, [redacted] out of [redacted] participants no longer required the use of a mobility aid, and [redacted] out of [redacted] participants still required the use of a mobility aid at last follow-up. [redacted] participants who did not require the use of a mobility aid at baseline, [redacted] still did not require the use of a mobility aid as of the analysis cut-off date.

Pain assessments - Section B.2.6.2.2.3 of the CS[10] reports pain assessment results for the UK MAA adult population.

For the purposes of the UK MAA, an improvement of less than 2 points in the Brief Pain Inventory - Short Form (BPI-SF) was used to determine whether treatment with AA was benefitting participants in the adult population. Overall, there was a [redacted] in BPI-SF scores in the adult population, [redacted]. Participants demonstrated a median [redacted] of [redacted] (min, max: [redacted]) in their BPI-SF score at Month [redacted] relative to baseline, [redacted].

Overall, [redacted] participants in the adult population were receiving [redacted] analgesic at enrolment in the UK MAA. Of these participants, [redacted] were receiving [redacted] analgesic at the time of UK MAA enrolment, and [redacted] started receiving [redacted] after enrolment. Overall, [redacted] participants continued to receive [redacted] analgesic as of the analysis cut-off date. The mean number of analgesics used at last follow-up in this population was [redacted] (SD: [redacted]).

Fractures – [redacted] participants in the adult population had ongoing fractures at the time of UK MAA enrolment. As of the analysis cut-off date, [redacted] new fractures occurred following enrolment in [redacted] participants in the adult population. See Section B.2.6.2.2.4. of the CS[10] for more information.

HRQoL - An improvement of more than 0.15 in EQ-5D-3L utility score was used to determine whether treatment with AA was benefitting participants and overall, participants in the adult population demonstrated EQ-5D-3L scores that indicated [redacted] compared with baseline. EQ-5D-3L scores increased from [redacted] (min, max: [redacted]) at baseline to [redacted] (min, max: [redacted]) at Month [redacted], corresponding to a median change from baseline of [redacted] (min, max: [redacted]), [redacted]. [redacted] participants [redacted] a more than 0.15 improvement specified in the UK MAA as of the analysis cut-off; the company provided the following additional information, about these participants, in their Factual Accuracy Check: [redacted]

4.2.1.1.4 Subgroup results: paediatric population

Subgroup analyses for the UK MAA paediatric population were conducted for participants <1 year of age at treatment initiation and for treatment-naïve and treatment-experienced patients to assess;

- Growth: Most ([redacted] participants in the paediatric population were <1 year of age at treatment initiation and demonstrated [redacted] and weight [redacted]; [redacted] participants who were <1 year of age at treatment initiation [redacted] From baseline to Month [redacted], a median change of [redacted] (min, max: [redacted]) percentiles was observed for height in participants <1 year of age at treatment initiation. See Appendix E.1.1.[50] for more information.

- BAMF scores: See Appendix E.1.2.[50] for change from baseline results in treatment-naïve and treatment experienced participants in the paediatric population (aged 1–4 years).

4.2.1.1.5 Safety results

Paediatric population - Adverse events of interest (EOI) in the paediatric population have been summarised in Table 4.6.

A total of [redacted] serious adverse events (SAEs) in [redacted] participants were reported in the paediatric safety population, [redacted] of which occurred during treatment or within 30 days of treatment discontinuation. [redacted] of the SAEs were assessed by the treating physician as definitely related to study treatment. The [redacted] of the SAEs were assessed as not related or unlikely to be related to study treatment.

As of the analysis cut-off date, [redacted] EOIs in [redacted] participants were reported, [redacted] of which occurred during study treatment or within 30 days of treatment discontinuation.[10] Of these [redacted], [redacted] events were assessed by the physician as related to study treatment and [redacted] events were assessed as not related to treatment. ISRs were the most frequently reported EOI in the paediatric safety population. Overall, [redacted] ISRs in [redacted] participants were reported, all of which were considered mild or moderate in severity.

As of the analysis cut-off date for this report, [redacted] participants in this population had died or discontinued due to an AE.

Adult population - Adverse EOIs in the adult population have been summarised in Table 4.7. As of the most recent data cut-off date ([redacted]), [redacted] was reported. [redacted].

A total of [redacted] SAEs were reported in [redacted] adult participants, [redacted] of which occurred on treatment or within 30 days of treatment discontinuation. [redacted] of the SAEs were assessed by the treating physician as definitely related to study treatment. The treating physician assessed the [redacted] remaining SAEs as not related or unlikely to be related to study treatment.

A total of [redacted] EOIs were reported in [redacted] adult participants, [redacted] of which occurred on treatment or within 30 days of treatment discontinuation. Of these, [redacted] events were mild or moderate in severity, [redacted] events were assessed by the treating physician as related to study treatment and [redacted] events were assessed as not related to study treatment. ISRs were the most frequently reported EOI in the adult safety population. Overall, [redacted] events were reported in [redacted] participants, all of which were considered mild or moderate in severity.

[redacted] participants discontinued the study due to an SAE or EOI.

EAG comment: The company were asked to clarify whether any patient (paediatric or adult), in the UK MAA, discontinued AA treatments due to treatment-emergent adverse events (TEAEs) or non-response[40] and confirmed that [redacted] participants in the UK MAA discontinued AA due to a TEAE or non-response.[9]

Table 4.6: Events of interest and SAEs during follow-up by relationship to treatment – Paediatric Safety Population (aged <18 years at baseline)

	Safety Population (N=[redacted])		
	All reported events		
	Any	Related	Not related
	n (%) E	n (%) E	n (%) E
Events of interest	[redacted]	[redacted]	[redacted]
Lack of efficacy/drug effect	[redacted]	[redacted]	[redacted]
Pneumonia	[redacted]	[redacted]	[redacted]
Craniosynostosis	[redacted]	[redacted]	[redacted]
Injection-associated reaction	[redacted]	[redacted]	[redacted]
Injection site reaction	[redacted]	[redacted]	[redacted]
Serious adverse events, n (%)	[redacted]	[redacted]	[redacted]
Congenital, familial, and genetic disorders	[redacted]	[redacted]	[redacted]
Craniosynostosis	[redacted]	[redacted]	[redacted]
Infections and infestations	[redacted]	[redacted]	[redacted]
Infectious mononucleosis	[redacted]	[redacted]	[redacted]
Pneumonia	[redacted]	[redacted]	[redacted]
Data pending	[redacted]	[redacted]	[redacted]
Data pending[a]	[redacted]	[redacted]	[redacted]
General disorders and administration site conditions	[redacted]	[redacted]	[redacted]
Injection site atrophy	[redacted]	[redacted]	[redacted]
Musculoskeletal and connective tissue disorders	[redacted]	[redacted]	[redacted]
Scoliosis	[redacted]	[redacted]	[redacted]
Respiratory, thoracic and mediastinal disorders	[redacted]	[redacted]	[redacted]
Respiratory distress	[redacted]	[redacted]	[redacted]

Table 93 of Appendix M[50]
E = number of events; N = number of participants; n = number of participants in a category; SAE = serious adverse event.
Notes: [a]The coded system organ call and preferred term were not available at data cut-off. Participant 0915-M01 had orthopaedic surgery for the insertion and removal of hemi epiphysiodesis at the time the SAE was reported.

Table 4.7: Events of interest and SAEs during follow-up by relationship to treatment – Adult Safety Population (aged ≥18 years at baseline)

	Safety Population (N=[redacted]) All reported events		
	Any	Related	Not related
	n (%) E	n (%) E	n (%) E
Events of interest, n (%)	[redacted]	[redacted]	[redacted]
Injection-associated reaction	[redacted]	[redacted]	[redacted]
Injection site reaction	[redacted]	[redacted]	[redacted]
Medication error	[redacted]	[redacted]	[redacted]
Serious adverse events, n (%)	[redacted]	[redacted]	[redacted]
Data pending	[redacted]	[redacted]	[redacted]

	Safety Population (N=[redacted])		
	All reported events		
	Any	Related	Not related
	n (%) E	n (%) E	n (%) E
Data pending[a]	[redacted]	[redacted]	[redacted]
General disorders and administration site condition	[redacted]	[redacted]	[redacted]
Injection site reaction	[redacted]	[redacted]	[redacted]
Musculoskeletal and connective tissue disorders	[redacted]	[redacted]	[redacted]
Flank pain	[redacted]	[redacted]	[redacted]
Nervous system disorders	[redacted]	[redacted]	[redacted]

Table 94 of Appendix M[50]
AA = asfotase alfa; E = number of events; MAA = Managed Access Agreement; N = number of participants; n = number of participants in a category; SAE = serious adverse event; UK = United Kingdom
Notes: All events occurred after enrolment in the UK MAA while the participant was on AA treatment or within 30 days of treatment discontinuation. Related events included those that were possibly related, probably related and definitely related. Baseline was considered the baseline/enrolment visit.
[a] The coded system organ call and preferred term were not available at data cut-off. Participant 0826-M02 had post-operative urinary retention and had surgery on their right femur at the time the SAE was reported.

EAG comment: In their response to clarification questions,[9] the company stated that [redacted] participants in the UK MAA discontinued AA due to a TEAE and [redacted] participants in the UK MAA died due to a TEAE.
The EAG considers that the informative potential of the UK MAA has been substantially limited by:

- Failure to categorise patients using the accepted definitions (perinatal-, infantile-, juvenile- and adult-onset HPP), as used in the NICE definition of the decision problem and in the Alexion clinical trials programme.
- Non-inclusion of data from the UK MAA in the meta-analysis used to provide estimates of overall efficacy.
- Lack of any comparison of outcomes for patients in the UK MAA with untreated controls.

4.2.1.2 Clinical trials: ENB-002-08/ ENB-003-08

A total of 11 patients were enrolled and treated with at least one dose of AA. The median treatment duration among the 11 patients was 2,416 days (min, max: 1, 2,743 days). Nine of the 11 patients had received at least 72 months of treatment with AA. One patient was discontinued from study drug and discontinued from ENB-002-08 because of injection associated reactions (IARs) during the initial intravenous (IV) AA infusion.

The remaining 10 patients all completed ENB-002-08 and continued participation into the extension study ENB-003-08. One patient died of sepsis during participation in ENB-002-08. The remaining nine patients completed participation in the extension study ENB-003-08.

Long term outcome results have been presented in this Section (last patient visit: [redacted]; extension up to 7 years) (see Table 4.4 for more information on study methodology).

4.2.1.2.1 Patient characteristics

Patient demographics and baseline characteristics have been summarised in Table 4.8. All participants in ENB-002-08/ENB-003-08 had infantile onset HPP.[10]

Table 4.8: ENB-002-08/ENB-003-08 patient demographics

Baseline characteristic	AA-treated patients (n=13)
Age (weeks)[a]	
Mean (SD)	[redacted]
Median (min, max)	[redacted]
Sex, n (%)	
Male	[redacted]
Female	[redacted]
Ethnicity, n (%)	
Hispanic or Latino	[redacted]
Not Hispanic or Latino	[redacted]
Race, n (%)	
White	[redacted]
Other	[redacted]
Baseline ventilation status, n (%)	
No support	[redacted]
Supplemental O_2 (without mechanical ventilation)	[redacted]
CPAP	[redacted]
Mechanical ventilation (invasive)	[redacted]
BPAP	[redacted]
Other[c]	[redacted]
Baseline RSS score (n=10)	
Mean (SD)	[redacted]
Median (min, max)	[redacted]
Baseline Z-scores (length) (n=11)[d]	
Mean (SD)	[redacted]
Median (min, max)	[redacted]
Baseline Z-scores (weight) (n=11)[c]	
Mean (SD)	[redacted]
Median (min, max)	[redacted]
Baseline alkaline phosphatase (U/L) (n=9)	
Mean (SD)	[redacted]
Median (min, max)	[redacted]
Baseline iPTH (pmol/L) (n=2)	
Mean (SD)	[redacted]
Median (min, max)	[redacted]

Baseline characteristic	AA-treated patients (n=13)
Baseline plasma PPi (μM) (n=8)[e]	
Mean (SD)	[redacted]
Median (min, max)	[redacted]
Baseline PLP (ng/ml) (n=9)[f]	
Mean (SD)	[redacted]
Median (min, max)	[redacted]
Baseline calcium (mmol/L) (n=11)[g]	
Mean (SD)	[redacted]
Median (min, max)	[redacted]

Table 53 of Appendix M[50]
AA = asfotase alfa; BPAP = bi-level or biphasic positive airway pressure; CDC = Centers for Disease Control; CPAP = continuous positive airway pressure; iPTH = intact parathyroid hormone; max = maximum; min = minimum; n = number of patients; O2 = oxygen; PPi = inorganic pyrophosphate; PLP = pyridoxal-5'-phosphate; RSS = Rickets Severity Scale; SD = standard deviation

Notes: Percentages are based on the number of patients in the treatment group column with non-missing data. Baseline is defined as the last value on or before the date of first dose of study drug in ENB-002-08.

[a]Age is the age at time of receiving first dose of study drug.
[b]The category for 'no support' at the baseline time point included patients with missing data at baseline. Information on respiratory support at baseline was missing/not available for Patients 002-01-01 and 002-09-02; these patients were categorised as needing 'no support' at baseline for the purpose of the tabulations here.
[c]O2 by nasal cannula (Patient 002-06-01).
[d]Z-scores for length and weight are based on CDC 2000 growth charts. The birth to 36 months chart was used for patients from birth to 36 months of age and the 2 to 20 years chart was used for patients older than 36 months.
[e]PPi normal reference range = 1.33 to 5.71 μM.
[f]PLP normal reference range = 11.76 to 68.37 ng/ml.
[g]Calcium normal ranges varied by laboratory.

4.2.1.2.2 Efficacy results

Overall survival - By the end of the study, [redacted] as only one (9.1%) of the 11 patients enrolled in the study had died. The OS data from this study was pooled with those from ENB-010-10 (see section 4.3 of this report).

Ventilator-free survival - [redacted]. Patients on respiratory support at baseline were excluded from the analysis. . [redacted] of the 11 enrolled patients were included in the analysis of VFS (including CPAP, BPAP, mechanical ventilation, and death), and [redacted] were included in the analysis of invasive VFS (including mechanical ventilation and death). The VFS data from this study was pooled with those from ENB-010-10 in the indirect comparison discussed in Section 4.3 of this report.

Respiratory support - At baseline, five (45%) of 11 patients required respiratory support, with three (27%) requiring mechanical ventilation, one (9%) receiving CPAP, and one (9%) receiving supplemental oxygen. By Year 2, three (33%) of nine patients required respiratory support, with one (11%) requiring mechanical ventilation and two (22%) receiving just supplemental oxygen. From 4.5 years of treatment until study end, none of the nine patients required respiratory support (including supplemental oxygen), representing a long-term, clinically significant improvement for the patients who initially had severe respiratory compromise.

Growth- Table 18 of the CS[10] details median Z-scores and change from baseline in growth (height/weight) over 7 years of treatment (Z-scores reflect the number of SDs each value falls from the

age-/sex-matched normal mean). Overall, four (44.0%) of nine patients had Z-scores within the normal range at last assessment. The mean increase from baseline in length or height Z-score was statistically significant at Year 3 (1.7 [SD = [redacted]]; p = 0.0385) and Year 4.5 (1.9 [SD = [redacted]]; p = 0.0346), but not at other timepoints. Median weight was 4.1 kg (range 2.1–9.2) at baseline (n=11) and 19.8 kg (range 15.1–31.4) at Year 7 (n=7). The mean increase from baseline in weight Z-score was statistically significant at Year 3 (2.4 [SD = [redacted]]; p = 0.0096) and Year 4.5 (2.5 [SD = [redacted]]; p = 0.0074), but not at other timepoints.

Motor function/functional assessments - Motor and cognitive development were assessed using three different tests, depending on the age of the patient - the Bayley Scales of Infant and Toddler Development®, 3rd Edition (BSID-III) was used to assess motor and cognitive function in patients up to 42 months of age, the Locomotion subtest of the Peabody Developmental Motor Scales, 2nd edition (PDMS-2) was used as an assessment of gross motor skills in patients aged 43–71 months who were considered to have evaluable functional abilities, and the BOT-2 Running Speed and Agility and Strength subtest was used to assess motor skills in patients 72 months of age or older.

The normal standard score mean (SD) for the BSID-III subscales is 10 (3) and at baseline or first assessment, nine (82%) of 11 patients had BSID-III Gross Motor scaled scores of 1, indicating profound developmental delays relative to healthy age-matched peers (three SDs below the normative mean). These patients had patients had serial BSID-III assessments and all nine patients showed improvements in age-equivalent scores on the Gross Motor, Fine Motor and Cognitive subscales over time. Median scaled Gross Motor scores improved from 1.0 (min, max: 1.0, 8.0) at baseline to 6.0 (min, max: 2.0, 8.0) at Year 3, indicating motor skill improvement and less developmental delay. Median scores on the Fine Motor and Cognitive subscales were low at baseline but normalised at Year 2 and Year 3.

The normal mean (SD) for PDMS-2 standard scores is 10 (3), with higher scores meaning better functioning. Eight (73%) patients advanced to complete serial PDMS-2 assessments. Of these, seven (88%) had standard scores more than one SD below the normal reference range (score <7) when they first completed the assessment; five (63%) of eight patients achieved scores within one SD of normal. Median Locomotion standard scores improved from [redacted] (min, max: [redacted] at Week 72 to [redacted] (min, max: [redacted]) at last overall assessment.

Eight (73%) of 11 patients transitioned to the BOT-2 and completed at least one assessment. All patients had received AA for at least 5 years when first tested. Seven (88%) of eight patients had initial scaled BOT-2 Running Speed and Agility subtest scores more than one SD below normal (scaled score <10; Figure 50 of Appendix M[50]). Three achieved normal scaled scores (≥10) by the end of the study. All six patients who completed serial BOT-2 assessments had improved age-equivalent BOT-2 scores during treatment.

Radiographic Global Impression of Change (RGI-C) and Rickets Severity Score (RSS) - Radiographs were used as the basis to assess changes in radiographic global impression of change (RGI-C) over time. Comparisons were made by three independent paediatric radiologists (qualified by training and experience). Median RGI-C scores documented significant improvements in HPP skeletal disease as early as Month 3 (median 1.2 [min, max: –1.0, 2.0]; p = 0.0313), which were typically sustained over 7 years of treatment (median 2.3 [min, max: 2.0, 3.0]; p = 0.016), with significant (p = <0.05) improvements at most visits.

Radiographs of the wrists and knees from each timepoint were also evaluated for severity of rickets using the rickets severity scale (RSS). Median RSS scores indicated that the significant improvements documented as early as Month 6 (median 4.0 [min, max: 0.5, 10.0]; p = 0.016) were sustained over 7

years of treatment (median 0.5 [min, max: 0, 5.5]; p = 0.016), with significant (p = <0.05) decreases suggesting improvement from baseline at most visits.

4.2.1.2.3 Safety results

Table 4.9 details adverse events (AEs) data from the ENB-002-08/ENB-003-08 trial safety set where 11 patients received AA treatment. A total of 794 TEAEs were observed over 7 years of treatment with AA; all 11 patients had at least one TEAE. The TEAEs were primarily mild (605 out of 794 [76%]) or moderate (151 out of 794 [19%]) in severity, and most were considered by investigators to be unrelated to the study drug (664 out of 794 [84%]). Events assessed by investigators as possibly, probably, or definitely related to AA in more than two patients were injection-site erythema (n=4), irritability (n=3), pyrexia (n=3), and vomiting (n=3). There were only 38 SAEs (in [redacted]

One patient withdrew because of AEs during the initial IV infusion of AA and one patient died from sepsis at around age 8 months, after 7.5 months of therapy.

Table 96 in Appendix M.4[50] details TEAEs that occurred in more than 20% of patients over 7 years of treatment with AA.

Table 4.9: Summary of all TEAEs over 7 years of treatment - ENB-002-08/ENB-003-08, safety set

Adverse event categories	**AA (n=11)**	
	Events, n	**Patients, n (%)**
Adverse events (AEs)	794	11 (100.0)
Not related AEs	664	[redacted]
Related AEs	130	[redacted]
Injection-site reactions (ISRs)	78	7 (63.6)
Hypersensitivity injection-associated reactions (IARs)	10	4 (36.4)
Mild	605	[redacted]
Moderate	151	[redacted]
Severe	38	[redacted]
AEs leading to discontinuation[a]	[redacted]	[redacted]
Serious adverse events (SAEs)	[redacted]	[redacted]
Not related SAEs	[redacted]	[redacted]
Related SAEs	[redacted]	[redacted]
ISRs	0	0 (0.0)
Hypersensitivity IARs	0	0 (0.0)
Mild	[redacted]	[redacted]
Moderate	[redacted]	[redacted]
Severe	37	8 (72.7)
SAEs leading to discontinuation	2	2 (18.2)
Deaths	-	1 (9.1)

Table 95 in Appendix M[50]
AA = asfotase alfa; AE = adverse event; IAR = injection-associated reaction; ISR = injection site reaction; SAE = serious adverse event; TEAE = treatment-emergent adverse event

Adverse event categories	AA (n=11)	
	Events, n	Patients, n (%)
Notes: TEAEs are events starting on or after the day of first dose of study drug. Patient percentages are based on the total number of patients in the treatment group column. Related AEs are defined as possible, probable, definitely related, or with a missing relationship. Unrelated AEs are defined as unrelated or unlikely related. All unique combinations of coded terms and verbatim text from AEs were reviewed by medical staff to flag events that may be IARs or ISRs. Those terms that were marked related by the recording clinician were considered IARs or ISRs. [redacted]		

EAG comment: The EAG notes that the starting dose of AA in this trial, was reported as 1 mg/kg, 3 times per week, increasing to a maximum of 3 mg/kg, 3 times per week (higher than the recommended dose);[46] the EAG could find no details of the actual doses received by individual patients and clinical efficacy and safety results were not reported in relation to dose received. The EAG further notes that the results of this study are for a subgroup of the population specified in the decision only (i.e., infantile-onset HPP).

4.2.1.3 Clinical trials: ENB-010-10

A total of 69 patients were enrolled and treated with AA. Sixty (87%) of the enrolled patients completed the study; nine (13%) patients died after initiating treatment with AA. One additional patient was consented for enrolment but died before receiving any treatment with study drug.

Long term outcome results have been presented in this section (last patients visit: [redacted]; extension up to 6 years) (see Table 4.4 for more information on study methodology).

4.2.1.3.1 Patient characteristics

Patient demographics and baseline characteristics have been summarised in Table 4.10.

Table 4.10: ENB-010-10 baseline demographics

Baseline characteristic	Enrolled patients (n=69)
Age at enrolment, month, median (min, max)	16.0 (0.3, 72.2)
Sex, n (%)	
Male	33 (48)
Race, n (%)	
White	54 (78)
Asian	7 (10)
Other	3 (4)
Unknown	5 (7)
Age at first signs of HPP, month, median (min, max)	1.0 (0, 5.5)
HPP-specific medical history, n (%)	
Abnormally shaped chest	58 (84)
History of respiratory compromise (up to and including respiratory failure)[a]	46 (67)
Seizures	17 (25)

Baseline characteristic	Enrolled patients (n=69)
Difficulty gaining weight, failure to thrive and/or difficulty eating/swallowing	60 (87)
Hypercalcaemia	61 (88)
Nephrocalcinosis	37 (54)
Fractures and/or delayed fracture healing	21 (30)
Length/height Z-score	n=67
Median (min, max)	-2.7 (-10.0, 1.0)
Weight Z-score	n=68
Median (min, max)	-2.5 (-24.0, 0)
RSS score	n=67
Median (min, max)	4.0 (0, 10.0)
ALP, U/L (normal range: 60–370 U/L)[b]	n=65
Median (min, max)	20 (18, 122)
PPi, mM (normal range: 1.3–5.7 mM)	n=65
Median (min, max)	6.3 (2.7, 13.3)
PLP, ng/ml (normal range: 11.8–68.4 ng/ml)[c]	n=60
Median (min, max)	521 (48, 24,600)
Calcium, mM [normal ranges: 2.25–2.74 mM (age: ≤2 years); 2.1–2.57 mM (age: >2 years)]	n=65
Median (min, max)	2.6 (1.8, 4.0)

Table 56 of Appendix M[50]
AA = asfotase alfa; ALP = alkaline phosphatase; HPP = hypophosphatasia; max = maximum; min = minimum; n = number of patients; O_2 = oxygen; PPi = inorganic pyrophosphate; PLP = pyridoxal-5'-phosphate; RSS = Rickets Severity Scale; SD = standard deviation
Notes:
[a]Respiratory compromise was defined as respiratory signs/symptoms that required institution of respiratory support measure(s), required medication(s) for management of symptom(s), and/or were associated with other respiratory complications (e.g., pneumonia, respiratory tract infection).
[b]Normal range for ALP activity, per ARUP Laboratories (University of Utah, Salt Lake City, UT), varies by age: 0–30 days: 60–320 U/L; 1–11 months: 70–350 U/L; 1–3 years: 125–320 U/L; 4–6 years: 150–370 U/L. Normal range also varies by sex in patients older than 10 years of age.
[c]Median (min, max) concentration for patients receiving vitamin B6 supplementation before dosing was 9,960 (65, 24,600) ng/ml and for those patients not receiving vitamin B6 supplementation before dosing was 417 (48, 13,100) ng/ml.

4.2.1.3.2 Efficacy results

Overall survival - By the end of the study, nine (13%) of the 69 patients enrolled in the study had died. Among all 69 patients, the Kaplan–Meier (KM) estimate of the OS rate at Year 6 was 80% (see Figure 4.1).

The OS data from this trial has been pooled with those from ENB-002-08/ENB-003-08 and discussed in Section 4.3 of this report.

Figure 4.1: ENB-010-10 Kaplan–Meier plot of overall survival – full analysis set

Figure 20 of CS[10]
CS = company submission; OS = overall survival
Note: Patients on respiratory support at baseline are excluded from the analysis, and patients without events are censored at the latest ventilator status assessment.

Ventilator-free survival - This analysis assessed the occurrence of death, CPAP, BPAP and invasive mechanical ventilation via intubation or tracheostomy. Thirty-eight of the 45 patients (84%) who were not receiving respiratory support at baseline remained ventilator-free. The KM estimate of the VFS rate at Year 6 for these patients was 84% (see Figure 4.2).

The VFS data from this trial has been pooled with those from ENB-002-08/ENB-003-08 and discussed in Section 4.3 of this report. See Section B.2.6.3.2.1.2 of the CS[10] for more information on the occurrence of death or mechanical ventilation via intubation or tracheostomy.

Figure 4.2: ENB-010-10 Kaplan–Meier plot of ventilator-free survival – full analysis set

Figure 21 of CS[10]
CS = company submission
Note: Patients on respiratory support at baseline are excluded from the analysis and patients without events are censored at the latest ventilator status assessment.

Respiratory support - Overall, 24 out of 69 (35%) patients required respiratory support at baseline (including invasive mechanical ventilation, CPAP, or supplemental oxygen). Of these patients, 11 (46%) no longer required respiratory support at last assessment. Of the 45 out of 69 (65%) patients who did not require respiratory support at baseline, 38 (84%) did not require respiratory support during the entire study period and 43 (96%) did not require respiratory support at the last assessment; one patient was receiving supplemental oxygen at Year 4, and one was receiving CPAP at Month 6. Three patients developed the need for respiratory support after baseline but were weaned before last assessment (by Month 9, Year 1.5, and Year 2.5).

Growth - Z-scores reflect the number of SDs each value falls from the age-/sex-matched normal mean. Length/height and weight Z-score generally improved over 6 years of treatment, reflecting improvements in growth relative to healthy peers. Median changes from baseline in length/height Z-scores were positive from Month 6 ([min, max: to Year 6 ([min, max:]), although the median remained more than 2 SDs below the mean for healthy age-matched and sex-matched peers at all timepoints expect Year 4 and Year 5. Median changes from baseline in weight Z-scores were positive from Month 6 ([min, max: to Year 6 ([min, max:]), and Z-scores increased to within two SDs of the mean for healthy age-matched and sex-matched peers from Year 2 to Year 6.

Motor function/functional assessments - Motor and cognitive development were assessed using three different tests, depending on the age of the patient - BSID-III in patients up to 42 months of age, the Locomotion subtest of the PDMS-2 in patients aged 43–71 months, and the BOT-2 Running Speed and Agility and Strength subtest in patients 72 months of age or older.

The BSID was administered to patients. Of these patients, had two or more assessments on at least one of the subscales. At baseline, mean (SD) scaled scores on the fine motor ( ]), gross motor]) and cognitive ( ]) subtests were at least one SD below the normal mean; this indicates that there were delays/impairments in the patients' abilities to perform fine motor, gross motor and cognitive tasks relative to healthy, age-matched peers. most patients with two or more assessments showed) in age-equivalent scores on at least one of the subtests: gross motor (fine motor ( ) or cognitive (

The PDMS-2 was administered to patients. Of these patients, had two or more assessments on the Locomotion subtest of the PDMS-2, an assessment of gross motor skills. At baseline, the mean (SD) standard score on the Locomotion subtest ( ]) was more than one SD below the normal mean, indicating impaired functioning. Median Locomotion standard scores improved from (min, max:) at baseline to (min, max:) at last overall assessment. Locomotion standard scores increased slightly in patients with scaled scores on two or more assessments. . Consistent with this, Locomotion age-equivalent scores in all patients with two or more assessments (%), .

Serial administrations of the BOT-2, which measures motor skills in individuals from four through 21 years of age, were performed in patients. All patients had also been tested with and shown improvements on the BSID-III and/or PDMS-2 prior to being transitioned to BOT-2, indicating functional improvement over time with AA treatment. Using the Running Speed and Agility subtest, regardless of their score at first assessment, patients (showed in age-equivalent scores from first to last assessment, . In addition, patients (%) showed in scaled scores, . Using the Strength subtest, regardless of their score at first assessment, patients (%) showed in age-equivalent scores from first to last assessment, , and patients (showed in scaled scores, .

Radiographic Global Impression of Change, and Rickets Severity Score - Radiographs were used as the basis to assess changes in RGI-C over time. Comparisons were made by three independent paediatric radiologists (qualified by training and experience). The proportion of patients classified as responders (RGI-C score ≥ +2) increased during the study, from 36% (24 out of 66 patients) at Month 3 to 73% (49 out of 67 patients) at last assessment. These long-term data demonstrate that treatment with AA results in sustainable and progressive improvements in skeletal manifestations over time. Radiographs of the wrists and knees from each timepoint were also evaluated for severity of rickets using the RSS. Consistent with RGI-C scores, significant (p = <0.05) improvements in RSS were observed as early as Month 3 (median change from baseline -1.0 [min, max: -8.0, 7.0]; p <0.05) and were sustained over 5 years of treatment (median -2.3 [min, max: -8.5, -1.0; p <0.05). These long-term data suggest ongoing improvements in rickets with long-term AA therapy.

4.2.1.3.3 Safety results

Table 4.11 details AEs data from the ENB-010-10 trial. A total of 3,052 TEAEs was observed over 5 years of treatment with AA; all 69 patients had at least one TEAE. Most TEAEs were mild (2,125 out of 3,052 [70%]) or moderate (728/3,052 [24%]) in severity. Most TEAEs were assessed by the investigator as unrelated to the study drug (2,409 out of 3,052 [79%]) and most related events were ISRs (593 out of 643 [92%]) and IARs (11 out of 643 [2%]), which occurred in 43 and six patients, respectively.

A total of 297 SAEs were reported in 50 (72%) patients. Of these, 286 (96%) were assessed by the investigator as unlikely to be related to or unrelated to the study drug. Of the 11 SAEs considered to be related to treatment, seven were ISRs or IARs in three patients. The remaining four occurred in three patients: craniosynostosis (n=1), pneumonia resulting in study drug withdrawal (n=1) and Arnold-Chiari type 1 malformation and syringomyelia (n=1).

Nine (13%) patients died during the study. Causes of death included: pneumonia (n=3); respiratory failure and cerebral death (n=1); HPP-related complications (n=1); severe respiratory failure (n=1); cardiopulmonary arrest (n=1); severe cardiopulmonary insufficiency (n=1); and trans tentorial and cerebellar tonsillar herniation as a result of cerebral oedema related to severe HPP (n=1).

Table 98 in Appendix M.4[50] details the most common TEAEs occurring in ≥10% of patients, regardless of the relationship to the study drug over 5 years of treatment with AA.

Table 4.11: Summary of all TEAEs over 5 years of treatment with AA - ENB-010-10, safety set

Adverse event categories	**AA (N = 69)**	
	Events, n	**Patients, n (%)[b]**
Patients with events	3052	69 (100.0)
Adverse events (AEs)[a]	3052	69 (100.0)
Not related AEs	2049	69 (100.0)
Related AEs[c]	643	49 (71.0)
ISRs[d]	593	43 (62.3)
IARs[e]	11	6 (8.7)
Mild	2125	68 (98.60
Moderate	728	64 (92.8)
Severe	[redacted]	[redacted]

Adverse event categories	AA (N = 69)	
	Events, n	Patients, n (%)[b]
AEs leading to withdrawal	[redacted]	[redacted]
AEs of special interest		
ISRs	[redacted]	[redacted]
Hypersensitivity IARs	[redacted]	[redacted]
Ectopic calcifications	[redacted]	[redacted]
Lipodystrophy	[redacted]	5 (7.2)
Craniosynostosis	46	28 (40.6)
Chronic hepatitis	22	13 (18.8)
Serious adverse events	297	50 (72.5)
Not related SAEs	286	47 (68.1)
Related SAEs	11	6 (8.7)
ISRs[d]	[redacted]	[redacted]
IARs[e]	[redacted]	[redacted]
Mild	[redacted]	[redacted]
Moderate	[redacted]	[redacted]
Severe	[redacted]	[redacted]
SAEs leading to withdrawal	[redacted]	[redacted]
Deaths	-	9 (13.0)

Table 97 of Appendix M[50]
AA = asfotase alfa; AE = adverse event; IAR = injection associated reaction; ISR = injection site reaction; SAE = serious adverse event; TEAE = treatment-emergent adverse event
Notes:
[a]TEAEs are events starting on or after the first dose of study drug
[b]Patient percentages are based on the total number of patients in the treatment group column (n=69)
[c]Related AEs are defined as possible, probable, or definitely related. Unrelated AEs are defined as not related or unlikely related
[d]ISRs include all AEs marked on the case report form as being ISRs. Additionally, all unique combinations of coded terms and verbatim text were reviewed by medical staff to flag additional events that may be ISRs
[e]All unique combinations of coded terms and verbatim text from AEs were reviewed by medical staff to flag events that may be IARs. Those terms that were marked as being related by the recording clinician were considered IARs.

EAG comment: The EAG notes that, although it appears that all participants received the recommended dose, either 1 mg/kg, 6 times per week, or 2 mg/kg, 3 times per week,[6] the EAG could find no details of the actual doses received by individual patients. In addition, the choice of dosing regimen was 'at the investigators' discretion' and it is unclear whether clinical efficacy and safety results may vary between different dosing regimens; results were not reported in relation to dose regimen received. The EAG further notes that the results of this study are for a subgroup of the population specified in the decision only (i.e., perinatal/infantile-onset HPP).

4.2.1.4 Clinical trials: ENB-006-09/ENB-008-10

All patients included in this study were aged ≥5 and ≤12 years and must, therefore, meet the definition of paediatric-onset (age <18 years at symptom onset) HPP.

Thirteen patients were randomised to AA treatment in ENB-006-09 at a dose of either 2 mg/kg 3 times per week (n=6) or 3 mg/kg 3 times per week (n=7). Sixteen historical control patients, selected from a natural history database of patients with HPP, were also included.

A total of 12 AA-treated patients completed the 24-week treatment period in ENB-006-09. All 12 patients that completed ENB-006-09 subsequently enrolled in ENB-008-10 and completed that study.

Long term outcome results have been presented in this Section (last patient visit: [redacted]; extension up to 7 years) (see Table 4.4 for more information on study methodology).

4.2.1.4.1 Patient characteristics

Patient demographics and baseline characteristics have been summarised in Table 4.12.

Table 4.12: ENB-006-09/ENB-008-10 baseline demographics

	Historical control patients (n=16)	**AA-treated patients (n=13)**
Age (years) at enrolment		
Mean ± SD	6.0 ± 1.8	8.8 ± 2.2
Median (min, max)	5.5 (4, 11)	8.6 (6, 12)
Sex, % (n)		
Male	69% (11)	85% (11)
Ethnicity, % (n)		
Not Hispanic or Latino	N/A	92% (12)
Race, % (n)		
White	N/A	92% (12)
Form of HPP, % (n)		
Infantile	44% (7)	38% (5)
Childhood (≥6 months to <18 years)	56% (9)	62% (8)
Age (months) at onset of HPP symptoms		
Mean ± SD	7.4 ± 9.5	10.5 ± 7.0
Median (min, max)	6.0 (0, 40)	12.0 (1, 22)
Baseline RSS (0 = normal, 10 = severe)		
Mean ± SD	1.44 ± 0.96	2.77 ± 1.33
Median (min, max)	1.0 (0.0, 3.5)	3.0 (0.5, 6.0)
Baseline plasma PPi (µM)		
Mean ± SD	N/A	5.01 ± 0.97
Median (min, max [normal range])	N/A	4.86 (3.74, 6.96 [0.75–5.71 µM])
Baseline serum PLP (ng/ml)		
Mean ± SD	323 ± 178	214 ± 127
Median (min, max [normal range])	328 (85, 726 [5.7–61.2 ng/ml])	218 (76, 527 [5.7–61.2 ng/ml])
Baseline serum calcium (mmol/l)		
Mean ± SD	2.5 ± 0.10	2.5 ± 0.10

	Historical control patients (n=16)	AA-treated patients (n=13)
Median (min, max [normal range])	2.52 (2.35, 2.78 [2.12–2.57 mmol/l])	2.50 (2.37, 2.67 [2.12–2.57 mmol/l])
HPP-related disease history, % (n)		
Unusual gait or running	N/A	100% (13)
Premature tooth loss	N/A	100% (13)
Delayed (≥15 months) walking	N/A	85% (11)
Knock knees	N/A	77% (10)
Muscle weakness	N/A	62% (8)
Elevated serum phosphorous	N/A	54% (7)
Difficulty eating/swallowing	N/A	46% (6)
Difficulty gaining weight	N/A	46% (6)
Hypermobility	N/A	46% (6)
Joint pain	N/A	46% (6)
Muscle pain	N/A	46% (6)
Abnormally shaped chest	N/A	46% (6)
Bone pain severe enough to limit activities	N/A	46% (6)
Bone pain severe enough to require medication	N/A	39% (5)
Bowing of legs	N/A	39% (5)

Table 59 of Appendix M[50]
AA = asfotase alfa; HPP = hypophosphatasia; max = maximum; min = minimum; N/A = not available; PLP = pyridoxal-5′ phosphate; PPi = inorganic pyrophosphate; RSS = Rickets Severity Score; SD = standard deviation

4.2.1.4.2 Efficacy results

Result tables and figures for trial efficacy outcomes reported in the submission including growth, mobility assessments, motor/functional assessments, pain and disability assessments, and RGI-C and RSS scores over 7 years of treatment, can be found in Sections B.2.6.3.3.1. to B.2.6.3.3.5. of the CS[10], and Appendix M.3.1.3.[50]

Growth - Median Z-scores for length/height and weight showed sustained improvements in growth in the treated patients from Month 6 until Year 7, although both remained more than two SDs below the mean for healthy age-matched and sex-matched peers at all timepoints. The median increase from baseline in length/height Z-score was statistically significant (p = <0.01) at Year 2 (median -0.78 [min, max: -6.4, 0.0) and then from Year 4 (median -0.74 [min, max: -5.9, 0.2) through Year 7 (median -0.69 [min, max: -5.4, 0.4). The median increase from baseline in weight Z-score was statistically significant (p <0.01) from Month 6 (median -0.71 [min, max: -7.7, 1.8) until Year 7 (median -0.15 [min, max: -5.4, 2.7) (See Table 21 of CS[10]).

Mobility assessments - All 13 patients attempted the 6MWT at baseline, and 11 patients completed the 6MWT at Year 7. Improvements in ambulation were rapid and reflected significant increases in both absolute (p = <0.0001) and percent of predicted (p = ≤ 0.001). The median distance walked increased from [redacted] metres (min, max [redacted]) at baseline to [redacted] metres (min, max [redacted]) after 7 years of treatment, which is higher than the MCID of 25 metres. In addition, median percent of predicted

increased significantly from 61% at baseline to 85% at Month 6 and was sustained at over 80% at all visits to Year 7, which is higher than the MCID of 10% improvement. These suggest a normalisation of ambulatory capacity independent of changes in age and height.

Motor function/ functional assessments - The BOT-2 Running Speed and Agility and Strength subtest was used to assess motor skills in patients 72 months of age or older. All 13 patients completed the BOT-2 at baseline, and 11 patients completed the BOT-2 at Year 7. Median composite standard scores for BOT-2 strength and agility significantly improved from 28 (min, max: 20.0, 37.0) at baseline to 37 (min, max: 28.0, 52.0) at Month 6 and remained significantly improved at all timepoints ($p = \leq 0.0002$) through 7 years. Median values were sustained within the normal reference range for healthy peers at all visits from one (median: 41 [min, max: 21.0, 48.0]) through 7 years (median: 51 [min, max: 34.0, 62.0]). As observed for the 6MWT and BOT-2 assessments, there was an early normalisation (6–12 months of treatment with AA) of mobility that was sustained over the 7 years of the study duration.

Pain and disability assessments - The Child Health Assessment Questionnaire (CHAQ), Pediatric Outcomes Data Collection Instrument (PODCI) and Pediatric Orthopaedic Society of North America (POSNA) were administered to assess post-treatment changes in parent-reported disability and pain.

Median CHAQ-DI score at baseline indicated some disability in these patients (See Figure 55, Appendix M.3.1.4.[50]). The change in median CHAQ-DI score from baseline was statistically significant following AA treatment at every assessment from Month 1 through Year 7, with achievement of a median score of zero (no disability detectable by CHAQ) at 2 years. Median CHAQ-DI score was maintained at zero through 7 years of treatment. Differences from baseline for the CHAQ were also [redacted]. Similarly, the mean CHAQ pain score decreased from [redacted] at baseline [redacted] at [redacted]), with significant decreases in the mean pain score for patients in the combined group at most assessments during the extension study.

For PODCI, [redacted]

Radiographic Global Impression of Change and Rickets Severity Score- Significant improvements in RGI-C scores were observed as early as Month 3 ([redacted]) and were sustained over 7 years of treatment ([redacted]). The proportion of patients classified as responders (RGI-C score ≥ +2) increased during the study, from [redacted] patients) at Month 3 to [redacted] ([redacted] patients) at Year 7. Improvements in RSS were observed as early as Month 6 (median RSS: 0.75 [min, max: 0, 4.5]) and were sustained over 7 years of treatment (median RSS: 0 [min, max: 0, 1.0). These long-term data suggest ongoing improvements in rickets with long-term AA therapy.

EAG comment: The EAG notes that 7/13 (53.8%) of participants in this study received an AA dose of 3 mg/kg, 3 times per week (higher than the recommended dose), during the first 24 weeks of the study,[47] and that clinical efficacy and safety data were not reported in relation to dose received. Although all patients (in the extension study) subsequently received 6 mg/kg/week (the recommended dose), the effects of AA are reported across the whole treatment period and the variation in dose during the first 24 weeks may, therefore, limit the applicability of the results of this study to UK clinical practice.

4.2.1.4.3 Subgroup results

Subgroup analyses were performed according to three disease subgroups:

- Infantile-onset is defined here as onset of HPP signs/symptoms <6 months of age (may include in utero onset)

- Juvenile-onset (or childhood-onset HPP) is defined as onset of HPP signs/symptoms ≥6 months to <18 years
- Adolescent, defined as patients who turned age 13–17 years at any time on study

See Sections E.2.1 to E.2.5 of Appendix E[50] for full results. The subgroup results for infantile- and juvenile-onset HPP have been summarised in this section.

