25 June 2015
EMA/CHMP/383178/2015
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Strensiq

International non-proprietary name: asfotase alfa

Procedure No. EMEA/H/C/003794/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

25-OH vitamin	25-hydroxy vitamin D
6MWT	Six-Minute Walk Test
ADA	Antidrug antibody
AE	Adverse event
AESI	
Alexion-defined age groups	Age groups defined by the Sponsor that align more closely with the enrolment criteria of the clinical studies
ALP	Alkaline phosphatase
ALPL	Alkaline phosphatase, liver/bone/kidney
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
ATS	American Thoracic Society
BiPAP	Biphasic positive airway pressure
BMC	Bone mineral content
BMI	Body mass index
BOT-2	Bruininks-Oseretsky Test of Motor Proficiency, Second Edition
BPI-SF	Brief Pain Inventory-Short Form
BSID-III	Bayley Scales of Infant and Toddler Development, Third Edition
BUN	Blood urea nitrose
CDC	Centers for Disease Control
CFB	Change from baseline
CHAQ	Child Health Assessment Questionnaire
CI	Confidence interval
CLIA	Chemical Laboratory Improvement Amendments
CNS	Central nervous system
CPAP	Continuous positive airway pressure
CSR	Clinical Study Report
DBil	Direct bilirubin
DEXA	Dual energy X-ray absorptiometry
DMD	Duchenne muscular dystrophy
EMA	European Medicines Agency
ERT	Enzyme replacement therapy
ETP	Extension treatment period
EU	European Union
FA	set Full analysis set
FDA	Food and Drug Administration (US)
FIH	First-in-human
FVC	Forced vital capacity
GLP	Good laboratory practice
Hct	Hematocrit

HEENT	Head, eyes, ears, nose, and throat
Hgb	Haemoglobin
HHD	Hand-held dynamometry
HPP	Hypophosphatasia
IAR	Injection-associated reaction
IAR	Injection- or infusion-associated reaction
IBil	Indirect bilirubin
Ig	Immunoglobulin
Infantile-onset HPP subgroup	A subgroup of patients with paediatric-onset HPP; patients in this subgroup experienced their first symptoms of HPP at <6 months of age
ISR	Injection site reaction
IV	Intravenous
Juvenile-onset HPP subgroup	A subgroup of patients with paediatric-onset HPP; patients in this subgroup experienced their first symptoms of HPP at ≥6 months but <18 years of age
KM	Kaplan-Meier
LEFS	Lower Extremity Functional Scale
max	Maximum
MCID	Minimum clinically important difference
MedDRA	Medical Dictionary for Regulatory Activities
min	Minimum
Mo	Month
NAb	Neutralizing antibody
NOAEL	No observed adverse effect level
O2	Oxygen
PD	Pharmacodynamics
PDMS-2	Peabody Developmental Motor Scales, Second Edition
PEA	Phosphoethanolamine
Pediatric-onset HPP	Patients whose first symptoms of HPP occurred at <18 years of age
Pi	Inorganic phosphate
PK	Pharmacokinetic(s)
PL	Pyridoxal
PLP	Pyridoxal-5'-phosphate
POSNA	PODCI Paediatric Orthopaedic Society of North America's Paediatric Outcomes Data
PP	set Per Protocol set
PPi	Inorganic pyrophosphate
PTH	Parathyroid hormone
PTP	Primary treatment period
PY	Patient-year
QD	Once daily
QoL	Quality of life
RGI-C	Radiographic Global Impression of Change

ROW	Rest of the world (geographically, not Asia, Europe, or the US/Canada)
RSS	Rickets Severity Scale
SAE	Serious adverse event
SC	Subcutaneous(ly)
SD	Standard deviation
SEM	Standard error of the mean
SOC	System organ class (MedDRA)
Tbil	Total bilirubin
TEAE	Treatment-emergent adverse event
TIW	Three times weekly
TNSALP	Tissue-nonspecific alkaline phosphatase
UAE	United Arab Emirates
UK	United Kingdom
ULN	Upper limit of the normal range
US	United States
wk(s)	Week(s)
yr	Year
AEX-HPLC	Anion-Exchange Chromatography
AS	Active Substance/ DS drug substance
CHMP	Committee for Medicinal Products for Human use
CHO	Chinese Hamster Ovary
CPP	Critical process parameter
CQA	Critical Quality Attribute
CVMP	Committee for Medicinal Products for Veterinary use
DP	Drug Product/ FP finished product
EC	European Commission
ELISA	Enzyme-Linked Immunosorbent Assay
EU	European Union
GMP	Good Manufacturing Practice
HA	Hydroxyapatite
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
KPA	Key Process Attribute
KPP	Key Process Parameter
LIVCA	Limit of *In Vitro* Cell Age
MALDI-TOF analysis	Matrix-Assisted Laser Desorption Ionisation Time-Of-Flight analysis
MCB	Master Cell Bank
MMV	Minute Virus of Mice
MuLV	Murine Leukaemia Virus
PDL	Population Doubling Level

Ph. Eur.	European Pharmacopoeia
pNPP	p-nitrophenyl phosphate
PPi	inorganic pyrophosphate
PRV	Pseudorabies Virus
QbD	Quality by Design
qRCR	quantitative
Reo	Reovirus
RVLPs	retrovirus-like particles
SEC-HPLC	Size Exclusion Chromatography
SmPC	Summary of Product Characteristics
SV40	Simian ***virus*** 40
TSE	Transmissible Spongiform Encephalopathy
USP	United States Pharmacopoeia
WCB	Working Cell Bank

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Alexion Europe SAS submitted on 1 June 2014 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Strensiq, through the centralised procedure falling within the Article 3(1) and point 4 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 30 May 2013.

Strensiq was designated as an orphan medicinal product EU/3/08/594 on 03/12/2008. Strensiq was designated as an orphan medicinal product in the following indication: Treatment of hypophosphatasia.

The applicant applied for the following indication: long-term enzyme replacement therapy in patients with paediatric-onset hypophosphatasia.

Following the CHMP positive opinion on this marketing authorisation, the Committee for Orphan Medicinal Products (COMP) reviewed the designation of Strensiq as an orphan medicinal product in the approved indication. The outcome of the COMP review can be found on the Agency's website: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/orphans/2009/11/human_orphan_000491.jsp&mid=WC0b01ac058001d12b

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application. The applicant indicated that asfotase alfa was considered to be a new active substance.

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0306/2013 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0306/2013 was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Applicant's requests for consideration

Marketing Authorisation under exceptional circumstances

The applicant requested consideration of its application for a Marketing Authorisation under exceptional circumstances in accordance with Article 14(8) of the above mentioned Regulation based on the following claims:

- Hypophosphatasia is a rare, serious, and life-threatening metabolic disorder. The incidence of the most severe forms of the disease is thought to be about 1:100,000 live births, although it is markedly higher in a small Canadian Mennonite population. The incidence of the most severe forms of HPP in Europe was recently estimated to be approximately 1:300,000.
- Given the extreme rarity of the disease, comprehensive data on the efficacy and safety under normal conditions of use cannot be provided at this point of time. The overall analysis set included in the submitted Marketing Authorization Application included a total of 71 patients who were treated with asfotase alfa. The efficacy and safety data in patients with HPP aged ≥18 years are limited. As requested by the CHMP, the Sponsor committed to conduct a study in the adult population in order to obtain (i) pharmacokinetic (PK) data on plasma levels of the enzyme in adults following administration of the dose advised in children, (ii) a dose response study in adults limited on biomarkers, and (iii) evidence of clinically significant benefit. However, based on the rarity of the disease, the sample size of this study is expecting to be small and data in this population will likely remain limited.
- Hypophosphatasia is a seriously debilitating and life-threatening metabolic disease. No product has been approved for this indication. There is a high unmet medical need to provide hypophosphatasia patients with a safe and effective therapy.

New active Substance status

The applicant requested the active substance asfotase alfa contained in the above medicinal product to be considered as a new active substance in itself, as the applicant claims that it is not a constituent of a product previously authorised within the Union.

Protocol Assistance

The applicant received Scientific Advice from the CHMP on 22/04/2010 and received Protocol Assistance from the CHMP on 17/03/2011, 19/09/2013 and 24/10/2013. The Scientific Advice and Protocol Assistance pertained to quality, non-clinical and clinical aspects of the dossier.

Licensing status

The product was not licensed in any country at the time of submission of the application.

1.2. Manufacturers

Manufacturer of bliological active substance

Lonza Biologics
101 International Drive
Pease International Tradeport
03801 Portsmouth
Unites States

Manufacturer responsible for batch release

Alexion Pharma International Trading
Park West, Block 10A, Nangor Road
Dublin 12
Ireland

1.3. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP:

Rapporteur: Greg Markey Co-Rapporteur: Daniela Melchiorri

- The application was received by the EMA on 1 June 2014.
- The procedure started on 23 July 2014.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 10 October 2014. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 11 October 2014.
- During the meeting on 6 November 2015 the Pharmacovigilance Risk Assessment Committee (PRAC) adopted the PRAC Advice on the submitted Risk Management Plan.
- During the meeting on 20 November 2014, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 20 November 2014.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 22 January 2015.
- The summary report of the inspection carried out at the Ajinomoto Althea Inc. site between 2 to 6 February 2015 was issued on 9th April 2015.
- The summary report of the inspection carried out at the Lonza Biologics site between 23rd and 27th March 2015 was issued on 9th June 2015.
- The Rapporteurs circulated the Joint Assessment Report on the applicant’s responses to the List of Questions to all CHMP members on 2 March 2015.
- During the meeting on 12 March 2015 the Pharmacovigilance Risk Assessment Committee (PRAC) adopted the PRAC Advice on the submitted Risk Management Plan.
- During the CHMP meeting on 26 March 2015, the CHMP agreed on a List of Outstanding Issues to be addressed in writing by the applicant.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 17 April 2015.
- The Rapporteurs circulated the Joint Assessment Report on the applicant’s responses to the List of Outstanding Issues to all CHMP members on 28 April 2015.
- During the meeting on 7 May 2015 the Pharmacovigilance Risk Assessment Committee (PRAC) adopted the PRAC Advice on the submitted Risk Management Plan.
- During the meeting on 21 May 2015, the CHMP agreed on a second List of Outstanding Issues to be addressed in writing by the applicant.
- The applicant submitted the responses to the second CHMP List of Outstanding Issues on 26 May 2015.
- The Rapporteurs circulated the Joint Assessment Report on the applicant’s responses to the second List of Outstanding Issues to all CHMP members on 9 June 2015.
- During the meeting on 11 June 2015 the Pharmacovigilance Risk Assessment Committee (PRAC) adopted the PRAC Advice on the submitted Risk Management Plan.

- During the meeting on 25 June 2015, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation under exceptional circumstances to Strensiq.

2. Scientific discussion

2.1. Introduction

Hypophosphatasia

Hypophosphatasia is a rare and sometimes fatal metabolic bone disease caused by a defect in the gene encoding tissue non-specific alkaline phosphatase. Tissue non-specific alkaline phosphatase is found on the outer surface of osteoblasts and chondrocytes and in the matrix vesicles released by these cells: it hydrolyses several substances including inorganic pyrophosphate and pyridoxal 5'-phosphate (a form of vitamin B6). In the presence of low enzyme activity:

- inorganic pyrophosphate accumulates and inhibits formation of bone mineralization so causing rickets in infants and children and osteomalacia in adults.
- pyridoxal 5'-phosphate cannot be dephosphorylated to let it cross into the cell: intracellular deficiency in the brain leads to seizures.

The presenting signs and symptoms of hypophosphatasia depend upon the age of presentation and vary from death *in utero* to relatively simple problems with dentition in adult life. Disease severity in hypophosphatasia is inversely related to the age at onset. The applicant did apply for a marketing authorisation for the treatment of the most severe form of the disease, i.e. paediatric-onset hypophosphatasia (see below).

Perinatal hypophosphatasia is the most clinically severe form of hypophosphatasia and presents *in utero* or at birth with profound hypo-mineralization of bone, deformed or shortened limbs and rapid death owing to respiratory failure caused by rachitic chest disease and hypoplastic lungs. Stillbirth is common. Epilepsy may occur. Excessive osteoid may encroach on the marrow space and result in anaemia. X-rays show marked under-mineralization of bones and severe rachitic changes. Long-term survival is unusual.

Infantile hypophosphatasia presents in the first 6 months of life. Postnatal development often appears normal until the onset of poor feeding, inadequate weight gain and rickets leading rib fractures, a flail chest, respiratory compromise and pneumonia. Defective mineralisation is associated with a 'functional' craniosynostosis. Hypercalcaemia, nephrocalcinosis and renal impairment may occur and present with recurrent vomiting. Radiographic features are generally less pronounced than those found in the perinatal form. Mortality is up to 50% in the first year of life.

Hypophosphatasia in childhood has variable clinical expression. Loss of deciduous teeth before the age of 5yrs occurs in association with characteristic dental x-ray findings.

Patients complain of stiffness and pain along with delayed walking and / or a waddling gait. Growth retardation and frequent fractures are common. A 'functional synostosis' of cranial sutures may occur leading to elevation of intracranial pressure.

X-rays show rachitic deformities and osteopenia.

Adult hypophosphatasia is associated with rickets / osteomalacia and premature loss of teeth. Dental disease may be the only clinical abnormality where radiographic and / or histologic studies show no evidence of rickets or osteomalacia. Some patients present with pseudogout consequent to raised

inorganic pyrophosphate concentrations. The applicant did only apply for a marketing authorisation for the treatment of paediatric-onset hypophosphatasia.

X-rays may show pseudofractures (typically of the proximal femora), stress fractures, chondrocalcinosis and osteopenia.

Inheritance

Perinatal and infantile hypophosphatasia are inherited as autosomal recessive traits.

The mode of inheritance for childhood and adult forms of hypophosphatasia can be either autosomal dominant or recessive.

The prevalence of perinatal and infantile hypophosphatasia is uncertain but is reckoned to be about 1:100,000. The prevalence of later-onset hypophosphatasia is even less certain because symptoms may escape notice.

The highest incidence of hypophosphatasia has been reported in the Mennonite community in Manitoba, Canada where one in every 25 people is a carrier and one in every 2,500 newborn infants has severe disease.

Diagnosis

A clinical diagnosis is made by a combination of clinical presentation, laboratory tests (low serum activity of alkaline phosphatase in association with raised concentrations of inorganic pyrophosphate, pyridoxal 5'-phosphate and phosphoethanolamine) and x-ray findings.

All clinical sub-types of hypophosphatasia are associated with mutations in the gene encoding tissue non-specific alkaline phosphatase, found on chromosome 1p36.1-34 in humans. Over 200 mutations have been described and about 80% are missense mutations. There is no clear correlation between genotype and phenotype in hypophosphatasia.

Treatment options

At time of review of this marketing authorisation application, no approved therapies for hypophosphatasia were available. Current management consists of maintaining calcium balance (by a combination of diet and calciuretics) and palliation of symptoms by use of analgesia, occupational therapy and dental and orthopaedic interventions as needed.

About the product

Asfotase alfa is a human recombinant tissue-nonspecific alkaline phosphatase-Fc-deca-aspartate fusion protein. It is intended as an enzyme replacement therapy for the treatment of patients with paediatric-onset hypophosphatasia. Patients with hypophosphatasia have reduced activity of tissue-nonspecific alkaline phosphatase leading to impaired skeletal integrity. Previous attempts to treat patients with infusions of tissue-nonspecific alkaline phosphatase did not correct the signs and symptoms of hypophosphatasia. It is thought that binding to cell membranes is needed for the enzyme to fulfil its functions and that previous products did not bear a domain to allow binding to cells. The current product has a deca-aspartate peptide domain that, according to the applicant, may promote attachment to cell membranes.

Asfotase alfa is intended for subcutaneous administration and is administered to patients with hypophosphatasia with a view to cleaving inorganic pyrophosphate, releasing inorganic phosphate to combine with calcium to form hydroxyapatite crystals that mineralise bone and so restore skeletal integrity.

2.2. Quality aspects

2.2.1. Introduction

Asfotase alfa is a human recombinant tissue-nonspecific alkaline phosphatase-Fc-deca-aspartate fusion protein. It is a soluble glycoprotein of 1452 amino acids made from the catalytic domain of human tissue-nonspecific alkaline phosphatase, the human immunoglobulin G1 Fc domain and a deca-aspartate peptide domain.

Asfotase alfa is expressed in an engineered Chinese hamster ovary cell line that maintains endogenous folding, sorting, disulfide bridging and N-linked glycosylation. The current product has a deca-aspartate peptide domain that is intended to promote attachment to cell membranes, which may enhance the effectiveness of the enzyme to fulfil its functions.

Asfotase alfa is administered to patients with hypophosphatasia with a view to cleaving inorganic pyrophosphate, releasing inorganic phosphate to combine with calcium to form hydroxyapatite crystals that mineralise bone and so restore skeletal integrity. Enzyme activity also permits pyridoxal to enter cells to act as a cofactor for many enzymatic reactions.

The finished product is intended for subcutaneous administration.

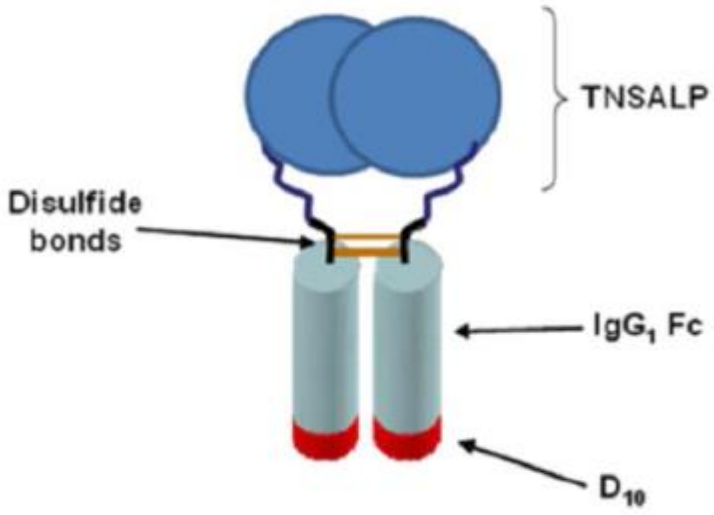
The product is presented as a sterile aqueous solution for injection, at two strengths: 100 mg/mL in a single presentation (80 mg in 0.8 mL) and 40 mg/mL in four presentations (12 mg in 0.3 mL, 18 mg in 0.45 mL, 28 mg in 0.7 mL and 40 mg in 1 mL) in single use Type I glass vials, for subcutaneous administration. The vials are stoppered with siliconised rubber stoppers and sealed with aluminium seals with polypropylene flip-off caps.

2.2.2. Active Substance

General information

The active substance, asfotase alfa is a soluble IgG1 Fc fusion glycoprotein comprised of two identical polypeptide chains, each with a length of 726 amino acids, covalently linked by two disulfide bonds. See Figure 1 below. Each polypeptide chain is comprised of a soluble catalytic domain of human tissue-nonspecific alkaline phosphatase, a human immunoglobulin IgG1 Fc domain and a deca-aspartate peptide domain intended to target bone. There are 6 N-glycosylation sites on each polypeptide chain; adequate details of the rationale for the fusion protein design have been presented.

Figure 1: Representation of the Asfotase Alfa Structure



Manufacture, characterisation and process controls

The active substance is manufactured by Lonza Biologics Inc., at their Portsmouth, New Hampshire facility in USA. It is produced by a Chinese Hamster Ovary (CHO) suspension cell line, which has been engineered for asfotase alfa expression. A flow chart for the manufacturing process is shown in Figure 2.

The upstream process is a conventional fermentation process, starting from the thawing of one vial of the Working Cell Bank (WCB). Cultures are progressively expanded using growth medium through a series of cell culture steps, and seed expansion bioreactors prior to inoculation into the production bioreactor. Upon completion of the cell culture, cells and cell debris are removed. Centrifugation and diafiltration steps follow.

The downstream asfotase alfa active substance manufacturing process includes a series of chromatography steps, a solvent/detergent viral inactivation step, virus filtration and sterile filtration steps prior to shipment to the finished product manufacturing facility. Each active substance batch will typically result in asfotase alfa at a concentration of approximately 100 mg/mL.

Control of materials

Sufficient information on raw materials used in the active substance manufacturing process has been submitted. Compendial raw materials are tested in accordance with the corresponding monograph, while specifications for non-compendial raw materials are presented. Acceptable documents have been provided for raw materials of biological origin used in the manufacturing process. Ovine and fish derived raw materials are used as media components for cell culture.

The host cell line chosen for production of asfotase alfa is the Chinese hamster ovary (CHO) cell line DG44, a non-secreting cell line. Production of asfotase alfa is achieved by insertion of a cDNA sequence encoding for a fusion protein of the soluble catalytic domain of human tissue-nonspecific alkaline phosphatase, the human immunoglobulin Fc domain terminated by a deca-aspartate peptide, along with regulatory sequences and a marker gene for drug selection into the genomic DNA of a CHO cell line. The insertion occurs as a result of integration of the transfected DNA fragment into the genome and results in the expression of asfotase alfa.

Translation of the asfotase alfa mRNA results in the synthesis of the asfotase alfa protein including a 17 amino acid signal peptide. The signal peptide is removed and a soluble, fully functional recombinant protein is secreted from the cell.

A two-tiered cell banking system is employed, consisting of a Master Cell Bank (MCB) from which a WCB is derived. Cell banks are stored in the vapour phase of liquid nitrogen. These cell banks are produced according to current good manufacturing practice (cGMP) regulations, and have been well characterised, including at the limit of *in vitro* age, to evaluate their ability to consistently produce the asfotase alfa active substance. A stability programme is in place for ongoing monitoring. However, discrepancies were observed with the establishment of gene copy number, which has been attributed to the test performance at different sites. Data obtained from the site that made the initial characterisation of cell banks are considered adequate, while there is a need to qualify the method used for gene copy number determination for the site listed in the dossier as a future characterisation and testing site. This is of particular importance in case further characterisation of cells will be needed in the future (i.e. a new cell bank will need to be established and compared to the original). The applicant has therefore been requested to provide new qualification data with respect to gene copy number to ensure that this procedure is appropriately established for the testing of future cell banks. The protocol as it has been presented for establishment and testing of new WCBs is acceptable, provided that the method for gene copy number is appropriately qualified i.e. there is a positive outcome following the review of the data requested in the relevant post-approval recommendation.

Control of critical steps and intermediates

A major objection had been raised on the control strategy. In responding to the major objection, the Applicant revised the control strategy, such that it is considered that the definition of critical/non-critical control steps, process controls in place and proposed actions in event of failure to comply with process parameters, are sufficient to provide assurance of the quality of the active substance. The Applicant also confirmed that it does not seek registration of a design space as defined by ICH Q8. The major objection has therefore been resolved (see discussion section for further details). Certain non-ICH terms are used for example, key process parameter (KPP) and key process attribute (KPA). A KPP is an input parameter that is controlled within an acceptable range and is essential for process performance. Maintenance of a KPP within its acceptable range is not known to impact critical quality attributes. Failure to maintain a KPP within its operating range will be investigated through the deviation process. A KPA is an output variable related to process repeatability and reliability that cannot be directly controlled but is an indicator that the process performs as expected. Failure to maintain a KPA within its output ranges will be investigated through the deviation process

Acceptable manufacturing process controls, key operating parameters and the respective acceptance criteria and ranges have been provided for the cell culture, primary recovery and purification stages. Points raised regarding the manufacturing process during the review process (including on starting materials, fermentation conditions, holding times, specification limits for intermediates and filters) have also been satisfactorily resolved. Steps at which reprocessing is permitted have been specified, as have lifetimes for chromatography resins. The active substance is processed continuously from cell vial thaw through to bulk fill with short term holding times of specified intermediates. These holding times have been presented (hold time and storage temperature) and validated. In summary, the measures in place can satisfactorily provide assurance of the control of the manufacturing process.

Process validation

Process validation studies were performed on four consecutive bulk active substance batches manufactured. The asfotase alfa commercial- scale manufacturing process was evaluated as a whole - from initial thaw through bulk fill - for the qualification of the entire process. Eleven operation units,

covering the entire manufacturing process, were evaluated individually and holistically to validate the asfotase alfa bulk active substance manufacturing process.

It was recommended that a preapproval inspection be conducted at the active substance manufacturing site (Lonza Biologics, Portsmouth, USA) with focus on fermentation, purification steps, process validation (PQR) and traceability with regard to the proposed batch numbering system. At inspection, the inspectors did specifically investigate issues arising. These were deemed to have eventually been appropriately addressed by the manufacturing facility. The outcome of the inspection of this site has been positive.

The shipping of the active substance from its manufacturing site to the site of manufacture of the finished product has been adequately validated.

The asfotase alfa active substance manufacturing process has been validated adequately demonstrating that the purification process can consistently produce active substance of reproducible quality that complies with the predetermined specification and in-process acceptance criteria.

Manufacturing process development

Initial active substance batches intended for clinical studies were manufactured at pilot cell-culture scale. The manufacturing process was scaled up to the commercial-scale cell culture process and transferred to Lonza Biologics to meet expected demand. Genealogy of batches used for non-clinical and clinical studies has been provided. A number of studies to support the changes in development have been provided and the comparability of the two process scales has been appropriately demonstrated. Of note, active substance from the final process at the commercial-scale has also been used in clinical studies. The history of the development of the manufacturing process has therefore been adequately described, with changes to the process during the clinical development clearly indicated and supported by relevant investigational work.

