



Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for asfotase alfa (rch)

Proprietary Product Name: Strensiq

Sponsor: Alexion Pharmaceuticals Australia Pty Ltd

July 2016

TGA Health Safety
Regulation

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- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <<https://www.tga.gov.au>>.

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- An Australian Public Assessment Report (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations and extensions of indications.
- An AusPAR is a static document; it provides information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

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Common abbreviations

Abbreviation	Meaning
6MWT	6 minute walk test
ACPM	Advisory Committee on Prescription Medicines
ACSOM	Advisory Committee on the Safety of Medicines
ADA	Anti-drug antibody
AE	Adverse event
AESI	Adverse events of special interest
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ASA	Australian Specific Annex
AST	Aspartate aminotransferase
AUC	Area under the concentration versus time curve
AUC _{0-168h}	Area under the concentration versus time curve from time 0 to 168 hours
BMC	Bone mineral content
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
C _{avg,ss}	Average steady-state concentration
CBRG	Cambridge Biomedical Research Group
CHAQ	Child Health Assessment Questionnaire
CHO	Chinese hamster ovary
CI	Confidence interval
CL	Clearance
CL/F	Apparent clearance
C _{max}	Peak serum concentration of a drug after administration

Abbreviation	Meaning
CMC	Chemistry, Manufacturing and Controls
CNS	Central nervous system
CSR	Clinical Study Report
CYP450	Cytochrome P450
DEXA	Dual Energy X ray Absorptiometry
DNA	Deoxyribonucleic acid
eCRF	Electronic case report form
eGFR	Estimated glomerular filtration rate
ED85	Near maximal effective dose
EMA	European Medicines Agency
E-R	Exposure response
ER _{AUC}	oestrogen receptor AUC
FDA	Food and Drug Administration (US)
GCP	Good Clinical Practice
HHD	Hand held dynamometry
HPP	Hypophosphatasia
IAR	Injection-associated reactions
ICH	International Conference on Harmonisation
Ig	Immunoglobulin
IgG1	Immunoglobulin G subclass 1
ISR	Injection-site reactions
IV	Intravenous
JP	Japanese Pharmacopeia
KM	Kaplan-Meier
LEFS	Lower Extremity Functional Scale
LSD	Lifesaving Drugs Program , Australian Department of Health

Abbreviation	Meaning
MCID	Minimally clinically important difference
NAb	Neutralising antibody
NOAEL	No observed adverse event level
PD	Pharmacodynamics
Ph. Eur.	European Pharmacopoeia
PK	Pharmacokinetic
PL	Pyridoxal
PLP	Pyridoxal-5'-phosphate
Pop PK	Population PK
POSNA PODCI	Paediatric Orthopaedic Society of North America's Paediatric Outcomes Data Collection Instrument
PPi	Inorganic pyrophosphate
PSUR	Periodic Safety Update Review
PY	Patient year(s)
QOL	Quality of life
RGI-C	Radiographic Global Impression of Change
RMP	Risk Management Plan
RSS	Rickets severity scale
SAE	Serious adverse event
SC	Subcutaneous
SD	Standard deviation
TEAE	Treatment emergent adverse event
T _{max}	Time taken to reach peak plasma concentration
TNSALP	Tissue nonspecific alkaline phosphatase
TSAC	Total sialic acid content
WML	Within normal limits

Abbreviation	Meaning
USP	United States Pharmacopeia

I. Introduction to product submission

Submission details

<i>Type of submission:</i>	New chemical entity
<i>Decision:</i>	Approved
<i>Date of decision:</i>	12 January 2016
<i>Date of entry onto ARTG</i>	14 January 2016
<i>Active ingredient:</i>	Asfotase alfa (rch)
<i>Product name:</i>	Strensiq
<i>Sponsor's name and address:</i>	Alexion Pharmaceuticals Australasia Pty Ltd Suite 401, 20 Rodborough Road Frenchs Forest NSW 2086
<i>Dose form:</i>	Solution for injection
<i>Strengths:</i>	12 mg/0.30 mL, 18 mg/0.45 mL, 28 mg/0.7 mL, 40 mg/1.0 mL and 80 mg/0.8 mL
<i>Container:</i>	2 mL glass vial
<i>Pack sizes:</i>	Single vial, pack of 12 vials
<i>Approved therapeutic use:</i>	<i>Indicated as enzyme replacement therapy in patients with paediatric onset hypophosphatasia</i>
<i>Route of administration:</i>	Subcutaneous
<i>Dosage:</i>	2 mg/kg of body weight administered three times per week, with a maximum injection volume of 1 mL or 1 mg/kg of body weight administered six times weekly. For full details please see the PI.
<i>ARTG numbers:</i>	232545, 232546, 266984, 266985, 266986

Product background

This AusPAR describes the application by Alexion Pharmaceuticals Australia Pty Ltd (the sponsor) to register Strensiq asfotase alfa (rch) as a new chemical entity for the indication of:

Strensiq asfotase alfa (rch) is indicated for long term enzyme replacement therapy in patients with paediatric onset hypophosphatasia.

Asfotase alfa is a human recombinant tissue nonspecific alkaline phosphatase-Fc-deca-aspartate fusion protein, produced by recombinant deoxyribonucleic acid (DNA) technology using mammalian Chinese hamster ovary (CHO) cell culture. It is not similar to

nor related to other previously approved drug substances. It is the first of its type for hypophosphatasia (HPP).

Hypophosphatasia is a rare, serious, and potentially fatal, genetic disorder caused by loss of function mutation(s) in the gene encoding tissue nonspecific alkaline phosphatase (TNSALP).¹ In patients with HPP, deficiency in TNSALP enzymatic activity leads to elevated concentrations of the TNSALP substrates, including inorganic pyrophosphate (PPi) and pyridoxal-5'-phosphate (PLP) which causes defective bone mineralization with skeletal deformities of rickets (abnormal mineralized bone, dysmorphic long bones and ribs and growth abnormalities) in infants and children and osteomalacia (softening of bones) in patients of all ages. The impaired phosphate and calcium regulation also leads to progressive damage to multiple vital organs including deformity and destruction of bones, pain and profound muscle weakness leading to impaired ambulation, shortened stature, respiratory failure and risk of ventilator dependence and premature death, vitamin B6 responsive seizures, impaired renal function, and dental abnormalities.

In HPP, death in paediatric patients is primarily due to respiratory failure. In the most severely affected paediatric patients, mortality ranges from 50 to 100%. In patients surviving to adolescence and adulthood, long term clinical sequelae include recurrent and non healing fractures, weakness, arthritis, dependence on internal fixation devices (due to the risk of recurrent fracture), severe and refractory pain, and the requirement for ambulatory assistive devices (wheelchairs, wheeled walkers and canes).

No specific therapy for HPP was currently registered in Australia at the time of approval. Treatment is otherwise generally directed towards preventing or correcting the symptoms or complications. Supportive symptomatic treatment in childhood and adult forms includes nonsteroidal anti-inflammatory drugs (children), teriparatide (adults) and orthopaedic management.

The sponsor states that: '*Asfotase (rch) combines the catalytic TNSALP enzyme domain and a bone targeting anchor, to allow a targeted enzyme replacement therapy to address the underlying cause of HPP, deficiency of TNSALP activity. Restoring TNSALP enzyme activity in HPP patients normalises the levels of TNSALP enzyme substrates, improves bone mineralisation and bone health, thereby preventing serious skeletal and systemic patient morbidity and premature death.*'

Regulatory status

At the time the TGA considered this application, a similar application had been approved in the EU (June 2015), Japan (July 2015), Canada (August 2015) and the USA (October 2015). The approved indications are as follows:

EU: *Strensiq is indicated for long-term enzyme replacement therapy in patients with paediatric onset hypophosphatasia to treat the bone manifestations of the disease.*

Canada: *Strensiq is indicated as enzyme replacement therapy for patients with confirmed diagnosis of paediatric onset hypophosphatasia. Patients should be advised about the conditional market authorization for this indication.*

USA: *Strensiq is indicated for the treatment of patients with perinatal/infantile-and juvenile-onset hypophosphatasia (HPP).*

Orphan drug status

Asfotase alfa (rch) was designated an orphan drug in Australia in October 2012.

¹ Millán JL, Plotkin H. Hypophosphatasia - pathophysiology and treatment. *Actual osteol.* 8: 164-182 (2012).

Product Information

The approved Product Information (PI) current at the time this AusPAR was prepared can be found as Attachment 1. For the most recent PI, please refer to the TGA website at <<https://www.tga.gov.au/product-information-pi>>.

II. Quality findings

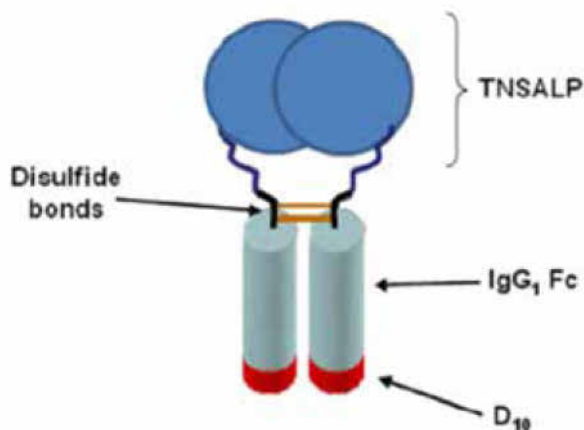
Introduction

Drug substance (active ingredient)

Asfotase alfa is a soluble fusion glycoprotein of 726 amino acids, comprised of two identical polypeptide chains. Each polypeptide chain contains the catalytic domain of human TNSALP, the human immunoglobulin (Ig) G1 Fc domain, and a deca-aspartate peptide domain used for bone targeting. The two polypeptide chains are connected by two inter chain disulphide bonds in the hinge region. Asfotase alfa is expressed in an engineered Chinese hamster ovary (CHO) cell line that maintains endogenous folding, sorting, disulphide bridging, and N-linked glycosylation. The novelty of the preparation is the fusion with a deca-aspartate peptide domain which facilitates bone targeting as it has been developed to treat a rare genetic disorder of the skeleton (bone) known as HPP.

Figure 1 (below) gives a diagrammatic representation of the overall physical structure of the asfotase alfa.

Figure 1. Representation of the asfotase alfa (rch) physical structure.



Drug product

Asfotase alfa (rch) is formulated in two concentrations, 40 and 100 mg/mL both combined with a 25 mM sodium phosphate (pH 7.4) buffer solution containing 150 mM sodium chloride. It is designed for subcutaneous injection only. The product comes in five presentations 12 mg/0.30 mL, 18 mg/0.45 mL, 28 mg/0.7 mL, 40 mg/1.0 mL and 80 mg/0.8 mL as shown in Table 1.

Table 1. Presentations and pack sized of Strensiq

Pack Size	Fill volume	Concentration	Strength
12 vials per pack or 1 vial per pack	0.30 mL	40 mg/mL	12 mg/vial
	0.45 mL		18 mg/vial
	0.70 mL		28 mg/vial
	1.00 mL		40 mg/vial
	0.80 mL	100 mg/mL	80 mg/vial

Stability

Stability data have been generated under stressed and real time conditions to characterise the stability profile of the product. Photo stability data indicate that the product is not photo stable. The proposed shelf life is 2 years when stored at 2 to 8°C.

A temperature cycling study determined asfotase alfa drug product should not be exposed to 37°C for more than 12 hours.

Biopharmaceutics

Evaluator's overall conclusions on pharmacokinetics

The pharmacokinetics (PK) of asfotase alfa in humans was derived from 5 interventional clinical studies (ENB-001-08, ENB-002-08/003-08, ENB-006-09/008-10, ENB-009-10 and ENB-010-10). One clinical trial was completed (ENB-001-08). Study ENB-003-08 is the extension phase of Study ENB-002-08 and Study ENB-008-10 is the extension phase of Study ENB-006-09. Study ENB-011-10 was a natural history study used as control for the perinatal/infantile subgroup patient population.

Extensive preclinical studies of the pharmacokinetics, pharmacodynamics and immunogenicity of asfotase alfa are reported and analysed in depth and extrapolated to the treatment of human subjects particularly infants and young people. Mammalian species including mice, rats, rabbits and monkeys shares a high protein sequence TNSALP homology (ranging from 86 to 97%) compared with the naturally occurring human sequence based on the alignment (performed using UniProt).

The final step from preclinical studies in experimental animal models was to simulate a dose to achieve the anticipated range of efficacious concentrations in humans using the available clinical asfotase alfa PK data from Study ENB-001-08.

For the first Phase II study in perinatal and infantile disease onset HPP subjects (Study ENB-002-08), a starting subcutaneous (SC) dose of 1 mg/kg SC three times weekly was chosen as it was determined that this dose was expected to provide serum asfotase alfa concentrations in the lower portion of the anticipated range of efficacious concentrations. Given the expected risk versus benefit in that patient population, this study included an initial intravenous (IV) dose of 2 mg/kg. Based on the available toxicological data and PK/safety data from Study ENB-001-08, a dose titration scheme centred on efficacy assessment was constructed. Following the starting dose of 1 mg/kg SC for the first month in Study ENB-002-08, the SC dose could be increased to 2 mg/kg according to lack of efficacy defined as two of the three following outcomes:

- Failure to show radiographic improvement in rickets

- Deterioration of pulmonary function
- Worsening of failure to thrive.

In Study ENB-006-09, children (aged ≥ 5 and ≤ 12 years) with open growth plates at the time of enrolment) with HPP were treated with asfotase alfa. The doses selected in this study were 2 mg/kg and 3 mg/kg SC three times weekly based on the available clinical PK data. These doses were expected to provide serum asfotase alfa concentrations in the anticipated range of efficacious concentrations. The subsequent experience with clinical efficacy and clinical safety established that the dose 6 mg/kg/week given as 6 daily divided doses subcutaneous injections 1 mg/kg is safe and efficacious in children and young people prior to growth plate closure. The Study ENB-008-10 is ongoing and PK data are being collected using a sparse sampling schedule.

Quality summary and conclusions

The administrative, product usage, chemical, pharmaceutical, microbiological data submitted in support of this application have been evaluated in accordance with the Australian legislation, pharmacopoeial standards and relevant technical guidelines adopted by the TGA. There are no outstanding issues.

The evaluator recommended Strensiq (asfotase alfa (rch)) as an injection solution in the proposed dosages should be approved and registration can be recommended with respect to chemistry, manufacturing and quality control aspects.

III. Nonclinical findings

Pharmacology

In vitro studies

Hydroxyapatite is a major inorganic component in hard tissues such as bone and teeth. Modification of proteins with a string of aspartate residues improves affinity to hydroxyapatite and can help target drugs to bones. In vitro, asfotase alfa had 17 to 32 fold greater affinity for purified hydroxyapatite than kidney TNSALP lacking the deca-aspartate peptide, supporting the premise that addition of the aspartate rich peptide promotes binding to hydroxyapatite. Specific targeting and sequestration of asfotase alfa to bone was demonstrated in vivo in tissue distribution studies in mice.

PPi is an inhibitor of hydroxyapatite crystal growth and PPi accumulation in HPP contributes to the impaired skeletal mineralisation. Mineralisation of clonal MC3T3-E1 cells isolated from newborn mouse calvaria was inhibited by the addition of PPi to the culture. This inhibition was reversed by the administration of asfotase alfa.

In vivo studies

In vivo studies were conducted in a murine knockout model of HPP (inactivation of TNSALP; designated Akp2-/-). This model displays most of the clinical features of the infantile form of HPP, such as impaired growth, abnormalities in skull development and morphology, episodes of apnoea and epileptic seizures. This model is considered an acceptable model of the disease.

In vivo efficacy studies examined prophylactic dosing regimens, beginning on postnatal day 1, and therapeutic dosing regimens, commencing 12 to 15 days after birth, a time at

which significant mineralisation defects are observed. Efficacy end points included levels of TNSALP substrates (PPi and PLP), bone mineralisation defects, enthesis mineralisation deficit, growth (including bone lengths) and survival. Dosing of asfotase alfa was via SC administration daily, every 3 days or weekly.

In the prophylactic dosing studies, asfotase alfa treatment reduced the severity of mineralisation defects, promoted normal mineralisation of bones of the hindpaw and partially prevented the mineralisation deficit at the calcaneus-Achilles tendon enthesis. Increasing the treatment from 16 to 43 days significantly improved the reversal of the mineralisation deficit at the calcaneus Achilles tendon enthesis. There was a dose related increase in survival. Inconsistent findings were observed with respect to PLP and PPi levels. One study indicated asfotase alfa treatment had no significant effect on plasma PLP or urine PPi levels, whereas another study indicated asfotase alfa treatment prevented the increase in plasma PPi and plasma PLP levels observed in *Akp2*^{-/-} mice. Nonetheless, the data collectively suggest that asfotase alfa greatly improved disease severity in *Akp2*^{-/-} mice but did not completely overcome the enzyme deficiency in this model. Based on radiographic image distribution data, the dose at which 85% of the animals had normal radiographs of paws (ED85, near maximal effective dose) was determined to be 2.7 mg/kg/day or 1451 U/kg/day asfotase alfa.

When dosing was initiated 12 or 15 days after birth, an age at or after which secondary ossification centres appear as asfotase alfa treatment had only minimal improvements on bone mineralisation and survival of animals. Asfotase alfa treatment during this period was clearly less efficacious using a therapeutic dosing regimen contrasted with a prophylactic dosing regimen. The submitted data also indicated that lower doses given more frequently (for example, daily) gave greater improvements than higher doses given at less frequent intervals (for example, every 3 days or weekly).

In general, the pharmacology studies support the use of asfotase alfa to alleviate the effects on bone mineralisation associated with defects in endogenous TNSALP activity when administered at an early age and prior to the commencement of significant postnatal mineralisation effects (for example, the appearance of secondary ossification sites).

Secondary pharmacodynamics and safety pharmacology

Asfotase alfa contains an Fc region from human IgG1 (immunoglobulin G subclass 1). There was no evidence of complement activation by asfotase alfa in serum collected from healthy volunteers.

Specialised safety pharmacology studies covered the central nervous system and respiratory function in rats, while cardiovascular effects were assessed in a 26 week repeat dose toxicity Study in cynomolgus monkeys. All studies were conducted under Good Laboratory Practice (GLP) conditions. Transient effects on behaviour (decreased activity and significant neuromuscular effects (for example, abnormal gait, altered landing foot splay) at ≥ 30 mg/kg IV) and respiration (depressed respiration) were attributed to a manifestation of an acute infusion reaction, rather than a direct drug related effect on these systems. Acute infusion reactions occurred at IV doses generally resulting in high peak plasma levels; C_{max} at ≥ 3 mg/kg IV in rats estimated to be 44.3 mg/L or 44,300 U/L (based on a specific activity of 1,000 U/mg); 17 times the clinical $C_{avg,ss}$.^{2,3}

Acute infusion reactions were observed in rats following IV dosing. Slowing the IV infusion or administering diphenhydramine or dexamethasone decreased but did not completely alleviate the acute response. The reactions did not appear to involve complement, but tryptase levels were elevated in animals that had clinical signs of an acute infusion

² C_{max} , Peak serum concentration of a drug after administration

³ $C_{avg,ss}$, Average plasma drug concentration at steady state

reaction, suggesting a possible anaphylactic/anaphylactoid reaction, though this was not fully elucidated. Acute infusion reactions were not seen in rats following SC dosing up to 180 mg/kg, in cynomolgus monkeys following IV or SC dosing (up to 180 mg/kg and 10 mg/kg, respectively) or in rabbits following IV dosing (up to 50 mg/kg). The relevance of the acute infusion reactions to human subjects is unknown, but is considered low, provided asfotase alfa is only administered via SC.

No adverse effects on cardiovascular function were observed in cynomolgus monkeys given ≤ 10 mg/kg/day SC for 26 weeks (C_{\max} 6.68 mg/L, 6,680 U/L; 2.6 times the clinical $C_{\text{avg,ss}}$). Although the exposure ratios are low, given the molecular weight of asfotase alfa, it is not expected to interact with ion channels in the heart. Altogether, asfotase alfa may be considered to have a low risk of adverse effects on cardiovascular function.

Pharmacokinetics

The pharmacokinetics of asfotase alfa were typical for this type of compound, characterised by a long apparent half-life (14 to 40 hours following IV dosing to mice, rats, rabbits and cynomolgus monkeys and 2.28 days following SC dosing to human subjects). Volume of distribution values were similar to total body water in mice, rats, rabbits and humans and lower than total body water in monkeys, suggesting low distribution of the test article into peripheral tissues. There were no consistent sex differences in pharmacokinetic parameters in mice, rats and cynomolgus monkeys. There were no pharmacokinetic differences between Akp2^{-/-} and wild-type mice. Bioavailability following SC dosing was variable, ranging from 34 to 100% across species at similar SC doses (2 to 5 mg/kg) and appeared to depend on sialic acid content. Lower bioavailability was observed with higher doses in rabbits given the same lot of asfotase alfa (10% at 50 mg/kg compared with 34% at 5 mg/kg). The rate of absorption following SC dosing was moderate to low in mice, rats, rabbits, cynomolgus monkeys and human subjects (T_{\max} 4 to 48 hours).⁴ There was no clear indication of accumulation following repeated weekly or daily IV dosing to juvenile rats or weekly IV dosing to cynomolgus monkeys. There was some indication of accumulation with daily SC dosing to cynomolgus monkeys. Following daily SC dosing to rats, lower exposures were seen on Day 28 compared to Day 1. This may be attributed to greater clearance as a result of anti-drug antibody (ADA) production.

Tissue distribution of radioactivity was monitored in mice after a single IV dose and repeated SC administration of radiolabelled asfotase alfa. Tissue AUC values were similar to or below blood AUC values, suggesting low distribution into tissues, with the exception of bone structures.⁵ High AUC values, long half-lives and relatively flat concentration-time profiles in the latter tissues are suggestive of specific targeting and sequestration in these tissues. There was minimal penetration of the blood brain barrier (brain AUC values 6 to 18% of blood values).

No metabolism or excretion studies were submitted, which is considered acceptable given the nature of the drug.

Overall, the pharmacokinetic profile of asfotase alfa is seen to be sufficiently similar in humans and the species used in toxicity studies (rats and monkeys) for these species to serve as appropriate models for toxicity

⁴ T_{\max} , Time taken to reach peak plasma concentration

⁵ AUC, Area under the plasma drug concentration-time curve (AUC) reflects the actual body exposure to drug after administration of a dose of the drug

Pharmacokinetic drug interactions

No pharmacokinetic drug interaction studies were submitted. Given the protein nature of asfotase alfa, pharmacokinetic drug interactions involving CYP450 enzymes are not expected.⁶

Toxicology

An exploratory, non GLP compliant single dose toxicity study was conducted in cynomolgus monkeys. Single IV escalating doses were examined. Increased serum alkaline phosphatase (ALP) levels were observed, consistent with increased serum levels of the test item. Mild increases in liver enzymes (alanine transaminase (ALT) and aspartate aminotransferase (AST)) were observed but have an unclear toxicological meaning. Animals were returned to the colony and were not subject to necropsy. The maximum non-lethal dose was 180 mg/kg IV.

Repeat dose toxicity

Repeat dose toxicity studies were conducted in juvenile rats following weekly or daily IV dosing up to 26 weeks and juvenile monkeys following weekly IV dosing (4 weeks) and daily SC dosing (26 weeks). The choice of species (rats and cynomolgus monkeys) for toxicity assessments is considered acceptable. Asfotase alfa was pharmacologically active in mice, the TNSALP homologues of rats and cynomolgus monkeys share 91% and 86%, respectively, sequence similarity with human TNSALP and the substrates of this enzyme are identical in humans and animal species. Therefore, asfotase alfa is expected to be pharmacologically active in rats and cynomolgus monkeys.