Growth - As expected for children, mean and median height, and mean and median weight [redacted] over the course of these studies for both patient subgroups (see Table 23 of Appendix E[50]). Mean and median changes from baseline in Z-scores for both height and weight also became [redacted], reflecting [redacted] in growth relative to healthy, same-aged peers.

Mobility assessments - A statistically significant [redacted] from baseline in distance walked (in metres) was observed for the infantile-onset subgroup as early as [redacted] using the 6MWT. Improvements in distance walked for the juvenile-onset subgroup was [redacted] from baseline for [redacted], as were percentage predicted values (i.e., obtained values were expressed as a percentage of those observed in sex, age and height-matched healthy children) (see Table 24 of Appendix E[50]).

Motor function/ functional assessments - A significant [redacted] from baseline in the mean Strength and Agility Composite Standard score from the BOT-2 test was observed for the infantile-onset subgroup at [redacted]; Table 26 of Appendix E[50]). In a similar way to the findings for the full analysis set, the [redacted] in the mean from baseline in Strength and Agility Composite Standard scores for the juvenile-onset was statistically significant at [redacted].

Pain and disability assessments - The mean changes from baseline for the CHAQ-disability index (CHAQ-DI) and the CHAQ pain score were [redacted] statistically significant for the infantile subgroup, although [redacted] in both scores were observed (see Table 26 of Appendix E[50]). For the juvenile-onset subgroup, statistically significant [redacted] were observed following AA treatment at most time points, from [redacted]. A similar [redacted] was observed in the CHAQ pain score for this subgroup, with statistically significant [redacted]

RGI-C over time - A similar [redacted] was observed in the CHAQ pain score for this subgroup, with statistically significant [redacted] (see Table 27 of Appendix E[50]). [redacted] infantile-onset patients were considered [redacted] patients in this subgroup considered [redacted].

4.2.1.4.4 Safety results

Table 4.13 details AEs data from the ENB-006-09/ENB-008-10 trial for the randomised treatment group (2 mg/kg and 3 mg/kg) and the combined dose group over 7 years of treatment with AA.

No patients discontinued treatment because of an AE and no SAEs or deaths were reported. See Section B.2.10.4 of the CS for more information.[10],

Table 100 in Appendix M.4[50] summarises the most common TEAEs occurring in ≥20% of patients, regardless of the relationship to the study drug over 7 years of treatment with AA. The most common TEAEs were generally related to ISRs and included erythema (85%), macule (69%), hypertrophy (62%) and pruritus (54%). Other common TEAEs included upper respiratory tract infection ([redacted]), procedural pain ([redacted]) and arthralgia ([redacted]).

Table 4.13: Summary of all TEAEs - ENB-006-09/ENB-008-10, safety set

	AA 2 mg/kg (n=6)		AA 3 mg/kg (n=7)		AA combined[a] (n=13)	
	Events, n	Patients, n (%)	Events, n	Patients, n (%)	Events, n	Patients, n (%)
AEs	[redacted]	6 (100.0)	[redacted]	7 (100.0)	[redacted]	13 (100.0)
Not related AEs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Related AEs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mild	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Moderate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Severe	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
AEs leading to discontinuation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ISRs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hypersensitivity IARs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ectopic calcification	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lipodystrophy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Craniosynostosis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Chronic hepatitis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SAEs	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)
Deaths	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)
Discontinuations due to AEs	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)

Table 99 of Appendix M[50]
AA = asfotase alfa; AE = adverse event; CSR = clinical study report; IAR = injection-associated reaction; ISR = infusion site reaction; SAE = serious adverse event; TEAEs = treatment-emergent adverse events
Notes: Percentages are based on the total number of patients in the treatment group column.
[a]All patients received their randomised dose for 24 weeks (Study ENB-00609), followed by dosing for most patients at 6 mg/kg per week for the majority of the extension study (Study ENB-008-10).

EAG comment: The EAG notes that no subgroup analyses, for the subgroups specified in the decision problem (infantile- and juvenile-onset HPP) were presented for safety results.

4.2.1.5 Clinical trials: ENB-009-10

Nineteen patients were randomised to receive AA treatment and all 19 (100.0%) patients were included in the safety set. During the primary treatment period (PTP), all patients received their randomised treatment (or were untreated controls) according to the randomisation schedule. In the extension treatment period (ETP), all patients received treatment with AA. Five patients (26.3%) discontinued from the study; three due to withdrawn consent, one due to non-compliance at Week 264 and another at Week 264 following two moderate SAEs.

All the patients originally randomised to AA (n=13) during the PTP received at least 96 weeks of exposure to AA. Of the six patients originally assigned to the control group during the PTP, all received at least 96 weeks of exposure to AA during the ETP, five received at least 192 weeks of exposure to AA during the ETP (one patient withdrew after 96 weeks of exposure), and four patients received 240 weeks of exposure (one patient was withdrawn due to noncompliance).

Long term outcome results have been presented in this Section (last patient visit: [redacted]; extension up to 5 years) (see Table 4.4 for more information on study methodology).

4.2.1.5.1 Patient characteristics

This study included adult and adolescent patients, aged 13 to 65 years. Patient demographics and baseline characteristics have been summarised in Table 4.14.

Table 4.14: ENB-009-10 baseline demographics and HPP-specific medical history[a]

	Total cohort (n=19)[b]	**Primary treatment period group assignment**	
		Control group (n=6)	**Treatment group[c] (n=13)**
Demographics			
Age at enrolment, years (range)	53 (13, 66)	21 (13, 58)	55 (14, 66)
Adults (age ≥18 years), n (%)	13 (68)	3 (50)	10 (77)
Adolescents (age 13–<18 years), n (%)	6 (32)	3 (50)	3 (23)
Age at HPP sign/symptom onset, years	2.0 (0, 36)	0.9 (0.2, 4)	2.0 (0, 36)
Adults (age ≥18 years)	3.0 (0.1, 36)	3.0 (0.8, 4)	2.5 (0.1, 36)
Adolescents (age 13–<18 years)	0.3 (0, 1)	0.5 (0.2, 1)	0.2 (0, 0.5)
≥18 years, n (%)	1 (5)	0 (0)	1 (8)
<18 years, n (%)	18 (95)	6 (100)	12 (92)
Female, n (%)	12 (63)	2 (33)	10 (77)
Race, White, n (%)	18 (95)	5 (83)	13 (100)
HPP-specific medical history			
Baseline serum ALP, U/L[d]	18.0 (18, 45)	23.5 (18, 45)	18.0 (18, 35)
Baseline plasma PLP, ng/ml[e]	267.0 (29, 1590)	237.0 (106, 906)	267.0 (29, 1590)
Baseline plasma PPi, µM[f]	5.2 (2.2, 12.1)	6.2 (4.2, 12.1)	5.1 (2.2, 8.2)
Patients with fractures, n (%)	18 (95)	6 (100)	12 (92)
Pseudo fractures, n (%)	12 (63)	5 (83)	7 (54)
Non-healing fractures, n (%)	6 (32)	1 (17)	5 (39)
Number of fractures	6 (1, 30)	5 (1, 8)	9.5 (1, 30)
Bone pain severity, n (%)			
Limits activity	18 (95)	5 (83)	13 (100)
Requires analgesics	16 (84)	5 (83)	11 (85)
Muscle complaints, n (%)			
Weakness	17 (90)	5 (83)	12 (92)
Pain	14 (74)	4 (67)	10 (77)
Joint complaints, n (%)			
Pain	17 (90)	5 (83)	12 (92)
Swelling	7 (37)	2 (33)	5 (39)
Unusual gait or walk/run, n (%)	15 (79)	4 (67)	11 (85)

	Total cohort (n=19)[b]	Primary treatment period group assignment	
		Control group (n=6)	Treatment group[c] (n=13)
Assistive devices (≥1) used at screening, n (%)	12 (63)	4 (67)	8 (62)
Craniosynostosis, n (%)	3 (16)	0	3 (23)
Premature loss of deciduous teeth, n (%)	16 (84)	5 (83)	11 (85)
Loss of adult teeth, n (%)	8 (42)	1 (17)	7 (54)
Number of adult teeth remaining	24 (0, 30)	26 (0, 28)	23 (0, 30)
Hypercalcaemia, n (%)	6 (32)	3 (50)	3 (23)
Hyperphosphataemia, n (%)	6 (32)	2 (33)	4 (31)
Gout, n (%)	5 (26)	2 (33)	3 (23)
Kidney stones[g] n (%)	4 (21)	2 (33)	2 (15)

Table 62 of Appendix M[50]
AA = asfotase alfa; ALP = alkaline phosphatase; HPP = hypophosphatasia; max = maximum; min = minimum; PLP = pyridoxal 5′-phosphate; PPi = inorganic pyrophosphate
Notes:
[a]Values presented medians (min, max) unless noted otherwise.
[b]Combined because all patients were treated in the extension phase.
[c]AA groups combined for analysis.
[d]Normal ALP ranges by age and sex per Covance, Inc.: males 10–<15 years (95–385 U/L), 15–<18 years (50–250 U/L), 18–<50 years (31–129 UL), 50–<60 years (35–131 U/L) and 60–<70 years (35–125 U/L); females 10–<15 years (51–300 U/L), 15–<18 years (31–110 U/L), 18–<50 years (31–106 U/L) and 50–<70 years (35–123 U/L).
[e]Normal PLP ranges by age category per Biotrial Bioanalytical Services: 5–18 years (5.7–61.2 ng/ml) and >18 years (2.8–26.7 ng/ml)
[f]Normal PPi ranges by age category per Charles River Laboratories: 13–18 years (<0.8–4.8 μM) and >18 years (1.0–5.8 μM)
[g]As reported in the patient's medical history

EAG comment: The EAG notes that participants in this study have not been grouped using age of symptom onset (perinatal, infantile, juvenile and adult-onset) categories, as defined for the population in the NICE scope and used in the Alexion clinical trials programme. The company were asked to provide the numbers of patients in each of perinatal, infantile, juvenile and adult-onset categories for all studies including the UK MAA and the Global HPP Registry (ALX-HPP-501);[40] these data were provided (see Section 3.3.1 of this report). The company were also asked to provide results grouped by these categories;[40] results, by age of onset category, were not provided (see Section 3.3.4 of this report).

The adolescent (age <18 years) patients in this study must meet the criteria for paediatric-onset (age <18 years at symptom onset) HPP. Based on the information provided in the CS, the EAG considered the results for the subgroup of adolescent patients, form this study, to be most relevant to the DP, since the age of symptom onset was not reported for adult study participants. The efficacy results for subgroup of adolescent patients, but not those for the overall population and adult subgroup, are summarised below. – The company provided additional information, in their Factual Accuracy Check, stating that 12 of the 13 adults in this study had paediatric-onset HPP. The ERG, therefore, accepts that results for the whole population of this study (presented in the CS) are relevant to the DP.

The EAG also notes that patients in this study were initially randomised to receive AA 0.3 mg/kg per day, AA 0.5 mg/kg per day or no AA for 24 weeks. During the 72 week extension phase, all participants (including previously un-treated controls) received 0.5 mg/kg per day for approximately 24 to 48 weeks and the dose was then increased to 1 mg/kg, 6 times per week (the recommended dose).[48] All patients in this study were included in the analyses for the efficacy and safety of AA, however, all patients received a dose which was lower than the recommended dose for the first 48 to 72 weeks of the study; the EAG considers that this may limit the applicability of the results of this study to UK clinical practice.

4.2.1.5.2 Efficacy results

Result tables and figures for trial efficacy outcomes reported in the submission including growth, mobility assessments (6MWT and use of mobility aids), motor/functional assessments, pain and disability assessments, and changes in PPi and PLP levels from baseline through Year 5 of treatment exposure, can be found in Sections B.2.6.3.4.1. to B.2.6.3.4.5. of the CS[10], and Appendix M.3.1.4.[50]

Growth - Growth was measured over time during the PTP and ETP for adolescent patients in the full analysis set. A total of [redacted] adolescent patients were evaluable for growth ([redacted] randomised to receive AA and [redacted] randomised to the untreated control group). The adolescent patients in the AA combined group showed [redacted]. Patients originally randomised to the control group also showed [redacted].

Mobility assessments - All 19 patients attempted the 6MWT at baseline, and 13 patients completed the 6MWT at Year 5. The median distance walked increased from 355 metres (min, max 10, 620; n=19) at baseline to 450 metres (min, max 280, 707; n=13) after 5 years of treatment, which is higher than the MCID of 25 metres. The increase from baseline was statistically significant at Month 6 and at Years 1, 2 and 3 (p = <0.05). The median percent of predicted was below normal (<84%) at baseline (76%; n=15) but improved to within the normal range after 6 months of treatment (85%; n=16) and was sustained at 88% (n=11) after 5 years of treatment, which is higher than the MCID of 10% improvement. The increase from baseline was statistically significant at Month 6 and Years 1, 2, 3, 4 and 5 (p = <0.05).

Use of assistive ambulatory devices was reported for five of the 19 patients who attempted the 6MWT at baseline (two in the control group, two in the AA 0.3 mg/kg per day group and one in the AA 0.5 mg/kg per day group) (see Section B.2.6.3.4.2.2. of the CS[10] for further narrative on the five patients).

Motor function/ functional assessments - The BOT-2 Running Speed and Agility and Strength subtest was used to assess motor skills in patients 72 months of age or older. From baseline to Month 6 concluding the PTP, median total (min, max) scores on the BOT-2 Running Speed and Agility subtest increased by 3 points (min, max: -1.0, 12.0) in the combined AA group (n=11), indicating better performance, and decreased by 0.5 points (min, max: -1.0, 0.0) in the control group (n=2). The median total scores on the Strength subtest increased by 2 points (min, max: -2.0, 8.0) in the AA group and by 4 points (min, max: 1.0, 7.0) in the control group. After 5 years of treatment with AA, the median changes from baseline were 4 points (min, max: -5.0, 18.0) in total Running Speed and Agility score (n=11) and 3.5 (min, max: -9.0, 9.0) points in total Strength score (n=12), indicating improvement.

At baseline, 18 patients completed the Lower Extremity Functional Scale (LEFS) and 15 completed it at Year 5. Overall, 14 of 18 patients (78%) with baseline data had improvements in LEFS scores at the last assessment, whereas four (22%) had either no change or decreased scores. For eight of these 18 patients, the changes represented clinically meaningful improvements (≥9-point increase) at the last assessment.

Pain and disability assessments - At baseline, the median (min, max) BPI-SF total pain severity score was [redacted] (min, max[redacted]) in all patients included in the ETP (n=19). The BPI-SF scores improved

over the ETP, with a median (min, max) decline from baseline of -1.0 (min, max: -21.0, 8.0) at Year 1 and -3.5 (min, max: -20.0, 5.0) up to 5 years of treatment.

Changes in inorganic pyrophosphate (PPi) and pyridoxal 5'-phosphate (PLP) levels from baseline through Year 5 of treatment exposure - When analysing the within-patient data for all patients who were treated during the ETP (n=19), significant (p = <0.05) reductions from baseline in plasma PLP concentrations were observed at 6 months (mean [95% CI] change from baseline: -318.4 [-521.6, -115.2]) of treatment and maintained through 5 years (mean [95% CI] change from baseline: -427.3 [-666.6, -188.0]) of treatment. In addition, significant (p = <0.05) reductions from baseline in plasma PPi concentrations were observed at 6 months (mean [95% CI] change from baseline: -2.0 [-2.5, -1.4]) of treatment and maintained through 5 years (mean [95% CI] change from baseline: -2.4 [-4.0, -0.7]) of treatment.

4.2.1.5.3 Subgroup results

The patient population was divided by age (patients ≥18 years versus <18 years) to assess the effects of AA on adult (n=13) and adolescent (n=6) patients with HPP, respectively. See Sections E.3.1 to E.3.3 of Appendix E[50] for full results. Results for the adolescent subgroup have been summarised in this section.

Growth - The adolescent combined group showed [redacted] in height and weight that were sustained in the ETP (Table 4.15). However, due to the limited number of patients and measurements over time, the clinical significance of these findings is unknown.

Table 4.15: ENB-009-10 growth in adolescent patients over 3 years of treatment

Endpoint/ parameter	Baseline	6 months	Year 1	Year 2	Year 3
Length/height Z-scores					
n	6	6	6	4	2
Mean (SD)	-3.1 (2.24)	-2.9 (2.07)	-2.7 (1.81)	-3.5 (1.99)	-4.5 (2.14)
Median (min, max)	-2.8 (-6.0, 0.0)	-2.8 (-5.0, 0.0)	-2.8 (-5.0, 0.0)	-3.3 (-6.0, -1.0)	-4.5 (-6.0, -3.0)
Weight Z-scores					
n	6	6	6	4	2
Mean (SD)	-1.4 (2.21)	-1.7 (2.92)	-1.8 (2.86)	-3.0 (4.11)	-4.3 (5.83)
Median (min, max)	-0.6 (-5.0, 0.0)	-0.8 (-7.0, 0.0)	-0.6 (-7.0, 0.0)	-1.9 (-9.0, 0.0)	-4.3 (-8.0, 0.0)
Based on Table 28 of Appendix E[50] AA = asfotase alfa; min = minimum; max = maximum; SD = standard deviation					

Mobility assessments- In the ETP, the combined adolescent group showed [redacted] up to [redacted] of exposure to treatment, with a median improvement of [redacted] metres [redacted]) (Table 4.16).

Table 4.16: ENB-009-10 6MWT distance walked and percent predicted over 5 years of treatment in adolescent patients

Endpoint/parameter	Baseline	6 months	Year 1	Year 2	Year 3	Year 4	Year 5
6MWT distance walked							
n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Endpoint/parameter	Baseline	6 months	Year 1	Year 2	Year 3	Year 4	Year 5
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median (min, max)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
6MWT percent predicted							
n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median (min, max)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Based on Table 29 of Appendix E[50] 6MWT = 6-minute walk test; min = minimum; max = maximum; SD = standard deviation							

Motor functional assessments - In the ETP, all changes from baseline in the combined adolescent group show [redacted] for running speed and agility, and [redacted] for strength using BOT-2 (Table 4.16). [redacted] The direction of the effect of AA on LEFS consistently [redacted] compared with baseline at each time point in adolescent patients (see Table 31 in Appendix E of the CS[50]).

Table 4.17: ENB-009-10 BOT-2 running speed and agility and strength scores over 5 years of treatment in adolescent patients

Endpoint/ parameter	Baseline	6 months	Year 1	Year 2	Year 3	Year 4	Year 5
BOT-2 running speed and agility total score							
n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median (min, max)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BOT-2 strength total score							
n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median (min, max)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Based on Table 30 of Appendix E[50] BOT-2 = Bruininks-Oseretsky Test of Motor Proficiency Edition 2; min = minimum; max = maximum; SD = standard deviation							

4.2.1.5.4 Safety results

Table 4.18 details AEs data from the ENB-009-10 trial. All 19 patients experienced a TEAE and there were 1,145 AEs during the study, the majority of which were mild (864 out of 1,145, 75.4%) and not related to the study drug (731 out of 1,145, 63.8%).

The most common TEAEs were ISRs (385 out of 1,145 [34%]), which occurred in all patients. Two patients experienced TEAEs categorised as hypersensitivity IARs, one patient experienced oral hypoesthesia and chills and one patient had an anaphylactoid reaction; each was considered moderate in intensity. The patient who had the anaphylactoid reaction withdrew from the study; [redacted]

No patients died during the study. Overall, 29 treatment-emergent SAEs were reported for nine patients following cumulative exposure to the study drug; the majority of events were moderate in intensity ([redacted]

Table 102 of Appendix M.4[50] details the most common TEAEs occurring in ≥20% of patients. The most common TEAEs were ISRs (385 out of 1,145 [34%]), which occurred in all patients. The most common

ISRs (≥5 patients) were erythema (13 [68%]), haematoma (10 [53%]), skin discoloration (nine [47%]), ISR not otherwise specified (seven [37%]), pain (six [32%]), atrophy (five [26%]), and pruritus (five [26%]). Other common TEAEs included arthralgia (13 [68%]), pain in the extremity (12 [63%]) and back pain (10 [53%]).

Table 4.18: Summary of all TEAEs over 5 years of treatment - ENB-009-10, safety set

Adverse event categories	**AA (N=19)**	
	Events, n	**Patients, n (%)**
Patients with events	1145	19 (100.0)
Adverse events (AEs)	1145	19 (100.0)
Not related AEs	[redacted]	[redacted]
Related AEs	[redacted]	[redacted]
Mild	864	[redacted]
Moderate	229	[redacted]
Severe	52	[redacted]
AEs leading to withdrawal	2	[redacted]
ISRs	385	19 (100.0)
IARs	[redacted]	[redacted]
Ectopic calcifications	[redacted]	[redacted]
Lipodystrophy	[redacted]	[redacted]
Craniosynostosis	[redacted]	[redacted]
Chronic hepatitis	[redacted]	[redacted]
Serious adverse events (SAEs)	29	9 (47.1)
Not related SAEs	21	8 (42.1)
Related SAEs	8	2 (10.5)
Mild	[redacted]	[redacted]
Moderate	[redacted]	[redacted]
Severe	[redacted]	[redacted]
SAEs leading to withdrawal	[redacted]	[redacted]
ISRs	[redacted]	[redacted]
IARs	[redacted]	[redacted]
Ectopic calcifications	[redacted]	[redacted]
Lipodystrophy	0	0 (0.0)
Craniosynostosis	[redacted]	[redacted]
Chronic hepatitis	[redacted]	[redacted]
Deaths	[redacted]	[redacted]

Table 101 of Appendix M[50]
AA = asfotase alfa; AE = adverse event; IAR = injection-associated reaction; ISR = injection site reaction; SAE = serious adverse event; TEAE = treatment-emergent adverse event
Notes: The TEAEs during the primary treatment period are events starting on or after the day of first dose of study drug (or randomisation for the control group). The TEAEs for the control group during the extension treatment period are events starting on or after the day of first dose of AA. Patient percentages are based on the total number of patients in each treatment group column. Related AEs are defined as possible, probable or definitely related. Unrelated AEs are defined as not related or unlikely related. All unique combinations of

Adverse event categories	AA (N=19)	
	Events, n	Patients, n (%)
coded terms and verbatim text from adverse events were reviewed by medical staff to flag events that may be IARs or ectopic calcification. Those terms that were marked related by the recording clinician were considered IARs or ectopic calcification. ISRs include all AEs marked on the CRF as being ISRs. Additionally, all unique combinations of coded terms and verbatim text were reviewed by medical staff to flag additional events that may be ISRs.		

4.2.2 Real world evidence studies of patients not treated with AA included in the submission

As reported in Section B.2 of the CS,[10] Table 4.19 provides a summary of the real world evidence studies included in the CS. The results of these studies are presented separately, by study, in the subsequent Sections 4.2.2.1 to 4.2.2.4.

EAG comment: For clarity and consistency, to allow comparison of data across sources and to facilitate the interpretation of all data against the DP specified in the scope, the company were asked to provide results tables, comparing results across all non-interventional natural history studies, including ALX-HPP-501, for each outcome measure; results should be grouped by age of onset category (perinatal-, infantile-, and juvenile-onset HPP).[40] These tables were not provided and the company stated:

'The Global HPP Registry was designed differently to the three natural history studies. The three natural history studies were designed to specifically assess the outcomes of patients with perinatal/infantile onset (ENB-011-10) and juvenile-onset HPP (ALX-HPP-502 and ALX-HPP-502s), whereas the Global HPP Registry focuses on the age of the patient and their symptoms at presentation. Within the Global HPP Registry, there are 2 distinct groups of patients based on current age < 18 years and ≥ 18 years.

In addition, some of the endpoints included in the Global HPP Registry (e.g., 6MWT, BPI-SF, PedsQL, SF-36v2) were not included in the natural history studies.

Therefore, efficacy data split by age disease onset are not available for all studies and the differences discussed above would make a comparison between the studies non-informative so summary tables have not been provided.'[9]

The EAG does not consider that this response provides sufficient justification for the inconsistent presentation of results. Where common outcomes were measured across studies, the EAG considers that the data could and should have been presented in a form which would facilitate meaningful comparison; information about the age of onset categories of patients in the Global HPP Registry and natural history studies was available and was provided by the company in their response to clarification questions (Table 3.6 and 3.7). [9]

4.2.2.1 Real world evidence: Global HPP Registry (ALX-HPP-501)

This study is currently ongoing and includes both AA-treated (ever-treated) and non-AA-treated (never-treated) patients. The Global HPP Registry was designed to collect data on HPP epidemiology, disease history, clinical course, symptoms, and burden of disease from patients of all ages who have a diagnosis of HPP and to evaluate the safety and effectiveness in patients who have/are receiving treatment with AA (see Table 4.19).

Table 4.19: Summary of clinical effectiveness evidence- Real world evidence studies

Study	Global HPP Registry (ALX-HPP-501)	EmPATHY study	Dahir et al. 2022
Study design	Multinational, multicentre, observational, prospective, long-term registry	Observational, retrospective chart review and prospective data collection, conducted at a single centre in Germany	Prospective, longitudinal telephone-based survey
Population	Patients of all ages with a confirmed diagnosis of hypophosphatasia (HPP)	Adult patients with paediatric-onset HPP, aged 19–78 years	Adult patients with paediatric-onset HPP, aged ≥18 years
Treatment duration and follow-up	Up to 4 years	Up to 2 years	Up to 6 months
Intervention(s)	Ever-treated with asfotase alfa (AA) (n=[redacted])	AA (n=21)	AA (n=[redacted])
Comparator(s)	Not applicable (N/A)	N/A	N/A
Indicate if study supports application for marketing authorisation	No	No	No
Indicate if study used in the economic model	Yes	No	No
Rationale if study not used in model	N/A	Small German real world evidence study, the United Kingdom (UK) Managed Access Agreement (MAA) and Global HPP Registry provide real-world evidence in a large number of patients more relevant to UK clinical practice.	The UK MAA and Global HPP Registry provide real world evidence in a large number of patients more relevant to UK clinical practice.
Reported outcomes specified in the decision problem	Mortality Pain	Pain	Health-related quality of life (HRQoL) (for patients and carers)

Study	Global HPP Registry (ALX-HPP-501)	EmPATHY study	Dahir et al. 2022
	Respiratory function Craniosynostosis and intracranial pressure Growth Tooth loss Cognitive development and motor skills Adverse effects of treatment HRQoL (for patients and carers)	Cognitive development and motor skills Adverse effects of treatment HRQoL (for patients and carers)	
All other reported outcomes	Mobility assessments Fractures	Mobility assessments	N/A

Based on Table 9 of CS[10]
AA = asfotase alfa; CS = company submission; HPP = hypophosphatasia; HRQoL = health-related quality of life; MAA = Managed Access Agreement; N/A = not applicable; UK = United Kingdom

4.2.2.1.1 Patient characteristics

As of the most recent analysis cut-off date ([redacted]), [redacted] patients had been enrolled in the Global HPP Registry. A total of [redacted] patients were excluded and [redacted] patients were included in the study population. Of these patients, [redacted] were <18 years of age and [redacted] were ≥18 years of age at baseline. Overall, [redacted] patients were never-treated, and [redacted] patients were ever-treated with AA. Of the ever-treated patients, [redacted] initiated treatment with AA prior to enrolment and [redacted] initiated AA on or after enrolment.

The baseline characteristics of never-treated and ever-treated patients have been summarised in Table 4.20. History of HPP has been summarised in Table 66 of Appendix M.[50]

Table 4.20: ALX-HPP-501 baseline characteristics

	Total (n=[redacted])	**Never treated (n=[redacted])**	**Ever treated (n=[redacted])**
Age at enrolment (years)			
Mean (SD)	[redacted]	[redacted]	[redacted]
Median (min, max)	[redacted]	[redacted]	[redacted]
Age at baseline (years)			
Mean (SD)	[redacted]	[redacted]	[redacted]
Median (min, max)	[redacted]	[redacted]	[redacted]
Age at last follow-up (years)			
Mean (SD)	[redacted]	[redacted]	[redacted]
Median (min, max)	[redacted]	[redacted]	[redacted]
Years from baseline to last registry follow-up			
Mean (SD)	[redacted]	[redacted]	[redacted]
Median (min, max)	[redacted]	[redacted]	[redacted]
Years from registry enrolment to last registry follow-up[a]			
Mean (SD)	[redacted]	[redacted]	[redacted]
Median (min, max)	[redacted]	[redacted]	[redacted]
Age group at enrolment, n (%)			
<18 years old	[redacted]	[redacted]	[redacted]
≥18 years old	[redacted]	[redacted]	[redacted]
HPP onset, n (%)			
n	[redacted]	[redacted]	[redacted]
Perinatal/infantile onset	[redacted]	[redacted]	[redacted]
Juvenile-onset HPP	[redacted]	[redacted]	[redacted]
Paediatric-onset HPP, specific type unknown	[redacted]	[redacted]	[redacted]
Adult-onset HPP	[redacted]	[redacted]	[redacted]

	Total (n=[redacted])	**Never treated (n=[redacted])**	**Ever treated (n=[redacted])**
Unknown	[redacted]	[redacted]	[redacted]
Sex, n (%)			
n	[redacted]	[redacted]	[redacted]
Male	[redacted]	[redacted]	[redacted]
Female	[redacted]	[redacted]	[redacted]
Ethnicity, n (%)			
n	[redacted]	[redacted]	[redacted]
Hispanic or Latino	[redacted]	[redacted]	[redacted]
Not Hispanic or Latino	[redacted]	[redacted]	[redacted]
Unknown/not reported	[redacted]	[redacted]	[redacted]
Race, n (%)			
n	[redacted]	[redacted]	[redacted]
American Indian or Alaskan native	[redacted]	[redacted]	[redacted]
Asian	[redacted]	[redacted]	[redacted]
Black or African American	[redacted]	[redacted]	[redacted]
Native Hawaiian or other Pacific Islander	[redacted]	[redacted]	[redacted]
White/Caucasian	[redacted]	[redacted]	[redacted]
Other/multiple	[redacted]	[redacted]	[redacted]
Unknown	[redacted]	[redacted]	[redacted]
Age at diagnosis of HPP (years)			
n	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]
Median (min, max)	[redacted]	[redacted]	[redacted]
Time from earliest signs/symptoms to diagnosis (years) (patients diagnosed prior to onset signs/symptoms)			
n	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]
Median (min, max)	[redacted]	[redacted]	[redacted]
Time from earliest signs/symptoms to diagnosis (years) (patients diagnosed after onset signs/symptoms)			
n	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]

	Total (n=[redacted])	**Never treated (n=[redacted])**	**Ever treated (n=[redacted])**
Statistic	Total [redacted]	Never-treated [redacted]	Ever-treated [redacted]
Median (min, max)	[redacted]	[redacted]	[redacted]
Baseline ALP, (U/L)[b]			
n	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]
Median (min, max)	[redacted]	[redacted]	[redacted]
ALP <LLN[c], n (%)	[redacted]	[redacted]	[redacted]
Patients who ever had ALP <LLN or an *ALPL* gene mutation[d], n (%)			
n	[redacted]	[redacted]	[redacted]
Yes	[redacted]	[redacted]	[redacted]
No	[redacted]	[redacted]	[redacted]

Table 65 of Appendix M[50]
ALP = alkaline phosphatase; *ALPL* = gene encoding the tissue non-specific alkaline phosphatase isoenzyme; HPP = hypophosphatasia; LLN = lower limit of normal; max = maximum; min = minimum; SD = standard deviation
Notes:
[a]Last follow-up regardless of treatment status at time of last follow-up
[b]For ever-treated patients ALP only prior and on baseline are considered. Based on current data, adults with ALP >193 U/L and children with ALP >700 U/L were identified as outliers and were excluded
[c]Lower limit of normal based on the entered range or CALIPER range
[d]Forever-treated patients ALP only prior and on baseline is considered. Based on current data, adults with ALP >193 U/L and children with ALP >700 U/L were identified as outliers and were excluded.

EAG comment: The EAG notes that although the baseline characteristics table above provides the numbers of participants in each age symptom onset category of HPP (perinatal/infantile-, juvenile- and adult-onset) categories, as defined for the population in the NICE scope and used in the Alexion clinical trials programme, efficacy and safety results were not presented by these subgroups or for the subgroup of all patients with paediatric-onset HPP; some subgroup analyses were presented for adults with paediatric-onset HPP. This makes it difficult to assess data on the efficacy and safety of AA from the Global HPP Registry (ALX-HPP-501) against the DP, as defined in the NICE scope, and to compare the results obtained from the Global HPP Registry (ALX-HPP-501) with those of the Alexion clinical trials. The company were asked to provide Global HPP Registry (ALX-HPP-501) results, AA-treated and untreated patients, by perinatal-, infantile-, juvenile- and adult-onset categories.[40] These data were not provided (see Section 3.3.4 of this report).

4.2.2.1.2 Efficacy results

Analysis results for interim data collected in the Global HPP Registry from start date [redacted] through to the most recent data cut-off date of [redacted] include respiratory support, growth, mobility assessments, pain assessments, fractures, and HRQoL assessments.

Respirator/ventilator use - Of the [redacted] patients aged <18 years at baseline with data on respirator/ventilator use[redacted] ever-treated patients and [redacted] never-treated patients had used respiratory support at any time during the study. The most frequently reported respiratory support was invasive

ventilation, which was reported in [redacted] ever-treated patients and none of the never-treated patients. Table 24 of the CS[10] presents full results for invasive ventilator use by duration of AA exposure in ever-treated patients. Of the [redacted] ever-treated patients ever on invasive ventilation, [redacted] were currently using invasive ventilation as of the patient's last reported observation. The age reported at diagnosis was <6 months for 10 patients and ≥6 months for [redacted] patient. This represents a clinically significant improvement for the patients who initially had severe respiratory compromise.

Of the [redacted] patients aged ≥18 years at baseline with historical data on respirator/ventilator use, [redacted] out of [redacted] ever-treated patients and [redacted] out of [redacted] never-treated patients had used respiratory support at any time during the study

Growth - This was analysed for patients <18 years of age at baseline. The results for median Z-scores and change from baseline for length/height and weight over 4 years of treatment have been presented in Table 25 of the CS.[10] The median change in height Z-score from baseline to the last assessment was [redacted] (min, max: [redacted]) for ever-treated patients and [redacted] (min, max: [redacted]) for never-treated patients. Median change in weight Z-score from baseline to last assessment was [redacted] (min, max: [redacted]) for ever-treated patients and [redacted] (min, max: -[redacted]) for never-treated patients.

Physical function – The MCID for 6MWT distance walked is considered 25 metres and/or a 10% improvement in distance walked from baseline. Results from baseline to last follow-up for distance walked and percent of predicted in the 6MWT has been presented in Table 26 of the CS.[10]

In patients aged <18 years, the median distance walked at baseline by ever-treated patients was [redacted] metres (min, max: [redacted] which increased by a median of [redacted] metres at last follow-up. The median distance walked by never-treated patients was [redacted] metres (min, max: [redacted]), which increased by a median of [redacted] metres at last follow-up. These results were both higher than the 25-metre MCID suggesting improvements in 6MWT.

In patients aged ≥18 years, the median distance walked at baseline by ever-treated patients was [redacted] metres (min, max: [redacted]), which increased by a median of [redacted] metres at last follow-up, suggesting an improvement in 6MWT. The median distance walked by never-treated patients was 503.0 metres (min, max: [redacted], which decreased by a median of [redacted] metres at last follow-up, indicating a reduction in walking ability.

Pain severity - In patients aged ≥18 years, self-reported pain was measured by the BPI-SF. Results have been published in Table 27 of CS.[10]

Pain severity is measured on a scale of 0 to 10, with a lower score indicating lesser pain. Data on pain severity from the BPI-SF were reported in [redacted] out of [redacted] ever-treated patients and [redacted] out of [redacted] never-treated patients at baseline and last follow-up. The median pain severity reported at baseline for ever-treated patients was [redacted] (min, max:[redacted] and decreased by a median of [redacted] at last follow-up, indicating a small improvement in pain severity during the study. For never-treated patients, the median pain severity reported at baseline was [redacted] (min, max[redacted] with [redacted] median decrease at last follow-up.

Pain interference was also measured with the BPI-SF on a scale of 0 to 10, with a lower score indicating less interference. For ever-treated patients, the median pain interference at baseline was [redacted] (min, max:[redacted] which decreased by a median of [redacted] at last follow-up. The median pain interference reported for never-treated patients at baseline [redacted] with [redacted] median decrease at last follow-up.

Fractures - Of the [redacted] patients with data, [redacted] out of [redacted] of ever-treated and [redacted] out [redacted] never-treated patients had a history of fractures/pseudo fractures at baseline (see Table 28 in CS[10]). However, the types of fractures differed between the groups. For example, femoral fractures were twice as common in ever-treated patients ([redacted] than in never-treated patients ([redacted] at baseline. After baseline, the proportion of patients with fractures decreased in both groups, with [redacted] out of [redacted] ever-treated patients and [redacted] out of [redacted] never-treated patients reported to have fractures/pseudo fractures.

HRQoL - See Sections B.2.6.4.1.6.1 to B.2.6.4.1.6.3 of the CS[10] for HRQoL assessment results using PedsQL for improvements in functioning, HAQ-DI for improvements in disability, and the SF-36, (Version 2) for improvements in QoL.

4.2.2.1.3 Subgroup results

Exploratory subgroup analyses were conducted using the ALX-HPP-501 data to characterise the treatment effects of AA in adults with paediatric-onset HPP.

As of the [redacted], [redacted] patients had been enrolled in the Global HPP Registry. Of these patients, [redacted] were ever-treated adults with paediatric-onset HPP and were included in the study population for this analysis. [redacted] patients initiated AA prior to enrolment, [redacted] initiated AA on or after enrolment and median treatment duration was [redacted] (min, max: [redacted]) years. The mean (SD) age at diagnosis was [redacted] years and [redacted] were female.

- Change from baseline in HRQoL as measured by the SF-36 (Version 2): SF-36 (Version 2) change from baseline results suggested [redacted] in physical HRQoL while on AA. See Section E.4.1 of Appendix E.[50]
- Change from baseline in self-reported pain and disability as measured by the BPI-SF and the HAQ-DI: BPI-SF results indicated improvements in pain over time while on AA, but HAQ-DI results showed [redacted] in disability over time while on AA. See Sections E.4.2 and E.4.3 of Appendix E.[50]
- Change from baseline in functional status as measured by the 6MWT: Results indicated improvements in ambulation following treatment with AA. See Section E.4.4 of Appendix E.[50]
- Occurrence of fractures/pseudo fractures and fracture location after treatment with AA: Of the [redacted] with available fracture data, [redacted] had any fractures or pseudo fractures, and the mean number of fractures per patients with fractures/pseudo fractures [redacted]. The most common types of fracture were other [redacted]

4.2.2.1.4 Safety results

As of the most recent data cut off ([redacted]), [redacted] patients aged <18 years and [redacted] patients aged ≥18 years had been exposed to AA treatment (ever-treated patients). The median age at initiation of treatment for patients aged <18 years was [redacted] years (min, max: [redacted] years), with a median of [redacted] (min, max: [redacted] years) from diagnosis to initiation of AA treatment. The median age at initiation of treatment for patients aged ≥18 years was [redacted] years (min, max: [redacted] years), with a median [redacted] years (min, max: [redacted] years) from diagnosis to initiation of AA treatment.

As of the most recent analysis cut-off date ([redacted]), targeted events and SAEs were reported for [redacted] ever-treated patients aged <18 years (see Table 21). A total of [redacted] targeted events or SAEs were reported by [redacted] ever-treated patients. The ISRs were the most frequently reported targeted events or SAEs ([redacted] out of [redacted] and a majority of these ISRs were [redacted].

As of the most recent analysis cut-off date ([redacted]), targeted events and SAEs were reported for [redacted] ever-treated patients aged ≥18 years. A total of [redacted] targeted events or SAEs were reported by [redacted]

ever-treated patients. The ISRs were the most frequently reported targeted events or SAEs ([redacted] out of [redacted] and most of these ISRs were[redacted]

Overall, a total of [redacted] deaths were reported; [redacted] deaths in patients <18 years (ever-treated) and [redacted] deaths in patients ≥18 years (never-treated). More information can be found in Section B.2.10.6 of the CS.[10]

Table 4.21: Targeted events and SAEs for ever-treated patients- ALX-HPP-501

	Total [redacted]		<18 years at baseline [redacted]		≥18 years at baseline [redacted]	
	n (%)	Events, n	n (%)	Events, n	n (%)	Events, n
Targeted events or SAEs reported	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lack of efficacy/drug effect	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Respiratory insufficiency or compromise	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pneumonia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Conductive deafness	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Craniosynostosis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ectopic calcification	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Injection-associated reaction	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Injection site reaction	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Severe hypersensitivity reaction	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Systemic immune complex-mediated reactions	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Reaction at administration	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hypocalcaemia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Effects of anti-AA antibody production	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SAEs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Not related	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Unlikely related	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Possibly related	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Probably related	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Definitely related	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Not applicable	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
General disorders and administration site conditions	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	Total [redacted]		<18 years at baseline [redacted]		≥18 years at baseline [redacted]	
	n (%)	Events, n	n (%)	Events, n	n (%)	Events, n
Drug ineffective	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Chest discomfort	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pyrexia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Congenital, familial and genetic disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Craniosynostosis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Arnold-Chiari malformation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gastrointestinal disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Abdominal pain upper	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ulcerative colitis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gastric ulcer	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gastric volvulus	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Haematochezia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hypoaesthesia oral	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Impaired gastric emptying	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Loose tooth	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Tooth loss	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Infections and infestations	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gastroenteritis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pneumonia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anal abscess	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Appendicitis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Beta haemolytic streptococcal infection	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Bronchitis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
COVID-19	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	Total [redacted]		<18 years at baseline [redacted]		≥18 years at baseline [redacted]	
	n (%)	Events, n	n (%)	Events, n	n (%)	Events, n
Device-related infection	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Exanthema subitum	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gastroenteritis viral	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lower respiratory tract infection	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Oral herpes	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Otitis media	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pneumonia bacterial	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Respiratory syncytial virus infection	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Salmonellosis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Sepsis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Tonsillitis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Urinary tract infection	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Investigations	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Oxygen saturation decreased	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Heart rate decreased	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weight decreased	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nervous system disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Brain injury	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cervical cord compression	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Encephalopathy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Epilepsy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Febrile convulsion	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Headache	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hydrocephalus	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	Total [redacted]		<18 years at baseline [redacted]		≥18 years at baseline [redacted]	
	n (%)	Events, n	n (%)	Events, n	n (%)	Events, n
Paraesthesia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pyramidal tract syndrome	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Seizure	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Status epilepticus	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Respiratory, thoracic and mediastinal disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Acute respiratory failure	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Asthma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Bronchopulmonary dysplasia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Bronchospasm	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Chronic respiratory failure	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dyspnoea	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Laryngeal stenosis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lung disorder	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Neonatal respiratory distress syndrome	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Obstructive airways disorder	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Respiratory failure	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Tracheomalacia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ear and labyrinth disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vertigo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Musculoskeletal and connective tissue disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Back pain	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Epiphyseal disorder	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	Total [redacted]		<18 years at baseline [redacted]		≥18 years at baseline [redacted]	
	n (%)	Events, n	n (%)	Events, n	n (%)	Events, n
Muscle twitching	[redacted]					
Osteoarthritis	[redacted]					
Rickets	[redacted]					
Neoplasms benign, malignant and unspecified (including cysts and polyps)	[redacted]					
Breast cancer	[redacted]					
Renal and urinary disorders	[redacted]					
Acute kidney injury	[redacted]					
Nephrolithiasis	[redacted]					
Blood and lymphatic system disorders	[redacted]					
Febrile neutropenia	[redacted]					
Lymphadenitis	[redacted]					
Cardiac disorders	[redacted]					
Cyanosis	[redacted]					
Eye disorders	[redacted]					
Retinal detachment	[redacted]					
Hepatobiliary disorders	[redacted]					
Cholelithiasis	[redacted]					
Immune system disorders	[redacted]					
Anaphylactic reaction	[redacted]					
Injury, poisoning and procedural complications	[redacted]					
Femoral neck fracture	[redacted]					
Femur fracture	[redacted]					

	Total [redacted]		<18 years at baseline [redacted]		≥18 years at baseline [redacted]	
	n (%)	Events, n	n (%)	Events, n	n (%)	Events, n
Forearm fracture	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Fracture	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Injection-related reaction	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Joint dislocation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Multiple fractures	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Wound	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Metabolism and nutrition disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dehydration	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hypercalcaemia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Psychiatric disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Substance abuse	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Surgical and medical procedures	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Medical device implantation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Unknown	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Unknown	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 103 of Appendix M[50]
AA = asfotase alfa; AE = adverse event; ALP = alkaline phosphatase; CSF = cerebrospinal fluid; HPP = hypophosphatasia; SAE = serious adverse event

Note: [redacted]

4.2.2.2 Real world evidence: the EmPATHY study

In 2018, Alexion supported, as an internal collaboration study the real world Evaluate and Monitor Physical Performance of Adults Treated with Asfotase Alfa for Hypophosphatasia (EmPATHY) study. This includes adult patients (≥18 years) diagnosed with paediatric-onset HPP who had received AA in routine clinical practice in Germany (see Table 4.19). Baseline characteristics for this population has been summarised in Table 69 of Appendix M.[50]

EmPATHY was not used to populate the economic model.