Characterisation

The biological function of asfotase alfa is provided by the soluble part of recombinant human TNSALP (a metallo-enzyme that catalyses the hydrolysis of phosphomonoesters with release of inorganic phosphate and alcohol). Asfotase alfa enzymatic activity is determined by using a synthetic substrate, p-nitrophenyl phosphate (pNPP), and the natural substrate, inorganic pyrophosphate (PPi). The ability of asfotase alfa to maintain its enzymatic activity once bound to bone is determined by an asfotase alfa and hydroxyapatite (HA) complex using pNPP as a substrate.

Characterisation of asfotase alfa was performed to provide a comprehensive understanding of the chemical structure and the biochemical, biophysical, and biological properties of the protein allowing a precise description of its quality attributes (the identity, purity, size, structure, glycosylation, charge profile, biological activity and immunochemical properties). The studies included investigation of a batch from the commercial-scale process. The rationale for the design of the fusion protein has been adequately described- the Fc domain is stated to be included primarily for purification purposes rather than for any influence on pharmacokinetics. Three different assays (pNPP-based alkaline phosphatase enzymatic assay, hydroxyapatite (HA)-bound asfotase alfa activity, and PPi hydrolysis assay) were used to test the ability of asfotase alfa to maintain target enzymatic activity *in vitro*. Several appropriate methods were used to evaluate the properties of asfotase alfa that relate to its primary, secondary, tertiary and quaternary protein structure. In addition, post-translational modifications related to glycosylation, cysteine bonding, putative oxidation and additional mass were included in the evaluation. The analytical results are consistent with the proposed structure.

An intact Fc region, as contained in asfotase alfa, could potentially bind to Fc receptors and activate the complement system. The activation of the complement system via the classical pathway occurs when complement factor C1q binds to the Fc fragment of antibodies bound to an antigen.

The potential of asfotase alfa to activate the complement in serum samples was evaluated using an enzyme-linked immunosorbent assay (ELISA) which determined the concentration of CH50 (total complement activity) in human serum samples. This study demonstrated that the Fc domain does not trigger an immunochemical response at the concentration intended in clinical settings. In summary, the characterisation is considered appropriate for this type of molecule.

Specification

The release and stability specifications for the active substance include tests for physical description, general characteristics, quantity, identity, purity and impurities (both product- and process-related), potency, and safety.

Three different assays are used to test the ability of asfotase alfa to maintain enzymatic activity *in vitro* (pNPP, HA binding and PPi).

pNPP-based alkaline phosphatase enzymatic assay - This method is used for the determination of asfotase alfa enzymatic activity to catalyse the hydrolysis of phosphomonoesters with a release of inorganic phosphate and alcohol.

HA-bound asfotase alfa activity - The ability of asfotase alfa to localize in bone tissue due to the C-terminus deca-aspartate high affinity for HA and maintain its enzymatic activity once bound to bone is determined by an asfotase alfa and HA complex using pNPP as a substrate. With regard to the HA binding assay, the Applicant states that the difference in activity between bound enzyme and control is expressed as a percentage of asfotase alfa bound to HA.

PPi hydrolysis assay - PPi, a natural alkaline phosphatase substrate is used to determine kinetic constants of asfotase alfa under physiological conditions (37°C, pH 7.4).

In some instances, a variety of tests are used to cover a single category such as purity. The analytical methods employed in the testing of the active substance have been adequately described and (non-compendial methods) appropriately validated in accordance with ICH guidelines.

The information provided in support of the justification of specification for both active substance and finished product is considered acceptable (see discussion). However, it is considered that for a number of active substance release parameters, although the proposed specifications are now acceptable based upon the data available and clinical justification, a greater control of the process/consistency may be needed to provide greater dose-to-dose consistency. Therefore, the Applicant has been requested to evaluate these specifications at a later stage, when further batch data are available. Alexion has committed to continuous monitoring of all active substance attributes in accordance with internal procedures and has implemented a long term process monitoring program for asfotase alfa active substance manufacturing to ensure the process is performing consistently. The Applicant has also committed to re-assess the release specification based on data generated under the process monitoring program and provide an update to the Agency at that time.

Process-related impurities were identified following the evaluation of the asfotase alfa manufacturing process in terms of process additives and substances generated during manufacturing. These include residual DNA and host cell proteins (HCP) from the CHO cells; materials used during early seed culture and fermentation; reagents used in viral inactivation and reagents used in purification. Studies demonstrated consistent reduction of process-related impurities for selected steps in the asfotase alfa bulk active substance manufacturing process to acceptable levels. The effective clearance of these

impurities was also confirmed during process validation. Residual HCP and DNA are also included in the active substance release specification. In summary, the capability of downstream processing operations in removal of process-related impurities has therefore been satisfactorily evaluated.

Product-related impurities are molecular variants that do not have the properties comparable to the desired product which include variants of the active substance with molecular weight other than the main band, aggregates and truncated molecule. SEC-HPLC is used as a purity assay by separating high molecular weight species (aggregate), asfotase alfa dimer and low molecular weight species (fragments). AEX basic peaks contain mainly asfotase alfa and possibly a small percentage of high molecular weight species. The AEX acidic peak contains asfotase alfa high molecular weight species. Basic and acidic species are product-related as confirmed by peptide finger printing by matrix-assisted laser desorption ionisation time-of-flight (MALDI-TOF) analysis. Studies have demonstrated consistent levels of product related impurities for selected steps in the asfotase alfa bulk active substance manufacturing process. This was demonstrated by measuring levels of selected impurities in samples collected from the process intermediate steps. The results demonstrate that these impurities are consistent and at low levels and will be continuously monitored at bulk active substance release, whereby the limits set are clinically justified.

Analytical results for several commercial batches manufactured during 2013 at the commercial- scale are demonstrated as complying fully with the proposed active substance specification. These include clinical, process validation and commercial lots. Data have been provided regarding the container closure system and satisfactory data clarifying the extractable / leachable data submitted.

Stability

A shelf-life for asfotase alfa active substance stored at 2 – 8°C protected from light was proposed.

Stability studies conducted in accordance with ICH Q5C, for active substance include long-term (2 - 8°C) storage and accelerated (23 - 27°C) storage, protected from light. All stability samples are placed into small volume (50 mL) bags of the same type and construction as the proposed container closure system.

All commercial-scale active substance batches were pooled (>10 batches) to support expiry which the Applicant justifies since there have been no significant changes during active substance manufacture at the commercial-scale. This is acceptable.

The documents submitted by the Applicant for the stability studies, to support the requested shelf-life are satisfactory. All the inspected quantitative attributes remain within specifications up to the proposed shelf-life and therefore the limit is approvable. Indeed, the Applicant has committed to continue the stress-stability study on three lots of active substance, mirroring the design of the finished product study. This commitment is acknowledged. However, in accordance with EU GMP guidelines,[1] the study results need only be reported to the authorities in case of out-of-specification results/ significant negative trend.

2.2.3. Finished Medicinal Product

Overall, the development, manufacture, characterisation and control of the finished product have been sufficiently described. The major objection related to the setting of specification, shared with the active

[1] 6.32 of Vol. 4 Part I of the Rules Governing Medicinal products in the European Union

substance, has been resolved. The specification is now acceptable, however it should be re-evaluated after accumulation of further data, as specified for active substance.

Description of the product and pharmaceutical development

The product is presented as a sterile aqueous solution for injection, prepared by aseptic filtration, at two strengths: 100 mg/mL in a single presentation (80 mg in 0.8 mL) and 40 mg/mL in four presentations (12 mg in 0.3 mL, 18 mg in 0.45 mL, 28 mg in 0.7 mL and 40 mg in 1 mL) in single use Type I glass vials, for subcutaneous administration. There is an overfill of 0.13 mL per vial for all presentations. The vials are stoppered with siliconised rubber stoppers and sealed with aluminium seals with polypropylene flip-off caps.

Excipients are well-known pharmaceutical ingredients and their quality is compliant with Ph.Eur. standards. There are no novel excipients used in the finished product formulation. The excipients used are: sodium chloride (tonicity agent), dibasic sodium phosphate heptahydrate (buffering agent), monobasic sodium phosphate monohydrate (buffering agent) and water for injection (solvent).

The physiochemical and biological properties of the finished product are identical to the physiochemical and biological properties of the active substance except for concentration. The formulation buffer composition has remained unchanged during non-clinical and clinical development.

Consideration has been given to the product properties, formulation development, manufacturing process development, suitability of the container closure system, microbiological attributes of the product and manufacturing process and compatibility of the product with commonly used administration devices.

Manufacture of the product and process controls

The physiochemical and biological properties of the asfotase alfa finished product are identical to the physiochemical and biological properties of the active substance except for concentration.

Asfotase alfa 100 mg/mL finished product is manufactured by filtration of the active substance with sterilising grade filters, followed by filling into a prepared container closure system using an automatic filling machine, then sealing the filled and stoppered vials. Due to the sensitivity of proteins to heat, terminal sterilisation of asfotase alfa finished product is not feasible. Therefore, the active substance is sterile filtered prior to vial filling. All manufacturing steps are performed using aseptic techniques. Each finished product batch consists of one active substance batch. A single active substance batch may be used to produce multiple finished product batches.

In-process controls are considered to be appropriate for the manufacturing operations carried out.

The asfotase alfa finished product manufacturing process had undergone two notable changes throughout clinical development. The first of these was a change in the finished product manufacturing facility. Comparability of material from the two sites has been effectively shown. The second change was adding a dilution process step for the formulation of 40 mg/mL asfotase alfa finished product concentration prior to filling.

The active substance was formulated at either 40 mg/mL or 100 mg/mL and filled without further formulation. In 2010, the active substance manufacturing was transferred to Lonza biologics and finished product manufacturing was also transferred to another manufacturer. Active substance is formulated at the 100 mg/mL concentration and filling of this concentration occurs without further formulation steps. The 100 mg/mL concentration is diluted with additional formulation buffer, to formulate the 40 mg/mL finished product presentation, prior to filling.

The manufacturing process has been successfully validated on the manufacture of several batches of 100 mg/mL product and several batches of 40 mg/mL product, to demonstrate the suitability and

robustness of the process. All major equipment such as the vial washer, autoclaves and depyrogenation oven were successfully qualified for cleaning, sterilisation of the container closure components and supportive materials for filling and cleaning.

The primary container closure system for both the 40 mg/mL and 100 mg/mL asfotase alfa concentrations consists of a 2 mL Ph. Eur. Type I glass vial, a 13 mm butyl rubber stopper (plug face laminated with Flurotec, entire stopper coated with B2-40 silicone) and an aluminium seal with a polypropylene flip-off cap. Data to demonstrate container suitability, chemical resistance and container closure integrity and investigations of extractable/ leachables have been submitted.

Product specification

The release and stability specifications for the finished product include tests for physical description, general characteristics, quantity, identity, purity and impurities (both product- and process-related), potency and safety. These specifications proposed for release and shelf-life of the finished product are similar to that applied to the active substance, with additional product specific tests including sterility, particulates and extractable volume.

The analytical methodology used for testing of the finished product is largely identical to that employed for testing of the active substance; some further validation to cover the analytical transfer to additional testing sites has been performed. Overall, the choice of the testing parameters for finished product is considered satisfactory. Adequate information on reference standards has been provided.

All release data from asfotase alfa finished product batches, including data from all batches used in non-clinical and clinical studies, process validation and commercial batches at both the 40 mg/mL and 100 mg/ mL concentrations have been presented in full against the specification that was in effect at the time of testing. Presented batch data include several commercial-scale, process validation batches of 100 mg/mL product and commercial-scale, process validation batches of 40 mg/mL product. These batches were used in clinical studies and complied with the specification in force at the time of testing. Furthermore, some finished product specification limits have subsequently been tightened to provide even further control of batch to batch consistency. The impurity profile is discussed in the active substance section of this report. No additional impurities are introduced during finished product manufacture. A recommendation has been made to review the finished product specification after manufacturing experience has been gained.

Stability of the product

Asfotase alfa finished product (40 mg/mL and 100 mg/ml concentrations) is stored at 2 – 8°C.

Stability studies conducted for finished product include stress studies, long-term (2 - 8°C) storage and accelerated (23 - 27°C) storage. A photostability study was performed on three finished product lots which included the two finished product concentrations (40 mg/mL and 100 mg/mL). In response to questions, further evidence has been provided to show that product-related impurities approaching the proposed specification limits were present in stability samples at time-points corresponding with the use of the same batches in clinical studies.

Stability data from earlier batches stored for 24 months show compliance to specifications, although no data for this time point have been presented for any of the validation batches that correspond to the proposed commercial fill volumes.

Finished product lots representing the clinical and commercial manufacturing process including several process validation lots for each finished product concentration have been placed on long term stability at 2 – 8°C and accelerated stability at 23 - 27°C, protected from light. These studies were conducted in containers representative of the commercial formulation. The statement in the SmPC that chemical

and physical in-use stability has been demonstrated for up to 1 hour at temperatures between 23°C to 27°C is justified based upon the data from the accelerated stability studies.

Many of the real-time test results from the 40 mg/ mL and the 100 mg/ mL lots do show compliance to the specification, however for a few key stability attributes, testing has not been performed up to the 18-month time-point and extrapolation is necessary. Furthermore, taken together with the fact that although specifications are clinically justified, they require review upon analysis of further batch data to provide greater assurance of dose-to-dose consistency, the finished product shelf-life is restricted to 15 months at this stage (See Discussion section and recommendations). This may be changed upon the availability of further data in a future variation procedure. Indeed, the commitment of the Applicant to monitor finished product stability in on-going studies is acknowledged, however in accordance with EU GMP guidelines[2] the study results need only be reported to the authorities in case of out-of-specification results/ significant negative trend.

Adventitious agents

Information regarding the raw materials of biological origin used in the manufacturing process of asfotase alfa active substance is deemed acceptable. A plant derived substance is used in the active substance manufacturing process. CHO cells originate from hamsters. Ovine and fish derived substances are used as media components for cell culture. The relevant certification has been presented. Compliance with the TSE Guideline (EMEA/410/01 – rev. 3) is considered sufficiently demonstrated.

The testing programme of cell banks and un-processed bulk harvest for virus contamination is considered adequate and in compliance with ICH Q5A. No adventitious viruses have been detected, while retrovirus-like particles (RVLPs) were observed. The retrovirus-like particles present are non-infectious and typical of the parental CHO cell line.

The manufacturing steps considered for virus validation studies are acceptable. Viral titrations were performed with the application of standard infectivity and qPCR methods. Viral removal/inactivation capacity by the asfotase alfa manufacturing process was evaluated for MuLV, PRV, Reo and MMV and SV40. The selected model viruses are appropriate, as enveloped and non-enveloped viruses are included.

Overall reduction factors are satisfactory and demonstrate the efficacy of the asfotase alfa manufacturing process to remove/inactivate possible viral contaminants. New resins as well as aged resins show a similar capability in removing viral particles.

The bulk harvest is routinely tested for mycoplasma and viruses. Bioburden and endotoxin testing are monitored throughout active substance and finished product manufacture. Detailed validation reports for the viral validation studies have been reviewed and found acceptable.

No materials of animal origin are used in the finished product manufacturing process. There are not considered to be any risks from adventitious agents resulting from the limited use of animal derived raw materials in the manufacturing processes of the active substance or finished product.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

The information presented in the dossier in relation to the manufacture of the active substance has followed the guidance laid down in ICH Q11. A major objection had been raised related to the control strategy for active substance manufacture. The Applicant has now adequately described the control strategy applied to the manufacture of the active substance, with definitions for Critical Quality Attributes (CQA), Critical Process Parameters (CPP) and the (non-ICH) terms of Key Process Attribute and Key Process Parameter (KPP).

A review of the process controls in place during inoculum expansion and fermentation has been performed that has resulted in the redefinition of two further process parameters

Furthermore, the process description has been amended to reflect tightening of cell culture process controls, in that any deviation from the target range is to be investigated for potential impact on product quality via the normal deviations procedure. The current in-process control defining the limit of *in vitro* cell age (LIVCA) with a limit for population doubling level (PDL) at inoculation of the production fermenter is not fully accepted, since it is considered that the *in vitro* cell age should cover the whole culture age including harvest. Therefore the Applicant has committed to ensure (by process controls or appropriate process characterisation data) that a LIVCA of population doublings is not exceeded at the end of each production run (at harvest).

Sections 3.2.S.2.2, 3.2.S.2.4 and 3.2.S.2.6 have been updated to reflect the clarification and amendments made in line with this tightening of the control strategy.

Justification is provided for the process controls applied during active substance manufacture. Target ranges or acceptance criteria applied are based on prior experience, work performed during manufacturing process development and during process validation.

In responding to the major objection, the Applicant has tightened the control strategy, such that it is considered that the process controls in place and proposed actions in event of failure to comply with process parameters are sufficient to provide assurance of the quality of the active substance. The major objection has therefore been resolved.

The active substance has been satisfactorily characterised employing a suite of orthogonal techniques, which have also been used to adequately demonstrate comparability between development, clinical study and commercial scale batches.

Manufacture of the finished product is straightforward, consisting of dilution with buffer (if required), sterile filtration and filling.

The active substance and finished product specifications are similar and are considered to cover appropriate parameters, employing orthogonal techniques. A major objection was however raised regarding the justification of specification and a complete reassessment in line with ICH Q6B was requested. The Applicant subsequently provided all the requested data to permit assessment of the justification of specification for quantitative attributes. The proposed rationale is now considered in agreement with the ICH Q6B. In particular:

- The requested tabulated summary has been provided and the concerns about the data used have been acceptably clarified.
- The Applicant clarified that the information about the PpK Index (statistical method) is not intended to support the setting of the acceptance criteria for the specification ranges.

Moreover, the Applicant presented 99%/95% Tolerance Intervals results; although they are not used as the main basis for setting the acceptance criteria for specifications; this is considered acceptable as Tolerance Intervals calculated on a limited number of batches (in general less than 20) are not endorsed as they would result in acceptance criteria ranges which are too large, to ensure desired quality. The Applicant should therefore re-evaluate specifications after further data (both for active substance and for finished product) are available.

Therefore, the major objection raised during initial assessment, for both active substance and finished product specifications, relating to the justification of specification, has been addressed. Specifications are supported by clinical studies and may be approved with the commitment from the Applicant to re-evaluate them after accumulation of data from active substance and finished product respectively.

Additionally, a point had been raised regarding expression of finished product potency. The Applicant was asked to investigate the feasibility of adapting the product presentation and posology in terms of determined potency units, rather than by product weight. However justification has been provided to continue to employ posology based on weight, with regard to patient compliance issues. In order to provide greater clarity regarding product administration, a dosing table has been included in the SmPC. Another point for clarification was raised with regard to this, concerning feasibility of accurate dose measurement. The Applicant has subsequently provided adequate reassurance with regard to the accuracy of dose measurement using widely available syringes for both proposed dosing regimens.

Stability data indicate that the active substance and finished product are fairly robust, not being overly susceptible to degradation.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

Approval of this product from a Quality perspective is recommended. The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. Data has been presented to give reassurance on viral/TSE safety. Recommendations for future quality development are given below.

2.2.6. Recommendation(s) for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP has recommended points for investigation as detailed in the report.

2.3. Non-clinical aspects

2.3.1. Introduction

Asfotase alfa is a soluble glycoprotein of 726 amino acids that contains a human tissue non-specific alkaline phosphatase (TNSALP) catalytic domain, a human immunoglobulin G1 Fc domain and a deca-aspartate peptide. The aspartate component is reported to bind directly to growing hydroxyapatite crystals in bone. In appropriate tissues, asfotase alfa is proposed to allow the TNSALP moiety to efficiently degrade excess local inorganic pyrophosphate (PPi) and restore normal mineralisation.

2.3.2. Pharmacology

Primary pharmacodynamic studies

In vitro, asfotase alfa was shown to have a 32-fold greater affinity to purified hydroxyapatite than kidney TNSALP lacking the deca-aspartate peptide. While the asfotase alfa's deca-aspartate peptide (D10) domain was intended to target the molecule/enzymatic activity to the bone tissue, there is a limited amount of non-clinical data to support this. In addition, although asfotase alfa was retained in bone tissues for longer periods than in other tissues examined, the D10-induced targeting of tissues was not conclusively demonstrated.

Following 5 days of ascorbic acid and β-GP-induced extracellular matrix deposition and mineralisation, MC3T3-E1 cell cultures were exposed to various treatments of PPi (± 5 μM) in the presence or absence of asfotase alfa (132 U/L) for one week. In MC3T3-E1 cell cultures, asfotase alfa abolished the PPi-induced reduction of calcium concentrations. None of the treatments affected collagen matrix deposition.

In vivo, preclinical efficacy studies with asfotase alfa were conducted in a murine knockout model (designated Akp2-/-) of human HPP. The Akp2-/- mice were characterised by a number of features including endogenous accumulation of the alkaline phosphatase (ALP) substrates PPi and pyridoxal-5' phosphate (PLP) in the plasma, excess of unmineralised bone matrix and impaired growth. They also exhibit a mineralisation deficit at the Achilles tendon enthesis, and abnormalities in skull development and morphology. Episodes of apnoea and epileptic seizures were also evident and reportedly contributed to early death. The clinical features of the Akp2-/- mouse were similar to those of the infantile form of human HPP. The Akp2-/- mouse was therefore reported to be a relevant model to evaluate asfotase alfa for the treatment of HPP. However, the Applicant states that the analyses of the effects of asfotase alfa on the craniofacial defects observed in the model Akp2-/- mouse model are still ongoing. The Applicant's responded to the request of additional data, by submitting the abstract of a study presented at the Association of Bone and Mineral Research 2014 Annual Meeting (Liu, 2014). It was indeed demonstrated that TNAP enzyme replacement starting in neonates rescues all craniofacial skeletal abnormalities seen in Alpl-/- mice. Micro-CT, histologic and digital caliper based analyses show that the skulls of treated P15 Alpl-/- mice (n=44) are significantly different than those of untreated Alpl-/- mice (n=44), but not significantly different than those of wild type mice (n=45). These findings suggest that post-natal TNAP enzyme replacement therapy is efficacious for preventing HPP-associated craniofacial skeletal abnormalities when initiated shortly after birth.

Results presented also indicate that the influence of TNAP on craniofacial skeletal development extends beyond that of promoting hydroxyapatite crystal growth, and includes both osteoblastic and chondrocytic differentiation mechanisms. Overall, the data are deemed to be acceptable.

In Akp2-/- mice, subcutaneous (SC) prophylactic treatment with asfotase alfa at doses of 0.5 to 8.2 mg/kg/day (corresponding to 303 to 8241 Units of alkaline phosphatase activity/kg/day) prevents hindpaw bone mineralisation-associated defects in a dose-dependent manner. In vehicle-treated Akp2-/- mice, the median survival time was reported to be 19.5 days. Prophylactic treatment of Akp2-/- mice with asfotase alfa significantly increased survival at all doses tested. A dose-response relationship was observed between the normalised daily dose of asfotase alfa (0.5 to 8.2 mg/kg/day) and survival.

Prophylactic treatment of Akp2-/- mice also demonstrated that asfotase alfa prevented accumulation of PPi and PLP in plasma, reduced enthesis mineralisation defects and reversed suppression of weight gain and bone growth. The lengths of the left tibiae and femurs from Akp2-/- mice treated with 8.2 mg/kg/day asfotase alfa for 43 days were similar to WT in one study but shorter than WT (by up to 6%) in another study. The differences in bone length observed between the two studies may represent a more sensitive parameter for efficacy evaluation at higher doses. Cessation of dosing reversed the effects of asfotase alfa prophylactic treatment on weight gain and survival, suggesting that continuous therapy with asfotase alfa was required for sustained benefit. Concerning the effects of asfotase alfa on PLP levels, the study ALP-PT-25.1 was conducted using a certified commercial laboratory rodent diet with no vitamin B6 supplementation. This way PLP (the primary vitamin B6 coenzymic form) measurements would not be affected by dietary intake. The evaluation was carried out as a pilot to a planned study ALP-PT-26, which confirmed the previously submitted results. It has been shown that continuous treatment of Akp2-/- mice with asfotase alfa for the full duration of the study (47 days), partially improved the reduced grip strength in the forelimbs, completely prevented the increase in both plasma PLP and liver glycogen levels, partially reversed the decreased bone length, and completely reversed the suppression of weight gain, in comparison to the 35-day asfotase alfa administration followed by 12 days vehicle injection.

In therapeutic preclinical studies, treatment with asfotase alfa was initiated 12 or 15 days after birth, a time point at which significant mineralisation-associated defects are observed in Akp2-/- mice. Treatment of Akp2-/- mice with asfotase alfa reduced mineralisation defects of bones and reversed

suppression of body weight gain. Therapeutic treatment with asfotase alfa significantly increased survival in the Akp2-/- mouse using various doses and SC dosing regimen. The daily dosing regimen was generally the most efficacious. These therapeutic effects were similar to those observed following prophylactic treatment.

