

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

125513Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	October 23, 2015
From	Anil Rajpal, MD, MPH, Clinical Team Leader Division of Gastroenterology and Inborn Errors Products
Subject	Cross-Discipline Team Leader Review
NDA/ BLA Supplement #	BLA 125513
Applicant	Alexion Pharmaceuticals
Date of Submission	December 23, 2014
PDUFA Goal Date	November 23, 2015 (includes 3-month extension due to Major Amendment)
Proprietary Name / Established (USAN) names	Strensiq / Asfotase alfa
Dosage forms / Strength	Sterile aqueous solution for subcutaneous (SC) injection; 18 mg/0.45 mL, 28 mg/0.7 mL, 40 mg/mL, or 80 mg/0.8 mL
Proposed Indication	(b) (4) in patients with infantile- and juvenile-onset hypophosphatasia (HPP)"
Recommended Action:	Approval

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1 Introduction

This rolling submission, final portion received December 22, 2014, is the initial Biologics License Application (BLA) for Strensiq (asfotase alfa). The Applicant proposes the following indication: "... for [REDACTED]^{(b)(4)} in patients with infantile- and juvenile-onset hypophosphatasia (HPP)."

Hypophosphatasia (HPP) is a rare genetic disorder caused by loss-of-function mutation(s) in the gene encoding tissue-nonspecific alkaline phosphatase (TNSALP), and is characterized by defective bone mineralization and impaired phosphate and calcium regulation, resulting in elevations of several TNSALP substrates including inorganic pyrophosphate (PPi) and pyridoxal-5'-phosphate (PLP).

Strensiq, a formulation of asfotase alfa, is a soluble glycoprotein composed of two identical polypeptide chains, each consisting of: (1) the catalytic domain of human TNSALP, (2) the human immunoglobulin G₁ Fc domain, and (3) a deca-aspartate peptide used as a bone targeting domain.

2 Background

2.1 Hypophosphatasia

Hypophosphatasia (HPP) is a rare genetic disorder caused by the loss-of-function mutation(s) in the gene encoding tissue-nonspecific alkaline phosphatase (TNSALP). HPP is characterized by defective bone mineralization and impaired phosphate and calcium regulation, resulting in elevations of several TNSALP substrates including inorganic pyrophosphate (PPi) and pyridoxal-5'-phosphate (PLP).

HPP is characterized by hypomineralization of the bones and premature shedding of primary teeth and/or severe dental caries. HPP is clinically heterogeneous, with disease severity ranging from death in utero to isolated dental loss in childhood or adulthood.¹ Six variants of the disease have been identified (see table below).

¹ Mornet E, Nunes ME, Hypophosphatasia, *GeneReviews* (<http://www.ncbi.nlm.nih.gov/books/NBK1150/>)

Variants	Characteristic Features
Perinatal (lethal) HPP	<ul style="list-style-type: none"> • Characterized by pulmonary insufficiency (the usual cause of mortality in this subgroup) and hypercalcemia. • Liveborn or stillborn infants may have a small thoracic cavity and short bowed legs.
Perinatal (benign) HPP	<ul style="list-style-type: none"> • Characterized by prenatal bone abnormalities and a childhood HPP or adult HPP phenotype later in life. • All reported cases of benign HPP have been born to mothers with biochemical evidence of HPP.
Infantile HPP	<ul style="list-style-type: none"> • Characterized by rickets with an onset between birth and six months of age.
Childhood HPP	<ul style="list-style-type: none"> • Characterized by rickets and fractures
Adult HPP	<ul style="list-style-type: none"> • Adult HPP characterized by early dental loss, stress fractures, and pseudofractures of the lower extremities
Odontohypo-phosphatasia	<ul style="list-style-type: none"> • Characterized by premature loss of primary teeth and/or dental caries as an isolated finding or as a clinical feature of other forms of HPP

Table above is summarized from the Clinical Review by Carla Epps.