Pivotal studies were GLP compliant, group sizes were reasonably acceptable (small group sizes are generally typical for studies conducted with cynomolgus monkeys) and were of acceptable duration (up to 6 months; ICH S6).⁷ The age of the animals at the start of dosing is considered appropriate given the age of the intended patient group (paediatric), though not all stages in postnatal bone development would have been covered.

The clinical route of administration (SC) was used in the pivotal cynomolgus monkey study, while the IV route was used in the remaining studies. This is considered acceptable as higher exposures were achieved via IV dosing compared to SC dosing. In rats, ADA production appeared to be higher and AUC lower with SC dosing compared with IV dosing. Therefore, use of the SC route for the longer term rat Study may have resulted in ADA production and lower exposures, potentially confounding the findings in that study. The dosing regimen was daily or weekly in contrast with the proposed clinical dosing regimen of 3 times per week or 6 times per week. This difference is not considered to affect the utility of the toxicity studies. Maximum tested doses were low, reaching only 4 times the clinical AUC in rats and 6 times the clinical AUC in cynomolgus monkeys. It may have been possible for higher exposures to have been achieved in cynomolgus monkeys, while dosing in the pivotal rat study seems appropriate based on clinical signs of toxicity and reduced bodyweight gain seen at higher doses in 4 week repeat dose toxicity studies in this species.

Relative exposure

Animal AUC data in mg/h/L were converted to data in U/h/L units using the specific activity of the asfotase alfa lot used in that particular study. The AUC values in U/h/L units

⁶ CYP450 enzymes are a group of over 50 enzymes, principally expressed in liver tissue and are essential for the metabolism of many medications as well as toxins and endogenous products of metabolism.

⁷ ICH, International Council on Harmonisation, S6 Guidance: 'Preclinical safety evaluation of biotechnology-derived pharmaceuticals'.

were corrected where necessary to correspond to a weekly exposure. The clinical $C_{avg,ss}$ was converted to a weekly exposure by multiplying by 168 hours. Relative exposures were determined by comparing animal area under the curve to 168 h after dosing (AUC_{0-168h}) in U·h/L units with human AUC_{0-168h} in U·h/L units (See Table 2 below).

Table 2. Relative exposure in repeat-dose toxicity studies

Species	Study duration (dosing frequency)	Dose (mg/kg)	AUC (mg·h/L)	AUC_{0-24h} (U·h/L)	AUC_{0-168h} (U·h/mL)	Exposure ratio [#]
Rat (SD)	26 weeks [daily; IV] ^a	1	12.3	9,840	68.9	0.2
		3	42.8	34,240	239.7	0.5
		13	331	264,800	1,853.6	4.2
Monkey (Cynomolgus)	4 weeks [weekly; IV] ^b	5	105		105	0.2
		15	524		524	1.2
		45	2670		2670	6.1
	26 weeks [daily; SC] ^b	0.43	7.23	7,230	50.6	0.1
		2.14	14.7	14,700	102.9	0.2
		10	124	124,000	868	2.0
Human (patients)	steady state [3 times weekly; SC]	2			436.8 ^c	

[#] = animal: human plasma AUC_{0-168h} ; = not relevant; data are the average across the sexes from the final sampling point; ^aspecific activity of lot used in the study was ~800 U/mg; ^bspecific activity of lot used in the study was approximately 1000 U/mg; ^cbased on a $C_{avg,ss}$ of 2600 U/L

Major toxicities

No consistent target organs for toxicity were identified. The main findings were acute infusion reactions following IV dosing to rats and injection site reactions following SC dosing to cynomolgus monkeys.

Following IV dosing to rats, transient acute infusion reactions (swelling of limbs, skin discolouration, reduced motor activity) beginning soon after dosing and ameliorating several hours after dosing, were observed. These reactions were seen as early as after the first dose and are discussed further above under 'Secondary pharmacodynamics and safety pharmacology'.

Injection site reactions (minimal to moderate granulomatous inflammation in the dermis and subcutis and minimal to moderate perivascular mononuclear cell infiltration with slight degeneration/necrosis of the underlying muscle) were observed following SC dosing to cynomolgus monkeys. The incidence and severity correlated with dose and were not seen following IV dosing. Injection site reactions are possible during clinical.

Significantly increased serum ALP levels were observed in both rats and cynomolgus monkeys. This is not considered to be of particular concern as the levels correlated with serum levels of aspartate aminotransferase, which has ALP activity.

Elevated serum phosphate levels, which may be expected in animals given excess TNSALP, was observed in only one repeat dose toxicity Study and only at relatively high IV doses to rats (90 mg/kg/week). Reduced bodyweight gain was seen in males (but not females), which correlated with apparently smaller bones in these animals (based on smaller bone area and/or bone mineral content). Therefore, moderately higher serum TNSALP levels do not appear to result in elevated serum phosphate levels.

Aside from the effects on bone development there were no consistent effects on bone development (based on biochemical markers of bone turnover and bone mineral density measurements) in either rats or cynomolgus monkeys. While mineralisation was observed at injection sites following dosing to cynomolgus monkeys, there was no evidence of ectopic calcification in any other tissue in any of the repeat dose toxicity studies.

There were no effects on physical or sexual development or behavioural parameters in rats.

Genotoxicity and carcinogenicity

No genotoxicity or carcinogenicity studies were submitted as is usual for most biotechnology derived pharmaceuticals.⁸ Based on its chemical nature, asfotase alfa is not expected to interact directly with DNA and therefore has a low potential for genotoxic effects.

Reproductive toxicity

Reproductive toxicity studies covered effects on fertility (rats), embryofetal development (rats and rabbits) and pre/postnatal development (rats). All studies were GLP compliant and were adequately conducted. Group sizes in the pivotal studies were appropriate. IV dosing was used in all studies, which is acceptable given that reasonably high exposures were achieved (up to 19 times the clinical AUC in rats and 50 times the clinical AUC in rabbits; though the presence of ADAs in rabbits may confound the exposure data) (See Table 3).

⁸ International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, "S6(R1): Preclinical safety evaluation of biotechnology-derived pharmaceuticals", 12 June 2011.

Table 3. Relative exposure in reproductive toxicity studies

Species	Study	Dose (IV)	AUC _{0-24h}	AUC _{0-24h}	Exposure ratio [#]
		mg/kg/day	mg.h/L	U h/L	
Rat	Embryofetal development	15	104	104,000	2
		25	128	128,000	2
		50	1,146	1,146,000	18
	Pre/post natal development	10	88.2	79,380	1
		25	340	306,000	5
		50	1,339	1,205,100	19
Rabbit (NZW)	Embryofetal development	10	332	289,800	5
		25	1,573	1,415,700	23
		50	3,435	3,091,500	50
Human	SS (3 x week)	2 mg/kg SC	-	62,400	-

[#] animal: human plasma AUC_{0-24h} clinical C_{avg,ss} (2,600 U/L) converted to human AUC_{0-24h} by multiplying by 24h

In rats, asfotase alfa treatment had no effect on oestrous cycling or on sperm parameters, and functional fertility was unaffected when both males and females were treated with high doses (≤ 50 mg/kg/day IV; estimated oestrogen receptor AUC (ER_{AUC}) 19).

Furthermore, sexual development was unaffected in the pre and postnatal study. Asfotase alfa treatment is not expected to affect fertility in human subjects.

Asfotase alfa crossed the placenta in mice with fetal plasma levels 70 to 90% of maternal levels. Asfotase alfa binds to the neonatal Fc receptor and placental transfer is likely to occur via this mechanism. No adverse effects on embryo/fetal development were seen in rats and rabbits following daily IV treatment to pregnant dams during the period of organogenesis (at ≤ 50 mg/kg/day IV; ER_{AUC} 18 in rats and 50 in rabbits). However, ADAs were detectable in approximately 70% of treated rabbits, which could affect exposures. Hence, it is considered that reproductive toxicity has not been adequately assessed in this species.

No adverse effects on pre/postnatal development were seen in rats (≤ 50 mg/kg/day IV; ER_{AUC} 19). It is unknown if asfotase alfa is excreted in milk during lactation.

Pregnancy classification

The sponsor has proposed Pregnancy Category B2.⁹ As the potential embryo/fetal development toxicity of asfotase alfa has not been adequately assessed in animals, and

⁹ Pregnancy Category B2: "Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed. Studies in animals are inadequate or may be lacking, but available data show no evidence of an increased occurrence of foetal damage."

taking into consideration the comments of the clinical evaluator, Category C is considered more appropriate.¹⁰

Local tolerance

No specific injection site reactions attributable to asfotase alfa were reported following IV administration to rats or cynomolgus monkeys. Asfotase alfa related injection site reactions observed following SC administration included minimal to moderate perivascular/subcutaneous mononuclear cell infiltrates in both rats and cynomolgus monkeys. Additional injection site findings in cynomolgus monkeys included skin scabs, skin dryness and/or skin redness at one or several injection sites with microscopic findings of minimal to moderate granulomatous inflammation in the dermis and subcutis and mineralisation (ectopic calcification). Slight degeneration to necrosis of the underlying muscle was noted in 1 animal. The study in monkeys indicated a dose related increase in incidence and severity of injection site reactions. The data suggest that injection site reactions may be seen in patients, with severity likely related to dose. The draft PI document indicates that injection sites should be rotated and carefully monitored for signs of potential reactions.

Immunogenicity

No significant ADAs were detected in rats given asfotase alfa via the IV route for up to 26 weeks, but ADAs were detected in rats given asfotase alfa via the SC route for up to 4 weeks, with significant effects on exposures. ADAs were also detected in cynomolgus monkeys given asfotase alfa via the IV route (for 4 weeks) and the SC route (for 26 weeks), but without an obvious effect on asfotase alfa exposures. In general, the incidence of ADAs appeared to be higher with asfotase alfa given via SC administration compared with IV administration. This is consistent with previously published reports with similar proteins administered via the two different administration routes and maybe reflective of differences in systemic absorption by the two routes of administration. Systemic absorption via the SC route occurs primarily through the lymphatic system and greater exposure to antigen presenting cells would be expected. While antibody production in animals is not always reflective of what may happen in human subjects, therefore, ADA production, and any adverse effects associated with it (such as reduced efficacy, hypersensitivity reactions), may be seen in patients.

Paediatric use

Asfotase alfa is intended for use in patients of all ages (neonates to adults). When given to juvenile rats and cynomolgus monkeys, there were no adverse effects on physical, reflex, neuro behavioural or sexual development. However, the age of animals used in the toxicity studies does not include the period for fusion of the secondary ossification centres (relevant to human years 11 to 20) that occurs at 15 to 162 weeks in rats and 2.25 to 6 years in cynomolgus monkeys). Therefore, the effect of asfotase alfa treatment on all stages of postnatal bone development has not been assessed.

¹⁰ Pregnancy Category C: "Drugs which, owing to their pharmacological effects, have caused or may be suspected of causing, harmful effects on the human fetus or neonate without causing malformations. These effects may be reversible. Accompanying texts should be consulted for further details."

Nonclinical summary and conclusions

Nonclinical summary

- The overall quality of the submitted dossier was reasonable and was in general compliance with the relevant guideline, ICH S6⁷
- In vitro, asfotase alfa had 17 to 32 fold greater affinity for purified hydroxyapatite than kidney TNSALP lacking the deca-aspartate peptide. Specific targeting and sequestration of asfotase alfa to bone was demonstrated in vivo in tissue distribution studies in mice. In vivo efficacy studies were conducted in a murine knockout model of HPP. When dosing was commenced on postnatal Day 1, asfotase alfa treatment reduced the severity of mineralisation defects, promoted normal mineralisation of bones of the hindpaw and partially prevented the mineralisation deficit at the calcaneus Achilles tendon enthesis. While asfotase alfa greatly improved disease severity, it did not completely overcome the enzyme deficiency in this model. Asfotase alfa treatment was clearly less efficacious using a therapeutic dosing regimen (that is, dosing during a period of active bone growth) contrasted with a prophylactic dosing regimen.
- Asfotase alfa did not activate complement in human serum.
- Specialised safety pharmacology studies covered the central nervous system and respiratory function in rats, while cardiovascular effects were assessed in a 26 week repeat dose toxicity Study in cynomolgus monkeys. In rats, transient effects on behaviour (decreased activity and significant neuromuscular effects (for example, abnormal gait, altered landing foot splay)) and respiration (depressed respiration) were attributed to a manifestation of an acute infusion reaction, rather than a direct drug-related effect on these systems. No adverse effects on cardiovascular function were seen in cynomolgus monkeys.
- The pharmacokinetics of asfotase alfa in laboratory species were typical for this type of compound, characterised by a long apparent half-life and low volume of distribution. Bioavailability following SC dosing was variable and dependent on sialic acid content. There was some indication of accumulation with daily SC dosing to cynomolgus monkeys. Aside from specific targeting and sequestration in bone structures, there was limited tissue distribution of radioactivity following dosing to mice. No metabolism, excretion or pharmacokinetic interaction studies were submitted.
- Repeat dose toxicity studies were conducted in juvenile rats following weekly or daily IV dosing up to 26 weeks and juvenile monkeys following weekly IV dosing (4 weeks) and daily SC dosing (26 weeks). No consistent target organs for toxicity were identified. The main findings were acute infusion reactions (swelling of limbs, skin discolouration, reduced motor activity) following IV dosing to rats and injection site reactions following SC dosing to cynomolgus monkeys.
- The age of the animals at the start of dosing in the repeat dose toxicity studies is considered appropriate given the age of the intended patient group (paediatric); however not all stages of postnatal bone development would have been covered in the submitted studies.
- No genotoxicity or carcinogenicity studies were submitted, which is considered acceptable for this type of product.
- Fertility (in rats), embryofetal development (in rats and rabbits) and pre/postnatal development (in rats) were unaffected by treatment with asfotase alfa at reasonably

high exposures. However, ADA production affects the utility of the study in rabbits to assess embryofetal development toxicity.

- ADAs were detected in rats following SC dosing and cynomolgus monkeys following SC and IV dosing. Reduced exposure in rats following repeat SC dosing correlated with ADA production.

Conclusions and recommendation

- The pharmacology studies support the use of asfotase alfa to alleviate the effects on bone mineralisation associated with defects in endogenous TNSALP activity when administered at an early age and prior to the commencement of significant postnatal mineralisation effects (for example, the appearance of secondary ossification sites).
- The following animal findings are considered to be potentially clinically relevant:
 - acute infusion reactions (IV route); the risk is considered low if administered by SC
 - injection site reactions
 - effects associated with ADA production are possible.
- There were no objections on nonclinical grounds to the proposed use of asfotase alfa.

The nonclinical evaluator also made recommendations regarding the PI but these are beyond the scope of the AusPAR.

IV. Clinical findings

Introduction

Clinical rationale

HPP is a rare, serious, and potentially fatal genetic disorder and to date management has been limited to symptomatic support.

HPP generally manifests in childhood with bone mineralisation defects as well as other systemic effects including inadequate respiratory function, seizures, muscle weakness, craniosynostosis and calcification in the kidneys (nephrocalcinosis).

The single or multiple loss of function mutations in the gene encoding TNSALP lead to the primary biochemical defect, a deficiency of TNSALP enzymatic activity. TNSALP is expressed throughout the body, but primarily in the liver, kidney, and bone tissues. In the bone tissue, TNSALP is localised on the entire cell surface of pre-osteoblasts, as well as the basolateral cell membrane of osteoblasts. It is also localized on hypertrophic cells in cartilage. In addition, TNSALP is anchored at the membrane of matrix vesicles released by osteoblasts and growth plate chondrocytes.

The disorders are usually suspected because of the finding of a low serum alkaline phosphatase on routine testing of bone and mineral metabolites or because of the finding of characteristic radiographic findings in skeletal X rays.

In reality, there is a wide age of onset of symptoms sufficient to result in referral for diagnosis. Nevertheless, a number of presentations (clinically recognised disorders) all with mutations in the TNSAP gene are generally described:

1. Perinatal: onset in utero resulting in stillbirth or severe illness in the newborn period, usually resulting in death from respiratory compromise.

2. Perinatal benign: manifest in utero bowing, suggesting perinatal HPP, but with spontaneous skeletal improvement after birth. Both autosomal recessive and autosomal dominant modes of inheritance are recorded. The latter is more characteristic of adult (onset) HPP.
3. Infantile (onset postnatal to 6 months).
4. Juvenile (onset 6 months to 18 years).
5. Adult onset: onset after 18 years.

Elevations in PPI inhibit bone mineralisation by blocking hydroxyapatite crystal formation, causing a pronounced accumulation of unmineralised bone matrix. Failure to mineralise bone matrix results in osteomalacia (softening of bones) in patients of all ages and skeletal deformities of rickets (abnormal mineralised bone) with striking radiographic changes at the end of tubular bones. In addition, there are dysplastic long bones and ribs, and growth abnormalities in infants and children.

TNSALP also dephosphorylates PLP into pyridoxal (PL), allowing it to cross the plasma membrane into the central nervous system (CNS). Deficiency in TNSALP results in vitamin B6 deficiency in the CNS, potentially leading to seizures. Progressive multisutural craniosynostosis is a relatively common feature of HPP and is particularly found in survivors of infantile and early juvenile HPP. Neurosurgical monitoring and in many cases intervention is needed. It is a serious complication.

Following puberty the growth plates at the centre ends of long bones mature and close over so that there is bone continuity. Deformities which may have developed during childhood or adolescence remain. There are patients who have primarily adult onset disease who may have had a history of mild rickets or premature loss of deciduous teeth. These patients manifest HPP characterised by recurrent poorly healing stress fractures. These are a particular nuisance in the feet but pseudo fractures may occur in various other areas of the skeleton particularly long bones. These non healing stress fractures are also known as 'pseudo fractures' (or Looser zones). Adult HPP may be associated with debilitating chronic bone pain.

Severe functional deficits may also be present including ambulation difficulties, weakness, shortened stature, and inability to carry out activities of daily living. In addition, osteomalacic changes in the chest including non healing stress fractures leads to the inability of the rib cage to support normal respiratory function and risk of ventilator dependence and premature death.

No approved treatment for HPP is currently available. Symptomatic treatment is the mainstay of patient management, though it does not prevent disease progression and the majority of patients experience significant morbidity. HPP is characterised by interdependent clinical manifestations, emanating from a failure to mineralise bone matrix due to elevated concentrations of the TNSALP substrates, including PPI and PLP.

There have been attempts over many years to trial purified natural TNSALP in the treatment of the bone disease, but these attempts have not been successful.

Asfotase alfa is a bone targeted enzyme replacement therapy designed to address the underlying cause of HPP, a deficiency of TNSALP activity, by replacing the defective enzyme and preventing or reversing the mineralisation defects of the skeleton, thereby preventing serious patient morbidity, risk of ventilator dependence and premature death.

Comment: The concept of protein/enzyme replacement is a well-accepted principle in the use of biopharmaceuticals and has been validated for many other proteins. In this instance the enzyme is targeted specifically to bone on the hypothesis that the primary pathology involves the regulation of PPI. It should be noted however that there are other body systems with a risk of ectopic calcification in the eye and kidney.

Guidance

A number of TGA adopted EU guidance documents are of relevance:

- EMEA/CHMP/EWP/147013/2004 Corr Guideline on the role of Pharmacokinetics in the Development of Medicinal Products in the Paediatric Population,
- CHMP/EWP/89249/2004 Guideline on the Clinical Investigation of the Pharmacokinetics of Therapeutic Proteins Effective: 6 January 2009,
- CPMP/ICH/2711/99 ICH Topic E 11 Note for Guidance on Clinical Investigation of Medicinal Products in the Paediatric Population Effective: 19 April 2001, pp. 127 - 132 of Rules 1998 (3C) - 3CC6a Clinical Investigation of Medicinal Products for Long-Term Use Replaces: pp. 163 - 165 of Rules 1989 Effective: 12 February 2002, ICH Topic E 1 Note for Guidance on Population Exposure: The Extent of Population Exposure to Assess Clinical Safety Effective: 12 February 2002

Contents of the clinical dossier

The submission contained the following clinical information:

- 1 population PK analysis.
- 1 renal function clearance report that may be related to the pop PK Study.
- 8 clinical studies that cover efficacy, safety, tolerability, PK and pharmacodynamics (PD).

The submission also contained; Clinical overview, clinical summaries including biopharmacology, clinical efficacy, clinical pharmacology, clinical safety, synopses of individual studies; nonclinical overview, nonclinical summaries including pharmacology, pharmacokinetics, toxicology, clinical pharmacology and literature references.

Paediatric data

The submission included paediatric pharmacokinetic, pharmacodynamics, efficacy and safety data which is as extensive as can be provided for an extremely rare genetic disorder.

Good clinical practice

The studies were conducted in accordance with the principles of Good Clinical Practice (GCP), as defined by relevant international guidelines.¹¹

Pharmacokinetics

Studies providing pharmacokinetic data

The PK of asfotase alfa in humans was derived from 5 interventional clinical studies (ENB-001-08, ENB-002-08/003-08, ENB-006-09/008-10, ENB-009-10 and ENB-010-10). One clinical trial was completed (ENB-001-08). Study ENB-003-08 is the extension phase of Study ENB-002-08 and Study ENB-008-10 is the extension phase of Study ENB-006-09.

¹¹ International Conference on Harmonisation the clinical studies in the submission complied with CPMP/ICH/135/95 Note for Guidance on Good Clinical Practice (ICH).

Study ENB-011-10 was a natural history study used as control for the perinatal/infantile subgroup patient population.

Table 4. Studies providing pharmacokinetic data

PK topic	Subtopic	Study ID		
PK in special populations	Target population [§]	Single dose	Not applicable	
		Multi dose	ENB-001-08 (FIH)	
	Neonates/infants/children/adolescents	Multi dose	ENB-002-08/ENB-003-08 (extension of ENB-002-08)	
			ENB-006-09/ ENB-008-10 (extension of ENB-006-09)	
			ENB-009-10	
			ENB-010-10	
			ENB-002-08/ENB-003-08 (extension of ENB-002-08)	
		Adolescent/Adult	ENB-006-09/ ENB-008-10 (extension of ENB-006-09)	
			ENB-009-10	
			ENB-010-10	
		Population PK analyses	Healthy subjects	Not applicable
			Target population	ENB-001-08 (FIH)
	ENB-002-08/ENB-003-08 (extension of ENB-002-08)			
	ENB-006-09/ ENB-008-10 (extension of ENB-006-09)			
ENB-009-10				
ENB-010-10				

[†]Bioequivalence of different formulations. [§]Subjects who would be eligible to receive the drug if approved for the proposed indication.

Evaluator's conclusions on pharmacokinetics

Extensive preclinical studies of the pharmacokinetics, pharmacodynamics and immunogenicity of asfotase alfa are reported and analysed in depth and extrapolated to the treatment of human subjects particularly infants and young people. Mammalian

species including mice, rats, rabbits and monkeys shares a high protein sequence TNSALP homology (ranging from 86 to 97%) compared with the naturally occurring human sequence based on the alignment (performed using UniProt).

The final step from preclinical studies in experimental animal models was to simulate a dose to achieve the anticipated range of efficacious concentrations in humans using the available clinical asfotase alfa PK data from Study ENB-001-08.

For the first Phase II study in perinatal and infantile disease onset HPP subjects (Study ENB-002-08), a starting SC dose of 1 mg/kg SC three times weekly was chosen as it was determined that this dose was expected to provide serum asfotase alfa concentrations in the lower portion of the anticipated range of efficacious concentrations. Given the expected risk/benefit in that patient population, this study included an initial IV dose of 2 mg/kg. Based on the available toxicological data and PK/safety data from Study ENB-001-08, a dose titration scheme centred on efficacy assessment was constructed.