Some differences were observed in AUC0-24 and Cmax in studies 902480 versus 902238, and 902236 versus 902237 employing batches 169466 (2000L) and 259248 (20000L scale process), respectively, therefore the Applicant is asked to provide a tabular overview of all the available exposure data (Cmax and AUC) derived by studies employing DS batches produced with 200, 2000 and 2000 L scale processes. There is no difference in scale process among studies 902480, 902238, 902236 and 902237. Drug substance batches 259248 and 169466 used in these studies have a same scale process of 20,000L, not 2,000L as noted by the Applicant. This is accepted.

Secondary pharmacodynamic studies

No secondary pharmacology studies with asfotase alfa were reported. This is acceptable.

Safety pharmacology programme

In a study in Akp2-/- mice administered either 1 or 4 SC doses of asfotase alfa at 8.2 mg/kg/day beginning on day 12, there was no induction of hypocalcaemia or hypophosphatemia.

The bolus intravenous (IV) administration of 180 mg/kg asfotase alfa produced acute reactions in rats. The administration of asfotase alfa by slow IV infusion or pre-treatments of diphenhydramine or dexamethasone SC reduced the reactions but did not completely alleviate the acute response. There was no evidence detected of a complement-based aetiology.

A single IV injection of asfotase alfa at dose levels of 30 and 88 mg/kg produced immediate but transient and reversible effects (abnormal gait and reduced mobility, reduced extensor thrust reflex, altered landing foot splay and lower grip strength) on the general behaviour of male rats. Paw swelling and redness, decreased body temperature, and irregular/laboured breathing were also seen in the 30 and 88 mg/kg dose groups. An IV dose of asfotase alfa at 3 mg/kg did not result in any measurable behavioural effects.

In a respiratory study in rats, asfotase alfa induced dose-dependent depressive effects on respiratory function. These effects were most notable during the first 2 hours after dosing. These effects coincided with the transient, acute infusion reactions observed in other rat IV toxicity studies and were not observed in rats administered asfotase alfa by SC administration.

No significant effects on ECG were seen in juvenile monkeys administered SC doses of up to 10 mg/kg/day asfotase alfa for 6 months.

Pharmacodynamic drug interactions

No specific pharmacodynamics drug interaction studies were conducted. This is acceptable.

2.3.3. Pharmacokinetics

The pharmacokinetic parameters of asfotase alfa have been studied in mice, rats, rabbits, and monkeys. The methods of analysis to determine levels of asfotase alfa from mouse, rat, rabbit, and monkey blood/serum and various tissues have been provided. Validation reports for the serum assays used in the GLP studies in rat, rabbit and monkey are considered adequate. The methods used are considered to be suitably validated. However, three assay parameters, i.e., calibration range, background subtraction and MRD, presented some variations. This was considered to potentially affect the quantitative enzyme determination. The Applicant adequately discussed the points related to the

differences encountered in the analytical assays developed for PK evaluations. It was clarified that all the three parameters evaluated (calibration range, background subtraction and MRD) do not present variations which could impact on the asfotase alfa PK parameters analysed in the GLP toxicology studies.

Absorption: Following a single IV administration, clearance (CL) of asfotase alfa ranged from 0.00504-0.0540 L/h/kg in mice, rats, rabbits and monkeys with apparent terminal t½ raging from ~30-40 hours. Vdss observed in these species suggest distribution of asfotase alfa into peripheral tissues. Linear kinetics, with an approximately constant CL over a dose range of 5-180 mg/kg, was observed in adult monkeys, while kinetic linearity was not assessed in mice, rats and rabbits because only one dose level was evaluated in the single dose PK studies.

Following repeated IV or SC administration of asfotase alfa for either 4 weeks or 26 weeks, AUC and/or Cmax values increased either proportionately (suggesting linear kinetics) or disproportionately (higher or lower, suggesting nonlinear kinetics) with increasing dose across the studies. Multiple factors, such as study design, drug lot, immunogenicity profile and/or age of animal may have affected the dose proportionality assessment, particularly between studies. Based on the estimated half-life values, the extent of drug accumulation in juvenile rats and monkeys were dependent on dosing frequency. At a weekly dosing schedule, no drug accumulation was observed. With a daily dosing regimen, drug accumulation was apparent. Sex differences in TK parameters were not observed in juvenile rats or juvenile monkeys.

A study was conducted where pregnant (CD-1) and non-pregnant (C57BL/6) mice were administered daily SC doses of 0 (vehicle), 0.5, 2 or 8.2 mg/kg/day asfotase alfa for 5 days on gestation days 13-17 (ALP-PT-15). Asfotase alfa concentrations were reported to be higher in non-pregnant mice. However, this could be due to strain differences. After repeated SC administration to pregnant mice at a dose range of 0.5-8.2 mg/kg, asfotase alfa levels were quantifiable in foetuses at all doses tested, suggesting cross-placental transport of asfotase alfa.

As asfotase alfa contains human immunoglobulin G1 (IgG1) Fc domain, an immunogenic response in animals was expected. Development of anti-drug antibody (ADA) was observed in 4 out of the 5 repeated dose studies. The incidence rate of ADA per time point per group was 0-100% in both rats and monkeys. The impact of ADA on systemic exposures in rats and monkeys varied from negligible to ~85% reduction in AUCs (relative to the corresponding group mean AUC values).

A toxicokinetic study of asfotase alfa was conducted in juvenile rats administered IV doses of 1, 3 or 13 mg/kg/day asfotase alfa for 26 weeks. Systemic exposures in Week 26 increased in a greater than dose proportional manner, suggesting non-linear kinetics. It was noted that drug lots of asfotase alfa with different TSAC levels (1.9 and 1.0) were used at weeks 1 to 19 and 20 to 26. Although some drug lots were expected to show a higher drug exposure, the reported exposure for week-26 was expected to be conservative compared to the exposures attained in the earlier phase of the study, i.e. week 1 through week 19. Therefore, the Week 26 exposure data was considered to be valid.

In a local tolerance study using male juvenile rats administered SC doses of 0, 0.84, 8.4 or 25.2 mg/kg/day asfotase alpha, ADA was detected in the blood samples from all dose groups including control animals.

In an embryo-foetal development study in pregnant rats administered daily IV doses of asfotase alfa at 13, 25 or 50 mg/kg on gestation days 6-19, Cmax increased in a greater than dose proportional manner, suggesting non-linear kinetics. In contrast to other studies, drug accumulation was not observed. The reason for this remained unclear.

In a pre and postnatal toxicology study of asfotase alfa in which pregnant rats were administered daily IV doses of asfotase alfa at 10, 25 or 50 mg/kg/day from gestation Days 6-19, the increase in systemic exposure was greater than dose proportional. The AUC values in this study were higher than those detected in pregnant rats of another study.

In an embryo-foetal development study in which pregnant rabbits were administered IV doses of asfotase alfa (with a TSAC of 2.7) at 10, 25 or 50 mg/kg/day from postcoitum days 7-19, systemic exposure increased in an equal to or greater than dose proportional manner. The AUC values in this study were higher than those detected in pregnant rabbits of a dose-range study. There was high inter-animal variability in serum concentrations of asfotase alfa and this was attributed to the possible development of ADAs. In pregnant rabbits administered IV doses of asfotase alfa at 10, 25 or 50 mg/kg/day, ADAs were detected in 70, 65 and 75% of animals, respectively.

In juvenile cynomolgus monkeys administered once weekly IV doses of 0, 5, 15 or 45 mg/kg/dose for 4 weeks, the increase in systemic exposure was equal to or greater than dose proportional. ADA was observed in all dose groups. However, the incidence was higher in the 45 mg/kg dose group.

In juvenile cynomolgus monkeys administered SC doses of 0.43, 2.14 or 10 mg/kg/day for 6 months, the increase in systemic exposure was equal to or slightly greater than dose proportional. Exposures were low in the 2.14 mg/kg/day dose group at Weeks 4 and 26 and the reason for this was unclear. Drug accumulation was seen at all doses. At Week 30, ADAs were detected in the 0.43 and 2.14 mg/kg/day dose groups (in 25 and 75% of animals tested, respectively) but not in the 10 mg/kg/day dose group. The reason for this remained unclear.

Distribution: Tissue distribution of asfotase alfa was characterised in juvenile mice administered a single IV dose of 5 mg/kg ^{125}I-asfotase alfa and newborn mice that received repeated SC doses of 4.3 mg/kg ^{125}I asfotase alfa for 14 days.

The distribution of ^{125}I-asfotase alfa to long bones was observed. AUC and Cmax were higher in bone tissue, femur, than that in soft tissue, such as kidney, liver, lung and muscle. Radioactivity remained in the long bones for at least 64 hours without a noticeable decline over the 96-168 hours of study period, suggesting bone retention. The radioactivity in blood/serum was eliminated more rapidly than that in bone tissues.

In the distribution study (ALP-PD-01), the protracted presence of ^{125}I-asfotase alfa in calvaria, tibia and femur, claimed by the Applicant, might indicate accumulation, retention or slow clearance of the component from these tissues. The Applicant regards this as bone targeting. However, this is considered to be drug retention in bone tissue as bone targeting was not conclusively demonstrated.

Metabolism and excretion: No specific non-clinical metabolism and/or excretion studies were performed with asfotase alfa. Such studies are not considered necessary for a biotechnology-derived product as the expected consequence of metabolism is the normal catabolic degradation to small peptides and amino acids.

No evidence of any unique clearance pathway for asfotase alfa was identified. The disposition of asfotase alfa is likely to be governed by the general mechanisms that are thought to play a role in the disposition of other Fc-fusion proteins.

Drug interaction: Non-clinical pharmacokinetic drug interaction studies were not conducted with asfotase alfa as the clearance pathways of therapeutic proteins differ from those of small molecules. Therefore, drug interactions between co-administered asfotase alfa and small molecules are unlikely to affect their pharmacokinetic profiles.

Other pharmacokinetic studies: Neonatal Fc receptor (FcRn) binding affinity of asfotase alfa was reported to be similar to two other positive controls, abatacept and etanercept (Fc domain-containing fusion proteins). The correlation analysis between FcRn binding affinity and clinical half-life showed that clinical half-life of asfotase alfa was comparable to abatacept and etanercept. These data were considered to suggest that the contribution of FcRn-mediated recycling to asfotase alfa clearance is similar to other Fc-fusion proteins.

2.3.4. Toxicology

A range of nonclinical studies was performed in support of the asfotase alfa development programme. These studies include single- and repeated-dose toxicology studies, reproductive and developmental toxicity studies. Toxicokinetic evaluations were performed in most of the repeated-dose studies. Anti-drug antibody (ADA) assessments were also conducted. In addition, local tolerance was also evaluated as part of the repeated dose studies.

The juvenile Sprague Dawley rat and juvenile cynomolgus monkey were selected as the appropriate rodent and non-rodent species, respectively, to evaluate the nonclinical safety of asfotase alfa.

Single dose toxicity: In a single dose study in juvenile cynomolgus monkeys, the IV administration of up to 180 mg/kg was considered to be well-tolerated. A marked dose-proportional increase in ALP activity was observed in all animals throughout the study due to the presence of circulating test article. Transient increases in serum ALT and AST activities were observed in three animals. These findings were not clinically or biologically relevant as they were not associated with any clinical sign or adverse findings.

Repeated dose toxicity: Weekly administration of asfotase alfa by the IV route to juvenile rats for 4 weeks at nominal doses of 0, 2.6, 26, 77 mg/kg was associated with a limited number of effects. The most consistent effect noted was a transient injection reaction (partially closed eyes, decreased muscle tone, lying on the side, hunched posture, cool to touch, uncoordinated movements, decreased activity, abnormal gait and/or blue, red and/or firm swollen hindpaws and/or forepaws) observed up to 60 minutes post dose. A reduction in the appendicular skeleton (femur and tibia) was also detected. However, no consistent effect on the axial skeleton and no effect in the crown to rump length was noted. Although the Applicant states that the small recovery group size, high variability and lack of consistency (with respect to gender) confounded these results.

Increased levels of serum phosphorus and total serum calcium, and decreased C-telopeptide values were observed in juvenile rats administered 77 mg/kg/week for 4 weeks. There were no effects observed on bone architecture.

The daily IV injection of 1, 3 or 13 mg/kg/day of asfotase alfa to juvenile rat for 26 weeks was associated with transient clinical signs including red and sometimes swollen muzzles, fore- and hind-paws for up to 1 hour post-dose throughout the dosing period and most consistently in the 13 mg/kg/day group. No toxicologically meaningful changes were seen in most of the parameters assessed during the study.

The increased serum ALP activities observed were attributed to circulating levels of asfotase alfa. Based on observations of transient clinical signs during the treatment period which were completely reversible, and did not result in any effect on the parameters used to assess toxicity at dose levels of 1, 3 or 13 mg/kg/day, the no observed adverse effect level (NOAEL) was considered to be 13 mg/kg/day.

A study was conducted to investigate the effects of asfotase alfa administered once weekly by slow IV injection to juvenile cynomolgus monkeys for 4 weeks followed by a 28-day recovery period. The only

affect seen was a dose-related increase in ALP activity. The Applicant attributed this to the presence of circulating recombinant ALP test article in the animals after each dose administration. The levels of ALP were generally similar to control values by the end of the recovery period. No effect on bone development was observed. No other toxicologically significant effects were reported.

Based on the results of this study, weekly IV injection of asfotase alfa to male and female cynomolgus monkeys for 4 weeks , at dose levels of 0, 5, 15 and 45 mg/kg, and followed by a 4-week recovery period, was without evidence of toxicity at any dose level. Therefore, the high dose level tested, 45 mg/kg/week, was considered to be the NOAEL.

The daily SC injection of asfotase alfa in juvenile monkeys for 6 months at 0.43, 2.14 or 10 mg/kg resulted in injection site observations, including skin scabs, skin dryness and/or skin redness. Asfotase alfa was not associated with any biologically relevant changes in body weight, food consumption, ophthalmology (including any evidence of ectopic calcification in the eyes), electrocardiography, haematology, clinical chemistry, urinalysis, biochemical markers of bone turnover, bone densitometry or bone geometry parameters, organ weights, macroscopic changes or microscopic findings during the study.

Increased serum alkaline phosphatase activity levels were attributed to circulating levels of asfotase alfa. There were trends for increased bone mass (at the tibia metaphysis and/or lumbar spine) and cortical thickness (at the tibia diaphysis) but no clear treatment-related effects. There was no indication that bone growth was slowed or in any way adversely affected by treatment, or any evidence of ectopic calcification in any tissue. The calvarium was examined from two sites containing the coronal and lambdoidal sutures. There were no abnormalities (e.g. premature suture closure) noted for the age of juvenile monkey used. Focal granulomatous inflammation with mineralisation (ectopic calcification) and mononuclear cell infiltration of the injection site was observed in animals from all treated groups and was partially to completely reversed following 4-weeks of recovery; focal minimal persistent inflammation remained in some injection sites from the high dose group. As the clinical signs at the injection sites (characterised as ectopic calcification or mineralisation) during the treatment period were partially to completely reversible and the injection was well tolerated, the NOAEL level was considered to be 10 mg/kg/day.

Although the rats (21 days) and monkeys (1 year) used in studies 670314 (rats) and 670388 (monkeys) cover the paediatric population aged >0.1 month to approximately 24 months, the animals used of both species had not reached the age at which the fusion of 2° ossification centres was complete (15-162 weeks in the rat and 3-6 years in the monkeys) (Zoetis 2003).

The Applicant discussed the relevance of ossification center fusion also in those animals covering paediatric patients aged 2-18, by clarifying that this aspect was taken into consideration in the 26 week study in rats (670315), although the ossification was not examined in the two repeat dose monkey studies. Taken together, these data are considered acceptable.

Toxicokinetics: The toxicokinetics of asfotase alfa have been investigated in a series of repeated dose IV and SC toxicity studies of up to 26 weeks duration in the rat, rabbit, and monkey. Following repeated IV or SC administration of asfotase alfa for either 4 weeks or 26 weeks, AUC and/or Cmax values increased either proportionately (suggesting linear kinetics) or disproportionately (higher or lower, suggesting nonlinear kinetics) with increasing dose across the studies. Multiple factors, such as study design, drug lot, immunogenicity profile and/or age of animal may have affected the dose proportionality assessment, particularly between studies. Based on the estimated half-life values, the extent of drug accumulation in juvenile rats and monkeys were dependent on dosing frequency. At a weekly dosing schedule, no drug accumulation was observed. With a daily dosing regimen, drug

accumulation was apparent. Sex differences in TK parameters were not observed in juvenile rats or juvenile monkeys.

The implications of the toxicological findings identified in preclinical studies for the risk of toxicity in man is unclear due an incomplete understanding of the asfotase alfa toxicokinetics, the great variability of ADA measurements in animals, and inconsistences among the AUC and Cmax values found in the study reports, PK written and toxicology written summaries, that do not allow firm conclusions to be made on the AUC values achieved at NOAELS and consequently on the safety margins.

For safety margin estimations, no extrapolation was used during AUC calculations since observed data were employed. Also, it was specified that safety margin calculations were appropriately conducted on the basis of both exposure and enzymatic activity data at 26 weeks. The Applicant acknowledged that sound conclusions about the impact of ADA on the non-clinical asfotase alfa PK cannot be made. However, an acceptable explanation was given about ADA impact on asfotase alfa clearance at the D150 step of the procedure, using the accumulation factor (AF) as an appropriate monitoring approach in relation to the drug half-life, where the AF is calculated as a ratio of AUC at the end of treatment (where ADA has been developed) to the AUC at the beginning of treatment (where the ADA is presumably close to zero).

Genotoxicity: No genotoxicity studies have been performed as asfotase alfa. This is acceptable.

Carcinogenicity: No carcinogenicity studies have been performed as asfotase alfa. This is acceptable.

Reproductive and developmental toxicity: In a fertility and early embryonic development study in rats, the administration of asfotase alfa at 10, 25 or 50 mg/kg/day by once daily IV injection was associated with acute injection reactions typical of those observed after previous studies utilising IV administration of asfotase alfa in rats. Males administered 50 mg/kg/day had slightly decreased body weights. Fertility and early embryofoetal development at doses ≤50 mg/kg/day were not different compared to vehicle-treated rats. Based on these results, the NOAEL was considered to be 25 mg/kg/day for males and 50 mg/kg/day for females. The NOAEL for the fertility and early embryofoetal development was considered to be 50 mg/kg/day.

In an embryofoetal development study in rats, the administration of asfotase alfa once daily by IV injection at dose levels of 13, 25 or 50 mg/kg/day from gestation Day 6 to 19 was associated with transient clinical signs. These clinical signs were typical of those seen in rats after IV administration of asfotase alfa.

There was no evidence of ectopic calcification in any fetal samples examined. Based on these results, the maternal NOAEL was considered to be 13 mg/kg/day (AUC=167 and 104 at gestation days 6 and 19, respectively mg.h/L). There was no evidence of foetotoxicity, embryolethality or teratogenicity associated with asfotase alfa in this study, therefore the NOAEL for embryofoetal development was considered to be 50 mg/kg/day (AUC=1096 and 1146 mg.h/L at gestation days 6 and 19, respectively).

In an embryofoetal development study in pregnant New Zealand white female rabbits administered IV doses of 10, 25, or 50 mg/kg/day asfotase alfa from gestation Days 7 to 19, inclusive, there was no evidence of foetal toxicity, teratogenicity or embryolethality; therefore, the NOAEL for embryofoetal development was considered to be 50 mg/kg/day. Renal tubular mineralisation was detected in2 pregnant animals administered 50 mg/kg/day. The maternal NOAEL was considered to be 25 mg/kg/day. As there was no evidence of foetal toxicity, teratogenicity or embryolethality, the NOAEL for embryofoetal development was considered to be 50 mg/kg/day. Renal tubular mineralisation was detected in 2 pregnant animals administered 50 mg/kg/day. The maternal NOAEL was considered to be

25 mg/kg/day (AUC=1978 and 1573 at gestation days 7 and 19 mg.h/L, respectively). In pregnant rabbits administered IV doses of asfotase alfa at 10, 25 or 50 mg/kg/day from gestation Days 7 to 19, anti-drug antibodies were detected in 70, 65 and 75% of animals, respectively. This could affect the detection of any embryofoetal toxicity.

A pre and postnatal development study was conducted in female rats administered 10, 25, or 50 mg/kg/day asfotase alfa by IV injection from Day 6 of gestation to Day 21 postpartum. For the F0 generation dams, transient clinical signs typically observed following IV injections of asfotase alfa were noted in all treated groups within 4 hours of dosing. A low incidence of pup cannibalism was noted for F0 dams in the mid and high dose groups. It is uncertain whether the cannibalism was treatment-related and its clinical relevance unclear. For the F1 generation adult males at 50 mg/kg/day, there were slightly lower body weight and food consumption values noted during the post weaning period. For offspring (F1 and F2 generation) there were no effects on survival, physical development, behaviour or reproductive performance. There was no evidence of treatment-related ectopic calcification. Based on these results, the NOAEL for the F0, F1 and F2 generations was considered to be 50 mg/kg/day (AUC 1339 mg.h/L).

Local tolerance: In most studies, mild local irritation was noted after SC injection, however these findings were generally reversible. In a local tolerance study, the IV injection of asfotase alfa to juvenile rats once weekly for 28 days caused transient adverse clinical signs at ≥30 mg/kg that reversed within 24 hours. The SC injection of asfotase alfa in juvenile rats once daily for 4 weeks was generally well-tolerated. Treatment-related findings included focal minimal to mild perivascular/subcutaneous mononuclear cell infiltrate at the injection sites at doses of ≥ 0.84 mg/kg/day, and axillary lymph node enlargement, that correlated with axillary lymph node minimal lymphoid hyperplasia in animals administered ≥ 8.4 mg/kg/day. As this study did not include a recovery period and the reversibility of these effects was not examined.

Impurities: There are no impurities in the drug product or drug substance that required further evaluation.

2.3.5. Ecotoxicity/environmental risk assessment

Asfotase alfa is a recombinant protein. The applicant provided justification that therefore asfotase alfa is not considered to provide a risk to the environment.

2.3.6. Discussion on non-clinical aspects

Asfotase alfa is a soluble IgG1 Fc fusion glycoprotein comprised of two identical polypeptide chains, each with a length of 726 amino acids. Each polypeptide chain is comprised of a soluble catalytic domain of human TNSALP and a human immunoglobulin IgG1 Fc domain, a deca-aspartate peptide (D10).

The non-clinical development programme for asfotase alfa consisted of a range of pharmacodynamic, pharmacokinetic and toxicology studies, in which the activity of asfotase alfa was investigated in vitro and in vivo. Pharmacokinetic studies examined the absorption and distribution profile of asfotase alfa. In the single and repeated dose toxicity studies, asfotase alfa was given intravenously and subcutaneously (which is the same route of administration used clinically). A local tolerance study was also conducted with asfotase alfa.

Asfotase alfa demonstrated preclinical efficacy in both prophylactic and therapeutic paradigms in a murine gene knockout model of hypophosphatasia, the Akp2-/- mouse model. In the prophylactic studies, asfotase alfa prevented the accumulation of circulating inorganic pyrophosphate and

pyridoxal-5' phosphate, reduced mineralisation defects of bones and had a beneficial effect on bone length and weight gain suppression. Survival time was also increased.

The positive effects of asfotase alfa on growth and survival were lost after dosing was discontinued suggesting that continuous therapy with asfotase alfa is required for sustained benefit. Therapeutic treatment with asfotase alfa promoted bone mineralisation, improved survival and reversed the weight gain suppression observed in Akp2-/- mice.

Safety pharmacology and toxicity studies were conducted in rats, rabbits and cynomolgus monkeys. Toxicokinetic and supportive ADA evaluations were conducted in several studies by measuring dose-proportional and transient IV infusion-associated reaction in rats. These reactions included depressed respiration, decreased motor activity, and swelling in the extremities. The injection response was not observed in monkeys (dosed either IV or SC), rabbits (dosed IV or SC) or in rats treated with equivalent SC doses. Injection site irritation was observed in the monkeys dosed by SC injection. These changes were mild and largely reversible. As these injection-related reactions were considered to be non-adverse and the NOAEL for each of the longer-term studies was generally considered to be the highest dose tested in each of the studies, the combined results from the toxicology studies provide some support to the clinical use of asfotase alfa.

There are no major objections or other concerns on non-clinical grounds.

2.3.7. Conclusion on the non-clinical aspects

Overall from a non-clinical perspective, no major objections or other unaddressed concerns remained in the view of the CHMP.