2.2 Asfotase Alfa

Asfotase alfa is a soluble IgG1 Fc fusion glycoprotein comprised of two identical polypeptide chains, each with a length of 726 amino acids. Each polypeptide chain is comprised of a soluble catalytic domain of human TNSALP, a human immunoglobulin IgG1 Fc domain, a deca-aspartate peptide (D10) used as a bone-targeting domain, and two amino acid long linkers between these domains. Each polypeptide chain contains (b) (4). The two polypeptides are covalently linked together by two disulfide bonds. The schematic figure is shown below.

TNSALP enables bone mineralization by locally cleaving inorganic pyrophosphate (Pi). Pi precipitates with calcium as calcium phosphate, which then mineralizes and becomes hydroxyapatite (HA). HA confers strength and rigidity to bones.

Figure 2: Representation of the Asfotase Alfa Structure



2.3 Current Treatments

There are no approved treatments for HPP.

Treatment is mainly symptomatic through pain control and orthopedic procedures to repair fractures and stabilize weakened bone.

Previously attempted treatments have not been successful.

- Serum from patients with Paget's disease: Four infants have been treated with serum from patients with Paget's disease, and all died of respiratory complications.
- Bisphosphonates: There are only a few case reports on the use of bisphosphonates to treat infants and adults with HPP. One infant died at 14 months of age and an adult patient did not show disease improvement after treatment with bisphosphonates.
- Experimental Bone Marrow Transplant: Two infants underwent experimental bone marrow transplant for HPP. All patients had initial improvement but continued to have disease progression.
- Recombinant human parathyroid hormone: One adult patient with HPP, who was treated with recombinant human parathyroid hormone (PTH), showed improvement in bone remodeling. Other PTH-treated patients did not show similar improvement. It should be noted that PTH is contraindicated in children with growing bone because nonclinical studies revealed an increased incidence of osteosarcoma in growing rats.

2.4 Regulatory History

The table below provides a summary of the pertinent regulatory activity of asfotase alfa prior to submission of the BLA.

Table 1. Pertinent Regulatory History of Asfotase Alfa (BLA 125513)*

Date	Event
June 14, 2007	The Division held a pre-IND meeting with the sponsor. Clinical discussions during the meeting included a discussion of the sponsor's plans and intended uses of asfotase alfa in the various HPP populations. The FDA expressed its concern about the potential for off-label use and recommended that all populations be studied in a timely manner.
June 4, 2008	IND 100,619 was opened for Protocol ENB-001-8, a study in adults, and Protocol ENB-002-08, a compassionate use protocol for patients with perinatal/infantile HPP.
June 7, 2008	The Division issued a Partial Clinical Hold due to insufficient nonclinical data to support dosing for the perinatal/infantile HPP protocol.
September 12, 2008	The Division held a Type C meeting with the sponsor to discuss nonclinical studies needed to support chronic dosing in clinical trials.
September 12, 2008	Asfotase alfa was granted Orphan Drug Designation.
November 19, 2008	The Division removed the Partial Clinical Hold.
May 14, 2009	Asfotase alfa was granted Fast Track Designation.
December 16, 2009	The Division held an End-of-Phase 1 meeting with the sponsor. During the meeting, the Division recommended that the sponsor establish natural history comparator groups for the intended study populations.
May 31, 2011	The Division held an End-of-Phase 2 meeting with the sponsor.
June 4, 2012	Sponsorship of IND 100,619 was transferred from Enobia Pharma Inc. to Alexion Pharma International Sàrl.
April 16, 2013	The Division held a Type C meeting with the sponsor to discuss the clinical development program. The Division agreed that the endpoints of overall survival and ventilator-free survival are appropriate for the perinatal/infantile population.
May 21, 2013	Asfotase alfa was granted Breakthrough Therapy Designation (BTD) for perinatal-, infantile- and juvenile-onset HPP. BTD was not granted for adult-onset HPP due to insufficient clinical evidence (b) (4)
September 3, 2013	The Division held a Post Breakthrough Therapy Designation meeting with the sponsor. During the meeting, the Division agreed that a historical control group may be acceptable for clinical trials to support an indication in the perinatal/infantile-onset and juvenile-onset populations. However, the Division noted that the sponsor may need to conduct other studies to support labeling for the juvenile-onset population.
November 26, 2013	The Division held a pre-BLA meeting with the sponsor to discuss CMC aspects of the BLA.