The starting dose for SC injections was 1 mg/kg. In the Phase II Study ENB-002-08, after one month of treatment, the SC dose could be increased to 2 mg/kg for lack of efficacy defined as two of the three following outcomes:

- Failure to show radiographic improvement in rickets
- Deterioration of pulmonary function
- Worsening of failure to thrive.

In Study ENB-006-09, children (age ≥ 5 and ≤ 12 years) with open growth plates at the time of enrolment) with HPP were treated with asfotase alfa. The doses selected in this Study were 2 mg/kg and 3 mg/kg SC thrice weekly based on the available clinical PK data. These doses were expected to provide serum asfotase alfa concentrations in the anticipated range of efficacious concentrations. The subsequent experience with clinical efficacy and safety established that the dose 6 mg/kg/week given as 6 daily divided doses subcutaneous injections 1 mg/kg is safe and efficacious in children and young people prior to growth plate closure. The Study ENB-008-10 is ongoing and PK data are being collected using a sparse sampling schedule.

Summary of population pharmacokinetic and pharmacodynamics report

The purpose of the analysis was to establish a basis for asfotase alfa dose and regimen selection for treatment of patients with HPP. The study included 60 subjects, of which 53 contributed data to the PK analysis and between 10 and 60 contributed data to subsequent PK-PD analyses. Median age was 7.5 y (range 1.5 day to 66.8 y).

On the basis of this evaluation, it was concluded:

- The final PK and PD models were successfully replicated, verifying the models and the reported PK-PD parameters in the report.
- The methodology was generally sound. The use of mixed effects modeling was appropriate given a mix of intensively sampled and primarily sparsely sampled PK and PD measurements over a period of up to 4 years. Modelling assumptions, model building methods, model selection criteria, evaluation methods and simulation methods used accepted approaches and were consistent with EMEA Guidelines. Minor deviations between the analysis plan and the Methods section of the PK-PD report were inconsequential to the outcomes of the analyses. Although the Methods stated that AIC would be used to discriminate between models, OFV was used. While inadequate for comparison of non-nested models (as in the PD analysis) the impact on final model selection would have been negligible given the battery of diagnostic checks appropriately utilised in conjunction with OFV.

- Several aspects relating to quality of data were identified but never fully discussed in the PK-PD report. Of note, the study population included only 60 subjects over a wide age range. There was a narrow dose range and no dose-ranging designs.
- There was substantial missing data requiring imputation of doses and covariates. A large proportion of doses (80%) in the master PK-PD were imputed. Missing serum creatinine values and subject heights were imputed to calculate eGFR for assessment of renal function on asfotase alfa clearance. Consequently the quality of the data was not ideal for supporting important clinical decisions. However, practically, the quality of the data must be balanced with the difficulty of collecting data in young patients with this rare disease (HPP).
- On the basis that an assessment of renal function was not considered in the primary PK-PD analysis because of paucity of data on which to base continuous eGFR calculations, the results of the renal evaluation on CL (companion report) should be considered exploratory in nature and insufficient to conclude a lack of effect of renal impairment on asfotase alfa CL.
- In the PK analysis, approximately 10% of samples were BLQ and were excluded. Perhaps these were pre-dose or suspect samples (BLQ when dosing suggested steady-state)? If not, then a sensitivity analysis should have been performed to confirm no effect on parameter estimation.
- In the PD analyses, outliers were excluded without adequate justification. Given the small numbers of subjects included in the analyses, adequate consideration should have been given to describing responses in all subjects, including those who differed from the norm. Data for 7 subjects (63 observations) taking concomitant vitamin B6 were excluded from the PK-PD analysis for PLP restricting interpretation of the data to subjects not taking concomitant vitamin B6. The effect of concomitant vitamin B6 on PLP response is therefore not known.
- Model evaluation using VPC for PK and PK-PD models were all deemed acceptable without adequate critique of the quality of the models. The PK model described SC data adequately but failed to adequately characterise the IV profile. Since subsequent exposure calculations and PK-PD modelling were conditioned on the final PK parameters and simulations to support dose selection were only relevant to SC dosing, it might have been appropriate to consider exclusion of the IV data from the analysis set for subsequent PK-PD analyses.
- For the PD models, poor fits were obtained for the adult-onset phenotype subset of the exposure-PLP model and the infantile-onset phenotype subset of the exposure-RSS-wrist model, limiting interpretation of the results of these models.
- Simulations using the final PK-PD models showed improvement in responses, deemed clinically meaningful, for biomarker, radiographic and functional efficacy endpoints at doses used in the clinical trials for the phenotypes evaluated.
- A dose of 6 mg/kg per week was selected as the optimal dosing regimen given near maximal responses for all endpoints. PK and response profiles were similar for 1 mg/kg 6 times per week and 2 mg/kg 3 times per week. This dose represents the predominant dose used in the clinical trials.

To summarise, a generally sound PK-PD modelling and simulation analysis was performed using data of less than ideal quality. Interpretation of the results in the context of the data quality was lacking. However, because the analysis findings were consistent with exploratory evaluations of the response data and simulations supported selection of a dose well represented in the tabulated exploratory response data, the dosage regimen selection is justified.

Clinically meaningful responses were obtained for the asfotase alfa doses and phenotypes assessed in the analysis. With respect to safety endpoints, while there was no exposure-response relationship for adverse events, there were a total of 552 treatment-related adverse events, including ectopic calcification, injection/infusion associated reactions and injection site reactions.

In the context of dosage regimen selection, the selected dose was justified on the basis that analysis findings were consistent with exploratory evaluations of the response data and simulations supported selection of a dose well represented in clinical investigations.

Pharmacodynamics

Studies providing pharmacodynamic data

Table 5. Submitted pharmacodynamic studies

PD Topic	Subtopic	Study ID
PD endpoints*	biomarkers, plasma PPI and PLP	ENB-001-08 (FIH)
		ENB-002-08/ ENB-003-08 (extension of ENB-002-08)
		ENB-006-09/ ENB-008-10 (extension of ENB-006-09)
		ENB-010-10
Gender other genetic and Age-Related Differences in PD Response	Effect of gender	Not applicable
	Effect of age of disease onset*	ENB-001-08 (FIH)
		ENB-002-08/ENB-003-08 (extension of ENB-002-08)
		ENB-006-09/ ENB-008-10 (extension of ENB-006-09)
	ENB-010-10	
Population PD and PK PD analyses	Healthy subjects	Not applicable
	Target population ^{§‡}	ENB-001-08 (FIH)
		ENB-002-08 (plus ENB-003-08 extension)
		ENB-006-09 (plus ENB-008-10 extension)
	ENB-010-10	

* Indicates the primary aim of the study. [§] Subjects who would be eligible to receive the drug if approved for the proposed indication. [‡] And adolescents if applicable.

None of the PD studies had deficiencies that excluded their results from consideration.

Evaluator's conclusions on pharmacodynamics

The scientific basis for the mode of action of asfotase alfa was confirmed by the drug induced reductions in key enzyme substrates of alkaline phosphatase including plasma PPI and PLP. The benefit of reduction in key enzyme substrates was evident from the data from HPP patients in which biopsies could be performed (Study ENB-006-09/008-10) that showed drug treatment normalised osteoid volume and thickness in a dose dependent direction indicating improved bone mineralisation.

Dosage selection for the pivotal studies

Dosage selection resulted from a sequential process of preclinical studies in animal models which permitted an in depth study of the PK and PD and Phase I/II dose ranging studies in volunteer adults (4 females and 2 males with HPP and the study in severely affected infants and children \leq 36 months old with onset of HPP signs prior to 6 months of age (ENB-002-08)).

Based on this assessment, a steady state concentration range of approximately 650 to 1,000 U/L, was considered to be therapeutically effective in humans. Notably, in animals receiving less frequent (once every 3 days) SC dosing at 2,071 to 13,390 U/kg of asfotase alfa, skeletal mineralisation defects were also effectively prevented). Early PK modelling of human data from Study ENB-001-08 suggested a dose of asfotase alfa of 1 mg/kg/day SC or 2.3 mg/kg SC 3 x weekly would provide serum asfotase alfa concentrations (activities) of approximately 1,000 Unit/L (**Alexion** report, CPR-000612), the upper range of concentration predicted as therapeutically effective using the Akp2^{-/-} mouse model.

Preclinical studies for human dose selection

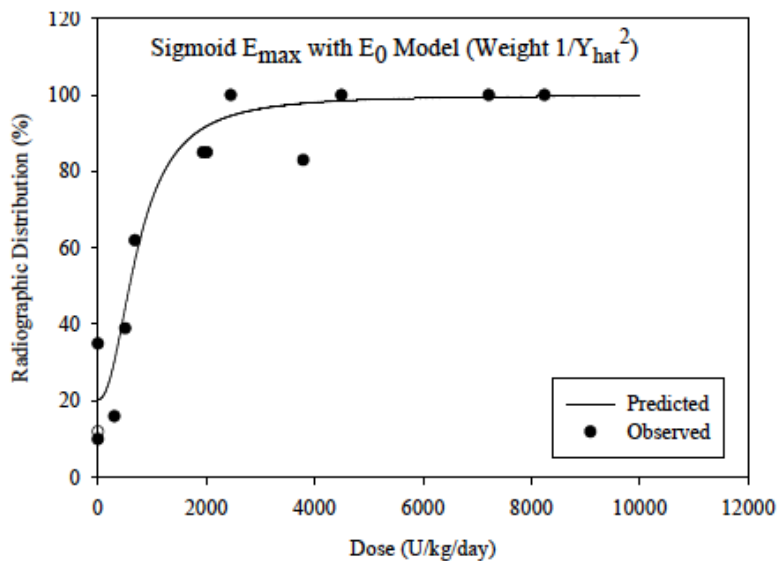
Overall approach

The following preclinical and toxicology data were used to support dose selection for Study ENB-001-08 and subsequently for other HPP studies.

- Pre-clinical efficacy and PK PD modelling studies in Akp2^{-/-} mice
- 4 week GLP intravenous (IV) and 4 week GLP subcutaneous (SC) toxicity studies in juvenile rats
- 4 week GLP IV and 6 month GLP SC toxicity studies in juvenile monkeys.

A dose-response relationship with respect to improvements in the bone mineralisation defects was established using the preclinical pharmacology efficacy studies in Akp2^{-/-} mice. Based on the dose response modelling (sigmoidal E_{max} model), the dose to achieve 85% of response (baseline unadjusted; internal consensus at preclinical level), or an ED85, was 1451 Unit/kg/day.

Figure 2. Dose response relationship of Study ENB-0040 in Akp2^{-/-} mice after daily SC dosing



Study ENB-001-08

Study ENB-001-08 was the first in human study in adults with HPP. The starting dose for this first in human (FIH) trial of asfotase alfa was selected based on sub-chronic (4 week) and chronic (6 month) toxicity studies in juvenile rats and cynomolgus monkeys. These species were selected because of similar protein sequence of tissue nonspecific alkaline phosphatase (TNSALP, the target enzyme) for these species and humans and the mechanism of action and biologic activity of TNSALP (enzymatic activity on several substrates, including PPi and PLP) are species independent. Comparing the findings from the 2 toxicity species evaluated, rat was considered to be the more sensitive species with the No Observed Adverse Event Level (NOAEL) of 30 mg/kg/dose after IV administration.

Based on these toxicology data, regimens consisting of an IV dose of 3 mg/kg followed by 3 weekly SC doses of either 1 or 2 mg/kg were considered to have adequate safety margin and were used in the FIH trial for asfotase alfa in HPP patients. Six adult subjects (4 female and 2 male) were studied for 3 weeks, in two cohorts receiving either 1 mg/kg or 2 mg/kg to assess safety and efficacy, PK, and bioavailability of asfotase alfa.

Study ENB-002-08

Study ENB-002-08 was the first study in severely affected infants and children ≤ 36 months old with onset of HPP signs prior to 6 months of age.

Dose selection for Study ENB-002-08 was developed in a stepwise approach:

- First, data from 6 preclinical pharmacology efficacy studies (see below) in Akp2^{-/-} mice were used to characterise the preclinical target effective dose.
- Then, a steady state concentration range for the preclinical target effective dose was estimated based on the 2 nonclinical mouse studies, a single dose PK study and a multiple repeated dose study. This preclinical steady state concentration range was defined as the anticipated range of efficacious concentrations for human trials.

As the final step, a dose to achieve the anticipated range of efficacious concentrations in humans was simulated using the available clinical asfotase alfa PK data from Study ENB-001-08.

The most commonly used dose of asfotase alfa was 6 mg/kg/week, administered SC in divided doses. The doses used in the clinical studies were chosen based on 2 to 6 week PD nonclinical studies in Akp2^{-/-} mice, toxicology studies in rat and monkey and a clinical safety and tolerability study in adults with HPP (ENB-001-08 CSR). A pooled PK exposure versus response (PK PD) modelling analysis examining multiple parameters was conducted to determine the appropriate dose for patients with paediatric onset HPP. The results of this modelling analysis supported the administration of 6 mg/kg/week asfotase alfa in daily divided doses SC for 6 days per week for the treatment of HPP as the lowest dose that provides near maximal efficacy for most patients.

In studies ENB-001-08 and ENB-002-08, patients were initially administered a dose of asfotase alfa via intravenous infusion for the assessment of pharmacokinetics and safety. In Study ENB-006-09, patients were randomised to a starting dose of either 6 mg/kg/week or 9 mg/kg/week. For all patients who completed Study ENB-006-09, participation in extension Study ENB-008-10 was offered, and the starting dose in the extension Study of 3 mg/kg/week was later increased to 6 mg/kg/week. In Study ENB-009-10, patients were randomised to a starting dose of either 2.1 or 3.5 mg/kg/week, escalating then to 3.5 mg/kg/week, and eventually 6 mg/kg week in the first and second parts of the extension. Dose adjustments were permitted in all studies for changes in body weight and for reasons of safety and efficacy. Dose increases to optimise efficacy were common among patients < 5 years of age. The most commonly used doses were between 6 and 9 mg/kg/week. The highest dose of asfotase alfa used in clinical studies was 28 mg/kg/week (for example 4 mg/kg per dose administered 7 times weekly).

Dose selection summary

The most commonly used dose of asfotase alfa was 6 mg/kg/week, administered SC in divided doses for 6 days per week. The results of the modelling analysis support the administration of 6 mg/kg/week asfotase alfa SC for the treatment of HPP as the lowest dose which provides near maximal efficacy for most patients.

Clinical pharmacology studies of total sialic acid content (TSAC) of the to be marketed product's Chemistry, Marketing and Controls (CMC) specification for TSAC (1.2 to 3.0 mol/mol) and specific activity (620 to 1,250 U/mg) should provide sufficient exposure at 6 mg/kg/week dose to see an efficacious change from baseline for the functional response of the 6 minute walk test (6MWT) consistent to that observed in the clinical trials.¹² This range of exposure is also representative of the exposures associated with efficacy based on other response variables (plasma PPI, plasma PLP, X-ray, RGI-C, Rickets severity scale (RSS), and Bruininks-Oseretsky Test of Motor Proficiency (BOT-2)) across the entire studied HPP patient population.^{13,14}

¹² 6MWT: The original purpose of the six minute walk was to test exercise tolerance in chronic respiratory disease and heart failure. The test has since been used as a performance-based measure of functional exercise capacity in other populations. <http://www.rheumatology.org/I-Am-A/Rheumatologist/Research/Clinician-Researchers/Six-Minute-Walk-Test-SMWT#sthash.L9fGHH2l.dpuf>

¹³ Ricketts Severity Scale. 10 point Radiographic scoring method for the assessment of the severity of nutritional rickets.

¹⁴ The Bruininks-Oseretsky Test of Motor Proficiency (Bruininks, 1978) is a standardized, norm-referenced measure used by physical therapists and occupational therapists in clinic and school practice settings. This test recently was revised and published as the Bruininks-Oseretsky Test of Motor Proficiency, Second Edition (BOT-2; Bruininks & Bruininks, 2005). The BOT-2 is an individually administered measure of fine and gross motor skills of children and youth, 4 through 21 years of age.

Efficacy

Studies providing efficacy data

Pivotal 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).

The sponsor initiated 6 efficacy and safety studies of asfotase alfa, including 4 original and 2 extension studies, in patients of all ages and in paediatric- and adult-onset HPP subgroups.

- Pivotal open label clinical Study ENB-002-08 and its extension, ENB-003-08 (ongoing), enrolled paediatric onset patients ≤ 3 years of age with onset of symptoms < 6 months of age (infantile onset subgroup)
- Pivotal open label clinical Study ENB-010-10 (ongoing and open for enrolment) enrolled paediatric onset patients ≤ 5 years of age with onset of symptoms < 6 months of age (infantile onset subgroup)
- Pivotal open label clinical Study ENB-006-09 and its extension ENB-008-10 (ongoing), enrolled paediatric onset patients 5 through 12 years of age
- A controlled, open label, supportive clinical Study ENB-009-10 (ongoing), enrolled adolescent and adult patients (13 to 66 years of age) regardless of age of symptom onset (paediatric and adult onset).

In addition to these interventional studies, a global, retrospective, epidemiological study (ENB-011-010) examining the natural history of patients with perinatal/infantile onset HPP has been completed. Historical control data from this study were used for comparison to survival and invasive ventilator-free survival results obtained in asfotase alfa treated patients.

All asfotase alfa studies were open label. Given the very high unmet medical need, the serious morbidity and mortality risk, the potential for irrevocable harm, and the absence of any alternative disease modifying treatments, no placebo or active comparator controls were used in the studies in infants and children. Nevertheless, historical controls were used for evaluating selected endpoints in Studies ENB-002-08/ENB-003-08, ENB-010-10, and ENB-006-09/ENB-008-10.

Study ENB-011-10 was a retrospective, non-interventional, epidemiological Study of the natural history of patients with severe perinatal/infantile onset HPP. Data was abstracted from medical records of qualifying children with perinatal/infantile HPP up to 5 years of age and served as the non-concurrent control group for survival analyses in perinatal/infantile HPP patients in Studies ENB-002-08/ENB-003-08 and ENB-010-10.

Study ENB-006-09/ENB-008-10 included historical control patients who had skeletal radiographic data available for the determination of rickets severity scoring. Study ENB-009-10, which was conducted in older patients, included a parallel untreated control group for the first 24 weeks. At 24 weeks, patients in the control group initiated asfotase alfa treatment and continued in the study.

In depth analysis of individual studies and pooled analyses of all used studies are available in Attachment 2.

Evaluator's conclusions on efficacy

Asfotase alfa is a particularly effective treatment to reverse the biochemical abnormalities arising from TNSAP deficiency, showing rapid correction of the abnormalities in PPI and calcium metabolism and the mineralisation defects in the skeleton of the growing child.

Asfotase alfa also demonstrated a favourable benefit profile in the treatment of patients over the age of thirteen years with non perinatally lethal paediatric onset HPP. Asfotase alfa lowered TNSALP substrates, PPI and PLP, consistent with its intended biological activity. In addition, treated adolescent and adult patients showed small improvements in histomorphometric parameters (osteoid volume, percentage osteoid thickness, and mineralisation lag time) after 48 weeks of exposure compared to the untreated control group. While there were no clear differences between treated and control patients in dual energy X ray absorptiometry (DEXA) results, treated patients did show modest, but statistically significant improvements from baseline in lumbar spine bone mineral density (BMD) after 24, 48, and 96 weeks of asfotase alfa exposure. Across the population studied, this biologic effect was associated with a trend toward improvement in strength, ambulation, and physical function. More importantly, a subset of patients with significant HPP disease burden at baseline experienced a clinically significant response, being able to come off of assistive devices for ambulation. Consequently, they markedly increased their functional capacity in a manner directly relevant to ambulation and the ability to conduct activities of daily living.

In human studies, not all patients have the profound deficiency of alkaline asfotase which is characteristic of patients with homozygous null gene mutations (contrast with the *Akp2*^{-/-} mouse). Accordingly, there is a wide spectrum of severity grading from historical studies ranging from infants with prenatal onset and perinatally lethal HPP through to infants with perinatal presentation but who are nevertheless ventilator independent. The spectrum continues to include patients with infantile onset, who were not ventilator dependent, and patients with juvenile and adult onset, who present with a broad range of severities. The definitions have been somewhat arbitrary but have served bone and mineral clinicians for several decades in decision making about management. The dramatic improvement in radiographic findings in the chest and growing centres reported in the clinical Study ENB-0040 which formed the report in the *New England Journal of Medicine* in 2012 shows an extreme severity a patient that would have been regarded as perinatally lethal.¹⁵ In the study report 5 out of 11 patients were diagnosed as perinatal onset and 9 out of 11 patients had significant respiratory failure at baseline.

In the pivotal study reports, there are a number of patients who show rapid healing of mineralisation defects after 24 weeks of therapy. For example in Study ENB-006-09, one subject illustrates in the radiographic studies, a marked reversal of the mineralisation defects in the growing centres (Figure 3). It is evident that the treatment for this patient with the diagnosis of juvenile HPP, shows healing of dysplastic lesions in wrist bones. The efficacy is mirrored in the progressive improvement in the functional assessment by the parent reported of this child paediatric outcomes data collected instrument (PODCI).

¹⁵ Whyte et al. Enzyme-Replacement Therapy in Life-Threatening Hypophosphatasia. *N Engl J Med* 2012; 366:904-913.

Figure 3. X ray of left wrist and knee film (baseline) (left) compared with film at 6 months (centre) and 36 months (right)



Asfotase alfa is, with some qualifications (see below), an effective therapy for skeletal involvement of young patients with HPP. The evidence for clinical efficacy in selected patients is very strong. A regimen of 1 mg/kg 6 times per week or 2 mg/kg 3 times per week, normalises mineral chemistry, increases whole body mineral content and results in radiographic evidence of healing rickets. This is true across the age groups from the perinatal period (those surviving the newborn period) through infantile and juvenile presentations.

Qualifications on the selection of patients and efficacy

Validity of the comparator case study of severe perinatal/infantile onset HPP

The comparator study has a number of limitations. It is not strictly an 'epidemiologic study' despite the title. It is a voluntary notification cohort study which has cases reported from multiple centres in different countries. The report of the study is more a case study of subjects from multiple sites from around the world and their characteristics. How representative they are of paediatric onset HPP in various regions of the world is questionable. The cohort of 15 Canadian patients (all of Mennonite origin with a common mutation) with perinatal HPP, appears to be a homogeneous cohort in which HPP was uniformly fatal and all patients died by 9 months of age. Only 1 Asian patient was included in the comparator study although there is known to be common mutations in East Asian subjects and possibly a higher frequency of HPP in East Asian populations. Thus, this historic cohort is unlikely to be unrepresentative even in North America.

Furthermore, the limitations of this multicentre, multinational retrospective chart review reflect a restricted physician base and did not include birth defect registers, skeletal dysplasias registers in centres other than the International Skeletal Dysplasia Register in Los Angeles and skeletal dysplasia patient management services patients in other centres around the world.

The studies which have been undertaken encompass a small number of patients in each of the pivotal studies and some these patients have also been included in Study ENB-011-10 which was a retrospective, non-interventional, 'epidemiological' study of the natural history with patients with severe perinatal/infantile onset HPP. ENB-011-10 is the study which is put forward as the comparator for all the other studies. It too is not strictly an 'epidemiologic study' but a case finding study from a limited number of sites in United States, Canada (again only Mennonite patients), Germany, Australia and single patients from Spain, Switzerland, Taiwan and other European or non-European sites. It is not analysed by radiographic severity grading at diagnosis nor by mutation and predicted phenotype extrapolated from mutation type and known structure function correlations. Mutation analysis was only determined for 35.4% of cases in the ENB-011-10 case series. It is even more disconcerting that 10 out of 48 (21%) cases included did not have radiographic confirmation.