2.4. Clinical aspects

2.4.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- **Tabular overview of clinical studies**

Table 1: Completed and Ongoing Clinical Studies with Asfotase Alfa

Descriptor	Study Number				
	ENB-001-08•	**ENB-002-08/ ENB-003-08•**	**ENB-010-10**	**ENB-006-09/ ENB-008-10•**	**ENB-009-10**
Study Design	Multicenter, multinational, open-label, dose-escalation, safety & efficacy, PK, PD	Multicenter, multinational, open-label, single-group assignment, safety & efficacy, PK, with extension	Multicenter, multinational, open-label, safety & efficacy, PK	Multicenter, multinational, open-label, dose-comparison, parallel-assignment, historical control, safety & efficacy, PK, PD, with extension	Randomized, multicenter, multinational, open-label, dose-ranging, concurrent control, safety & efficacy, PK
Countries	Canada, USA	Canada, UAE, UK, USA	Canada, Germany, Japan, Taiwan, Turkey, USA	Canada, USA	Canada, USA
Study Status	Completed	Completed/ Ongoing	Currently enrolling and ongoing	Completed/ Ongoing	Ongoing
Number of Patients Enrolled	6	11/10	28•	13/12	19
Number of Patients Completed[(1)]	6	10/9[(1)]	24[(1),(2)]	12/12[(1)]	18[(1)]
Age at Inclusion	24 to 58 years	0.5 to 35 months	0 to 72 months	5 to 12 years	13 to 66 years
Number of Patients by Age at Disease Onset (age at onset of first signs and/or symptoms of HPP)					
Pediatric-onset	4	11	28	13	16
Perinatal/Infantile (<6 months)	1	11	28	5	4
Juvenile (6 months <18 years)	3	0	0	8	12
Adult-onset (≥18 Years)	0	0	0	0	2
Unknown-onset	2	0	0	0	1
Included in Clinical Pharmacology Analysis	yes	yes	yes	yes	yes
Included in Integrated Efficacy Analysis (n=52)	no	yes	yes	yes	no
Included in Integrated Safety Analysis (n=71)	no	yes	yes	yes	yes

Table 1: Completed and Ongoing Clinical Studies with Asfotase Alfa (Continued)

Descriptor	Study Number				
	ENB-001-08[1]	ENB-002-08/ ENB-003-08[2]	ENB-010-10	ENB-006-09/ ENB-008-10[3]	ENB-009-10
Dosing Regimen	Cohort 1: Single 3 mg/kg IV dose followed by 1 mg/kg SC dose once weekly for 3 weeks Cohort 2: Single 3 mg/kg IV dose followed by 2 mg/kg SC dose once weekly for 3 weeks	Single 2 mg/kg IV dose followed by1 mg/kg SC TIW, with dose adjustments per protocol	2 mg/kg SC TIW or 1 mg/kg SC 6×/week, with dose adjustments per protocol	2 mg/kg SC TIW or 3 mg/kg SC TIW, with dose adjustments /1 mg/kg SC TIW later changed to 2 mg/kg SC TIW or 1 mg/kg SC 6×/week, with dose adjustments per protocol	No treatment (control) or 0.3 mg/kg SC QD or 0.5 mg/kg SC QD Extension 1: 0.5 mg/kg SC QD starting at Week 24 Extension 2: 1.0 mg/kg SC 6×/week
Analysis cutoff Date for CSR	NA	16 NOV 2012	22 NOV 2013	22 JAN 2013	29 JAN 2013
Analysis cutoff Date for Integrated Analyses	NA	22 NOV 2013	22 NOV 2013	05 NOV 2013	30 OCT 2013

[1] Study ENB-001-08 is not included in the pooled efficacy and safety analyses. Four of the 6 patients who enrolled in ENB-001-08 also enrolled in ENB-009-10 and are only counted once.

[2] Study ENB-003-08 is the extension study for Study ENB-002-08. Patients who rolled over from the parent study to the extension study were only counted once.

[3] Study ENB-008-10 is the extension study for Study ENB-006-09. Patients who rolled over from the parent study to the extension study were only counted once.

[4] Study ENB-010-10 is continuing to enroll patients.

(1) For ongoing studies, the number of completed patients is reflective of the number of patients that were continuing asfotase alfa treatment as of the analysis cutoff date for the integrated analyses.

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Abbreviations: CSR = clinical study report; HPP = hypophosphatasia; IV = intravenous; NA = not applicable; PD = pharmacodynamic; PK = pharmacokinetic; QD = once daily; SC = subcutaneous; TIW = 3 times weekly; UAE = United Arab Emirates; UK = United Kingdom; USA = United States of America.

2.4.2. Pharmacokinetics

Absorption
ENB-0040 bioavailability after s/c dosing ranged from 62.9% to 98.4% after the first dose of ENB-0040 1 mg/kg and 54.2% to 71.3% after the first dose of ENB-0040 2 mg/kg.

Distribution
n/a

Elimination
n/a

Dose proportionality and time dependencies
After s/c dosing, median Tmax was 24 to 48 hours with dose-proportional increases in mean Cmax and AUC0-168h between cohorts.

Within the limits of variability and the small patient number, Cmax was comparable after first and third SC doses for both cohorts, as was AUC0-168h for Cohort 2. Since AUC0-168h could be estimated at Week 4 only for 1 patient in Cohort 1, no comparison can be made.

Mean t½ after s/c dosing was relatively consistent between cohorts and between Weeks 2 and 4; individual patient values ranged from 111 to 166 hours. The longer t½ after s/c dosing is most likely a consequence of slower absorption from the s/c injection site.

Pharmacokinetic studies

Pharmacokinetics of asfotase alfa were evaluated in a 1-month, multi-centre, open-label, dose-escalating study in adults with hypophosphatasia.

- Cohort 1 (n=3) of the study received asfotase alfa 3 mg/kg intravenously the first week followed by 3 doses at 1 mg/kg subcutaneous at weekly intervals from weeks 2 to 4.
- Cohort 2 (n=3) received asfotase alfa 3 mg/kg IV the first week followed by 3 doses at 2 mg/kg subcutaneous at weekly intervals from weeks 2 to 4.
- After the 3 mg/kg for 1.08 hours intravenous infusion, the median time (Tmax) ranged between 1.25 to 1.50 hours, and the mean (SD) Cmax ranged between 42694 (8443) and 46890 (6635) U/L over the studied cohorts.
- The absolute bioavailability after the first and third subcutaneous administration ranged from 45.8 to 98.4%, with median Tmax ranging between 24.2 to 48.1 hours.
- After the 1 mg/kg weekly subcutaneous administration in Cohort 1 the mean (SD) AUC over the dosing interval (AUC_τ) was 66034 (19241) and 40444 (N=1) U*h/L following the first and the third dose, respectively.
- After the 2 mg/kg weekly subcutaneous administration in Cohort 2 the mean (SD) AUC_τ was 138595 (6958) and 136109 (41875) following the first and the third dose, respectively.

Population pharmacokinetics

Pharmacokinetic data from all asfotase alfa clinical trials were analysed using population PK methods. The pharmacokinetic variables characterized by population PK analysis represent the overall

hypophosphatasia patient population with age range from 1 day to 66 years and subcutaneous doses of up to 28 mg/kg/week.

Based on the results of population pharmacokinetic analysis it was concluded that asfotase alfa exhibits linear pharmacokinetics up to subcutaneous doses of 28 mg/kg/week.

The model identified body weight to affect asfotase alfa clearance and volume of distribution parameters. It is expected that PK exposures will increase with body weight.

The impact of immunogenicity on asfotase alfa PK overall was estimated to decrease PK exposures by less than 20%.

2.4.3. Pharmacodynamics

Mechanism of action

Asfotase alfa is an enzyme supplement therapy for the treatment of paediatric-onset hypophosphatasia. Deficiency in tissue nonspecific alkaline phosphatase activity leads to raised blood concentrations of substrates such as inorganic pyrophosphate and pyridoxal-5'-phosphate.

Asfotase alfa is a human recombinant tissue-nonspecific alkaline phosphatase-Fc-deca-aspartate fusion protein. It is a soluble glycoprotein of 726 amino acids made from the catalytic domain of human tissue nonspecific alkaline phosphatase, the human immunoglobulin G1 Fc domain (to facilitate purification) and a deca-aspartate peptide domain.

Administration of asfotase alfa to patients with paediatric-onset hypophosphatasia is proposed to promote bone mineralization and so improve skeletal structure.

Primary and Secondary pharmacology

Pharmacodynamics were evaluated in the following clinical studies:

Study 06-09/08-10

Study 06-09/08-10 was an open-label, non-randomised study. 13 patients were enrolled and 12 patients are on-going in the study. 5 patients presented with hypophosphatasia at under 6 months age and 8 patients presented between 6 months and 18yrs age. Age at inclusion in the study was between 5 and 12 years old. The study employed historical controls from the same centre as patients who received asfotase alfa and who had been subject to a similar protocol of clinical management.

<u>The effects of asfotase alfa on x-ray appearance</u>

Trained radiologists evaluated pre- and post-baseline x-rays of wrists and knees of patients for the following signs: apparent physeal widening, metaphyseal flaring, irregularity of provisional zone of calcification, metaphyseal radiolucencies, metadiaphyseal sclerosis, osteopenia, 'popcorn' calcification in metadiaphysis, demineralization of distal metaphysis, transverse subphyseal band of lucency and tongues of radiolucency. X-ray changes from baseline were then rated using the Radiographic Global Impression of Change rating scale as follows: -3=severe worsening, -2=moderate worsening, -1=minimal worsening, 0=no change, +1=minimal healing, +2=substantial healing, +3= near-complete or complete healing. Patients who received asfotase alfa moved to scores of +2 and +3 over the first 6 months of exposure and this was sustained with on-going treatment. Historical controls did not show change over time.

Bone biopsy

Tetracycline for bone-labelling was administered in two 3-day courses (separated by a 14-day interval) prior to acquisition of the bone biopsy. Trans-iliac crest bone biopsies were obtained by standard procedure. Histological analysis of biopsies used Osteomeasure software (Osteometrics, USA). Nomenclature, symbols and units followed recommendations of the American Society for Bone and Mineral Research. For 10 patients in the per-protocol set (excludes those patients who received oral vitamin D between baseline and week 24) who underwent biopsy of the trans-iliac bone crest before and after receiving asfotase alfa:

- Mean (SD) osteoid thickness was 12.8(3.5)µm at baseline and 9.5(5.1)µm at week 24
- Mean (SD) osteoid volume / bone volume was 11.8(5.9)% at baseline and 8.6(7.2)% at week 24
- Mean (SD) mineralisation lag-time was 93 (70) days at baseline and 119 (225) days at week 24

Growth

Height, weight and head circumference were plotted on growth charts (series of percentile curves that illustrate distribution) available from the Centers for Disease Control and Prevention, USA. These reference data were drawn from a representative sample of healthy children and are not specific for children with special health care needs: they have been used in the absence of growth charts for children with hypophosphatasia.

For those patients who received asfotase alfa: 9/13 patients displayed persistent apparent catch-up height-gain as shown by movement over time to a higher percentile on CDC growth charts. 3/13 patients did not display apparent catch-up height-gain and 1 patient did not have enough data to permit judgement. Progress through Tanner stages appeared appropriate.

For the time period of observation of historical controls: 1/16 patients displayed apparent catch-up height-gain, 12/16 patients did not display apparent catch-up height-gain and data were inconclusive in 3/16 patients.

Study 02-08/03-08

Study 02-08/03-08 was an open-label, non-randomised, non-controlled study. 11 patients were enrolled and 9 patients are on-going in the study. Onset of hypophosphatasia was under 6 months in all patients. Age at inclusion in the study was between 0.5 to 35 months.

The effects of asfotase alfa on x-ray appearance

7/11 patients in the full analysis set achieved Radiographic Global Impression of Change scores of +2 at Week 24 compared to baseline radiographs.

Growth

5/11 subjects displayed apparent catch-up height-gain. Fluctuation in height-gain was apparent and may reflect the more severe disease and higher rate of morbidity in these younger patients.

Study 09-10

Study 09-10 was an open-label, randomised study. 19 patients were enrolled and 18 patients are on-going in the study. Onset of hypophosphatasia was under 6 months in 16 patients, between 6 months and 18yrs in 4 patients and over 18yrs in 2 patients. Age of onset was not known for 1 patient. Age at inclusion was from 13 to 66yrs.

Growth

The adolescent (and adult) patients in this study did not display apparent height-gain.

Bone biopsy

Patients underwent biopsy of the trans-iliac bone crest either as part of a control group or before and after exposure to asfotase alfa:

	Control group 5 evaluable patients		0.3mg/kg/day asfotase alfa group 4 evaluable patients		0.5mg/kg/day asfotase alfa group 5 evaluable patients	
	baseline	Week 24	baseline	Week 48	baseline	Week 48
Osteoid thickness mean (SD)	13µm (1.6)	11.9µm (7.6)	7.6µm (2.2)	8.5µm (4.1)	7.1µm (2.5)	6.3µm (2.0)
Osteoid volume per bone volume mean (SD)	11.1% (5.0)	11.6% (8.7)	6.6% (3.7)	8.9% (3.3)	5.3% (2.0)	3.2% (1.9)
Mineralisation lag-time mean (SD)	226 (248) days	304 (211) days	1236 (1468) days	328 (200) days	257 (146) days	130 (142) days8

- For the 9 evaluable patients who received asfotase alfa, mean (SD) mineralisation lag-time was 692 (1041) days at baseline and 218 (189) days at week 48

Modelling exercise

Clinical pharmacology data (pharmacokinetic, pharmacodynamic and immunogenicity data) collected up to 28th Jan 2013 were analysed.

The final Pop-PK model analysed the iv and s/c data simultaneously producing a final pharmacokinetic model with first-order absorption following s/c administration and a two-compartment disposition with elimination from the central compartment.

Dose proportionality was inferred up to the studied s/c dose of 28.0 mg/kg/wk based on the Pop-PK model analysis.

Covariate Effects

The model was used to investigate effects of (i) formulation factors on bioavailability, (ii) demographics on clearance and volume of distribution and (iii) immunogenicity effects on clearance.

A model-based assessment of the impact of assay on estimated Pop- PK model parameters was made. The model shows minimum impact of assay in all cases.

Monte Carlo simulations using final Pop-PK model and variable estimates were conducted to evaluate the covariate effects on asfotase alfa PK. Simulations by varying parameters such as batch size, immunogenicity and body weight content were carried out. Covariates such as age, sex, renal function

and liver function tests (AST and ALT) along with bioanalytical method for measuring PK of asfotase alfa as activity were not found to be significant.

Population-pharmacokinetic and pooled pharmacokinetic-pharmacodynamic analyses were conducted to characterise independent exposure vs. response relationships for change in biomarkers such as plasma pyridoxal phosphate and inorganic pyrophosphate, radiologic pharmacodynamic endpoints such as the Radiographic Global Impression of Change, Rickets Severity Scale and functional efficacy endpoints such as the Bruininks-Oserestsky Test of Motor Proficiency and the 6-minute walk test.

An evaluation of population exposure-response relationships for the adverse events of ectopic calcification, injection / infusion associated reactions and injection site reaction events during the entire treatment duration for all studies in the PK-PD analysis data set. 552 events occurred across the 3 endpoints.

Given the subject specific Cavg over the entire study, rate of adverse event incidence (number of events/time) vs. quartiles of exposure were constructed. When viewed as a function of exposure quartiles, adverse event summaries revealed no dependence on exposure.

Justification of product specifications

One of the product specifications for the manufacture of asfotase alfa that impact the exposure - response relationship are specific activity (U/mg, drug potency).

Based on a covariate sensitivity analysis performed using the developed Pop-PK one parameter was identified as having a impact on exposure in hypophosphatasia patients.

Since this parameter and specific activity differs from lot to lot within the set formulation specifications, a model based simulation analysis was conducted to assess the magnitude of pharmacokinetic exposure changes and its subsequent impact on efficacy as a result of formulation factors.

From the modelling exercise:

- The to-be-marketed product's CMC specification should provide sufficient exposure at 6 mg/kg/week dose to see efficacy
- The maximum exposure of ~4000 U/L predicted using the maximum specific activity values specified for the to-be-marketed product's CMC specification is well below the >5000 U/L exposure resulting from the NOAEL dose from the 26 week GLP toxicology study in monkey.

The specifications proposed were questioned, as there was a limited number of subjects who achieved drug exposures represented by the upper limits. Nevertheless, it is viewed as important to achieve sufficient drug exposure. For this reason and because the proposed specification is supported by batches used in clinical studies, the specification is agreed. To provide additional supportive data, the Applicant will record batch numbers in the planned study ALX-HPP-501 (registry).

2.4.4. Discussion on clinical pharmacology

It is acknowledged that hypophosphatasia is a rare condition and that the company has had a limited pool of patients upon which to conduct studies of clinical pharmacology.

Overall, pharmacokinetic characteristics of asfotase alfa presented do not give rise to concerns.

The modelling exercise carried out by the company supports a drug exposure of 6mg/kg/week for clinical efficacy. Higher exposures were likely to be associated with the clinical safety issue of ectopic calcification.

The pharmacodynamic results suggest that exposure to asfotase alfa results in improvement of x-ray appearances of wrists and knees associated with a reduced mineralisation time-lag on bone biopsy. Many patients display apparent catch-up height-gain.

There is considered to be a differential pharmacodynamics response to exposure to asfotase alfa. Thus, patients with long-standing hypophosphatasia have osteoarthritis superimposed on the underlying osteomalacia condition. The physes are "closed" and so metaphyseal changes are absent or minimal. For these reasons, it is considered that the RGI-C score will be confounded in adults with hypophosphatasia i.e. the RGI-C score is not informative in the adult population. Interpretation of bone biopsy in an adult population with hypophosphatasia may be hampered by previous exposure to medications such as bisphosphonates and by co-existing morbidities that have been acquired during life and that affect bone histology. There may be large error from one biopsy to the next in the same person. Change in bone architecture may take years to achieve, not weeks. Further, the natural history of bone histology in patients with hypophosphatasia has not been established (and may be different to those with vitamin D sensitive osteomalacia). It may be considered that the more informative measurement in the adult population is mineralisation lag time because the measurement is a dynamic measure of cellular activity and does not require conversion to a 3-dimensional unit (i.e. it is not needed to assume isotropy of the iliac bone crest).

Data on blood concentrations of pyridoxal phosphate and inorganic pyrophosphate, the Rickets Severity Scale, the Bruininks-Oserestsky Test of Motor Proficiency and the 6-minute walk test were provided by the company: However, the data were found to not meet standards required to make claims on clinical efficacy, and were therefore considered as supportive only by CHMP.

2.4.5. Conclusions on clinical pharmacology

Overall, results of the clinical pharmacology exercise did not show any particular concerns, and were found to be acceptable by CHMP.

2.5. Clinical efficacy

The clinical studies in the asfotase alfa development program include:

- Pivotal (according to the company) open-label studies include ENB-002-08 and its extension, ENB-003-08 (ongoing); ENB-010-10 (ongoing); and ENB-006-09 and its extension ENB-008-10 (ongoing).
- A controlled, open-label supportive study ENB-009-10 (ongoing).
- A retrospective, non-interventional, epidemiological study ENB-011-10 (complete).
- Additional studies include ENB-001-08, a short-term 30-day safety & tolerability and PK study (complete).

The overall analysis set included a total of 71 patients who were treated with asfotase alfa (68 with paediatric-onset hypophosphatasia [48 with perinatal/infantile-onset hypophosphatasia, 20 with juvenile-onset hypophosphatasia], 2 with adult-onset, and 1 patient with an unknown form of hypophosphatasia).

Patients ranged from 1 day to 66 years of age at initiation of treatment. For integrated efficacy analyses by age of hypophosphatasia onset, the population included 44 patients with perinatal/infantile-onset hypophosphatasia and 8 patients with juvenile-onset hypophosphatasia.

Untreated historical controls were used for evaluating selected endpoints in studies ENB-002-08/ENB-003-08, ENB-010-10, and ENB-006-09.

2.5.1. Main studies

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Main studies ENB-006-09 / ENB-008-10

- **Table A: Summary of efficacy for trial ENB-006-09 / ENB-008-10**

Title: A Randomised, Open-Label, Multicentre, Multinational, Dose-Ranging, Historical Control Study of the Safety, Efficacy, Pharmacokinetics, and Pharmacodynamics of ENB-0040 (Human Recombinant Tissue-Nonspecific Alkaline Phosphatase Fusion Protein) in Children with Hypophosphatasia (HPP)		
Study identifier	ENB-006-09	
.	.	
Extension study title: Extension Study of Protocol ENB-006-09 Evaluating the Long-Term Safety and Efficacy of ENB-0040 (Human Recombinant Tissue-Nonspecific Alkaline Phosphatase Fusion Protein) in Children with Hypophosphatasia (HPP)		
Extension study identifier	ENB-008-10 The extension study is on-going	
.	.	
Design	a randomised, open-label, multicentre, multinational, dose-ranging study using historical controls. The open-label extension study ENB-008-10 used a fixed dose.	
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	24 weeks not applicable On-going
Hypothesis	That exposure to asfotase alfa will improve the skeletal manifestations of hypophosphatasia as compared to historical controls. A phase 2 study	
	The ages of patients ranged from 5 to 12yrs.	
Treatments groups	Study ENB-006-09	13 patients were randomised to asfotase alfa 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).
	Study ENB-008-10 (extension study)	Patients initially received a total of 3 mg/kg/week of asfotase alfa. Upon analysis of emerging data, the dose of asfotase alfa was increased to 6 mg/kg/week.

	Historical control group		16 historical control patients. These patients are in the Full Analysis set for skeletal radiographic assessments.
Endpoints and definitions	Main efficacy evaluation	RGI-C	Changes in rickets severity from Baseline to Week 24, based on skeletal radiographs measured by the Radiographic Global Impression of Change (a company-produced rating scale). Radiographs were assessed by 3 separate readers.
	Other evaluations	.	Changes in bone mineralization assessed by DEXA and bone biopsy, growth measurements, walking ability, muscle strength, motor function, pain and disability over time and forced vital capacity by pulmonary function tests. The Rickets Severity Score was recorded.
Analysis Cut-off Date	22nd January 2013		

Results and Analysis

Analysis description	**Primary Analysis**			
Analysis population	Full analysis set			
Descriptive statistics	Treatment group	ENB-006-09	ENB-008-10 (extension study)	Historical control group
	Number of subjects	13	12	16
	RGI-C	**Radiographic Global Impression of Change rating scale** X-ray changes at wrists and knees from baseline were rated using the Radiographic Global Impression of Change rating scale as follows: -3=severe worsening, -2=moderate worsening, -1=minimal worsening, 0=no change, +1=minimal healing, +2=substantial healing, +3= near-complete or complete healing. Patients who received asfotase alfa moved to scores of +2 and +3 over the first 6 months of exposure and this was sustained with on-going treatment. Historical controls did not show change over time.		

Analysis description	Other analysis
	Biopsy of trans-iliac crest bone For 10 patients in the per-protocol set (excludes those patients who received oral vitamin D between baseline and week 24) who underwent biopsy of the trans-iliac bone crest: • Mean (SD) osteoid thickness was 12.8(3.5)µm at baseline and 9.5(5.1)µm at week 24 • Mean (SD) osteoid volume / bone volume was 11.8(5.9)% at baseline and 8.6(7.2)% at week 24 • Mean (SD) mineralisation lag-time was 93 (70) days at baseline and 119 (225) days at week 24 **Growth** For those patients who received asfotase alfa: 9/13 patients displayed persistent apparent catch-up height-gain as shown by movement over time to a higher percentile on CDC growth charts. 3/13 patients did not display apparent catch-up height-gain and 1 patient did not have enough data to permit judgement. Progress through Tanner stages appeared appropriate. For the time period of observation of historical controls: 1/16 patients displayed apparent catch-up height-gain, 12/16 patients did not display apparent catch-up height-gain and data were inconclusive in 3/16 patients. **In addition:** Changes in bone mineralization assessed by DEXA, the Rickets Severity Score and results of tests of quality of life / physical activity are considered to be generally supportive.

Supportive studies ENB-002-08 / ENB-003-08, ENB-009-10, ENB-010-10, ENB-011-10

Table B. Summary of efficacy for trial ENB-002-08 / ENB-003-08

Title: A multicenter, open-label study of the safety, tolerability, and pharmacology of ENB-0040 (Enobia's human recombinant tissue-nonspecific alkaline phosphatase fusion protein) in up to 10 severely affected patients with infantile hypophosphatasia	
Study identifier	ENB-002-08
.	.
Extension study title: Extension study of ENB-0040 (human recombinant tissue-nonspecific alkaline phosphatase fusion protein) in severely affected infants and young children with hypophosphatasia	
Study identifier	ENB-003-08

.	.		
Design	an open-label, multi-centre, non-randomised, non-controlled multinational study		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		6 months not applicable Up to 60 months (study is on-going)
Hypothesis	That exposure to asfotase alfa will improve the skeletal manifestations of hypophosphatasia in patients with infantile onset. A phase 2 study.		
	There were 11 subjects in study ENB-002-08 The age of patients ranged from 2.9 to 158.1 weeks, onset of symptoms before 6 months age.		
Treatments	Study ENB-02-08		Patients received an initial single iv infusion of 2 mg/kg asfotase alfa followed 1 week later by regular administration of s/c injections of 1 mg/kg asfotase alfa 3 times/week (total 3 mg/kg per week). Dose adjustments could be made for changes in weight and / or for safety concerns or for lack of efficacy.
	Study ENB-003-08		The initial asfotase alfa dose was the same dose being administered at the patient's Week 24 visit in Study ENB-002-08. Dose is adjusted for weight every 6 months.
Endpoints and definitions	Main efficacy evaluation	RGI-C	Changes in rickets severity from Baseline to Week 24, based on skeletal radiographs measured by the Radiographic Global Impression of Change (a company-produced rating scale). Radiographs were assessed by 3 separate readers.
	Other evaluations	..	Other assessments were of the Rickets Severity Score (a company-produced rating scale), growth, tests / questionnaires of physical ability, assessment of respiratory support and overall survival.
	..	..	..
Analysis Cut-off Date	16th November 2012		
Results and Analysis			

Analysis description	**Primary Analysis**	
Analysis population	Full analysis set	
Descriptive statistics	Number of subjects	11 in study ENB-002-08 10 in extension study ENB-003-08
	RGI-C	7/11 patients in the full analysis set achieved Radiographic Global Impression of Change scores of +2 at Week 24 compared to baseline radiographs.
Analysis description	**Other analyses**	
	Growth 5/11 subjects displayed apparent catch-up height-gain **In addition:** Other analyses of overall survival, need for respiratory support and results of tests of quality of life / physical activity are considered to be generally supportive.	