Date	Event
January 14, 2014	The Division held Post Breakthrough Therapy meetings with the sponsor to discuss the overall immunology, clinical pharmacology, and clinical plans for asfotase alfa.
March 21, 2014	The Division granted the sponsor's request for a rolling submission and review of their BLA.
March 31, 2014	The sponsor submitted the first part (Wave 1) of its rolling submission.
June 30, 2014	The Sponsor submitted the second part (Wave 2) of its rolling submission.
July 8, 2014	The Division held a pre-BLA meeting with the sponsor. During the meeting, the sponsor clarified that the primary efficacy endpoint for the juvenile-onset HPP population would be gait assessment.
December 23, 2014	The sponsor submitted the third and final part (Wave 3) of its rolling submission.

*IND 100619

Above is modified from the Clinical Review by Carla Epps

Key agreements are highlighted; see also Section 7 of this CDTL Review.

See the Clinical Review by Carla Epps for additional details of the regulatory history.

2.5 Current Application

This application was submitted as a rolling submission. The first portion of the application was submitted on March 27, 2014, and the final portion of the application was submitted on December 23, 2014. It was classified as a six-month submission with a PDUFA deadline of August 23, 2015. Because of a major amendment, the PDUFA date was extended to November 23, 2015.

No Advisory Committee meeting was convened to discuss this application.

The relevant review disciplines have all written review documents. The primary review documents relied upon were the following:

- (1) Clinical Review by Carla Epps, dated October 22, 2015
- (2) Statistics Review by Benjamin Vali, dated September 19, 2015
- (3) Clinical Pharmacology Review by Christine Yuen-Yi Hon, dated August 7, 2015
- (4) Pharmacology/Toxicology Review by Dinesh Gautam, dated August 27, 2015
- (5) Quality Reviews:
 - (a) Drug Substance and Drug Product Reviews:
 - (i) Drug Substance Review by Joslyn Brunelle, dated August 6, 2015
 - (ii) Drug Product Review by Gunther Boekhoudt, dated August 7, 2015
 - (iii) Addendum to Drug Substance and Product Reviews by Joslyn Brunelle and Gunther Boekhoudt, dated September 8, 2015
 - (b) Microbiology Reviews:
 - (i) Microbiology Review by Candace Gomez-Broughton, dated August 21, 2015
 - (ii) Addendum to Microbiology Review by Candace Gomez-Broughton, dated September 22, 2015

- (c) Facilities Reviews:
 - (i) Facilities Review by Steven Fong, dated August 12, 2015
 - (ii) Addendum to Facilities Review dated September 23, 2015
- (d) Other Reviews:
 - (i) Complement Activation - Drug Substance Review by Mate Tolnay, dated August 6, 2015
 - (ii) Immunogenicity Review by Frederick Mills, dated August 6, 2015
- (e) Integrated Summary Quality Review by Cristina Ausin-Moreno, dated September 30, 2015
- (6) Consult Reviews:
 - (a) Division of Neurology Products (DNP) Consult Review by Teresa Buracchio, dated June 24, 2015
 - (b) Division of Bone, Reproductive, and Urologic Products (DBRUP) Consult Review by Stephen Voss, dated April 16, 2015
 - (c) Office of Scientific Investigations (OSI) Clinical Inspection Summary by Susan Leibenhaut, dated July 30, 2015
- (7) Office of Surveillance and Epidemiology Reviews:
 - (a) Division of Risk Management's (DRISK) Review by Jasminder Kumar, dated October 22, 2015
 - (b) Division of Epidemiology (DEPI) Review by Joel Weissfeld, dated October 2, 2015
- (8) Labeling Reviews:
 - (a) Division of Pediatric and Maternal Health (DPMH) Reviews:
 - (i) Maternal Health Labeling Recommendations Review by Carrie Ceresa, dated August 6, 2015
 - (ii) Pediatric Labeling Recommendations Review by Ethan Hausman, dated June 29, 2015
 - (b) Division of Medication Error Prevention and Analysis (DMEPA) Reviews:
 - (i) Label, Labeling and Packaging Review by Matthew Barlow, dated August 3, 2015
 - (ii) DMEPA Proprietary Name Review by Matthew Barlow, dated April 13, 2015
 - (c) Office of Prescription Drug Promotion (OPDP) and Division of Medical Policy Programs (DMPP) Reviews
 - (i) Review of Package Insert (PI), Patient Package Insert (PPI), and Carton/Container Labeling by Adewale Adeleye (OPDP), dated August 3, 2015
 - (ii) Review of Patient Labeling (Patient Package Insert [PPI] and Instructions for Use [IFU]) by Shawna Hutchins (DMPP) and Adewale Adeleye (OPDP), dated September 11, 2015