4.2.2.2.1 Efficacy results

Physical function outcomes - Overall, 13 patients completed the 6MWT assessments at each timepoint. At baseline, the median distance walked was 267.0 metres (interquartile range [IQR]: 0, 368.0 metres), which increased to 320.0 metres (IQR: 234.0, 469.0) after 12 months of treatment, corresponding to a 20% improvement. The MCID for the 6MWT distance walked is considered 25 metres and/or a 10% improvement in distance walked from baseline. Results indicate a significant improvement in the 6MWT. Seven of the evaluable patients required assistive devices to complete the 6MWT at baseline (three patients used crutches; four used a rolling walker), however, none of the patients who walked unassisted at baseline required assistance at any point during the study. Figure 4.3A illustrates the results from baseline to 12 months for physical function outcomes among adults, with paediatric-onset HPP, treated with AA. Results of the Timed Up and Go (TUG), short physical performance battery and grip strength test are shown in Figure 4.3B, Figure 4.3C and Figure 4.3D, respectively.

Pain prevalence - Figure 4.4D illustrates the results of change from baseline in pain intensity quantitated using a 10-item Likert scale (1 = minimal pain; 10 = maximum possible pain). Median pain intensity at baseline was 6 (IQR: 4.0, 8.3) points, which decreased to 5 (IQR: 4.0, 6.0) points after 12 months of treatment, which corresponds to a 17% improvement. Although there was a significant decrease in pain intensity from baseline to Month 6, changes in median pain intensity from baseline to Month 3 and Month 12 were not statistically significant. Twelve patients were using pain medication before AA treatment and had pain medication data available at baseline, and over the course of the study, four patients reduced their use of pain medication from daily use to an on-demand basis, with only one patient not using pain medication at Month 12.

Health-related quality of life - Nine patients completed the SF-36 (Version 2) at all four timepoints. Figure 4.4B and C illustrates the results of change from baseline in the Mental Component Summary (MCS) and Physical Component Summary (PCS). At baseline, the median PCS score was 26 (IQR: 21, 31), which increased to 33 (IQR: 26, 45) after 12 months of treatment ($p = 0.010$), corresponding to a 27% improvement whilst the median MCS score was 53 (IQR: 33, 60) at baseline and 56 (IQR: 39, 60) after 12 months of treatment, corresponding to a non-statistically significant 5% improvement.

Figure 4.3: EmPATHY primary outcomes of physical function among adults treated with AA for paediatric-onset HPP

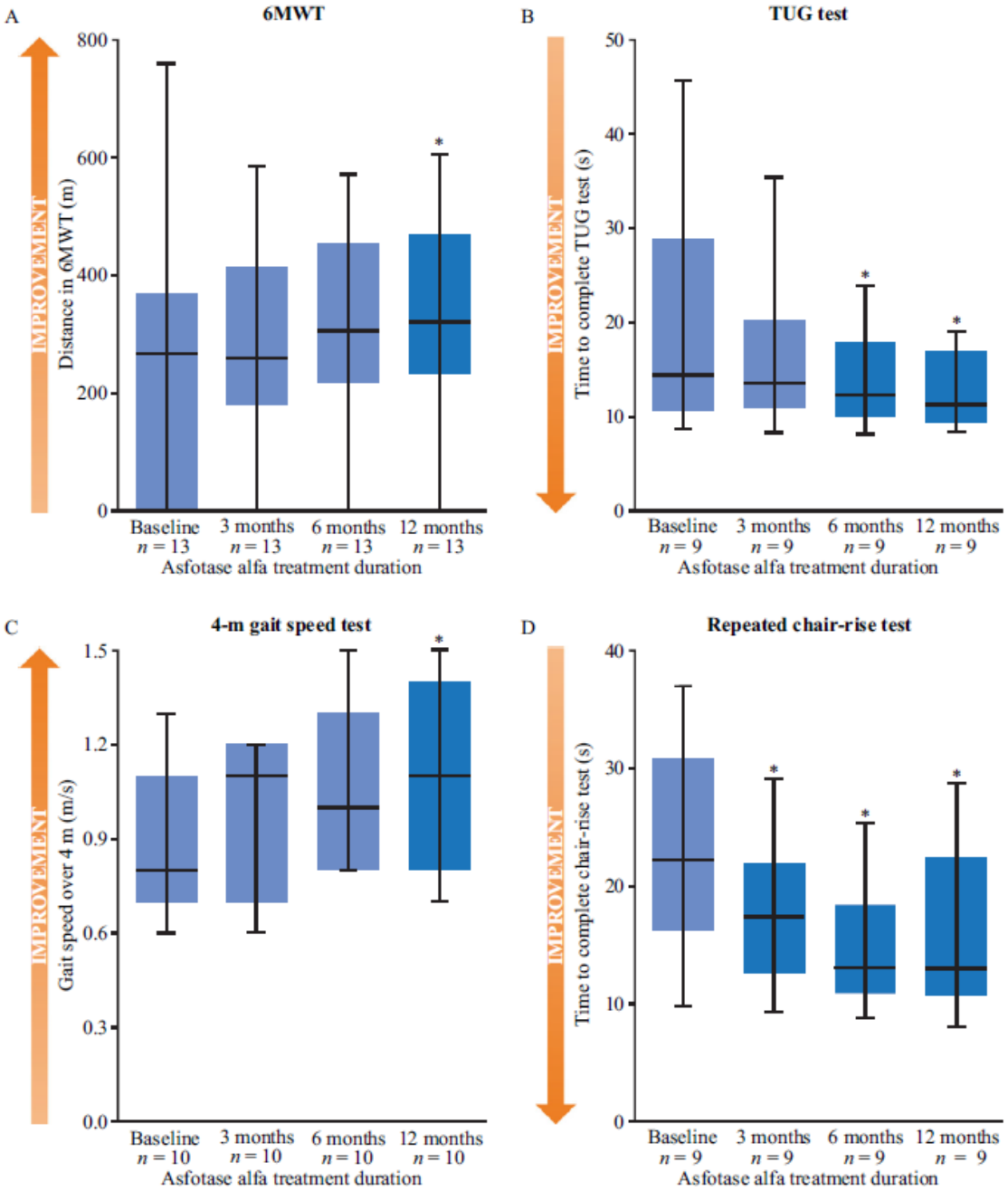


Figure 25 of CS[10]

6MWT = 6-Minute Walk Test; CS = company submission; HPP = hypophosphatasia; SPPB = Short Physical Performance Battery; TUG = Timed Up and Go

Notes:

(A) 6MWT distance, (B) TUG test time, (C) 4 minute gait speed test, and (D) repeated chair-rise test at baseline, 3, 6, and 12 months of treatment.

* p = <0.05 versus baseline. The lower and upper boundaries of blue boxes represent the 25th and 75th percentiles, respectively. Horizontal black lines represent the medians; whiskers represent the maximum and minimum values.

Figure 4.4: EmPATHY secondary outcome measures of patient-reported physical function among adults treated with AA for paediatric-onset HPP

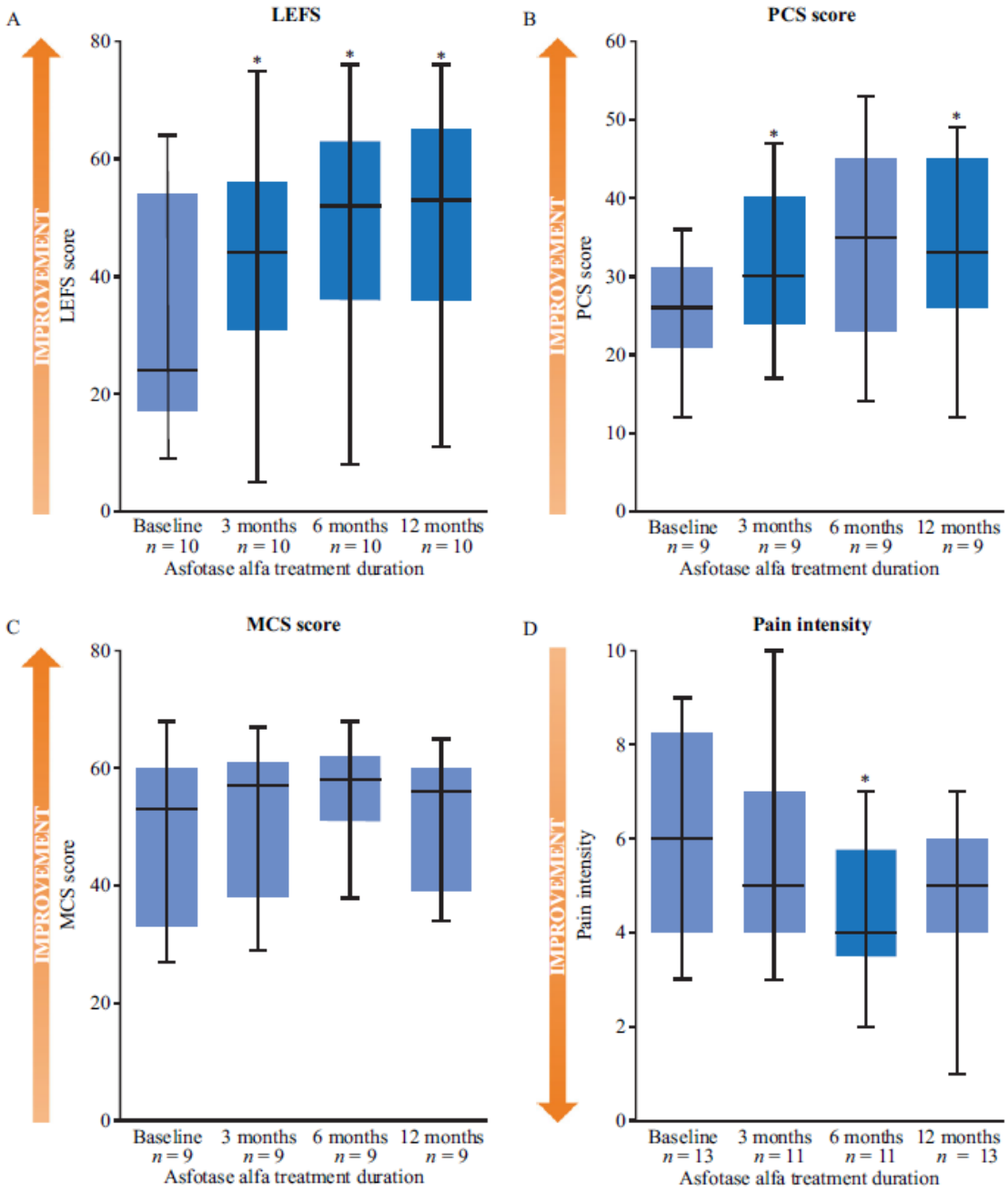


Figure 26 of CS[10]

CS = company submission; HPP = hypophosphatasia; LEFS = Lower Extremity Functional Scale; MCS = Mental Component Summary; PCS = Physical Component Summary; SF-36v2 = 36-Item Short-Form Health Survey (Version 2)

Notes: (A) LEFS, (B, C) SF-36v2, and (D) pain intensity questionnaire at baseline, 3, 6, and 12 months of treatment.

* p = <0.05 versus baseline. The lower and upper boundaries of blue boxes represent the 25th and 75th percentiles, respectively. Horizontal black lines represent medians; whiskers represent the maximum and minimum values.

Additional efficacy data on mobility (the Timed Up and Go test [TUG], short physical performance battery [SPPB], and grip strength tests), and motor function/functional assessments (LEFS), can be found in Section M.3.2.2. of Appendix M.[50]

4.2.2.2.2 Safety results

All 14 patients experienced at least one AE with 46 AEs being recorded in the patients being treated with AA for 12 months. Most of these events (n=33) were judged to not be, or unlikely to not be associated with AA treatment. They were said to be associated with underlying disease and/or comorbidities, such as degenerative disease of the spine, lower back pain/lumbago, knee osteoarthritis, myogelosis (muscle tension/stiffness), greater trochanteric pain syndrome and skin irritation.

The 13 AEs reported as being possibly related to treatment with AA were: fatigue (n=2); weight gain (n=2): headache (n=2); and back pain, increase in pain, performance loss in daily activities, insufficiency fracture, raised intraocular pressure, small bowel ileus and skin irritation (n=1 each).

The most common AEs were ISRs, with 11 (79%) patients noting reddening and/or tenderness at injection sites with variable intensity and duration sometime during the first 3 months of treatment. This increased to 13 patients following 12 months of treatment.

4.2.2.3 Real world evidence: Dahir et al. 2022

This is a prospective, longitudinal telephone-based survey that includes adults (≥18 years) with paediatric-onset HPP on AA treatment, reporting on the symptoms and humanistic burden in patients over [redacted] period (see Table 4.19). Dahir et al. 2022 was not used to populate the economic model.

[redacted] patients were enrolled in the study, of which [redacted] were evaluable at [redacted] Patients' mean age at baseline was [redacted] years, and [redacted] were female.

[redacted] Based on the Work Productivity and Activity Impairment – Specific Health Problem (WPAI-SHP), there was no significant [redacted] in employment between baseline ([redacted] and [redacted] ([redacted]). The WPAI-SHP domains showed significant improvement at [redacted] in: absenteeism ([redacted]), presenteeism ([redacted]), activity impairment ([redacted]), and work productivity loss ([redacted]). A [redacted] of patients ([redacted] continued on AA at [redacted].

4.2.2.4 Natural history studies

Three non-interventional historical controls, ENB-011-10, ALX-HPP-502 and ALX-HPP-502s also formed part of the submission and have been presented in this Section.

EAG comment: The EAG notes that, as indicated in Section B.2.6.4.4 of the CS,[10] the results of non-interventional natural history studies are those that were presented in the original submission and that the SLR, conducted for this submission, did not seek to identify natural history studies: *'no treatment was an exclusion criteria'.*[9]

4.2.2.4.1 ENB-011-10

ENB-011-10 was a global, non-interventional, retrospective, epidemiologic chart review study in which patients comprised the non-concurrent, historical-control group for comparison with a subset of patients with infantile-onset HPP from the open-label ENB-002-08/ ENB-003-08 and ENB-010-10 studies.

Of the 65 patients screened, 48 were eligible and enrolled from 12 sites (six in the US [n=26] and one each in Australia [n=2], Canada [n=11], Germany [n=6], Spain [n=1], Switzerland [n=1] and Taiwan [n=1]). Patients were born between 1970 and 2011; among them 13 (27%) were diagnosed with

hypophosphatasia before 1990, 14 (29%) between 1990 and 1999 and 21 (44%) during or after 2000. Thirteen (27%) were alive (median [min, max] age: 7.7 [2–20] years) and 35 (73%) had died (KM median [95% confidence interval (CI) age at death]: 0.7 [0.4, 1.2] years). Baseline characteristics have been summarised in Table 72 of Appendix M.[50]

Overall survival - Of the 48 enrolled patients, 35 were dead at the time of data abstraction and 13 patients who were alive were censored. [redacted]

Respiratory support requirements and invasive ventilation-free survival – Forty-five (94%) of the 48 patients had documented respiratory status. Of these 45 patients, 29 had received either 'non-invasive' or 'invasive' respiratory support. Invasive ventilation was necessary for 19 of the 29 patients, and death occurred for 18 of the 19 who received invasive ventilation (see Figure 4.5). Among the 48 patients, the median invasive VFS was 7.8 months (95% CI: 2.6, 9.9). The KM estimate of the probability of being alive and not invasively ventilated during the first year of life was 63% at 3 months, 54% at 6 months and 31% at 12 months. Only 25% of patients were alive at 5 years of age.

Figure 4.5: ENB-011-10 respiratory support administration

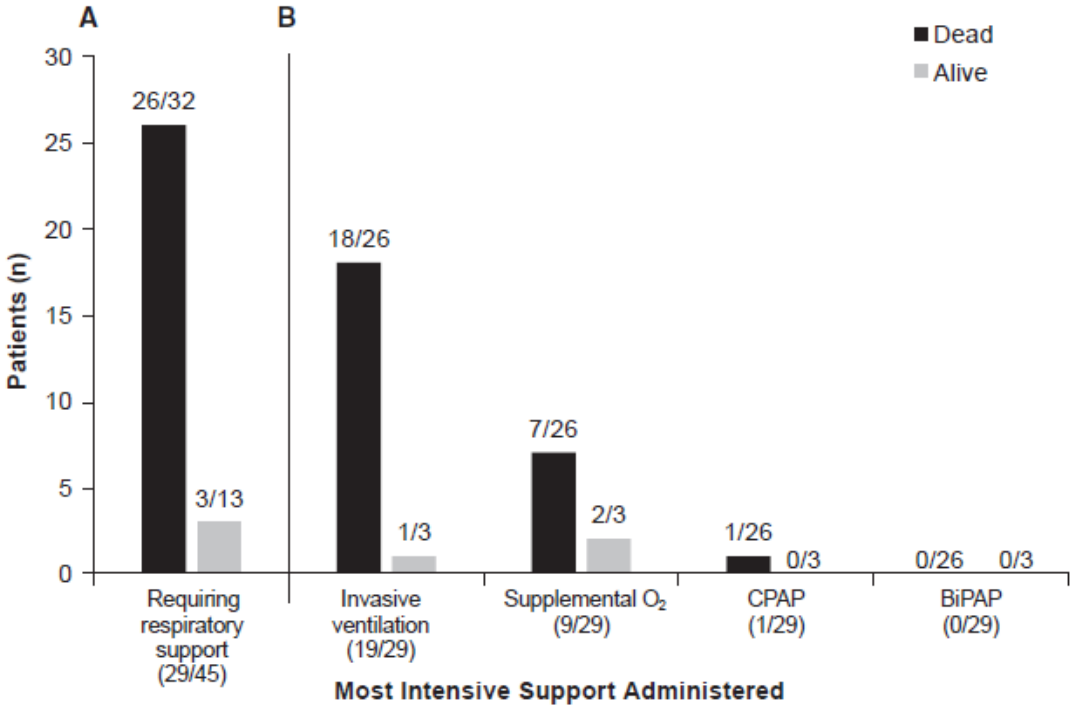


Figure 62 of Appendix M[50]
BiPAP = bilevel or biphasic positive airway pressure; CPAP = continuous positive airway pressure
Notes:
[A]Distribution of living and dead patients who had required respiratory support.
[B]Greatest required support stratified by type and number of patients alive versus dead at data collection. Values along the x-axis represent the total number of patients (dead and alive combined) who received the specific type of support compared with the total number of patients for whom were available.

4.2.2.4.2 ALX-HPP-502 (Global HPP Registry)

Of the [redacted] patients with juvenile-onset HPP who were screened for this study, [redacted] were enrolled at multinational sites. All patients were alive at the time of data abstraction. Baseline characteristics for the enrolled patients have been summarised in Table 75 of Appendix M.[50]

Rickets Severity Scale (RSS)- Median changes from baseline in total RSS scores varied over time, but there were [redacted] from baseline at any time point. [redacted] in rickets severity was observed in this group of historical-control patients (in terms of skeletal radiographs collected for enrolled patients).

Growth (height) - There were no significant [redacted] in height Z-scores at any time point in this historical-control population, including at the last assessment (median [min, max] change from baseline Z-score of [redacted]

Growth (weight)- As with the height Z-scores, patients had notably [redacted] weight Z-scores at baseline, with a mean (min, max) Z-score of [redacted] percentile). No [redacted] in weight over time were observed in this historical-control population.

Overall survival - [redacted]

4.2.2.4.3 ALX-HPP-502s

This was a single-centre, non-interventional functional natural history sub-study of ALX-HPP-502 in patients with juvenile-onset HPP who were selected as the historical-control population for ENB-006-09. [redacted] Baseline characteristics for these enrolled patients have been summarised in Table 78 of Appendix M.[50]

Change in gait performance (MPOMA-G) - Change in gait performance from the first recorded evaluable video (baseline) to subsequent video(s), measured by the Modified Performance Oriented Mobility Assessment-Gait (MPOMA-G), a 12-point scale on which a score of 12 indicates no impairment and lower scores indicate increasing impairment. The patients in this study had only one pair of videos each available for evaluation; therefore, results are presented for baseline and each patient's single post-baseline or last assessment in Table 4.22. The mean (min, max) time difference between the baseline and last assessment video for the [redacted] patients was [redacted] months.

Table 4.22: ALX-HPP-502s: MPOMA-G scores

Visit[a]	Statistic	Actual value	Change from baseline
Baseline	n	[redacted]	[redacted]
	Mean (SD)	[redacted]	[redacted]
	Median	[redacted]	[redacted]
	Min, max	[redacted]	[redacted]
Last overall	n	[redacted]	[redacted]
	Mean (SD)	[redacted]	[redacted]
	Median	[redacted]	[redacted]
	Min, max	[redacted]	[redacted]
	P value[b]	[redacted]	[redacted]

Table 91 of Appendix M[50]
max = maximum; min = minimum; MPOMA-G = Modified Performance Oriented Mobility Assessment-Gait; N/A = not applicable; SD = standard deviation
[a]Baseline is defined as the earliest recorded evaluable video within the period from 5 to 15 years of age for each patient.
[b]p value based on non-parametric sign test to test whether the median of change from baseline in MPOMA-G score differed from 0.

4.2.3 Quality assessment of included studies

EAG comment: As previously discussed in Section 4.1.4 of this report, quality assessments appear to have been performed by one reviewer and checked by another. The CS[10] surmised that *'Most studies were of good quality, with all of the studies assessed as having a low risk of bias in terms of randomisation, withdrawals, outcome selection and reporting and statistical analysis. There was a high risk of bias in terms of allocation concealment and blinding with all of the studies. In terms of baseline comparability between the treatment groups, the risk of bias was low in two-thirds of studies.'*

The EAG is reasonably satisfied with the results of the quality assessment of included studies, but notes that the use of a quality assessment tool for RCTs is of limited relevance, because none of these studies included in the submission were used as RCTs. ENB-006-09/ENB 008-10 randomised participants by AA dose and compared to historic controls and ENB-009-10 did include a control group in the randomisation, however, for both trials, the data for all treated patients were combined and used as single arm studies of AA.

4.2.3.1 Clinical trials

The company utilised the standard NICE checklist in their critical appraisal of included trials. See appraisal conclusions in Table 4.23.

Table 4.23: Quality assessment of ENB-006-09/ENB 008-10 and ENB-009-10

Questions/justification	Study name	
	ENB-006-09/ENB 008-10	**ENB-009-10**
Was randomisation carried out appropriately?	No	Yes
Justification	No, method of randomisation was not reported.	No information was given on how patients were randomised.
Was the concealment of treatment allocation adequate?	No	No
Justification	This was an open-label study.	No information was given regarding concealment of treatment allocation.
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes	No
Justification	No significance difference was observed between the groups.	There were imbalances between the control and treatment groups with regard to some baseline characteristics, so the control group may have had more substantial disease burden.
Were the care providers, participants and outcome assessors blind to treatment allocation?	No	No
Justification	This was an open-label study.	This was an open-label study.

Questions/justification	Study name	
	ENB-006-09/ENB 008-10	**ENB-009-10**
Were there any unexpected imbalances in drop-outs between groups?	No	No
Justification	No	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No unexpected missing data was observed.	There were no unexpected imbalances in drop-outs between groups.
Justification	No	No
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes	Yes
Justification	Modified intent-to-treat was used in analysis.	Intent-to-treat analysis was performed to determine efficacy and safety.
Adapted from Table 20 of Appendix D[50]		

4.2.3.2 Single-arm trials and observational studies

The company utilised the Downs and Black checklist in appraising single-arm trials and observational studies; see appraisal conclusions in Table 4.2.4.

Table 4.24: Quality assessment of single-arm trials and observational studies

Number	Question	Study name				
		UK MAA	ENB-002-08/ ENB-003-08	ENB-010-10	ALX-HPP-501	EMPATHY
1	Is the hypothesis/aim/objective of the study clearly described?	Yes	Yes	Yes	Yes	Yes
2	Are the main outcomes to be measured clearly described in the introduction or methods section?	Yes	Yes	Yes	Yes	Yes
3	Are the characteristics of the patients included in the study clearly described?	Yes	Yes	UTD	Yes	Yes
4	Are the interventions of interest clearly described?	Yes	Yes	Yes	Yes	Yes
5	Are the distributions of principal confounders in each group of patients to be compared clearly described?	UTD	Yes	Yes	UTD	UTD
6	Are the main findings of the study clearly described?	Yes	Yes	Yes	Yes	Yes
7	Does the study provide estimates of the random variability in the data for the main outcomes?	UTD	Yes	Yes	UTD	UTD
8	Have all important adverse events that may be a consequence of the intervention been reported?	Yes	Yes	Yes	Yes	Yes
9	Have the characteristics of patients lost to follow-up been described?	Yes	No	Yes	Yes	No
10	Have actual probability values been reported (e.g., 0.035 rather than <0.05) for the main outcomes except where the probability value is less than 0.001?	N/A	Yes	Yes	Yes	Yes
11	Were the subjects asked to participate in the study representative of the entire population from which they were recruited?	Yes	Yes	N/A	Yes	Yes
12	Were those subjects who were prepared to participate representative of the entire population from which they were recruited?	Yes	UTD	UTD	Yes	Yes

Number	Question	Study name				
		UK MAA	ENB-002-08/ ENB-003-08	ENB-010-10	ALX-HPP-501	EMPATHY
13	Were the staff, places, and facilities where the patients were treated representative of the treatment the majority of patients receive?	Yes	UTD	UTD	Yes	UTD
14	Was an attempt made to blind study subjects to the intervention they have received?	N/A	No	No	N/A	N/A
15	Was an attempt made to blind those measuring the main outcomes of the intervention?	N/A	No	Yes	N/A	N/A
16	If any of the results of the study were based on 'data dredging', was this made clear?	UTD	No	Yes	UTD	UTD
17	In trials and cohort studies, do the analyses adjust for different lengths of follow-up of patients, or in case-control studies, is the time period between the intervention and outcome the same for cases and controls?	Yes	Yes	UTD	Yes	Yes
18	Were the statistical tests used to assess the main outcomes appropriate?	N/A	Yes	Yes	N/A	Yes
19	Was compliance with the intervention(s) reliable?	Yes	Yes	Yes	UTD	UTD
20	Were the main outcome measures used accurate (valid and reliable)?	Yes	Yes	Yes	Yes	Yes
21	Were the patients in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited from the same population?	Yes	Yes	Yes	Yes	Yes
22	Were study subjects in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited over the same period of time?	N/A	Yes	Yes	Yes	Yes
23	Were study subjects randomised to intervention groups?	No	No	Yes	No	No

Number	Question	Study name				
		UK MAA	**ENB-002-08/ ENB-003-08**	**ENB-010-10**	**ALX-HPP-501**	**EMPATHY**
24	Was the randomised intervention assignment concealed from both patients and health care staff until recruitment was complete and irrevocable?	No	No	Yes	No	No
25	Was there adequate adjustment for confounding in the analyses from which the main findings were drawn?	UTD	Yes	Yes	UTD	UTD
26	Were losses of patients to follow-up taken into account?	Yes	Yes	Yes	Yes	Yes

Table 21 of Appendix D[50]
N/A = not applicable; UTD = unable to determine

4.2.3.3 Retrospective non-interventional, natural history epidemiological studies

The company assessed historical control studies using the 2009 CRD guidance (see Table 4.25).[57]

Table 4.25: Quality assessment of historical control studies

	ENB-011-10	ALX-HPP-502	ALX-HPP-502s
Is the study based on a representative sample selected from a relevant population?	Unclear	Unclear	Unclear
Are criteria for inclusion explicit?	Yes	Yes	Yes
Was follow-up long enough for important events to occur?	Yes	Yes	Yes
Drop-outs?	No	No	No
Were outcomes assessed using objective criteria or was blinding used?	Partly	No	No
If comparisons of sub-series, was there sufficient description of the series and distribution of prognostic factors?	None reported	None reported	None reported
Adapted from Table 22 of Appendix D[50]			

4.3 Results of the Meta-analyses/ITC

Section B.2.9 of the CS comprised the following statement: *'Indirect treatment comparisons were not considered appropriate. However, 2 retrospective, non-interventional retrospective studies and 1 sub-study were conducted to provide control data to use in the comparative analyses of selected endpoints in ENB-002-08/ENB-003-08, ENB-010-10 and ENB-006-09/ENB-008-10. ENB-011-10 served as the historical control population for patients with perinatal-/infantile-onset HPP for long-term assessment of OS and VFS (ENB-002-08/ENB-003-08 and ENB-010-10). These comparisons are presented in Section B.2.8.1.'*[10]

EAG comment: The EAG considers these analyses to be a form of ITC, but notes that the methods used are substantively flawed.

The CS included comparative analyses, for the outcomes OS and VFS, using data for AA-treated patients taken from ENB-002-08/ENB-003-08 (n=11) and ENB-010-10 (n=69), and data for untreated patients taken from *'untreated historical controls of similar age and with similar HPP characteristics from a retrospective natural history study (ENB-011-10)'*.[10, 29] Section B.8.1.1 of the CS further states that: *'The demographic, baseline and HPP-specific medical histories of the AA-treated patient cohort and the historical control group are presented in Appendix M.3, and indicate that the 2 groups are clinically similar.'*[10]

EAG comment: The EAG notes that Appendix M of the CS does not include a comparison of baseline characteristics for the studies used in the comparative analyses. Table 4.26, below has been constructed from the baseline characteristics tables for the individual studies, presented elsewhere in the CS. The EAG does not consider that sufficient information has been provided to support the statement that *'the demographic, baseline and HPP-specific medical histories of the AA-treated patient cohort and the historical control group are presented in Appendix M.3 and indicate that the 2 groups are clinically similar'*; the comparability of these study populations is unclear. In addition, it is not clear whether all participants in the natural history study, ENB-011-10, were included in the comparative analyses. The

EAG also considers that the care received by patients in ENB-011-10 may not be representative of current BSC, in that the last patient data were abstracted for this study on 18 April 2013 and 13/48 (27%) of participants were diagnosed before 1990.

The EAG notes the following key points with respect to the comparative analyses presented in the CS:

- Comparative analyses were only provided for survival outcomes (OS and VFS) and for a subgroup of the population specified in the decision problem (perinatal/infantile-onset HPP).
- No attempt appears to have been made to match AA-treated patients and untreated controls, with respect to key demographic and clinical characteristics, or to adjust for potential confounders.
- With respect to control data used in the reported comparative survival analyses, the EAG considers that historical control data used may not be representative of current BSC in that 27% of the included patients were diagnosed before 1990. It should be noted that an exploratory analysis of survival data by year, reported in the CSR for ENB-011-10,[2] showed the probability of survival to 3 months of age [redacted].
- Potential for immortal time bias - immortal time bias can occur, in observational studies, where there is a delay to the start of treatment; this wait period is considered immortal because individuals who enter the treatment group have survive (be alive and event free) until the treatment definition is met.[3] Bias, which necessarily favours the treatment under study, is introduced when the immortal period is either misclassified with respect to treatment status or is excluded from the analysis.[3] The EAG report for the previous assessment notes that, with respect to ENB-011-10, [redacted] These data were redacted from the publicly available version of the EAG report and were not included in the current submission. Given that the median age at baseline, for patients AA-treated patients (ENB-002-08/ENB-003-08), was [redacted].
- The comparative analyses, presented in Section B.2.8.1.1 of the CS,[10] did not include any data from the UK MAA; this was inconsistent with the mortality analysis used to inform cost effectiveness modelling, presented in Section B.3.3.1.1.1[10] which included [redacted] of the [redacted] patients from the UK MAA who had perinatal/infantile-onset HPP.
- The comparative analyses did not use the Global HPP Registry (ALX-HPP-501) as a source of data for untreated patients; this study included a total of [redacted] patients with paediatric-onset HPP who were 'never treated' with AA, ([redacted] with perinatal/infantile-onset HPP, [redacted] with juvenile-onset HPP and [redacted] with paediatric-onset HPP of unknown type).

The company were asked to conduct the following additional analyses:[40]

- Please conduct analyses comparing AA with BSC (using natural history control data) for all outcomes mentioned in the scope, including adverse effects. Please include all study data relevant to the DP population, as reported in Table 1 or excluding juvenile-onset HPP if an amended DP (perinatal/infantile-onset HPP only) is proposed. Please ensure that these analyses include data from the UK MAA and from the wider Global HPP Registry (ALX-HPP-501), as well as all other relevant AA treated and natural history data sources.
- Please conduct all of these analyses using appropriate methods for adjusting for potential confounders according to the methods described in NICE TSD 17 (National Institute for Health and Care Excellence. Decision Support Unit. Utilities TSD series. Available from: http://nicedsu.org.uk/technical-support-documents/utilities-tsd-series).
- Please conduct subgroup analyses for all outcomes comparing AA to BSC according to age of onset category i.e., at least to match the subgroups in the cost effectiveness

section i.e., perinatal/infantile and juvenile, using the most appropriate evidence from all studies for each subgroup.

The company did not submit additional analyses and provided the following response:[9]

'Disease onset age can be a proxy for disease severity, however, as HPP is multisystemic heterogenous disease, it can affect patients to different extents throughout their lifetime. The age of onset of symptoms is a predictor of disease severity, but HPP is multisystemic heterogenous disease that can affect patients to different extents throughout their lifetime. Therefore, grouping patients by age of disease onset, would result in highly variable groups in terms of symptoms severity and affected QoL. As such, the age of the patient at the point of treatment initiation is more important (with the exception of perinatal/infantile-onset cases with high mortality risk), as it reflects the current state of the disease and can result in a group of patients with similar baseline characteristics that make assessment of efficacy and safety of AA more reliable and less biased. This rationale was applied when the AA clinical trials were designed.

Regarding the comparison with BSC, it would be challenging to find (from natural history studies) a matching BSC population of HPP patients, as severely affected patients have been included in the AA clinical trials and the UK MAA, and it would be challenging to find similar patients who are untreated. Where possible, the Alexion clinical trials have included a comparison with BSC for the primary endpoint and a pooled analysis of perinatal/infantile AA treated patients compared with BSC historical controls is included in the submission. Furthermore, the available natural history studies do not contain data for all relevant endpoints, so a comparison on all endpoints would not be possible.

Moreover, even if it were possible to find matching BSC patients, this would require re-writing the ESAP for our AA clinical trials and the UK MAA which, would need at least 6-12 months-worth of delay to materialise; this is not feasible in the time available.'

The EAG does not consider that the ESAP for the AA clinical trials, which pre-date the inception of the UK MAA, provide any justification for not conducting summary analyses which include data from the UK MAA. The EAG also notes an apparent inconsistency, in that Section B.3.3.1.1.1 of the CS reports that [redacted] patients from the UK MAA, with perinatal/infantile-onset HPP, were included in the survival analysis used to inform cost effectiveness modelling.[10] It is, however, unclear why only [redacted], of the total of [redacted] patients with perinatal/infantile-onset HPP from the UK MAA (see Table 3.4),[9] were included in the survival analysis used to inform cost effectiveness modelling.

The EAG does not consider that all potential sources of data for matched BSC patients have been adequately explored (see Sections 3.3 and 4.2.1.9 of this report).

Table 4.26: Comparison of baseline characteristics for studies used in the comparative analyses

Baseline characteristic	ENB-002-08/ENB-003-08 (n=13)[a]	ENB-010-10 (n=69)	ENB-011-10 (n=48)
Age			
Mean (SD)	[redacted] (weeks)[b]	NR	NR
Median (min, max)	[redacted] (weeks)[b]	16.0 (0.3, 72.2) (months)	NR
Gestational age at birth (weeks)			
Median (min, max)	[redacted]	NR	39.0 (30, 41) (n=36)
Age at data abstraction if alive (years)			
Median (min, max)	[redacted]	NR	7.7 (2.0, 20.0) (n=13)
Age at first signs of HPP (months)			
Median (min, max)	[redacted]	1.0 (0, 5.5)	2.0 (0, 179) (n=47)
Sex, n (%)			
Male	[redacted]	33 (48)	26 (54)
Female	[redacted]	36 (52)	22 (46)
Ethnicity, n (%)			
White	[redacted]	54 (78)	NR
Asian	[redacted]	7 (10)	NR
Hispanic or Latino	[redacted]	NR	NR
Other	[redacted]	3 (4)	NR
Unknown	[redacted]	3 (4)	NR
HPP-specific medical history, n (%)			
Abnormally shaped chest	[redacted]	58 (84)	32 (67)
Seizures	[redacted]	17 (25)	NR
Difficulty gaining weight, failure to thrive and/or difficulty eating/swallowing	[redacted]	60 (87)	NR

Baseline characteristic	**ENB-002-08/ENB-003-08 (n=13)[a]**	**ENB-010-10 (n=69)**	**ENB-011-10 (n=48)**
Hypercalcaemia	[redacted]	61 (88)	NR
Nephrocalcinosis	[redacted]	37 (54)	NR
Fractures and/or delayed fracture healing	[redacted]	21 (30)	NR
Radiological Findings	[redacted]	NR	38 (79.2)
Signs/symptoms[c]	[redacted]	NR	25 (52.1)
Baseline ventilation status, n (%)			
No support	[redacted]	23 (33)	NR
History of respiratory compromise (up to and including respiratory failure)[e]	[redacted]	46 (67)	NR
Supplemental O_2 (without mechanical ventilation)	[redacted]	NR	NR
CPAP	[redacted]	NR	NR
Mechanical ventilation (invasive)	[redacted]	NR	NR
BPAP	[redacted]	NR	NR
Other	[redacted]	NR	NR
Baseline RSS score			
Mean (SD)	[redacted]	NR	NR
Median (min, max)	[redacted]	4.0 (0, 10.0) (n=67)	NR
Baseline Z-scores (length)			
Mean (SD)	[redacted]	NR	NR
Median (min, max)	[redacted]	-2.7 (-10.0, 1.0) (n=67)	NR
Baseline Z-scores (weight)			
Mean (SD)	[redacted]	NR	NR
Median (min, max)	[redacted]	-2.5 (-24.0, 0) (n=68)	NR

Baseline characteristic	ENB-002-08/ENB-003-08 (n=13)[a]	ENB-010-10 (n=69)	ENB-011-10 (n=48)
Baseline alkaline phosphatase (U/L)			
Mean (SD)	[redacted]	NR	NR
Median (min, max)	[redacted]	20 (18, 122)[h] (n=65)	NR
Baseline iPTH (pmol/L)			
Mean (SD)	[redacted]	NR	NR
Median (min, max)	[redacted]	NR	NR
Baseline plasma PPi (µM)			
Mean (SD)	[redacted]	NR	NR
Median (min, max)	[redacted]	6.3 (2.7, 13.3) (n=65)	NR
Baseline PLP (ng/ml)			
Mean (SD)	[redacted]	NR	NR
Median (min, max)	[redacted]	521 (48, 24,600) (n=60)[k]	NR
Baseline calcium (mmol/L)			
Mean (SD)	[redacted]	NR	NR
Median (min, max)	[redacted]	2.6 (1.8, 4.0) (n=65)	NR

Tables 53, 56 and 72 of Appendix M [50]

AA = asfotase alfa; BPAP = bi-level or biphasic positive airway pressure; CDC = Centres for Disease Control; CPAP = continuous positive airway pressure; HPP = hypophosphatasia; iPTH = intact parathyroid hormone; max = maximum; min = minimum; n = number of patients; NA = not applicable; NR = not reported; O2 = oxygen; PPi = inorganic pyrophosphate; PLP = pyridoxal-5'-phosphate; RSS = Rickets Severity Scale; SD = standard deviation

Notes: Percentages are based on the number of patients in the treatment group column with non-missing data. Baseline is defined as the last value on or before the date of first dose of study drug in ENB-002-08.

[a]11/13 patients from this study were included in the pooled analysis (baseline data were not provided for this subset of patients)

[b]Age is the age at time of receiving first dose of study drug

[c]Presence or absence of respiratory compromise or other respiratory complications, pyridoxine responsive seizures, chest deformity, failure to thrive, nephrocalcinosis, craniosynostosis, tooth loss, other clinical signs and symptoms of HPP

[d]The category for 'no support' at the baseline time point included patients with missing data at baseline. Information on respiratory support at baseline was missing/not available for Patients 002-01-01 and 002-09-02; these patients were categorised as needing 'no support' at baseline for the purpose of the tabulations here

[e]Respiratory compromise was defined as respiratory signs/symptoms that required institution of respiratory support measure(s), required medication(s) for management of symptom(s), and/or were associated with other respiratory complications (e.g., pneumonia, respiratory tract infection)

Baseline characteristic	ENB-002-08/ENB-003-08 (n=13)[a]	ENB-010-10 (n=69)	ENB-011-10 (n=48)
[f]O2 by nasal cannula (Patient 002-06-01) [g]Z-scores for length and weight are based on CDC 2000 growth charts. The birth to 36 months chart was used for patients from birth to 36 months of age and the 2 to 20 years chart was used for patients older than 36 months [h]Normal range for ALP activity, per ARUP Laboratories (University of Utah, Salt Lake City, UT), varies by age: 0–30 days: 60–320 U/L; 1–11 months: 70–350 U/L; 1–3 years: 125–320 U/L; 4–6 years: 150–370 U/L [i]PPi normal reference range = 1.33 to 5.71 µM [j]PLP normal reference range = 11.76 to 68.37 ng/ml [k]Median (min, max) concentration for patients receiving vitamin B6 supplementation before dosing was 9,960 (65, 24,600) ng/ml and for those patients not receiving vitamin B6 supplementation before dosing was 417 (48, 13,100) ng/ml [l]Calcium normal ranges varied by laboratory			

The following Sections summarise the results of the comparative analyses and the results of additional, non-comparative pooled analyses of outcomes for AA-treated patients, presented in Section B.2.8 of the CS.[10]

4.3.1 Comparative analyses of survival outcomes

The results of the comparative analyses indicated that AA improved OS in patients with perinatal/infantile-onset HPP compared to untreated historical control patients; the probability (95% CI) of survival at 7 years for AA-treated patients was 87% (0.77, 0.93) compared to 27% (0.15, 0.40) for untreated historical controls.[10]

Figure 4.6: Pooled analysis – OS in infants and children with paediatric-onset HPP treated with AA versus historical control patients

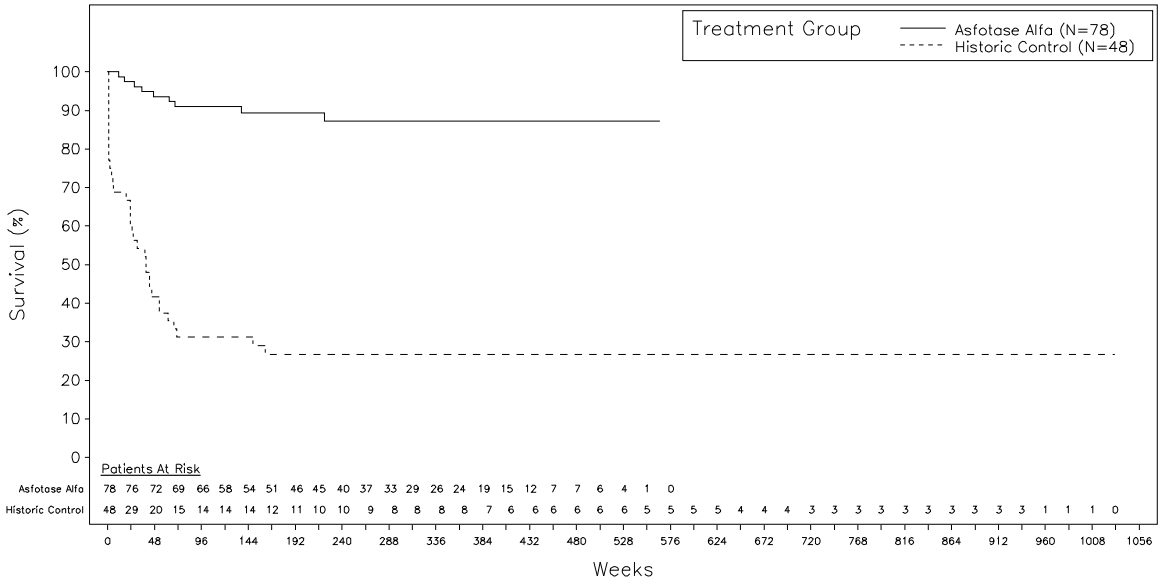


Figure 27, Section B.2.8.1 of the CS[10]
AA = asfotase alfa; CS = company submission; HPP = hypophosphatasia; OS = overall survival

Notes:
*A patient for whom survival time cannot be determined. Censoring was counted if patients withdrew from the study, or, in the case of historical controls, were lost to follow-up. Data were included for infants and children with paediatric-onset HPP from ENB-002-08/ENB-003-08 and ENB-010-10. These patients were treated with AA and their data were compared to data obtained from a group of comparable untreated historical control patients (ENB-011-10).