Table C. Summary of efficacy for trial ENB-009-10

Title: A randomised, open-label, multicentre, multinational, dose-ranging, concurrent control study of the safety, efficacy, and pharmacokinetics of ENB-0040 (Human Recombinant Tissue-Nonspecific Alkaline Phosphatase Fusion Protein) in adolescents and adults with Hypophosphatasia		
Study identifier	ENB-009-10	
Design	randomised, open-label, concurrent control, multi-centre, multinational study.	
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	24 weeks not applicable On-going
Hypothesis	That exposure of patients to asfotase alfa will reduce plasma concentrations of inorganic pyrophosphate and pryidoxal phosphate	
Treatments groups	Patient age ranged from 13 to 66 years 22 patients were planned, 19 have enrolled	
	Group 1	Asfotase alfa 2.1mg/kg/week for 24 weeks
	Group 2	Asfotase alfa 3.5mg/kg/week for 24 weeks

	concurrent control	24 weeks
	Upon completion of the 24-week primary treatment period, all patients were eligible to continue in the open-label Extension Treatment Period of this study. Amendment 5 (20th October 2011) increased the permitted dosage to 6mg/kg/week after the first 6 months of the extension period. The study is on-going.	
Endpoints and definitions	Co-primary evaluation	Reduction in plasma concentrations of inorganic pyrophosphate and pryidoxal phosphate
	Secondary evaluations	Change in osteoid content of bone biopsy, change in bone mineral content as measured by DEXA, change in walking distance over 6 minutes.
Analysis Cut-off Date	29th January 2013	

Results and Analysis

Analysis description	**Primary Analysis**			
Analysis population	Full analysis set			
Descriptive statistics	Treatment group	Group 1	Group 2	concurrent control
	Number of subjects	6	7	6
	plasma concentrations of inorganic pyrophosphate and pryidoxal phosphate	Data submitted by the company do not convince of significant reductions in plasma concentrations of either inorganic pyrophosphate or pryidoxal phosphate		
Analysis description	**Other analyses**			

	Biopsy of trans-iliac crest bone Patients underwent biopsy of the trans-iliac bone crest either as part of a control group or before and after exposure to asfotase alfa: • Control group, standard of care (5 evaluable patients): mean (SD) mineralisation lag-time was 226 (248) days at baseline and 304 (211) days at week 24 • 0.3mg/kg/week asfotase alfa group (4 evaluable patients): mean (SD) mineralisation lag-time was 1236 (1468) days at baseline and 328 (200) days at week 48 • 0.5mg/kg/week asfotase alfa group (5 evaluable patients): mean (SD) mineralisation lag-time was 257 (146) days at baseline and 130 (142) days at week 48 **In addition:** Data submitted by the company for DEXA scans are inconclusive. Data submitted by the company do not convince of significant changes in walking distance over 6 minutes.

Table D. Summary of efficacy for trial ENB-010-10

Title: An Open-Label, Multicenter, Multinational Study of the Safety, Efficacy, and Pharmacokinetics of Asfotase Alfa (human recombinant tissue-nonspecific alkaline phosphatase fusion protein) in Infants and Children ≤5 Years of Age with Hypophosphatasia		
Study identifier	ENB-010-10	
Design	a non-randomised, open-label, multicentre, multinational study 28 patients reported (60 planned, study is on-going). A study of children ≤5yrs age.	
	Duration of main phase:	24 weeks An interim report is submitted for subjects who have completed 3 months.
	Duration of Run-in phase:	not applicable
	Duration of Extension phase:	not applicable

Hypothesis	That exposure to asfotase alfa will improve the skeletal manifestations of hypophosphatasia in patients with infantile onset. A phase 2 study.	
Treatment	6 mg/kg/week of asfotase alfa given s/c	
Endpoints and definitions	Main efficacy evaluation	Changes in rickets severity from Baseline to Week 24, based on skeletal radiographs measured by the Radiographic Global Impression of Change (RGI-C, a company-produced rating scale). Radiographs were assessed by 3 separate readers.
	Secondary evaluations	Rickets Severity Scale (a company-produced rating scale), overall survival, need for respiratory support, growth
Analysis Cut-off Date	22nd November 2013	
Results and Analysis		

Analysis description	**Primary Analysis**	
Analysis population	Full Analysis Set	
Descriptive statistics	Number of subjects	28 patients reported (60 planned).
	RGI-C	At Week 24, 21/28 patients achieved Radiographic Global Impression of Change scores of 1 or greater.
Analysis description	**Other analyses**	
	Other analyses are considered to be generally supportive towards the main efficacy evaluation. Safety evaluations contributed towards understanding of product clinical safety.	

Table E. Summary of efficacy for trial ENB-011-10

Title: A Retrospective, Non-Interventional Epidemiologic Study of the Natural History of Patients with Severe Perinatal and Infantile Hypophosphatasia	
Study identifier	ENB-011-10

<table>
<tr><td>Design</td><td colspan="2">Multi-centre, multinational, retrospective, chart review study.

127 subjects were identified, 48 patients were enrolled.

Patients had presented with symptoms at <6 months age</td></tr>
<tr><td rowspan="2">Endpoints</td><td>Primary endpoint</td><td>overall survival defined as time from birth to death</td></tr>
<tr><td>Secondary endpoint</td><td>invasive ventilator-free survival time</td></tr>
<tr><td colspan="3">First patient data abstracted 25th Sept 2012, last patient data abstracted 18th April 2013.</td></tr>
<tr><td colspan="3"><u>Results</u>
Median overall survival = 270.5 days
Median invasive ventilator free survival = 236 days</td></tr>
<tr><td colspan="3">.</td></tr>
<tr><td colspan="2">Comparative survival analysis: data collected from ENB-011-10 served as the non-concurrent control group for the combined analysis of patients from study ENB-002-08 and its extension study ENB-003-08 and study ENB-010-10 that matched the inclusion criteria for Study ENB-011-10.

25 patients from studies ENB-002-08/ENB-003-08 and ENB-010-10 met inclusion criteria.
Data cutoff for studies ENB-002-08/ENB-003-08 and ENB-010-10 was November 2012.

A comparison of overall survival and invasive-ventilator-free survival is made</td><td>Advances in supportive clinical care and technologies (in particular for respiratory support) prevent acceptance of claims made by the company on the basis of the submitted historical comparison.

Data of clinical safety of study 11-10 have contributed towards analysis of adverse events in those subjects exposed to Strensiq in the clinical studies submitted by the company.</td></tr>
</table>

2.5.2. Discussion on clinical efficacy

- **Design and conduct of clinical studies**

71 patients with hypophosphatasia have taken part in the following clinical studies submitted by the company:

- Pivotal (according to the company) open-label studies include ENB-002-08 and its extension, ENB-003-08 (ongoing); ENB-010-10 (ongoing); and ENB-006-09 and its extension ENB-008-10 (ongoing).
- A controlled, open-label supportive study ENB-009-10 (ongoing).
- A retrospective, non-interventional, epidemiological study ENB-011-10 (complete).
- Additional studies include ENB-001-08, a short-term 30-day safety & tolerability and PK study (complete).

The company's pivotal studies are described as "phase 2" and are open-label, non-controlled, non-randomised. The rationale put forward for study design is that hypophosphatasia:

- is rare
- has high unmet medical need
- is associated with serious morbidity and mortality risk
- bears potential for irrevocable harm
- does not have any alternative treatments

CHMP acknowledged that the prevalence of the severe forms of hypophosphatasia is low (about 1/100,000) although in some communities the severe form occurs more frequently such as the Mennonite population in Canada where the prevalence of the severe forms in newborn infants is (about) 1/2,500 (Mornet E. Hypophosphatasia. Orphanet J Rare Dis. 2007;2:40-7). Many of the participants in the studies submitted by the company were from the Manitoba region in Canada and it is presumed that they came from the local Mennonite community.

The prevalence of the less severe or moderate forms of hypophosphatasia is not established but has been estimated to be (about) 1/5000 in the European population (Mornet E et al. A molecular-based estimation of the prevalence of hypophosphatasia in the European population. Ann Hum Genet. 2011;75:439-45). The prevalence is likely to be higher in the Mennonite community where all forms are known to be over-represented.

It has been noted that, during the course of clinical studies, the main objectives were variously changed with regard to the primary endpoint, and how the primary endpoint was interpreted. In addition, based on the basis of emerging data, changes were made to the dosage of study drug and the inclusion / exclusion criteria of study subjects. For these reasons, cautious interpretation of data submitted is required.

Interpretation of submitted data was further hampered by use of baseline-comparison (in the absence of a suitable control group). Only one study (study 09-10) has had a concurrent control albeit non-treated as opposed to placebo. There was concern that the open-label, non-controlled, non-randomised, baseline-comparison nature of the studies is associated with high bias towards favouring the study drug. There were additional concerns that (i) studies have been carried out with the presumption of therapeutic competence and that (ii) studies have employed an ambitious array of test strategies. Therefore it would have been preferred if study designs had been concurrent, blinded, randomised controls and had been focussed on only a few significant outcomes of interest.

The use of historical control data in study 11-10 was considered generally supportive for the purposes of illustration but it was considered that improvements in supportive care and technologies (especially those of respiratory support) hamper comparison with clinical efficacy data generated by the studies

submitted by the company (information from study 11-10 has informed assessment of adverse events occurring in response to exposure to asfotase alfa). The company has observed that some subjects exposed to Strensiq in studies 02-08/03-08 and 10-10 were successfully weaned off ventilation (when ventilation has been needed): a comparison has been made with the natural history of untreated subjects in study 11-10 where there was a high mortality if ventilation was clinically required, however this comparison exercise must be interpreted with caution because of the potential of bias and confounding elements to interfere.

The above discussion is informed by:

ICH E8 General Considerations for Clinical Trials, CPMP/ICH/291/95, March 1998

ICH E9 Statistical Principles for Clinical Trials, CPMP/ICH/363/96, September 1998, January 2001

ICH E10 Choice of Control Group and Related Issues in Clinical Trials, CPMP/ICH/364/96, January 2001

Efficacy data and additional analyses

The patient population studied is acceptable as representative of subjects with hypophosphatasia. The main clinical efficacy outcomes submitted by the company are (i) the Radiographic Clinical Impression of Change, a technique to assess change in x-ray appearance over time, (ii) growth as assessed by serial measurements of height, weight and head circumference and (iii) change over time in bone histology.

The Radiographic Clinical Impression of Change tool

Trained radiologists evaluated pre- and post-baseline x-rays of wrists and knees of patients for the following signs: apparent physeal widening, metaphyseal flaring, irregularity of provisional zone of calcification, metaphyseal radiolucencies, metadiaphyseal sclerosis, osteopenia, 'popcorn' calcification in metadiaphysis, demineralization of distal metaphysis, transverse subphyseal band of lucency and tongues of radiolucency. X-ray changes from baseline were then rated using the Radiographic Global Impression of Change (RGI-C) rating scale as follows: -3=severe worsening, -2=moderate worsening, -1=minimal worsening, 0=no change, +1=minimal healing, +2=substantial healing, +3= near-complete or complete healing.

Study 06-09/08-10

Study 06-09/08-10 is considered to be the most informative study. This was an open-label study of 24 weeks duration with an on-going extension. 13 patients aged 5 to 12yrs were enrolled and, on the basis of emerging data, were exposed to 6mg/kg/week study drug. This study also enrolled 16 historical controls.

The use of historical controls within study 06-09/08-10 has been accepted in the analysis of the Radiographic Clinical Impression of Change tool and in growth measurement on the grounds that:

- Historical patient have received precisely defined standard treatment that is the same for the trial patients
- The method of treatment evaluation is the same
- Historical patient characteristics are sufficiently comparable to the trial patients
- Management has been done by same organisation and (largely the) same investigators
- No other issues making one expect differing results compared to current trial group are apparent at this time.

Regarding use of historical controls in study 06-09/08-10, the company has submitted a statement signed and dated by the main investigator physician that patients have been subject to the same core protocol in place at the one institution over the last (about) 30yrs.

X-ray appearances of wrists and knees assessed by the RGI-C tool

Data for study 06-09 suggest that subjects display improvement in the x-ray appearances of wrists and knees (as assessed by the Radiographic Impression of Change tool). Patients who received asfotase alfa moved to scores of +2 and +3 over the first 6 months of exposure and this was sustained with on-going treatment. By contrast, a change in the RGI-C score over a comparable time period was not apparent in historical controls.

Bone biopsies

The following results were obtained for 10 patients in the per-protocol set (excludes those patients who received oral vitamin D between baseline and week 24) who underwent biopsy of the trans-iliac bone crest before and after receiving asfotase alfa:

- Mean (SD) osteoid thickness was 12.8(3.5)µm at baseline and 9.5(5.1)µm at week 24
- Mean (SD) osteoid volume / bone volume was 11.8(5.9)% at baseline and 8.6(7.2)% at week 24
- Mean (SD) mineralisation lag-time was 93 (70) days at baseline and 119 (225) days at week 24

Apparent "catch-up growth" in response to exposure to study drug

For those patients who received asfotase alfa: 9/13 patients displayed persistent apparent catch-up height-gain as shown by movement over time to a higher percentile on CDC growth charts. 3/13 patients did not display apparent catch-up height-gain and 1 patient did not have enough data to permit judgement. Progress through Tanner stages appeared appropriate.

By contrast, for the time period of observation of historical controls: 1/16 patients displayed apparent catch-up height-gain, 12/16 patients did not display apparent catch-up height-gain and data were inconclusive in 3/16 patients.

<u>Studies 02-08/03-08 and 10/10</u>

The company has submitted the following observations on the need for ventilation support in studies 02-08/03-08 and 10/10 (patients aged 0.1 to 270 weeks at baseline):

21 patients required ventilation support:

- 14 patients required invasive ventilation support (intubation or tracheostomy) at baseline (one had a brief period of non-invasive ventilation at baseline before transfer).
    - ❖ 7 patients were weaned off ventilation (time on ventilation from 24 to 168 weeks), all had achieved an RGI-C score ≥2
    - ❖ 3 patients continued with ventilation support, RGI-C score ≤2
    - ❖ 3 patients died whilst on ventilation support
    - ❖ 1 patient withdrew consent
- 7 patients started non-invasive ventilation (BiPAP or CPAP) after baseline (2 patients required brief support with invasive ventilation).
    - ❖ 5 patients were weaned off ventilation (time on ventilation from 4 weeks to 48 weeks)

- ❖ 2 patients died

The natural history of untreated infant hypophosphatasia patients described in study 11-10 suggests a high mortality if ventilation is required.

Study 09-10

Results of clinical efficacy from study 09-10 are generally supportive though highlight that data are very limited in adult subjects. Further data on adult subjects will be generated by the applicant as a post-authorisation commitment.

Further information from the studies

Patients / parents / guardians report mainly positive effects on physical activity within the first 6 months of exposure (with the caveat that there are concerns over the high potential for the open-label, non-controlled nature of the phase 2 studies submitted by the company to be associated with bias in favour of the current product).

The company measured serum concentrations of inorganic pyrophosphate and pyridoxal phosphate in response to exposure to asfotase alfa, but due to issues with the collection and measurement of those data these could not be taken into account by CHMP.

2.5.3. Conclusions on the clinical efficacy

It is acknowledged that hypophosphatasia is a rare condition and that the company has had a limited pool of patients upon which to make claims of clinical efficacy.

Hypophosphatasia is characterised by failure to mineralise bone. The Radiographic Global Impression of Change tool was developed to assess change over time in skeletal mineralization in patients with hypophosphatasia in response to asfotase alfa treatment and was chosen by the company as the primary endpoint for the main clinical studies of asfotase alfa in paediatric-onset hypophosphatasia. The tool was developed by an expert panel that identified the most important radiographic features for evaluating the skeletal manifestations of hypophosphatasia. The ability of the tool to assess mineralisation of bone would make it clinically relevant in the assessment of response of patients with hypophosphatasia to exposure to asfotase alfa.

Validation of the Radiographic Global Impression of Change tool is considered to be an essential component of the current application. Thus:

- Results obtained using the RGI-C tool have demonstrated an acceptable level of agreement in inter-rater and intra-rater scores.
- Sensitivity to change of the Radiographic Global Impression of Change tool may be inferred (internal to the tool) from the pattern of response of subjects to Strensiq who move from a score of "0" to between "+2" and "+3" over the first 6 months of exposure and then fluctuate between "+2" and "+3" thereafter upon continued exposure.
- Sensitivity to change of the Radiographic Global Impression of Change tool may be inferred (external to the tool) by the concomitant display of (i) apparent catch-up height gain and (ii) the apparent improvement in histological appearance of bone biopsies over the first 6 months of exposure.

It is recognised that the company encountered difficulties conducting clinical studies on such a rare condition with multiple, serious morbidities that may blunt demonstration of clinical efficacy.

The CHMP considered that with regard to 1) the improvement in x-ray appearance as assessed by the Radiographic Clinical Impression of Change tool, 2) the histological appearance of bone biopsy material and 3) the apparent catch-up height-gain demonstrated by patients, these clinical effects showed:

Biological plausibility: supplementing a deficient enzyme that is involved in bone mineralisation is likely to lead to improved appearance of bone histology and improved x-ray appearances of bones and joints. It was therefore found to be plausible that there would be consequent gain in height and may have improved respiratory ability.

Biological coherence: pre-clinical studies submitted by the company further supported the claims for clinical efficacy.

A temporal relationship: the effects became evident subsequent to exposure and persisted with continuing exposure.

Direction of effect: the changes in x-ray appearance and bone histology were in the direction anticipated.

Consistency: the effects did occur in most (though not all) patients and were found in more than one study under similar circumstances.

Specificity of outcome: it was not apparent that organs other than bone were affected. There may be an indirect effect on muscle strength but the studies (such as the 6-minute walk test) were not able to show this conclusively.

The bulk of evidence submitted in support of clinical efficacy is in subjects under 13 yrs of age (between 0.5 months and 12 yrs of age at time of inclusion in the studies).

The data for subjects between 13 to 18 yrs of age is very limited, and the applicant has not been able to provide a robust presentation of this population in its studies. Therefore, the CHMP considered the following measure necessary to address the issue of limited efficacy data in this specific sub-population age-range:

Extension of studies ENB-008-10 and ENB-009-10 is expected to provide more data (such as, but not limited to RGI-C scores, height and weight change, biomarkers measurement) in patients 13 to 18 year-old of age, although data in this population will likely remain limited.

The applicant should submit these data to the CHMP to substantiate evidence of efficacy in this age group no later than March 2017.

Concerns over the limited amount of clinical data are particularly pronounced for subjects ≥18yrs. For treatment of patients ≥18 years, as key data on both optimal dose and schedule of administration in this specific patient sub-population are limited. Therefore, the CHMP considered the following measure necessary to address this issue:

Multicentre, randomized, open-label, Phase 2a study of Strensiq in adult patients with hypophosphatasia (HPP) to:

(i) evaluate pharmacokinetics (PK) of Strensiq in adults following administration of the dose advised in children;

(ii) provide dose response data on plasma inorganic pyrophosphate (PPi) and pyridoxal-5` -phosphate (PLP) and to explore evidence of clinical benefit. In order to ensure that the data are reliable, the MAH should submit a study protocol including acceptable techniques for blood collection, storage and assay for the PPi and PLP biomarkers, to be agreed by CHMP before the start of the study.

The applicant should submit these data to the CHMP no later than March 2017.

The CHMP agreed with the applicant's argumentation that the patient population of paediatric onset hypophosphatasia is encountered so rarely that the applicant cannot reasonably be expected to provide comprehensive clinical data on the safety and efficacy of this medicinal product. The incidence of the most severe forms of the disease is very low and thought to be about 1:100,000 live births, although markedly higher in some small populations, and recently estimated to be approximately 1:300,000 in Europe. As a consequence, the applicant will be obliged to set up a registry in order to provide, on an ongoing bases, further evidence as specific obligations relating in particular to efficacy and safety as follows:

Observational, Longitudinal, Prospective, Long-Term Registry of Patients with HPP to collect information on the epidemiology of the disease, including clinical outcomes and quality of life, and to evaluate safety and effectiveness data in patients treated with Strensiq. Specifically, more information is to be collected on the variability, progression and natural history of the disease in all age groups, the disease burden, clinical outcomes, and quality of life, and to collect and evaluate safety and effectiveness data specific to the use of asfotase alfa.

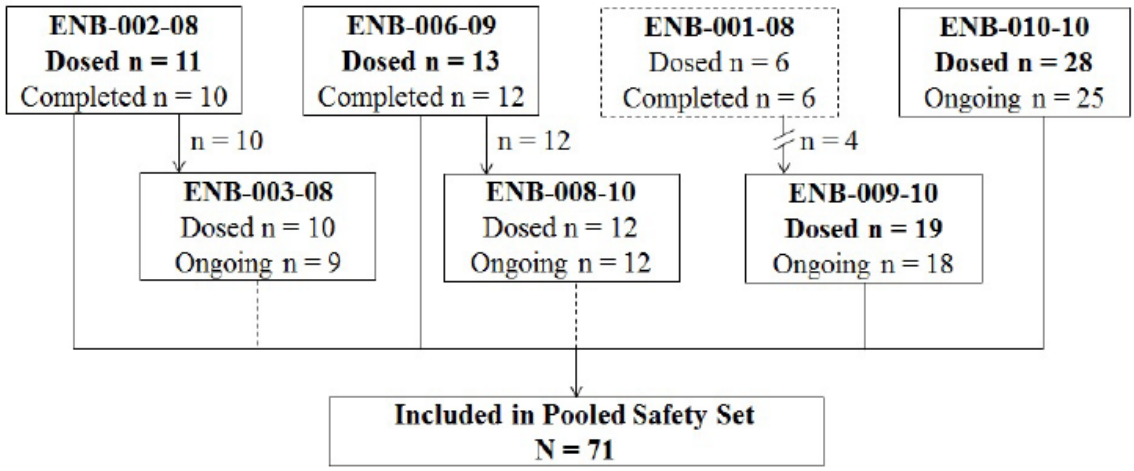
These specific obligations shall be reassessed annually.

Based on 1) the improvement in x-ray appearance as assessed by the Radiographic Clinical Impression of Change tool, 2) the histological appearance of bone biopsy material and 3) the apparent catch-up height-gain demonstrated in some patients, CHMP considered, although the data is very limited, that the totality of evidence submitted supports a specific and limited claim for clinical efficacy.

2.6. Clinical safety

The asfotase alfa clinical programme includes 7 ongoing or completed clinical studies of 71 patients as shown in the following diagram:

Figure 1: Flow of Patients from Clinical Studies into the Pooled Safety Set



The number of patients from each study included in the Pooled Safety Set is shown in bold font.
With the exception of Study ENB-001-08, the safety experience from all studies in which patients received asfotase alfa are included in the integrated analyses. Four patients who participated in Study ENB-001-08 were subsequently allowed to participate in Study ENB-009-10; however, their safety experience in Study ENB-001-08 was not included in the integrated analyses. Safety findings from Study ENB-001-08 are discussed separately.

The safety data from ENB-001-08 study are presented separately (4 patients of study ENB-001-08 were enrolled in study ENB-009-10 and so contribute towards the Pooled Safety Set).

Additionally, 11 patients have been treated under compassionate use programmes.

The 71 patients make up the Pooled Safety Set. Evaluable patients (those who received at least 1 dose of asfotase alfa) were pooled across studies and then grouped according to age at onset of first signs and / or symptoms of hypophosphatasia as shown in the following table:

Table 1: Overview of Hypophosphatasia Onset Categories and Studies Included for Pooling of Safety Data

HPP Onset Category	Subgroup	Age at Onset of First Signs/Symptoms	Studies Included in Pooled Data
Pediatric-onset	Infantile-onset	<6 months of age	ENB-002-08/ENB-003-08 ENB-006-09/ENB-008-10 ENB-009-10 ENB-010-10
	Juvenile-onset	≥6 months to <18 years of age	ENB-006-09/ENB-008-10 ENB-009-10
Adult-onset	NA	≥18 years of age	ENB-009-10
Unknown	NA	Age at onset was unknown	ENB-009-10

HPP = hypophosphatasia; NA = not applicable
Source: Integrated Safety Analysis Plan for 2.7.4

Demographics

Pooled Safety Set

Demographics for the Pooled Safety Set overall and by age at disease onset are summarised in the following table:

Table 4: Patient Demographics in the Pooled Safety Set, Overall and by Age at Disease Onset

	Pediatric Onset (N=68)				
Variable Statistic/Category	Perinatal/ Infantile Onset (N=48)	Juvenile Onset (N=20)	Adult Onset (N=2)	Unknown Onset (N=1)	All Patients (N=71)
Age at First Dose (years)					
n	48	20	2	1	71
Mean (SD)	4.69 (8.683)	29.33 (22.3.11)	55.75 (15.575)	64.24 (NA)	13.91 (20.042)
Median	2.13	16.86	55.75	64.24	5.42
Min, Max	0.0, 56.2	6.2, 59.3	44.7, 66.8	64.2, 64.2	0.0, 66.8
Age at First Dose (months)					
n	48	20	2	1	71
Mean (SD)	56.25 (104.192)	351.98 (267.729)	668.96 (186.897)	770.92 (NA)	166.88 (240.502)
Median	25.61	202.30	668.96	770.92	65.02
Min, Max	0.1, 674.5	74.2, 711.2	536.8, 801.1	770.9, 770.9	0.1, 801.1
Sex, n (%)					
Male	23 (47.9)	10 (50.0)	0	1 (100.0)	34 (47.9)
Female	25 (52.1)	10 (50.0)	2 (100.0)	0	37 (52.1)
Race, n (%)					
Asian	6 (12.5)	0	0	0	6 (8.5)
White	39 (81.3)	19 (95.0)	2 (100.0)	1 (100.0)	61 (85.9)
Other	3 (6.3)	1 (5.0)	0	0	4 (5.6)
Ethnicity, n (%)					
Hispanic or Latino	1 (2.1)	1 (5.0)	0	0	2 (2.8)
Not Hispanic or Latino	47 (97.9)	19 (95.0)	2 (100.0)	1 (100.0)	69 (97.2)

Max = maximum; Min=minimum; NA = not applicable; SD = standard deviation.
Source: Table 1.1.1.1.1

There were 34 (47.9%) males and 37 (52.1%) females. Most patients were White (61 patients; 85.9%), 2 (2.8%) patients were Hispanic or Latino and there were 6 (8.5%) Asian patients.