The studies reported in ENB-011-10 encompass a small number of subjects with diverse disease severities. The largest group of patients is from a perinatal/infantile onset with age of onset under 5 years of age. These patients are survivors of a large group of infants born but in whom the mortality is exceedingly high. In this case series, of those in whom there was documentation of prenatal evidence of HPP 14 out of 29 (48%) cases were documented as having signs of prenatal HPP. It is not made clear in the conclusions of the study that these infants would almost all have had the diagnosis of perinatally lethal HPP in whom the mortality is exceedingly high. Not only would they have rarely survived for treatment, these infants would have needed invasive ventilatory support. In addition these infants were at high risk for Vitamin B6 responsive seizures, a group with a virtually 100% probability of death with none (0 out of 11) surviving at > 3 to 5 years and often marked disturbance of mineral metabolism.

In the prospective asfotase alfa interventional studies, craniosynostosis developed in 11.3% of subjects. The Comparator group (ENB-011-10) had a frequency of craniosynostosis in the Deceased group of 52.6% and the Alive group of 75%, but was not strictly comparable given a high frequency of cases ascertained with severe even prenatal onset disease.

Perinatal onset

The perinatal group includes a sub group of patients who have prenatal onset with marked skeletal abnormalities. Radiographic studies in those patients show missing skeletal elements, skeletal deformity, extremely severe mineralisation defects and retarded in utero growth. There is respiratory distress at birth and the majority of these babies would not survive without invasive chronic ventilation. There is good evidence that the same effect seen across the genetic skeletal dysplasias on the maturation of lungs as a result of poor growth of the chest as well as the muscular weakness which accompanies HPP, results in an immaturity in the development of the broncho alveolar system.

If these infants are sustained on chronic ventilation, these pathological lung features cannot always be reversed despite restoration of bone strength and development. Those infants who have persistent pulmonary immaturity may require tracheostomy for long term airway management. This sub group may have pulmonary outcomes similar to those described by Langston and Bishop.¹⁶ (also see Clinical Efficacy section in Attachment 2 for Strensiq Asfotase alfa (rch)). On the other hand, there are infants with a perinatal presentation who are somewhat milder and may be ascertained because of their skeletal features or seizures in the first 2 years of life. While there is continuum in the severity of these skeletal phenotypic effects, there is clinical discontinuity because of the known historic outcomes prior to the development of an innovative therapy such as asfotase alfa.

¹⁶ Langston C and Bishop M. Diffuse Lung Disease in Infancy: A Proposed Classification Applied to 259 Diagnostic Biopsies. *Paediatric and Developmental Pathology* 2009; 12: 421-437.

Non perinatally lethal infantile and juvenile patients of ≤ 18 years of age

These children with HPP have skeletal changes of variable severity. The evidence for clinical efficacy is very strong in this group of patients. A regimen of 1 mg/kg 6 times per week or 2 mg/kg 3 times per week, normalises mineral chemistry, increases whole body mineral content and results in radiographic evidence of healing rickets. A sub group of children have very mild changes and do not appear to be included in these study groups. As previously noted this group includes a relatively large group of children in Australia who have odontohypophosphatasia who have no evidence of generalised skeletal disease assessed with skeletal radiology and bone densitometry yet have premature loss of deciduous teeth. At present it is not proposed that this latter group will need therapy. It is important to note that the 'long term' natural history of patients with odontohypophosphatasia is not known. In particular, it is not known whether these patients (all children) will develop symptomatic adult onset osteomalacia.

Adult patients

The growing centres of the long bones are closed at puberty and in adult life. These patients have persistent osteomalacia and propensity to pain and debilitating stress fractures. The case definition of paediatric onset HPP is not precise.

Asfotase alfa in the adolescent and adult case series with HPP (ENB-009-10) demonstrated a favourable benefit profile series. In this trial, patients were randomised to one of two dosage regimens (2.1 or 3.5 mg/kg/week) for the first 24 weeks only. Following the primary treatment period, the dose was increased to the 6 mg/kg/week. Most functional outcomes were obtained after the 24 week period on the 6 mg/kg/week dosing. This observation foreshadows the question about asfotase alfa authorisation and whether a firm recommendation can be made for an adult dosage regimen.

Should 'long term' be included in the indication?

When a firm clinical diagnosis with the full range of signs and symptoms and radiographic findings is made in childhood, it is inevitable that the disorder will have 'long term' clinical consequences. Once patients reach adult life, it is not clear whether therapy should be ceased. Nor is it clear what the indications will be for continuing therapy and what the dose and frequency of administration of asfotase alfa should be. It is reported that some patients have remissions of their symptoms and signs in young adult life but the usual course historically is one of fluctuating bone pain and episodic stress fractures.¹⁷ Historically younger and older adults prior to asfotase alfa therapy have required complex orthopaedic surgeries and have required protracted rehabilitation. The population prevalence in post pubertal subjects is unknown.

Therapy commenced at any stage of childhood will need to be reviewed when patients reach adult life and perhaps be continued for life. There is very little documentation and evaluation of asfotase alfa therapy, its dose, frequency and monitoring requirements in subjects over the age of 18 and insufficient data to continue therapy without review of the need for ongoing therapy indications. Study ENB-009-10 would suggest that a regimen clearly needs to be derived from the available studies. As with other biopharmaceuticals introduced for disorders treated from childhood, guidelines are needed for a change in dosage at puberty if paediatric dosing can be reduce which is indicated as the trials undertaken by the sponsor indicate the dosage regimens 2.1 mg/kg/week or 3.5 mg/kg/week were both efficacious.

Given the different genetic structure of world populations, the potential for endogamy in some populations and the variability in mutations and phenotypes as listed in the

¹⁷ Whyte et al. Enzyme-Replacement Therapy in Life-Threatening Hypophosphatasia. *N Engl J Med* 2012; 366:904-913.

international TNSAP register it will be important that centres of expertise offering clinical management for patients with HPP, establish their own national or state wide databases of the patterns of the mortality, morbidity and natural history of these disorders.¹⁸ With some assistance from the organisers of a proposed post marketing (PM) surveillance program as outlined (ALX-HPP -501), it would be possible for local state based registers to harmonise with this PM surveillance database (included in proposed Risk Management Plan (RMP)).

Evidence for the age ranges of patients

Perinatal age range

This age range encompasses children with HPP with perinatally lethal HPP who almost universally will have underdevelopment of the lungs of prenatal onset and subsequent failure to wean from invasive ventilation because of irreversible lung damage. It will be important to establish comprehensive assessment and recommended exclusion criteria where hypoplasia of the lungs is irreversible and the prospect for weaning to invasive ventilator free ventilation is achievable.

Transition from juvenile to adult pharmaceutical responsiveness

As with many therapies primarily trialled in affected children particularly those where the therapy may be life extending, care will need to be taken to determine the effective therapeutic dose post puberty. ENB-009-10 had a study design which was case controlled and did not have a major bias. Doses of 2.1 mg/kg/weekly and 3.5 mg/kg weekly in 7 SC divided doses gave a favourable response. The evaluator recommended that the commencing adult dose be 2.1 mg/kg weekly with an option to increase to 3.5 mg/kg weekly if an increase is needed.

Adults with paediatric onset of HPP

Special consideration must be given to indications for treatment of adults given that inclusion/exclusion criteria for adults will need to be quite specific. Study ENB-009-10 included dosing studies to determine minimum effective doses and confirmed that this may be lower for adults compared to the paediatric dose. ENB-009-10 had a study design which was case controlled and did not have a major bias. Doses of 2.1 mg/kg/weekly and 3.5 mg/kg weekly in 7 SC divided doses gave a favourable response.

In adults without paediatric onset HPP but clinically proven to have HPP and osteomalacia, there will be the temptation to use asfotase alfa with adults with symptoms and complications of osteomalacia but with a questionable paediatric history of involvement. Future trials in adults with symptomatic osteomalacia need to be undertaken but commencing at the lower 2.1 mg/kg weekly dose.

Safety

Studies providing safety data

The following studies provided evaluable safety data:

- ENB-001-08
- ENB-002-08/ENB-003-08
- ENB-006-09/ENB-008-10

¹⁸ Mornet E. The Tissue Nonspecific Alkaline Phosphatase Gene Mutations Database. Laboratoire SESEP. Last update: August 27, 2013. http://www.sesep.uversusq.fr/03_hypo_mutations.php.

- ENB-009-10
- ENB-010-10.

Pivotal efficacy studies

In the pivotal efficacy studies, the following safety data were collected:

- Spontaneously reported adverse events (AEs)
- Infusion/injection associated reactions (IARs)
- Laboratory assessments (chemistry, haematology, urinalysis, calcium and phosphorus, and 25(OH) vitamin D)
- Vital signs
- Physical examinations (including fundoscopic examinations)
- 12 lead electrocardiograms (ECGs)
- Clinical laboratory tests
- Anti asfotase alfa antibody testing were assessed for changes from baseline.

Pivotal studies that assessed safety as a primary outcome

The following were studies that assessed safety as a primary outcome:

- ENB-001-08
- ENB-002-08/ENB-003-08
- ENB-006-09/ENB-008-10
- ENB-009-10
- ENB-010-10.

Methodology for evaluation of asfotase alfa safety and tolerability were comparable across the clinical trials. As part of continuous AE assessment, 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 potential ectopic calcifications as these are known to be influenced by disturbances in calcium homeostasis associated with HPP. Considering that asfotase alfa is an exogenous protein, monitoring for the development of anti asfotase alfa antibodies and neutralising antibodies was also routinely performed. Other common safety assessments performed in clinical trials of asfotase alfa included physical examinations, vital signs, and routine clinical laboratory testing (haematology, blood chemistries, and urinalysis). Any clinically significant changes from baseline in safety assessments, including worsening of pre-existing conditions(s) from baseline, were to be reported as AEs.

For further details of the evaluation of the safety data please see Attachment 2.

Adverse events of particular interest

Adverse events of special interest were identified based on the mechanism of action of asfotase alfa, the natural history of HPP, and review of the safety data; additional safety analyses for these events were performed to assist in characterisation of the safety profile of asfotase alfa.

Predefined Adverse Events of Special Interest (AESIs) were injection-associated reactions (IARs) and injection site reactions (ISRs) lipohypertrophy (as a subset of ISRs), ectopic calcification, pancreatitis, pneumonia/respiratory distress, chronic hepatitis, conductive deafness, and craniosynostosis.

Patient exposure

The integrated safety analyses (n = 71) included paediatric onset HPP patients (68 of 71 (95.8%) patients), 2 patients with adult onset HPP and 1 patient with undetermined disease onset. For this reason, data summaries and presentations are focused on the overall population. Safety observations relevant to infantile onset and juvenile onset subgroups of paediatric onset HPP patients are provided, where appropriate.

A summary of patient exposure to asfotase alfa in the pooled safety set overall and by age at disease onset is provided in Table 6 (see below). Exposure to asfotase alfa ranged from 0.1 to 260.9 weeks. Median exposure for all patients in the Pooled Safety Set was 2.53 patient years (PYs). A majority of patients (n = 42) received at least 120 weeks of treatment, with 29 patients receiving ≥ 144 weeks of treatment. As HPP is a rare disease and the ability to enrol and treat these patients in clinical studies is challenging, data from patients with > 3 years of exposure are limited.

Table 6. Summary of exposure to asfotase alfa in the pooled safety set, overall and age at disease onset

Variable Statistic/ Category	Pediatric Onset (N=68)			Unknown Onset (N=1)	All Patients (N=71)
	Perinatal/ Infantile Onset (N=48)	Juvenile Onset (N=20)	Adult Onset (N=2)		
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

Table 7 below provides a summary of the PYs of asfotase alfa exposure by total weekly dose. There have been a total of 169.17 PYs of asfotase alfa exposure, with 97.50 PYs of exposure in patients who received weekly doses ≥ 6 mg/kg and 155.64 PYs of exposure in patients who have received weekly doses < 9 mg/kg. Exposure at higher weekly doses has been limited, with approximately 13.5 PYs exposure at total weekly doses ≥ 9 mg/kg, and < 6 PYs exposure at total weekly doses ≥ 12 mg/kg. The majority of the exposure experience has been at total weekly doses ≥ 3 mg/kg to < 9 mg/kg per week (147.40 PYs);

this was largely driven by the design of the clinical studies wherein patients initially received lower doses (for example, 3 mg/kg/week) over the duration of a 24 week primary treatment period followed by an increase in total weekly dose (for example, 6 mg/kg/week).

Table 7. Patient years of exposure to asfotase alfa by weekly dose, pooled safety set, overall and 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](#)

Adverse events

All AEs (irrespective of relationship to study treatment)

Pivotal studies

All 71 patients in the pooled safety set experienced at least 1 TEAE; 2,706 TEAEs were reported through encompassing the subjects in the pivotal studies analysis cut off dates for the integrated analyses. The majority of TEAEs (1,800 out of 2,706 events reported in 70 out of 71 (98.6%) patients) were considered by the investigator to be not related to asfotase alfa, and the majority of TEAEs (2050 out of 2706 events reported in 69 out of 71 (97.2%) patients) were mild in intensity. There were 6 TEAEs in 3 patients that led to discontinuation of treatment and Study withdrawal. Almost half (1,314 out of 2,706) of the TEAEs reported occurred within the first 24 weeks of treatment, with all (100%) patients experiencing at least 1 TEAE during that time period. Approximately one third of all TEAEs were ISRs or IARs; these events accounted for the majority of TEAEs that were considered to be related to asfotase alfa (by definition, ISRs and IARs were considered to be related to asfotase alfa).

More TEAEs (1,848 out of 2,706 events) were reported by patients in the infantile onset HPP subgroup compared with patients in the juvenile onset HPP subgroup (752 out of 2,706 events) and patients with adult onset HPP (26 out of 2,706 events); this was not remarkable since patients in the infantile onset HPP subgroup (n = 48) accounted for more than half the pooled safety set (n = 71) and because the manifestations of HPP tend to be more severe in those patients. The majority of TEAEs (1,371 out of 1,848 events) in patients in the infantile onset HPP subgroup were considered by the investigator to be not related to asfotase alfa, whereas approximately half (347 out of 752) of the events in patients in the juvenile onset HPP subgroup and approximately one third (9 out of 26) of the events in patients with adult onset HPP were considered by the investigator to be not related to asfotase alfa treatment. Of the related TEAEs, 449 out of 477 events in patients

in the infantile onset HPP subgroup, 385 out of 405 events in patients in the juvenile onset HPP subgroup, and 15 out of 17 events in patients with adult onset HPP were reported as ISRs or IARs. Proportionally more patients in the infantile onset HPP subgroup (50.0%) experienced severe TEAEs compared to patients in the juvenile onset HPP subgroup (20.0%) and patients with adult onset HPP (0%). All 3 of the patients who experienced TEAEs that led to treatment discontinuation and study withdrawal were in the infantile onset HPP subgroup. In patients with infantile, juvenile, and adult onset HPP, 44.6%, 56.4%, and 46.2% of the TEAEs, respectively, were experienced by patients during the first 24 weeks of treatment (defined as early onset events).

Treatment related adverse events (adverse drug reactions)

There were 906 related TEAEs experienced by 60 (84.5%) patients in the pooled safety set, with an overall incidence rate of 535.0 events/100 PYs asfotase alfa exposure, that were considered by the investigator to be related to asfotase alfa treatment. The only SOC in which $\geq 50\%$ of patients reported related TEAEs was general disorders and administration site conditions (77.5%); the 764 related events reported within this SOC accounted for nearly 85% of all related TEAEs in the pooled safety set. Given that the majority of ISRs and IARs were coded to preferred terms within this SOC and that ISRs and IARs were, by definition, considered to be related to asfotase alfa treatment. Other SOCs in which $\geq 5\%$ of patients in the pooled safety set reported related TEAEs included:

- Skin and subcutaneous tissue disorders (22.5%)
- Eye disorders (19.7%)
- Gastrointestinal disorders (9.9%)
- Musculoskeletal and connective tissue disorders (8.5%)
- Injury, poisoning and procedural complications; vascular disorders; and renal and urinary disorders (5.6%, each)

Related TEAEs (preferred terms) reported by $\geq 15\%$ of patients were:

- Injection site erythema (52.1%)
- Injection site discolouration (23.9%)
- Injection site pain (22.5%)
- Injection site pruritus (19.7%)
- Injection site macule and injection site swelling (15.5% each).

Preferred terms with an incidence rate ≥ 15 events/100 PYs of exposure to asfotase alfa included:

- Injection site erythema (159.4 events/100 PYs)
- Injection site discolouration (47.2 events/100 PYs)
- Injection site macule (44.3 events/100 PYs)
- Injection site pain (30.1 events/100 PYs)
- Injection site pruritus (27.2 events/100 PYs)
- Injection site reaction (23.6 events/100 PYs)
- Injection site induration (23.0 events/100 PYs)
- Injection site swelling (20.1 events/100 PYs)
- Injection site hypertrophy (17.1 events/100 PYs)

- Erythema (16.5 events/100 PYs)

More TEAEs (1,848 out of 2,706 events) were reported by patients in the infantile onset HPP subgroup compared with patients in the juvenile onset HPP subgroup (752 out of 2,706 events) and patients with adult onset HPP (26 out of 2,706 events); this was not remarkable since patients in the infantile onset HPP subgroup (n = 48) accounted for more than half the pooled safety set (n = 71) and because the manifestations of HPP tend to be more severe in those patients. The majority of TEAEs (1,371 out of 1,848 events) in patients in the infantile onset HPP subgroup were considered by the investigator to be not related to asfotase alfa, whereas approximately half (347 out of 752) of the events in patients in the juvenile onset HPP subgroup and approximately one third (9 out of 26) of the events in patients with adult onset HPP were considered by the investigator to be not related to asfotase alfa treatment. Of the related TEAEs, 449 out of 477 events in patients in the infantile onset HPP subgroup, 385 out of 405 events in patients in the juvenile onset HPP subgroup, and 15 out of 17 events in patients with adult onset HPP were reported as ISRs or IARs.

Proportionally more patients in the infantile onset HPP subgroup (50.0%) experienced severe TEAEs compared to patients in the juvenile onset HPP subgroup (20.0%) and patients with adult onset HPP (0%). All 3 of the patients who experienced TEAEs that led to treatment discontinuation and study withdrawal were in the infantile onset HPP subgroup. In patients with infantile, juvenile, and adult onset HPP, 44.6%, 56.4%, and 46.2% of the TEAEs, respectively, were experienced by patients during the first 24 weeks of treatment (defined as early onset events).

The majority of nonfatal SAEs reported (172/183 events) were experienced by 27 (56.3%) patients in the infantile onset HPP subgroup; only 11 nonfatal SAEs were experienced by 5 (25.0%) patients in the juvenile onset HPP subgroup, and no SAEs were experienced by patients with adult onset HPP. All but 5 of the nonfatal SAEs experienced by patients in the infantile onset HPP subgroup were considered by the Investigator to be not related to asfotase alfa treatment, and almost half (5 out of 11) of the nonfatal SAEs experienced by patients in the juvenile-onset HPP subgroup were considered to be not related.

Consistent with the analysis of all in the pooled safety set TEAEs, proportionally more patients who received a majority of their weekly dosing at ≥ 6 mg/kg (93.3%) experienced nonfatal SAEs compared with those who received the majority of their total weekly dosing at < 6 mg/kg (32.7%). The preferred terms for which $\geq 10\%$ of patients who received a majority of their total weekly dosing at ≥ 6 mg/kg experienced nonfatal SAEs compared with patients who received a majority of their total weekly dosing at < 6 mg/kg were respiratory disorder, pneumothorax, respiratory distress, pneumonia, upper respiratory tract infection, bronchiolitis, viral infection, craniosynostosis, pyrexia, irritability, feeding tube complication, food intolerance, and feeding disorder of infancy or early childhood.

Deaths and other serious adverse events

All treatment emergent deaths reported during the clinical studies were in patients in the infantile onset HPP subgroup.

In the pooled safety set, total of 183 nonfatal SAEs were reported by 32 (45.1%) patients; all but 11 of these events (in 4 patients) were considered by the investigator to be not related to asfotase alfa. One nonfatal SAE led to treatment discontinuation and study withdrawal. No ISRs were reported as SAEs. Five deaths were reported in the clinical database, 4 deaths were considered to be treatment emergent and included in the integrated analyses; one death was reported prior to the first dose of asfotase alfa.

All deaths occurred in patients who were < 1 year of age at enrolment, were in the infantile onset HPP subgroup, and had 1 or more prognostic factors for poor outcome (that

is, rachitic chest deformity, respiratory compromise, and/or vitamin B6 responsive seizures). Three patients died within approximately 8 months of treatment initiation; 1 of these patients died within approximately 3 weeks of treatment initiation. Two patients received an asfotase alfa dose > 6 mg/kg/week for disease related management; 1 patient received a dose of 14 mg/kg/week at initiation of treatment due to general disease severity at enrolment, and 1 patient had a dose increase to 9 mg/kg/week for hypercalcaemia. Events preceding death were generally consistent with complications of underlying infantile onset HPP and assessed by the investigator as being unrelated to asfotase alfa; 1 death due to pneumonia was assessed by the investigator as being possibly related to asfotase alfa.