The results of the comparative analyses also indicated that AA improved invasive VFS in patients with perinatal/infantile-onset HPP compared to untreated historical control patients; the probability (95% CI) of VFS at 7 years for AA-treated patients was 81% (0.68, 0.89) versus 25% (0.14, 0.38) for untreated historical controls.[10]

Figure 4.7: Pooled analysis – invasive VFS in infants and children with paediatric-onset HPP treated with AA versus historical control patients

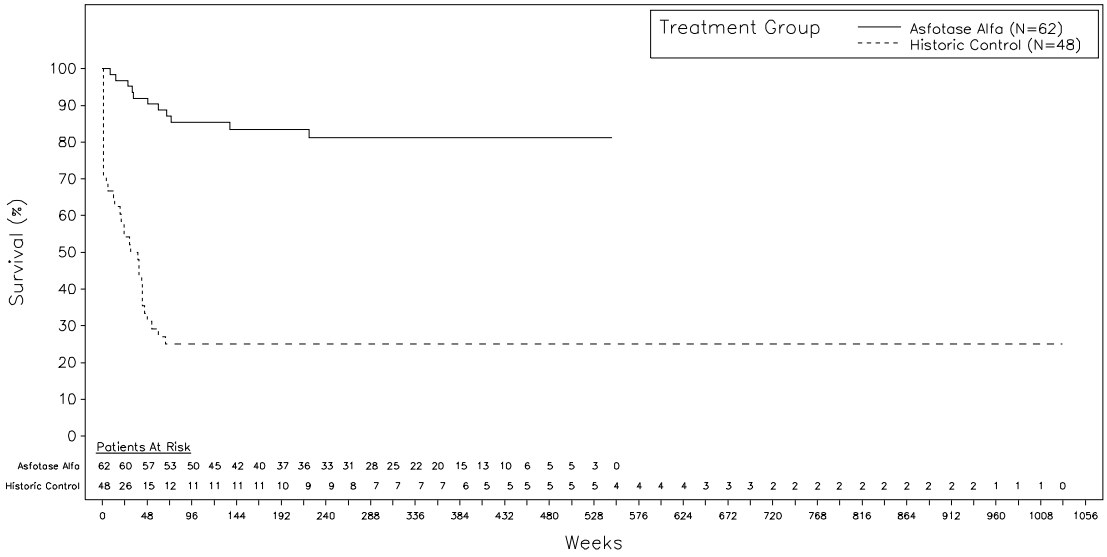


Figure 28, Section B.2.8.1 of the CS[10]
AA = asfotase alfa; CS = company submission; HPP = hypophosphatasia; VFS = ventilator-free survival
Notes:
*A patient for whom survival time cannot be determined. Censoring was counted if patients withdrew from the study, or, in the case of historical controls, were lost to follow-up. Data were included for infants and children with paediatric-onset HPP from ENB-002-08/ENB-003-08 and ENB-010-10. These patients were treated with AA and their data were compared to data obtained from a group of comparable untreated historical control patients (ENB-011-10).

EAG comment: The EAG notes that the CS stated that the analyses showed that treatment with AA markedly improved OS and invasive VFS in infants and children with paediatric-onset HPP, compared to the OS observed in untreated historical control patients.[10] However, according to Section B.2.8.1 of the CS, all AA-treated patients included in the comparative survival analyses were from ENB-002-08/ENB-003-08 and ENB-010-10 (studies which included only patients with perinatal/infantile-onset HPP), therefore, the EAG does not consider that these analyses provide evidence about the relative efficacy of AA in patients with juvenile onset HPP. The EAG further notes that, of the 80 AA patients included in the pooled analysis data set, 78 were included in the comparative analysis of OS and 62 were included in the comparative analysis of VFS.

4.3.2 Pooled analysis of growth in asfotase alpha-treated patients

The pooled analysis for growth included AA-treated patients in ENB-002-08/ENB-003-08, ENB-010-10 and ENB-006-09/ENB-008-10.[10]

The CS presented pooled median Z-score changes from baseline for length/height and weight over 8 years of treatment. The median length/height Z-scores were higher than at baseline from month 3 (0.07 [min, max: -2.0, 5.9]) until year 8 (0.64 [min, max: -0.7, 2.7]) and the median increase from baseline in length or height Z-score was statistically significant at month 6, year 1, year 2, year 3 and year 6 ($p = <0.05$ for all), but not at other timepoints.[10]

Figure 4.8: Pooled analysis – change from baseline in length/height Z-scores over time in infants and children with paediatric-onset HPP

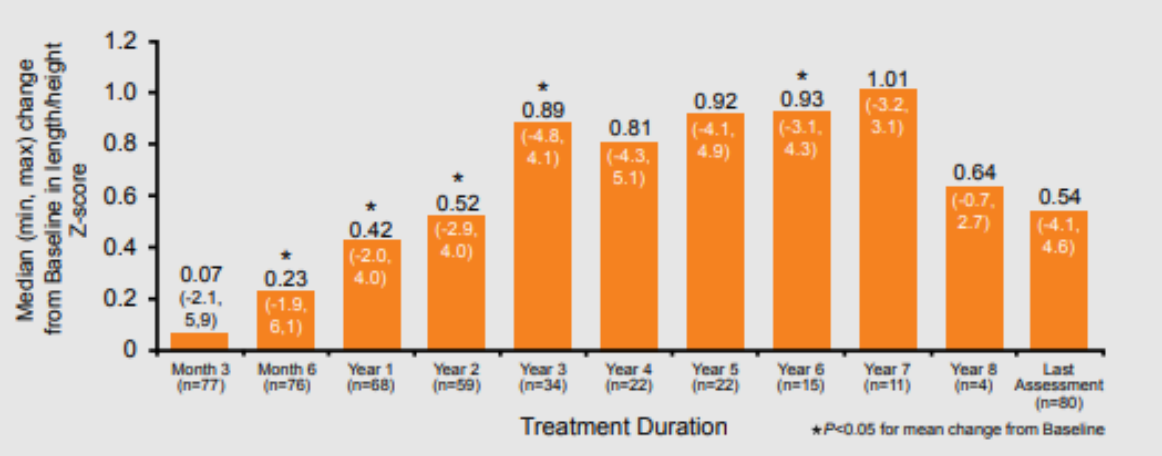


Figure 29 in the CS[10]
CS = company submission; HPP = hypophosphatasia; max = maximum; min = minimum

Similarly, the pooled median weight Z-scores were higher than at baseline from Month 3 (0.21 [min, max: -1.7, 2.3]) until Year 8 (3.09 [min, max: 0.8, 5.2]) and the change from baseline was statistically significant (p = <0.05) at all points.[10]

Figure 4.9: Pooled analysis – change from baseline in weight Z-scores over 8 years of treatment in infants and children with paediatric-onset HPP

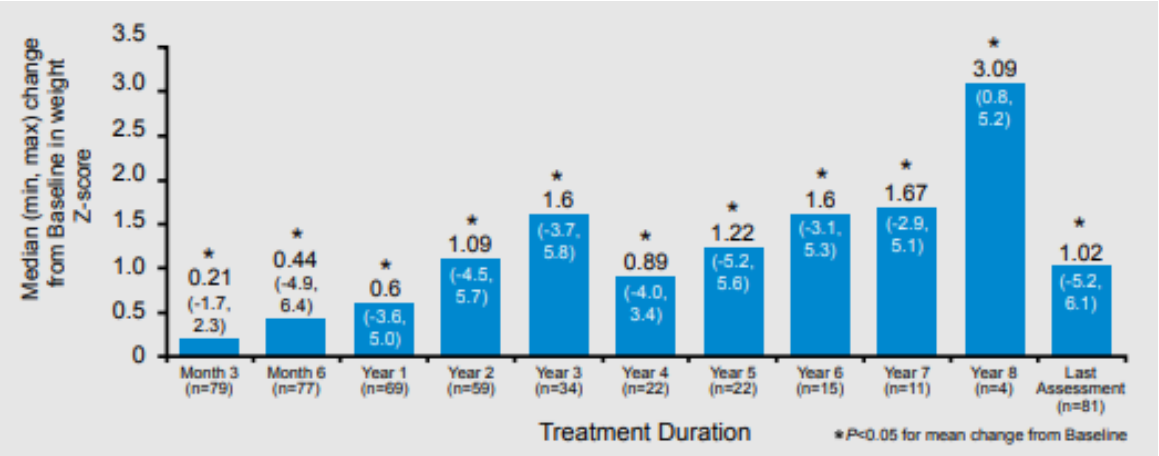


Figure 30 in the CS[10]
CS = company submission; HPP = hypophosphatasia; maximum = maximum; min = minimum

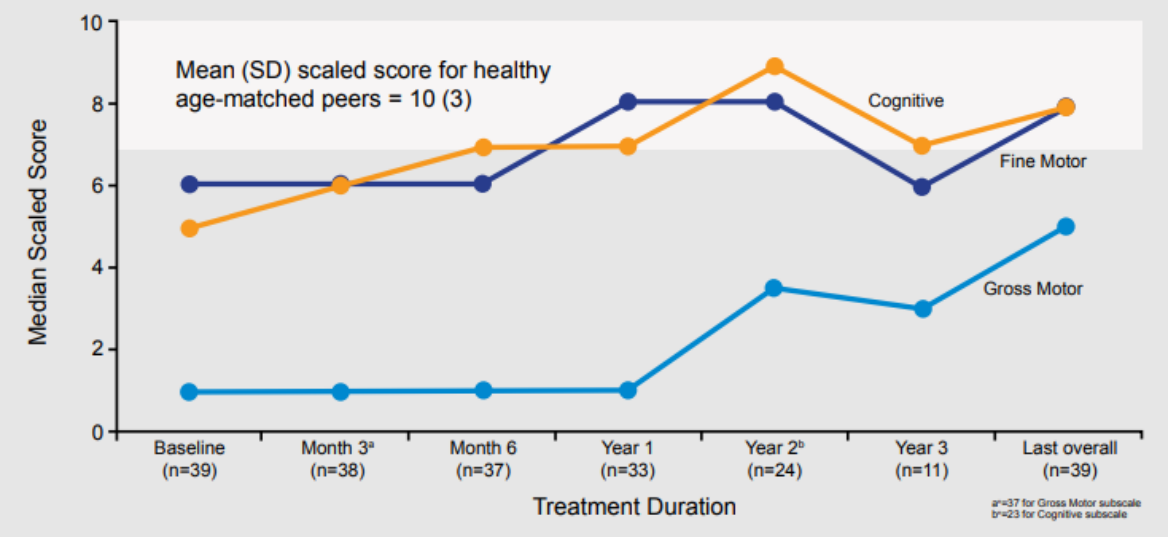
EAG comment: The EAG notes that, although information provided in Tables 14 and 15, Appendix D of the CS[50] indicates that 9/11 AA-treated patients in ENB-002-08/ENB-003-08 and 60/69 AA-treated patients in ENB-010-10 completed these studies, the number of patients included in the pooled analyses of growth outcomes progressively declined over the 8 years of treatment and at year 8 only four patients were included in the pooled analyses length/height Z-score and weight Z-score; no details of loss to follow-up were provided and the planned study durations and hence the definitions of 'completion' were unclear.

The EAG further notes that all data included in the pooled analyses of growth outcomes were for patients with perinatal-/infantile-onset HPP only, i.e., for a subgroup of the population specified in the decision problem.

4.3.3 Pooled analysis of BSID-III scores, over time, in asfotase alpha-treated patients

Section B.2.8.1.3 of the CS states that: improvements were observed in median BSID-III Gross Motor, Fine Motor, and Cognitive scaled scores over time in infants and toddlers (<2 years) with paediatric-onset HPP treated with AA.[10] Data form these outcomes were presented in graph form.

Figure 4.10: Pooled analysis – median BSID-III Gross Motor, Fine Motor, and Cognitive scaled scores over time in infants and toddlers (<2 years) with paediatric-onset HPP treated with AA



Based on Figure 31 in the CS[10]

AA = asfotase alfa; BSID-III = Bayley Scales of Infant and Toddler Development®, 3rd Edition; CS = company submission; HPP = hypophosphatasia; SD = standard deviation

Notes: Term newborn infants (age 0 to 27 days; n=3) and children (age 2 to 11 years; n=8) also generally showed improvements on the BSID-III after treatment with AA. However, results were variable because of the low number of patients with available data in each group. Data were included for infants and children with paediatric-onset HPP from ENB-002-08/ENB-003-08 and ENB-010-10. Scaled scores range from 1 to 19 with a normal mean (SD) of 10 (3), with higher scores meaning better motor and cognitive function.

EAG comment: The EAG notes that, as with the pooled analyses of growth outcomes in AA-treated patients, the pooled analysis of BSID-III scores appears to have included only a subset of the AA-treated patients in studies ENB-002-08/ENB-003-08 and ENB-010-10 and the number of patients included in the analyses progressively declined over the reported treatment period. Although the BSID-III score data and the growth (Z-score) data were taken from the same studies, the treatment duration for which these outcomes were reported differs (8 years for growth data versus 3 years for BSID-III data). No information was provided about the source of data for 'healthy age-matched peers' used to scale scores.

The EAG further notes that all data included in the pooled analyses of BSID-III scores were for patients with perinatal-/infantile-onset HPP only, i.e., for a subgroup of the population specified in the DP.

4.3.4 Pooled analysis RGI-C scores and RSS, over time, in asfotase alpha-treated patients

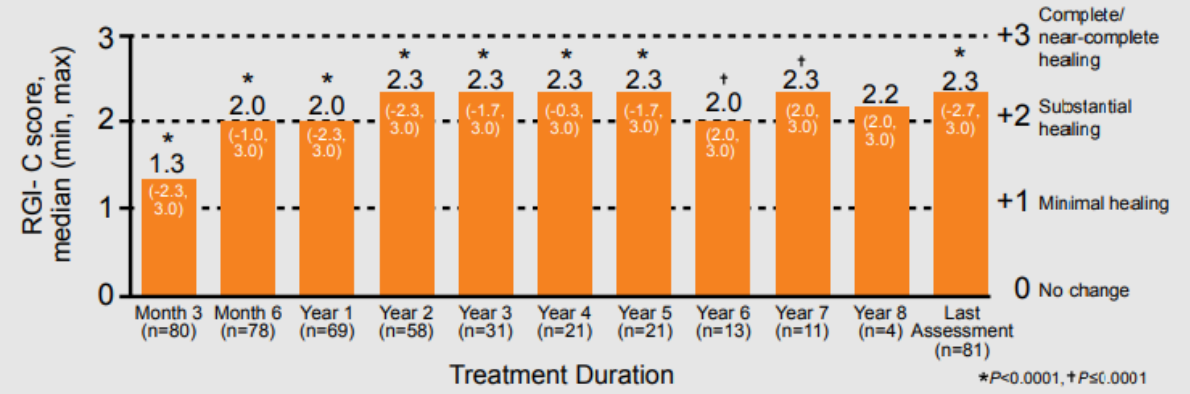
The pooled analysis for changes in RGI-C scores and RSS included AA-treated patients in ENB-002-08/ENB-003-08, ENB-010-10 and ENB-006-09/ENB-008-10.[10]

The complete data set, as reported in Section B.2.8.1 of the CS, comprised 85 patients: ENB-002-08/ENB-003-08 (n=11 patients with infantile-onset HPP); ENB-010-10 (n=69 patients with perinatal/infantile-onset HPP); ENB-006-09/ENB-008-10 (n=5 children with unspecifies paediatric -onset HPP).

Median RGI-C scores indicated that improvements in HPP-related skeletal disease occurred from month 3 (median 1.3 [min, max: -2.3, 3.0]; p = <0.0001) and appeared to be sustained over 8 years of treatment (median 2.2 [min, max: 2.0, 3.0]).

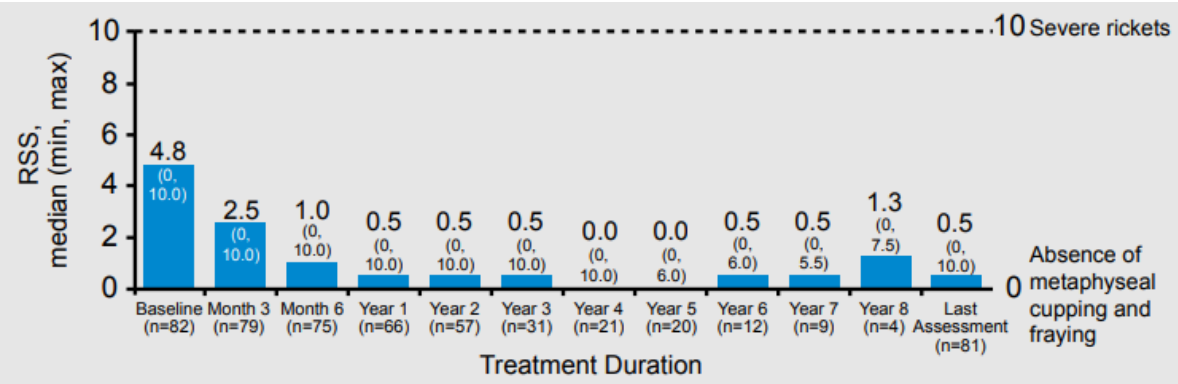
Similarly, median RSS scores indicated that the improvements occurred from month 3 (median 2.5 [min, max: 0.0, 10.0]) and appeared to be sustained over 8 years of treatment (median 1.3 [min, max: 0.0, 7.5]).

Figure 4.11: Pooled analysis – median RGI-C scores over 8 years of treatment in infants and children with paediatric-onset HPP



Based on Figure 32 in the CS[10]
CS = company submission; HPP = hypophosphatasia; max = maximum; min = minimum; RGI-C = Radiographic Global Impression of Change
Notes: The RGI-C is a 7-point scale (–3 [severe worsening] to +3 [complete/near-complete healing]) used to assess radiographic changes from baseline in the most common skeletal characteristics of HPP. Data were included for infants and children with paediatric-onset HPP from ENB-002-08/ENB-003-08, ENB-010-10 and ENB-006-09/ENB-008-10.

Figure 4.12: Pooled analysis – median RSS over 8 years of treatment in infants and children with paediatric-onset HPP



Based on Figure 33 in the CS[10]
CS = company submission; HPP = hypophosphatasia; max = maximum; min = minimum; RSS = rickets severity scale
Notes: The RSS is a 10-point scale (0 = absence of metaphyseal cupping and fraying [both characteristic of rickets] to 10 = severe rickets; maximum of 4 points for the wrists and 6 points for the knees). It was originally developed to assess severity of nutritional rickets in the wrists and knees. Data were included for infants and children with paediatric-onset HPP from ENB-002-08/ENB-003-08, ENB-010-10 and ENB-006-09/ENB-008-10.

EAG comment: The CS states that: *'median RGI-C scores documented improvements in HPP-related skeletal disease in infants and children with paediatric-onset HPP'* The EAG notes that is unclear how many, if any, of the patients from ENB-006-09/ENB-008-10 had juvenile-onset HPP and that most (80/85) of the patients in the complete data set were taken from studies that included only patients with perinatal-/infantile-onset HPP; the EAG, therefore, considers that the pooled analyses of RGI-C and RSS scores provide evidence for the subgroup of patients with perinatal-/infantile-onset HPP only.

The EAG notes that the pooled analyses for RGI-C and RSS scores do not appear to have included all 85 patients from the complete data set for ENB-002-08/ENB-003-08, ENB-010-10 and ENB-006-09/ENB-008-10, and that the number of patients included in the pooled analyses progressively declined over the 8 years of treatment with only four patients being included at year 8; no details of loss to follow-up were provided.

4.3.5 Pooled analysis of safety data

The CS (Section B.8.2) presented pooled safety data from four completed studies of AA: in children aged ≤ 3 years (ENB-002-08/ENB-003-08; n=11) and children aged ≤ 5 years (ENB-010-10; n=69) with onset of HPP symptoms before the age of 6 months; and children aged 5–12 years (ENB-006-09/ENB-008-10; n=13) and adolescents and adults aged 13–65 years with onset of HPP at any age (ENB-009-10; n=19).[10] The CS stated that patients in the pooled safety set: *'represented a broad spectrum of patients with HPP as shown in the medical history and baseline characteristics, and according to both age of onset of first symptoms, age of first fracture and number of fractures.'*[10]

EAG comment: The EAG notes that no subgroup analyses, by age of onset category, were provided for pooled safety data.

The exposure of patients included in the pooled safety set varied; 83 (75%) patients received 2 mg/kg AA administered 3 times per week and 28 (25%) received 1 mg/kg AA administered 6 times per week. Median (min, max) treatment duration was 2.7 years (1 day, 7.5 years) and the median average weekly total dose was 6.0 mg/kg, with a range of 2.1 to 11.9 mg/kg.[10]

All patients experienced at least one TEAE. In total, 1,466 TEAEs in 91 patients were considered treatment-related. Most treatment-related adverse events (TRAEs) (1,310 [89.4%] in 82 patients) were ISRs, with the majority being mild (74%) or moderate (21%) in severity. The most common ISRs were erythema (54%), discoloration (24%) and pain (19%). The ISRs occurred most frequently within the first 3 months of treatment (565 events in 53 patients), then generally decreased over time (207 events in 33 patients from 3 to 6 months; 178 events in 35 patients from 6 months to 1 year; 125 events in 32 patients from 1 to 2 years; and 247 events in 45 patients from 2 to 7 years).[10]

The CS stated that: *'SAEs of special interest were craniosynostosis (28%; including 6 surgeries), injection-associated reactions (6%; including 2 anaphylactoid reactions), ectopic calcifications (2%; including nephrolithiasis), and elevated transaminases or chronic hepatitis (2%; including chronic hepatitis and elevated liver enzymes).'*[10]

EAG comment: The EAG notes that the overall number of patients, in the pooled safety set, who experienced any SAE, is not clear. It is also unclear whether the percentages reported refer to the percentage of patients in the pooled safety set who experienced the specified SAE, or the percentage of SAEs which were, for example, craniosynostosis.

Ten deaths occurred, all of which occurred in patients with severe HPP (perinatal or infantile HPP). One death was considered to be possibly related to AA treatment and was attributed to pneumonia,

while the remaining nine deaths were considered to be unrelated to treatment. Six deaths were a result of the following complications: respiratory failure and cerebral death; HPP-related complications; severe respiratory failure; cardiopulmonary arrest; severe cardiopulmonary insufficiency; and trans tentorial and cerebellar tonsillar herniation due to cerebral oedema. Three deaths were due to pneumonia and/or sepsis.[10]

4.4 Additional work on clinical effectiveness undertaken by the EAG

No additional work was undertaken by the EAG.

4.5 Conclusions of the clinical effectiveness section

4.5.1 Completeness of the CS with regard to relevant clinical studies and relevant data within those studies

The EAG is confident that all relevant studies (published and unpublished) of AA were included in the CS, including data from the UK MAA. The EAG notes that, as indicated in Section B.2.6.4.4 of the CS,[10] the results of non-interventional natural history studies are those that were presented in the original submission and that the SLR, conducted for this submission, did not seek to identify natural history studies: *'no treatment was an exclusion criteria'.*[9] Therefore, the EAG is not confident that all potential sources of comparator data have been fully explored.

Despite the relative completeness of the CS with respect to included studies, the EAG considers that the results have not been provided in a way which allows for ready comparison across studies and for interpretation against the DP specified in the scope. In particular, results were not consistently presented by age of onset category (perinatal/infantile- and juvenile-onset) and the company have declined to provide results by age of onset category, even though the provision of baseline data for age of onset category appears to indicate that sufficient data are available to support this.

Following the previous assessment of AA, in this indication, in 2015/2016,[42] a UK MAA was put in place to allow collection of further data.[1] Although the CS includes results from the UK MAA, the EAG does not consider that these results have been appropriately used in the analyses of clinical effectiveness presented. No data from the UK MAA were included in any of the pooled analyses of efficacy or comparative efficacy presented in the clinical effectiveness sections of the CS (Section B.2.8) and[10] and the company declined to repeat these analyses including all relevant data from the UK MAA, stating that: *'no further pooled analyses are available and it would not be feasible to conduct a pooled analysis across all populations due to the limited availability of historical control data across all populations and all endpoints, and such an analysis would require re-designing the ESAP for all studies and would require several months to complete.'*[9] The EAG considers that this response and the presentation of data in the clinical effectiveness section of the CS is inconsistent with the company's approach to providing inputs for their cost effectiveness modelling, where, for example, [redacted] of the [redacted] patients from the UK MAA, with perinatal/infantile-onset HPP, were included in the survival analysis (Section B.3.3.1 of the CS).[10]

4.5.2 Interpretation of treatment effects reported in the CS in relation to relevant population, interventions, comparator, and outcomes

There is some evidence to indicate that AA may improve survival in patients diagnosed with perinatal/infantile-onset HPP (the most severely affected patient group). The CS (Section B.2.12.2) states that: *'AA improved OS from 27% to 87% compared with historical controls in a pooled analysis of patients with perinatal- and infantile-onset HPP (ENB-002-08/ENB-003-08 and ENB-010-10) after 7 years of treatment.'*[10] and that *'AA markedly increased the probability of invasive VFS in patients with*

perinatal- and infantile-onset HPP (ENB-002-08/ENB-003-08 and ENB-010-10) compared with untreated historical patients, with VFS rates of 81% after 7 years of AA treatment compared with 25% for untreated historical controls.'[10]

These were the only comparative effectiveness data presented in the clinical effectiveness section of the CS.[10] The OS analysis used data for 78 AA-treated patients from clinical trials and the VFS analysis used data for 82 AA-treated patients from the same trials, and both analyses used the same group of 48 historical controls that were used in the previous submission.[10] Neither analysis included any data for the additional [redacted] AA-treated patients, with perinatal-/infantile-onset HPP, from the UK MAA or any data for the [redacted] 'ever-treated' with AA patients, with perinatal-/infantile-onset HPP, from the Global HPP Registry. Despite not including these patients in the pooled analyses, the CS (Section B.2.12.2) did report data from the UK MAA and the Global HPP Registry in support of the proposition that AA improves OS and VFS, stating:

'As of the most recent analysis cut-off date for the UK MAA, v participants in the Paediatric Population had died. [redacted] participants were classified as the most severely affected by HPP (perinatal- and infantile-onset).'

'In the Global HPP Registry, [redacted] ever-treated patients in the < 18 years and perinatal-/infantile-onset group were on invasive ventilation. Of these patients, [redacted] patients stopped invasive ventilation following AA treatment. In addition, as of the most recent analysis cut-off date for the UK MAA, no patients in the Paediatric Population required respiratory support including invasive ventilation support, [redacted] of whom were classified as the most severely affected by HPP (perinatal- and infantile-onset).'

With respect to control data used in the reported comparative survival analyses, the EAG considers that historical control data used may not be representative of current BSC in that 27% of the included patients were diagnosed before 1990. It should be noted that an exploratory analysis of survival data by year, reported in the CSR for ENB-011-10,[2] showed the probability of survival to 3 months of age [redacted] There is also a potential issue with immortal time bias in the survival analysis.[3] Immortal time bias can occur, in observational studies, where there is a delay to the start of treatment; this wait period is considered immortal because individuals who enter the treatment group have survive (be alive and event free) until the treatment definition is met.[3] Bias, which necessarily favours the treatment under study, is introduced when the immortal period is either misclassified with respect to treatment status or is excluded from the analysis.[3] The EAG report for the previous assessment notes that, with respect to ENB-011-10, [redacted] These data were redacted from the publicly available version of the EAG report and were not included in the current submission. Given that the median age at baseline, for patients AA-treated patients (ENB-002-08/ENB-003-08), was [redacted] The CS did not report any attempt to explore the potential use of 'never treated' patients from the Global HPP Registry to improve the comparator data set. The EAG does not consider that all potential sources of comparator data have been adequately explored.

In addition, no attempt appears to have been made to match AA-treated patients and untreated controls, with respect to key demographic and clinical characteristics, or to adjust for potential confounders. The EAG, therefore, considers these analyses to be fundamentally flawed.

The CS did not include any data about potential long-term survival benefit for patients with juvenile-onset HPP, who are treated with AA. Although these patients are less severely affected and therefore have less potential for immediate gain, it is unclear whether the morbidities associated juvenile onset

HPP have any effect on long-term life expectancy and hence whether treatment with AA has any effect on long-term survival.

The clinical effectiveness section of the CS did not include any information about the comparative efficacy of AA versus BSC, with respect to growth or functional outcomes, either for babies born with HPP who survive, following treatment with AA, or for those with juvenile-onset HPP (less severe disease). All of the conclusions about the beneficial effects of AA on growth and functional outcomes, presented in the clinical effectiveness section of the CS (Section B.12.2),[10] were based on changes from baseline observed in individual studies. Mean and median changes from baseline in Z-scores for height and weight increased over time and with treatment, reflecting improvements in growth relative to healthy, same-aged peers. Results for studies of AA-treated patients are summarised in Section 4.2.1.

5 COST EFFECTIVENESS

5.1 Introduction

This Section provides an assessment of whether AA for treating paediatric onset patients with HPP represents value for money for the NHS in England. The main source of evidence used to inform this assessment is the CS and the electronic cost effectiveness model. This chapter provides a summary of the literature review performed by the company to search for economic evidence, the structure of the economic model, the evidence used to inform the input parameters of the economic analyses, the results of the company cost effectiveness analyses (CEAs) and a critique of all these aspects conducted by the EAG.

5.2 EAG comment on company's review of cost effectiveness evidence

Two systematic literature searches were performed to identify cost effectiveness studies, health-state utility values, and cost and healthcare resource use studies (CS Appendix G, Appendix H and Appendix I).[50]

5.2.1 Searches performed for cost effectiveness section

The following paragraphs contain summaries and critiques of all searches related to cost effectiveness presented in the CS.[10, 50] The CADTH evidence-based checklist for the PRESS, was used to inform this critique.[51, 52] The CS was checked against the STA and HST evaluation specification for company/sponsor submission of evidence.[53]

Appendix G, Appendix H and Appendix I of the CS reported the literature searches used to identify cost effectiveness studies, health-state utility values, and cost and healthcare resource use studies.[50] Searches were conducted in July 2021, and updated in February 2022.

A summary of the resources searched is provided in Table 5.1.

Table 5.1: Resources searched for the economic literature reviews (as reported in CS)

Resource	Host/Source	Date Ranges	Dates searched
Electronic databases			
MEDLINE In-Process	PubMed	Not applicable Not applicable	07/07/21 07/02/22
Embase and MEDLINE	embase.com	Not reported Not reported	07/07/21 07/02/22
Health Technology Assessment (HTA) Database	Centre for Reviews and Dissemination (CRD) interface	Not reported Not reported	07/07/21 07/02/22
National Health Service Economic Evaluation Database (NHS EED)	CRD interface	Not reported Not reported	07/07/21 07/02/22
Cochrane Central Register of Controlled Trials (CENTRAL)	Cochrane Library	Not reported Not reported	07/07/21 07/02/22
Cochrane Database of Systematic Reviews (CDSR)	Cochrane Library	Not reported Not reported	07/07/21 07/02/22
EconLit	EBSCO	Not reported	07/07/21

Resource	Host/Source	Date Ranges	Dates searched
		Not reported	07/02/22
Conference proceedings			
Annual Meeting of the American Society for Bone and Mineral Research	Not reported	2019-2022 2019-2022	July 2021 February 2022
Annual Meeting of the Endocrine Society	Not reported	2019-2022 2019-2022	July 2021 February 2022
European Society for Paediatric Endocrinology	Not reported	2019-2022 2019-2022	July 2021 February 2022
International Conference on Children's Bone Health	Not reported	2019-2022 2019-2022	July 2021 February 2022
International Society for Pharmacoeconomics and Outcomes Research: European Meeting	Not reported	2019-2022 2019-2022	July 2021 February 2022
HTA organisations			
National Institute for Health and Care Excellence (NICE)	Not reported	- -	July 2021 February 2022
Scottish Medicines Consortium	Not reported	- -	July 2021 February 2022
All Wales Medicines Strategy Group	Not reported	- -	July 2021 February 2022

EAG comment:

- The CS provided full details of the literature searches for the EAG to appraise.[10, 50]
- A good range of databases, conference proceedings, and HTA organisation websites were searched.
- Full details of the database searches, including the database name, host platform, and date searched, were provided.
- Details of the conference proceedings searched were provided, including the date range. The search terms used, URL links, specific date of searches, and results, were not reported.
- A list of the HTA organisation websites searched was provided. The search terms used, URL links, specific date of searches, and results, were not reported.
- The database search strategies were well structured, transparent and reproducible. They included truncation, proximity operators, synonyms, and subject headings (MeSH and EMTREE in embase.com, and MeSH in the Cochrane Library and CRD databases).
- There were no language or date limits for the health-state utility values searches. There were no language limits for the cost effectiveness, and cost and resource use searches, but there was a 10-year date limit. It was not clear why this date limit was applied.
- MEDLINE was searched using embase.com on the understanding that Embase contains all MEDLINE content. This approach is not recommended as MEDLINE records are indexed

differently in Embase; MeSH terms are replaced with EMTREE subject headings.[54] To fully utilise MeSH indexing it is preferable to search MEDLINE separately.

- It would have been preferable for the database search strategies to be presented exactly as run, rather than copied into a tabular format, as item 8 of the PRISMA-S reporting checklist recommends.[55] The Cochrane Handbook also recommends that *"...bibliographic database search strategies should be copied and pasted into an appendix exactly as run and in full, together with the search set numbers and the total number of records retrieved by each search strategy. The search strategies should not be re-typed, because this can introduce errors"*.[54]
- Study design search filters for economic evaluations, utilities and HRQoL, and cost and resource use were included. The search filters were not cited, as current practice recommends.[55]
- The facet of study design search filters was run as a one-line search, making it very difficult to read, decipher what the search was designed to identify, and to spot any errors. A more transparent, and easier to read approach would have been to structure the search strategy using multiple search lines.
- The search strategies were designed to combine the population (HPP) with study design search filters (economic evaluations, utilities and HRQoL, and costs). As the population of interest (HPP) has a relatively small literature, it might have been beneficial to conduct the searches without the facet of study design search filters. This sensitive approach would have ensured that no relevant studies were missed.
- There was a spelling mistake in the population facet: (phosphatase NEAR/3 (**defecien** * OR disorder*)):ab,ti,kw. This error was repeated in the Cochrane, PubMed and EconLit searches, and the update searches. There was also a spelling mistake in the 'economic evaluation and cost and resource use' facet: (cost NEAR/3 (effect* OR utility* OR benefit OR conseq* OR minimi* OR increment* OR qaly* OR **ly*** OR 'quality adjusted life year*' OR 'life year*')):ab,ti,kw. This error was repeated in the update searches.
- There were numerous redundant search terms included in the 'economic evaluation and cost and resource use' facet: 'quality adjusted life year* OR life year*'; 'hidden Markov model/exp' OR 'markov chain/exp'; 'cost near/3 qaly' OR 'qaly'; 'qaly NEAR/3 cost' OR 'cost NEAR/3 qaly', etc.
- The CS reported that MEDLINE In-Process was searched using PubMed. This is inaccurate, as the search limit used in PubMed identifies recently added records, not in-process records: (publisher[sb] NOT pubstatusnihms NOT pubstatuspmcsd NOT pmcbook) OR (pubstatusaheadofprint). The correct subset to use is 'inprocess[sb]'. MEDLINE In-process records were excluded from the company's PubMed search.
- The CS reported searching the NHS EED and HTA databases via the CRD interface, but the search strategy suggested that the DARE was also searched, and the results for all three databases retrieved.
- There was no reason to search the CRD databases for the update (February 2022), as NHS EED and DARE have not been updated since March 2015 and the HTA database has not been updated since October 2018. A better approach would have been to search the International HTA Database which has superseded the CRD HTA database.
- The Cochrane search strategy did not report the database issue numbers or differentiate the results for CENTRAL from CDSR.
- For the update of the economic searches, a table of databases searched was provided (Table 1) in the embedded Updated SLR in Appendix G. The table reported that NHS EED and the HTA database were searched via 'online.wiley.com' when they were actually searched via the CRD interface. The host URL links for PubMed and Cochrane were incorrect. The 'filter used for study design' did not cite the search filters used.

5.2.2 Review process and results

The search methods and results for the economic SLR are shown in Appendix G of the CS.[10]

The SLR identified no pharmacoeconomic models or CEA evaluating treatments of paediatric-onset HPP.

The SLR identified one previous HST appraisal for HPP.[4] This was a NICE submission in 2017 which assessed the cost effectiveness of AA treatment for patients with paediatric-onset HPP and was the preceding submission of the current technology assessment. The current submission concerns the same product and indication as the 2017 NICE submission and is developed following the completion of the MAA.[4]

5.3 Exposition of the company's model

5.3.1 Economic evaluation scope

Table 5.2 provides an assessment of the adherence of the company model to the NICE reference case.

Table 5.2: Adherence to the reference case principles relevant to highly specialised technologies

Element of economic analysis	Reference case	EAG comment
Defining the decision problem	The scope developed by the National Institute for Care and Health Excellence (NICE).	The scope of the economic analysis is generally in line with the scope developed by NICE.
Comparator	Therapies routinely used in the National Health Service (NHS), including technologies regarded as the current best practice.	Best supportive care (BSC) including surgical interventions, hospitalisations, intensive care unit (ICU) services, respiratory assistance, outpatient visits, consultations. However, medication for e.g., seizures, infection and respiratory problems were not included.
Perspective on costs	NHS and Personal Social Services (PSS).	NHS and PSS perspective was considered.
Perspective on outcomes	All health effects on individuals.	Patient and caregiver health benefits are included.
Type of economic evaluation	Cost effectiveness analysis (CEA).	Incremental costs and benefits are assessed in the form of a quality adjusted (QA) life year (LY)-based cost-utility analysis.
Time horizon	Sufficient to capture differences in costs and outcomes.	Lifetime time horizon was used.
Synthesis of evidence on outcomes	Based on a systematic review.	The effectiveness of asfotase alfa (AA) is based on pooled analyses of patient-level data from prospective single-arm studies and the United Kingdom (UK) Market Access Agreement (MAA). BSC effectiveness in terms of mortality and invasive ventilation support was based on a retrospective chart review of the natural history of the disease. BSC effectiveness in terms of 6-minute walk test (6MWT) was based on screening pre-test period recordings from single-arm

Element of economic analysis	Reference case	EAG comment
		interventional studies. Inputs for both AA and BSC groups were augmented using other literature and expert opinion.
Measure of health effects	QALYs and LYs.	Health outcomes are valued in terms of LYs and QALYs gained.
Source of data for measurement of HRQoL	Reported directly by patients and/or carers.	The utility values in the model were derived from the clinical expert elicitation study, which was designed to elicit utility estimates for the health states defined in the CEA (by the need for invasive ventilation for patients under 5 years old and by severity level for those age 5 and over). Standardised sets of UK preference weights were used and were mapped to 3 Level (3L) values, aligning with NICE's recommendation prior to the new 2022 guidance.
Source of preference data for valuation of changes in HRQoL	Representative sample of the public.	
Discount rate	An annual rate of 3.5% on both costs and health effects.	Costs and health outcomes were discounted at 3.5%.
Equity weighting	An additional weighting can be applied for Highly Specialised Technology (HST) producing incremental QALYs greater than or equal to 10.[60]	The company base-case estimated undiscounted results for QALY gains greater than 30 and implemented therefore a QALY weight of 3.

AA = asfotase alfa; BSC = best supportive care; CEA = cost effectiveness analysis; EAG = Evidence Assessment Group; HRQoL = health-related quality of life; HST = Highly Specialised Technology; ICU = Intensive Care Unit; LY = life year; NHS = National Health Service; NICE = National Institute of Health and Care Excellence; MAA = Managed Access Agreement; PSS = Personal Social Services; QALY = quality-adjusted life year; UK = United Kingdom; 3L = 3 level; 6MWT = 6-minute walk test

5.3.2 Model structure

An Excel-based Markov model was developed to perform the CEAs of AA in patients with paediatric-onset HPP. The modelling approach is similar to the economic model submitted in the original HST appraisal in 2017.[4] A major difference in the current submission is that the model is structured differently for patients aged <5 years old at HPP onset than for patients aged 5+ years at HPP onset. This is to reflect differences in disease manifestations and potential impact of treatments. For patients aged <5 years, the model simulates the disease severity by ventilation status and accounts for HPP-related mortality, whereas for patients aged 5+ years, disease progression is simulated by using 6MWT as a surrogate for disease severity and HPP-related mortality is not considered, in patients receiving either AA or BSC. That is because younger patients face elevated risks of HPP-related mortality and respiratory complications requiring invasive ventilation compared to older patients. Disease impact in the submitted cost effectiveness model is estimated in terms of costs, HRQoL for patients and caregivers, and, for patients aged <5 years only, also in terms of HPP-related survival.