The median age at the time of the first dose was 5.17 years

Study ENB-001-08

The 6 patients who enrolled in Study ENB-001-08 were 24 to 58 years of age. All patients (2 male and 4 female) were Caucasian.

Cohort 1 (1 mg/kg/wk s/c): mean and median age of patients was 40 and 38 years, respectively.

Cohort 2 (2 mg/kg/wk s/c): mean and median age of patients was 50 and 52 years, respectively.

Baseline Disease Characteristics

[Baseline disease characteristics were not collected in Studies ENB-002-08/ENB-003-08].

Medical / surgical histories reported for patients included in the integrated safety analyses were consistent with the manifestations and complications of hypophosphatasia and reflected the spectrum of comorbidities seen in patients with this disease.

The more commonly reported medical / surgical histories reported included:

- skeletal deformities e.g. craniosynostosis, limb asymmetry, deformed thorax, talipes
- fractures and treatment for fractures, internal fixation
- developmental and neurological conditions e.g. developmental delay, failure to thrive, gross motor delay, speech disorder, convulsion
- musculo-skeletal conditions e.g. gait disturbance, arthralgia, arthritis, muscular weakness, myalgia, bone pain, use of orthosis, hypotonia, hypermobility, rickets
- Dental conditions e.g. dental caries, tooth development disorder, tooth loss, endodontic procedure, tooth abscess
- Gastrointestinal events and conditions e.g. constipation, gastro-oesophageal reflux disease, dysphagia
- Renal conditions e.g. nephrocalcinosis, renal failure, nephrolithiasis
- Abnormal clinical laboratory values e.g. anaemia, blood calcium abnormal, blood calcium increased, blood phosphorus increased, hypokalaemia

Other conditions noted in the overall medical history included dyspnoea, pneumonia, chronic sinusitis, hypertension, hypothyroidism, seasonal allergy, hypersensitivity, depression and anxiety, history of respiratory compromise, the need for respiratory support and vitamin B6-responsive seizures.

At Baseline, mean and median alkaline phosphatase activities were below the lower limit of normal, mean and median inorganic pyrophosphate concentrations tended to be towards the upper limits of normal, mean and median pyridoxal phosphate concentrations were highly variable and towards the upper limits of normal and mean and median parathyroid hormone concentrations were variable.

The age at onset of the first symptoms of hypophosphatasia, age when the first fracture occurred and the number of fractures per patient are presented in the following table:

Table 5: Baseline Disease Characteristics in the Pooled Safety Set, Overall and by Age at Disease Onset

Variable Statistic	Pediatric Onset (N=68) Perinatal/ Infantile Onset (N=37)[a]	Pediatric Onset (N=68) Juvenile Onset (N=20)	Adult Onset (N=2)	Unknown Onset (N=1)	All Patients (N=60)
Age at Onset of Hypophosphatasia Symptoms (years)					
n	37	20	2	0	59
Mean (SD)	0.13 (0.145)	1.71 (0.938)	33.00 (4.243)	--	1.78 (5.997)
Median	0.08	1.54	33.00	--	0.25
Min, Max	0.0, 0.5	0.5, 4.0	30.0, 36.0	--	0.0, 36.0
Age at Onset of Hypophosphatasia Symptoms (months)					
n	37	20	2	0	59
Mean (SD)	1.54 (1.738)	20.55 (11.260)	396.00 (50.912)	--	21.35 (71.964)
Median	1.00	18.50	396.0	--	3.00
Min, Max	0.0, 5.5	6.0, 48.0	360.0, 432.0	--	0.0, 432.0
Age When First Fracture Occurred (months)					
n	11	13	2	0	26
Mean (SD)	32.73 (42.219)	128.31 (76.113)	396.00 (50.912)	--	108.46 (113.755)
Median	12.00	120.00	396.00	--	78.00
Min, Max	0.0, 132.0	12.0, 240.0	360.0, 432.0	--	0.0, 432.0
Number of Fractures per Patient					
n	12	13	2	1	28
Mean (SD)	3.3 (2.99)	7.9 (7.27)	9.5 (6.36)	30.0 (NA)	6.8 (7.44)
Median	2.0	6.0	9.5	30.0	4.5
Min, Max	1, 9	1, 25	5, 14	30, 30	1, 30

Max = maximum; Min=minimum; NA = not applicable; SD = standard deviation.
[a] This analysis does not include Studies ENB-002-08/ENB-003-08.
Source: Table 1.1.1.1.1 and Table 1.1.3.2.1.1

47 (66.2%) patients in the Pooled Safety Set reported taking medications between the time their informed consent was signed and the administration of the first dose of asfotase alfa.

In general, prior medications taken by patients in the Pooled Safety Set were unremarkable and reflected those substances that would be taken for pain management (eg opioids, analgesics), neurologic disorders (eg antiepileptics) and procedures related to the management or assessment of hypophosphatasia (eg anaesthetics, iv solutions, tetracycline [for bone labelling]).

Patient exposure

71 patients were in the Pooled Safety Set and 64 of these are involved in on-going studies.

A summary of exposure (overall and by age of onset) is shown in the following table:

Table 2: Summary of Exposure to Asfotase Alfa in the Pooled Safety Set, Overall and by Age at Disease Onset

Variable Statistic/ Category	Pediatric Onset (N=68) Perinatal/ Infantile Onset (N=48)	Pediatric Onset (N=68) Juvenile Onset (N=20)	Adult Onset (N=2)	Unknown Onset (N=1)	All Patients (N=71)
Treatment Duration[a] (weeks)					
n	48	20	2	1	71
Mean (SD)	113.07 (78.098)	150.11 (35.973)	131.64 (16.061)	143.86 (NA)	124.46 (68.804)
Median	121.71	143.86	131.64	143.86	132.00
Min, Max	0.1, 260.9	95.7, 207.9	120.3, 143.0	143.9, 143.9	0.1, 260.9
Q1, Q3	28.6, 181.4	120.3, 181.3	120.3, 143.0	143.9, 143.9	60.1, 180.9
Treatment Duration Category[a] (weeks)					
<24	5 (10.4)	0	0	0	5 (7.0)
≥24 to <48	10 (20.8)	0	0	0	10 (14.1)
≥48 to <72	4 (8.3)	0	0	0	4 (5.6)
≥72 to <96	2 (4.2)	1 (5.0)	0	0	3 (4.2)
≥96 to <120	0	3 (15.0)	0	0	3 (4.2)
≥120 to <144	7 (14.6)	7 (35.0)	2 (100.0)	1 (100.0)	17 (23.9)
≥144	20 (41.7)	9 (45.0)	0	0	29 (40.8)
Patient-Years of Exposure					
n	48	20	2	1	71
Mean (SD)	2.17 (1.497)	2.88 (0.689)	2.52 (0.308)	2.76 (NA)	2.39 (1.319)
Median	2.33	2.76	2.52	2.76	2.53
Min, Max	0.0, 5.0	1.8, 4.0	2.3, 2.7	2.8, 2.8	0.0, 5.0
Q1, Q3	0.5, 3.5	2.3, 3.5	2.3, 2.7	2.8, 2.8	1.2, 3.5
Total	104.0	57.5	5.0	2.8	169.3

Max = maximum; Min=minimum; NA = not applicable; Q1 = 25th percentile; Q3 = 75th percentile; SD = standard deviation.

[a] Treatment Duration=Last dose date of asfotase alfa minus first dose date of asfotase alfa plus 1 day. For Studies ENB-002-08/ENB-003-08 and ENB-006-09/ENB-008-10, the last dose date was the last available dose of the respective extension study. Dosing interruptions or adjustments were not considered in this calculation.

Source: Table 1.3.8.1.1

Exposure to asfotase alfa ranged from 0.1 to 260.9 weeks with a median exposure for all patients of 2.53 patient-years. 49/71 patients were exposed for ≥96 weeks.

The following table provides a summary of the patient years of asfotase alfa exposure by total weekly dose:

Table 3: Patient-Years of Exposure to Asfotase Alfa by Total Weekly Dose, Pooled Safety Set Overall and by Age at Disease Onset

Dose (mg/kg/wk) Statistic/ Category	Pediatric Onset (N=68), PYs (n)		Adult Onset (N=2) PYs, n	Unknown Onset (N=1) PYs, n	All Patients (N=71) PYs, n
	Perinatal/ Infantile Onset (N=48)	Juvenile Onset (N=20)			
>0 to <3	1.33 (24)	5.09 (11)	0.91 (2)	0.92 (1)	8.24 (38)
≥3 to <6	32.23 (46)	27.99 (20)	1.40 (2)	1.82 (1)	63.44 (69)
≥6 to <9	57.62 (44)	23.59 (19)	2.74 (2)	0 (0)	83.96 (66)
≥9 to <12	7.19 (13)	0.80 (5)	0 (0)	0 (0)	8.00 (18)
≥12 to <15	3.87 (6)	0.07 (3)	0 (0)	0 (0)	3.94 (9)
≥15 to <18	0.58 (2)	0 (0)	0 (0)	0 (0)	0.58 (2)
≥18 to ≤30	1.02 (1)	0 (0)	0 (0)	0 (0)	1.02 (1)
Total	103.84 (47)[a]	57.54 (20)	5.05 (2)	2.76 (1)	169.17 (70)
Total <6	33.56 (47)	33.07 (20)	2.31 (2)	2.74 (1)	71.68 (70)
Total ≥6	70.28 (46)	24.46 (19)	2.74 (2)	0.02 (1)	97.50 (68)

PYs = patient-years.
Patients who had changes in their dose of asfotase alfa may show up in multiple total dose/week categories; therefore, the sum of patients exceeds the number of patients in each phenotype.
[a] One patient in the infantile-onset HPP subgroup discontinued the study during administration of an initial IV dose of asfotase alfa and prior to any SC dose; therefore, this patient is not included in the exposure summary.
Source: Table 1.3.8.1.3

There has been a total of 169.17 patient years of asfotase alfa exposure.

155.64 patient years of asfotase alfa exposure were in patients who received weekly doses <9 mg/kg.

Most asfotase alfa exposure experience was at total weekly doses ≥3 mg/kg and <9 mg/kg per week (147.40 patient years, mainly arising from those studies where patients received 3mg/kg/week for the first 24 weeks before increasing to 6mg/kg/week).

Exposure at higher weekly doses has been limited, with about 13.5 patient years exposure at total weekly doses ≥9 mg/kg, and <6 patient years exposure at total weekly doses ≥12 mg/kg. Treatment at higher total weekly doses primarily occurred in the infantile-onset hypophosphatasia subgroup.

Adverse events

Investigators were instructed to monitor patients for potential signs of asfotase alfa-related reactions, both systemic and localised. Clinical studies also included routine renal ultrasounds and eye examinations, including fundoscopy, to monitor for ectopic calcification.

2706 treatment-emergent adverse events were reported for the 71 patients included in the integrated safety analyses, as summarised in the following table:

Table 7: Overview of Treatment-Emergent Adverse Events in the Pooled Safety Set, Overall and by Age at Disease Onset

AE Category	Pediatric Onset (N=68)									
	Perinatal/ Infantile Onset (N=48)		Juvenile Onset (N=20)		Adult Onset (N=2)		Unknown Onset (N=1)		All Patients (N=71)	
Subcategory	n[a]	n (%)[b]	n[a]	n (%)[b]	n[a]	n (%)[b]	n[a]	n (%)[b]	n[a]	n (%)[b]
Any TEAE	1848	48 (100.0)	752	20 (100.0)	26	2 (100.0)	80	1 (100.0)	2706	71 (100.0)
Not Related[c]	1371	47 (97.9)	347	20 (100.0)	9	2 (100.0)	73	1 (100.0)	1800	70 (98.6)
Related[d,e]	477	37 (77.1)	405	20 (100.0)	17	2 (100.0)	7	1 (100.0)	906	60 (84.5)
Mild	1389	46 (95.8)	622	20 (100.0)	21	2 (100.0)	18	1 (100.0)	2050	69 (97.2)
Moderate	368	41 (85.4)	125	20 (100.0)	5	2 (100.0)	31	1 (100.0)	529	64 (90.1)
Severe	91	24 (50.0)	5	4 (20.0)	0	0	31	1 (100.0)	127	29 (40.8)
Early Onset AE[f]	824	48 (100.0)	424	20 (100.0)	12	2 (100.0)	54	1 (100.0)	1314	71 (100.0)
SAEs (nonfatal)	172	27 (56.3)	11	5 (25.0)	0	0	0	0	183	32 (45.1)
Not Related[c]	167	26 (54.2)	5	4 (20.0)	0	0	0	0	172	30 (42.3)
Related[d]	5	3 (6.3)	6	1 (5.0)	0	0	0	0	11	4 (5.6)
Mild	33	10 (20.8)	0	0	0	0	0	0	33	10 (14.1)
Moderate	76	23 (47.9)	11	5 (25.0)	0	0	0	0	87	28 (39.4)
Severe	63	17 (35.4)	0	0	0	0	0	0	63	17 (23.9)
Deaths[g]	4	4 (8.3)	0	0	0	0	0	0	4	4 (5.6)

SAE = serious adverse event; TEAE = treatment-emergent adverse event.
[a] Number of events
[b] Number and percentage of patients
[c] Considered by the Investigator to be not related or have an unlikely relationship to asfotase alfa.
[d] Considered by the Investigator to be possibly, probably, or definitely related to asfotase alfa.
[e] There were 3 ISRs that were not assessed by the Investigator as being related to asfotase alfa; 1 event in a patient in the infantile-onset HPP subgroup, and 2 events in a patient in the juvenile-onset HPP subgroup. By definition, ISRs were supposed to be considered related to asfotase alfa.
[f] Defined as any event that occurred within the first 24 weeks of asfotase alfa treatment.
[g] Treatment-emergent deaths in the clinical database. One additional death occurred pretreatment, and another occurred after the database for the integrated analyses were locked. See Section 2.1.6.
Treatment-emergent adverse events are events that started on or after the day of the first dose of asfotase alfa. All events in extension studies ENB-003-08 and ENB-008-10 were considered to be treatment-emergent. For ENB-009-10 patients in the control group, only those events that occurred on or after the day of the first dose of asfotase alfa were included.
Source: Table 1.3.1.1.1.1

Treatment-emergent adverse events observed were largely consistent with the manifestations and complications of underlying hypophosphatasia or were injection-related reactions. Treatment-emergent adverse events reported by ≥25% of patients in the integrated safety analyses) included:

- Injection site erythema (53.5%)
- Upper respiratory tract infection (39.4%)
- Pyrexia (29.6%)
- Pain in extremity (28.2%)
- Vomiting (26.8%)

Related to Asfotase Alfa

Pooled Safety Set

A summary of the most frequently reported (in ≥3 patients in the Pooled Safety Set) treatment emergent adverse events considered by the Investigator to be related to asfotase alfa treatment is provided in the following table:

Table 22: Related Treatment-Emergent Adverse Events Reported in ≥3 Patients in the Pooled Safety Set, Overall and by Age at Disease Onset

MedDRA SOC Preferred Term	Pediatric Onset (N=68), n (%) Perinatal/ Infantile Onset (N=48)	Pediatric Onset (N=68), n (%) Juvenile Onset (N=20)	Adult Onset (N=2) n (%)	Unknown Onset (N=1) n (%)	All Patients (N=71) n (%)
Any Related Adverse Event	37 (77.1)	20 (100.0)	2 (100.0)	1 (100.0)	60 (84.5)
General Disorders and Administration Site Conditions	33 (68.8)	19 (95.0)	2 (100.0)	1 (100.0)	55 (77.5)
Injection site erythema	21 (43.8)	14 (70.0)	1 (50.0)	1 (100.0)	37 (52.1)
Injection site discolouration	10 (20.8)	7 (35.0)	0	0	17 (23.9)
Injection site pain	7 (14.6)	8 (40.0)	1 (50.0)	0	16 (22.5)
Injection site pruritus	6 (12.5)	7 (35.0)	0	1 (100.0)	14 (19.7)
Injection site macule	4 (8.3)	7 (35.0)	0	0	11 (15.5)
Injection site swelling	5 (10.4)	6 (30.0)	0	0	11 (15.5)
Injection site bruising	4 (8.3)	3 (15.0)	2 (100.0)	0	9 (12.7)
Injection site hypertrophy	4 (8.3)	5 (25.0)	0	0	9 (12.7)
Injection site induration	6 (12.5)	3 (15.0)	0	0	9 (12.7)
Injection site reaction	3 (6.3)	5 (25.0)	1 (50.0)	0	9 (12.7)
Injection site atrophy	4 (8.3)	4 (20.0)	0	0	8 (11.3)
Injection site nodule	2 (4.2)	2 (10.0)	0	0	4 (5.6)
Injection site rash	4 (8.3)	0	0	0	4 (5.6)
Pyrexia	4 (8.3)	0	0	0	4 (5.6)
Chills	2 (4.2)	1 (5.0)	0	0	3 (4.2)
Injection site papule	3 (6.3)	0	0	0	3 (4.2)
Irritability	3 (6.3)	0	0	0	3 (4.2)
Skin and Subcutaneous Tissue Disorders	9 (18.8)	5 (25.0)	1 (50.0)	1 (100.0)	16 (22.5)
Erythema	2 (4.2)	3 (15.0)	0	0	5 (7.0)
Lipohypertrophy	4 (8.3)	1 (5.0)	0	0	5 (7.0)
Eye Disorders	2 (4.2)	11 (55.0)	1 (50.0)	0	14 (19.7)
Deposit eye	0	6 (30.0)	1 (50.0)	0	7 (9.9)
Conjunctival deposit	2 (4.2)	4 (20.0)	0	0	6 (8.5)
Gastrointestinal Disorders	5 (10.4)	2 (10.0)	0	0	7 (9.9)
Vomiting	3 (6.3)	0	0	0	3 (4.2)
Musculoskeletal and Connective Tissue Disorders	3 (6.3)	3 (15.0)	0	0	6 (8.5)
Pain in extremity	1 (2.1)	2 (10.0)	0	0	3 (4.2)
Injury, Poisoning and Procedural Complications	1 (2.1)	3 (15.0)	0	0	4 (5.6)
Contusion	1 (2.1)	3 (15.0)	0	0	4 (5.6)
Renal and Urinary Disorders	1 (2.1)	3 (15.0)	0	0	4 (5.6)
Nephrolithiasis	1 (2.1)	2 (10.0)	0	0	3 (4.2)

MedDRA = Medical Dictionary for Regulatory Activities; SOC = system organ class.
Treatment-emergent adverse events are events that started on or after the day of the first dose of asfotase alfa. All events in extension studies ENB-003-08 and ENB-008-10 were considered to be treatment-emergent. For ENB-009-10 patients in the control group, only those events that occurred on or after the day of the first dose of asfotase alfa were included.
Related adverse events were those considered by the investigator to have a possible, probable, or definite relationship to asfotase alfa.
An SOC was included only if a preferred term within the SOC was reported in ≥3 patients in the Pooled Safety Set overall.
If a patient had more than one event for a particular SOC or preferred term, the patient was counted only once for that SOC or preferred term.
Patient percentages were based on the total number of patients in each column.
Source: Table 1.3.1.2.1.4 and Table 1.3.1.1.1.11

Of the 2706 treatment emergent adverse events reported for the 71 patient included in the integrated safety analyses, there were 906 treatment emergent adverse events experienced by 60 (84.5%) patients assessed as related to asfotase alfa by the Investigator. The most common were localised injection site reactions.

When injection site reactions were excluded from the analysis, there were a total of 50 treatment emergent adverse events assessed as treatment-related experienced by 29 (40.8%) patients. Events among these (reported by ≥3 patients) included:

- Deposit eye (7 patients; 9.9%)
- Conjunctival deposit (6 patients; 8.5%)
- Nephrolithiasis (3 patients; 4.2%)
- Pain in extremity (3 patients; 4.2%)

Although assessed as asfotase alfa treatment related, deposit eye, conjunctival deposit and nephrolithiasis are known features of hypophosphatasia.

Adverse events of special interest

Injection site reactions and lipohypertrophy

Most injection-site reactions were mild and self-limiting and none was assessed as serious.

Events reported included pyrexia (5.6%), injection site erythema (5.6%), chills (4.2%), irritability (4.2%) and vomiting (4.2%).

Cases of anaphylaxis were not identified.

Two patients experienced injection-site reactions that led to asfotase alfa dose reduction.

There were 12 treatment-emergent adverse events of lipohypertrophy experienced by 5 patients, mostly at injection sites on the arm and abdomen, and were all assessed as non-serious and mild or moderate in intensity by the Investigator. Analysis by age at first dose of asfotase alfa revealed lipohypertrophy was generally reported in patients 5 to 17 years of age.

One patient who experienced multiple injection-site reactions for which asfotase alfa was reduced, subsequently withdrew consent for clinical trial participation and discontinued treatment. Histological examination of a biopsy specimen from the injection site of this patient showed the presence of large adipocytes of normal morphology without evidence of lipoblasts, increased cellularity or other pathology.

As part of the risk management plan, patient education materials have been developed for asfotase alfa administration that instruct patients to rotate injection sites, considered part of standard clinical care for management of injection site reactions in patients receiving chronic treatment with injectables and carefully monitor these for signs of potential injection site reactions.

Craniosynostosis

11 patients (all in the infantile-onset hypophosphatasia subgroup, mostly in patients <2 years of age) experienced 16 treatment-emergent adverse events of craniosynostosis. One such event was considered serious and possibly related to asfotase alfa treatment by the Investigator and was associated with conductive deafness as described above.

Based on known natural history of the condition, the occurrence of craniosynostosis is known to occur in hypophosphatasia patients.

Ectopic Calcification

22 patients included in the integrated safety analyses experienced a total of 25 events included as potential events of ectopic calcification.

Events reported in ≥2 patients included:

- deposit eye (11.3%)
- conjunctival deposit and nephrocalcinosis (8.5% each)
- corneal deposit (2.8%)

All events were mild or moderate in intensity. One event of nephrocalcinosis (in the juvenile-onset hypophosphatasia subgroup) was considered to be related to asfotase alfa by the Investigator; most of

the ophthalmic calcifications were considered to be related to asfotase alfa. Visual disturbances were not reported in conjunction with the ophthalmic calcifications.

Based on known natural history of the condition, the occurrence of ectopic calcification is not uncommon in hypophosphatasia patients.

Summary of events of craniosynostosis and ectopic calcification according to clinical studies submitted by the company:

Study 02-08 / 03-08

3 patients had a history of craniosynostosis at baseline. 1 of these patients had a further episode at 128 days after starting study drug.

4 patients without a history of craniosynostosis at baseline went on to develop one or more episodes of craniosynostosis at or beyond 142 days after exposure to study drug. Craniosynostosis was managed medically and surgically.

None of the patients was found to develop ectopic calcification during the clinical study.

Study 06-09 / 08-10

3 patients at baseline had a history of craniosynostosis treated surgically. None of the subjects reported new craniosynostosis during the clinical study.

Ectopic calcification was observed in 4 patients; all 4 events were conjunctival deposits found on eye examination (slit lab examination).

Study 09-10

3 patients at baseline had a history at baseline of craniosynostosis managed surgically. None of the subjects reported new craniosynostosis during the clinical study.

6 patients developed ectopic calcification. All cases were identified during an eye examination and were located either at the conjunctiva or cornea. 1 occurred at week 24 and the others were detected beyond week 72.

Study 10-10

There were 5 new events of craniosynostosis at 8 weeks of study drug exposure or beyond.

2 events of ectopic calcification of the eye were reported as treatment-emergent. There were also 3 events of nephrocalcinosis reported as treatment emergent.