Correspondence that was cited by this reviewer consisted of the following:

- Proprietary Name Request Conditionally Acceptable Letter sent to Alexion Pharmaceuticals, Inc., dated April 13, 2015 (signed by Todd Bridges, Deputy Director, DMEPA)
- OSI Staff Letter (Sponsor Monitor NAI Letter) sent to Alexion Pharmaceuticals, Inc., dated August 14, 2015 (signed by Susan Thompson, Team Leader, Good Clinical Practice Assessment Branch, Division of Good Clinical Practice Compliance, OSI)

The reviews should be consulted for more specific details of the current application.

3 CMC

The reader is referred to the Drug Substance Review, Drug Product Review, Immunogenicity Review, Complement Activation - Drug Substance Review, Integrated Summary Quality Review, Microbiology Review, and Facilities Review for complete information.

See Section 2.2 of this CDTL Review for a description of asfotase alfa.

3.1 Drug Substance

Potency Assay:

(b) (4)

- *Quality Reviewers' Conclusion:* Because the assay demonstrates that bound asfotase alfa is still active, this information is sufficient.

Potential for Complement Activation:

- Asfotase alfa contains intact Fc region [redacted] (b) (4) and can potentially bind to C1q and trigger activation of the complement system.
- *Quality Reviewers' Conclusions / Recommendation for PMR:* Because the adverse events reported during the clinical studies do not indicate instances of complement activation, it is not necessary to resolve this concern pre-licensure; the sponsor will develop an assay to evaluate the complement activating capacity of asfotase alfa compared to that of human IgG1 post licensure (see **Quality PMR 1** below).

Total (b) (4) Content:

- According to the Clinical Pharmacology Reviewers (see Section 5 of this CDTL Review), (b) (4)
- The DS Reviewer noted the following: (b) (4)
- *Quality Reviewers' Conclusions / Recommendation for PMC: To achieve greater control (b) (4) the sponsor should assess and implement a revised control strategy (b) (4) Because the information provided in the BLA shows that Alexion can consistently produce asfotase alfa that is safe, pure, and potent, the studies may be conducted post licensure as a Post Marketing Commitment (see **Quality PMC 2** below).*

Reference Material(s):

- The current reference standard (RS) RS12150413 was derived from asfotase alfa lot 338971.
- The RS is stored in (b) (4).
- The qualification includes release testing and extensive physicochemical characterization.
- The stability testing includes the same assays as the DS stability protocol (except bioburden and endotoxin testing).
- The RS is (b) (4).
- The acceptance criteria for purity assays are (b) (4) than the release specifications.
- *Quality Reviewers' Conclusions/Comments: Qualification and requalification protocols were reviewed and found to be acceptable.* (b) (4)

Cell Bank System:

- The parental host cell line was CHO cell line (b) (4) obtained from the (b) (4)



(b) (4)

Animal Derived Materials:



(b) (4)

Manufacturing Process -



(b) (4)

(b) (4)

- *Quality Reviewers' Conclusions:* The process is well controlled; microbial controls are in place and are adequate.
- *Quality Reviewers' Recommendation for PMC:* The Quality Reviewers recommended a Post Marketing Commitment to re-evaluate the (b) (4) endotoxin limits (b) (4) (b) (4) see additional discussion in Microbiology section below, and see **Microbiology Quality PMC 1** below).