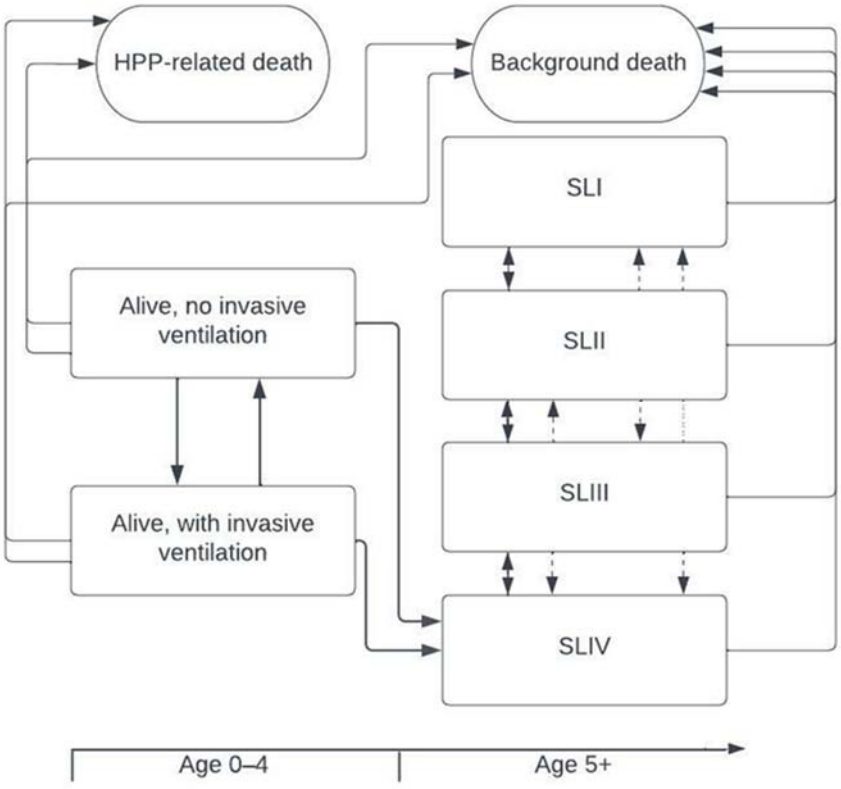
For patients aged <5 years, the model consists of a death state and two mutually exclusive health states indicating whether the patient requires invasive ventilation or not. Death for patients aged <5 years is represented by two absorbing states including the HPP-related death state and background mortality

state. Invasive ventilation is included as a toll state, representing the patients that were <5 years in the trials and required invasive ventilation. Invasive ventilation leads to health utility decrements and additional direct medical costs.

For patients aged 5+ years, the model consists of four mutually exclusive health states with distinctive severity levels (SL) (SLI; SLII; SLIII; SLIV) and a death state for background mortality. The severity levels of the HPP disease are defined based on the percentage of observed versus predicted 6MWT (observed 6MWT/predicted 6MWT) measure indicating the relative 6MWT performance of a patient with respect to the expected average 6MWT performance of the healthy subjects of the same gender and similar age range. Perinatal-/infantile-onset HPP patients surviving to the age of 5 are assumed to enter the model in the health state SLIV.

Figure 5.1 provides the graphical presentation of the model as reported by the company.

Figure 5.1: Model structure



Based on Figure 34 of the CS[10]
CS = company submission; HPP = hypophosphatasia; SL= severity level

For patients aged <5 years, transitions to invasive ventilation are constant and independent of age. Transitions between the health states and death are all age dependent. Age-specific background mortality risks are estimated from UK life tables. HPP mortality rates for BSC and AA treatment are estimated based on KM curves obtained from trial observations and the UK MAA. Invasive ventilation rates for BSC and AA treatment are estimated based on survival estimates obtained from trial observations at 5 and 1.8 years, respectively.[13] For patients aged 5+ years, transition probabilities between the disease severity levels are obtained from ordered probit models run separately for BSC and AA arms based on patients' observed health state transitions, age and the days elapsed between visits.

Derivation of the invasive ventilation/HPP mortality risks and transitions between the different severity levels health states are further explained in Section 5.3.3.

The categorisation of severity levels for patients aged 5+ years is defined based on predicted thresholds, which used the minimum clinically important difference (MCID) of 30.2 metres estimated via the "*one third of the standard deviation method*" and represented 8.8% of the baseline 6MWT distance.[61] This approach is aligned with the MCID for the Duchenne's muscular dystrophy (DMD), which is considered to be closely related to HPP disease, as estimated in McDonald et al. 2013.[62] In the study of McDonald et al. 2013[62] MCID for 6MWT and percentage predicted 6MWT were calculated at 31.7 meters and 8.9%, respectively, based on the same method of "*one third of the standard deviation*". In the CS model, the number of alive health states was chosen arbitrarily at four. Furthermore, the range defining each severity level was based on two times the MCID as a percentage of the baseline 6MWT distance (17.6%).

Therefore, the severity level based on the 6MWT as a percentage of predicted distance for patients aged 5+ are defined as shown in Table 5.3.

Table 5.3: Health state definitions, based on the 6MWT as a percentage of predicted distance

Health state	6MWT as a percent (%) of predicted		
	Age 5–12 years	**Age 13–17 years**	**Age ≥18 years**
SLI (Lowest impact on ambulation)	82.5–100	82.7–100	84.1–100
SLII	64.9–82.4	65.3–82.6	68.1–84.0
SLIII	47.3–64.8	47.9–65.2	52.1–68.0
SLIV* (Highest impact on ambulation)	≤ 47.2	≤ 47.8	≤ 52.0

Based on Table 36 of the CS[10]
CS = company submission; 6MWT = 6-minute walk test; SL = severity level
*Patients who could not complete the 6MWT were categorized in SLIV

The company indicated that clinical experts who reviewed the framework did not feel that the severity levels based on percentage of predicted 6MWT adequately captured the full extent of the disease burden for patients living with HPP, although they could not define a more appropriate modelling approach. During the original appraisal of AA in 2017, the committee also accepted that using the percentage of predicted 6MWT to define health states was relatively reasonable, considering the lack of evidence that could be used to define alternative structures. Nonetheless, the committee stated that a model structure capturing all symptoms of HPP would be preferred.[4]

The model uses a lifetime time horizon and adopts an NHS perspective. A cycle length of 12 weeks is used. The model employs a half-cycle correction and a discount rate of 3.5% per year for costs and effects. In the base-case of the patient population aged <5 year, a mean age of onset of 0-month-old is used based on the mean age of onset (1 month) rounded using the model's 12-week cycle length.[5] In the base-case of the patient population aged 5+ years, a starting age of 5.0, based on the mean age at first admission,[63] and an initial severity level distribution of 10.53%, 26.32%, 42.11% and 21.05% is used respectively for SLI, SLII, SLIII, SLIV, based on the ENB-006-09 and ENB-009-10 AA clinical studies and the UK MAA dataset including patients aged 5–17 years at baseline (n=19).

EAG comments: The EAG considers that there is uncertainty regarding the assumption that perinatal-/infantile-onset HPP patients surviving to the age of 5 enter the model in the health state SLIV. In

response to clarification question B1d, the company indicated that this assumption was validated with clinical experts.[9] However, in response to clarification question B8 on the scenario analysis based on the UK MAA data in which there were no patients requiring invasive ventilation support, the company mentioned that "*as a consequence of 100% of patients being invasive-ventilation free, it was assumed that 50% of perinatal-/infantile-onset patients receiving AA and surviving at age 5 enter the model in health state SLIII, with the remaining 50% entering health state SLIV*", and emphasised the "*lower severity of disease associated with patients not requiring invasive ventilation*".[9] While this seems a reasonable assumption, it contradicts the base-case assumption that also all patients with no invasive ventilation move to SLIV. The assumption that all patients with no invasive ventilation move to SLIV is also in contradiction with the assumption that the caregiver disutility of patients with no invasive ventilation is equal to that of patients in SLIII, as well as the expert opinion that *"SLIV and invasive ventilation should result in the worst decrement, followed by SLIII and no invasive ventilation."*

Adverse events were not included in the model because the most commonly reported AEs were ISRs for AA treatment, whereas for BSC, AEs have never been evaluated accordingly. The EAG understands the challenges of incorporating AEs into the model considering the lack of comparative studies and expects that inclusion of AEs would have limited impact on the total costs and health effects. See Section 5.3.3.4 for further details.

5.3.3 Evidence used to inform the company's model parameters

This Section presents a summary of the evidence sources used to inform the company's model parameters. The main sources used in the CS are the clinical trials ENB-002-08/ENB-003-08, ENB-010-10, ENB-006-09/ENB-008-10, ENB-009-10, and the UK MAA for AA patients, and for BSC patients the ENB-011-10 natural history study.[2, 6, 7, 46-48] A detailed description of model parameter values and sources is presented below.

5.3.3.1 Population

The patient population considered in the cost effectiveness model is defined as patients with paediatric onset HPP, which consists of patients with perinatal-/infantile-onset HPP (onset before or at birth/onset at 0–6 months) and patients with juvenile-onset HPP (onset 6 months–17 years). This is consistent with the final NICE scope and the DP. The patient population in the economic analysis was subdivided in two patient groups, patients aged <5 years and patients aged 5+ years, to reflect the elevated risks of HPP-related mortality and respiratory complications requiring invasive ventilation for younger patients compared to older patients. For older patients, the company indicated that management of HPP symptoms is the focus of care, as there is a lack of evidence regarding excess HPP-related mortality at patients aged 5+ years.

Demographic data inputs to the CEA were obtained from the baseline characteristics of participants in the HPP trials and the natural history/non-interventional studies providing data of historical controls as shown in below:

Table 5.4: Baseline model cohort characteristics

Characteristic	Model input	Source
Initial age (years)		
Patients aged <5 years	0.0	The mean age of onset is 1 month old rounded down to 0 months based on the model's 12-week cycle length. Whyte et al. 2016[5]

Characteristic	Model input	Source
Patients aged 5+	5.0	Assumed that all patients with juvenile-onset HPP begin treatment at age of admission. Whyte et al. 2016[63]
Percentage of female patients (%)		
Percentage of females	46.7%	ENB-002-08/ENB-003-08, ENB-010-10, ENB-006-09/ENB-008-10, ENB-009-10, ENB-011-10, and ALX-HPP-502.[2, 6, 46-48, 64]
Based on Table 33 and Section B.3.2.1 of the CS[10] CS = company submission; HPP = hypophosphatasia		

EAG comments: The EAG questioned if the patient characteristics included in the model are representative for the UK patient population (Question B3 in the clarification letter).[40] The company acknowledged that although the AA clinical trial programme included limited numbers of UK patients, the disease pathophysiology and clinical progression are common among all patients with HPP, strengthening the company's expectation that patients in AA trials are representative of the UK patients.[9] Nonetheless, it is unclear to the EAG why the company did not use the UK MAA data to inform the baseline cohort characteristics given the UK MAA data is the source for the majority of the new data about AA-treated patients included in this resubmission (see Section 3.3.1).

5.3.3.2 Intervention and comparators

The cost effectiveness of the intervention, AA, is compared against BSC alone, which may include: i) medical management of symptoms and functional disorders such as seizures, chronic muscle and/or skeletal pain, respiratory complications, renal complications, and gastrointestinal complications; ii) neurosurgical interventions for craniosynostosis; iii) physical therapy to help improve muscle function, conditioning and strength, as well as mobility; iv) orthopaedic management of fractures and pseudo fractures; and v) dental monitoring, including preventative care and dental hygiene aimed at avoiding a bacterial invasion.

5.3.3.3 Transition probabilities

Table 5.5 presents a summary of evidence sources used to inform the company's model parameters for transition probabilities. These key efficacy inputs will be elaborated on in the subsections below. At the end of each subsection, issues surrounding the appropriateness of selected sources and the derivation and application of the model parameter values and will be discussed under the "EAG Comments" sections.

The model structure implies that several key efficacy inputs have been considered including:

- Transitions between invasive ventilation and HPP-related/background death for patients aged <5 years.
- Transitions between severity states based on the 6MWT model, and background death for patients aged 5+ years.

Table 5.5: Summary of evidence sources used to inform transition probabilities in the company's model

Parameter group	Source of parameter values
Perinatal/infantile onset	
Transition probabilities for hypophosphatasia (HPP) mortality in the asfotase alfa (AA) arm	AA interventional clinical trials, analysis on the ENB-002-08/ENB-003-08 (n=11) and ENB-010-10 (n=69) trials with two patients excluded and the United Kingdom (UK) Management Access Agreement (MAA) ([redacted]
Transition probabilities for HPP mortality in the best supportive care (BSC) arm	Historical control study analysis on the ENB-011-10 (n=48) study with seven patients excluded (patients who died on the first day were excluded from the analysis as it was considered likely that these patients would not be started on AA treatment)
Transition probabilities for invasive ventilation in the AA arm	Whyte et al. 2014[13]
Transition probabilities for invasive ventilation in the BSC arm	Whyte et al. 2014[13]
Juvenile onset	
Transition probabilities for disease severity states based on percentage predicted 6-minute walk test (6MWT) in the AA arm	AA clinical trials, analysis on the ENB-006-09/008-09 (n=13) and ENB-009-010 trials (n=19) with five patients excluded and the UK MAA (n=24)
Transition probabilities for disease severity states based on percentage predicted 6MWT in the BSC arm	AA Clinical trials, analysis on the ENB-006-09/008-09 (n=13) and ENB-009-010 trials (n=19) with six patients excluded
Other-cause mortality	UK life tables from the Office for National Statistics (ONS)[65]
Based on Table 33 and section B.3.3.1.3- of the CS[10] AA = asfotase alfa; CS = company submission; HPP = hypophosphatasia; MAA = Managed Access Agreement; ONS = Office for National Statistics; UK = United Kingdom; 6MWT = 6-minute walk test	

Transition probabilities for HPP mortality and background mortality

HPP-related mortality was only considered for patients <5 years of age, whereas for patients aged 5+ years it was assumed that they have the same mortality risk as the general population. The transition probabilities for HPP-related mortality in the model were based on the survival data from the ENB-002-08/ENB-003-08 (11 patients) and ENB-010-10 (26 patients) trials as reported by Whyte et al. 2016,[5] with the addition of 43 treated patients from the ENB-010-10 trial,[6] which were enrolled in the study since the last cut-off date, and 11 patients from the UK MAA for AA patients.[7] For BSC patients, the respective transition probabilities were based on 48 patients from the ENB-011-10 trial.[2]

The ENB-002-08/ENB-003-08 and ENB-010-10 trials, which were used to derive the HPP mortality data for the AA arm, were interventional studies including patients aged ≤3 and ≤5 years at enrolment, respectively. All patients were required to have a documented diagnosis of HPP (with perinatal/infantile onset) and to have presented symptoms prior to 6 months of age. Two patients from ENB-010-10 did not meet these criteria, leading to a total number of 91 patients in the AA arm. For BSC, the ENB-011-10 trial results were used to derive HPP-related mortality. ENB-011-10 was a retrospective, multinational, noninterventional natural history study in which data extracted from the chart reviews of patients with perinatal/infantile onset HPP was analysed. Patients in the ENB-011-10 trial who died on the first day were excluded from the analysis as these patients would not be considered to start on AA treatment, resulting in a total of 41 patients being included in the BSC arm. Survival data from the

clinical trials were then translated into a KM curve, measuring survival times from birth to death as shown in Figure 5.2.

Figure 5.2: Overall survival for HPP: Kaplan–Meier curves for AA and BSC

Based on figure provided in response to clarification question B4.[9]
AA = asfotase alfa; BSC = best supportive care; HPP = hypophosphatasia

For both BSC and AA arms, 12-week HPP-related mortality rates (cycle length = 12 weeks) were calculated as shown in Table 5.6 and were implemented uniformly for the two alive health states: invasive ventilation, and no invasive ventilation. Parametric survival modelling was not explored in this analysis, as HPP-related mortality was only applied for the first 5 years in the model and the trial data were assumed to be mature enough. Of note, the follow-up time for ENB-002-08/ENB-003-08 and ENB-010-10 trials were up to 6 and 7 years, respectively, whereas in the UK MAA follow-up duration was up to 4 years.

Background age-specific death rates for both patient populations, aged <5 years and aged 5+ years, were included using life tales for the UK from the Office for National Statistics (ONS).[65]

Table 5.6: HPP-related mortality in the first 10 cycles for patients aged <5 years

Week	Age (years)	AA		BSC	
		S(t)*	f(t)	S(t)*	f(t)
0	0.00	[redacted]	[redacted]	1.000	0.195
12	0.23	[redacted]	[redacted]	0.805	0.152
24	0.46	[redacted]	[redacted]	0.683	0.107
36	0.69	[redacted]	[redacted]	0.610	0.280
48	0.92	[redacted]	[redacted]	0.439	0.000

Week	Age (years)	AA		BSC	
		S(t)*	f(t)	S(t)*	f(t)
60	1.15	[redacted]	[redacted]	0.439	0.167
72	1.38	[redacted]	[redacted]	0.366	0.000
84	1.61	[redacted]	[redacted]	0.366	0.000
96	1.84	[redacted]	[redacted]	0.366	0.000
108	2.07	[redacted]	[redacted]	0.366	0.000
120	2.30	[redacted]	[redacted]	0.366	0.000

Based on Table 38 and Table 39 of the CS[10]
AA = asfotase alfa; BSC = best supportive care; CS = company submission; f(t) = the proportion of the remaining population from the prior time period who died in the current time period; HPP = hypophosphatasia; S(t) = the proportion of the original population alive at time t.

*S(t) is calculated as 1- ([number of deaths observed at time t]/N). An approximation of f(t) is calculated as 1-(S[t]/S[t-1]), where t is the current 12-week time interval, and t-1 is the prior 12-week time interval, indexed for a given age.

To reflect uncertainty within the OS data in the PSA, the company used a hazard ratio (HR) to the KM estimates. A normal distribution was assumed for the HR and the standard deviation (SD) was calculated through a calibration method using the Solver function in Microsoft Excel®.

EAG comments: To model the impact of treatment on HPP-related mortality for patients aged <5 years, mortality rates based on unadjusted survival from birth data for both treatment arms were compared. The difference in survival from birth between AA treated patients and historical controls is assumed to reflect a treatment effect. The EAG considers that this approach may have potential biases as survival curves may not be aligned with treatment initiation (see also Sections 4.3 and 4.5.2). The KM curves based on "survival from birth" can erroneously indicate that AA patients were treated from birth, whereas they were treated only after the study enrolment (see Section 4.3 EAG comment regarding immortal time bias). The company in clarification question B4 responded that considering the lack of a randomised control study comparing AA and BSC arms, and the fact that BSC patients by definition do not have a treatment initiation time, it is not possible to use time from treatment initiation for this comparison.[9] They argued that using survival since treatment initiation for AA and survival since birth for BSC would be inappropriate as AA patients begin treatment at an age greater than 0. Furthermore, the company noted that HPP symptoms onset was close to birth for all patients, with the average age of 1 month for patients in the ENB-010-10 trial and Whyte et al. 2016 study,[5, 6] and 0 years for the UK MAA patients, whereas on average, patients started treatment at approximately 1 year of age across all studies (response to clarification question B4).[9] As per the company's answer, considering the average treatment initiation is at 1 year, the EAG questions what is the reason the curves are so different right from the start of Figure 5.2. For example, after 12 weeks, in the AA group 2% has died versus 20% in the BSC group. That likely indicates that AA patients present better survival from birth, as they can only initiate treatment if they live long enough to be treated. The EAG also noticed that HPP-related mortality data for BSC in patients <5 years were similar as in the original submitted appraisal, while data from the global HPP Registry (ALX-HPP-501) were not used to inform the HPP-related mortality for BSC (see Section 3.3.3).[4] The only difference compared with the original submission is that the seven patients in the ENB-011-10 trial who died on the first day were excluded from the analysis, resulting in a total of 41 patients instead of 48 in the original submission. Considering this exclusion, the CS states that "for the BSC arm, the current base-case aligns with the EAG's preferences to the

original NICE submission, where patients who died on the first day were excluded from the analysis as it was considered likely that these patients would not be started on AA treatment". However, the EAG in the original submission found this comparison of survival data to be still biased when AA and historical control patients are not matched (see also Section 4.3). The EAG in the original appraisal, considered additional evidence provided by the company and noticed that the probability of survival for people with infantile onset HPP had improved over the years and in the BSC only 21 patients were diagnosed after 2000 compared with AA patients being diagnosed after 2005. To address these biases, the EAG in the original appraisal considering additional evidence provided by the company, also removed BSC patients who were diagnosed before the year 2000 in addition to the seven patients who died on the first day. The committee in the original appraisal found this approach more appropriate when comparing OS data for AA with BSC.[4] The committee noted that the estimate of incremental life years reduced by 1 life year when using survival data from people in the historical control group who were diagnosed in 2000 or later compared with using survival data from all historical controls. Furthermore, a matched analysis was requested by the EAG, not only because risk factors between the two groups would need to be comparable, such as the year of diagnosis, but also because matched patients in the BSC arm had to be alive when 'their' AA patient started treatment. To address the bias due to survival estimated from birth in the BSC group compared with from the start of treatment in people receiving AA, the company provided additional analysis retrospectively matching patients from its historical control data with patients having AA from its clinical studies. The survival benefit in the matched analysis was lower than the unmatched analysis.[4] In the current resubmission, the company did not consider this evidence and continued presenting an unmatched survival analysis between BSC and AA arms. The EAG therefore thinks the limitations reported during the original appraisal still pertain in the current analysis, agrees with the conclusion of the EAG and committee in the original appraisal and considers that the company failed to appropriately address these concerns in the current submission. The EAG is unable to make any changes to address these suggestions due to lack of access to patient-level data.

The EAG also considers that the company could have used parametric extrapolation methods as per the NICE Decision Support Unit (DSU) Technical Support Document 21 (TSD 21)[66] to allow for flexibility in HPP-related survival estimates. The EAG in the original appraisal found that among six parametric models, the Gompertz distribution provided a better fit, especially towards the end of the observation period, for both the AA and BSC arm.[4] The unadjusted survival data in Figure 5.2 above shows that most HPP-related deaths occur within the first 75 weeks while the numbers at risk slowly decrease thereafter, with censoring increasing uncertainty. It is also questionable to the EAG why the company considers the 5 years as cut-off for HPP-related survival when there are very limited number of deaths observed after 2 years (Figure 5.2).

In clarification question B5, the EAG asked the company to provide further details on the magnitude and methods used to estimate the "hazard ratio" ("HRs") used in the PSA to reflect uncertainty within the OS data, but also to describe in detail the implementation approach for the PSA.[9] The company answered that two separate "HRs" to the KM estimates of AA and BSC arms (B5a in the clarification letter) were estimated to estimate the amount of variation in the probabilistic analysis.[9] The so-called HR was therefore assumed to be 1 for the deterministic analysis. The calibration method that was used to estimate these probabilistic "HRs" minimises the total sum of the squared differences between the minimum and maximum values obtained from the statistical KM curve estimates, and those estimated with the calibrated SD when applying a normal distribution centred around a value of 1 to the observed KM curve. The EAG assumes that the company estimated an 'uncertainty/variation factor' that was multiplied with the f(t) values in Table 5.7, and the boundaries defined below reflect the 95% CI around

the KM curve. Therefore, what is mentioned as an HR by the company is considered to be a variation factor by the EAG, as reflected in Table 5.7.

Table 5.7: Factors applied to the mortality rates (f(t)) based on the Kaplan-Meier estimates used in PSA analysis

Arm	Calibrated SD	95% CI LB factor	95% CI UB factor
BSC	0.190	0.627005	1.372995
AA	0.355	0.303296	1.696704

Based on Table 10 of the clarification letter[9]
AA = asfotase alfa; BSC = best supportive care; CI = confidence interval; LB = lower bound; PSA = probabilistic sensitivity analysis; SD = standard deviation; UB = upper bound

The EAG noticed that the SD for the AA 'uncertainty/variation factor' in Table 5.7 is higher than for BSC and consequently the CI is wider. This seems to be counterintuitive since for AA there are more patient data than for BSC. The EAG cannot explain why this happens. Furthermore, as also confirmed by the company in the clarification letter,[9] the two 'uncertainty/variation factors' are not correlated in the PSA, which might lead to implausible results in some PSA iterations. As indicated by the company, assuming that the 'uncertainty/variation factor' are not correlated when in fact they are leads to an overestimation of the uncertainty.

Transition probabilities for invasive ventilation
Invasive ventilation was considered only for patients <5 years of age. Transition probabilities for invasive ventilation were estimated using the same trials mentioned above for HPP-related mortality. Nonetheless, transition probabilities for invasive ventilation were modelled independent of age.

The company estimated transition probabilities using the study of Whyte et al. 2014,[13] which, according to the CS, reported on ENB-002-08/ENB-003-08, ENB-010-10, and ENB-011-10 trials. For the AA arm, an 84% rate of invasive VFS over 1.8 years was translated to a constant rate of 0.0223 per 12-week period using data from 37 patients in Whyte et al. 2014.[13] Similarly, for the BSC arm, a 25% rate of invasive VFS over 5.0 years was translated to a constant rate of 0.0638 per 12-week period using data from 48 patients in Whyte et al. 2014.[13] The rates were then converted to probabilities resulting in a 12-week probability of receiving invasive ventilation of 0.0220 for AA and 0.0618 for BSC.

The company noted that in the UK MAA data, there were [redacted] reported to require invasive ventilation at any of the follow-up time, whilst [redacted] treatment-naïve patients were on invasive ventilation at registry enrolment. Therefore, the UK MAA data were not used as a data source to inform transitions to invasive ventilation for patients aged <5 years in the base-case analysis. To address the lack of patients on invasive ventilation in the UK MAA dataset, a scenario analysis was conducted in which [redacted] of patients in the AA arm are expected to be invasive ventilation-free. Because of this assumption, 50% of perinatal-/infantile-onset patients receiving AA and surviving at age 5 entered the model in health state SLIII, with the remaining 50% entered the model in health state SLIV.

EAG comments: The EAG could not validate the values used to estimate transition probabilities for invasive ventilation referenced to Whyte et al. 2014.[13] The reference of Whyte et al. 2014[13] used by the company is only an abstract that refers to a natural history study of 48 patients with perinatal and infantile onset and does not include patients from the AA arm, nor reports a 25% rate of invasive VFS over 5.0 years for BSC patients.

In response to clarification question B7b,[67] the company indicated that "*at t=0, the proportion of patients on invasive ventilation is equal to the risk of invasive ventilation at each cycle. For AA there are 2.2% of patients on invasive ventilation. For BSC, 6.2% are on invasive ventilation*".[9] However, the EAG considers that this is not completely correct since at t=0, treatment has not started yet and therefore both risks should be equal. Therefore, the EAG in their preferred base-case set invasive ventilation risk at t=0 to be equal to 6.2% in both treatment arms.

Risks for invasive ventilation in the patient population aged <5 years are assumed to be age independent. Since HPP disease severity manifests differently in younger than older patients and HPP-related mortality in patients aged <5 years is modelled dependent on age, the EAG asked for the rationale for uniformly applying invasive ventilation risks across all ages for patients aged <5 years (Question B7 in the clarification letter).[67] The company responded that applying a constant risk of receiving invasive ventilation across the first 5 years of age was deemed more appropriate to capture the potential need of patients for repeated invasive ventilation support during this time period rather than using time to event data and parametric survival models for invasive VFS.[67] Also, in response to B7d,[67] the company acknowledged the uncertainty about assuming a constant rate of invasive ventilation. However, this assumption cannot be changed in the model. Therefore, it is unclear why the company also mentioned that changing the ventilation rate is not a driver of the model results, when in the model it is only possible to consider a constant rate. A more flexible approach (e.g., parametric extrapolations) could have helped addressing this uncertainty. When the EAG asked for the rationale for uniformly applying invasive ventilation risks across all ages for patients aged <5 years (Question B7 in the clarification letter) and requested survival data for invasive ventilation to be included in the model,[40] the company responded that applying a constant risk of receiving invasive ventilation across the first 5 years of age was deemed more appropriate to capture the potential need of patients for repeated invasive ventilation support during this time period rather than using time to event data and parametric survival models for invasive VFS.[67] The EAG agrees that if there are many patients requiring repeated ventilation support, then a time to event analysis would not be the most appropriate approach. However, the company did not provide any additional evidence in the clarification letter to show the breakdown of patients requiring repeated ventilation support. If the number of patients with repeated ventilation support is low, then a time to event analysis would still be more informative than a constant risk. Therefore, the EAG is still unable to assess the suitability of the approach with the evidence provided.

Transition probabilities for 6MWT-defined health states

Transition probabilities between severity levels were only considered for patients aged 5+ years. The 6MWT was used to reflect progression through disease severity levels. The distance walked in meters was assessed at each visit and the percentage of observed versus predicted 6MWT was used to allocate patients across the severity levels. As described in Section 5.3.2, severity levels were defined based on predicted thresholds, which used the MCID of 30.2 metres estimated via the "*one third of the standard deviation method*", representing 8.8% of the baseline 6MWT distance. The threshold values of 6MWT as percentage of predicted were assumed to vary by age-group (Table 5.3).

The 6MWT performance measure was included as outcome measure in the ENB-006-09/ENB-008-10 (n=13, age 5-12 years) trials, the ENB-009-10 (n=19, age 13-66 years) trial and in the UK MAA (n=45). Patients completed the 6MWT at each visit and patients who were under the age of 65 (no normative values for 6MWT were available for patients aged over 65 years) considered in the analysis. Patients who could not complete the 6MWT were assumed to be in the most severe health state (i.e., SLIV).

Data were collected from pre-baseline visit through a maximum of 264 weeks post-baseline. For AA patients, outcomes were obtained using all visits in which patients received AA (i.e., post-baseline

visits). For BSC patients, the analysis was conducted using screening/pre-baseline and baseline visits of all patients included in the AA analysis, as well as post-baseline visits for patients in ENB-009-10 treated with BSC during the 24-week primary treatment period.

To determine transition probabilities, patients with at least two 6MWT assessments on AA or BSC were included so that a severity level transition could be observed. In total, the AA and BSC arms included respectively 51 and 26 patients. In the AA arm, 27 patients were included from the clinical studies and 24 from the UK MAA. Baseline characteristics for patients considered in the 6MWT analyses are similar for AA and BSC as shown in Table 5.8, except for the number of visits (mean number of visits for AA: 9.5; for BSC: 2.2) and follow-up length (mean number of follow-up in months for AA: 44.2; mean number of follow-up in months for BSC: 2.6). The differences in the number of visits and follow-up time are justified by the fact that most of the BSC patients were trial participants during the screening and pre-baseline visits.

Table 5.8: Baseline characteristics for 6MWT analyses

Descriptor	AA	BSC
Sample size	51	26
Male (n, %)	25 (49.0%)	14 (53.8%)
White (n, %)	26 (96.3%)	25 (96.2%)
Visits		
Mean	9.5	2.2
Standard deviation	5.4	0.7
Min	2	2
Max	17	4
Follow-up length in months		
Mean	44.2	2.6
Standard deviation	25.6	2.1
Min	3.0	0.7
Max	79.1	8.4
Age at first visit (years)		
Mean	26.5	28.0
Standard deviation	21.3	22.5
Min	5	6.0
Max	64	64
Age at onset (years)		
Mean	1.9	1.4
Standard deviation	2.8	1.2
Min	0	0
Max	14	4
Height (cm)		
Mean	138.3	142.3
Standard deviation	26.9	22.8
Min	89.0	89.0

Descriptor	AA	BSC
Max	180.0	174.0
Weight (kg)		
Mean	47.8	51.2
Standard deviation	26.0	25.7
Min	11.4	11.4
Max	97.0	90.7

Based on Table 41 of the CS[10]
AA = asfotase alfa; BSC = best supportive care; CS = company submission; 6MWT = 6-minute walk test; kg = kilogram; Max= maximum; Min = minimum

For the AA arm, there were in total 432 transitions observed from the two consecutive 6MWT recordings, and for the BSC arm there were in total 32 transitions observed (Table 5.9). Table 5.9 shows the number of transitions from previous to the most recent visits. For BSC patients, there were no transitions observed from SLIV to lower severity level health states, whereas for AA patients 21 out of 64 transitions in SLIV were to less severe states (SLI–III).

Table 5.9: Observed state transitions for AA and BSC

	State at current visit				
State at prior visit	**SLI_t**	**$SLII_t$**	**$SLIII_t$**	**$SLIV_t$**	**Row Total**
AA group					
SLI_{t-1}	152	23	2	2	**179**
$SLII_{t-1}$	33	64	15	6	**118**
$SLIII_{t-1}$	3	27	34	7	**71**
$SLIV_{t-1}$	2	6	13	43	**64**
Column Total	**190**	**120**	**64**	**58**	**432**
BSC group					
SLI_{t-1}	5	3	0	0	**8**
$SLII_{t-1}$	2	5	3	0	**10**
$SLIII_{t-1}$	0	2	7	2	**11**
$SLIV_{t-1}$	0	0	0	3	**3**
Column Total	**7**	**10**	**10**	**5**	**32**

Based on Table 44 and Table 45 of the CS[10]
AA = asfotase alfa; BSC = best supportive care; CS = company submission; SL = severity level;

Aligned with the NICE submission in 2017,[4] multivariate ordered probit models were fitted separately to both AA and BSC arms, based on the observed health state transitions and controlling for patient age and the days elapsed between visits. This approach assumes that a latent continuous metric (e.g., disease severity) underlies the ordinal observations (e.g., health states based on percentage predicted 6MWT). The resulting coefficient estimates of a probit model can be used to generate predicted probabilities for a transition matrix, which provides the age-specific probability of being in a given health state conditional on prior health state.

Three model specifications were tested where each specification was run separately for BSC and AA arms.

- Model with specification 1 estimates current health state (severity level) based on prior health state in terms of severity level, days elapsed between visits and intercept.
- Model with specification 2 estimates current health state (severity level) based on prior health state in terms of severity level, patient's age at visit, days elapsed between visits and intercept.
- Model with specification 3 estimates current health state (severity level) based on prior health state in terms of severity level, patient's age at visit, days elapsed between visits, interactions between age and previous health states- (severity levels) and intercept.

The three specifications produced comparable goodness-of-fit statistics measured with log likelihood tests and the McFadden's pseudo R^2 measure of fit. Specification 2 was considered more appropriate for the base-case analysis, since it produced age-specific transition probabilities, which were deemed necessary for the model. That was because the likelihood of being in different disease severity levels was expected to be age-specific and the selected model would need to generate out-of-sample predictions for patients older than 65 years old. Specification 2 was also preferred over specification 3, as it included fewer covariates relative to the number of observations needed to be considered in the model to avoid model overspecification. In the CS, the company stated that the last was especially problematic for BSC for which specification 3 resulted in coefficient estimates that did not statistically significantly differ from zero due to the limited number of observations.

Hence, in the CS base-case, specification 2 was used to generate age-specific predicted probabilities for the transition matrix of each treatment arm, whereas specification 3 was used in the sensitivity analysis. To generate transition probabilities for each treatment and age, it was assumed that 84 days elapsed between visits (one model cycle of 12 weeks). Table 5.10 presents the transition probability matrix for patients aged 5.0 years old. Note, that BSC patients entering in SLIV were assumed to remain in SLIV.

Table 5.10 Transition probability matrix at age 5.0 years for AA and BSC

State at prior visit	State at current visit			
	SLI_t	**$SLII_t$**	**$SLIII_t$**	**$SLIV_t$**
AA group				
SLI_{t-1}	90%	9%	0%	0%
$SLII_{t-1}$	40%	46%	11%	2%
$SLIII_{t-1}$	12%	45%	30%	13%
$SLIV_{t-1}$	1%	16%	33%	51%
BSC group				
SLI_{t-1}	65%	33%	2%	0%
$SLII_{t-1}$	10%	58%	31%	1%
$SLIII_{t-1}$	1%	20%	68%	12%
$SLIV_{t-1}$	0%	0%	0%	100%

Based on Table 47 and Table 48 of the CS[10]
AA = asfotase alfa; BSC = best supportive care; CS = company submission; SL = severity level

EAG comments: In response to clarification question B16,[9] the company indicated that limited 6MWT data were collected in the Global HPP Registry. However, these data were not used to in the model to estimate transition probabilities for 6MWT-defined health states (see Section 4.2.2.1 for further details)

As in the original NICE submission of 2017, the number of patients in the BSC arm in the current submission is the same.[4] Therefore, the number of observations used to estimate transition probabilities between the severity health states in the BSC arm is small, implying a large uncertainty associated to these input parameters which was not resolved when compared with the original appraisal. In clarification question B12,[40] the EAG asked the company to apply the Laplace's rule of succession to the BSC observation matrix (i.e., to add +1 to unobserved transitions). In their response, the company argued that "*without the addition of more data points, the recommendation to add +1 observations to all transitions that were unobserved is problematic due to the small sample size*".[9] The EAG acknowledges the problems associated with the small sample size, but given the low number of observed transitions, and that several transitions remained unobserved, the current approach can be deemed as problematic too. The EAG also understands that the addition of +1 observations is likely to introduce bias, but drawing conclusions such as "*the observed data indicate no patient on BSC improved from SLIV to a less severe state*",[9] which is based on three observations only, is likely to be biased as well. Therefore, despite the limitations, the EAG still considers that Laplace's rule of succession a valid approach and would have wanted to see the requested scenario conducted. The results of this scenario should have been interpreted with caution, but it could have been used to illustrate the potential uncertainty associated with the BSC transition probabilities. However, this scenario was not provided by the company. The EAG appreciates that the company presented an alternative scenario, but unfortunately that scenario was not completely appropriate to illustrate the purpose of the clarification question.

Three specifications were provided for probit regression models developed separately for the AA and BSC arms to estimate transition probabilities between the severity levels (refer to Table 46 of the CS).[10] The first specification included the previous severity state and days between visits into the model. The second specification added age at visit in the first model specification, and the third specification was similar to the second, but also including interaction terms between age at visit and previous severity states. The EAG noticed that the three specifications produced comparable goodness-of-fit statistics and that in both the second and third specifications, in which age at visit was included as a covariate, the estimated coefficients for age at visit were not statistically significant, while in the second specification, age at visit had a positive coefficient for AA (+0.002) and a negative coefficient for BSC (-0.012), indicating a relatively small impact. Similarly, the covariate measuring days between visits had a positive coefficient for AA (+0.003) and a negative coefficient for BSC (varied from -0.017 to -0.009). When asked on the appropriateness of the signs of the coefficients according to prior expectations, the company did not provide any further clarifications in clarification question B13.[9]

Aligned with the previous EAG preference during the original NICE submission of 2017 to use one single model for both treatment arms, the EAG asked the company to provide the coefficients of the probit regression models for all patients (BSC and AA) including a treatment effect as covariate in all model specifications (clarification question B9).[67] Considering the limited number of observations, especially for BSC patients, it was considered by the EAG that having one probit model for all patients (BSC and AA) including a treatment effect as covariate may provide more reliable results than fitting separate models for both arms. The company's reaction to this request was to provide model results for a specification including a treatment indicator, but also interactions of the treatment indicator with the lag of severity level parameters.[67] The company's rationale was that to achieve the same flexibility as the separate models, the joint model with a treatment-indicator covariate would require interaction terms of the treatment indicator with each covariate. To avoid model overfit by the inclusion of so many covariates while maintaining adequate flexibility in the modelling of the AA treatment effect, the abovementioned model specification was considered more adequate according to the company.[67] The

EAG appreciates that the company presented an alternative model specification, but does not consider that this model specification addresses the EAG's concerns on the stability of the results due to the small number of observations for BSC and would have preferred a more parsimonious model without interaction terms.

Therefore, considering the uncertainty around model predictions due to the limited number of observations, especially for BSC, the EAG agrees with the company's preferred model and considers the second specification more appropriate for the base-case analysis. Nonetheless, as explained above, the EAG also has concerns around the inclusion of age as a covariate and considers the most parsimonious model of the first specification appropriate for inclusion in the scenario analyses. In the CS, the scenario analyses only explored the impact of using the third instead of the second specification, completely neglecting the most parsimonious specification 1.

5.3.3.4 Adverse events

Adverse events were not included in the model and in the CS, it was mentioned that most of the TEAEs were HPP-related but not treatment-related, with the most common TRAEs being ISRs. Furthermore, the CS states that AEs from BSC treatment have never been previously evaluated prohibiting their inclusion in the cost effectiveness model.

EAG comments: Although most of the AA TEAEs were assessed not to be related to the study treatment, the EAG has concerns on the exclusion of the AEs (Key issue 4 in Section 1.4). As reported in Section B.2.10 of the CS,[10] and the company response to clarification question A.19,[9] the incidence for severe AEs is not negligible. The EAG also thinks that no systematic approach was followed to distinguish study TRAEs from disease related complications.

However, the EAG understands the challenges of incorporating AEs into the model considering the lack of comparative studies and expects that inclusion of AEs would have limited impact on the total costs and health effects.

5.3.3.5 Health-related quality of life

Health-related quality of life of patients

The same source as in the original submission was used to inform the utility values for the health states in the model. This was a vignette study done with HPP clinical experts in the UK.[68] However, one input value was altered: the utility in the under 5 years on ventilation stage was -0.09 in the study publication and in the original submission, but it has been changed to 0.00 in the current submission (Table 5.11). No rationale was given for this change. As in the original submission, no effects of AEs on HRQoL were included.

Table 5.11: Utility values used in the health economic model

Health state	Mean utility value	Standard error
Under 5 years – no invasive ventilation	0.24	0.12
Under 5 years – invasive ventilation	0.00	0.17
Age 5 and over - SLI	0.86	0.04
Age 5 and over – SLII	0.67	0.03
Age 5 and over – SLIII	0.54	0.03
Age 5 and over - SLIV	0.23	0.08

Health state	Mean utility value	Standard error
Based on Table 55 of the CS[10] CS = company submission; SL = severity level		

A number of alternative sources of utility data were considered but dismissed by the company. These included a more recent vignette study that aimed to obtain utility estimates for three age groups (5-12 years, 13-17 years, and 18 and older).[69] Clinical experts rated vignettes using the EQ-5D-5L and EQ-5D-Y questionnaires. The resulting utility values were considered extremely implausible and therefore deemed not suitable to be used in the model.

As part of the UK MAA, HRQoL data were collected from 18 adult and 14 paediatric patients. The data were considered unsuitable for use in the model due to the small sample size.

The international HPP registry collected HRQoL data. These data were not used in the model for two reasons. First, over 80% of the adult records in the registry were not matched to the 6MWT percent of predicted. Second, the utility values were too high to be deemed plausible by experts.

EAG comments: The EAG considers it a limitation that HRQoL data obtained from patients were not used. The same vignette study as in the original submission was used to inform health state utilities in the base-case. As such, the EAG comments on that submission still hold. In particular, the design of the vignette study made it prone to lead to similar utility values being assigned to health states by experts, therefore suggesting a lower variability in health-related quality of life than could be expected in reality. This limitation was not addressed in the PSA (e.g., by increasing uncertainty beyond that was observed in the vignette study), while the univariate sensitivity analyses showed that the model results are quite sensitive to changes in the health state utility input values.

The NICE reference case states that HRQoL must be measured/reported in patients. Two sources could have potentially provided patient reported HRQoL data: the UK MAA and the Global HPP Registry. Only a small sample of HRQoL data were available from the UK MAA, limiting its value for the economic model. The use of the HRQoL data from the Global HPP Registry was complicated due to a limited number of patient records being matched to the 6MWT percent predicted. Nonetheless, it would be valuable to use the available data in an explorative manner to validate the utilities from the vignette study or explore its impact in a scenario analysis. Whereas the available data from the UK MAA was presented in the CS, the data from the Global HPP Registry was not shown, even though it was clarified in the response to the clarification questions that utility values were calculated for the health states. There was no explanation as to why this data were not presented in the CS or the response to the clarification questions, which prevents further exploration of this data in an EAG scenario analysis.

Health-related quality of life of caregivers

The impact of caring for patients with HPP on the HRQoL of caregivers was taken into account in the current model (it was not in the original submission). No published data on the burden of caring for patients with HPP was available. Rather, data from an observational study on the caregiver burden of patients with DMD was used, as this was considered a condition with similar burden on caregivers.[70] This study reports the QoL of caregivers for Duchenne patients for four categories of caregiver perceptions of patients' heath (excellent, very good, good, fair/poor). Quality of life of caregivers was measured using the EQ-5D-3L and valued using the UK value set. The study found a QoL of caregivers of patients in 'Excellent' health (utility of 0.88) and that of caregivers of patients in 'fair/poor' health (utility of 0.71). The difference between these two utility values (0.17) was used as the utility decrement in caregivers of patients under 5 that required invasive ventilation, as well as patients 5 years and older

in the most severe health state (SLIV). It was assumed that no disutility was experienced by caregivers of patients in the least severe health state (SLI). For the two intermediate health states (SLII and SLIII) the disutility for caregiver burden was calculated by weighing the maximum disutility (as applied to caregivers of patients in SLIV) with the ratio of the difference between the best health state (SLI) and the intermediate health state (SLII or SLII) and the difference between the best (SLI) and worst (SLIV) health state. For example, the caregiver burden utility decrement for patients in health state SLII was assumed to be:

$$SLII\ caregiver\ disutility = invasive\ ventilation\ disutility * \frac{SLI\ utility - SLII\ utility}{SLI\ utility - SLIV\ utility}$$

It was assumed that caregivers for patients under 5 not requiring invasive ventilation experienced the same utility decrement as caregivers of patients in the SLIII health state. An overview of the caregiver disutilities for each health state are shown in Table 5.12. The caregiver disutility is counted for one caregiver until the patient reaches an age of 60 years. As no information on parameter uncertainty was available, a standard error of 10% of the mean (-0.017) was assumed.