The company reports on cases of craniosynostosis that have been detected after starting asfotase alfa or that have progressed in spite of exposure to asfotase alfa. The association between craniosynostosis and asfotase alfa may be real or be coincidental: there are not enough cases to distinguish. Similarly, the association between ectopic calcification and asfotase alfa may be real or be coincidental: there are not enough cases to distinguish. It is considered, therefore, that there are insufficient data at present to establish a causal role of asfotase alfa in the development / progression of craniosynostosis or ectopic calcification.

Craniosynostosis and ectopic calcification are identified as potential risks in the RMP.

Conductive Deafness

One patient in the infantile-onset hypophosphatasia subgroup was reported to have a treatment-emergent adverse event of conductive deafness, which was reported in association with a treatment-

emergent adverse event of craniosynostosis. Both events were assessed as serious and possibly related to asfotase alfa treatment by the Investigator.

Based on known natural history of the condition, the occurrence of conductive deafness is known to occur in hypophosphatasia patients.

Pneumonia / Respiratory Distress

24 patients included in the integrated safety analyses experienced a total of 137 events broadly included as potential events of pneumonia / respiratory distress.

Events reported in ≥5 patients included

- pneumonia (13 patients)
- respiratory distress (6 patients)
- respiratory disorder (5 patients).

Of the 137 events reported, 133 occurred in 20 (41.7%) patients in the infantile-onset hypophosphatasia subgroup and were more common in patients <2 years of age.

Based on known natural history of the condition, the occurrence of pneumonia / respiratory distress is known to occur in hypophosphatasia patients.

Chronic Hepatitis and Pancreatitis

There was one event of chronic hepatitis (occurring in infantile-onset hypophosphatasia patient receiving concomitant treatment with montelukast sodium, known to be associated with hepatitis) assessed as serious and possibly related to asfotase alfa by the Investigator.

One patient in the infantile-onset hypophosphatasia subgroup experienced pancreatitis assessed as serious and unlikely related to asfotase alfa by the Investigator for which asfotase alfa dosing was interrupted. The patient recovered and asfotase alfa dosing was resumed without recurrence of pancreatitis.

Chronic hepatitis is not considered to be an adverse reaction to asfotase alfa.

Serious adverse events and deaths

Serious Adverse Events

183 non-fatal serious adverse events were experienced by 32 (45.1%) patients included in the integrated safety analyses and were generally consistent with the manifestations and complications of hypophosphatasia.

Non-fatal serious adverse events reported by >5% of patients in the integrated safety analyses included:

- Craniosynostosis (11.3%)
- Pneumonia (7.0%)
- Respiratory disorder (5.6%)

By patient age at first dose of asfotase alfa, about 84% of non-fatal serious adverse events were reported by 19 patients <2 years of age, and over 92% of non-fatal serious adverse events were reported by 25 patients ≤4 years of age in the infantile-onset hypophosphatasia subgroup, a subgroup

of hypophosphatasia patients that is generally characterised as having more severe disease-related manifestations and life-threatening complications.

11 non-fatal serious adverse events in 3 infantile-onset patients and 1 juvenile-onset hypophosphatasia patient were assessed as related to asfotase alfa treatment by the Investigator:

- 2 patients had infusion-associated reactions (considered important medical events by the Investigator),
- 1 patient developed craniosynostosis and conductive deafness
- The fourth patient experienced chronic hepatitis while receiving concomitant treatment with montelukast sodium at the time of onset of the event. Treatment with montelukast sodium was discontinued with eventual normalization of liver function tests without interruption of asfotase alfa treatment. Hepatobiliary disorders have been reported in patients treated with montelukast sodium.

Deaths

Five patients died during participation in clinical trials of asfotase alfa prior to the analysis cut-off dates for the integrated analyses.

All deaths occurred in patients who were <1 year of age at enrolment, were in the infantile-onset hypophosphatasia subgroup and had 1 or more prognostic factors for poor outcome i.e. rachitic chest deformity, respiratory compromise and / or vitamin B6-responsive seizures.

Death for 1 patient occurred prior to administration of asfotase alfa. Death for 1 patient occurred within 3 weeks of treatment initiation. 3 further patients died within 60 weeks of treatment initiation. One death due to pneumonia was assessed by the Investigator as being possibly related to asfotase alfa.

Narratives of patients are provided.

After the analysis cut-off date for the integrated analyses, the Sponsor received reports of 2 additional deaths in Study ENB-010-10, as described below:

Patient, a female patient who was approximately 7 months old at the time of her first dose of asfotase alfa, had a medical history significant for rachitic rosary, dysphagia, developmental delay with poor head control, hypercalcaemia, nephrocalcinosis and bulging fontanelle. The patient was found unresponsive in her car seat en route to the Week 6 study visit; attempts at resuscitation were unsuccessful. An autopsy confirmed the death was due to complications of hypophosphatasia.

Patient, a female patient who was approximately 20.5 months old at the time of her first dose of asfotase alfa, was admitted to the hospital approximately 10.5 months after her first dose of asfotase alfa with an serious adverse event of pneumonia which was accompanied by pyrexia and respiratory failure. Several days later, the Sponsor received a report that the patient died due to respiratory failure on an unknown date; the respiratory failure was considered by the Investigator to have an unlikely relationship to asfotase alfa.

A summary of deaths occurring up to the original cut-off point is provided in the following table:

Table: Summary of deaths (n=5):

HPP Onset Category	Age at Study Entry/Sex	Days from First Dose to Event Onset (to Death)	Dose (mg/kg)/ Frequency at Event Onset	Verbatim Term/ Preferred Term	Relationship to Asfotase Alfa[a]
Infantile-onset	2.9 wk/Male	214 d (221 d)	2 mg/kg/ TIW	Septic shock/ Septic shock	Unrelated
Infantile-onset	0.1 wk/Male	436 d (436 d)	2 mg/kg/ 7×/wk	Cardiopulmonary arrest resulting in death/ Cardio-respiratory arrest	Unrelated
Infantile-onset	6.6 wk/Male	7 d (22 d)	2 mg/kg/ TIW	Abnormal neurological findings/ Neurological examination abnormal	Unlikely
Infantile-onset	38.9 wk/Male	94 d (203 d)	3 mg/kg/ TIW	Pneumonia/ Pneumonia	Possible
Infantile-onset	33.4 wk/Male	Not dosed	NA	Respiratory failure/ Respiratory failure	Unrelated

HPP = hypophosphatasia; MedDRA = Medical Dictionary for Regulatory Activities; TIW = 3 times weekly.
[a] As assessed by the Investigator.

Laboratory findings

Overall, baseline clinical laboratory measurements of interest such as alkaline phosphatase, serum calcium and parathyroid hormone were consistent with the underlying manifestations of hypophosphatasia.

Clinical chemistry

Parathyroid hormone concentration increased, most notably over the first 12 weeks of treatment, likely associated with the bone mineralization process.

Urinalysis

There were no consistent changes in urinalysis over the course of asfotase alfa treatment.

Haematology

A summary of treatment-emergent adverse events potentially associated with abnormal haematology laboratory results experienced by patients in the Pooled Safety Set overall and by age at disease onset is provided in the following table:

Table 16: Treatment-Emergent Adverse Events Potentially Associated with Abnormal Hematology Laboratory Results in Patients in the Pooled Safety Set, Overall and by Age at Disease Onset

	Pediatric Onset (N=68), n (%)		Adult Onset (N=2) n (%)	Unknown Onset (N=1) n (%)	All Patients (N=71) n (%)
MedDRA Preferred Term	Perinatal/ Infantile Onset (N=48)	Juvenile Onset (N=20)			
Haemoglobin decreased	6 (12.5)	0	0	0	6 (8.5)
Anaemia	3 (6.3)	1 (5.0)	0	0	4 (5.6)
Lymphocyte count increased	0	1 (5.0)	0	0	1 (1.4)
Neutrophil count increased	0	1 (5.0)	0	0	1 (1.4)
Neutropenia	1 (2.1)	0	0	0	1 (1.4)
Thrombocytosis	1 (2.1)	0	0	0	1 (1.4)
White blood cell count increased	0	1 (5.0)	0	0	1 (1.4)

MedDRA = Medical Dictionary for Regulatory Activities.
Source: Table 1.3.1.1.1.3

Of the events listed in, only the event of neutropenia was considered by the Investigator to be related to asfotase alfa.

Safety in special populations

By Age at First Dose

Safety analyses were performed using the age groups defined in ICH Guideline E11 and also by groups defined by the company (infants / toddlers <2 years of age; children 2 to 4 years of age; children 5 to 12 years of age; adolescents 13 to 17 years of age and adults ≥18 years of age) to align more closely with the enrolment criteria in the clinical studies.

It was noted that some types of events tended to occur in higher proportions of younger patients, particularly patients <2 years of age compared with older patients, such as: respiratory, renal, cardiac and central nervous system events that are known features of hypophosphatasia. Also more common were gastro-intestinal and skin events that are more common in children than adults.

Children and adolescents were more likely to report injection site reactions and lipohypertrophy.

Older patients were more likely to report pain and eye deposits / calcifications.

By Gender

Overall, there appeared to be no clinically meaningful differences in the safety profile of male and female patients treated with asfotase alfa.

By Race

Patients in Japan had a disproportionately high number of injection site reactions. Otherwise, overall, the types and rates of events noted in White patients and patients of "Other" races, including severe and nonfatal serious adverse events, followed the same general patterns observed in the overall Pooled Safety Set.

Immunological events

Pooled Safety Set

Of the 69 patients for whom post-Baseline antibody data were available, 56 (81.2%) tested positive for anti-drug antibodies at some point post Baseline.

Anti-drug antibodies titres ranged from 0 to 2048 (median peak titre of 64.0).

The median time to first anti-drug antibody positive result was 37.0 days (range of 14 to 1072 days).

Not all patients who tested positive for anti-drug antibodies post Baseline remained consistently positive for these antibodies after the initial positive result.

Continuously Positive or Not Continuously Positive Antidrug Antibody Status

In order to be categorised as continuously positive for anti-drug antibodies, a patient must have achieved and sustained uninterrupted positive results for anti-drug antibodies during and through the end of their series of anti-drug antibody measurements while receiving treatment. At a minimum, a patient must have been positive for the last 2 anti-drug antibody measurements while on treatment.

More patients categorized as continuously anti-drug antibody positive reported treatment emergent adverse events than patients categorised as not continuously anti-drug antibody positive as follows:

- injection site erythema (64.3% vs. 37.0%)
- injection site pain (31.0% vs. 11.1%)
- injection site pruritus (26.2% vs. 11.1%);

- injection site macule and injection site swelling (21.4% vs. 7.4%, each).

The incidence rates for these events were:

- Injection site erythema (174.6 vs. 139.6 events/100 patient years)
- Injection site pain (44.7 vs. 10.9 events/100 patient years)
- Injection site pruritus (37.4 vs. 13.7 events/100 patient years)
- Injection site macule (40.5 vs 49.3 events/100 patient years)
- Injection site swelling (27.0 vs. 10.9 events/100 patient years)

The incidence rates of the events commonly associated with injection site reactions were generally not greater in patients categorised as continuously anti-drug antibody positive compared with patients categorised as not continuously anti-drug antibody positive, even though a greater proportion of patients categorised as continuously anti-drug antibody positive reported these types of events.

Overall, the incidence rate for treatment emergent adverse events experienced by patients before becoming continuously anti-drug antibody positive (1938.8 events/100 patient-years of exposure to asfotase alfa) was greater than the incidence rate for treatment emergent adverse events experienced by patients after becoming continuously anti-drug antibody positive (1144.1 events/100 patient-years).

Ever Positive or Always Negative for Antidrug Antibodies

Proportionally more patients who ever had a positive anti-drug antibody result experienced treatment emergent adverse events considered by the Investigator to be related to asfotase alfa (89.3%) compared with patients who were always negative for anti-drug antibody (69.2%). This observation was mainly influenced by the greater proportion of patients who were ever positive for anti-drug antibody who experienced an injection site reaction.

The incidence rates for treatment emergent adverse events were generally greater before patients had a positive anti-drug antibody result compared to the rates after patients had a positive anti-drug antibody result. Incidence rates in the SOC of General Disorders and Administration Site Conditions, in which many of the preferred terms for injection site reactions are coded, were 856.5 events/100 patient years of exposure to asfotase alfa before patients had any positive anti-drug antibody results (which includes patients who were always negative for anti-drug antibody), and 387.9 events/100 patient years after patients had any positive anti-drug antibody results.

By Peak Antibody Titre Category

Overall, more patients who ever had an anti-drug antibody titre >128 experienced injection site reactions compared to patients who had anti-drug antibody titres ≤128 (91.7% vs 75.0%); however, the number of patients who ever had an anti-drug antibody titre >128 was small (n=12). In the SOC of General Disorders and Administration Site Condition, wherein many of the preferred terms for injection site reactions are coded, the proportions of patients who experienced events were comparable between patients who ever had an anti-drug antibody titre >128 and those who always had anti-drug antibody titres ≤128 (91.7% vs. 90.9%)

Neutralising Antibody Analyses

Of the 69 patients in the Pooled Safety Set for whom antibody data were available, 56 (81.2%) tested positive for anti-drug antibody at some time point post Baseline and were included in the analyses for neutralising antibodies.

25 of these patients were positive for neutralising antibodies at some time point post Baseline i.e. had a neutralising antibodies inhibition result >4.478%.

As with anti-drug antibodies, patients who tested positive for neutralising antibodies at some point post Baseline were not consistently positive for neutralising antibodies after the first positive result.

The median peak inhibition values for neutralising antibodies in the 56 patients who were ever positive for anti-drug antibody was 3.870% with a range of 5.696% to 16.868%.

A greater proportion of patients who were ever positive for neutralising antibodies experienced treatment emergent adverse events considered by the investigator to be related to asfotase alfa compared with patients who were always negative for neutralising antibodies (92.0% vs. 81.8%). This was mainly influenced by the proportions of patients who experienced injection-associated reactions.

The incidence rate for overall treatment emergent adverse events experienced by patients after they experienced their first positive neutralising antibody result (1198.4 events/100 patient years of exposure to asfotase alfa) was lower than that for patients before their first positive neutralising antibody result (1691.5 events/100 patient years).

Overall

Overall, the magnitude of the immunogenicity response was considered small and time-variant in patients.

Results of analyses performed for patients who had continuously positive anti-drug antibody results (defined as positive results for at least the last 2 available post-Baseline assessments, regardless of length of exposure to asfotase alfa), patients who ever had any positive post-Baseline anti-drug antibody result ("ever positive"), and patients with at least 1 post-Baseline anti-drug antibody titre >128 did not suggest there was an appreciable impact of anti-drug antibodies on the safety profile of asfotase alfa.

There were not any indications of anaphylaxis with s/c administration of asfotase alfa.

While no consistent pattern between antibody titre and any of the pharmacodynamic measurements or radiographic assessments could be discerned, no firm conclusions can be drawn from this informal analysis given the small sample size.

Safety related to drug-drug interactions and other interactions

- Drug Interactions
- No interaction studies have been performed with asfotase alfa. Based on its structure and pharmacokinetics, asfotase alfa is an unlikely candidate for cytochrome P450-mediated interactions.
- Interactions with Food
- Asfotase alfa is administered s/c. Studies designed to investigate the effect of food on asfotase alfa have not been conducted. Given the s/c route of administration, food effects are not anticipated.

By Geographic Region

There are 71 patients in the Pooled Safety Set. 54 patients were treated at sites in the USA / Canada, 9 patients were treated at sites in Europe, 5 patients were treated at sites in Japan and 3 patients were treated at sites throughout the rest of the world.

5 patients treated in Japan were all in the infantile-onset hypophosphatasia subgroup and had a disproportionate number of injection-site reactions compared with the other geographic regions. For example, the incidence rate for injection site erythema for patients in Japan was more than 27 times greater than what was observed in patients treated in Europe.

Overall, the types and rates of events noted in patients treated at sites in Europe, including severe and nonfatal serious adverse events, followed the same general patterns observed in the overall Pooled Safety Set.

Discontinuation due to AES

Discontinuations

- Excluding deaths, 2 patients discontinued asfotase alfa in association with treatment-emergent adverse events:
    - One patient in the infantile-onset subgroup experienced non-serious infusion associated reactions of pyrexia, chills, pilo-erection and irritability in association with the single iv infusion of asfotase alfa (in study ENB-002-08/ENB-003-08).
    - The second patient (in study ENB-009-10, in the juvenile-onset subgroup) experienced multiple injection site reactions (including injection site discolouration assessed as severe by the Investigator) and subsequently withdrew consent for clinical trial participation and discontinued treatment.

Temporary interruptions

Four patients (all in the infantile-onset hypophosphatasia subgroup) had temporary interruptions in asfotase alfa dosing due to treatment-emergent adverse events during clinical trial participation. None of these treatment-emergent adverse events (cases of change in neurological status, haematuria, false positive pregnancy test and pneumonia) was assessed as asfotase alfa treatment-related.

In addition, 7 patients (4 in the infantile-onset and 3 in the juvenile-onset hypophosphatasia subgroup) had 1 or more dose modifications as a result of treatment-emergent adverse events (mostly injection site events) or because of signs / symptoms associated with the underlying hypophosphatasia (cases of bone fracture, pneumonia, muscular weakness).

In addition:

Use in Pregnancy and Lactation

Asfotase alfa has not been studied in pregnant or lactating women.

Overdose

Patients have received asfotase alfa at doses up to 28 mg/kg/wk s/c. No dose-related toxicity has been observed in clinical studies to date.

No change in the safety profile has been seen with higher doses by mg/kg, absolute dose, or by serum concentration.

Drug Abuse

The potential for drug abuse was not investigated or reported in human trials of asfotase alfa.

Withdrawal and Rebound

The possibility of withdrawal and rebound has not been studied (life-long treatment is anticipated).

Effects on Ability to Drive or Operate Machinery or Impairment of Mental Ability

The effects of asfotase alfa treatment on the ability to drive or operate machinery or whether treatment with asfotase alfa may impair mental ability have not been studied.

Post marketing experience

n/a

2.6.1. Discussion on clinical safety

From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics.

The total patient exposure to study drug is limited: allowance for this has been made in the assessment process, however, because of the rarity of the hypophosphatasia condition.

Each study submitted in the current application included collection of data on safety, as required. The company has reported on 2706 treatment-emergent adverse events in the 71 patients included in the integrated safety analyses. A relatedness exercise carried out by the company has identified "injection site reactions" and "injection associated reactions" as the most common adverse events and these were recorded in all studies. Anaphylaxis was not recorded. There was broad agreement on the nature of the adverse events found in both infantile-onset and juvenile-onset hypophosphatasia.

When injection site reactions were excluded from the analysis, there were 50 treatment emergent adverse events assessed as treatment-related experienced by 29/71 patients. Events among these included: deposit eye, conjunctival deposit, nephrolithiasis and pain in extremity.

Ectopic calcification may be a feature of hypophosphatasia. Modelling studies submitted by the company suggest that ectopic calcification may also be more likely if asfotase alfa is administered at a dosage higher than 6mg/kg/week (which would be higher than the recommended dose). Information on ectopic calcification is included in the SmPC section 4.4.

The issue of low vitamin D status, and a possible need for vitamin D supplementation, consequent to exposure to asfotase alfa, is addressed in sections 4.4 and 5.1 of the SmPC.

The issue of some patients displaying a rise in weight out of proportion to the increase in height is addressed in section 4.4 of the SmPC.

The analysis of immunogenicity has not given rise to any particular concern (with the caveat that antibody status after a study-drug free period of 4-5 half-lives has not been tested, but instead the dissociation technique described was employed).

Hypophosphatasia is known to be associated with appreciable morbidity and mortality at a young age. Those serious adverse events and deaths recorded during studies conducted by the company have been described in detail by the company: the relatedness exercise carried out by the company has found that such events were (mainly) owing to the underlying hypophosphatasia; there was insufficient evidence to establish whether or not there is a causal relationship between exposure to Strensiq and craniosynostosis or ectopic calcification. The explanations of the company were found to be acceptable by CHMP. Craniosynostosis and ectopic calcification are both identified in the Risk Management Plan as important potential risks and are also described appropriately in the SmPC.

2.6.2. Conclusions on the clinical safety

The total patient exposure to study drug was very limited with 71 patients included in the integrated safety analyses. Taken that limitation into account, aspects of clinical safety reported by the company did not give rise to any particular, serious concern and were considered to be clinically manageable.

The issue of low vitamin D status, and a possible need for vitamin D supplementation, consequent to exposure to asfotase alfa is addressed in sections 4.4 and 5.1 of the SmPC.

The issue of some patients displaying a rise in weight out of proportion to the increase in height is addressed in section 4.4 of the SmPC.

There was insufficient evidence to establish whether or not there is a causal relationship between exposure to Strensiq and craniosynostosis or ectopic calcification.

The CHMP agreed with the applicant's argumentation that the patient population of paediatric onset hypophosphatasia is encountered so rarely that the applicant cannot reasonably be expected to provide comprehensive clinical data on the safety and efficacy of this medicinal product. The incidence of the most severe forms of the disease is very low and thought to be about 1:100,000 live births, although markedly higher in some small populations, and recently estimated to be approximately 1:300,000 in Europe. As a consequence, the applicant will be obliged to set up a registry in order to provide, on an ongoing bases, further evidence as specific obligations relating in particular to efficacy and safety as follows:

Observational, Longitudinal, Prospective, Long-Term Registry of Patients with HPP to collect information on the epidemiology of the disease, including clinical outcomes and quality of life, and to evaluate safety and effectiveness data in patients treated with Strensiq. Specifically, more information is to be collected on the variability, progression and natural history of the disease in all age groups, the disease burden, clinical outcomes, and quality of life, and to collect and evaluate safety and effectiveness data specific to the use of asfotase alfa.

These specific obligations shall be reassessed annually.

2.7. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the Pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.8. Risk Management Plan

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 1.3 is acceptable. In addition, minor revisions were recommended to be taken into account with the next RMP update. The PRAC endorsed PRAC Rapporteur assessment report is attached.

The CHMP endorsed the Risk Management Plan version 1.3 with the following content:

Safety concerns

Summary of safety concerns	
Important identified risks	Injection site reactions (ISRs) Immunogenicity (Formation of Anti-asfotase alfa antibodies) Injection associated reactions (IARs)
Important potential risks	Craniosynostosis Ectopic calcification Medication errors
Missing information	Use in pregnant and lactating women Use in elderly Use in patients with hepatic or renal impairment Long-term safety and efficacy Use in non-Caucasian patients

Pharmacovigilance plan

Study/activity Type, title and category (1-3)	Objectives	Safety concerns addressed	Status (planned, started)	Date for submission of interim or final reports (planned or actual)
ALX-HPP-501: An Observational, Longitudinal, Prospective, Long-term Registry of Patients with Hypophosphatasia. (Category 1) .	• To collect information on the variability, progression, and natural history of HPP from patients of all ages, including infants, children, and adults with HPP, regardless of age at onset. • To characterize the epidemiology of the HPP population. Inclusion of all classifications of HPP is planned: perinatal, infantile, juvenile, adult, and odontohypophosphatasia. • To evaluate the burden of disease for HPP and the multi-system aspects of HPP, including clinical outcomes and quality of life, in a "real-life" setting. • To collect and evaluate safety and effectiveness data specific to the use of asfotase alfa in patients with HPP. (This study will enroll patients treated with asfotase alfa after MAA approval)	Missing information, important identified and potential risks.	Planned The registry started enrolling patients with HPP (without asfotase alfa treatment) in Q1 2015. HPP patients treated with Asfotase alfa will be enrolled after MAA approval.	The final protocol will be submitted within 30 days of EC decision. The dates for submission of interim and final reports will be based on agreement with CHMP
Assess the receipt of the educational material. Assess the incidence rate and characteristics of injection site reactions and medication errors from post-marketing	• The registry will track receipt of the educational material and therefore will allow to assess the receipt rate. • The registry will collect detailed information on injection site reactions (ISRs) and dosing. Information collected	Injection site reactions and medication errors	Planned	Based on agreement with CHMP

Study/activity Type, title and category (1-3)	Objectives	Safety concerns addressed	Status (planned, started)	Date for submission of interim or final reports (planned or actual)
data (including the HPP registry)	will include the site of the ISR, if the patient/care giver has been rotating injection sites as recommended in the educational material, and dosing information. The periodic safety reports will include comprehensive assessment of ISRs and medication errors from post-marketing data (including information from the registry).			