(b) (4)

(b) (4)

- Long-term stability results will be included in the annual report.

Container Closure:

(b) (4)

- Based on data from extractable evaluation (b) (4), the applicant performed a leachables evaluation of 6 DS lots (b) (4)

Dating Period and Storage Conditions:

(b) (4)

3.2 Drug Product (DP)

Immunogenicity:

- Immunogenicity assays for anti-product antibodies to asfotase alfa are appropriately validated with adequate sensitivity.
- Approximately 80 % of patients became binding Ab positive.
- Approximately 50 % of binding antibody positive samples are neutralizing.
- *Immunogenicity Reviewer's Comments/Conclusions: The high incidence of binding Ab positivity is expected, since asfotase is not a native protein, but a fusion of TNSALP domain with an IgG1 Fc and a D10 bone targeting peptide, together with two amino acid linker segments. Although there is a correlation of infusion reaction with antibody responses, they do not appear to affect clinical course. Therefore, the Immunogenicity Reviewer found no immunogenicity issue that would prevent approval.*
- *Immunogenicity Reviewers' Recommendation for PMR: The Sponsor is being asked to provide a PMC to formalize a pre-BLA commitment to develop an assay for Cross Reactive Immunological Material (CRIM), which in this case is endogenous TNSALP. This assay will help identify patients without endogenous TNSALP, who are most at risk for producing antibodies that may result in loss of asfotase efficacy. (See **Quality PMC 1** below.)*

Strength:

- Strensiq is supplied at two asfotase alfa concentrations, 40 mg/mL and 100 mg/mL.
- At the 40 mg/mL concentration, it is supplied as a single use vial at (b) (4) 0.45, 0.70, and 1.0 mL volumes containing (b) (4) 18, 28, and 40 mg of asfotase alfa respectively.
- At the 100 mg/mL concentration it is supplied in a single-use vial at 0.80 mL volume containing 80 mg of asfotase alfa.

Summary of Product Design:

- Strensiq is supplied in single-use 2 mL vials.

List of Excipients:

- (b) (4) sodium chloride, (b) (4) dibasic sodium phosphate, (b) (4) monobasic sodium phosphate

Reference Material(s):

- The same reference material is used for drug substance and drug product

Manufacturing Process:

- The manufacturing process of drug product consists of (b) (4)
(b) (4)
- *Quality Reviewers' Conclusions: The control strategy is appropriate to ensure (b) (4) consistently accurate fill and adequate critical quality attributes.*

Container Closure:

- The primary container closure system is a 2 mL Type I glass vial with a 13 mm (b) (4) stopper, (b) (4) aluminium seal with a (b) (4) flip-off cap.
- *Quality Reviewers' Conclusions: Appropriate compatibility studies were performed for the container closure system.*

Expiration Date and Storage Conditions:

- 24 months at 2-8°C

3.3 Microbiology (Drug Substance and Drug Product)

See the description of the DS manufacturing process (b) (4) and the DP manufacturing process in Sections 3.1 and 3.2, respectively, of this CDTL Review.

Drug Substance Manufacturing - (b) (4) :

(b) (4)

Drug Substance Manufacturing - [REDACTED] (b) (4)



Drug Substance Manufacturing - Overall Process:

- *Microbiology Reviewer's Conclusion:* The manufacturing process has been adequately described. Microbial controls are in place.

Drug Substance Manufacturing - [REDACTED] (b) (4) Microbial Hold Validation:

- The Applicant was requested by the Microbiology Reviewer to provide data to validate the hold time for the [REDACTED] (b) (4) vessel including bioburden and endotoxin data [REDACTED] (b) (4) and to report the correct growth promoting medium used in the hold time studies.
- *Microbiology Reviewer's Conclusions:* Both of these requests were satisfactorily addressed by the applicant. The applicant provided rationale demonstrating that the current [REDACTED] (b) (4) procedure, storage conditions, and [REDACTED] (b) (4) operational controls are capable of maintaining microbial control over [REDACTED] (b) (4) hold time regardless of the number of internal intrusions. Also, the applicant listed the correct medium [REDACTED] (b) (4) in the hold studies.