There were 183 nonfatal SAEs experienced by 32 (45.1%) patients in the pooled safety set, with an overall incidence rate of 108.1 events/100 PYs asfotase alfa exposure. The SOCs in which $\geq 10\%$ of patients reported nonfatal SAEs were:

- Respiratory, thoracic and mediastinal disorders (22.5%)
- Infections and infestations (21.1%)
- Nervous system disorders (12.7%)
- Investigations and congenital, familial and genetic disorders (11.3%)

Nonfatal SAEs (preferred terms) reported by > 5% of patients in the pooled safety set included:

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

The preferred terms with incidence rates ≥ 3 events/100 PYs exposure to asfotase alfa included:

- Craniosynostosis (5.3 events/100 PYs)
- Pneumonia (4.7 events/100 PYs)
- Dyspnoea (4.1 events/100 PYs)
- Respiratory disorder and feeding tube complication (3.5 events/100 PYs, each)

Table 8. Treatment emergent non-fatal serious adverse events reported in ≥ 2 patients in the pooled safety set, overall and by age of onset

MedDRA SOC Preferred Term	Pediatric Onset (N=68), n (%)		Adult Onset (N=2) n (%)	Unknown Onset (N=1) n (%)	All Patients (N=71) n (%)
	Perinatal/ Infantile Onset (N=48)	Juvenile Onset (N=20)			
Any Nonfatal Serious Adverse Event	27 (56.3)	5 (25.0)	0	0	32 (45.1)
Respiratory, Thoracic and Mediastinal Disorders	16 (33.3)	0	0	0	16 (22.5)
Respiratory disorder	4 (8.3)	0	0	0	4 (5.6)
Hypoxia	2 (4.2)	0	0	0	2 (2.8)
Obstructive airways disorder	2 (4.2)	0	0	0	2 (2.8)
Pneumothorax	2 (4.2)	0	0	0	2 (2.8)
Respiratory distress	2 (4.2)	0	0	0	2 (2.8)
Respiratory failure	2 (4.2)	0	0	0	2 (2.8)
Restrictive pulmonary disease	2 (4.2)	0	0	0	2 (2.8)
Infections and Infestations	15 (31.3)	0	0	0	15 (21.1)
Pneumonia	5 (10.4)	0	0	0	5 (7.0)
Upper respiratory tract infection	3 (6.3)	0	0	0	3 (4.2)
Bronchiolitis	2 (4.2)	0	0	0	2 (2.8)
Sepsis	2 (4.2)	0	0	0	2 (2.8)
Viral infection	2 (4.2)	0	0	0	2 (2.8)
Nervous System Disorders	7 (14.6)	2 (10.0)	0	0	9 (12.7)
Convulsion	2 (4.2)	1 (5.0)	0	0	3 (4.2)
Intracranial pressure increased	2 (4.2)	0	0	0	2 (2.8)
Congenital, Familial and Genetic Disorders	8 (16.7)	0	0	0	8 (11.3)
Craniosynostosis	8 (16.7)	0	0	0	8 (11.3)
Investigations	8 (16.7)	0	0	0	8 (11.3)
CSF pressure	2 (4.2)	0	0	0	2 (2.8)
Oxygen saturation decreased	2 (4.2)	0	0	0	2 (2.8)
General Disorders and Administration Site Conditions	6 (12.5)	1 (5.0)	0	0	7 (9.9)
Pyrexia	3 (6.3)	0	0	0	3 (4.2)
Chills	1 (2.1)	1 (5.0)	0	0	2 (2.8)
Device dislocation	2 (4.2)	0	0	0	2 (2.8)
Irritability	2 (4.2)	0	0	0	2 (2.8)
Injury, Poisoning and Procedural Complications	6 (12.5)	0	0	0	6 (8.5)
Feeding tube complication	2 (4.2)	0	0	0	2 (2.8)
Metabolism and Nutrition Disorders	6 (12.5)	0	0	0	6 (8.5)
Food intolerance	3 (6.3)	0	0	0	3 (4.2)
Feeding disorder of infancy or early childhood	2 (4.2)	0	0	0	2 (2.8)
Musculoskeletal and Connective Tissue Disorders	2 (4.2)	2 (10.0)	0	0	4 (5.6)
Pain in extremity	0	2 (10.0)	0	0	2 (2.8)

MedDRA SOC Preferred Term	Pediatric Onset (N=68), n (%)		Adult Onset (N=2) n (%)	Unknown Onset (N=1) n (%)	All Patients (N=71) n (%)
	Perinatal/ Infantile Onset (N=48)	Juvenile Onset (N=20)			
Surgical and Medical Procedures	4 (8.3)	0	0	0	4 (5.6)
Tracheostomy tube removal	2 (4.2)	0	0	0	2 (2.8)
Vascular Disorders	2 (4.2)	0	0	0	2 (2.8)
Deep vein thrombosis	2 (4.2)	0	0	0	2 (2.8)

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.

An SOC was included only if a preferred term within the SOC was reported in ≥ 2 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 1.3.1.1.1.5](#)

Discontinuation due to AEs

Three patients experienced TEAEs that led to discontinuation of study drug; all 3 patients were in the infantile onset HPP subgroup. Two patients came from ENB-002-08/ENB-003-08 and one from ENB-010-10.

A fourth patient (who experienced pneumonia) was shown as having discontinued study drug; however, this patient subsequently resumed dosing. Due to the design of the case report form for this early study, it was not possible for the investigator to describe that the patient experienced an interruption in dosing except in the notes.

Laboratory tests

Other clinical chemistry

A summary of TEAEs potentially associated with abnormal clinical chemistry values noted for patients in the Pooled Safety Set overall and by age at disease onset is provided in Table 9 below.

Table 9. Treatment emergent adverse events associated with abnormal clinical chemistry laboratory results in patients in the pooled safety set, overall and by age at disease onset

MedDRA Preferred Term	Pediatric Onset (N=68), n (%)		Adult Onset (N=2) n (%)	Unknown Onset (N=1) n (%)	All Patients (N=71) n (%)
	Perinatal/Infantile Onset (N=48)	Juvenile Onset (N=20)			
Alanine aminotransferase increased	4 (8.3)	0	0	0	4 (5.6)
Aspartate aminotransferase increased	3 (6.3)	0	0	0	3 (4.2)
Urine calcium/creatinine ratio increased	3 (6.3)	0	0	0	3 (4.2)
Hyperphosphataemia	2 (4.2)	0	0	0	2 (2.8)
Hypokalaemia	2 (4.2)	0	0	0	2 (2.8)
Hyponatraemia	2 (4.2)	0	0	0	2 (2.8)
Vitamin D decreased	2 (4.2)	0	0	0	2 (2.8)
Vitamin D increased	1 (2.1)	1 (5.0)	0	0	2 (2.8)
Blood 1,25-dihydroxycholecalciferol decreased	0	1 (5.0)	0	0	1 (1.4)
Blood 25-dihydroxycholecalciferol decreased	1 (2.1)	0	0	0	1 (1.4)
Blood 25-dihydroxycholecalciferol increased	0	1 (5.0)	0	0	1 (1.4)
Blood potassium decreased	1 (2.1)	0	0	0	1 (1.4)
Blood urea increased	1 (2.1) ^a	0	0	0	1 (1.4)
Blood sodium decreased	1 (2.1)	0	0	0	1 (1.4)
Gamma-glutamyltransferase increased	1 (2.1)	0	0	0	1 (1.4)
Hepatic enzyme increased	1 (2.1) ^a	0	0	0	1 (1.4)
Metabolic acidosis	1 (2.1)	0	0	0	1 (1.4)
Metabolic alkalosis	1 (2.1)	0	0	0	1 (1.4)
Hypophosphataemia	1 (2.1)	0	0	0	1 (1.4)
Hypoglycaemia	1 (2.1)	0	0	0	1 (1.4)
Chronic hepatitis	1 (2.1) ^a	0	0	0	1 (1.4)
Pancreatitis	1 (2.1) ^a	0	0	0	1 (1.4)
Renal failure	1 (2.1) ^a	0	0	0	1 (1.4)

MedDRA = Medical Dictionary for Regulatory Activities.

^a Reported as a nonfatal serious adverse event.

Patient percentages were based on the total number of patients in each column.

Source: [Table 1.3.1.1.1.3](#)

A summary of TEAEs potentially associated with abnormal clinical laboratory parameters that are of interest for patients in the Pooled Safety Set overall and by age at disease onset is provided in Table 10 below.

Table 10. TEAEs potentially associated with abnormal clinical chemistry laboratory parameters of interest in patients in the pooled safety set, overall and by age at disease onset

MedDRA Preferred Term	Pediatric Onset (N=68), n (%)		Adult Onset (N=2) n (%)	Unknown Onset (N=1) n (%)	All Patients (N=71) n (%)
	Perinatal/Infantile Onset (N=48)	Juvenile Onset (N=20)			
Hypercalcaemia	4 (8.3)	0	0	0	4 (5.6)
Hypocalcaemia	3 (6.3)	0	0	0	3 (4.2)
Blood parathyroid hormone increased	1 (2.1)	2 (10.0)	0	0	3 (4.2)
Blood alkaline phosphatase abnormal	1 (2.1)	0	0	0	1 (1.4)
Vitamin B ₆ decreased	0	1 (5.0)	0	0	1 (1.4)

MedDRA = Medical Dictionary for Regulatory Activities.

Patient percentages were based on the total number of patients in each column.

Source: Table 1.3.1.1.1.3

Haematology

There were no consistent changes in routine haematology.

A summary of TEAEs 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 Table 11 below. Of the events listed in the table only the event of neutropenia was considered by the investigator to be related to asfotase alfa.

Table 11. TEAEs potentially associated with abnormal haematology laboratory results in patients in the pooled safety set, overall and by age at disease onset

MedDRA Preferred Term	Pediatric Onset (N=68), n (%)		Adult Onset (N=2) n (%)	Unknown Onset (N=1) n (%)	All Patients (N=71) n (%)
	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

No events potentially associated with abnormal haematology laboratory parameters were reported as SAEs in the Pooled Safety Set.

Clinical chemistry

Select clinical chemistry laboratory parameters including ALT, AST, ALP, total bilirubin (TBil), direct bilirubin (DBil), indirect bilirubin (IBil), blood urea nitrogen (BUN), creatinine, urine calcium/creatinine ratio, albumin, potassium, calcium, phosphate, 25-hydroxy vitamin D (25-OH vitamin D), PTH, PLP, and PPi showed no significant change. Due to the unique nature of some of these parameters and their potential association with other facets of efficacy and safety, ALP, calcium, PTH, PLP, and PPi (as well as eosinophils and eosinophil/leukocyte ratio) were considered to be clinical laboratory tests of interest.

Generally, mean and median clinical chemistry test results associated with hepatic function (ALT, AST, TBil, DBil, and IBil) were relatively stable over time. Mean and median serum BUN and creatinine values tended to decrease from Baseline to Week 24, but these values were slightly higher at the last visit compared with Baseline values.

Changes over time for other clinical chemistry parameters, including potassium, phosphate, and 25-OH vitamin D were not clinically meaningful. Any variability seen in 25-

OH vitamin D results may be reflective of concomitant vitamin D supplements taken by some patients (see Table 12 below for more details).

Table 1. TEAEs associated with abnormal clinical chemistry laboratory results in patients in the Pooled Safety Set, overall and by age at disease onset

MedDRA Preferred Term	Pediatric Onset (N=68), n (%)		Adult Onset (N=2) n (%)	Unknown Onset (N=1) n (%)	All Patients (N=71) n (%)
	Perinatal/ Infantile Onset (N=48)	Juvenile Onset (N=20)			
Alanine aminotransferase increased	4 (8.3)	0	0	0	4 (5.6)
Aspartate aminotransferase increased	3 (6.3)	0	0	0	3 (4.2)
Urine calcium/creatinine ratio increased	3 (6.3)	0	0	0	3 (4.2)
Hyperphosphataemia	2 (4.2)	0	0	0	2 (2.8)
Hypokalaemia	2 (4.2)	0	0	0	2 (2.8)
Hyponatraemia	2 (4.2)	0	0	0	2 (2.8)
Vitamin D decreased	2 (4.2)	0	0	0	2 (2.8)
Vitamin D increased	1 (2.1)	1 (5.0)	0	0	2 (2.8)
Blood 1,25-dihydroxycholecalciferol decreased	0	1 (5.0)	0	0	1 (1.4)
Blood 25-dihydroxycholecalciferol decreased	1 (2.1)	0	0	0	1 (1.4)
Blood 25-dihydroxycholecalciferol increased	0	1 (5.0)	0	0	1 (1.4)
Blood potassium decreased	1 (2.1)	0	0	0	1 (1.4)
Blood urea increased	1 (2.1) ^a	0	0	0	1 (1.4)
Blood sodium decreased	1 (2.1)	0	0	0	1 (1.4)
Gamma-glutamyltransferase increased	1 (2.1)	0	0	0	1 (1.4)
Hepatic enzyme increased	1 (2.1) ^a	0	0	0	1 (1.4)
Metabolic acidosis	1 (2.1)	0	0	0	1 (1.4)
Metabolic alkalosis	1 (2.1)	0	0	0	1 (1.4)
Hypophosphataemia	1 (2.1)	0	0	0	1 (1.4)
Hypoglycaemia	1 (2.1)	0	0	0	1 (1.4)
Chronic hepatitis	1 (2.1) ^a	0	0	0	1 (1.4)
Pancreatitis	1 (2.1) ^a	0	0	0	1 (1.4)
Renal failure	1 (2.1) ^a	0	0	0	1 (1.4)

MedDRA = Medical Dictionary for Regulatory Activities.

^a Reported as a nonfatal serious adverse event.

Patient percentages were based on the total number of patients in each column.

Source: [Table 1.3.1.1.1.3](#)

Anti asfotase alfa antibodies and neutralising antibodies

Overall, the incidence rate for TEAEs experienced by patients before becoming continuously ADA positive (1,938.8 events/100 PYs of exposure to asfotase alfa) was greater than the incidence rate for TEAEs experienced by patients after becoming continuously ADA positive (1,144.1 events/100 PYs). With the exception of injection site macule and tooth loss, all of the preferred terms noted above (those reported by $\geq 10\%$ more patients categorized as continuously ADA positive compared with patients categorised as not continuously ADA positive) had higher incidence rates before patients became continuously ADA positive than after patients became continuously ADA positive. The incidence rates for these events were:

- Injection site erythema (174.6 versus 139.6 events/100 PYs)
- Injection site pain (44.7 versus 10.9 events/100 PYs)
- Injection site pruritus (37.4 versus 13.7 events/100 PYs)
- Injection site macule (40.5 versus 49.3 events/100 PYs)
- Injection site swelling (27.0 versus 10.9 events/100 PYs)
- Tooth loss (10.4 versus 31.5 events/100 PYs)
- Myalgia (6.2 versus 1.4 events/100 PYs)

These data suggest that, the incidence rates of the events commonly associated with ISRs were generally not greater in patients categorised as continuously ADA positive compared

with patients categorised as not continuously ADA positive, even though a greater proportion of patients categorised as continuously ADA positive reported these types of events.

Vital signs

Throughout the clinical studies of asfotase alfa, vital sign measurements were performed as part of the routine safety monitoring. Clinically significant vital sign measurements were to be recorded as AEs.

Analyses of marked, sustained vital sign abnormalities were performed to assess the numbers and proportions of patients who experienced hypertension, increased heart rates, or decreased heart rates.

A summary of TEAEs potentially associated with abnormal vital signs in patients in the Pooled Safety Set, overall and by age at disease onset, is provided in Table 13 (see below). All but 2 TEAEs potentially associated with abnormal vital signs were experienced by patients in the infantile onset HPP subgroup. This finding was not unexpected given the more severe manifestations of HPP typically observed for patients in this subgroup; the other 2 events were experienced by patients in the juvenile onset HPP subgroup.

Table 2. TEAEs potentially associated with abnormal vital signs in patients in the pooled safety set, overall and by age at disease onset

MedDRA Preferred Term	Pediatric Onset (N=68), n (%)		Adult Onset (N=2) n (%)	Unknown Onset (N=1) n (%)	All Patients (N=71) n (%)
	Perinatal/ Infantile Onset (N=48)	Juvenile Onset (N=20)			
Pyrexia	21 (43.8)	0	0	0	21 (29.6)
Respiratory distress	6 (12.5)	0	0	0	6 (8.5)
Hypertension	5 (10.4)	0	0	0	5 (7.0)
Bradycardia	4 (8.3)	0	0	0	4 (5.6)
Tachycardia	4 (8.3)	0	0	0	4 (5.6)
Dyspnoea	3 (6.3)	0	0	0	3 (4.2)
Acute respiratory failure	2 (4.2)	0	0	0	2 (2.8)
Apnoea	2 (4.2)	0	0	0	2 (2.8)
Respiratory failure	2 (4.2)	0	0	0	2 (2.8)
Restrictive pulmonary disease	2 (4.2)	0	0	0	2 (2.8)
Sleep apnoea syndrome	2 (4.2)	0	0	0	2 (2.8)
Tachypnoea	2 (4.2)	0	0	0	2 (2.8)
Acute respiratory distress syndrome	1 (2.1)	0	0	0	1 (1.4)
Apnoeic attack	1 (2.1)	0	0	0	1 (1.4)
Arrhythmia	1 (2.1)	0	0	0	1 (1.4)
Asthma	1 (2.1)	0	0	0	1 (1.4)
Blood pressure increased	0	1 (5.0)	0	0	1 (1.4)
Breath holding	1 (2.1)	0	0	0	1 (1.4)
Cardiac arrest	1 (2.1)	0	0	0	1 (1.4)
Cardio-respiratory arrest	1 (2.1)	0	0	0	1 (1.4)
Febrile convulsion	1 (2.1)	0	0	0	1 (1.4)
Heart rate abnormal	1 (2.1)	0	0	0	1 (1.4)
Heart rate decreased	1 (2.1)	0	0	0	1 (1.4)
Heart rate increased	0	1 (5.0)	0	0	1 (1.4)
Hypothermia	1 (2.1)	0	0	0	1 (1.4)
Pulmonary hypertension	1 (2.1)	0	0	0	1 (1.4)
Respiratory arrest	1 (2.1)	0	0	0	1 (1.4)
Respiratory depression	1 (2.1)	0	0	0	1 (1.4)
Respiratory rate increased	1 (2.1)	0	0	0	1 (1.4)
Right ventricular systolic pressure increased	1 (2.1)	0	0	0	1 (1.4)
Secondary hypertension	1 (2.1)	0	0	0	1 (1.4)

MedDRA = Medical Dictionary for Regulatory Activities.

Source: Table 1.3.1.1.1.3

Safety issues with the potential for major regulatory impact***Haematological toxicity***

Asfotase alfa is bone targeted. There is no evidence of haematological toxicity from the clinical trials reported by the sponsor.

Serious skin reactions

The high frequency of local site reactions with asfotase alfa SC injections need to be highlighted and guidelines for preventing them need to be clear and communicated clearly to parents and patients.

Cardiovascular safety

Asfotase alfa is bone targeted. There are no pharmacologic effects of asfotase on the heart myocardium.

Secondary pulmonary hypertension may be present pre-treatment in severely affected infants with severe immature lung disease and chronic ventilator dependency.

Unwanted immunological events

Of the 69 patients for whom post Baseline ADA data were available, 56 (81.2%) tested positive for ADAs at some point post baseline. Generally, ADA titres were low, and ranged from 0 to 2,048 (median peak titre of 64.0). The median time to first ADA positive result was 37.0 days (range of 14 to 1,072 days). Of note, not all patients who tested positive for

ADAs post baseline remained consistently positive for these antibodies after the initial positive result.

Proportionally more patients categorised as continuously ADA positive experienced TEAEs considered to be related to asfotase alfa (92.9%) compared with patients categorised as not continuously positive (74.1%); this observation was primarily influenced by the greater proportion of patients categorised as continuously ADA positive who experienced ISRs and IARs.

However, the overall incidence rate for TEAEs experienced by patients before becoming continuously ADA positive (1,938.8 events/100 PYs of exposure to asfotase alfa) was greater than the incidence rate for TEAEs experienced by patients after becoming continuously ADA positive (1,144.1 events/100 PYs).

Other safety issues

Safety in special populations

Pregnancy and breast feeding

- *Pregnancy. Asfotase alfa should not be used during pregnancy unless medically necessary.*

At the present time, there are no reports of human exposure in utero and no reports of its safety. There are no human or higher animal studies. From extrapolation in animal studies, it is assumed that Strensiq given to the mother crosses the placenta and appears in the fetal circulation. The study of PK and pharmacotoxicity in mice is insufficient data on which to base a statement about reassurance in human pregnancies. These are far more complex. For example, exposure to chronic vitamin D deficiency on the developing foetus has an impact on mineralisation of the fetal skeleton. Asfotase alfa crosses the placenta where it can impact on the fetal skeleton particularly in the second and third trimester when the fetal skeleton is rapidly accreting mineralisation. The genetic condition of hyperphosphatasia does exist so that it will be important to demonstrate that there are no fetal effects similar to hyperphosphatasia or Caffey disease reflecting chronic exposure of the fetal skeleton which is mineralising between the 5th and 40th weeks of gestation. Until this reassurance can be provided, the proposed use in pregnancy category needs to be changed to C¹⁰ the category which recognises that there are likely pharmacologic effects on the developing human skeleton but this is not assessable in animal safety studies at the present time.

It is recommended that the PI be changed to 'Use in Pregnancy – Category C' until further knowledge can provide reassurance that there are no long term pathophysiological effects from long term exposure on the fetal skeleton.

The Alexion Pregnancy Reporting and Outcome Form/Breast Feeding is incorporated into the Australian Specific Annex (ASA) of the EU RMP version 1 December 2014 and its use is supported. Although the risks to the foetus are unknown, experience with other genetic innovative therapies is that some women who are fully informed of the lack of knowledge at the present time will continue with therapy through their pregnancy.

Safety related to drug-drug interactions and other interactions

There was no evidence of drug-drug or protein/protein interactions which would preclude clinical use.

Postmarketing data

Asfotase alfa is not currently marketed in any country; therefore, no reports of post-marketing experience are included.

However, Alexion supports a compassionate use program globally. Reporting of death in the treatment program and in compassionate use program globally, is valuable to understand the multiple targets of therapy which are needed to ensure the best outcome.

A report of deaths in the compassionate use programs is summarised below in Table 14 below.

Table 14. Compassionate use programs: Fatal SAEs

Patient details, diagnosis	Fatal SAEs
Patient had a medical history significant for hyperammonaemia, pulmonary hypoplasia, pulmonary hypertension, chronic lung disease, multiple bullae, and tracheotomy.	The direct cause of death was reported to be due to huge bullae and chronic lung disease. The treating physician considered the events of pulmonary bulla, pulmonary hypertension, pneumothorax, and cardiac tamponade to be unrelated to asfotase alfa treatment, but a natural course of HPP when ventilated for a long time.
Patient had a medical history significant for severe infantile-onset HPP requiring ventilatory support and tracheostomy.	After approximately 8 weeks of asfotase alfa treatment, the patient vomited and became profoundly hypoxic. The treating physician considered the fatal event of severe, acute airway obstruction to be unrelated to asfotase alfa treatment.
Patient had a medical history significant for respiratory difficulties with ventilator dependency since birth	At 7 months of age, the patient developed severe respiratory insufficiency with decreased oxygen saturations and died.

Comment: Several observations can be made about Compassionate use programs and the challenge of introducing potentially lifesaving therapies in clinical practice. These three deaths during the course of treatment of 3 perinatal cases are instructive however for they support the requirement of the EMEA for post-marketing surveillance and the clear need to document the outcomes of post-marketing experience with asfotase alfa, particularly from the perspective of TEAEs.

There is an urgent need for clinicians and clinician scientists to re-examine the criteria for case selection of perinatal cases for treatment and case exclusion. Other clinician groups have undertaken this for therapies in disorders where there is therapeutic evidence of poor survival or unacceptable disability outcomes in some subsets of the disorder where the clinical evidence suggested an almost universally poor survival, for example, Investigators using Myozyme for Infantile Pompe disease have been guided by a research Study which showed that long term survival of newborns who were ventilator dependent despite Myozyme treatment had very poor outcomes. This led to recommendations which provided families with clear and supportive care guidelines about treatment options.

Evaluator's conclusions on safety

Safety data from is derived from 71 patients from the pooled safety dataset of whom 68 Paediatric onset patients had an asfotase exposure of 169.17 PYs with a 97.5 PYs of exposure in patients who received weekly doses of > 6 mg/kg.

Although asfotase alfa is a protein, no incidences of anaphylaxis have been observed in the per protocol dose range. Nevertheless there is a high frequency of local site reactions (ISRs) which would be expected for a subcutaneous dosage regimen. The CMI provides clear guidelines on steps to reduce and minimise ISRs. Injection associated reactions are fortunately rare. The per protocol treatment regimen does not recommend IV infusion. A review of data on ectopic calcification concludes that monitoring for both kidney and eye calcification should be carried out. Fortunately the vascular, kidney and eye calcifications are of low clinical significance. It will be essential that these are monitored and reported in the post-market surveillance.

Treatment emergent adverse effects are likely to be seen in patients with a perinatal onset compared to patients with juvenile onset HPP. This may reflect the greater severity in patients who are included on the basis of a class diagnosis of HPP rather than following a protocol of assessments which might predict outcomes.

This evaluator has written questions about:

- Development of inclusion and exclusion guidelines for babies with prenatal diagnosis of HPP and perinatal HPP.
- This assessor has raised concerns about treatment in adult HPP or paediatric onset HPP in adults where there is inadequate trial data about outcomes and safety.