Risk minimisation measures

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Injection Site Reactions	(Proposed) text in SmPC:	Patient and caregiver educational

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	Section 4.4 Special warnings and precautions of use: "Administration of Strensiq may result in local injection site reactions (including, but not limited to, erythema, rash, discoloration, pruritus, pain, papule, nodule, atrophy) defined as any related adverse event occurring during the injection or until the end of the injection day (see section 4.8). Rotation of injection sites usually helps effectively manage these reactions. These have been generally assessed as non-serious, mild to moderate in severity and self-limiting. 1 patient out of 71 patients treated in clinical trials experienced a severe injection site reaction of injection site discolouration which led to the discontinuation of Strensiq. Strensiq administration should be interrupted in all patients experiencing severe injection reactions and appropriate medical therapy administered." Section 4.8 Undesirable effects: ISRs are included in the table of adverse drug reactions with an incidence of "very common". Also in the Description of selected adverse reactions in section 4.8 the following is included: "Injection site reactions : Injection site reactions (including injection site: erythema, discolouration, pain, pruritus, macule, swelling, bruising, hypertrophy, induration, reaction, atrophy, nodule, rash, papule, haematoma, inflammation, urticarial, warmth, haemorrhage, cellulitis and mass) are the most common adverse reactions observed in about 73% of the patient in the clinical studies. The frequency of injection site	material

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	reactions was higher in patients with juvenile-onset hypophosphatasia and in patients who received injections 6 times/week (compared to 3 times /week)Most injection site reactions were mild and self-limiting, and none was reported as a serious adverse events. Two patients experienced injection site reactions that led to reductions of their asfotase alfa dose." (Proposed) text in Package leaflet: "You may experience a reaction at the injection site. Read section 4 carefully to know what side effects can occur before using this medicine When injecting regularly, the injection site should be rotated between different parts of the body to help reduce potential pain and irritation. Areas with a substantial amount of fat below the skin are the most suitable areas to inject. Please discuss with you healthcare professional the best sites for you." Injection site reactions are mentioned in section 4 (possible side effects) In addition, the section on how to inject Strensiq provides instructions on proper injection technique.	
Immunogenicity	(Proposed) text in SmPC: Section 4.8 "Immunogenicity There is potential for immunogenicity. Among 69 hypophosphatasia patients enrolled in the clinical trials, 56 (81.2%) were tested positive for anti-drug antibodies at some point after receiving Strensiq treatment. Among those 56 patients, 25 (44.6%) also showed presence of neutralizing antibodies. The antibody	None proposed

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	response (with or without presence of neutralizing antibodies) was time variant. The development of antibodies has not shown to affect clinical efficacy and safety. (see Section 5.2). No trends in adverse events in clinical trials based on antibody status. Furthermore, patients confirmed positive for antibodies have not shown signs of hypersensitivity or tachyphylaxis following subcutaneous administration of Strensiq. " (Proposed) text in Package leaflet Section 2 details the potential risk of allergic reaction. "Strensiq can cause allergic reactions in some people. Symptoms of such reactions include low blood pressure, vomiting, difficulty breathing, fast heart rate, hives or rash. If you experience any of these symptoms, tell your doctor immediately. You may need to be given additional medicines to prevent an allergic reaction (antihistamines or corticosteroids)." In addition the following is included in section 4 (Possible side effects) "You may experience allergic reactions to Strensiq. Please tell your doctor immediately, if you have any of the symptoms described in section 2."	
Injection Associated Reactions	(Proposed) text in SmPC: Section 4.3 Contraindications: "Hypersensitivity to the active substance(s) or to any of the excipients listed in section 6.1." Section 4.4 Special warnings and precautions of use "Hypersensitivity: Hypersensitivity reactions have not been observed with Strensiq. As with any protein product, severe allergic-type	None proposed

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	hypersensitivity reactions are however possible, including urticaria, difficulty breathing, cardiovascular collapse. If these reactions occur, immediate discontinuation of Strensiq treatment is recommended and appropriate medical treatment should be initiated. The current medical standards for emergency treatment should be observed. There have been no adverse drug reactions related to anti-asfotase alfa antibody status in clinical trials Furthermore, patients confirmed positive for anti-drug antibodies have not shown signs of hypersensitivity or tachyphylaxis with Strensiq administration Injection Reaction No reports of anaphylaxis or anaphylactoid reactions have been noted following treatment with Strensiq in any clinical trials. Strensiq administration should be interrupted in all patients experiencing severe injection reactions and appropriate medical therapy administered." (Proposed) text in Package leaflet Section 2 details the potential risk of allergic reaction. "Strensiq can cause allergic reactions in some people. Symptoms of such reactions include low blood pressure, vomiting, difficulty breathing, fast heart rate, hives or rash. If you experience any of these symptoms, tell your doctor immediately. You may need to be given additional medicines to prevent an allergic reaction (antihistamines or corticosteroids)." In addition the following is included in section 4 (Possible side effects) "You may experience allergic	

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	reactions to Strensiq. Please tell your doctor immediately, if you have any of the symptoms described in section 2."	
Ectopic Calcification	(Proposed) text in SmPC: Section 4.4 Special warnings and precautions of use "Ectopic Calcification In asfotase alfa clinical studies ophthalmic (conjunctival and corneal) calcification and nephrocalcinosis have been reported in hypophosphatasia patients. An association between asfotase alfa treatment and ectopic calcification worsening has not been established. These events are likely related to underlying disease. Ophthalmic (conjunctival and corneal) calcification and nephrocalcinosis as manifestations of hypophosphatasia are documented in published literature. Nephrocalcinosis occurred in 51.6% of patients between birth and 5 years of age in a natural history study of untreated infantile-onset hypophosphatasia patients. Periodic ophthalmology examination and renal ultrasounds are recommended." (Proposed) text in Package leaflet Section 2. "Some eye-related side-effects have been reported in clinical trials with and without the use of Strensiq, probably associated with hypophosphatasia, talk to your doctor in case of vision trouble."	None proposed
Craniosynostosis	(Proposed) text in SmPC: Section 4.4 Special warnings and precautions of use "Craniosynostosis In asfotase alfa clinical studies adverse events of craniosynostosis (associated with increased intracranial pressure), including worsening of pre-existing craniosynostosis have been reported in	None proposed

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	hypophosphatasia patients < 5 years of age. . An association between asfotase alfa treatment and craniosynostosis progression has not been established. These events are likely related to underlying disease. Craniosynostosis as a manifestation of hypophosphatasia is documented in published literature and occurred in 61.3% of patients between birth and 5 years of age in a natural history study of untreated infantile-onset hypophosphatasia patients. Craniosynostosis can lead to increased intracranial pressure. Periodic monitoring (including fundoscopy for signs of papilloedema) and prompt intervention for increased intracranial pressure is recommended in hypophosphatasia patients below 5 years of age." (Proposed) text in Package leaflet "Early fusion of the bones of the head in children below 5 years of age has been reported in clinical studies of infants with Hypophosphatasia, with and without use of Strensiq. Talk to your doctor if you notice any change in the shape of your infant's head."	
Medication errors	(Proposed) text in SmPC: Section 4.2 Posology and method of administration "Strensiq treatment should be initiated by a physician experienced in the management of patients with metabolic or bone disorders. Posology Recommended dosage regimen of asfotase alfa is 2 mg/kg of body weight administered subcutaneously three times per week, or a dosage regimen of 1 mg/kg of body weight administered six times per week."	Patient and caregiver educational material

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	Method of administration Strensiq should be administered as subcutaneous injection. The maximum volume of medication per injection should not exceed 1 ml. If more than 1 ml is required, multiple injections may be administered at the same time. Injections sites should be rotated and carefully monitored for signs of potential reactions (see section 4.4)." (Proposed) text in Package leaflet 3. How to use Strensiq Strensiq will be explained to you by a doctor who is experienced in the management of patients with metabolic diseases. After being trained by the doctor, you can inject Strensiq by yourself at home. Always use this medicine exactly as described in this leaflet or as your doctor, or pharmacist or nurse has told you. Check with your doctor, pharmacist or nurse if you are not sure. Dosage • The dose you receive is based on your body weight. • The correct dose will be calculated by your doctor and consists of a total of 6 mg per kg of body weight and per week of asfotase alfa, administered by injection under the skin (subcutaneous). • You may receive either 1 mg/kg asfotase alfa 6 times per week or 2 mg/kg asfotase alfa 3 times per week depending on the recommendation of your doctor. Use in children and adolescents The recommended dosage of Strensiq in children and adolescents is the same as in adults. Before injecting Strensiq, please read the following instructions carefully	

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	• Strensiq is administered only by injection under the skin (subcutaneous injection). • Strensiq will be given to you under the supervision of a doctor who is experienced in the management of patients with metabolic diseases. • Each vial is for single use and should only be punctured once. Only clear and colourless to slightly yellow solution without visible signs of deterioration should be used. Any unused medicinal product or waste material should be disposed of immediately. • If you are injecting this medicine yourself, you will be shown how to prepare and give the injection by your doctor, pharmacist or nurse. Do not inject this medicine yourself unless you have received training and you understand the procedure." In addition, in the "How to inject Strensiq section" detailed instruction (with illustrations/diagrams) on proper administration of Strensiq is provided.	
Use in pregnant and lactating women	(Proposed) text in SmPC: Section 4.6 Fertility, pregnancy and lactation "Pregnancy There is no data from the use of asfotase alfa in pregnant women. Following repeated subcutaneous administration to pregnant mice in the therapeutic dose range (> 0.5 mg/kg), asfotase alfa levels were quantifiable in fetuses at all doses tested, suggesting cross-placental transport of asfotase alfa. Animal studies, however, did not indicate direct or indirect harmful effects with respect with respect to reproductive toxicity (see section 5.3). As a precautionary measure, Strensiq should not be used during pregnancy unless medically	None proposed

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	necessary. Breast-feeding There is insufficient information on the excretion of asfotase alfa in human milk. A risk to the newborns/infants cannot be excluded. Breast-feeding should be discontinued during treatment with Strensiq. Fertility Pre clinical fertility studies were conducted and shown no evidence of effect on fertility and embryo-fetal development." (Proposed) text Package Leaflet: Section 2. Pregnancy and breast-feeding Strensiq should not be used during pregnancy or breast-feeding unless medically necessary. If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.	
Use in patients with hepatic or renal impairment	(Proposed) text in SmPC: Section 4.2 Posology and method of administration Patients with renal impairment "The safety and efficacy of asfotase alfa have not been studied in patients with renal impairment." Patients with hepatic impairment Safety and efficacy of Strensiq have not been studied in patients with hepatic impairment."	None proposed
Use in elderly	(Proposed) text in SmPC: Section 4.2 Posology and method of administration "Efficacy and safety data in patients with HPP >18 years old are limited." Elderly people There is no evidence for special	None proposed

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	considerations when Strensiq is administered to elderly patients.	
Long-term safety and efficacy	(Proposed) text in SmPC The duration of the patient exposure in clinical studies is provided in section 5.1 Pharmacodynamic properties (Clinical efficacy and safety)	None proposed
Use in non-Caucasian patients	(Proposed) text in SmPC The description of clinical studies is provided in section 5.1 Pharmacodynamic properties (Clinical efficacy and safety)	None proposed

2.9. Product information

2.9.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

2.9.2. Labelling exemptions

A request of partial translation exemption of the labelling (outer carton and vial label) and package leaflet as per Article.63(1) of Directive 2001/83/EC has been submitted by the applicant and has been found unacceptable by the QRD Group.

The request was rejected due the fact that the product can be self-administered by the patient at home and the applicant has been asked to attempt multilingual combinations first for the outer carton and vial label.

The applicant has also been offered the option of using Art. 63(3) on the basis of severe availability issues and, therefore, could approach each Member State at national level.

2.9.3. Quick Response (QR) Code

A QR code linking to educational materials has been included in the package leaflet, as requested by PRAC.

3. Benefit-Risk Balance

Benefits

Beneficial effects

The company has recruited patients with hypophosphatasia to take part in 3 open-label, non controlled, non-randomised phase 2 clinical studies of exposure to asfotase alfa. Studies ENB-002-08 and ENB-006-09 are complete (their extensions are on-going). Study ENB-010-10 is on-going.

Also submitted were studies ENB-009-10 (concurrent non-treated control, open label), a retrospective, non-interventional, epidemiological study ENB-011-10 (complete) and study ENB-001-08, a short-term 30-day safety & tolerability and PK study (complete).

71 patients have been recruited to the above studies in addition to historical controls.

The main endpoint of all studies was the outcome of the Radiographic Impression of Change (RGI-C) score, a radiographic assessment tool devised by the company to emulate the practice of radiologists in assessing changes in x-rays of the wrists, hands and knees. X-ray changes from baseline were then rated as follows: -3=severe worsening, -2=moderate worsening, -1=minimal worsening, 0=no change, +1=minimal healing, +2=substantial healing, +3= near-complete or complete healing.

Study 06-09/08-10

It is considered that study 06-09/08-10 is the most informative study submitted by the company. Patients who received asfotase alfa moved to RGI-C scores of +2 and +3 over the first 6 months of exposure and this was sustained with on-going treatment. By contrast, historical controls did not show change over time.

For 10 patients in the per-protocol set of study 06-09/08-10 (excludes those patients who received oral vitamin D between baseline and week 24) who underwent biopsy of the trans-iliac bone crest before and after receiving asfotase alfa:

- Mean (SD) osteoid thickness was 13.3(3.6)µm at baseline and 9.7(5.0)µm at week 24
- Mean (SD) osteoid volume / bone volume was 13.9(7.9)% at baseline and 8.4(7.3)% at week 24
- Mean (SD) mineralisation lag-time was 163 (269) days at baseline and 114 (225) days at week 24

The improvements in both static and dynamic measurements of bone pathophysiology shown by histological analysis are considered to be clinically relevant.

Height, weight and head circumference were plotted on growth charts (series of percentile curves that illustrate distribution) available from the Centers for Disease Control and Prevention, USA. These reference data were drawn from a representative sample of healthy children and are not specific for children with special health care needs: they have been used in the absence of growth charts for children with hypophosphatasia. For those patients who received asfotase alfa: 9/13 patients displayed persistent apparent catch-up height-gain as shown by movement over time to a higher percentile on CDC growth charts. 3/13 patients did not display apparent catch-up height-gain and 1 patient did not have enough data to permit judgement. Progress through Tanner stages appeared appropriate.

By contrast, for the time period of observation of historical controls: 1/16 patients displayed apparent catch-up height-gain, 12/16 patients did not display apparent catch-up height-gain and data were inconclusive in 3/16 patients.

Studies 02-08/03-08, 09-10, 10-10 and 11-10

Observation analysis of studies 02-08/03-08 and 10/10 has described 12/21 patients who were exposed to Strensiq and who were successfully weaned off ventilation support (when ventilation support has been needed). By contrast, the natural history of untreated infant hypophosphatasia patients in study 11-10 suggests a high mortality if ventilation is required.

Results of clinical efficacy from study 09-10 were generally supportive of clinical benefit, though highlight that data are very limited in adult subjects. The company will provide further data on adult subjects as a post-marketing commitment.

Uncertainty in the knowledge about the beneficial effects

'Heterogeneity of clinical effect'

The bulk of evidence submitted to support claims of clinical efficacy was from subjects under 13 yrs of age.

On the basis of the RGI-C score change, bone histology change (osteoid thickness, osteoid volume and mineralisation lag time) and apparent catch-up height-gain over time, efficacy was most convincingly demonstrated in the 5 to 12 yrs age group of study 06-09/08-10.

There was evidence of a positive clinical efficacy outcome, though less strong, also in the population age group 0.5 to 35 months that took part in study 02-08/03-08: "only" 7/11 patients achieved an RGI-C score of +2 at week 24 whilst height-gain appears to fluctuate, probably reflecting the more severe disease and higher rate of co-existing morbidity in these younger patients.

There was a lack of sufficient evidence of clinical efficacy for patients aged 13 to 66 yrs of age taking part in study 09-10. Results of bone biopsies in this age group suggest that there may be a decrease in mineralisation lag time of bone consequent to exposure to asfotase alfa. Interpretation of results is hampered, however, by the inherent difficulties associated with the technique of serial bone biopsy, the small number of patients involved in this exercise and because subjects were exposed to doses of asfotase alfa below that currently recommended [it is noted that osteoid thickness and volume did not change, unlike subjects in study 06-09 who were <13yrs age]. Furthermore, there was also a lack of data that convince of a clinically significant consequence of possible improvement in bone pathophysiology in the age group of 13 to 66 yrs of age in study 09-10. Concerns over lack of convincing clinical data are most pronounced for subjects ≥18 yrs (in particular those who initiate treatment when ≥18yrs age).

It is considered that the apparently differential response based on age may be a manifestation of 'heterogeneity of clinical effect'.

The data for subjects between 13 to 18 yrs of age is very limited, and the applicant has not been able to provide a robust presentation of this population in its studies. Therefore, the CHMP considered it necessary that the applicant will obtain further data to substantiate evidence of efficacy in this age group. Concerns over the limited amount of clinical data are particularly pronounced for subjects ≥18yrs. For treatment of patients ≥18 years, key data on both optimal dose and schedule of administration are missing. Therefore, the applicant is required to generate data in a dedicated pharmacokinetics (PK) study of Strensiq in adults following administration of the dose advised in children and to provide dose response data and to explore evidence of clinical benefit in this patient population. (see section 2.5.3: Conclusion on clinical efficacy)

It has been noted that, during the course of clinical studies, the main objectives were variously changed with regard to the primary endpoint, how the primary endpoint was interpreted. In addition, on the basis of emerging data, changes were made to the dosage of study drug and inclusion / exclusion criteria of study subjects. Cautious interpretation of data submitted is therefore required.

Interpretation of submitted data was further hampered by use of baseline-comparison (in the absence of a suitable control group). Only one study (study 09-10) has had a concurrent control albeit non-treated as opposed to placebo. There was concern that the open-label, non-controlled, non-randomised, baseline-comparison nature of the studies is associated with high bias towards favouring the study drug. There were additional concerns that (i) studies have been carried out with the presumption of therapeutic competence and that (ii) studies have employed an ambitious array of test strategies.

Of concern is that apparent catch-up height-gain over time shown with the use of asfotase alfa may be a non-specific effect of more attention being paid to patients during the studies. However, as previous management strategies (e.g. plasma replacement, teriparatide, bone marrow transplant) have not shown similar clinical efficacy with regard to catch-up height-gain it seems plausible that the clinical efficacy claimed for asfotase alfa is not non-specific.

The use of historical control data in study 11-10 was considered generally supportive for the purposes of illustration but it was considered that improvements in supportive care and technologies (especially those of respiratory support) hamper direct comparison with clinical efficacy data generated by the studies. Study 11-10 has informed overall analysis of clinical safety of the current product. The company has observed that some subjects exposed to Strensiq in studies 02-08/03-08 and 10-10 were successfully weaned off ventilation (when ventilation has been needed): a comparison has been made with the natural history of untreated subjects in study 11-10 where there was a high mortality if ventilation was clinically required, however this comparison exercise must be interpreted with caution because of the potential of bias and confounding elements to interfere.

Output data from the modelling exercise carried out by the company has to be interpreted with caution due to the limitations of the quality of data put in to the model.

The CHMP did not accept results of serum concentrations of inorganic pyrophosphate and pyridoxal phosphate in response to exposure to asfotase alfa because of concerns over sample collection and analysis. Irrespective, results of inorganic pyrophosphate and pyridoxal phosphate were not considered to be crucial by CHMP to the application from the overall clinical perspective.

The applicant has committed to use acceptable techniques for blood collection, storage and assay for those biomarkers in future studies.

Risks

Unfavourable effects

Each study submitted in the current application included collection of data on safety, as required. The company has reported on 2706 treatment-emergent adverse events in the 71 patients included in the integrated safety analyses. A relatedness exercise carried out by the company has identified "injection site reactions" and "injection associated reactions" as the most common adverse events. These events were clinically manageable and were overall found to be acceptable by CHMP.

There is concern that the metabolic stress consequent to exposure to asfotase alfa leads to a relative vitamin D deficiency and secondary hyperparathyroidism. This concern is addressed by advice and information given in sections 4.4 and 5.1 of the SmPC.

Disproportionate weight gain has occurred consequent to exposure to asfotase alfa. This concern is addressed by information in section 4.4 of the SmPC.

Uncertainty in the knowledge about the unfavourable effects

Uncertainty about unfavourable effects did arise because of the small population studied (there were only 71 patients exposed in all studies) thereby making it difficult to detect adverse events other than those that may be regarded as 'common' or striking in nature. Uncertainty also did arise because a high background morbidity associated with the hypophosphatasia condition may mask adverse events caused by asfotase alfa.

It is considered that there are insufficient data to establish a causal association between Strensiq and either development or progression of craniosynostosis or ectopic calcification [both of which may occur during the natural history of hypophosphatasia].

Overall, the total patient exposure to study drug was very limited with 71 patients included in the integrated safety analyses and uncertainty regarding unfavourable effects remain. Continuous collection of further data on clinical efficacy and safety is required as a specific obligation in the context of a marketing authorisation under exceptional circumstances:

Observational, Longitudinal, Prospective, Long-Term Registry of Patients with HPP to collect information on the epidemiology of the disease, including clinical outcomes and quality of life, and to evaluate safety and effectiveness data in patients treated with Strensiq.

The specific obligation shall be reassessed annually.

Balance

Importance of favourable and unfavourable effects

The commonly encountered unfavourable effects of injection site reactions are considered to be tolerable by patients and clinically manageable. Other unfavourable effects described were also considered to be manageable by the agreed risk management plan and pharmacovigilance activities.

The clinical benefit of exposure to asfotase alfa for patients with hypophosphatasia was considered positive by CHMP from the clinical perspective [with caveats consequent to the open-label, non-controlled nature of the phase 2 studies submitted in support of the current product].

Benefit-risk balance

Although based on a very limited set of data due to the rarity of the underlying disease, the potential improvement in bone health and growth were considered by CHMP to outweigh the unfavourable effects of injection reactions and other adverse events which are considered to be either tolerable or clinically manageable.

Discussion on the benefit-risk assessment

Whilst the CHMP had concerns over the open-label, non-controlled nature of the phase 2 studies submitted leading to possible bias in favour of the current product, the apparent improvements in x-ray appearance of knees and hands and wrists were relevant (along with the apparent "catch up" in growth) and are further supported by a patient population that reports mainly positive physical effects within the first 6 months of exposure.

The company has submitted arguments in favour of granting a marketing authorisation under exceptional circumstances in accord with EU regulation 726/2004 and EU directive 2001/83/EC, as amended. The CHMP agreed with the justification, considering that:

- Hypophosphatasia is a rare, serious, and life-threatening metabolic disorder. The incidence of the most severe forms of the disease is thought to be about 1:100,000 live births, although it is markedly higher in a small Canadian Mennonite population. The incidence of the most severe forms of HPP in Europe was recently estimated to be approximately 1:300,000.

Given the extreme rarity of the disease, comprehensive data on the efficacy and safety cannot be provided and data in this population will likely remain limited. Besides, Hypophosphatasia is a seriously debilitating and life-threatening metabolic disease. No product has been approved for this

indication. There is a high unmet medical need to provide hypophosphatasia patients with a safe and effective therapy.

The overall benefit / risk of asfotase alfa is considered to be positive.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the risk-benefit balance of Strensiq in the indication for long-term enzyme replacement therapy in patients with paediatric-onset hypophosphatasia to treat the bone manifestations of the disease is favourable and therefore recommends the granting of the marketing authorisation under exceptional circumstances subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Conditions and requirements of the Marketing Authorisation

- **Periodic Safety Update Reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- **Additional risk minimisation measures**

Prior to launch of Strensiq in each Member State the Marketing Authorisation Holder (MAH) must agree about the content and format of the educational programme, including communication media, distribution modalities, and any other aspects of the programme, with the National Competent Authority.

The educational programme is aimed to provide instruction to patients and carers for proper administration techniques to address the risks of medication errors and injection site reactions.

The MAH shall ensure that in each Member State where Strensiq is marketed all patients/parents or caregivers who are expected to use Strensiq have access are provided with the following educational package:

- Patient information leaflet
- Self-injection guide for patients
- Injection guide for parents or caregivers with infant patients

The Patient/parents or caregivers guides shall contain the following key messages:

- Warning and precautions on the potential risk of medication errors and injection site reactions associated with the use of Strensiq
- Instructions on the correct dose to be administered
- Instruction on how the injection site is chosen and how the injection is carried out and recorded
- Detailed description on how Strensiq is injected using aseptic techniques
- Information on cold chain management for Strensiq during storage and travel
- Information on reporting side effect

- **Obligation to complete post-authorisation measures**

The MAH shall complete, within the stated timeframe, the below measures:

Description	Due date
The MAH should conduct a multicentre, randomized, open-label, Phase 2a study of Strensiq in patients with hypophosphatasia (HPP) to: (i) evaluate pharmacokinetics (PK) of Strensiq in adults following administration of the dose advised in children; (ii) provide dose response data on plasma inorganic pyrophosphate (PPi) and pyridoxal-5` -phosphate (PLP) and to explore evidence of clinical benefit. In order to ensure that the data are reliable, the MAH should submit a study protocol including acceptable techniques for blood collection, storage and assay for the PPi and PLP biomarkers, to be agreed by CHMP before the start of the study.	31 March 2017
The MAH should extend the studies ENB-008-10 and ENB-009-10 to provide efficacy data (such as, but not limited to RGI-C scores, height and weight change, biomarkers measurement) in patients 13 to 18 year-old of age.	31 March 2017

Specific Obligation to complete post-authorisation measures for the marketing authorisation under exceptional circumstances

This being a marketing authorisation under exceptional circumstances and pursuant to Article 14(8) of Regulation (EC) No 726/2004, the MAH shall complete, within the stated timeframe, the following measures:

Description	Due date
The MAH should set up an observational, longitudinal, prospective, long-term registry of patients with HPP to collect information on the epidemiology of the disease, including clinical outcomes and quality of life, and to evaluate safety and effectiveness data in patients treated with Strensiq.	Annually within annual reassessment

Conditions or restrictions with regard to the safe and effective use of the medicinal product

to be implemented by the Member States.

Not applicable.

New Active Substance Status

Based on the CHMP review of data on the quality properties of the active substance, the CHMP considers that asfotase alfa is qualified as a new active substance.

Paediatric Data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/0306/2013 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.