Drug Product Manufacturing - [REDACTED] (b) (4) :

- The Microbiology Reviewer requested the Applicant to provide action and alert levels used for environmental monitoring during the [REDACTED] (b) (4) process; the Applicant stated that these were determined in accordance with [REDACTED] (b) (4)
- *Microbiology Reviewer's Comments (Initial Review):* The sponsor's response is inadequate. [REDACTED] (b) (4) is not an adequate reference for determining environmental monitoring limits for an [REDACTED] (b) (4) process. In addition, the environmental monitoring limits were not clearly stated. This information was requested from the sponsor.

- *Microbiology Reviewer's Comments (Addendum): The sponsor's response was deemed satisfactory; the Microbiology Reviewer concluded that drug product (b) (4) and the action and alert limits for these areas are listed in a table of the applicant's response and are adequate.*

Drug Product Manufacturing - Container Closure System and Stability:

- The Applicant has submitted the protocol and method validation for a container closure integrity test to be completed in lieu of sterility for drug product placed on stability.
- *Microbiology Reviewer's Comments: The sponsor's response was deemed satisfactory; the Microbiology Reviewer concluded that the (b) (4) detection method for container closure integrity is suitable for its intended use.*

Drug Product Manufacturing - Overall Process:

- Process controls used to ensure microbial quality during manufacturing include (b) (4)
- *Microbiology Reviewer's Conclusion: The manufacturing process has been adequately described.*

3.4 Facilities

Initial Review (August 12, 2015)

The applicant proposed nine sites for asfotase alfa manufacture (see table below).

Table 2. Proposed Sites for Asfotase Alfa Manufacture

Drug Substance Manufacture, Cell Banking and Testing Operations	
Site	Responsibilities
(b) (4)	(b) (4)
Alexion Pharmaceuticals, Inc.; Smithfield RI	<ul style="list-style-type: none"> • Storage of master & working cell bank
Drug Product Manufacture, Testing, Packaging and Labeling	
Site	Responsibilities
(b) (4)	(b) (4)
Alexion Pharmaceuticals; Smithfield RI	<ul style="list-style-type: none"> • Drug release and stability testing • Drug product stability testing • Drug product release testing • Drug product release testing

Table above modified from the Clinical Review. Source is the Facilities Review.

The Facilities Reviewer concluded that adequate descriptions were provided for the (b) (4) facilities proposed for asfotase alfa DS and DP manufacture, respectively. All proposed manufacturing and testing sites except for the (b) (4) DP release testing site were recommended for approval from a facilities assessment standpoint; however, a final facilities recommendation was not made in the August 12, 2015 Facilities Review because compliance decisions were still pending for the following:

Addendum (September 23, 2015)

The Addendum was written to follow up on the compliance decisions for the (b) (4) DP Release Testing site.

The Facilities Reviewer noted the following:

- (b) (4) A Compliance decision of Approve has now been rendered for the (b) (4) DS site. See table above.
- (b) (4) This site has an OAI status. The Applicant submitted an amendment on September 3, 2015 withdrawing (b) (4) as a testing facility. DP release testing will be conducted at one site only: (b) (4). See table above.

The Facilities Reviewer concluded that all listed facilities are now currently in a state of compliance.