Comment: In view of the extreme rarity and reported low frequency of experience in the management of patients with paediatric onset HPP in Australia, this evaluator recommends that the use of asfotase alfa Enzyme Replacement Therapy be initiated and monitored by centres of expertise with experience in genetic bone and mineral disorders, and allied health expertise to evaluate the functional outcomes, including occupational therapy, physiotherapy and experience in a clinical trials setting. There will need to be regular reporting of outcomes of therapy and close monitoring (see the post-market pharmacovigilance data collection instrument, ALX-HPP-501). Furthermore the high frequency of injection site reactions requires sympathetic and supportive therapy coordination.

First round benefit-risk assessment

First round assessment of benefits

The benefits of asfotase alfa in the proposed usage are:

- Asfotase alfa has been well demonstrated to be an effective therapy for skeletal involvement of young patients with HPP. The evidence for clinical all patients, excepting infants with prenatal diagnosis of severe disease who are ventilator dependent from birth and who remain ventilator dependent despite a trial of therapy, is very strong. A regimen of 1 mg/kg 6 times per week or 2 mg/kg 3 times per week, normalises mineral chemistry, increases whole body mineral content and results in radiographic evidence of healing rickets. The effect on the growing centres in the skeleton (metaphyses) is rapid and seen within the first 6 months of therapy. This is true across the age groups from the perinatal period (those surviving the newborn period) through infantile and juvenile presentations. It is associated with normalisation of walking and physical activity and improved quality of life.

- For children with severe disease there is improvement in respiratory failure and in some children, it has been possible to wean from ventilator dependency and improve their mobility and quality of life.

First round assessment of risks

The major risks are:

- A high frequency of ISRs give the mode of subcutaneous administration.
- A possibly higher risk from chronic use in pregnancy and the need for further preclinical or other experimental data to establish safety. In the meantime, the need to revise categorisation of risk in pregnancy to the C category¹⁰.
- A significant proportion of Infants with a prenatal diagnosis will have irreversible lung immaturity, and become invasive ventilator dependent and accordingly not be suitable for institution of long term therapy. In keeping with the greater severity in this group of children there is a much higher frequency of TEAEs and mortality. Weaning from invasive ventilator support may not be feasible.
- There need to be clinical guidelines outlining indications to treat. These (guidelines) need to recognise that there has historically been a high mortality in the subsets of patients with prenatally diagnosed HPP, the majority of whom have perinatally lethal HPP and are chronically ventilator dependent. Similarly there needs to be a clear clinical guideline in the case of the additional subset of babies with HPP with (vitamin B6 responsive seizures who despite seizure control historically have had a high infant mortality.

First round assessment of benefit-risk balance

As discussed above, asfotase alfa given in the dose and recommended regimen is an effective therapy in selected cases of HPP of paediatric onset.

The benefit-risk balance of asfotase alfa (rch), given the proposed usage, is favourable.

Uncertainties

- The number of separate subjects in the human studies reported is still small. This is particularly true in certain age cohorts, for example, subjects over 18 years of age. The sponsors have planned and requested post-market studies as a requirement of use of asfotase alfa by clinicians.
- There is a high frequency of TEAEs.
- Just as management has been facilitated in clinical trials settings, achievement of Australian centres of expertise to initiate and monitor therapies will be needed to meet the requirements for high proficiency of monitoring (as proposed by the sponsor).
- Potential outcomes of pregnancy and breast feeding: It is recommended that protocols for management in the case of pregnancy (accidental or intended) be developed rapidly to avoid confusion as to whether a pregnancy should be terminated in the accidental situation. In addition, use of the monitoring protocol Alexion Pregnancy Reporting and Outcome Form/Breast Feeding in subjects who elect to continue with their pregnancy is recommended.
- The sponsor should seek additional expert opinion and scientific findings from learned societies in the bone and mineral medicine field to examine the potential effects on the developing fetal skeleton in the case of inadvertent use in pregnancy.

First round recommendation regarding authorisation

This evaluator having considered all the documentation, recommends that Strensiq be authorised for long term enzyme replacement therapy in patients with paediatric onset HPP: The evaluator further recommends that the authorisation be subject to the following conditions:

- Use in patients 0 to 18 years (or skeletal maturity) should employ a dose of 6 mg/kg/SC weekly.
- Use in patients with prenatal diagnosis who are assessed to be extremely severe, and ventilator dependent from birth, the authorisation should be limited to a defined period subject to a review of responsiveness within 2 years of commencing therapy. These infants may have evidence of congenital pulmonary immaturity, in whom there is irreversible lung damage and poor chance of ventilator independent survival. Consideration may be given to withdrawal of therapy in this interval if the patient is unresponsive to therapy.
- For use in adolescent and adult patients after 18 years of age subject to a decision about the minimal effective dose for commencement of therapy and a maintenance dose following the first year reassessment. The commencement and maintenance therapy dose will be guided by the data analysis of the outcomes of ENB-009-10, a patient review every 2 years and review of periodic safety update reports (PSURs).
- That an Australian register of patients who could potentially benefit from asfotase alfa therapy be developed with the cooperation of the Centres of Expertise in each state (see the post-market pharmacovigilance data collection instrument, ALX-HPP-501).
- That management of patients with paediatric onset HPP should be coordinated through centres of expertise.

Additional expert input

The sponsor should seek additional expert opinion and scientific findings from learned societies in the bone and mineral medicine field to examine the potential effects on the developing foetal skeleton in the case of inadvertent use in pregnancy.

Clinical questions

1. Does the sponsor have further pharmacologic and/or clinical trials data which would inform a statement of dosage and dose frequency in post-pubertal subjects?
2. Does the sponsor have advice on dosage and dose frequency in postmenopausal patients with HPP?
3. Can the sponsor provide documentation as to whether there are interactions with anti resorptive medications such as the bisphosphonates, denosumab, etcetera, as these are sometimes used in treatment particularly in the post-menopausal period where there may be additive pathologies?

There were no further questions regarding pharmacokinetics, pharmacodynamics, efficacy or safety.

Second round evaluation

The details of the sponsor's responses to the clinical questions and the evaluator's comments on these responses are detailed in Attachment 2.

Second round assessment of benefits

The benefits of asfotase alfa in the proposed usage are:

1. Asfotase alfa has been well demonstrated to be an effective therapy for skeletal involvement of paediatric onset patients with HPP. The clinical trials evidence for all patients, excepting infants with perinatal diagnosis of severe disease who are ventilator dependent from birth and who remain ventilator dependent despite a trial of therapy, is very strong. A regimen of 1 mg/kg 6 times per week or 2 mg/kg 3 times per week, normalises mineral chemistry, increases whole body mineral content and results in radiographic evidence of healing rickets. The effect on the growing centres in the skeleton (metaphyses) is rapid and seen within the first 6 months of therapy. This is true across the age groups from the perinatal period (those surviving the newborn period) through Infantile and Juvenile Presentations. It is associated with normalisation of walking and physical activity and improved quality of life.
2. For children with severe disease from birth there is improvement in respiratory failure and in some children, it has been possible to wean from ventilator dependency and improve their mobility and quality of life.

Second round assessment of risks

The risks of asfotase alfa in the proposed usage are outlined in detail in the first round assessment of risks. The major risks are:

1. A high frequency of Infusion Site Reactions give the mode of subcutaneous administration.
2. An unknown but possibly small risk for modification to the density of the foetal skeleton from chronic use in pregnancy. Monitoring and reporting of all pregnancies will be mandatory. Skeletal outcomes may be dependent on the genetic status in the foetus. The outcomes of pregnancy and breast feeding will be subject to reporting. In the meantime there is need to revise Categorisation of Risk in pregnancy to the C category.
3. A proportion of infants with a perinatal diagnosis may have irreversible lung immaturity or postnatal lung pathology, and become invasive ventilator dependent. Institution of therapy in face of long-term invasive ventilation is associated with its own morbidity and mortality independent of the effectiveness of asfotase alfa in reversing the mineralisation defect.
4. There need to be clinical guidelines outlining indications to treat. These need to recognise that there has historically been a high mortality in the subsets of patients with prenatally diagnosed HPP, the majority of whom have perinatally lethal HPP and are chronically ventilator dependent. Similarly there needs to be a clear clinical guideline in the case of the additional subset of babies with HPP with B6 responsive seizures who despite seizure control historically have had a high infant mortality.

Second round assessment of benefit-risk balance

Asfotase alfa given in the dose and recommended regimen is an effective therapy in selected cases of Hypophosphatasia of paediatric onset.

The benefit-risk balance of asfotase alfa (rch), given the proposed usage, is favourable.

Uncertainties

- The number of separate subjects in the human studies reported is still small. Post-market studies will be a requirement of use of asfotase alfa by clinicians.
- There is a high frequency of treatment emergent adverse events. Adequate recommendations are given in the PI and CMI.
- The sponsors support the concept of Australian centres of expertise to initiate and monitor therapies which will be needed to meet the requirements for high proficiency monitoring and coordination of care.
- Pregnancy and breast feeding will be required to be notified to supervising physicians. A monitoring protocol Alexion Pregnancy Reporting and Outcome Form/Breast Feeding will be required of subjects who elect to continue therapy while pregnant.
- The sponsor agrees to seek additional expert opinion and scientific findings from learned societies in the bone and mineral medicine field to examine the potential effects on the developing fetal skeleton in the case of inadvertent use in pregnancy.

Second round recommendation regarding authorisation

This evaluator having considered all the documentation, recommends that Strensiq be authorised for long term enzyme replacement therapy in patients with paediatric onset HPP: The evaluator further recommends that the authorisation be subject to the following conditions:

- Use in patients 0 to 18 years (or skeletal maturity) and adults should employ a dose of 6 mg/kg SC weekly or 2 mg/kg 3 times per week.
- Post-market experience should be reported for patients with perinatal diagnosis who are assessed to be extremely severe, and ventilator dependent from birth, and post-market experience soon after 2 years of age should be analysed as a separate subset for data analysis. Adverse reports indicate that some proportion of infants commenced in the first 2 years of life may have evidence of congenital pulmonary immaturity or chronic lung disease These may have irreversible lung damage and poor chance of ventilator independent survival. Consideration may be given to withdrawal of therapy in this interval if the patient is unresponsive to therapy.
- That an Australian register of patients who could potentially benefit from asfotase alfa therapy be developed with the cooperation of the centres of expertise in each state (see the post-market pharmacovigilance data collection instrument, ALX-HPP-501). This would also involve a specific agreement to separately report the analysis of data on Australian patients collected via the ALX-HPP-501 protocol. That management of patients with paediatric onset HPP should be coordinated through centres of expertise.

V. Pharmacovigilance findings

Risk management plan

The sponsor submitted an EU-RMP Version 01.3 (dated 22 May 2015, Data Lock Point 30 November 2013) and Australian Specific Annexe (ASA) Version 1.1 (dated July 2015), which was reviewed by the RMP evaluator.

Safety specification

The sponsor provided a summary of ongoing safety concerns which are shown on Table 15 below.

Table 15. Ongoing safety concerns for Strensiq

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
Missing information:	Use in pregnant or lactating women Use in elderly Use in patients with hepatic or renal impairment Long term safety

RMP evaluator's comment

- Notwithstanding the evaluation of the nonclinical and clinical aspects of the safety specification, there are no definite objections to the list of safety concerns and missing information items provided in the context of this application. However, the list is not considered complete. The following changes are recommended: 'skin disorders' should be added as an important identified risk (as seen in clinical trials).
- 'Hypersensitivity' should be added as an important potential risk.
- 'Medication errors' should be added an important potential risk.

Pharmacovigilance plan

Proposed pharmacovigilance activities

The sponsor proposes routine pharmacovigilance activities for important identified and potential risks and missing information. Furthermore, an additional activity is planned for all safety concerns and missing information. These activities are summarised in Table 16 below.

Table 16. Additional pharmacovigilance activities planned by the sponsor

Additional activity	Assigned safety concern	Actions/outcome proposed	Estimated planned submission of final data
<p>ALX-HPP-501: An observational, longitudinal, prospective, long term registry of patients with HPP.</p> <p>Planned: The registry is planned to start enrolling patients with HPP in Q4 2014. HPP patients treated with Asfotase alfa will be enrolled after approval</p>	<p>Missing information, important identified and potential risks.</p>	<ul style="list-style-type: none"> • 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 characterise 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 approval.) 	<p>Based on agreement with CHMP</p>

RMP evaluator's comment

There is no definite objection to the pharmacovigilance plan proposed by the sponsor in the context of this application. However, the following recommendations are made:

- Details of Study ALX-HPP-501 (including dates of submission of data) should be provided
- Updates from Study ALX-HPP-501 should be provided with Periodic Safety Update Reviews (PSURs).

It is noted that the sponsor is currently conducting the following study:

- Study ENB-010-10; an open label, multicentre, 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 (HPP).
- The sponsor should commit to all studies conducted by the sponsor to be reported in PSURs and to inform future updates of the risk management plan.

Risk minimisation activities

Sponsor's conclusion in regard to the need for risk minimisation activities

The sponsor is not proposing additional risk minimisation activities for the Australian market.

In the EU-RMP, additional risk minimisation activities include patient and caregiver educational material for all safety concerns. However, the sponsor committed to providing the same information contained in the patient and caregiver educational material in the CMI document.

RMP evaluator's comment

The sponsor should conduct the same additional risk minimisation activities as the activities planned in the EU jurisdiction.

Potential for medication errors

For the purposes of this RMP evaluation different types of medication errors, as suggested have been considered.¹⁹

With regard to medication errors, the sponsor states the following:

The potential for medication error with asfotase alfa is low:

- The naming of the product is sufficiently different from existing medications therefore the likelihood of error in dispensing is low.*
- Patients will start treatment in the hospital. After an initial Phase of training under the supervision of a healthcare professional in the hospital where clear explanation and training related to the weight based dosing will be provided. Asfotase alfa will be self-administered by patients or their caregivers.*
- Educational materials regarding dosing and proper administration of asfotase alfa will be provided to patients and caregivers.*

There is no definite objection to the sponsor's proposed actions. However, given that, for the Australian market, the sponsor does not intend to conduct additional risk minimisation activities, the risk of medication errors is increased, if the product is self-administered.

The sponsor should state, whether, for the Australian market, self-administration of Strensiq by patients, or administration by carers/parents is intended, or whether administration by a health professional is intended.

Given that self or carer administration is likely to occur, proper education of those groups is vital to prevent medication errors, in particular over or under dosing.

Potential for overdose

With regard to overdose, the sponsor states the following:

The maximum dose of asfotase alfa used in clinical studies is 28 mg/kg/week. No dose related toxicity or change in the safety profile has been observed in clinical studies to date; therefore, no overdose level has been determined.

¹⁹ Ferner RE, Aronson JK. Clarification of terminology in medication errors: definitions and classification. Drug Saf. 2006;29(11):1011-22.

The risk for intentional overdose is minimal, if administered by a health care professional or patient or carer sufficiently trained in the administration. In the proposed PI, over dosage has been discussed to a satisfactory standard given the limited information available.

Potential for off-label use

With regard to off-label use, the sponsor states the following:

Due to its specific mechanism of action, it is unlikely that asfotase alfa will be used for indications other than its intended use.

This is acceptable.

Risk minimisation plan

Planned actions

Routine risk minimisation activities are proposed for all safety concerns. No additional risk minimisation activities are planned for the Australian market.

Additional risk minimisation activities

The nature and objectives of the planned additional activities in Europe (as described by the sponsor) are as follows:

- 'Educational material will be provided to patients and caregivers by the physician. these will include separate injection guides for patients who self-inject and for parents/caregivers who inject infant patients.'
- An animated injection guide will also be made available
- The injection guides will provide information on how to inject using aseptic techniques
- Information on warnings and precautions and side effects based on approved Summary of product characteristics (SmPC)
- Information on reporting side effects
- Dosing chart based on approved SmPC
- Detailed instructions with clear diagrams will demonstrate how the injection site is chosen and how the injection is carried out and recorded. Essential information on cold chain management for Strensiq during storage and travel will also be included.

RMP reviewer comment

The sponsor should conduct the same or equivalent risk minimisation activities in Australia as planned in the EU. This is particularly desirable given that the product is a first in class new chemical entity.

The education material proposed for the EU has not been supplied with the submission and should be provided.

The education material for patients and caretakers should ideally include a patient card, individual information on dosing and administration (notably where individualised dosing information can be added by the prescriber), and information on adverse events (in particular injection site reactions, hypersensitivity and immunogenicity) and cold chain management.

Prior to approval, the sponsor should provide the TGA with the following details for agreement:

- All draft education materials
- A clear distribution plan
- A clear plan to measure the effectiveness of the education program as an additional risk minimisation activity.

Reconciliation of issues outlined in the RMP report

The following section summarises the OPR's first round evaluation of the RMP, the sponsor's responses to issues raised by the OPR, and the OPR's evaluation of the sponsor's responses.

Table 17: Reconciliation of issues outlined in the RMP report.

Recommendation in RMP evaluation report	Sponsor's response (or summary of the response)	RMP evaluator's comment
Safety considerations may be raised by the nonclinical and clinical evaluators through the consolidated TGA request for information and/or the nonclinical and clinical evaluation reports, respectively. It is important to ensure that the information provided in response to these includes a consideration of the relevance for the RMP, and any specific information needed to address this issue in the RMP. For any safety considerations so raised, please provide information that is relevant and necessary to address the issue in the RMP.	Alexion will evaluate any safety consideration raised in the nonclinical and clinical evaluation reports for inclusion as important risks in the RMP.	The sponsor's response has been noted.
Any ASA updates should be provided in the current ASA format.	The updated ASA (version 1.1) provided with this response is in the new ASA format.	This is acceptable in the context of this application.
A version number should be attached to the ASA.	The updated ASA (version 1.1) provided with this response is in the new ASA format.	This is acceptable in the context of this application.
'Skin disorders' should be added as an important identified risk (as seen in clinical trials).	Skin disorders reported in the clinical studies that were considered as related to asfotase alfa were primarily at the injection site (for example stretched skin at injection site) and are hence considered as ISRs. ISRs are included as an important identified risk in the RMP. The evaluation of ISRs for the periodic safety updates (as proposed in the EU-RMP) includes a comprehensive list of MedDRA terms (including 'skin disorders'). Hence, Alexion does not consider 'skin disorders' as a separate risk to be included in the RMP.	This is acceptable in the context of this application.

Recommendation in RMP evaluation report	Sponsor's response (or summary of the response)	RMP evaluator's comment
'Hypersensitivity' should be added as an important potential risk.	IARs and Immunogenicity are included as important identified risks in the RMP. IARs are systemic reactions to asfotase alfa and include hypersensitivity. The evaluation of IARs and immunogenicity for the periodic safety updates (as proposed in the EU-RMP) will include the SMQ for 'hypersensitivity'. Hence, Alexion does not consider 'hypersensitivity as a separate risk to be included in the RMP. Period safety updates will be provided to the TGA.	This is acceptable in the context of this application.
'Medication errors' should be added as an important potential risk.	<p>Medication error is included as an important potential risk in the EU RMP recently approved by the CHMP. Routine and additional PV activities (Study ALX-HPP-501) have been included for this risk. Patient educational materials (additional risk minimization activities) provide information to patients and care giver/guardians on proper injection technique (see response below).</p> <p>Additionally, the following updates have been made to the EU-RMP since the version submitted to the TGA.</p> <p>"Long-term safety and efficacy" and "Use in non-Caucasian patients" have been added as missing information.</p> <p>These updates have been captured in the ASA +provided with this response.</p>	This is acceptable in the context of this application.
Details of Study ALX-HPP-501 (including dates of submission of data) should be provided.	<p>The final protocol for ALX-HPP-501 will be submitted in the EU within 30 days of EC decision (estimated September 2015). The dates for submission of interim and final reports will be based on agreement with CHMP. The TGA will continue to be informed of these dates via updates to the RMP.</p> <p>Alexion provides the assurance that updates from Study ALX-HPP-501 will be provided in annual periodic benefit-risk evaluation report (PBRERs) submitted to the TGA. Furthermore, Alexion commits to report outcomes of all studies stated in the pharmacovigilance plan in annual PBRERs and inform the TGA of any updates to the RMP.</p>	This is acceptable in the context of this application.
Updates from Study ALX-HPP-501 should be provided with PSURs.	<p>The final protocol for ALX-HPP-501 will be submitted in the EU within 30 days of EC decision (estimated September 2015). The dates for submission of interim and final reports will be based on agreement with CHMP. The TGA will continue to be informed of these dates via updates to the RMP.</p>	This is acceptable in the context of this application.

Recommendation in RMP evaluation report	Sponsor's response (or summary of the response)	RMP evaluator's comment
	<p>Alexion provides the assurance that updates from Study ALX-HPP-501 will be provided in annual PBRERs submitted to the TGA. Furthermore, Alexion commits to report outcomes of all studies stated in the Pharmacovigilance Plan in annual PBRERs and inform the TGA of any updates to the RMP.</p>	
<p>The sponsor should commit to all studies conducted by the sponsor to be reported in PSURs and to inform future updates of the risk management plan.</p>	<p>The final protocol for ALX-HPP-501 will be submitted in the EU within 30 days of EC decision (estimated September 2015). The dates for submission of interim and final reports will be based on agreement with CHMP. The TGA will continue to be informed of these dates via updates to the RMP.</p> <p>Alexion provides the assurance that updates from Study ALX-HPP-501 will be provided in annual PBRERs submitted to the TGA. Furthermore, Alexion commits to report outcomes of all studies stated in the Pharmacovigilance Plan in annual PBRERs and inform the TGA of any updates to the RMP.</p>	<p>This is acceptable in the context of this application.</p>
<p>The sponsor should state, whether, for the Australian market, self-administration of Strensiq by patients, or administration by carers/parents is intended, or whether administration by a health professional is intended.</p>	<p>Alexion confirms self-administration of Strensiq by patients or carers/parents is intended in Australia.</p>	<p>The sponsor's response has been noted.</p>
<p>The sponsor should conduct the same or equivalent risk minimisation activities in Australia as planned in the EU. This is particularly desirable given that the product is a first in class new chemical entity.</p>	<p>Alexion agrees to conduct equivalent risk minimization activities in Australia as in the EU (please refer to the updated ASA (version 1.1)).</p>	<p>This is acceptable in the context of this application.</p>
<p>The education material proposed for the EU has not been supplied with the submission and should be provided.</p>	<p>The proposed EU educational material were provided in the submitted EU-RMP; however, the materials have since been updated (during the registration procedure by the EMA). The CHMP approved EU-RMP is provided in this response. The final SmPC and the EU educational materials are provided.</p>	<p>This is acceptable in the context of this application.</p>
<p>Prior to approval, the sponsor should provide the TGA with the following details for agreement:</p> <ul style="list-style-type: none"> · All draft education materials; · A clear distribution plan; and 	<p>As per the EU-RMP, the Australian education materials will provide instructions to patients and carers for proper administration techniques to address the risks of medication error and injection site reactions.</p> <p>Alexion agrees to provide copies of the final AU education materials (patient tool kit) prior to</p>	<p>This is acceptable in the context of this application.</p>

Recommendation in RMP evaluation report	Sponsor's response (or summary of the response)	RMP evaluator's comment
<ul style="list-style-type: none"> A clear plan to measure the effectiveness of the education program as an additional risk minimisation activity. 	<p>TGA approval of Strensiq. The patient tool kit will be as per the CHMP approved EU materials (as enclosed in the EU-RMP).</p> <p>The patient tool kit will be distributed as part of the enrolment in the HPP Registry (ALX-HPP-501). Assessment of the access and receipt of the tool kit will be performed in the Registry, upon enrolment and annually thereafter.</p> <p>Data from the HPP registry will be used to assess the effectiveness of risk minimisation measures in the EU-RMP. The registry will collect detailed information on ISRs and dosing. Information collected 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 (including information from the registry).</p>	

Advice from the Advisory Committee on the Safety of Medicines (ACSOM)

1. *Can the committee comment on the adequacy of the proposed additional risk minimisation activities to address the risks associated with asfotase alfa (rch), taking into account the small patient population affected by hypophosphatasia? If not considered adequate, can the committee advise which additional activities might be required?*

The committee noted that the sponsor has undertaken to conduct the same risk minimisation activities in Australia as will be conducted in Europe. Educational materials will be provided for patients undertaking self-administration, and also for caregivers. The range of materials includes an animated injection guide and pamphlets. Information covered includes aseptic technique for injection; warnings/precautions and side effects; how to report side effects; dosing chart; diagrams/instructions for injection site selection; record keeping; cold chain management; and storage.