Table 5.12: Utility decrements representing caregiver burden used in the health economic model

Health state	Disutility	Standard error
Under 5 years – no invasive ventilation	-0.09	N/A
Under 5 years – invasive ventilation	-0.17	-0.017
Age 5 and over - SLI	0.00	N/A
Age 5 and over – SLII	-0.05	N/A
Age 5 and over – SLIII	-0.09	N/A
Age 5 and over - SLIV	-0.17	-0.017
Based on Table 55 of the CS[10] CS = company submission; SL = severity level		

The effect of infant death on the HRQoL of parents was also included in the model. An estimate of the effect size published in literature was used as this same effect was used in a previous NICE HST.[71, 72] A reduction in utility of 0.04 in both parents was applied for the remainder of their lives.

EAG comments: The EAG considers the use of evidence on caregiver burden from caregivers for DMD patients reasonable, given the evidence available. However, the CS only presented one source of caregiver burden and no indication that a literature search was conducted.[10] The company's answers to the clarification questions included a limited overview of relevant data from the recent review of carer HRQoL in NICE appraisals.[73] This showed that in NICE HST3 a disutility of 0.11 was used for caregivers of DMD patients.[74] We consider this value a more appropriate estimate for use in the base-case. In addition, in NICE HST8 which assessed burosumab for treating X-linked hypophosphataemia in children and young people, arguably a condition with similarities to HPP, a disutility of 0.08 was used.[73] The uncertainty of this estimate, as well as the number of caregivers to which this disutility is applied, is explored in scenario analyses.

In the model, caregiver disutility is only applied to patients who at a certain timepoint are alive under both treatment arms. In practice this means that caregiver disutility is only applied in both arms based on the patients alive in the BSC arm at a given timepoint, as mortality is lower in the AA treatment arm. As the source of caregiver disutility is the provision of care to the patient, the disutility should be applied as long as the patient that is cared for is alive. Therefore, this has been corrected in the EAG base-case.

The inclusion of disutility accounting for bereavement in NICE appraisals is rare. Two instances cited in the CS are TA588 (Nusinersen for treating spinal muscular atrophy)[75] and HST7 (Strimvelis for treating adenosine deaminase deficiency–severe combined immunodeficiency).[72] In TA588, a disutility of 0.04 was included in the base-case, whereas in HST7 a disutility of 9% of the child's QALY loss in a scenario. In the current submission the same disutility of 0.04 as used in TA588 was used, the source of which is a study by Song et al. 2010.[71] This study was conducted in the US and the extent to which this applies to a UK setting is unknown. The EAG is of the opinion that a conservative approach is warranted given the uncertainty of this estimate and the scarcity of prior examples in which disutility for bereavement has been included in NICE appraisals. Therefore, disutility for bereavement is not included in the EAG base-case, but rather in a scenario analysis. Another matter of uncertainty is the duration for which a disutility for bereavement is experienced. In the company base-case, this disutility is applied for the remaining lifetime of both bereaved parents. No justification was given for this assumption. The impact of this assumption is explored in scenario analyses where the disutility is applied for a shorter period of 25 years. In the study by Song et al. 2010 the average time since death of the child corresponding to the disutility estimate used was 21 years.

Health-related quality of life in the general population

A model from Ara and Brazier was used to determine age specific general population utilities.[76] These utilities are then used as a multiplication factor on the utilities in the model for all patients 18 years and older.

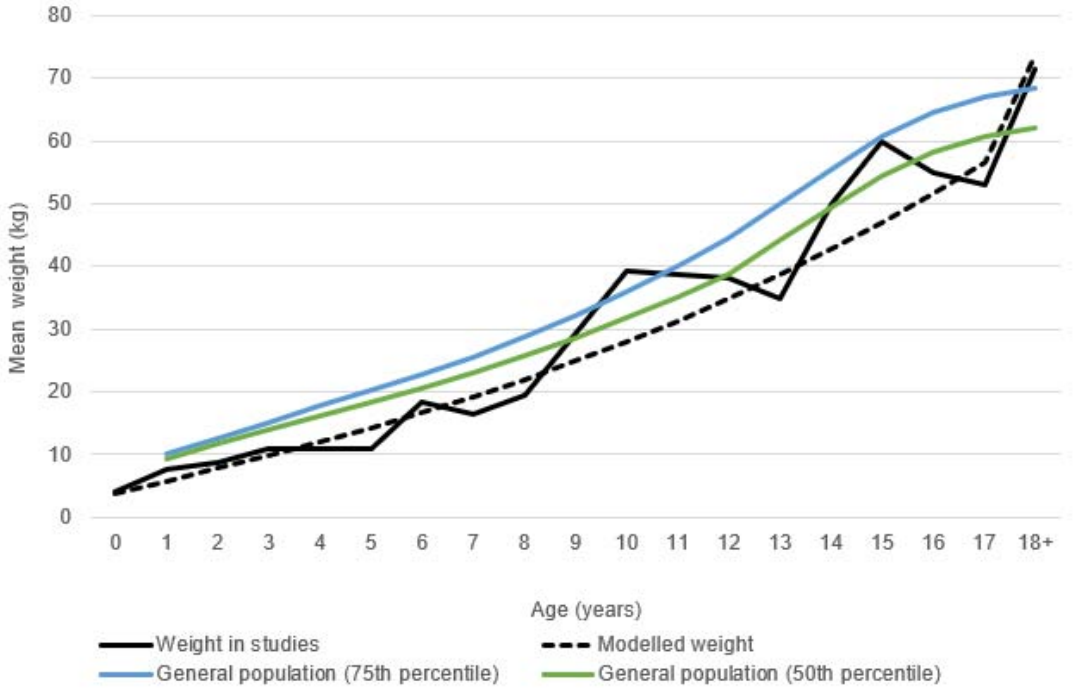
5.3.3.8 Resources and costs

AA acquisition and administration costs

Treatment costs of AA consist only of drug acquisition costs and depend on the dosing schedule, which varies by patient weight. AA is administered 2 mg/kg of body weight subcutaneously 3 times per week, or 1 mg/kg of body weight administered subcutaneously 6 times per week. No administration costs were considered in the model. AA treatment costs were calculated using the list price of AA in the UK at £58.80 per mg. A simple patient access scheme (PAS) discount of [redacted] was applied, leading to a discounted cost of [redacted] per mg. The model further assumes that loss of exclusivity in 7 years from the start of the model's horizon will lead to 58.5% decrease in the list price of AA.

The age-specific weight used to calculate AA treatment costs was estimated based on the average weight observed in different age ranges of patients from the ENB-002-08/ENB-003-08, ENB-006-09/ENB-008-10, ENB-009-10, ENB-010-10 clinical trials and the MAA UK study. Smoothing was applied to the mean weight value curves using a third-degree polynomial model, as for some of the ages, trial data were deviating from the weight patterns observed in the general population as shown in Figure 5.3 below.

Figure 5.3: Comparison of weight from studies, modelled prediction and general population



Based on Figure 36 provided in CS.[10]
AA = asfotase alfa; CS = company submission; HPP = hypophosphatasia.
Sources: ENB-002-08/ENB-003-08, ENB-006-09/ENB-008-10, ENB-009-10, ENB-010-10 and the MAA UK study; General population weight based on UK-WHO growth charts.[77]

The model considers wastage as partially used vials of AA are not administered to another patient while the excess AA is considered in drug cost calculations. The company based on interviews with two clinical experts argued that in practice clinicians make an effort to minimise drug wastage by rounding down the dose per administration if the dose was not reduced by more than 3–4 mg per administration. Therefore, the company's base-case analysis, accounted for rounding down if the administered dose was 12 mg less than the required weekly dose. Table 5.13 presents the weekly, 12-week and annual AA drug costs per age-group, calculated by average HPP patients' weight, dosing by weight range, and price per vial of AA following PAS discount values.

Table 5.13 Average weight by age for patients with HPP

Age group	Average weight (kg)	Weekly Purchased Dose (mg)*	Vials per administration	Weekly AA Drug Cost (£)	12-Week AA Drug Costs (£)	Annual AA Drug Costs (£)
0–1 year	3.92	54	1 x 18 mg	[redacted]	[redacted]	[redacted]
1 year	5.84	54	1 x 18 mg	[redacted]	[redacted]	[redacted]
2 years	7.82	54	1 x 18 mg	[redacted]	[redacted]	[redacted]
3 years	9.89	54	1 x 18 mg	[redacted]	[redacted]	[redacted]
4 years	12.05	84	1 x 28 mg	[redacted]	[redacted]	[redacted]
5 years	14.33	84	1 x 28 mg	[redacted]	[redacted]	[redacted]
6 years	16.74	84	1 x 28 mg	[redacted]	[redacted]	[redacted]
7 years	19.30	108	2 x 18 mg	[redacted]	[redacted]	[redacted]

Age group	Average weight (kg)	Weekly Purchased Dose (mg)*	Vials per administration	Weekly AA Drug Cost (£)	12-Week AA Drug Costs (£)	Annual AA Drug Costs (£)
8 years	22.02	120	1 x 40 mg	[redacted]	[redacted]	[redacted]
9 years	24.92	138	1 x 18 mg & 1 x 28 mg	[redacted]	[redacted]	[redacted]
10 years	28.03	168	2 x 28 mg	[redacted]	[redacted]	[redacted]
11 years	31.34	174	1 x 18 mg & 1 x 40 mg	[redacted]	[redacted]	[redacted]
12 years	34.89	204	1 x 28 mg & 1 x 40 mg	[redacted]	[redacted]	[redacted]
13 years	38.68	240	1 x 80 mg	[redacted]	[redacted]	[redacted]
14 years	42.74	240	1 x 80 mg	[redacted]	[redacted]	[redacted]
15 years	47.08	294	1 x 18 mg & 1 x 80 mg	[redacted]	[redacted]	[redacted]
16 years	51.72	324	1 x 28 mg & 1 x 80 mg	[redacted]	[redacted]	[redacted]
17 years	56.67	360	1 x 40 mg & 1 x 80 mg	[redacted]	[redacted]	[redacted]
18+ years	73.58	480	2 x 80 mg	[redacted]	[redacted]	[redacted]

Based on Table 57, Table 58 and Table 59 of the CS[10]
AA = asfotase alfa; CS = company submission; kg = kilogram; mg = milligram
*The values in this column are not aligned with the respective values in Table 50 of the CS, as the EAG considers that the values in Table 59 are erroneously calculated

Furthermore, the model accounts for a treatment compliance rate of [redacted], informed from the UK MAA study, and an annual discontinuation rate [redacted] (translated in a 12-week discontinuation probability of [redacted] informed from the ENB-002-08/ENB-003-08, ENB-010-10, ENB-006-09/ENB-008-10 clinical trials, the UK MAA, and the Global HPP Registry.

BSC costs

For BSC, there are no treatment costs applied in the model. All costs related to managing HPP were assumed to be covered by health state costs for patients with HPP presented in the next subsection.

Health state costs

Resource use costs associated with the different HPP health states were primarily based on the previous NICE submission of 2017.[4] Resource use of discrete clinical events remained relatively aligned with the NICE submission of 2017, following clinical experts' confirmation that clinical practice for HPP treatment has remained relatively unchanged since 2016. Small adjustments included addition of pain management services, addition of dietician visits and inclusion of mental health services, as patients with HPP may experience mental health difficulties related to the disease. Unit costs for resource use associated with HPP health states were updated accordingly and inflated to 2020-21 if values were prior 2021 using the NHS Cost Inflation Index from the 2021 Personal Social Services Research Unit.[8] The cost estimates per year per health state are presented in Table 5.14.

Table 5.14: Resource use costs by health state

Health state	Annual cost	Cost per cycle (12 weeks)
Age <5 years		
No invasive ventilation	£66,162.18	£15,216.94
With invasive ventilation	£608,926.80	£140,040. 66

Health state	Annual cost	Cost per cycle (12 weeks)
Age 5+ years		
SLI	£3,308.87	£760.97
SLII	£5,646.83	£1,298.66
SLIII	£11,027.83	£2,536.18
SLIV	£20,258.85	£4,659.12
Based on Table 63 of the CS.[10] CS = company submission; SL = severity level		

Adverse event costs

Costs of AEs were not included in the analysis.

EAG comments: The company's base-case analysis accounted for a price reduction of 58.5% in AA treatment costs to account for patent expiration in 7 years from now. The EAG does not consider this assumption reasonable for the base-case analysis since it is only based on the company's expectations and not on evidence. To further support this, the rationale for the magnitude of the price reduction (58.5%) was based on reports of prices for biosimilar infliximab suggesting price reductions of 45–72% versus the originator product.[78] Clarification (B18) was requested by the EAG on what the reasoning is behind the company's expectation that biosimilars for AA would lead to similar price reductions.[40] The response was that there is a paucity of data for price reduction in rare diseases due to the introduction of biosimilars, and the infliximab price reduction was selected as a reference drug for price reduction by the company due to the data availability.[9] The EAG questions the assumption that a generic version of the drug will replace AA after patent expiry. Furthermore, as the EAG noted in the original appraisal of 2017,[42] the number of existing biosimilars for orphan diseases is very limited, likely attributed to the economically unattractiveness of producing biosimilars for orphan diseases targeting small populations. The committee in the original appraisal of 2017, also acknowledged that there was no robust basis for assuming a price reduction due to future patent expiry and stated that it had not previously considered price reductions resulting from the potential introduction of generics or biosimilars because this is speculative, and the impact of their introduction is unknown. Therefore, the EAG's preferred base-case analysis in Section 6.2 does not consider a potential price reduction for AA treatment due to future patent expiry.

To estimate AA treatment costs the company used mean weight value curves using a third-degree polynomial model fitted to data from AA clinical trials and the UK MAA study. Firstly, the EAG noticed that the company used average weight values per patient's age using discrete values, as reported in Table 57 of the CS,[10] instead of a continuous scale, and implemented a rounding down function for age in the model. That means that if a patient is for instance 19.8 years, the AA dosing schedule is underestimated by assuming that this patient weighs as a patient at the age of 19. The EAG corrected this functionality in the model. Secondly, the EAG notices that the modelled patient's weight based on the polynomial model is much lower than the weight of the general population as shown in Figure 5.3. The company did not provide any information on the goodness-of-fit for the polynomial model and on other smoothing curves that they have been potentially exploring. The EAG also noted that for the higher age range (i.e., above the age of 13), the difference between the smoothed curve and the curves from the general population are stronger than for the respective differences in the younger ages (Figure 5.3). The 50th percentile weight curve of the general population based on UK-World Health Organization growth charts is about 1.15-1.90 times higher than the smoothed curve. Thirdly, considering that the AA underlying mechanism of action leads to renewed bone development and improvements in rickets and growth, it could be expected that patient's weight on AA treatment would

improve. Therefore, the EAG's sensitivity analysis considered a scenario in which the patients' weight followed the median values of the general population as shown in Figure 36 of the CS.[10, 77] As data from the Royal College of Paediatrics and Child Health cover people up to the age of 17, the weight from the smoothed curve and the lower bound of the differences between the 50th percentile weight curve and the smoothed curve was used to estimate the weight for people aged 18+ (i.e. 1.15) in the EAG scenario analysis.

The model accounts for drug wastage for the excess drugs of AA vials not administered to patients. The company's base-case analysis accounted for partial wastage, by rounding down the AA treatment costs if the administered dose was 12 mg less than the required weekly dose, indicating that patients would receive a lower dose than recommended to avoid drug wastage. This assumption was based on interviews with two clinical experts mentioning that efforts were made to minimise drug wastage by rounding down the per administration dose if this was not reduced by more than 3–4 mg per administration. The EAG noticed that the model included two additional functionalities to account for wastage which were not explained in detail in the CS.[10] These were the 'rounding up' and 'closest'. In the clarification response (B17),[9] the company explained that the option of 'rounding up' is the same as assuming complete wastage based on the total vials required to purchase the required dose, whereas the 'closest' option selects the option that is the closest to the required dose between the 'rounding down with 12 mg cap' (partial wastage) or 'rounding up' (complete wastage). Considering that efforts to minimise drug wastage are not aligned with the recommended dosage in the SmPC[79, 80], the EAG's preferred base-case analysis considers complete drug wastage for the remainder of the AA vials that are not used as part of the required dose, hence chose the 'rounding up' option. Note that in the SmPC a vial size of 12 mg/0.3 ml is also available, which has not been considered in the current submission by the company to limit drug wastage by the use of bigger vial sizes. The impact of the other two wastage options in the model was explored in the EAG's scenario analysis.

The company estimated an annual AA treatment discontinuation rate of [redacted] combining data from the ENB-002-08/ENB-003-08, ENB-010-10, ENB-006-09/ENB-008-10 clinical trials and the UK MAA (Table 60 of the CS). However, as questioned in the clarification letter (B19) it was unclear to the EAG how the data from the aforementioned sources were used to estimate this value. The company explained that in order to avoid double counting, patients who died in any of the studies were excluded from the data, as these patients were counted in the model not to receive AA due to death.[9] In contradiction to the CS, which states that data from ENB-002-08/ENB-003-08 trials were used to define the annual discontinuation rate (Section B.3.5.1 of the CS),[10] the company further indicated in the clarification response (B19) that data from ENB-002-08/ENB-003-08 was not included in the final calculation as there was no information available on the mean number of exposure days, which is contradicting Table 60 of the CS reporting the mean number of exposure to be at 2,066 days.[10] It is unclear to the EAG what is the reason for this discrepancy. Apart from the discontinuation rate, the company's base-case analysis also accounts for a treatment compliance rate of [redacted] This was informed from the UK MAA study based on patients who missed or interrupted doses because they forgot, ran out of the drug, was asked to skip doses by physician, experienced an AE or because of their own decision.

The EAG noticed that changing both parameters, the compliance and discontinuation rates, has an impact the cost effectiveness outcomes. Specifically, the higher the discontinuation rate and the lower the compliance rate, the more favourable the cost effectiveness outcomes of AA treatment versus BSC. That is because the higher the discontinuation rate and the lower the compliance rate the lower the AA treatment costs, whereas the impact of those two parameters on health effects is assumed to remain unaltered in the model. The EAG has concerns around this modelling assumption, since under this approach, patients on AA treatment who discontinue or do not comply with the treatment are assumed

to get the full health impact of the treatment. It would be expected that patients who discontinue or do not comply with the treatment would encounter a reduced AA treatment efficacy compared to treatment compliers. Considering the rarity of the data, the EAG understands that an analysis focussing on treatment compliance to measure efficacy would be difficult to be performed. On the other side, ignoring treatment compliance and discontinuation parameters would bias cost effectiveness results. Therefore, the EAG agrees with the company on the use of compliance the discontinuation rates in base-case analysis but explored the impact of using 100% compliance and no discontinuation rate in the scenario analysis.

5.3.4 Model evaluation

The health economic analyses for treating paediatric onset HPP are presented in terms of the incremental QALYs and incremental costs for AA treatment compared to BSC. The CS also included the results of one-way DSA and a PSA.

In the DSA analysis, parameters were varied one by one using the upper and lower bound values of 95% CIs. If no standard error was available to calculate the 95% CI, a standard error of 10% of the mean value was assumed. A list of all input including the upper and lower bounds and distributions for the PSA can be found in Appendix Q of the CS.[10] In the DSA analysis, the ICER was recorded for each upper and lower bound of the parameters, and the 10 parameters with the largest impact on the ICER were presented in a tornado diagram.

In the PSA, probability distributions were assigned to the model input parameters to assess the uncertainty around all parameters simultaneously. In the PSA, the following groups of parameters were sampled:

- Initial baseline severity distribution (SLI-SLIV)
- Baseline proportion of females
- Patient's weight
- Health state utility values
- Utility decrement due to infant death
- Caregiver utility decrement
- Annual frequency of resource use
- Unit costs of resource use
- Discontinuation rate
- Transition probabilities for invasive ventilation for AA/BSC
- Probit estimates for AA/BSC (i.e., transition probabilities between severity states for AA/BSC)

The PSA was conducted using 1,000 simulations. Results were recorded in the form of incremental costs and incremental QALYs and were plotted on a cost effectiveness plane. A cost effectiveness acceptability curve (CEAC) was estimated from the results of the PSA. Finally, several scenario analyses were also explored by the company to assess the impact of varying modelling assumptions on the cost effectiveness results.

5.4 Headline results reported within the CS

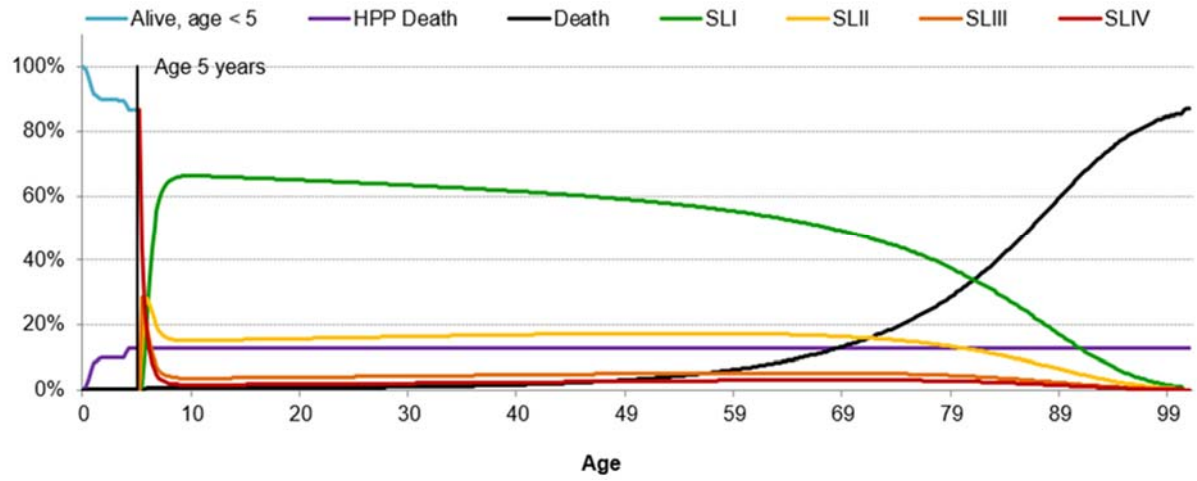
This Section summarises the results of the CEA as presented in the CS.

5.4.1 Deterministic results of the company (base-case)

Figure 5.4 and Figure 5.5 present the base-case distribution of patients per health-state over time (Markov traces) for AA and BSC, respectively, in the perinatal-/infantile-onset HPP patient population.

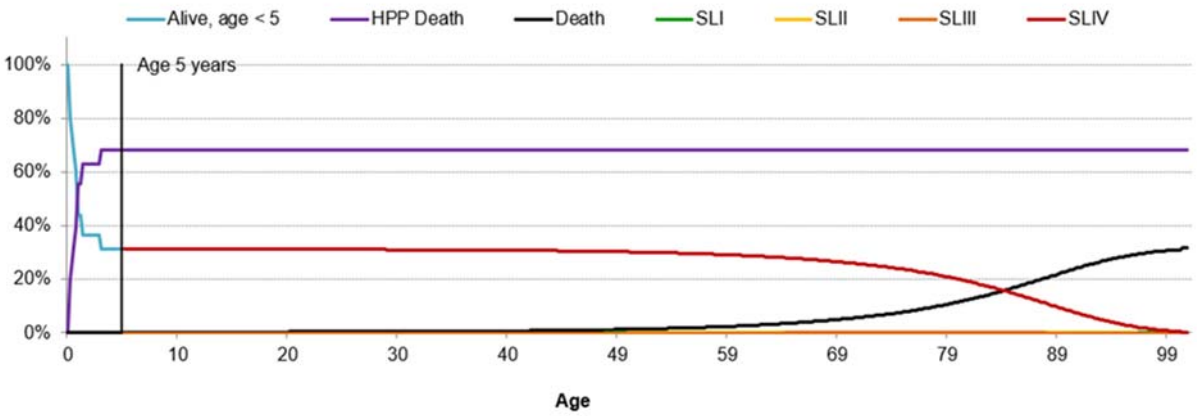
For patients aged <5 years, there is a large proportion of patients with HPP in the BSC arm who do not survive to the age of 5 (Figure 5.5), whereas this proportion is much lower in the AA arm (Figure 5.4), reflecting the OS gain of AA treatment in the perinatal-/infantile-onset HPP patients.

Figure 5.4: Markov trace: AA base-case for perinatal-/infantile-onset HPP



Based on Figure 37 of the CS.[10]
AA = asfotase alfa; CS = company submission; HPP = hypophosphatasia; SL = severity level

Figure 5.5: Markov trace: BSC base-case for perinatal-/infantile-onset HPP



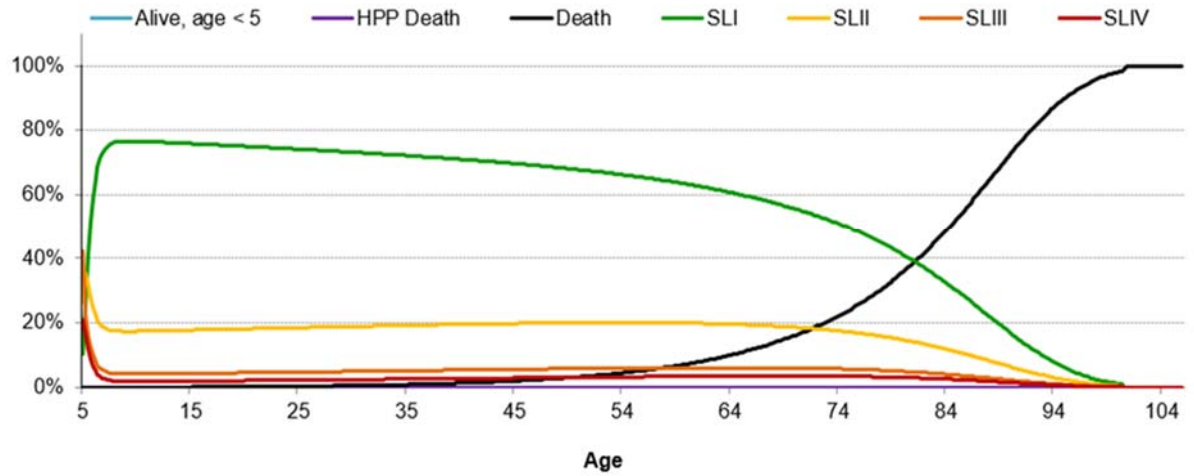
Based on Figure 38 of the CS.[10]
BSC = best supportive care; CS = company submission; HPP = hypophosphatasia; SL = severity level

Figure 5.6 and Figure 5.7 present the base-case distribution of patients per health-state over time (Markov traces) for AA and BSC, respectively, in the juvenile-onset HPP patient population.

For patients aged 5+ years, there is no OS gain for AA in the base-case, therefore there is no survival difference between the Figure 5.6 and Figure 5.7 (juvenile-onset HPP patients).

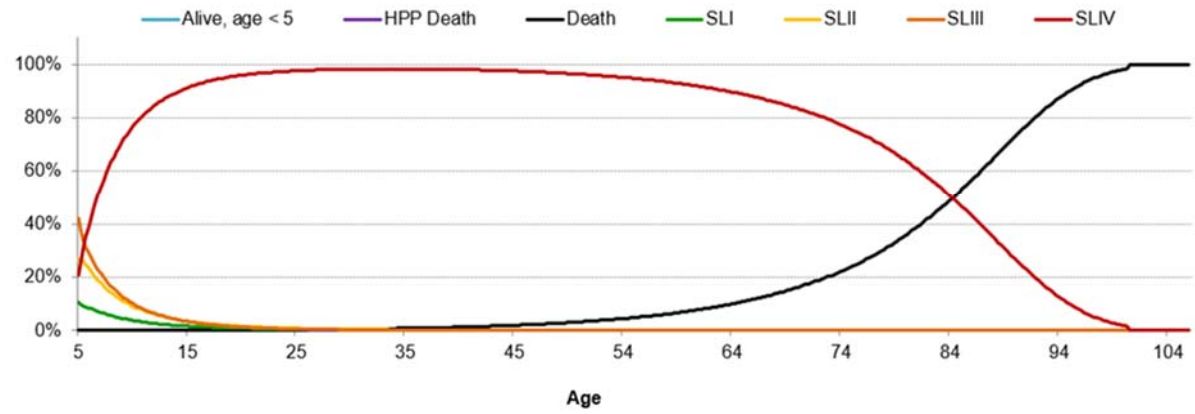
The Markov traces also show that for both populations (perinatal-/infantile- and juvenile-onset HPP), patients treated with AA are expected to spend most of their time alive in SLI while patients treated with BSC are expected to spend most of their time alive in SLIV.

Figure 5.6: Markov trace: AA base-case for juvenile-onset HPP



Based on Figure 39 of the CS.[10]
AA = asfotase alfa; CS = company submission; HPP = hypophosphatasia; SL = severity level

Figure 5.7: Markov trace: BSC base-case for juvenile-onset HPP



Based on Figure 40 of the CS[10]
BSC = best supportive care; CS = company submission; HPP = hypophosphatasia; SL = severity level

Applying a 3.5% discount rate for both costs and effects, the company base-case results in Table 5.15 showed that compared with BSC, AA is associated with [redacted] incremental life years, [redacted] incremental QALYs, and [redacted] incremental costs in the perinatal-/infantile-onset group. In the juvenile-onset group AA is associated with [redacted] incremental life years, [redacted] incremental QALYs, and [redacted] incremental costs versus BSC. The ICER is £240,279 per QALY gained in the perinatal-/infantile-onset group and £295,536 per QALY gained in the juvenile-onset group.

Table 5.15: Company discounted base-case results without QALY weight

Technologies	Total costs (£)	Total LYG	Total QALYs	Inc. costs (£)	Inc. LYG	Inc. QALYs	ICER (£) without QALY weight
Population: Perinatal-/infantile-onset HPP							
BSC	[redacted]	[redacted]	[redacted]				
AA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£240,279

Technologies	Total costs (£)	Total LYG	Total QALYs	Inc. costs (£)	Inc. LYG	Inc. QALYs	ICER (£) without QALY weight
Population: Patients with juvenile-onset HPP							
BSC	[redacted]	[redacted]	[redacted]				
AA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£295,536

Based on Table 66 of the CS.[10]
AA = asfotase alfa; CS = company submission; BSC = best supportive care; HPP = hypophosphatasia; ICER = incremental cost-effectiveness ratio; Inc. = incremental; LYG = life years gained; QALY = quality-adjusted life year

When no discount rate is applied, the company's model estimates that perinatal-/infantile-onset patients treated with AA gain [redacted] QALYs compared to BSC. For juvenile-onset HPP patients, treatment with AA resulted in [redacted] undiscounted QALYs gain. As the company base-case estimated undiscounted results for QALY gains greater than 30, a QALY weight of 3 was implemented for health gains. Therefore, Table 5.16 presents the same results as Table 5.15 while accounting for a QALY weight of 3 for the health gains in both arms. Compared with Table 5.16, costs and life years remain unchanged in Table 5.15, whilst the incremental QALY gain for the perinatal-/infantile-onset patients increased to v, dropping the ICER to £80,093 per QALY gain. For patients with juvenile-onset HPP, the incremental QALYs increased to [redacted] and the ICER reduced to £98,512 per QALY gain.

Table 5.16: Company discounted base-case results with QALY weight

Technologies	Total costs (£)	Total LYG	Total QALYs	Inc. costs (£)	Inc. LYG	Inc. QALYs	ICER (£) with QALY weight
Population: Perinatal-/infantile-onset HPP							
BSC	[redacted]	[redacted]	[redacted]				
AA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£80,093
Population: Patients with juvenile-onset HPP							
BSC	[redacted]	[redacted]	[redacted]				
AA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£98,512

Based on Table 67 of the CS[10]
AA = asfotase alfa; CS = company submission; BSC = best supportive care; HPP = hypophosphatasia; ICER = incremental cost-effectiveness ratio; Inc. = incremental; LYG = life years gained; QALY = quality-adjusted life year

5.4.2 Sensitivity analyses presented within the company's submission

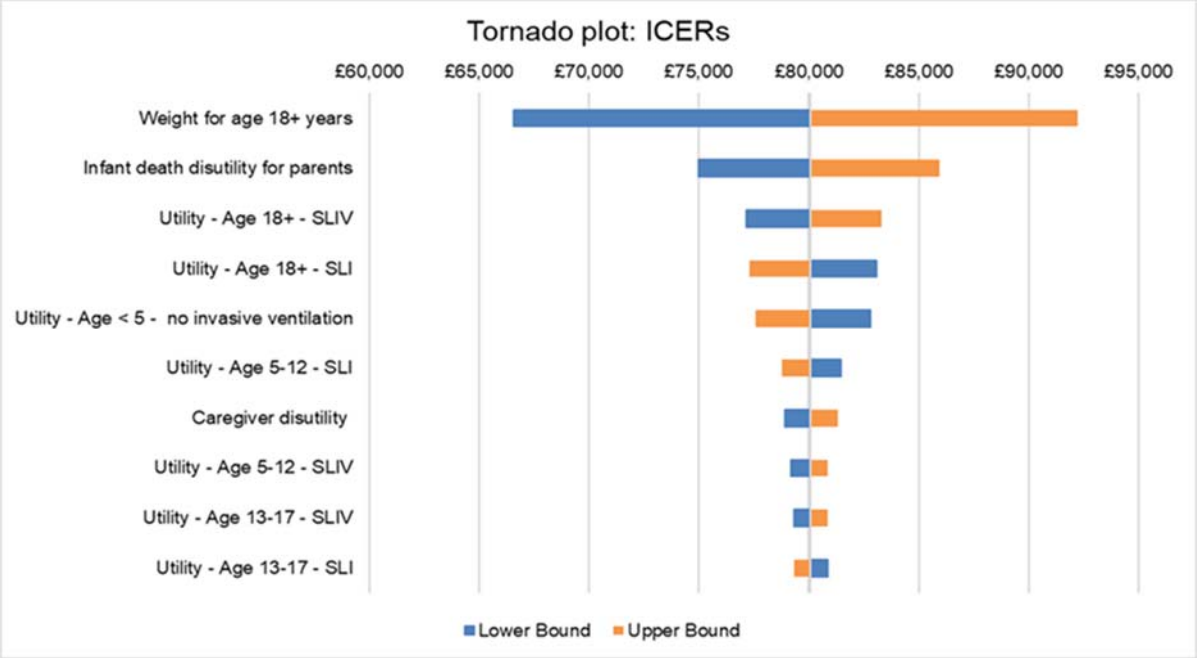
The company conducted one-way DSA and PSAs, as well as several scenario analyses. The results of these analyses are summarised in the remaining of this Section. Note that only discounted results are discussed in this Section.

5.4.2.1 One-way deterministic sensitivity analyses

In the DSA, the variables that were varied included the proportion of females, the utility values associated with health states, the disutilities, the resource use estimates, the healthcare costs, the patient

weight, and the 12-week risk of invasive ventilation. The results of the DSA are presented in Figure 5.8 and Figure 5.9 for perinatal-/infantile-onset and juvenile-onset HPP patients, respectively. The parameters with the greatest impact on the ICER are the weight for patients aged 18 years and over, which is a key parameter in the definition of the AA treatment costs, the health state utility values, the infant death disutility for parents of patients with the perinatal-/infantile-onset HPP, and the caregiver disutility values.

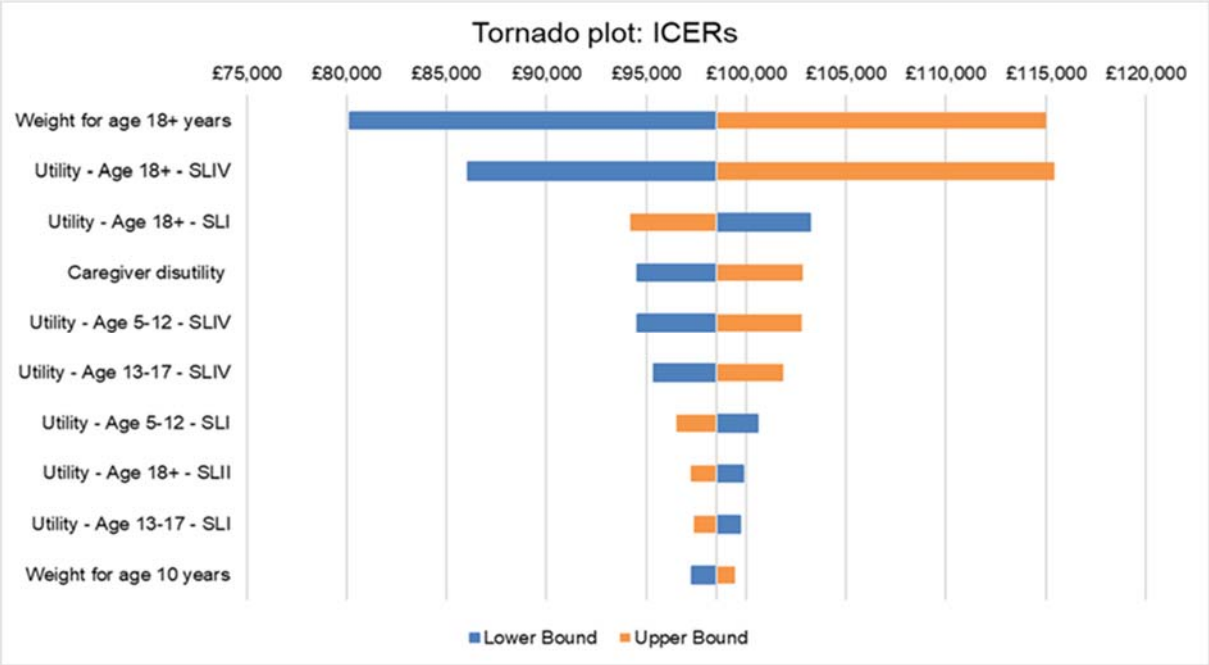
Figure 5.8: One-way sensitivity analysis for perinatal-/infantile-onset HPP patients - ICER results after applying QALY weighting



Based on Figure 45 of the CS.[10]

CS = company submission; HPP = hypophosphatasia; ICER = incremental cost effectiveness ratio; QALY = quality-adjusted life-year; SL = severity level

Figure 5.9: One-way sensitivity analysis for juvenile-onset HPP patients - ICER results after applying QALY weighting



Based on Figure 46 of the CS.[10]
CS = company submission; HPP = hypophosphatasia; ICER = incremental cost effectiveness ratio; QALY = quality-adjusted life-year; SL = severity level

5.4.2.2 Probabilistic sensitivity analysis

Results of the PSA are given in Table 5.17. The difference between PSA and deterministic outcomes is relatively large for patients with juvenile-onset HPP, for which the probabilistic ICER increased to £106,799 per QALY gain compared to the deterministic ICER of £98,512 per QALY gain (Table 5.16). The probabilistic and deterministic are quite similar for the perinatal-/infantile-onset group. That is also evident in Figure 5.11, in which incremental costs and QALYs vary in a wider range compared to Figure 5.10. The difference between probabilistic and deterministic ICER is partly attributed to the asymmetrical uncertainty distributions of regression analysis parameters (for the transition probabilities between health states) leading to a non-normal distribution of sampled outcomes. The difference in the PSA for patients with juvenile-onset HPP compared to the perinatal-/infantile-onset group, is that for the latter group a large proportion of patients in the BSC arm die before the age of 5 when the regression analysis is applied in the model for transition probabilities.[10] Hence, the asymmetries apply to a much smaller group of patients than for the juvenile-onset HPP group.

Table 5.17: Company probabilistic base-case results with QALY weight

Technologies	Total costs (£)	Total LYG	Total QALYs	Inc. costs (£)	Inc. LYG	Inc. QALYs	ICER (£)
Population: Perinatal-/infantile-onset HPP							
BSC	[redacted]	[redacted]	[redacted]				
AA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£80,661
Population: Patients with juvenile-onset HPP							
BSC	[redacted]	[redacted]	[redacted]				

Technologies	Total costs (£)	Total LYG	Total QALYs	Inc. costs (£)	Inc. LYG	Inc. QALYs	ICER (£)
AA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£106,799

Based on Table 69 and Table 70 of the CS.[10]
AA = asfotase alfa; CS = company submission; BSC = best supportive care; HPP = hypophosphatasia; ICER = incremental cost-effectiveness ratio; Inc. = incremental; LYG = life years gained; QALY = quality-adjusted life year

Figure 5.10: Probabilistic sensitivity analysis scatterplot company base-case - patients with perinatal-/infantile-onset HPP

[redacted]

Based on Figure 41 in the original CS.[10]
CS = company submission; HPP = hypophosphatasia; PSA = probabilistic sensitivity analysis; QALY = quality-adjusted life-year

Figure 5.11: Probabilistic sensitivity analysis scatterplot company base-case - patients with juvenile-onset HPP

[redacted]

Based on Figure 42 in the original CS.[10]

CS = company submission; HPP = hypophosphatasia; PSA = probabilistic sensitivity analysis; QALY = quality-adjusted life-year

5.4.2.3 Scenario analyses

The company further presented results of nine scenarios per patient population in the CS to explore structural uncertainty of the model. A summary of the scenarios explored with respective results are summarised in Table 5.18 below.

From the scenarios explored in the perinatal-/infantile-onset HPP patients, the scenarios that had the greatest impact were the use of a 25-year time horizon (instead of lifetime in base-case), the use of 1.5% discount rate for health outcomes (instead of 3.5% in base-case) and the application of a different discount rate in AA costs following the loss of patent exclusivity (45% or 72% instead of 58.5% in the base-case). It is noteworthy, that the 25-year time horizon analysis resulted in a substantially larger ICER, as the QALY weighting could not be applied in this scenario due to the lower QALY gains.

From the scenarios explored in the juvenile-onset HPP patients, the scenarios that had the greatest impact were the use a higher baseline age at 26.5 years (instead of 5.0 in the base-case), the use of a 25-year time horizon (instead of lifetime in base-case), the use of 1.5% discount rate for health outcomes (instead of 3.5% in base-case), and the application of a different discount rate in AA costs following the loss of patent exclusivity (45% or 72% instead of 58.5% in the base-case).