While this approach appeared appropriate, the committee suggested that the following points should be addressed in information for prescribers, patients and carers:

- Clear instructions regarding the subcutaneous injection technique. The technique described in the injection guide may result in loss of control of the needle or its breakage. The need for rotation of injection sites and rotation frequency (for example at every injection) should be highlighted in the animated injection guide.
- Clear directions on cold chain management relevant to the Australian climate ('room temperature') and environment, and applicable to domestic storage and when travelling (including in motor vehicles). There needs to be clear advice on both the minimum time required for the medicine to reach 'room temperature' and the maximum permitted time outside refrigeration, consistent with product stability. The temperature of the injection solution can affect the patient's discomfort and so the patient may reasonably prefer injection of the medicine at a particular temperature.
- Clear directions on how to implement 'protect from light', relevant to the Australian climate and environment.

- Advice on selection of the syringe and legibility of its graduations; advice on carriage and disposal of sharps.
- The presence of what appears like particulate matter is common for biologicals when taken from refrigerated storage but this often disappears (goes into solution) once the solution has been warmed up to room temperature. This should be addressed, if relevant.
- Photographs to depict the different product strengths and dosages, which are colour-coded.
- As the patient is expected to gain weight, and dosage is weight based, the need for regular recording of body weight and review of the appropriate dosage should be emphasised. For example, a digital diary could be provided, with alerts at body weight points that should trigger review of the dosage.
- Advice for males on the possible effect on fertility; advice for females on contraception and pregnancy testing.
- The statement in the CMI that 'breastfeeding should be discontinued during treatment' should be reviewed to be relevant to patients using asfotase alfa, which will not be used intermittently.

It may be useful to seek comment from any current users on the adequacy of the educational material.

The committee noted that an observational, longitudinal, prospective, long-term registry study of patients with HPP is planned (Study ALX-HPP-501). The committee commented that the patient registry would serve as both a pharmacovigilance activity and as a risk minimisation activity.

The Study ALX-HPP-501 protocol, includes that female patients will be requested to provide information on pregnancy history, and to report any pregnancy occurring during the study, along with information regarding the outcome of pregnancy and neonatal condition. The committee advised that similar information should be sought from male patients (in relation to their spouses and any offspring) as asfotase alfa treatment of male patients with severe forms of paediatric onset HPP may allow them to reach reproductive age and treatment will be lifelong.

The registry study will include Australian patients. While the reporting requirements for the registry study appear burdensome, there appeared to be no practical alternative for systematic and long term investigation of safety (and efficacy) for such a rare disease. The committee noted that advice on the practicalities of coordinating and funding such a registry is outside of the ACSOM terms of reference.

A majority of patients in the clinical trials developed anti asfotase alfa antibodies. Immunogenicity to asfotase alfa has the potential to lead to immune reactions and a reduction in asfotase alfa efficacy. While it was noted that the appearance of antibodies did not appear to influence clinical outcomes in trials to date, the registry study is expected to provide further information on such reactions.

Treatment should be restricted to initiation by a physician experienced in the management of patients with metabolic or bone disorders.

Other

The committee noted the claims that, compared with patients considered as untreated historical controls, asfotase alfa treatment has demonstrated marked improvements in bone structure, growth, agility, walking distance, the requirement for mechanical ventilation and overall patient survival. The committee was unaware of the historic era from which the 'historical control' data was obtained and if the claims for efficacy of

asfotase alfa took account of incremental improvements in standard clinical care that may have occurred since that time.

The committee advised that reporting to the regulator on the status and outcomes of ongoing clinical trials should be a requirement of the pharmacovigilance plan.

The committee agreed with the TGA that the list of 'important potential risks' should include medication errors and hypersensitivity reactions (urticaria, dyspnoea, cardiovascular collapse); additionally, weight gain is an 'important identified risk'.

Comments on the safety specification of the RMP

Clinical evaluation report

The clinical evaluator made comments in the first and second round evaluations with regard to safety specifications in the draft RMP. The second round comments were:

The document entitled Pregnancy Reporting Outcome Form/Breast Feeding is a general document which might be instituted for monitoring pregnancies outcomes in response to concerns about any new medication.

The focus of the evaluator's concerns remains as to whether there could be an effect on bone and mineral metabolism in the developing foetus in terms of increasing bone formation particularly in parts of the skeleton where that might matter. The screening document does not focus on this specific issue which is discussed in the evaluator's question.

This matter could be addressed by converting column 11 on page 3 of the screening document to the wording 'Assessment of Newborn skeleton'. This would require a specific annotation.

Nonclinical evaluation report

The nonclinical evaluator made the following comment in regard to safety specifications in the draft RMP:

Results and conclusions drawn from the nonclinical program for asfotase alfa detailed in the sponsor's draft RMP (RMP submitted with the Section 31 response, letter dated 29 July 2015) are in general concordance with those of the nonclinical evaluator.

Summary of recommendations

- The sponsor should provide the educational materials intended for Australian patients. The sponsor should consider the recommendations given by the Advisory Committee on the Safety of Medicines (ACSOM) with regard to the materials (see below), where practical.
- With regard to Study ALX-HPP-501, the sponsor should consider obtaining a pregnancy history from male patients (in relation to their spouses and any offspring).
- As per recommendation in the clinical evaluation report, the sponsor should consider updating the pregnancy reporting form to include an 'assessment of newborn skeleton' item.

VI. Overall conclusion and risk/benefit assessment

The submission was summarised in the following Delegate's overview and recommendations:

Quality

The biological evaluator has no objections to the registration of Strensiq (asfotase alfa (rch)) including with regards to formulation, manufacture, stability, shelf life, sterility, specifications, labelling and microbiology. Asfotase alfa is a human recombinant TNSALP-Fc-deca-aspartate fusion protein with enzymatic activity, produced by recombinant DNA technology using mammalian CHO cell culture which has been engineered for asfotase alfa expression. Cell cultures undergo multiple processes to remove cells and cell debris (centrifugation, depth filtration, diafiltration) prior to a viral inactivation step. The downstream asfotase alfa drug substance manufacturing process includes three concentration and diafiltration steps along with three chromatography steps, and a virus filtration step. All viral/prion safety issues have been addressed, including use of animal derived excipients, supplements in the fermentation process and in cell banking. The real time data submitted support a shelf life of 2 years stored at 2 to 8°C protected from light.

The sponsor is required as a condition of registration to provide, as a minimum, the first five independent batches of the product for TGA's assessment prior to supply.

Nonclinical

The nonclinical evaluator has no objections on nonclinical grounds to the registration of asfotase alfa (rch) for the proposed indication. The studies were considered to be appropriately designed and conducted in compliance with GLP (with the exception of an exploratory single dose toxicity study).

Results of the in vitro and in vivo studies support the mechanism of action proposed by the sponsor. Asfotase alpha showed a high affinity for purified hydroxyapatite, and reversed the inhibition of mineralisation caused by PPI. The in vivo murine prophylactic dosing studies of asfotase alfa reduced the severity of mineralisation defects, promoted normal mineralisation of bones of the hindpaw and partially prevented the mineralisation deficit at the calcaneus-Achilles tendon enthesis when administered at an early age and prior to the commencement of significant postnatal mineralisation effects (for example, the appearance of secondary ossification sites). No consistent organ targets for toxic effects were identified in repeat dose toxicity studies in either juvenile rats or monkeys (not all animal ages were included with regard to postnatal bone development; in particular the period for fusion of the secondary ossification centres (relevant to human years 11 to 20)).

Acute infusion reactions (swelling of limbs, skin discolouration, reduced motor activity) were observed in rats following IV dosing, and injection site reactions were observed in monkeys following SC dosing. The reactions did not appear to involve complement, but elevated tryptase levels suggested a possible anaphylactic/anaphylactoid reaction. There were no observed adverse cardiovascular effects. Repeat dosing in animals showed anti-drug antibodies (SC > IV) resulting in reduced drug exposure in rats but not monkeys. Fertility (in rats), embryofetal development (in rats and rabbits) and pre/postnatal development (in rats) were unaffected by treatment with asfotase alfa at reasonably high exposures. However, anti-drug antibody (ADA) production affects the utility of the study in rabbits to assess embryofetal development toxicity. No genotoxicity or carcinogenicity studies were submitted, but this was considered acceptable by the evaluator for this type of product. Following IV administration there was a long apparent half-life and low volume of distribution. Bioavailability following SC dosing was variable, ranging from 34 to 100% across species at similar SC doses (2 to 5 mg/kg). The rate of absorption following SC dosing was moderate to low in mice, rats, rabbits, cynomolgus monkeys and human subjects (T_{max} 4 to 48 hours).

Clinical

The clinical evaluator has reviewed the submitted data, which included:

- 1 population PK analysis
- 1 renal function clearance report that may be related to the pop PK Study
- 7 clinical studies (including 2 extension studies) that cover efficacy and/or safety, tolerability, PK and PD
- 1 retrospective natural history study.

The clinical evaluator recommended approval in the clinical evaluation report, subject to a number of conditions, including:

- Post market experience should be reported for patients with perinatal diagnosis who are assessed to be extremely severe, and ventilator dependent from birth, and post market experience soon after 2 years of age should be analysed as a separate subset for data analysis. Adverse reports indicate that some proportion of infants commenced in the first 2 years of life may have evidence of congenital pulmonary immaturity or chronic lung disease. These infants may have irreversible lung damage and a poor chance of ventilator independent survival. Consideration may be given to withdrawal of therapy in this interval if the patient is unresponsive to therapy.
- That an Australian register of patients who could potentially benefit from asfotase alfa therapy be developed with the cooperation of the centres of expertise in each state. This would also involve a specific agreement to separately report the analysis of data on Australian patients collected via the post market pharmacovigilance data collection instrument (ALX-HPP-501) protocol. That management of patients with paediatric onset HPP should be coordinated through centres of expertise.

The following concerns were highlighted by the evaluator:

- A high frequency of ISRs given the mode of subcutaneous administration.
- An unknown but possibly small risk for modification to the density of the fetal skeleton from chronic use in pregnancy. Monitoring and reporting of all pregnancies will be mandatory. Skeletal outcomes may be dependent on the genetic status in the foetus. The outcomes of pregnancy and breast feeding will be subject to reporting.
- A proportion of infants with a perinatal diagnosis may have irreversible lung immaturity or postnatal lung pathology, and become invasive ventilator dependent. Institution of therapy in face of long-term invasive ventilation is associated with its own morbidity and mortality independent of the effectiveness of asfotase alfa in reversing the mineralisation defect.
- A need for clinical guidelines outlining indications to treat. The guidelines need to recognise that there has historically been a high mortality in the subsets of patients with prenatally diagnosed HPP, the majority of whom have perinatally lethal HPP and are chronically ventilator dependent. Similarly, there needs to be a clear clinical guideline in the case of the additional subset of babies with HPP with vitamin B6 responsive seizures who despite seizure control historically have had a high infant mortality.

Pharmacology

The pharmacology studies noted the following pharmacokinetic findings:

- The absolute bioavailability of SC asfotase alfa ranged from 46% to 98%

- Mean CL and volume of distribution (V_d) values ranged from 7.90 to 11.4 mL/min (11.4 to 16.4 L/day) and 39.7 to 71.0 L, respectively
- Median T_{max} values were 24 to 48 hours after SC injection
- C_{max} and $AUC_{0\text{ to }168\text{ h}}$ of asfotase alfa increased in a dose-proportional manner from 1 mg/kg to 2 mg/kg following SC injection
- After SC dosing, asfotase alfa exhibits flip-flop kinetics, where the effective $t_{1/2}$ is rate limited by the relatively slower absorption kinetics. The elimination $t_{1/2}$ was independent of dose after both IV (59 to 73 hours) and SC dosing (112 to 135 hours)
- Pop PK modelling identified sialic acid content (TSAC), body weight and immunogenicity status as significant covariates, with TSAC and body weight considered clinically relevant.

The pharmacology studies noted the following pharmacodynamic findings:

- Asfotase alfa reduced the key enzyme substrates of alkaline phosphatase including plasma PPI and pyridoxal 5-phosphate (PLP). Onset was rapid, and the response sustained during treatment
- Bone biopsies demonstrated normalising osteoid volume and thickness indicating improved bone mineralisation

The population PK evaluator made the following comments:

- To summarise, a generally sound PK PD modelling and simulation analysis was performed using data of less than ideal quality. Interpretation of the results in the context of the data quality was lacking. However, because the analysis findings were consistent with exploratory evaluations of the response data and simulations supported selection of a dose well represented in the tabulated exploratory response data, the dosage regimen selection is justified.
- A dose of 6 mg/kg per week was selected as the optimal dosing regimen given near maximal responses for all endpoints. PK and response profiles were similar for 1 mg/kg 6 times per week and 2 mg/kg 3 times per week. This dose represents the predominant dose used in the clinical trials.
- Data for 7 subjects (63 observations) taking concomitant vitamin B6 were excluded from the PK PD analysis for PLP restricting interpretation of the data to subjects not taking concomitant vitamin B6. The effect of concomitant vitamin B6 on PLP response is therefore not known.
- A number of PI suggestions have also been made.
- Pharmaceutical Subcommittee advice for Chemistry (PSC): The PSC noted the lack of data regarding dosing in renal failure but advised that this should not be used as a reason to conclude that no dose adjustment is needed in renal failure. Overall, the PSC supported the external pharmacometric evaluator's conclusions.

Efficacy

- Study ENB-002-08 / ENB-003-08 (pivotal): ENB-002-08 was a Phase II, 6 month, international, open label study in 11 patients to assess the safety, tolerability, and pharmacology of asfotase alfa in severely affected infants and young children ≤ 36 months of age with infantile onset HPP (onset of signs/symptoms prior to 6 months of age) based on clinical, radiographic and biochemical features. Key exclusion criteria were: current or prior clinically significant condition/disease; low serum calcium, phosphate, or 25-hydroxy vitamin D (25-OH vitamin D); current evidence of a treatable form of rickets; and prior treatment with a bisphosphonate.

Patients received an initial single IV infusion of 2 mg/kg asfotase alfa followed 1 week later by 1 mg/kg SC 3 times/week which could be titrated up to 2 mg/kg 3 times/week after 1 month, and up to 3 mg/kg 3 times/week after 3 months. Patients who completed ENB-002-08 could enrol in the extension study (ENB-003-08, ongoing) for up to an additional 54 months treatment.

- The primary efficacy endpoint was change in rickets severity from baseline to Week 24, based on skeletal radiographs measured by the radiographic global impression of change (RGI-C). This rating scale was developed by the sponsor using an expert panel. Each patient's RGI-C score at each post Baseline time point was the mean of 3 independent, blinded assessors. The RGI-C improved from Baseline to Week 24, with 7 out of 11 patients achieving a RGI-C score of + 2 or greater (indicative of substantial healing of rickets); these patients were considered 'responders'. Improvements in RGI-C appeared as early as Week 12, and were maintained in the majority of patients out to Week 144. Patients also showed improvement in the RSS scores, respiratory status (with the majority of patients being able to be weaned off respiratory support), and there was evidence of improvement in growth parameters (length, weight, BMI, head circumference) and in gross motor, fine motor, and cognitive functioning (as measured by the BSID-III, PDMS-2), and/or the BOT-2)).
- Study ENB-010-10 (pivotal): This is an ongoing, open label, multinational study of the safety, efficacy, and PK of asfotase alfa in 60 infants and children ≤ 5 years of age with perinatal/infantile onset HPP. Exclusion criteria were similar to those for ENB-002-08. Patients received a total of 6 mg/kg/week of asfotase alfa administered by SC injection, either 1 mg/kg asfotase alfa 6 times per week or 2 mg/kg asfotase alfa 3 times per week.
- In an interim analysis of 28 patients, there was an improvement in RGI C of 1.67 ($p < 0.0001$), with 21 out of 28 patients (75%) achieving a RGI-C score of + 1 or greater (indicative of at least minimal healing of rickets), 13 out of 28 patients (46.4%) achieving a RGI-C score of + 2 or greater, and 4 out of 28 patients (14.3%) achieving a score of + 3 (indicating complete or near complete healing of rickets) at Week 24. These results were generally maintained at Week 48 and beyond. Improvements were also seen in RSS scores, respiratory status, growth measurements, and motor and cognitive function.
- Study ENB-006-09/ENB-008-10 (pivotal): ENB-006-09 was a 24 week, randomised, multicentre (USA and Canada), dose ranging, open label, historical control study in 13 patients (16 historical controls) aged 5 to 12 years with infantile or juvenile onset HPP. ENB-008-10 is an ongoing, open-label extension study in 12 patients who previously completed ENB-006-09. Patients were randomised to receive SC injections of 2 or 3 mg/kg asfotase alfa 3 times a week for 24 weeks. In ENB-008-10 patients initially received 3 mg/kg/week which increased to 6 mg/kg/week. Radiographic results (RGI-C and RSS scores) were compared with historical controls.
- The majority of asfotase alfa treated patients (9 out of 13 (69%)) achieved RGI-C scores of + 2 or greater at Week 24 (i.e. were "responders"), compared with 1 out of 16 (6.3%) of historical controls. There were no differences in efficacy between the 2 dose groups at Week 24. The RSS scores decreased (improved) over time, and the median change from baseline was better in patients receiving asfotase than in the historical control group at Weeks 24, 48 and 96. Improvements were also seen in DEXA parameters, bone biopsies, growth measurements, motor function, pain and disability.
- Study ENB-009-10 (supportive): This is an ongoing, international, multicentre, open label, concurrent control study to assess the safety, efficacy, and pharmacology of asfotase alfa, in 19 adolescent ($n = 6$) and adult ($n = 13$) patients aged 13 to 65 years with infantile, juvenile, or adult onset HPP. Patients were randomised to 1 of 3

treatment groups for the first 24 weeks: a daily SC dose of 0.3 mg/kg or 0.5 mg/kg of asfotase alfa, or no treatment (control). All patients subsequently received 0.5 mg/kg/day of asfotase alfa for approximately a further 24 weeks, which then increased to 1 mg/kg 6 times per week. The median age of the control group was much lower than the combined asfotase alfa treatment group (21.0 years (range: 13, 58) versus 55 years (range: 14, 66), respectively).

- Results for the co-primary pharmacodynamic endpoints of mean change from Baseline to Week 24 in PPi and PLP showed greater reductions in the combined asfotase treatment group than the control group for both parameters (-2.100 μM versus -1.052 μM ; and -397.72 ng/mL versus + 3.13 ng/mL, respectively), but the result was only statistically significant for PLP. There were no differences in efficacy between the 2 dose groups at Week 24. Reductions in PPi and PLP were maintained during 96 weeks of follow-up. Improvements were also seen in histomorphometric parameters (osteoid volume per bone volume percentage, osteoid thickness, and mineralization lag time) and lumbar spine BMD, but not in DEXA results. There was a trend towards greater clinical improvement in the combined treated versus control patients on measures of function and disability.
- Efficacy was also assessed by pooling the data from studies ENB-002-08/ENB-003-08, ENB-010-10 and ENB-006-09/ENB-008-10. In these 52 patients, the improvements in PPi, PLP, bone mineralisation, RGI-C, growth, and physical function at Week 24 were generally consistent regardless of age at treatment initiation. Improvements were also seen in level of disability, and quality of life.
- Survival and invasive ventilator free survival were assessed in a subset of 37 infantile onset HPP patients from studies ENB-002-08/ENB-003-08 and ENB-010-10 and compared to 48 untreated non concurrent historical control patients from a global, retrospective, epidemiological study of the natural history of patients with perinatal/infantile onset HPP (Study ENB-011-10). Asfotase alfa treatment was associated with improved survival and invasive ventilator free survival regardless of the number of risk factors for mortality and morbidity. The benefit was generally retained after analyses were adjusted for 2 major sources of bias: period/year of diagnosis of control patients and age of treated patients at enrolment.

Safety

- In the pooled safety set (including studies ENB-002-08/ENB-003-08, ENB-006-09/ENB-008-10, ENB-009-10 and ENB-010-10), there were 71 patients exposed to asfotase alfa for a mean 124.5 weeks (range 0.1, 260.9). Overall, 56 out of 71 (79%) patients had ≥ 48 weeks of exposure. The majority of patients ($n = 68$) had paediatric onset HPP.
- Demographics in the pooled safety set: 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 5.42 years.
- All 71 patients experienced at least one TEAE, $n = 2,706$, with most (76%) being mild in intensity and not considered by the Investigator to be related to asfotase alfa (67%). Injection site reactions (ISRs) and injection associated reactions (IARs, such as urticaria, hypotension) accounted for 32% of all TEAEs. After excluding ISRs and IARs, the most common TEAEs were upper respiratory tract infection (39.4%), pyrexia (29.6%), and pain in extremity (28.2%). The majority of adverse drug reactions were ISRs or IARs (856 out of 906, 94%). The most common ADRs (after excluding ISRs and IARs) were deposit eye (9.9%), conjunctival deposit (8.5%), pain in extremity and nephrolithiasis (4.2%, each).

- There were 5 deaths reported (including 1 reported prior to the first dose of asfotase alfa) all occurring in patients < 1 year of age at enrolment who had 1 or more prognostic factors for poor outcome (namely rachitic chest deformity, respiratory compromise, and/or vitamin B6 responsive seizures). Only 1 death was considered possibly related to asfotase alfa (pneumonia). In total 183 non-fatal SAEs occurred in 32 patients. The most common SAEs were: craniosynostosis (11.3%), pneumonia (7.0%), respiratory disorder (5.6%), upper respiratory tract infection (URTI), convulsion, pyrexia and food intolerance (4.2%, each). Three patients discontinued because of TEAEs. Anaemia/Hb decreased, increased ALT and/or AST, increased urine calcium/creatinine ratio, hypercalcaemia, hypocalcaemia, and increased parathyroid hormone were all reported in 3 or more patients. Antidrug antibodies were detected in 56 out of 69 (81%) of patients with post Baseline antibody data available. Patients with continuously positive ADA status were more likely to experience TEAEs (93%) than those not continuously positive (74%), influenced primarily by a higher proportion of ISRs and IARs. ADA status was not positively associated with SAEs.

Risk management plan

The Pharmacovigilance and Special Access Branch (PSAB) has provisionally accepted the EU Risk Management Plan for Strensiq (asfotase alfa), version 01.3, dated 22 May 2015 (data lock point 30 November 2013), with the Australian Specific Annex (ASA), version 1.1, dated July 2015. Further amendments may be required.

The following were outstanding matters and should be followed up with PSAB and in the Pre ACPM Response where required:

- The sponsor should provide the educational materials intended for Australian patients. The sponsor should consider the following recommendations given by the ACSOM with regard to the materials provided for prescribers, patients and carers, where practical: Clear instructions regarding the subcutaneous injection technique. The technique described in the injection guide may result in loss of control of the needle or its breakage. The need for rotation of injection sites and rotation frequency (for example is it needed at every injection?) should be highlighted in the animated injection guide.
- Clear directions on cold chain management relevant to the Australian climate ('room temperature') and environment, and applicable to domestic storage and when travelling (including in motor vehicles). There needs to be clear advice on both the minimum time required for the medicine to reach 'room temperature' and the maximum permitted time outside refrigeration, consistent with product stability. The temperature of the injection solution can affect the patient's discomfort and so the patient may reasonably prefer injection of the medicine at a particular temperature.
- Clear directions on how to implement 'protect from light', relevant to the Australian climate and environment.
- Advice on selection of the syringe and legibility of its graduations; advice on carriage and disposal of sharps.
- The presence of what appears like particulate matter is common for biologicals when taken from refrigerated storage but this often disappears (goes into solution) once the solution has been warmed up to room temperature. This should be addressed, if relevant.
- Photographs to depict the different product strengths and dosages, which are colour-coded.

- As the patient is expected to gain weight, and dosage is weight based, the need for regular recording of body weight and review of the appropriate dosage should be emphasised. For example, a digital diary could be provided, with alerts at body weight points that should trigger review of the dosage.
- Advice for males on the possible effect on fertility; advice for females on contraception and pregnancy testing.
- With regard to the post market pharmacovigilance data collection instrument (ALX-HPP-501), the sponsor should consider obtaining a pregnancy history from male patients (in relation to their spouses and any offspring).
- As per recommendation in the CER, the sponsor should consider updating the pregnancy reporting form to include an 'assessment of newborn skeleton' item.

Delegates considerations

Efficacy

The efficacy of asfotase alfa is based on 3 pivotal Phase II studies with two extension studies, and 1 supportive study in 71 patients with paediatric (n = 68) or adult (n = 2) onset HPP (1 patient had an unknown form of HPP). Although based on a small number of patients, the clinical development program for asfotase alfa is considered adequate for this rare, potentially fatal disease given the unmet need for an effective treatment option. There is no specific guideline for HPP; the efficacy endpoints chosen by the sponsor appear acceptable based on the pathophysiology of the disease, however there were a large number of endpoints used, and they were not uniform between the studies. This complicates the interpretation of the results, however in general the effect of asfotase on each endpoint was consistent across the studies. Where measured, rickets severity (based on RGI-C and RSS scores) improved over 24 weeks, with 46 to 69% responding (achieving a RGI-C score of + 2 or greater) and RSS scores decreased from baseline. These results were generally maintained for the duration of follow up and appeared to be consistent across the age groups studied. Improvements in biochemical parameters and clinically relevant improvements in growth, physical function, and respiratory status were also observed and provided supportive evidence of efficacy to the radiographic endpoints. Asfotase treatment improved survival and ventilator free survival in paediatric HPP patients compared with historical controls. Only one study (ENB-009-10) had a concurrent control (no treatment) group which demonstrated the superiority of asfotase alfa on PPI and PLP. The historical control data is of limited use as the relative contribution of asfotase versus improvements in supportive care in the comparison is not clear; however this should not affect interpretation of the radiographic assessments. Four studies are ongoing.

Dose

It should be noted that during the course of the studies, the dose of asfotase varied from 1 mg/kg three times weekly, 1 mg/kg six times weekly, up to 3 mg/kg three times weekly. The proposed dose (2 mg/kg 3 times per week, or 1 mg/kg 6 times per week) appears reasonable based on preclinical pharmacology, first in human and simulated PK study results.

Safety and RMP

Asfotase alfa (rch) has been studied in a limited number of patients with HPP with exposure exceeding the 12 months required for long-term treatment. As could be expected

with a SC route of administration, the majority of ADRs were ISRs or IARs, but these were generally mild to moderate in severity and self-limiting. Anti-drug antibody development was high and may lead to increased adverse events. The most common SAEs were: craniosynostosis, pneumonia, and respiratory disorder. Four deaths occurred on asfotase alfa, but each patient had one or more poor prognostic factors. An RMP has been provisionally accepted and the sponsor has been requested to give specific consideration to the content of the educational material, and additional data that should be collected in the post marketing study. The sponsor should respond to the outstanding RMP matters.

Data deficiencies

Efficacy and safety data are based on Phase II studies with limited patient numbers and methodological limitations (for example open label, lack of control arm, inconsistency of endpoints used and so on). There were even fewer patients aged between 13 and 18 years and ≥ 18 years as is to be expected based on the natural history of HPP. Data from the study extensions and ongoing studies is required to supplement these data, although it will remain limited because of the rarity of HPP.

Conditions of registration

The following were proposed as conditions of registration:

- The implementation in Australia of the EU Risk Management Plan for Strensiq (asfotase alfa), version 01.3, dated 22 May 2015 (data lock point 30 November 2013), with the Australian Specific Annex (ASA), version 1.1, dated July 2015 and Pre-ACPM Response of (date), included with submission PM-2014-03845-1-3, and any subsequent revisions, as agreed with the TGA.
- It is a condition of registration that, as a minimum, the first five independent batches of asfotase alfa (Strensiq) imported into/manufactured in Australia are not released for sale until the manufacturer's release data have been assessed and endorsed for release by the TGA Laboratories Branch.
- The following study reports must be submitted to the TGA, as soon as possible after completion, for evaluation as a Category 1 submission(s):
 - Study ENB-003-08: Extension study of ENB-0040 (human recombinant tissue-nonspecific alkaline phosphatase fusion protein) in severely affected infants and young children with hypophosphatasia (HPP).
 - Study ENB-009-10: A Randomized, 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 (HPP).
 - Study ENB-008-10: 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).
 - Study ENB-010-10: An Open-Label, Multicentre, 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 (HPP).
 - Study in adult patients with HPP as required by the CHMP in their Assessment report (Procedure No. EMEA/H/C/003794/0000).
 - Prospective, long-term, observational study in STRENSIQ (asfotase alfa) treated patients with perinatal/infantile-onset and juvenile-onset hypophosphatasia

(HPP) from ages birth and older, as required by the FDA in their BLA APPROVAL letter dated 23 October 2015.

- Establishment of a long-term registry of patients with HPP.

Summary of issues

The primary issues with this submission are as follows:

1. Safety and efficacy are based on limited, uncontrolled, Phase II data in 71 patients with HPP. Is this acceptable given HPP is rare and there is an unmet clinical need.
2. Lack of data in patients aged 13 to 18 years, and > 18 years, consistent with natural history of HPP.

Proposed action

The Delegate had no reason to say, at this time, that the application for asfotase alfa should not be approved for registration.

Delegate's questions for the sponsor

1. *The FDA label provides safety and efficacy data for 99 patients compared with the 71 patients evaluated by the TGA. The FDA label also highlights additional safety issues, in particular a single hypersensitivity reaction consistent with anaphylaxis, lipodystrophy and nephrocalcinosis.*

Please provide a summary in the pre-ACPM response of this additional data and identify the source of the additional data in the FDA label. If based on additional interim reports or final reports not previously submitted to the TGA, these data should be submitted for evaluation post registration.

Please update the PI with the relevant safety data.

2. *The sponsor is requested to respond to the clinical evaluator's second round recommendations and issues of concern/uncertainty.*
3. *The sponsor is requested to respond to the population PK report and its recommendations and PI comments.*
4. *The sponsor is requested to respond to the outstanding RMP matters identified with the RMP section.*

Request for ACPM advice

The ACPM was requested by the Delegate to provide advice on the following specific issues:

1. The sufficiency of the data to support long term treatment of patients with paediatric onset HPP, given:
 - a. Small number of patients studied (n = 71), particularly in the age groups of 13 to 18 years, and > 18 years.
 - b. Limited period of follow-up to assess rare safety events.
 - c. Design of the clinical trials.
2. Does the PI require a dosing chart similar to that in the EU SmPC or FDA Label?

The committee was also requested to provide advice on any other issues that it thinks may be relevant to a decision on whether or not to approve this application.

Response from sponsor***Sponsor's responses to Delegate's questions***

1. *The FDA label provides safety and efficacy data for 99 patients compared with the 71 patients evaluated by the TGA. The FDA label also highlights additional safety issues, in particular a single hypersensitivity reaction consistent with anaphylaxis, lipodystrophy and nephrocalcinosis.*

Please provide a summary in the pre-ACPM response of this additional data and identify the source of the additional data in the FDA label. If based on additional interim reports or final reports not previously submitted to the TGA, these data should be submitted for evaluation post registration.

Please update the PI with the relevant safety data.

Sponsor's response:

The integrated data in the Australia (and EMA) submission was based on a November 2013 data cut. During the review of the US-BLA, as required by the FDA a Day 120 Safety Report was submitted in April 2015 (with a data cut of November 2014). The single case of hypersensitivity was included in the Day 120 Safety Report.

The Australian PI is based on data from the 71 patients. Hence, for consistency, the efficacy and safety sections are based on the final approved EU SmPC.

2. *The sponsor is requested to respond to the clinical evaluator's second round recommendations and issues of concern/uncertainty.*

Sponsor's response:

The sponsor has initiated a global HPP disease registry (ALX-HPP-501) that will enrol approximately 500 patients and record data from these patients for at least 5 years. The registry will be initiated in Australia and include patients treated with asfotase alfa as well as untreated patients to expand understanding of the natural history of HPP and the effects, including adverse experiences, of asfotase alfa treatment.

Alexion is, as always, committed to supporting physicians and their patients with severe and life threatening rare diseases. Alexion is experienced in coordinating patient care, physician education, and managing Registries for ultra-rare diseases. The Australian HPP registry (ALX-HPP-501) will support the monitoring of Strensiq treatment in Australian HPP patients.

Alexion wishes to highlight that the proposed dosing regimen is 6mg/kg/sc weekly, administered as 1 mg/kg 6 times a week or 2 mg/kg 3 times a week.

Alexion will provide data on post-market experience from the HPP Registry (ALX-HPP-501) for patients with perinatal diagnosis who are assessed to be extremely severe, and ventilator dependent from birth. Furthermore, post-market experience soon after 2 years of age will be analysed as a separate subset of these data in the ALX-HPP-501 study report.

As stated by the evaluator, the Post marketing Pharmacovigilance data collection instrument, ALX-HPP-501 (HPP Registry) will collect information on the natural history of HPP patients of all ages and characterize the epidemiology of the Australian HPP population, generating a Register of patients who could potentially benefit from asfotase alfa therapy. This Disease Registry will be coordinated by Alexion under the advice of an expert advisory committee. As per the sponsor's response above, the management of patients with paediatric-onset HPP will be coordinated with healthcare professionals to ensure high proficiency monitoring and patient care.

3. *The sponsor is requested to respond to the population PK report and its recommendations and PI comments.*

Population PK report recommendations and PI comments:

- *'To summarise, a generally sound PK-PD modelling and simulation analysis was performed using data of less than ideal quality. Interpretation of the results in the context of the data quality was lacking. However, because the analysis findings were consistent with exploratory evaluations of the response data and simulations supported selection of a dose well represented in the tabulated exploratory response data, the dosage regimen selection is justified.'*
- *'A dose of 6 mg/kg per week was selected as the optimal dosing regimen given near maximal responses for all endpoints. PK and response profiles were similar for 1 mg/kg 6 times per week and 2 mg/kg 3 times per week. This dose represents the predominant dose used in the clinical trials.'*
- *'Data for 7 subjects (63 observations) taking concomitant vitamin B6 were excluded from the PK-PD analysis for PLP restricting interpretation of the data to subjects not taking concomitant vitamin B6. The effect of concomitant vitamin B6 on PLP response is therefore not known.'*
- *'A number of PI suggestions have also been made.'*
- *'PSC advice: The PSC noted the lack of data regarding dosing in renal failure but advised that this should not be used as a reason to conclude that no dose adjustment is needed in renal failure. Overall, the PSC supported the external pharmacometric evaluator's conclusions.'*

Sponsor's response:

The evaluator's comments are noted. Please refer to the sponsor's comment on the PI for response to the PI suggestions.

4. *The sponsor is requested to respond to the outstanding RMP matters identified with the RMP section.*
 - a. *The sponsor should provide the educational materials intended for Australian patients. The sponsor should consider the following recommendations given by the ACSOM with regard to the materials provided for prescribers, patients and carers, where practical.*

Sponsor's response:

At this time, Alexion is assessing external vendors to provide support for Australian patients being treated with Strensiq, which will include guidance on the various considerations posed by ACSOM (dosing chart, injection technique; medicine storage, including when traveling; and alerts for dosage adjustments, considering the weight based dosing). Alexion agree to consider ACSOM's recommendations when finalizing the Australian specific RMP materials which will be incorporated into Alexion's patient support.

Alexion is, as always, committed to supporting patients with rare diseases. As the details for the program are still to be determined, Alexion propose to submit the RMP materials to the TGA Post-market Surveillance Branch (PMSB) for approval, with the objective of implementing within 3 months of TGA approval (as per the final RMP evaluation report).

Alexion wishes to note that the 2 Australian HPP patients currently being treated with Strensiq are adequately trained for, and are currently administering, home injections. These patients and prescribers will be provided with the PMSB approved RMP materials upon finalization and offered to be enrolled into the HPP Registry.

- b. *With regard to the post market pharmacovigilance data collection instrument (ALX-HPP-501), the sponsor should consider obtaining a pregnancy history from male patients (in relation to their spouses and any offspring).*

Sponsor's response:

Alexion will collect pregnancy history (history of HPP) for the spouses and offspring of male patients in the HPP Registry.

- c. *As per recommendation in the CER, the sponsor should consider updating the pregnancy reporting form to include an 'assessment of newborn skeleton' item.*

Sponsor's response:

The pregnancy reporting and outcome form is a global standard form used to monitor pregnancy outcomes in clinical trials and post-marketing surveillance for all Alexion products. Reporter assessment of the newborn skeleton following maternal or paternal drug exposure is an outcome specific for Strensiq and therefore an outcome that was not considered for inclusion in the standard form. This specific request for newborn skeletal assessment is best sought at the time of follow up of delivery and pregnancy outcome.

Alexion will seek to provide specific instructions to the reporter to provide comment on the newborn skeleton as part of the neonatal assessment for maternal and paternal drug exposure reports. The procedure to request the reporter to provide pregnancy report follow up and assessment of the newborn skeleton will be incorporated into Alexion Pharmacovigilance procedures in Australia.

Response from sponsor to Delegate's request for ACPM advice

1. *The sufficiency of the data to support long term treatment of patients with paediatric onset HPP, given:*
 - a. *Small number of patients studied (n = 71), particularly in the age groups of 13 to 18 years, and > 18 years.*
 - b. *Limited period of follow-up to assess rare safety events.*
 - c. *Design of the clinical trials*
2. *Does the PI require a dosing chart similar to that in the EU SmPC or FDA Label?*

Sponsor's response:

Alexion acknowledge the Delegate's recommendation that they have no reason to say, at this time, that the application for asfotase alfa should not be approved for registration.

HPP is an extremely rare, serious, and life threatening metabolic disorder. The incidence of the most severe forms of the disease is thought to be about 1 in 100,000 live births, demonstrating the extreme rarity of HPP and the small population of patients available for clinical studies to assess the efficacy and safety of new treatments for the indication. Currently, there are no treatments registered for this debilitating condition in Australia.

Paediatric onset HPP is associated with significant mortality (as high as 50%) and morbidity, including multiple bone manifestations such as rickets/osteomalacia, altered calcium and phosphate metabolism, impaired growth and mobility, respiratory compromise that may require ventilation, and vitamin B6 responsive seizures. Available therapies do not correct the underlying cause of the disease and have no impact on the bone hypomineralisation characteristic of the disease. Thus, there is a high unmet medical need to provide HPP patients with a safe and effective therapy.

The clinical development of asfotase alfa was complicated by the fact that the presenting signs and symptoms of HPP depend upon the age of presentation. As a result, clinical studies to assess the efficacy and safety of new treatments for the condition involved

recruitment of patients of different ages with varying presentation of the disease (that is, perinatal/infantile onset HPP, juvenile onset HPP, and adult onset HPP). The overall analysis set included in the submitted application includes a total of 71 patients who were treated with asfotase alfa (48 patients with infantile onset HPP, 20 with juvenile onset HPP, 2 with adult onset HPP, and 1 HPP patient with time of disease onset not known). Patients ranged from 1 day to 66 years of age at initiation of treatment. The asfotase alfa clinical development program included 13 adult patients (either adult patients with paediatric onset HPP or patients with adult onset HPP).

Due to the rarity and serious debilitating nature of HPP, the asfotase alfa clinical development program did not include randomized placebo controlled clinical trials. Employment of placebo control would have resulted in withholding a potentially effective treatment, leading to serious irreversible harm. The use of a non concurrent, matched historical control reference is recognized as an important component in the clinical development of therapies for potentially devastating diseases with no other available treatment options.²⁰ Given these factors, along with the absence of any alternative treatments, patients were assigned to active treatment and a non concurrent historical control group was used as a comparator.

Although comprehensive data are not available, the totality of the clinical data collected to date, including demonstrated clinically meaningful benefits across disease relevant endpoints with a 3 year follow up, supports a favourable benefit over risk profile for treatment with asfotase alfa in patients of any age with paediatric onset HPP.

The sponsor considers that the completion of the ongoing studies (ENB-002-08/ENB-003-08, ENB-006-09/ENB-008-10, ENB-010-10, and ENB-009-10) planned by January 2017, as well as the establishment of a long term surveillance program/patient registry to monitor long term efficacy and safety of asfotase alfa in HPP patients, will provide adequate data to confirm the benefit/risk profile of asfotase alfa on a regular basis.

Advisory committee considerations

The ACPM resolved to recommend to the TGA delegate of the Minister and Secretary that:

The ACPM, taking into account the submitted evidence of efficacy, safety and quality, agreed with the delegate and considered STRENSIQ aqueous solution for injection containing 40 mg/mL, 100 mg/mL of asfotase alfa to have an overall positive benefit-risk profile for the indication;

Strensiq (asfotase alfa rch) is indicated for long-term enzyme replacement therapy in patients with paediatric-onset hypophosphatasia.

In making this recommendation the ACPM was of the view that there was sufficient evidence to support long-term therapy.

Proposed conditions of registration

The ACPM agreed with the Delegate on the proposed conditions of registration.

Proposed Product Information (PI)/Consumer Medicine Information (CMI) amendments

The ACPM agreed with the Delegate to the proposed amendments to the PI and CMI and specifically advised on the inclusion of the following:

A dosing chart should be included in the PI similar to the EU SmPC or the US PI.

²⁰ Guidance documents ICH E10 CPMP, ICH 364 96

Specific advice

The Advisory Committee on Prescription Medicines (ACPM), having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, advised the following:

1. *The sufficiency of the data to support long-term treatment of patients with paediatric onset HPP, given:*
 - a. *Small number of patients studied (n = 71), particularly in the age groups of 13 to 18 years, and > 18 years*
 - b. *Limited period of follow-up to assess rare safety events.*
 - c. *Design of the clinical trials*

The ACPM noted that this is a very rare chronic disease which will probably require long term treatment. The ACPM noted the lack of patients in the age group of 13 to 17 years of age was probably a result of the severity of the disease with death often occurring at the perinatal or infantile stage. Patients with a milder form of the disease are much rarer, limiting the pool of patients available. The ACPM acknowledged that the data to support long-term treatment are currently limited. However, there is no evidence that patients requiring treatment would be cured and not require ongoing therapy. Further trials could address the impact of therapy cessation once biochemical and radiological correction is achieved.

The ACPM considered that ongoing data collection to demonstrate the long term outcomes of patients exposed to novel treatments such as asfotase is essential. The post-marketing surveillance proposal of the sponsor is satisfactory for this purpose, but requires the treating physicians to enter data. The ACPM advised that therapy would be best supervised by a centre of excellence to ensure proper data collection.

Overall, the ACPM advised that there is sufficient data to support long-term treatment and noted that ongoing studies will provide further information about the treatment of HPP. The ACPM also was of the view that post-market surveillance was essential particularly with regard to collecting data on adverse events. The ACPM considered that an international registry would also provide further essential information on the treatment of HPP.

2. *Does the PI require a dosing chart similar to that in the EU SmPC or FDA Label?*

The ACPM noted that two dosage schedules were proposed, which might cause confusion. In addition, the rationale for the choice of dosing regimens was unclear. Therefore, it was essential that a dosage chart is provided in the PI, similar to the EU SmPC or the US PI.

The ACPM advised that implementation by the sponsor of the recommendations outlined above to the satisfaction of the TGA, in addition to the evidence of efficacy and safety provided would support the safe and effective use of these products.

Outcome

Based on a review of quality, safety and efficacy the TGA approved the registration of Strensiq asfotase alfa (rch) solution for administration in 80 mg/0.80 mL, 12 mg/0.30 mL, 18 mg/0.45 mL, 28mg/0.70 mL and 40 mg/1.00mL indicated for:

Strensiq is indicated as enzyme replacement therapy in patients with paediatric onset hypophosphatasia.

Specific conditions of registration applying to these goods

1. The Strensiq (asfotase alfa), EU-Risk Management Plan (EU-RMP), version 01.3, dated 22 May 2015 (data lock point 30 November 2013), with the Australian Specific Annex (ASA), version 1.1, dated July 2015 and Pre-ACPM Response of 16 November 2015, included with submission PM-2014-03845-1-3, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.
2. Batch Release testing by OLSS: It is a condition of registration that, as a minimum, the first five independent batches of asfotase alfa (STRENSIQ) imported into/manufactured in Australia are not released for sale until the manufacturer's release data have been assessed and endorsed for release by the TGA Laboratories Branch.

The sponsor must supply:

- a. Certificates of Analysis of all active ingredient (drug substance) and final product.
 - b. Information on the number of doses to be released in Australia with accompanying expiry dates for the product and diluents (if included).
 - c. Evidence of the maintenance of registered storage conditions during transport to Australia.
 - d. 5 vials of each batch for testing by the Therapeutic Goods Administration LB together with any necessary standards, impurities and active pharmaceutical ingredients (with their Certificates of Analysis) required for method development and validation.
3. The following study reports must be submitted to the TGA, as soon as possible after completion, for evaluation as a Category 1 submission(s):
 - a. Study ENB-003-08: Extension study of ENB-0040 (human recombinant tissue-nonspecific alkaline phosphatase fusion protein) in severely affected infants and young children with hypophosphatasia (HPP).
 - b. Study ENB-009-10: A Randomized, Open-Label, Multicenter, 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 (HPP).
 - c. Study ENB-008-10: 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).
 - d. Study ENB-010-10: 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 (HPP).
 - e. Study in adult patients with HPP as required by the CHMP in their Assessment report (Procedure No. EMEA/H/C/003794/0000).
 - f. Prospective, long-term, observational study in STRENSIQ (asfotase alfa) treated patients with perinatal/infantile-onset and juvenile-onset hypophosphatasia (HPP) from ages birth and older, as required by the FDA in their BLA APPROVAL letter dated 23 October 2015.
 - g. The Day 120 Safety Report submitted to the FDA
 4. Establishment of a long-term registry, with regular reporting to the TGA as per the agreed RMP requirements, that includes Australian patients with hypophosphatasia

to monitor the long term efficacy and safety of asfotase and includes patients with perinatal diagnosis who are severe and ventilator dependent from birth (to be reported as a specific subset of the data).

Attachment 1. Product Information

The PI approved for Stensiq at the time this AusPAR was published is at Attachment 1. For the most recent PI, please refer to the TGA website at <<https://www.tga.gov.au/product-information-pi>>.

Attachment 2. Extract from the Clinical Evaluation Report

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