Table 5.18: Scenario analyses results with QALY weight*^

Scenario	Incremental costs (£)	Incremental QALYs	ICER (£)	Change versus base-case
Patients with perinatal-/infantile-onset HPP				
Base-case	[redacted]	[redacted]	**£80,093**	
Time horizon 25 years	[redacted]	[redacted]	£144,947	£64,854
Time horizon 50 years	[redacted]	[redacted]	£78,912	-£1,181
Discounting 1.5% for health benefits, 3.5% for costs	[redacted]	[redacted]	£46,612	-£33,481
Probability of invasive ventilation in AA arm = 0.00%; 50:50 split of alive patients entering SLIII and SLIV at age 5 in AA arm	[redacted]	[redacted]	£78,535	-£1,558
Include costs associated with productivity loss	[redacted]	[redacted]	£74,689	-£5,404
Stopping rule applied after age 18	[redacted]	[redacted]	£79,895	-£198
Discount after loss of exclusivity: 45%	[redacted]	[redacted]	£103,236	£23,143
Discount after loss of exclusivity: 72%	[redacted]	[redacted]	£58,224	-£21,869

Scenario	Incremental costs (£)	Incremental QALYs	ICER (£)	Change versus base-case
Model specification 3	[redacted]	[redacted]	£79,965	-£128
Patients with juvenile-onset HPP				
Base-case	[redacted]	[redacted]	**£98,512**	
Time horizon 25 years	[redacted]	[redacted]	£219,990	£121,478
Time horizon 50 years	[redacted]	[redacted]	£109,939	£11,427
Discounting 1.5% for health benefits, 3.5% for costs	[redacted]	[redacted]	£64,543	-£33,969
Include costs associated with productivity loss	[redacted]	[redacted]	£98,303	-£209
Stopping rule applied after the age of 18	[redacted]	[redacted]	£105,659	£7,147
Baseline age at 26.5 years	[redacted]	[redacted]	£237,728	£139,216
Discount after loss of exclusivity: 45%	[redacted]	[redacted]	£134,537	£36,025
Discount after loss of exclusivity: 72%	[redacted]	[redacted]	£76,075	-£22,438
Model specification 3	[redacted]	[redacted]	£111,430	£12,918

Based on Table 73 of the CS.[10]
AA – asfotase alfa; CS = company submission; HPP = hypophosphatasia; ICER = incremental cost-effectiveness ratio; SL = severity level; QALY = quality-adjusted life-year
*The EAG was unable to replicate the results of the scenario analyses included in this table.
^The EAG also noticed some of the scenarios reported in this table are producing unreasonable changes. For instance, when including costs associated with productivity loss or when using a different price reduction upon patent expiry, the incremental QALYs also change, which is not aligned with expectations.

5.4.3 Validation

The company indicated in Section B.3.13 of the CS that the model has been quality checked.[10] The quality checklist used to assess the CE model of AA treatment in paediatric-onset HPP was based on publicly available and peer-reviewed checklists of known modelling errors and questioning of assumptions, including extreme value testing, logical tests, and consistency checks.[81-83] The company also indicated that the model has been updated following feedback from the EAG in the preceding NICE submission in 2017 and submissions in other HTA agencies.

The company further solicited expert opinion to validate key model inputs and assumptions from a clinical perspective. Two UK-based HPP clinical experts were approached to validate standard treatment protocols for patients with varying severities of disease used to inform disease resource use. Another validation exercise was performed for the underlying assumption on perinatal-/infantile-onset survivors to age 5 entering the model in health state SLIV. This was validated with a clinical expert who indicated that perinatal-/infantile-onset patients surviving to age 5 on BSC would likely be in a high-severity state. Clinicians were further used to validate caregiver utility decrements, the UK MAA-derived utilities, and the effort to avoid drug wastage for AA by rounding down of dose per administration. The UK MAA-derived utilities were deemed unsuitable to inform the economic model,

but they were also considered to validate the clinician-derived utility values. Other validations were on the 6MWT severity states and 6MWT results, the model predictions and observed outcomes were compared. From these assessments, the company suggests that there is face validity to the model's predictions.

EAG comments: The EAG requested in the clarification letter (B20),[9] a further comparison of the results in the current submission with those submitted in HTA agencies of other countries such as the CADTH, the Institut national d'excellence en santé et en services sociaux (INESSS), Sweden, the Netherlands, France, and Australia, aiming to understand differences between results in terms of outcome values (e.g. life expectancy or QALYs). However, the company refused to provide such a comparison arguing the HTA requirements in other countries differ from the UK and is therefore not deemed applicable to the current submission.

5.5 Discussion of the available evidence relating to value for money for the NHS and PSS

The discounted company base-case results using a PAS discount of [redacted] for AA showed that, compared to BSC, AA is associated with [redacted] incremental QALYs at an additional cost of [redacted] in the perinatal-/infantile-onset group. In the juvenile-onset group, AA is associated with [redacted] incremental QALYs at an additional cost of [redacted] versus BSC. These correspond to ICERs of £240,279 per QALY gained in the perinatal-/infantile-onset group and £295,536 per QALY gained in the juvenile-onset group.

The undiscounted gain in QALYs with AA was [redacted] in the perinatal-/infantile-onset HPP patients and [redacted] in the juvenile-onset HPP patients compared to BSC, indicating that a weighting of [redacted] can be used to calculate a weighted threshold (of [redacted]).

The company explored various scenarios. From the scenarios explored in both the perinatal-/infantile-onset and the juvenile-onset HPP patients, the use of a 25-year time horizon (instead of lifetime in base-case) has a very large impact on the ICER, leading to a substantial increase. Using a 1.5% discount rate for health outcomes (instead of 3.5% in base-case) or applying a higher price discount in AA costs following the loss of patent exclusivity (72% instead of 58.5% in the base-case), decreased the ICERs in both patient populations. On the other side, applying a lower price discount for AA costs following the loss of patent exclusivity (45% instead of 58.5% in the base-case) substantially increased the ICERs in both patient populations. In the juvenile-onset HPP patients, the scenario that had the greatest impact was the use of a higher baseline age at 26.5 years (instead of 5.0 in the base-case), leading to a higher ICER.

The EAG's preferences regarding alternative assumptions led to changes for the following input:

- The caregiver utility decrement value.
- The caregiver disutility applied to those surviving in each of the treatment arms.
- The parental disutility due to infant death.
- The price reduction for AA following patent expiry.
- The drug wastage for AA treatment.

The impact of these EAG changes on the ICER is presented in Section 6.3 below.

The EAG also explored some other scenarios, i.e., using alternative model specifications to estimate transition probabilities between severity levels, applying different caregiver disutilities, using alternative options to incorporate parental disutility due to infant death, applying alternative options for drug wastage, assuming 100% compliance and no discontinuation rate. These scenarios are presented in Section 6.4.

6 IMPACT ON THE COST-CONSEQUENCE ANALYSIS OF ADDITIONAL EXPLORATORY CLINICAL AND ECONOMIC ANALYSES UNDERTAKEN BY THE EAG

6.1 New company analyses after the request for clarification

The company did not submit a revised base-case in response to the clarification letter.

6.2 Exploratory and sensitivity analyses undertaken by the EAG

6.2.1 Explanation of the EAG adjustments

The changes made by the EAG to the cost effectiveness model provided by the company are outlined in this Section. These changes were divided into the following three categories (as defined by Kaltenthaler 2016):[84]

1. Fixing errors (correcting the model where the company's electronic model was unequivocally wrong).
2. Fixing violations (correcting the model where the EAG considered that the NICE reference case, scope, or best practice has not been adhered to).
3. Matters of judgement (amending the model where the EAG considered that reasonable alternative assumptions are preferred).

These changes were implemented in the company's model to define the EAG base-case. Additionally, scenario analyses were explored by the EAG in order to assess the impact of alternative assumptions on the cost effectiveness results.

6.2.1.1 Fixing errors

As outlined in Section 5.3.3, an error was made by considering that at t=0, the proportion of patients on invasive ventilation is equal to the risk of invasive ventilation at each cycle, which was 2.2% for AA patients and 6.2% for BSC patients. The EAG corrected the invasive ventilation risk at t=0 to be equal to 6.2% in both treatment arms. Additionally, as mentioned in Section 5.3.3.8, the rounding down function for age used in the model to calculate AA treatment costs was removed.

6.2.1.2 Fixing violations

No violations were identified by the EAG in the economic model (see Section 5.3.1).

6.2.1.3 Matters of judgement

The EAG's preferences regarding alternative assumptions led to the following changes to the company base-case analysis:

- The utility decrement in caregivers of patients under 5 that required invasive ventilation, as well as patients 5 years and older in the most severe health state (SLIV) was assumed to be 0.17. The EAG prefers to assume that the caregiver disutility of 0.11 is a more suitable value (see Section 5.3.3.5).
- The assumption made by the company that caregiver disutility is only applied to those surviving in both treatment arms is changed. Caregiver disutility is considered appropriate to be applied to those surviving in each of the treatment arms (see Section 5.3.3.5).
- The effect of infant death on the HRQoL of parents was not included in the EAG's preferred base-case due to the limited evidence around this modelling assumption (see Section 5.3.3.5).

- The price reduction for AA of 58.5% after 7 years was excluded. Price reductions resulting from the potential introduction of generics or biosimilars are uncertain and the impact of their introduction is unknown (see Section 5.3.3.8).
- The rounding down option for drug wastage creates for some patients a deviation in AA dose received from the recommended dosing schedule based on their weight. Full wastage is assumed for AA treatment costs to align dosing strategy with the recommended dosage in SmpC of AA for all patients (see Section 5.3.3.8).[79, 80]

6.3 Impact on the ICER of additional clinical and economic analyses undertaken by the EAG

The results from the EAG deterministic base-case are shown in Table 6.1. The results are presented without QALY weighting. It is clear that the five changes together have a very large impact on the ICER. Applying a 3.5% discount rate for both costs and effects, the EAG base-case results showed that compared with BSC, AA is associated with [redacted] incremental QALYs, and [redacted] incremental costs in the perinatal-/infantile-onset group. In the juvenile-onset group AA is associated with [redacted] incremental QALYs and [redacted] incremental costs versus BSC. The ICER is £621,370 per QALY gained in the perinatal-/infantile-onset group and £739,120 per QALY gained in the juvenile-onset group. When no discount rate is applied, the EAG's base-case estimates show that perinatal-/infantile-onset patients treated with AA gain [redacted] QALYs compared to BSC, and for juvenile-onset HPP patients, the respective gain is [redacted] undiscounted QALYs, indicating that a weighting [redacted] can be used to calculate a weighted threshold. With QALY weighting, the ICER for patients with perinatal/infantile-onset HPP is £207,123 per QALY gained and for patients with juvenile-onset HPP £246,373 per QALY gained.

Table 6.1: EAG discounted base-case results without QALY weight

Technologies	Total costs (£)	Total LYG	Total QALYs	Inc. costs (£)	Inc. LYG	Inc. QALYs	ICER (£)
Population: Perinatal-/infantile-onset HPP							
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	621,370
AA	[redacted]	[redacted]	[redacted]				
Population: Patients with juvenile-onset HPP							
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	739,120
AA	[redacted]	[redacted]	[redacted]				

Based on Table 69 and Table 70 of the CS.[10]
AA = asfotase alfa; BSC = best supportive care; CS = company submission; EAG = External Assessment Group; HPP = hypophosphatasia; ICER = incremental cost-effectiveness ratio; Inc. = incremental; LYG = life years gained; QALY = quality-adjusted life year

In Table 6.2 we can see which of the changes had the largest impact i.e., the exclusion of price reduction for AA after 7 years due to patent expiry in both patient populations. Excluding the parental disutility due to infant death and applying the caregiver disutility to survivors in each of the treatment arms separately also have a clear impact, whereas the error correction and the change from partial to full wastage have relatively little impact in the perinatal-/infantile-onset HPP patients. In the juvenile-onset HPP patients, changing the caregiver disutility and implementing full wastage instead of partial wastage also have a clear impact, whereas the error correction has a relatively little impact. The exclusion of parental disutility due to infant death and the implementation of the caregiver disutility to survivors in each of the treatment arms separately have no impact in the cost effectiveness of the juvenile-onset HPP patients.

Table 6.2: Isolated impact of the EAG's preferred model assumptions without QALY weight

Preferred assumption	Section in EAG report	Inc. Costs (£)	Inc. QALYs	ICER (£/QALY)
Population: Perinatal-/infantile-onset HPP				
Company base-case	**5.4.1**	[redacted]	[redacted]	**£240,279**
Company base-case after error correction on the invasive ventilation risk at t=0	6.2.1.1	[redacted]	[redacted]	240,473
Company base-case after error correction on rounding down of age	5.3.3.8	[redacted]	[redacted]	241,839
EAG change 1 – Caregiver disutility 0.11	5.3.3.5	[redacted]	[redacted]	246,933
EAG change 2 – Caregiver disutility applied survivors in each of the treatment arms	5.3.3.5	[redacted]	[redacted]	248,179
EAG change 3 - Parental disutility due to infant death not included	5.3.3.5	[redacted]	[redacted]	258,200
EAG change 4 - Exclude price reduction for AA after 7 years	5.3.3.8	[redacted]	[redacted]	529,032
EAG change 5 - Consider full wastage of AA	5.3.3.8	[redacted]	[redacted]	245,067
EAG base-case – all 5 changes combined	-	[redacted]	[redacted]	621,370
Population: Patients with juvenile-onset HPP				
Company base-case	**5.4.1**	[redacted]	[redacted]	**£295,536**
Company base-case after error correction on the invasive ventilation risk at t=0	6.2.1.1	[redacted]	[redacted]	295,536
Company base-case after error correction on rounding down of age	5.3.3.8	[redacted]	[redacted]	299,737
EAG change 1 – Caregiver disutility 0.11	5.3.3.5	[redacted]	[redacted]	319,773

Preferred assumption	Section in EAG report	Inc. Costs (£)	Inc. QALYs	ICER (£/QALY)
EAG change 2 – Caregiver disutility applied survivors in each of the treatment arms	5.3.3.5	[redacted]	[redacted]	295,537
EAG change 3 - Parental disutility due to infant death not included	5.3.3.5	[redacted]	[redacted]	295,536
EAG change 4 - Exclude price reduction for AA after 7 years	5.3.3.8	[redacted]	[redacted]	658,265
EAG change 5 - Consider full wastage of AA	5.3.3.8	[redacted]	[redacted]	305,114
EAG base-case – all 5 changes combined	-	[redacted]	[redacted]	739,120
AA = asfotase alfa; EAG = External Assessment Group; HPP = hypophosphatasia; ICER = incremental cost-effectiveness ratio; Inc. = incremental; QALY = quality-adjusted life year				

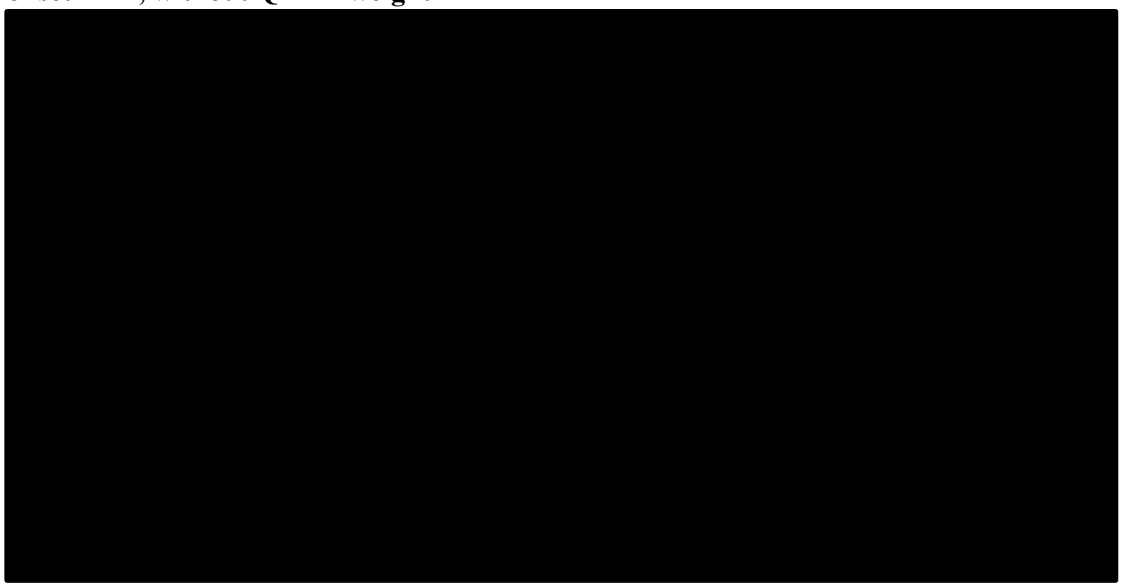
The EAG also conducted a PSA on their preferred base-case, with results shown in Table 6.3. The probabilistic ICER, averaged over 1,000 simulations, was £628,435 for the perinatal-/infantile-onset HPP patients, which is relatively close to the deterministic ICER shown in Table 6.1. The probabilistic ICER, averaged over 1,000 simulations, was £792,796 for the juvenile-onset HPP patients, which is slightly higher than the deterministic ICER shown in Table 6.1.

Table 6.3: EAG probabilistic base-case results without QALY weight

Technologies	Total costs (£)	Total QALYs	Inc. costs (£)	Inc. QALYs	ICER (£)
Population: Perinatal-/infantile-onset HPP					
BSC	[redacted]	[redacted]	[redacted]	[redacted]	628,435
AA	[redacted]	[redacted]			
Population: Patients with juvenile-onset HPP					
BSC	[redacted]	[redacted]	[redacted]	[redacted]	792,796
AA	[redacted]	[redacted]			
AA = asfotase alfa; BSC = best supportive care; EAG = External Assessment Group; HPP = hypophosphatasia; ICER = incremental cost effectiveness ratio; Inc. = incremental; QALY = quality-adjusted life year					

Figure 6.1 shows the scatterplot of the PSA outcomes on the CE-plane for perinatal-/infantile-onset HPP patients. [redacted]. Based on these, the CEAC was derived and shown in Figure 6.2. At the threshold ICER of £300,000 per QALY gained, the probability that AA is cost effective compared to BSC was [redacted].

Figure 6.1: Probabilistic sensitivity analysis scatterplot EAG base-case for perinatal-/infantile-onset HPP, without QALY weight



Based on electronic model with EAG preferred assumptions
EAG = Evidence Assessment Group; HPP = hypophosphatasia; PSA = probabilistic sensitivity analysis; QALY = quality-adjusted life-year

Figure 6.2: Cost effectiveness acceptability curve EAG base-case for perinatal-/infantile-onset HPP

Based on electronic model with EAG preferred assumptions
AA = asfotase alfa; BSC = best supportive care; EAG = Evidence Assessment Group; HPP = hypophosphatasia

Figure 6.3 shows the scatterplot of the PSA outcomes on the CE-plane for juvenile-onset HPP patients. [redacted]. Based on these, the CEAC was derived and shown in Figure 6.4. At the threshold ICER of £300,000 per QALY gained, the probability that AA is cost effective compared to BSC was [redacted].

Figure 6.3: Probabilistic sensitivity analysis scatterplot EAG base-case for juvenile-onset HPP, without QALY weight

Based on electronic model with EAG preferred assumptions
EAG = Evidence Assessment Group; HPP = hypophosphatasia; PSA = probabilistic sensitivity analysis; QALY = quality-adjusted life-year

Figure 6.4: Cost effectiveness acceptability curve EAG base-case for juvenile-onset HPP

Based on electronic model with EAG preferred assumptions
AA = asfotase alfa; BSC = best supportive care; EAG = Evidence Assessment Group; HPP = hypophosphatasia

6.4 Exploratory scenario analyses conducted by the EAG

The EAG conducted several additional scenario analyses to explore model uncertainties. The results of these scenarios are summarised in Table 6.4 and described below.

6.4.1 Scenario set 1: Transition probabilities between severity levels

Use of first model specification: Three specifications were provided for probit regression models developed separately for the AA and BSC arms to estimate transition probabilities between the severity

levels. The first specification included the previous severity state and days between visits into the model. The EAG noticed that the three specifications produced comparable goodness-of-fit statistics and that in both the second and thirds specifications, in which age at visit was included as a covariate, the estimated coefficients for age at visit were not statistically significant. To address the EAG's concerns on the stability of the results due to the small number of observations for the BSC arm, (see Section 5.3.3.) the most parsimonious specification 1 was used in the scenario analysis.

Use of third model specification: The second model specification for transition probabilities between the severity levels added age at visit in the first model specification, while the third specification was like the second, but also including interaction terms between age at visit and previous severity states. Specification 2 was considered more appropriate for the base-case analysis according to both the company and EAG, as it produced age-specific transition probabilities, which were deemed necessary for the model, whilst it included fewer covariates avoiding model overspecification (see Section 5.3.3.). Therefore, the scenario analyses also explored the impact of using the third instead of the second specification.

The results of the scenario analyses (Table 6.4) showed that for perinatal/infantile onset HPP patients, using alternative model specifications for transitions between health states had a minor impact on results. For juvenile-onset HPP patients, the most parsimonious first specification substantially increased the ICER to £945,924 per QALY gained, whereas the impact on the ICER was slightly lower for the third specification at £744,319 per QALY gained.

6.4.2 Scenario set 2: Health-related quality of life

Caregiver burden disutility: The disutility associated with caregiver burden was changed to 0.11 in the EAG base-case from 0.17 in the company base-case. As this estimate remains uncertain, the impact of this is explored in two scenarios where caregiver burden disutility is lower and higher. A scenario with a lower estimate of 0.08 was based on the value used in NICE HST8 for caring for patients with X-linked hypophosphataemia (see Section 5.3.3.5). The company base-case value of 0.17 was also used as the higher scenario. In an additional scenario, we explore the effect of applying the disutility to two rather than one caregiver.

Bereavement disutility: In the EAG base-case, bereavement disutility is not included. To explore the impact of including this, as well as the assumption on the duration of it, three scenarios are included where bereavement disutility is applied for different durations (i.e., a disutility value of 0.04 for 15 years, 30 years, and lifetime) (see Section 5.3.3.5).

In Table 6.4 it is shown that when the caregiver disutility value changed to the value of 0.08, the ICER of the perinatal/infantile-onset HPP patients increased to £626,948 per QALY gained, whereas if the caregiver disutility value was set equal to the value used in the company base-case analysis the ICER decreased to £610,506 per QALY gained. Similarly, when the caregiver disutility value changed to the value of 0.08, the ICER of the juvenile-onset HPP patients increased to £770,722 per QALY gained, whereas if the caregiver disutility value was set equal to the value used in the company base-case analysis the ICER decreased to £683,102 per QALY gained. Assuming that the number of caregivers would be two instead of one in the base-case analysis, lowered the ICER at £601,738 per QALY gained for the perinatal/infantile-onset HPP patients and at £642,520 per QALY gained for the juvenile-onset HPP patients.

Accounting for disutility in both parents due to infant death for a time horizon of 15 years, 30 years and lifetime decreased the ICER of the perinatal/infantile-onset HPP patients at £598,612, £586,150, and

£576,087 per QALY gained respectively. These scenarios had no impact in the ICER of the juvenile-onset HPP patients as no survival benefit from AA treatment is assumed in this population.

6.4.3 Scenario set 3: Resource use and costs

Weight of patients: To estimate AA treatment costs the company used mean weight value curves using a third-degree polynomial model fitted to data from AA clinical trials and the UK MAA study. The EAG noted that for the older ages the difference in weight from the smoothed curve and the curves from the general population are larger than for younger ages (Figure 5.3). Also, considering that the AA underlying mechanism of action leads to renewed bone development and improvements in rickets and growth, it could be expected that patient's weight on AA treatment would increase. Therefore, the EAG's sensitivity analysis considered a scenario in which the patients' weight followed the median values of the general population as shown in Figure 5.3 (see Section 5.3.3.8).

AA drug wastage: The EAG's preferred base-case analysis considers complete drug wastage for the remainder of the AA vials that are not used as part of the required dose, hence the 'rounding up' option. (see Section 5.3.3.8.). The model also includes a 'rounding down' option based on which the AA treatment costs are rounded down if the administered dose is 12 mg less than the required weekly dose, and the 'closest' option which selects the option that is the closest to the required dose between the 'rounding down with 12 mg cap' (partial wastage) or 'rounding up' (complete wastage) (see Section 5.3.3.8.). The impact of both scenarios was explored in the EAG's scenario analysis.

Discontinuation and Compliance: The company estimated an annual AA treatment discontinuation rate of [redacted] combining data from the ENB-002-08/ENB-003-08, ENB-010-10, ENB-006-09/ENB-008-10 clinical trials and the UK MAA and a treatment compliance rate of [redacted] based on data from the UK MAA study. The EAG noticed that changing both parameters, the compliance and discontinuation rates impact the cost effectiveness outcomes. The EAG has concerns around this modelling assumptions and explored the impact of using 100% compliance and no discontinuation rate in the scenario analysis (see Section 5.3.3.8.).

Table 6.4 shows that when the patient weight followed the pattern of the weight in the general population, the ICER of the perinatal/infantile-onset HPP patients increased to £770,947 per QALY gained, whereas the ICER of the juvenile-onset HPP patients increased to £917,000 per QALY gained.

Changing the drug wastage to the 'rounding down with 12 mg cap' option lowered the ICER of the perinatal/infantile-onset HPP patients to £609,600 per QALY gained, whereas the ICER of the juvenile-onset HPP patients reduced to £724,158 per QALY gained. Also, selecting the 'closest' option for drug wastage decreased the ICERs to £613,185 per QALY gained for the perinatal/infantile-onset HPP patients and to £728,643 per QALY gained for the juvenile-onset HPP patients.

Assuming no discontinuation rate and complete compliance rates increased the ICER of the perinatal/infantile-onset HPP patients at £756,998 and at £886,344 per QALY gained for the juvenile-onset HPP patients, with the impact being stronger for the discontinuation rate.

Table 6.4: EAG scenario analyses results, without QALY weight

Scenario	Assumptions	Inc. costs (£)	Inc. QALYs	ICER (£)
Population: Perinatal-/infantile-onset HPP				
EAG base-case		[redacted]	[redacted]	**621,370**
Transition probabilities for SLs	First model specification	[redacted]	[redacted]	620,130
	Third model specification	[redacted]	[redacted]	613,194
Caregiver disutility	0.08	[redacted]	[redacted]	626,948
	0.17	[redacted]	[redacted]	610,506
Number of carers to which disutility is applied	2	[redacted]	[redacted]	601,738
Disutility Bereavement	0.04 for 15 years	[redacted]	[redacted]	598,612
	0.04 for 30 years	[redacted]	[redacted]	586,150
	0.04 for lifetime	[redacted]	[redacted]	576,087
Weight function	Weight of the general population	[redacted]	[redacted]	770,947
Drug Wastage	'Round down' option	[redacted]	[redacted]	609,600
	'Closest' option	[redacted]	[redacted]	613,185
Discontinuation and Compliance	0% discontinuation rate	[redacted]	[redacted]	745,730
	100% compliance rate	[redacted]	[redacted]	630,744
	0% discontinuation and 100% compliance rate	[redacted]	[redacted]	756,998
Population: Patients with juvenile-onset HPP				
EAG base-case		[redacted]	[redacted]	**739,120**
Transition probabilities for SLs	First model specification	[redacted]	[redacted]	945,924
	Third model specification	[redacted]	[redacted]	744,319
Caregiver disutility	0.08	[redacted]	[redacted]	770,722
	0.17	[redacted]	[redacted]	683,102
Number of carers to which disutility is applied	2	[redacted]	[redacted]	642,520
Disutility Bereavement	0.04 for 15 years	[redacted]	[redacted]	739,120
	0.04 for 30 years	[redacted]	[redacted]	739,120
	0.04 for lifetime	[redacted]	[redacted]	739,120
Weight function	Weight of the general population	[redacted]	[redacted]	917,000

Scenario	Assumptions	Inc. costs (£)	Inc. QALYs	ICER (£)
Drug Wastage	'Round down' option	[redacted]	[redacted]	724,158
	'Closest' option	[redacted]	[redacted]	728,643
Discontinuation and Compliance	0% discontinuation rate	[redacted]	[redacted]	872,668
	100% compliance rate	[redacted]	[redacted]	750,762
	0% discontinuation and 100% compliance rate	[redacted]	[redacted]	886,344

EAG = External Assessment Group; HPP = hypophosphatasia; ICER = incremental cost effectiveness ratio; Inc. = incremental; QALY = quality-adjusted life year; SL = severity level

7 COST TO THE NHS AND PSS AND OTHER SECTORS

7.1 Summary of submitted evidence relating to the costs to the NHS and PSS

The budget impact analysis (BIA) was updated from the previous submission. In the current submission, the size of the patient population and its age distribution were estimated using data from the UK MAA. All patients that were on AA treatment in the UK MAA at the most recent data cut-off (6 January 2022) were assumed to form the patient population in the first year after AA introduction. The change in size of the target population in the following 4 years (i.e., years 2 to 5 in the BIA) was based on the enrolment in the UK MAA during the four-year period from 2018 up to and including 2021. The total patient population on AA treatment in each year of the BIA is shown in Table 7.1. In terms of uptake and market share of AA, it was assumed that all newly diagnosed patients would receive AA treatment, taking into consideration the compliance and discontinuation rates as used in the cost effectiveness model. Resource use and costs for the BIA were taken from the cost effectiveness model (i.e., costs for HPP treatment and for invasive ventilation). The percentage of the patient population requiring invasive ventilation was also the same as in the cost effectiveness model.

Table 7.1: Results of the budget impact analysis

	Year 1	Year 2	Year 3	Year 4	Year 5
Patients on AA treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario without AA market access					
Invasive ventilation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other non-AA costs (<5 years)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other non-AA costs (≥5 years)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total cost of treatment pathway without AA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario with AA market access					
Invasive ventilation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other non-AA costs (<5 years)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other non-AA costs (≥5 years)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
AA costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total cost of treatment pathway with AA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Net budget impact					
Difference between scenario with and without AA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Based on Table76 of the CS.[10]
AA = asfotase alfa; CS = company submission

7.2 EAG critique of the company's budget impact analysis

A potential limitation of using the UK MAA enrolment data is that it presents the minimum number of patients to be treated, as we know for certain that those enrolled in the UK MAA are eligible and willing to take the treatment. It may, however, be an underestimation of the potential future treatment population.

8 IMPACT OF THE TECHNOLOGY BEYOND DIRECT HEALTH BENEFITS AND ON THE DELIVERY OF THE SPECIALISED SERVICE

8.1 Summary of cost savings estimated within the CS

8.1.1 Proportion of costs or benefits which fall outside of the NHS and PSS

The company have not estimated the proportion of costs outside of the NHS and PSS that may be saved due to treatment with AA. The only benefits outside the NHS and PSS explicitly taken into account in the CS are productivity losses, which are included as a scenario analysis in the CEA.

8.1.2 Societal costs

The average value of a person's productivity in the UK for a 12-week cycle was based on the average weekly earnings for the UK and the unemployment rate. This amounted to £6,323 per 12-week cycle. It is assumed that the productivity losses occur in one of the caregivers for patients younger than 18 years, and in the patient themselves in case of adult patients. The extent to which productivity is lost depends on the age of the patient and disease severity. For patients under 1 year of age, no productivity loss is assumed due to parental leave regulations. For patients aged 1-4 years, no productivity losses are assumed if the patient does not need invasive ventilation, and a 50% loss of productivity in case invasive ventilation is needed. For patients of 5 years and older, the loss of productivity depends on the disease severity. For patients in the SLI state, no losses are assumed. In more severe health states, the productivity loss is based on the proportion of the utility in that heath state to the utility in the SLI health state. An overview of the proportion of productivity lost and the value of lost productivity is shown in Table 8.1.

Table 8.1: Productivity losses and associated costs used in the cost effectiveness model

Patient age	Health state	Proportion of patients or caregivers (in case patient <18 years) able to work	Average productivity loss per patient per cycle
0–1 year	All	N/A	£0.00
1-4 years	No ventilation	50%	£3,438.00
	Invasive ventilation	0%	£6,876.00
5-12 years	SLI	100%	£0.00
	SLII	77%	£1,559.20
	SLIII	62%	£2,591.89
	SLIV	27%	£5,018.33
13-17 years	SLI	100%	£0.00
	SLII	77%	£1,559.20
	SLIII	62%	£2,591.89
	SLIV	27%	£5,018.33
18-65 years	SLI	100%	£0.00
	SLII	77%	£1,559.20
	SLIII	62%	£2,591.89

Patient age	Health state	Proportion of patients or caregivers (in case patient <18 years) able to work	Average productivity loss per patient per cycle
	SLIV	27%	£5,018.33
N/A = not applicable; SL = severity level			

8.1.3 Costs borne by patients

In Section B.1.3.3.2 of the CS it is mentioned that HPP is associated with additional costs borne by patients.[10] Examples given are home modifications and frequent hospital visits (resulting in travel expenses and time lost). Data from a survey among adult HPP patients indicated that 32% of patients required home modifications.[31] However, these costs were not quantified in the CS.

8.1.4 Other carer costs

Caring for patients with HPP presents a considerable burden for caregivers. This burden is captured in part in the economic model by including effects on caregiver HRQoL and productivity. However, there is an additional burden in the form of time invested that could otherwise be used for leisure by the caregiver. This cost is not taken into account in the CS.

EAG comments: Costs or benefits that fall outside of the NHS and PSS were considered in greater detail in the previous submission, when compared to the current submission. In the original submission, data from the European HPP survey was used to inform the extent of productivity losses. It is unclear why the company decided to rely purely on assumptions in the current submission. Additionally, the previous submission explicitly took other societal costs into account, such as the costs for special schooling, out of pocket expenditures for transportation, costs for the adaptation of cars and homes, and the value of informal care. These costs are only mentioned but not taken into account in the current submission. To illustrate, the patient borne costs estimated for the BSC treatment alternative in the previous submissions were £1,642 for juvenile-onset HPP and £646 for adult patients with paediatric-onset HPP, most of which was assumed to be avoided under AA treatment. Overall, the EAG considers it a missed opportunity that the current submission omits the estimation of costs beyond direct health benefits that was present in the previous submission. That said, this omission does constitute a conservative estimate of the economic impact of AA, as it is expected that AA treatment leads to a reduction in non-healthcare costs.

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Asfotase alfa for treating paediatric-onset hypophosphatasia (review of HST6) [ID3927]

Company response to EAG Report

Name of Company: Alexion AstraZeneca Rare Disease
Date: 16/09/2022

Contents

This document provides the Company's responses to each of the key EAG issues, including:

Below, the Company first seeks to clarify the new data included in the re-submission and collected under the UK Managed Access Agreement (MAA). Responses are then provided for each of the 9 key issues that the EAG references.

New evidence in the re-submission

Alexion has already provided, within the current submission dossier, all the available asfotase alfa (AA) data sets in accordance with the hypophosphatasia (HPP) patient population as defined in NICE's final scope document "People with paediatric-onset HPP". Moreover, the data presented are also in line with AA licensed indication "Paediatric-onset HPP".

In comparison with the original submission (HST6), the current submission contains a range of additional data including 3 new datasets (UK Managed Access Agreement (MAA), Empathy study, HPP Global Registry) as well as 12-30 months additional follow up data for AA registration studies – all of them on patients with paediatric-onset HPP. Table 5 provides further detail on the new evidence included in this submission.

EAG comment:

The EAG has acknowledged the completeness of the submission with respect to the available AA data sets (see section 4.5.1 of the EAG report): *'The EAG is confident that all relevant studies (published and unpublished) of AA were included in the CS, including data from the UK MAA.'*
The key issues highlighted by the EAG pertain to how these data were presented and to the analyses undertaken or not undertaken.

Alexion also provides further explanations of the way the clinical evidence is presented, in line with the population defined in the decision problem. The MAA, as agreed between NICE, NHSE, Clinical experts & Patient Advocates, was established to generate real world data from UK clinical practice to address the clinical uncertainties identified during the previous appraisal. For clarity, age of HPP onset and outcomes in BSC patients **were not** identified as key parameters of clinical uncertainty and as such, the MAA was not set up to capture data to address these issues. Rather, the MAA focuses on the evaluation of uncertainties for clinically relevant outcomes (survival, functional (including 6MWT), HRQoL) where uncertainties remained from the 2015 submission.

Consequently, MAA treatment eligibility criteria are based on the patient age at the time of presentation at the designated treatment centres. Moreover, the data collection and sharing agreement (Appendix E, MAA) does not include any requirement to collect and report AA data based on age of HPP onset or comparison with BSC.

EAG comment:

The EAG notes that the starting rules of the MAA do distinguish between patients with perinatal- and infantile-onset HPP, for whom it is stated that: 'Patients below 1 year of age with symptoms and signs of HPP should be initiated on asfotase alfa therapy as soon as is possible,' and other patients (adults and children) with childhood-onset HPP, for whom more restrictive starting rules are specified (relating to the observed effects of HPP in the individual patient).

Alexion's clinical development program for AA was not designed based on age of HPP onset, as the historical classification (perinatal, infantile, juvenile) is not directly relevant to the disease prognosis, how the patients are diagnosed, and treatment decisions are made in clinical practice. Alexion has, however, included within this dossier data on juvenile-onset HPP where they were available, and attempted to distinguish the value for money according to the subgroups that NICE requested in the decision problem. More details around the availability of data on juvenile-onset HPP as well as why additional subgroup analyses would not be feasible with the currently available data-sets are provided below, in the responses to the Key Issues raised by the EAG.

EAG comment:

The EAG notes that company were able to provide age of onset data for all studies, in their response to clarification questions (Tables 3.4.to 3.7 in the EAG report), indicating that data are likely to be available to support the subgroup analyses requested by the EAG.

Alexion also provides below the rationale for why the Global HPP Registry data set could not be used as a source to inform comparative efficacy estimates of AA vs BSC, due to:

1. Lack of collection of relevant outcomes in the registry
2. Lack of consistency in measurement (method, time interval, etc.), when they were collected
3. Lack of longitudinality, for assessment of change
4. Selection bias / confounding, vs. the population expected to receive treatment in England (i.e., meeting MAA start criteria)

Table 6 and Table 7 provide a detailed overview of the differences in baseline demographics between the untreated patients in the Registry and the AA treated patients. This indicates that a comparative efficacy analysis would be severely biased.

Moreover, although BSC standards may have improved after 2010, the-long term survival of patients with the severe perinatal/infantile form of HPP has not changed. Patients may survive a few more weeks within the NICU/PICU but they eventually pass away.

EAG comment:

The EAG has acknowledged that all of the potential sources of comparator data presented have limitations (see section 3.3.3 of the EAG report):
'The EAG acknowledges the limitations of the Global HPP Registry data, but notes that the natural history studies also have substantial limitations as sources of data for comparable non-AA treated patients. The EAG therefore considers that it would be preferrable to present analyses based on both potential sources of control data; use of all available data, with appropriate consideration of limitations/risk of bias, could inform considerations of the uncertainty in estimates of relative efficacy.'

The EAG, therefore, maintains the view that is reasonable to request that all potential sources of comparator data be fully explored, with a view to providing matched non-AA-treated patients and comparative efficacy analyses in-line with the methods described in NICE TSD 17 (National Institute for Health and Care Excellence. Decision Support Unit. Utilities TSD series. Available from: http://nicedsu.org.uk/technical-support-documents/utilities-tsd-series).
The EAG notes that the presence of population-level differences in baseline demographics between the untreated patients in the Registry and the AA treated patients does not preclude the possibility of identifying individual patients suitable for matching.

Alexion's responses below to the key issues identified by the EAG provide additional context.

Key Issue 1

Discrepancy between the population in decision problem and the main source of efficacy data

Juvenile onset data

The definition of the population in NICE's final scope document is "People with paediatric onset HPP". Alexion has provided all the available data sets from AA studies in patients with paediatric onset HPP (Table 5). Within these data sets the following are related to patients with juvenile-onset HPP:

- Study ENB-006-09/ENB-008-10, 9/16 (56%) had juvenile onset HPP
- Study ENB-009-10, 9/13 (69%) had juvenile onset HPP
- UK MAA, [redacted] patients had juvenile onset HPP

Moreover, the following efficacy subgroup analysis is available within the clinical study report (pages 113-131) **Study ENB-006-09/ENB-008-10:** patients with perinatal/infantile & patients with juvenile onset HPP. The findings of this subgroup analysis confirm those of the main data set.

Comparative efficacy for juvenile-onset patients

Studies ENB-006-09/ENB-008-10 & ENB-009-10 (that include 56% & 69% juvenile onset patients respectively) included a comparator arm (historical control & active comparator, respectively). This comparison was used to provide comparative estimate of AA treatment for the primary endpoint of the studies – following 6 months treatment duration.

EAG comment:

The EAG acknowledges the inclusion of the subgroups analyses indicated (in the CSR for study ENB-006-09/ENB-008-10) and the inclusion of historical control and active comparator arms in studies ENB-006-09/ENB-008-10 and ENB-009-10, respectively. However, the EAG notes that clinical effectiveness section of section B of the CS describes the outcomes for AA-treated patients in studies ENB-006-09/ENB-008-10 and ENB-009-10, rather than describing comparative efficacy (vs control/BSC). Overall, the EAG does not consider that the question of the comparative efficacy of AA vs BSC has been adequately addressed for all populations and all outcomes specified in the NICE scope. In particular, there is deficiency, with respect to comparative efficacy data, for outcomes

other than survival (both with respect to the whole paediatric-onset population and to the subgroups of interest specified in the NICE scope).

Alexion does not consider it appropriate to conduct the suggested pooled analysis for the juvenile-onset HPP patients for the following reasons:

1. With the exception of patients that present with HPP symptoms prior to the age of 1 y.o. and are likely to have the life-threatening form of HPP, the historical classification of HPP falls short of describing the reality of HPP and the longitudinal course of the disease and is not directly relevant to the disease prognosis, how the patients are diagnosed, and treatment decisions that are made in clinical practice. The disease evolves over time and therefore the current clinical status and the degree of disability are likely more meaningful in making treatment decisions than age-of-onset categorization.

EAG comment:

As indicated by the company, patients presenting before 1 year of age (perinatal/infantile-onset) are likely to have a more severe form of HPP. The EAG therefore considers that it is relevant to conduct subgroup analyses in order to explore potential differences in the efficacy of AA for the management of the long-term manifestations of HPP between patients in this category (who survive infancy) and those with less severe (juvenile-onset) form of HPP. The relevance of these subgroup analyses is reflected by the inclusion of these subgroups in the NICE scope.

2. The AA clinical program was not designed around age of onset classification. With the exception of one study (ENB-010-10), all other registration studies were based on age at time of enrolment.

EAG comment:

The EAG notes that company were able to provide age of onset data for all studies, in their response to clarification questions (Tables 3.4.to 3.7 in the EAG report), indicating that data are likely to be available to support the subgroup analyses requested.

3. During the discussion of the MAA terms between all stakeholders (NICE, NHSE, clinical experts, PAGs, Alexion) at the time of the initial appraisal, age of onset of patients was NOT identified as a key parameter of clinical uncertainty for which data collection was required. All treatment eligibility criteria in the MAA were based on the age of patients at the time of presentation at the designated treatment centres. The only requirement was that patients had evidence of paediatric-onset HPP, in order to comply with AA licensed indication. Additionally, data analysis by age of onset was not one of the parameters agreed between NHSE and Alexion as specified within the MAA Data Collection & Sharing Agreement (MAA Appendix E).

EAG comment:

The EAG notes that, for patients other than those with perinatal- and infantile-onset HPP, the starting rules for the MAA did include specific, disease-severity-based criteria (as indicated in the company's point 5, below).

4. The need for subgroup analysis based on age of onset, was also NOT identified when Alexion presented an interim analysis of the MAA data to the MAA Oversight Committee meeting in Q1 2021.

EAG comment:

The EAG cannot comment on discussions between Alexion and the MAA Oversight Committee, but notes that the subgroups of interest were specified in both the NICE scope for HST6 and in the current NICE scope.

5. A pooled analysis of patients with juvenile-onset HPP would also be challenging given the significant differences in inclusion criteria for studies ENB-006-09/ENB-008-10, ENB-009-10 and the UK MAA, which only includes patients with more severe disease who satisfy the strict criteria for treatment.

EAG comment:

The EAG acknowledges this issue, but considers that it would have been reasonable for the company to either conduct such an analysis and present the results alongside a description of the issues, or to provide a structured narrative synthesis comparing the results from the UK MAA with those from the Alexion clinical trials and exploring potential reasons for any differences observed.

6. The only pooled subgroup analysis that Alexion has conducted is for the patients that presented with perinatal/infantile HPP in the AA clinical studies ENB-002-08/ENB-003-08, ENB-010-10 & ENB-006-09/ENB-008-10. This subgroup analysis was not performed specifically for this reappraisal process but does provide data on the long-term survival of the patient population with the form of HPP which can be life-threatening.

EAG comment:

The EAG notes that company did not conduct any pooled subgroup analyses specifically for the purpose of addressing the decision problem as specified in the NICE scope.

7. Survival analyses in patients with juvenile onset of HPP is not particularly meaningful or relevant given the disease in this population is associated with significant morbidity but is not typically life-threatening.

EAG comment:

The EAG acknowledges that survival analysis is likely to be less meaningful for patients with juvenile-onset HPP than for those with perinatal/infantile-onset HPP.

Use of untreated cohort in global registry data for comparative analysis

Alexion believes that using the HPP Global Registry as a source for conducting comparative efficacy analysis is inappropriate and would produce highly biased results and generate additional uncertainties. The reasons are presented below:

- The Registry is a prospective observational study that does not mandate any specific data collection or schedule of clinical assessments for the participating patients/sites. Data are input based as per routine medical practice at each site. This results in limited data availability for variables relevant to this re-appraisal, especially for the never-treated population that would be used in a comparative efficacy estimate. For example, **EQ5D & Bleck score** are not collected in the Registry, only 1 never-treated patient required ventilation support and 2/210 never treated paediatric patients had a brief (2m) course of respiratory support . Moreover, the scarcity of data availability for the 6MWT **(which mainly informs the CEA model in the submission)** is more profound with only 13/559 never-treated patients having multiple percent-predicted 6MWT measures in the registry, and the majority of these patients do not match MAA start criteria in terms of prognostic factors (see response to Key Issue 5).
- Comparison of the never-treated population in the registry with the UK MAA treated cohort would be inappropriate as the cohorts are very different in terms of baseline characteristics (disease burden and severity, especially functional & HRQoL outcomes). Consequently, comparison would not be fair and balanced and would produce biased results (please see Table 6 and Table 7 for details of the differences among the disease-specific variables relevant for this submission). In response to the EAG's request to conduct a matched analysis of change in percent-predicted 6MWT between the UK MAA and the registry, Alexion explored matching patients based on prognostic factors defining start criteria in the MAA; this indicated that a minority (4 patients) of the already severely limited sample (13 patients with multiple measures) met the MAA start criteria, illustrating the systematic differences between these populations.

EAG comment:

The EAG acknowledges that the above text describes some exploration of the potential of the registry data set to provide matched patients form comparative analyses. However, no detail is provided for the 'prognostic factors' explored, and it is not clear whether the historical control patients used in the company's analysis would have similar matching problems if the same criteria were applied.

Key Issue 2

Non-standard subgrouping of study participants

Presentation of data by perinatal/infantile and juvenile onset

The MAA terms and conditions were agreed between all the relevant stakeholders (NICE, NHSE, Clinical Experts, PAGs, Alexion). The purpose of the MAA was to address the clinical uncertainties identified during the initial appraisal and discussed within the Committee Meetings. The only requirement in terms of HPP onset, as agreed within the MAA, was for the patients to have documented paediatric onset HPP. All other clinical criteria for treatment initiation were based on age of patients at diagnosis/presentation to treatment centres. Moreover, the data collection and sharing agreement (Appendix E of the MAA) as well as the MAA ESAP (submitted to NICE's MAA Oversight Committee) do not include any requirement for analysing/presenting the MAA data according to age of HPP symptoms onset.

Study ENB-009-10 age inclusion criterion was patients aged ≥13 y.o. The study prospectively enrolled 19 patients with 18/19 having paediatric-onset HPP (i.e., matching the decision problem). The data from this study are almost entirely driven by patients with paediatric onset HPP.

EAG comment:

Regardless of any historical requirements for categorisation of patients by age of onset, the NICE scope makes it clear that age of onset as a means of defining the population and any subgroups was expected. This would require that at a minimum an attempt to categorise all relevant evidence including the UK MAA and the Global HPP Registry was made and presented in a way that enabled comparison between treatment with AA and BSC. It would also require that an attempt was made when conducting any comparative analyses to adjust for confounding e.g., though matching and using all relevant data.

Presentation of subgroup analyses

Alexion, as per the responses above, has presented the data according to the defined population in the decision problem; i.e., "people with paediatric onset HPP", and has provided subgroup analyses where available. In summary:

- Studies **ENB-002-08/ENB-003-08 & ENB-010-10** included solely patients with perinatal/infantile onset HPP
- Study **ENB-006-08/ENB-008-10** included patients with perinatal/infantile and juvenile onset disease. A subgroup analysis for this study is available (as detailed above); the findings of this analysis confirms the full data set analysis
- Study **ENB-009-10** included 18/19 **(94.7%)** patients with paediatric-onset HPP – no subgroup analysis is available for these 18 patients, but it is safe to say that the study results are driven by patients with paediatric-onset HPP

The MAA was not designed based on age of HPP onset. Also, the age of onset and the need to analyse the data by age of onset subgroups was not identified as a requirement during the finalization of the MAA (NICE, NHSE, clinical experts, PAGs, Alexion) nor during its implementation at the MAA Oversight Committee meetings.

Alexion has presented, within the response to Key Issue 1, the reasons for only conducting a pooled analysis of the perinatal/infantile patients from studies **ENB-002-08/ENB-003-08, ENB-010-10 & ENB-006-08/ENB-008-10.** In summary:

- HPP can be life-threatening only in those patients that present with symptoms before the age of 1 year old (perinatal/infantile HPP).
- HPP traditional classification falls short of describing the reality of HPP and the longitudinal course of the disease, and is not directly relevant to the disease prognosis, how the patients are diagnosed, and treatment decisions made in clinical practice.

AA clinical trials (with one exception) and the MAA were not designed based on HPP onset but based on the age of patient at baseline.

EAG comment

The EAG acknowledges that in the comparative analysis some data in a perinatal/infantile subgroup were analysed, but as presented in the EAG report, not all relevant data that might have been

available for subgroups covering the whole paediatric population, including the MAA or the Global HPP Registry.

Key Issue 3

Use of historical controls in comparative survival analyses

Impact of improvements in respiratory support

Leading clinical experts in HPP, as detailed in Whyte et al. (2016)[1], have clearly stated that advances in supportive respiratory care are unlikely to impact on mortality of the BSC patients. In the Whyte paper, it is noted that while patients diagnosed since 2000 onwards tended to survive longer, their ultimate prognosis was unchanged and all eventually died as respiratory support did not affect their underlying course of disease.

Improved survival of patients treated with asfotase alfa is attributed to improved skeletal mineralization, stabilization of chest structure and thus support of the lungs that allows the patient to be weaned off ventilation. With only ventilation support, BSC patients do not experience these improvements.

While Alexion did provide a separate survival analysis for BSC patients diagnosed from 2000 in the original NICE appraisal process, the results in overall long-term survival rates did not change for the post 2000 cohort compared with the whole cohort. The survival rates from these different periods of diagnosis (80s, 90s, 2000s) were not statistically significantly different, owing to the small samples introduced with subgrouping (N = 13, 14, and 21, respectively). Accordingly, survival outcomes for BSC patients were not identified as requiring further data collection in BSC patients in the context of the MAA.

ENB-011-10 study was a retrospective study looking at medical records of patients with HPP diagnosis before 6 months of age and having any of the following inclusion criteria

- Rachitic features
- Ventilation Support
- B-6 responsive seizures

These inclusion criteria allow for selection of the most severely affected patients from the perinatal/infantile onset group where the likelihood of mortality (within 1 year) is high.

In contrast, ENB-002-08/ENB-003-08 prospectively included any patient with HPP and age at enrolment ≤3 years old. This allowed for enrolment of patients with perinatal/infantile disease who had survived infancy, thus contributing to higher median baseline age at treatment initiation.

[1] Whyte MP, Rockman-Greenberg C, Ozono K, Riese R, Moseley S, Melian A, Thompson DD, Bishop N, Hofmann C. Asfotase Alfa Treatment Improves Survival for Perinatal and Infantile Hypophosphatasia. J Clin Endocrinol Metab. 2016 Jan;101(1):334-42.

The clinical story is clear – for perinatal/infantile-onset patients meeting the MAA start criteria for treatment, if untreated, they would either die in their early years or, if they survive, they would have significant morbidity and severely compromised HRQoL.

- Given the significant morbidity that surviving patients treated with BSC would continue to experience, uncertainty in survival rates may have limited impact on value for money.
- This is shown in the cost-effectiveness model with any surviving perinatal/infantile onset BSC patients entering and remaining in the health state SL4 representing the most severe disease (see response to Key Issue 6 below).

EAG comment

The company appear to make a contradictory statement regarding the change in life expectancy of BSC treated patients: *"it is noted that while patients diagnosed since 2000 onwards tended to survive longer, their ultimate prognosis was unchanged"*: clearly if they are surviving longer then their prognosis has changed, notwithstanding that some events including death will still occur, but later. The company report that an analysis by year of diagnosis (pre- and post- 2000) was presented in the previous submission, but this has not been represented for consideration by the committee and neither has one with all of the data that is now available including the Global HPP Registry. The company also verify the EAG's assertion of likely immortal time bias by noting that, in contrast to the natural history study, ENB-011-10, the AA study, *"ENB-002-08/ENB-003-08 prospectively included any patient with HPP and age at enrolment ≤3 years old. This allowed for enrolment of patients with perinatal/infantile disease who had survived infancy,…"*. Therefore, if these data are being used for a comparison with historical controls where death before treatment with AA could have begun, there will be a bias in favour of AA.

Use of BSC data from Global HPP Registry

Alexion has stated, within the response in Key issue 1, why the Global HPP Registry could not be used to provide comparative efficacy estimates for patients with paediatric onset HPP.

Additional reasons that the Global Registry is not a suitable data source for a non-treated population with perinatal/infantile onset HPP are the following:

- The Registry was first established in Q1 2015, coinciding with the availability of asfotase alfa. Due to the severity of the disease and the increased mortality in patients presenting with HPP <1 year old, almost all patients with perinatal/infantile form of the disease in the registry would have been treated with asfotase alfa either within clinical trials (from 2009) or with commercial drug (from Aug 2015). As such, there would be very few, if any patients with severe perinatal/infantile HPP in the Registry who would have been left untreated (from 2009 onwards) to inform a meaningful comparative analysis with more recently diagnosed patients.
- Within the Global Registry, there are only 7 never-treated patients who received some form of respiratory support – 6 received a short course of nasal oxygen or CPAP and only one received invasive ventilation support. This is a clear indicator that the never treated patients do not have as severe disease as those who perinatal/infantile-onset patients who are treated.
- Any known untreated patients with severe perinatal/infantile HPP who had died between 2009-2015 would not have been captured in the Registry as its inclusion criteria did not allow for posthumous enrollment.

EAG comment:

The EAG notes that the number of never-treated patients who received some form of respiratory support has been updated from [redacted] to 7. The EAG acknowledges the difference between ever-treated (with AA) and never-treated patients of [redacted] vs. [redacted] (as in CS), which might suggest a selection bias where the patient with better prognosis remain untreated with AA. However, this is a hypothesis and even if true, it might be that the treatment effect on patients with a better prognosis might be less than on those with a worse prognosis. Given that there is already a high-risk bias in favour of AA by using historical controls from the distant past e.g., pre-2000 from ENB-011-10, it therefore seems reasonable to include the Global HPP Registry patients despite there also being a risk of bias in the other direction.

Key Issue 4

Inclusion of selected outcomes for the comparative efficacy analyses and weak comparator data

The EAG states that:
"Comparative analyses should be conducted for all specified outcomes, using all available data for AA-treated patients, including data from the MAA. The Global HPP Registry (ALX-HPP-502) should have been used to provide comparator data for patients not treated with AA as well as natural history data sources."

Alexion's submission for the re-evaluation provided extensive documentation of the evidence collected for patients treated with AA under the MAA. However, the MAA only captured data for treated patients; it was not designed to assess comparator (i.e., BSC) outcomes.

The EAG suggests that the Global HPP Registry (ALX-HPP-502) could have been used to provide BSC data, to act as controls for the patients treated with AA under the MAA. While Alexion considered this in developing the re-submission, for key outcomes informing the value for money of AA vs. BSC, it was determined that the registry could not provide suitable data for comparison. This is because:

Perinatal/infantile onset:

- In the registry, there was only 1 never-treated patient with reported perinatal/infantile onset disease.
  - Of note, the patient was age >60 years at enrolment in the registry, raising suspicion regarding classification of age of onset earlier than 6 months of age.
- The lack of observations of never-treated perinatal/infantile-onset patients in the registry likely arises for two reasons:
  - The registry began enrolment in 2015, when infants at risk of mortality likely would have been treated with AA.
  - The registry's inclusion criteria do not allow for posthumous enrolment. For infants with severe disease eligible for AA but who did not receive it, survival outcomes, therefore, most likely would not be observed.

Juvenile onset:

- In the registry, percent-predicted 6MWT was measured for only 16/559 of never-treated patients, of whom only 13 had multiple measures.
  - Administration and measurement of the 6MWT may have also been inconsistent in method and timing across the different healthcare settings in which it was administered.
- For the 13 never-treated patients with multiple percent-predicted 6MWT measures (for whom BSC transitions could be estimated), confounding due to imbalance of prognostic factors is of particular concern.
  - A well-recognized limitation of registry data is that untreated patients have lesser propensity for treatment (e.g., have less severe disease, and accordingly less need for/likelihood of receiving treatment).
  - This dynamic reflects in comparison of the population treated under the MAA vs. the never-treated patients with multiple percent-predicted 6MWT measures in the registry, as [redacted] of the MAA patients fell into the two most severe health states of the economic model (SL3 and SL4) at baseline, while only 23% did in the sample available from the registry.

EAG comment:

There is an inconsistency in the number of never-treated patients with perinatal/infantile onset disease: 1 above and [redacted] in the CS (see Table 3.6 in the EAG report). The EAG also notes a discrepancy in total number of juvenile never-treated patient: 559 above and [redacted] in the CS, although perhaps the company is referring to all never-treated patients ([redacted] in the CS). The company also only refer to one of several outcomes in the NICE scope. Generally, scarcity of data does not preclude an orderly comparison of all outcomes using all relevant data in the relevant population and subgroups. As already referred to, the EAG acknowledges the risks of bias in using observational data for a comparison, which is all the more reason to present all outcome data in an orderly manner and to attempt to adjust for confounding in any comparative analysis, as recommended in NICE TSD 17.

Alexion's response to Key Issue 5 expands on the reasons that matching could not be conducted to leverage the registry's percent-predicted 6MWT data while adjusting for confounding.

Key Issue 5

Inappropriate methods used to calculate estimates of comparative efficacy

The EAG states that comparative analyses should be conducted of the UK MAA vs. control / natural-history data from the Global HPP Registry (ALX-HPP-501), and should use appropriate methods for adjusting for potential confounders according to the methods described in NICE DSU TSD 17[2].

As described in Alexion's response to Key Issue 4, data on survival of perinatal/infantile-onset patients on BSC could not be sourced from the registry, as only one perinatal/infantile-onset never-treated patient was observed in the registry. As described above, this is likely due to enrolment in

[2] Faria R, Alava MH, Manca A, Wailoo A, editors. NICE DSU TECHNICAL SUPPORT DOCUMENT 17: The Use of Observational Data to Inform Estimated of Treatment Effectiveness in Technology Appraisal: Methods for Comparative Individual Patient Data. 2015. URL: https://www.sheffield.ac.uk/media/34204/download?attachment

the registry starting in 2015, when infants at risk of mortality likely would have been treated with AA, and that the registry does not allow for posthumous enrolment. Mortality was only observed for 3 never-treated patients in the registry, all among patients enrolled at age ≥18 years, among a total sample of 363.

For juvenile-onset patients, it was deemed that the sample of 13 (of 559) never-treated patients with multiple percent-predicted 6MWT measures would be insufficient to contribute meaningful comparator data. However, following the EAG's request, Alexion has explored use of percent-predicted 6MWT data for never-treated patients in the registry, based on the recommendations of NICE DSU TSD 17. The TSD indicates that when non-randomized individual patient data (IPD) are available to act as a comparator, they should be assessed for confounding, which if likely to be present, should be addressed by trimming/matching the treatment groups based on prognostic factors. If the balance of prognostic factors remains poor, comparative analyses may not be feasible.

To assess potential confounding in comparison of the UK MAA (treated) and registry (untreated) data, we inspected balance of prognostic factors, which were considered to be the MAA's start criteria, as these represent characteristics agreed to signal poor prognosis. The MAA's start criteria are summarized in

Table 1 below for patients aged ≥5 at start of treatment.

Table 1. Start criteria in the UK MAA, for patients aged ≥5 at enrolment

Ages 5-17	Ages 18+
ONE of the following: • Limited mobility assessed by a specialist according to the modified Bleck Ambulation Efficiency Scoring and with a Bleck score between 1-6, ranging from non-walker older than 2 years of age to able to walk less than 300m with the use of crutches or sticks. • Continuing or recurring musculoskeletal pain where there is significant pain that affects daily activities which: o Affects quality of life o Has not improved with 2 different types of painkiller which have been recommended by a national pain specialist	TWO of the following: • Limited mobility assessed by a specialist according to the modified Bleck Ambulation Efficiency Scoring and with a Bleck score between 1-6, ranging from non-walker older than 2 years of age to able to walk less than 300m with the use of crutches or sticks. • Continuing or recurring musculoskeletal pain where there is significant pain that affects daily activities which: o Affects quality of life o Has not improved with 2 different types of painkillers which have been recommended by a national pain specialist • 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).

Among the 13 never-treated patients with multiple percent-predicted 6MWT observations, 2 were from the UK. Considering that these patients did not initiate treatment under the MAA, it was assumed that they did not meet the MAA start criteria. The remaining 11 patients included 8 aged < 18 years and 3 aged ≥ 18 years, of whom 10 were from the USA and 1 from Germany. None of the 11 patients used assistive devices for walking. Impaired mobility, chronic musculoskeletal pain, and recurring fractures were identified from data on baseline signs and symptoms at enrolment in the registry. As presented in

Table **2** below, only 4 patients met the MAA start criteria, and would contribute one transition each to the analysis (as each had only 2 observations).

Table 2. Registry patients with multiple percent-predicted 6MWT measures, and summary of prognostic factors

Patient ID	pp6MWT at BL	pp6MWT measures	Age at BL	Sex	Country	Impaired mobility[a]	Chronic pain[b]	Recurring fractures[c]	Meets UK MAA criteria
0099-033	0.75	2	43.8	Male	United States	0	1	1	1
0150-040	0.54	2	26.0	Male	United States	1	1	1	1
0401-004	1.02	2	11.1	Male	Germany	0	0	0	0
0680-005	0.71	5	16.0	Female	United States	0	0	0	0
0680-006	0.76	3	19.3	Male	United States	0	1	0	0
0680-007	0.69	7	6.8	Female	United States	0	0	0	0
0680-009	0.57	2	16.6	Female	United States	1	1	0	1
0680-010	0.66	2	13.2	Female	United States	0	1	1	1
0680-011	0.71	5	8.3	Female	United States	0	0	0	0
0680-012	0.72	2	16.9	Female	United States	0	0	0	0
0680-013	0.74	3	13.8	Male	United States	0	0	0	0

Abbreviations: BL – baseline; MAA – managed access agreement; pp6MWT – percent predicted six-minute walk test.

Notes:

a. Identified as any sign/symptom including: "ABNORMAL GAIT", "RICKETS (BY X-RAY)", "WEAKNESS", or percent-predicted 6MWT in SL3 or SL4 (i.e., < 64.4%).

b. Identified as any sign/symptom including: "CHRONIC BONE PAIN", "CHRONIC MUSCLE PAIN", or "GENERALIZED BODY PAIN".

c. Identified as the sign/symptom "RECURRENT AND POORLY HEALING FRACTURES/ PSEUDOFRACTURES".

d. Rows highlighted in blue indicate patients identified as potentially meeting the UK MAA start criteria.

Based on the limited sample size, balance and overlap of prognostic factors, and longitudinality (number of observations over time) that could be contributed, Alexion did not use the registry data for comparative analyses of percent-predicted 6MWT.

EAG comment:

The company's opening statement is appears to be misleading: *"The EAG states that comparative analyses should be conducted of the UK MAA vs. control / natural-history data from the Global HPP Registry (ALX-HPP-501)"*. The EAG stated that all relevant data should be used, "*including*" the UK MAA and the Global HPP Registry. For an assessment of potential for a comparative analysis with adjustment for confounding the company then only examine the Global HPP Registry and not ENB-011-10. As already mentioned in Key Issue 4, there is also that discrepancy in the number of never-treated perinatal/infantile onset patients in the Global HPP Registry. Also, as already mentioned in Key Issue 4, the company then only focus on one outcome i.e., 6MWT for an assessment of the feasibility of analysis, for which they seem to have made some choices that are not well supported:

- Assuming the two UK patients are not able to be included because they were not included in the MAA
- Lack of transparency in how patients did or did not meet the MAA criteria
- Lack of justification for the choice of prognostic factors

As already stated in the EAG report and the previous Key Issues, the EAG acknowledge the challenges of a comparative analysis given limited observational data, which is why the EAG have

requested that all relevant data from all sources, both for the AA treated and the non-AA treated be included in analyses for the relevant patient populations.

Key Issue 6

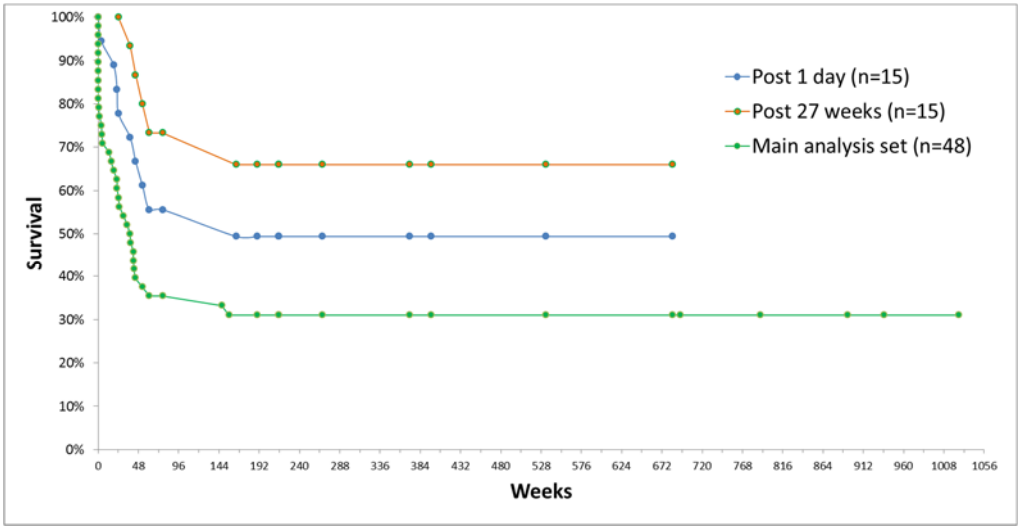
Uncertainty in transition probabilities

Overall survival in perinatal/infantile onset

The EAG states that Alexion should have conducted a matched analysis to estimate HPP-related mortality for patients aged <5 years, such as those conducted by the ERG in the original submission, matching on period of diagnosis (2000 or later) and time survived after baseline (to avoid "immortal time bias").

Alexion would like to clarify that, as noted in response to Key Issue 3, and described in Whyte et al. (2016)[3], the data used in the re-submission did include matching. The 48 historical controls compared to treated patients from studies ENB-002/003-08 and ENB-010-10 were required to have one or more of three life-threatening complications in HPP. Further, to align with the ERG's preferences from the original NICE submission, in the re-submission BSC patients who died on the first day after baseline were excluded from the analysis as it was considered likely that these patients would not be started on AA treatment. The benefit of further matching in the survival analyses appears uncertain. For example, restricting to patients treated from 2000 onwards restricts the BSC sample from 41 to 18 (Table 4.14 of the EAG report from the original submission), adding considerable uncertainty. It also implies overall survival with BSC appearing inconsistently high (i.e., >60% at 5+ years) vs. clinical characterization of perinatal/infantile-onset HPP, as reflected in Figure 4.2 of the ERG's report for the original submission, replicated as Figure 1 below.

Figure 1. Scenarios of overall survival in historical-control perinatal/infantile-onset HPP patients, considered by the ERG in the original submission



[3] Whyte MP, Rockman-Greenberg C, Ozono K, Riese R, Moseley S, Melian A, Thompson DD, Bishop N, Hofmann C. Asfotase Alfa Treatment Improves Survival for Perinatal and Infantile Hypophosphatasia. J Clin Endocrinol Metab. 2016 Jan;101(1):334-42.

Further, it should be noted that the ICER for the perinatal/infantile-onset subgroup in the CEA is relatively insensitive to the variation of overall survival estimates depicted above. This is because, for perinatal/infantile-onset patients meeting the MAA start criteria for treatment, even if kept alive with BSC, long-term prognosis would include significant morbidity (i.e., patients would remain in SL4 for the model's horizon), such that a surviving patient's utility would be close to death (0.23). For example, using the ERG's post-1 day and post-27 weeks scenarios above, the perinatal/infantile-onset ICER changes from [redacted] to [redacted] and [redacted].

EAG comment:

The EAG would like to thank the company for the additional clarification and scenarios. Please refer to the response to Key Issue 3 for additional details.

Time-to-event modelling of invasive-ventilation risk in perinatal/infantile onset

The EAG states that for modelling invasive-ventilation risk, a time-to-event analysis would be more informative than a constant risk of ventilation support, as Alexion modelled in the re-submission. The EAG acknowledges, however, that if many patients require repeated ventilation support, then a time-to-event analysis would not be the most appropriate approach as argued by the company in response to EAG's clarification question.

As described in response to the EAG's clarification question, time-to-event analysis was not used for modelling invasive ventilation, as a transition to invasive ventilation would be "absorbing" – i.e., patients would not transition off invasive ventilation for the remainder of the period under age 5 years in the CEA. This is inconsistent with the evidence from Whyte et al. (2016)[4] (see Figure 2 of the publication), in which 14 of the 37 AA-treated patients who were on invasive ventilation at baseline were weaned off while on treatment. Given this, it remains unclear to Alexion that a time-to-event analysis of invasive ventilation would be appropriate.

It should be noted, however, that the modelling of invasive-ventilation risk is unlikely to meaningfully change CEA results. For example, setting the per-cycle probability of invasive ventilation to 0.00 for BSC and AA (i.e., removing any risk) only changes the perinatal/infantile-onset ICER from [redacted] to [redacted].

EAG comment:

The EAG would like to clarify that a time to event analysis would be more informative than a constant risk of invasive ventilation support, if the number of patients with repeated ventilation support was low, and that this information was missing from the submission and the clarification response.

[4] Whyte MP, Rockman-Greenberg C, Ozono K, Riese R, Moseley S, Melian A, Thompson DD, Bishop N, Hofmann C. Asfotase Alfa Treatment Improves Survival for Perinatal and Infantile Hypophosphatasia. J Clin Endocrinol Metab. 2016 Jan;101(1):334-42

In the clarification response (question #B7), the company stated that "given that patients do not permanently move to invasive ventilation, a constant probability was applied in the model to allow patients to enter invasive ventilation more than once throughout the model, rather than modelling parametric survival models of invasive-ventilation free survival." This statement suggests that in the data there are patients moving to invasive ventilation support more than once. However, the number of patients requiring repeated ventilation support in the data were not provided neither in the company submission nor in the clarification response. In the clarification response only, the company referred to the study of Whyte et al. (2016), but in this study there is only 1 patient in the AA arm requiring repeated invasive ventilation support.

Severity-level transitions in juvenile onset

The EAG states that data from the Global HPP Registry on the 6MWT could have been used to reduce uncertainty around model predictions for the BSC arm. Further, while the EAG agrees with Alexion's preference of the ordered-probit Model Specification 2 for estimation of transition probabilities in the base case, the EAG suggests that the more parsimonious (i.e., with fewer covariates) Model Specification 1 should be considered, as it is associated with a higher ICER for juvenile-onset HPP patients.

Alexion recommends against use of Model Specification 1 for the order-probit estimation of transition probabilities. As listed in Table 46 of Section B.3.3.1.3.5 of Alexion's re-submission, log likelihood and pseudo-R2 statistics support that Model Specifications 2 and 3 provide better fits to the data that Model Specification 1.

With regards to use of the registry 6MWT data to inform BSC transitions in the CEA, as described in response to Key Issue 5, only 13 of 559 never-treated patients had multiple percent-predicted 6MWT measures in the registry, only 4 of whom may match the profile of prognostic factors in patients treated under the MAA. Consequently, the registry would only have been able to provide 4 additional observations of BSC transitions (SL3 → SL3, SL2 → SL2, SL3 → SL2, and SL2 → SL1).

Most importantly, the need for predicting BSC transitions, and the resulting influence of uncertainty from potential misspecification, is reduced in the context of the MAA. In the MAA, start criteria ensured that only patients with severe disease-initiated treatment. Accordingly, in CEA analyses informing the MAA, in the original submission, the NICE EC allowed modelling juvenile-onset patients starting from SL4, and remaining in severe states. This approach is supported by actual enrolment in the MAA; among the n=[redacted] patients who initiated treatment under the MAA and were not <5 years of age (at which the 6MWT was not collected), at baseline [redacted] % were in SL4 (or could not complete the 6MWT), [redacted] % in SL3, and [redacted] % in SL2. There is, thus, little uncertainty that patients treated under the MAA would be in a severe disease state in the absence of treatment.

In the CEA, starting juvenile-onset patients from the MAA severity-level distribution reduces the base case ICER from [redacted] to [redacted], and to [redacted] if all patients start from SL4.

EAG comment:

The EAG would like to thank the company for the additional clarification. The EAG found that the three specifications produced comparable goodness-of-fit statistics with relatively small differences in log likelihood and pseudo-R2 statistics (Table 46 of Section B.3.3.1.3.5 of Alexion's re-submission) and that in the 2nd and 3rd specifications, in which age at visit was included as a covariate, the estimated coefficients for age at visit were not statistically significant. Furthermore, while in the 2nd specification age at visit had a positive coefficient for AA (+0.002), it had a negative coefficient for BSC (-0.012), indicating a relatively small impact. Similarly, the covariate measuring days between visits had a positive coefficient for AA (+0.003) and a negative coefficient for BSC (varied from -0.017 to -0.009). When asked on the appropriateness of the signs of the coefficients according to prior expectations, the company did not provide any further clarifications in clarification phase. Therefore, the EAG considers that there is uncertainty around these model predictions, likely attributed to the limited number of observations, especially for BSC. The EAG concluded that the company's preferred model would be most appropriate for the base case analysis but had concerns around the inclusion of age as a covariate and considered the most parsimonious model of the 1st specification appropriate for inclusion in the scenario analyses.

The number of observations for the BSC arms remains small even with the addition of the patients in the registry and, therefore, uncertain.

The initial severity level distribution can have a non-negligible impact on the ICER, as shown in the scenario results provided by the company. The different assumptions regarding this initial distribution should be discussed by the Committee and it should be decided which one is considered as more plausible.

Key Issue 7

Uncertainty in utility values and carer disutilities

The EAG states that HRQoL data reported by patients, rather than clinicians scoring vignettes, should be used in the CEA, and that data from the UK MAA and/or the Global HPP Registry should be used to inform the utility values. The EAG also states that the disutility of infant death experienced by parent/caregivers is uncertain in size and duration for which it is experienced, so the EAG prefer that it be evaluated in a scenario rather than the base case.

Alexion understands NICE's preference for use of HRQoL responses from patients vs. vignettes. However, this was not possible due to lack of HRQoL measurements across the range of 6MWT (underpinning severity levels of the CEA model) in the MAA. Due to start criteria ensuring that only patients with severe disease-initiated treatment, among the N= [redacted] patients aged ≥5 at baseline of the MAA, [redacted] % were in SL3 or SL4 (or could not complete the 6MWT). Due to visit restrictions during COVID, limited observations were obtained at improved 6MWT levels. Per Table 52 of the re-

submission, replicated as Table 3 below, utility estimates stratified by 6MWT were therefore concentrated in the more severe states, limiting sample size in SL1-2, preventing use of the MAA data in the CUA.

Table 3. xxxx

Where the MAA did provide sufficient sample size, utility estimates for SL3 and SL4 of [redacted] and [redacted] validate those estimated with the vignettes (0.23 and 0.54). When not stratifying utilities by percent-predicted 6MWT ranges, the MAA demonstrated the significant utility benefits associated with AA treatment. As described in Alexion's re-submission, median change from baseline of the EQ-5D was [redacted] (min, max[redacted]), supporting the large improvements modelled in the CUA.

Alexion understands that there is uncertainty around the size and duration of the disutility for parents/caregivers associated with infant death. However, the scope for the evaluation indicated that outcomes should include, "health-related quality of life (for patients and carers)". Alexion therefore believes that parental disutility associated with infant death should be considered in the base case. Of note, however, results of the CEA are relatively insensitive to this parameter; for the perinatal/infantile-onset scenario, removing this disutility changes the ICER from [redacted] to [redacted].

EAG comment:

The EAG would like to thank the company for the additional clarification. We understand the limitations of the data and we also consider that the different position in terms of the size and duration of the disutility for parents/caregivers associated with infant death is a matter of different judgement between the company and the EAG. Therefore, the EAG would like to reiterate its preference for the assumptions made in its base-case. These different assumptions should be discussed by the Committee, and it should be decided which one is considered as more plausible.

Additionally, the EAG would like to note that, besides the aspects discussed above, Key Issue 7 also underlines a shortcoming in the way uncertainty in the utility values was incorporated in the model. This aspect has not been further clarified in the response above.

Key Issue 8

Price reduction due to patent expiry

The EAG states the price reduction due to future patent expiry of AA treatment should be omitted from the base-case analysis, as it relies on assumptions/expectations rather than evidence, and the number of existing biosimilars for orphan diseases is very limited, likely attributed to producing biosimilars for orphan diseases targeting small populations being economically unattractive.

Alexion acknowledges that there is uncertainty around future biosimilar competition. However, the AA patent is due to expire in 2030, and data from Europe show significant variance in price differentials between reference products and biosimilars. For example, recent reports of prices for biosimilar infliximab have suggested price reductions of 45–72% versus the originator product. NICE has stated that "biosimilars have the potential to offer the NHS considerable cost savings, especially as they are often used to treat long-term conditions". Alexion also currently faces emerging biosimilar competition for an ultra-rare disease therapy, such that in the company's view, this expectation is informed by evidence, though subject to uncertainty.

Removing the LOE price reduction from the base case increases the ICER for the perinatal/infantile-onset scenario from [redacted] to [redacted], and for the juvenile-onset scenario from [redacted] to [redacted]. However, Alexion is submitting an updated PAS to PASLU, representing a per-vial discount of [redacted] which yields CEA results aligning with Alexion's base case analyses.

EAG comment:

The EAG would like to thank the company for the additional clarification. The scenarios with the updated PAS are relevant for the Committee discussion.

Key Issue 9

Resource use and costs

The EAG states that patient weight modelled in the CEA is significantly lower than the general population, based on a polynomial fit of weight-for-age data from the clinical trials and UK MAA. The EAG states that the company did not provide any information on the goodness-of-fit for the polynomial model and on other smoothing curves that were explored. The EAG conducted a sensitivity analysis in which patients' weight followed the median values of the general population, and found that this increased base-case ICERs significantly.

Alexion would like to note that HPP patients, especially those aged < 18 years, have body weight distinctly lower than the median values of the general population. More specifically, the median baseline and last follow up weight values for AA treated patients in the clinical studies included in the current submission are as reflected in Table 4 below.

Table 4. Weight-for-age Z scores across paediatric-onset HPP populations

	ENB-002-08/ENB-003-08	ENB-010-10	ENB-006-09/ENB-008-10	ENB-009-10	MAA (Paediatric patients)	ALX-HPP-501 GLOBAL REGISTRY (Paediatric patients)
Baseline weight	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Last follow up	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

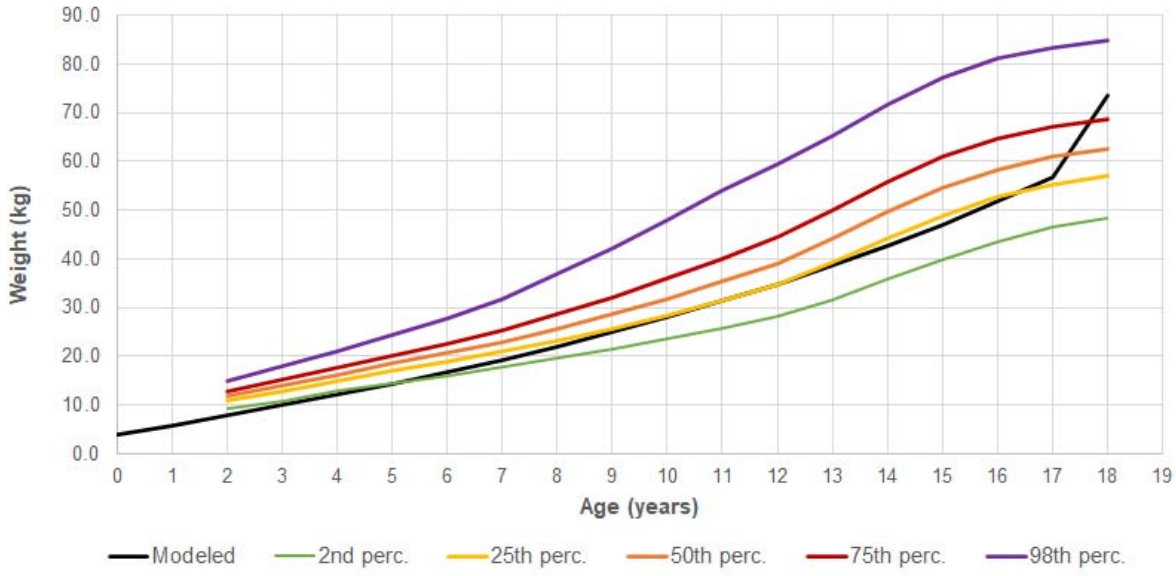
Following AA treatment, as shown by the AA treatment follow up data, there is a slow catch up for the majority of patients that will take well into adulthood until weight reaches the median values of the population.

In the CEA, weight for age was modelled based on a third-degree polynomial fit of baseline weight by age in the clinical trials and MAA. Alexion explored 1st, 2nd, and 3rd degree polynomial fits, as well as an exponential, and found that the 3rd-degree polynomial provided best fit based on AIC and BIC. These goodness-of-fit tests were not requested in the EAG's clarification questions, but could have been provided. Before age 18, the modelled weight-for-age curve tracks the 25th percentile of the UK population, according to the Royal College of Paediatrics and Child Health (RCPCH)[5], as reflected in Figure 2 below. This is consistent with the clinical data reported above, that children with HPP typically have body weight 1-2 Z scores below the general population's.

[5] Royal College of Paediatrics and Child Health. GIRLS - UK Growth chart 2-18 years. January, 2013. URL: https://www.rcpch.ac.uk/sites/default/files/Girls_2-18_years_growth_chart.pdf
Royal College of Paediatrics and Child Health. BOYS - UK Growth chart 2-18 years. January, 2013. URL: https://www.rcpch.ac.uk/sites/default/files/Boys_2-18_years_growth_chart.pdf

In adults with HPP, the CEA models a mean weight of 73.6 kg, based on the polynomial fit of the clinical-trials and MAA data. This is slightly lower than the 50%-50% male-female mean for the UK general population of 78.0 kg according to NHS England[6]. However, AA dosing remains at the same level (2 vials of 80 mg, 3x per week) from body weight of 63 kg to 82 kg; only at 83 kg would dosing increase. Consequently, modelling the UK adult mean weight would not affect CEA results. Of note, exposure data from the UK MAA validate that the majority of adults receive dosing consistent with that modelled in the CEA.

Figure 2. Weight-for-age modelled in the CEA, compared to RCPCH growth charts for the UK



EAG comment:

The EAG would like to thank the company for the additional clarification. However, a transparent explanation of how to interpret the data in Table 4 and the information about the goodness-of-fit for the polynomial model and on other smoothing curves that were explored are however still missing. Based on the information presented above, the EAG considers that modelling the UK adult mean weight would not indeed affect CEA results. Regarding children, the company indicated that "*the modelled weight-for-age curve tracks the 25th percentile of the UK population*". However, based on Figure 2, this only occurs after 8 or 9 years of age. Before that the modelled weight is lower. Therefore, the EAG still considers that the scenarios with the change in patient weight are relevant for the Committee discussion.

[6] NHS England. Health Survey for England 2016: Adult health trends. Excel Tables - Table 3. December 13, 2017. URL: https://digital.nhs.uk/data-and-information/publications/statistical/health-survey-for-england/health-survey-for-england-2016#summary

Demographics comparison tables

Table 5. Comparison of data included in the 2015 Asfotase Alfa HST submission (HST6) and current re-submission

	ENB-002-08/ ENB-003-08	ENB-010-10	ENB-006-09/ ENB-008-10	ENB-009-10	EMPATHY	MAA	ALX-HPP-501 GLOBAL REGISTRY
Key Demographics	11 AA treated patients Patients ≤ 3y.o. Perinatal/infantile HPP	69 AA treated patients Patients ≤ 5y.o. & symptoms onset <6 m.o.	13 AA treated patients Patients 6-12 y.o. Perinatal/infantile HPP (5) Juvenile HPP (8)	19 AA treated patients Patients ≥13 y.o; 18 pts with paed-onset HPP;1 pt with adult onset HPP Perinatal/infantile HPP (4) Juvenile HPP (14)	14 AA treated patients Adults with paed-onset HPP	[redacted]	347 AA treated patients Children & adults with paed-onset HPP
Appraisal 2017 – Submission 21 Jul 2015	Efficacy & Safety data for AA – duration of follow up 54 months	Efficacy & Safety data for AA – duration of follow up to 48 months *(on-going)*	Efficacy & Safety data for AA – duration of follow up 48 months *(on-going)*	Efficacy & Safety data for AA – duration of follow up to 48 months *(on-going)*	**N/A**	**N/A**	**N/A**

RE-appraisal – Current submission June 2022	Efficacy & Safety data for AA – duration of follow up to 84 months	Efficacy & Safety data for AA – duration of follow up 60 months	Efficacy & Safety data for AA – duration of follow up 84 months Subgroup analysis: 1. Perinatal/infantile 2. Juvenile	Efficacy & Safety data for AA – duration of follow up 60 months Subgroup analysis 1. Patients with paed -onset HPP	Efficacy & Safety data for AA – duration of follow up, 12 months	[redacted]	Efficacy and safety data Ventilation support Height & Weight 6mWT BPI-SF PedsQL Fractures SF36
Summary	Additional 30 months follow up data on AA treatment	Additional 12 months follow up data on AA treatment	Additional 36 months follow up data on AA treatment	Additional 12 months follow up data on AA treatment	New dataset	New dataset	New dataset

Table 6. Baseline differences between MAA adult patient population, the HPP Global Registry never-treated adult population & study ENB-009-10

Baseline variable	UK MAA study - AA treated pts >18 y.o.; [redacted]	ALX-HPP-501, never treated >18 y.o. baseline; 362 patients	ENB-009-10 19 patients
Fractures (current & history)	[redacted]	129/272 (37%)	6/19 (31.6%)
BPI-SF median (pain)	[redacted]	3.0	15
Analgesics use	[redacted]	Not reported	16/19 (84.2%)
6mWT (median)	[redacted]	503 (75.88% predicted)	402 (72.5% predicted)
Bleck Score (median)	[redacted]	Not captured	Not captured
EQ5D-3L utility	[redacted]	Not captured	Not captured

Table 7. Baseline differences between MAA paediatric patient population, the HPP Global Registry never-treated paediatric population & study ENB-006-09/008-10

Baseline variable	UK MAA study - AA treated pts <18 y.o.; v	ALX-HPP-501, never treated <18 y.o. baseline; 210 patients	ENB-006-09/ENB-008-10 13 patients
Analgesics use	[redacted]	Not reported; BPI -SF (median)= 3.0	11/13 (84.6%)
6mWT (median)	[redacted]	478m (71.97% predicted)	350m (60.98% predicted)
Bleck Score (median)	[redacted]	Not captured	Not captured
PedsQL	[redacted]	84.24	
Height (median)	[redacted]	-0.32 (Z)	-1.26 (Z)
Weight	[redacted]	-0.14 (Z)	-1.21 (Z)
BAMF upper	[redacted]	Not captured	Not captured
BAMF lower	[redacted]	Not captured	Not captured