3.5 Recommendation

Quality:

The Quality Reviewers recommended that this product be approved for human use under conditions specified in the package insert. The Quality Reviewers commented that the data submitted in this application are adequate to support the conclusion that the manufacture of Strensiq is well controlled and leads to a product that is pure and potent. The following post-marketing requirements and commitments were recommended:

Quality PMR 1: Develop an assay to directly compare the complement activating capacity of STRENSIQ (asfotase alfa) to that of human IgG1. The assay should be set up under conditions to readily detect complement activation by IgG1. A dose response curve to demonstrate the sensitivity of the assay is recommended

Quality PMC 1: Develop a validated cross-reactive immunologic material (CRIM) assay for patients with hypophosphatasia (HPP) and test patient samples in a cohort of untreated patients. Results should be correlated with antibody response (binding and neutralizing), genetic mutations, enzyme activity level and clinical outcome in patients who are receiving STRENSIQ (asfotase alfa) treatment. (b) (4)

(b) (4)

Quality PMC 2: Evaluate the STRENSIQ (asfotase alfa) manufacturing process and develop a control strategy (b) (4)

Provide detailed summaries of all data utilized to propose the revised control strategy (b) (4)

Quality Microbiology:

An Approval Action is the recommendation by the Quality Microbiology discipline with the following post-marketing commitment:

Quality Microbiology PMC 1: Re-evaluate the (b) (4) endotoxin limits for the (b) (4) after data from thirty batches is available and (b) (4) the (b) (4) limits to reflect manufacturing process capability.

Facilities:

An Approval Action is the recommendation from a Facilities assessment standpoint.

4 Nonclinical Pharmacology/Toxicology

The reader is referred to the Nonclinical Pharmacology/Toxicology Review by Dinesh Gautam, dated August 27, 2015, for complete information.

4.1 Issues

The Nonclinical Reviewer noted that the applicant submitted reports of primary pharmacology, safety pharmacology, pharmacokinetics, single and repeated dose toxicity studies in juvenile rats and juvenile monkeys, and reproductive and development toxicology studies in rats and rabbits.

The Nonclinical Reviewer noted the following results of these studies:

- *In vitro* pharmacology studies showed that asfotase alfa binds with a high affinity (up to 97%) to hydroxyapatite (HA), the most common mineral component of bone. Asfotase alfa can rescue the inhibition of mineralization induced by inorganic pyrophosphate (PPi).
- The efficacy of asfotase alfa was evaluated in *Akp2^{-/-}* (an HPP knockout mouse model) mice (immediately after birth to 15-day-old) following SC administration at dose levels of up to 15.2 mg/kg for up to 52 days. Following SC administration to *Akp2^{-/-}* mice, asfotase alfa caused a reduction of plasma PPi (inorganic

pyrophosphate) levels, and caused a significant increase in bone mineralization of the feet, rib cages and pelvic limbs, and improved body weight gain and survival rate.

- Following IV administration of single dose of asfotase alfa, to normal rats, it caused a bradypneic effect with a decrease in minute volume. In normal rats, treatment with asfotase alfa was associated with reduced motor activity, reduced reactivity to stimuli, abnormal gait and reduced mobility, altered landing foot splay and lower grip strength.
- Asfotase alfa had no effects on ECG parameters in juvenile Cynomolgus monkeys when administered by SC injection at dose levels up to 10 mg/kg.
- The pharmacokinetics (PK) of asfotase alfa was characterized in mice, rats and monkeys. The plasma clearance (CL) of asfotase alfa ranged from 0.00504-0.0540 L/h/kg and apparent terminal half-lives ranged from 14-40 hours across the species. Distribution studies with radiolabeled asfotase alfa showed that it is distributed into peripheral tissues, including bones. The PK profiles following SC dosing suggest a slow absorption of the enzyme and the SC bioavailability ranged from 25 to 56% in the species tested.
- The toxicity profile of asfotase alfa was assessed in a single-dose toxicity study in monkeys, and repeated dose toxicity studies of up to 6-months duration in rats and monkeys after intravenous and subcutaneous administration. Common clinical signs observed in rats were partly closed eyes, decreased muscle tone, lying on the side, hunched posture, cold to touch, uncoordinated movements, decreased activity, abnormal gait and/or blue, red and/or firm swollen hindpaws and/or forepaws and swollen muzzle. These observations were transient and did not occur on non-dosing days or during the recovery period. A dose related increase in alkaline phosphatase level was observed in all test article treated animals (rats and monkeys) throughout the treatment period. Since the test article is recombinant soluble form of tissue nonspecific alkaline phosphatase, this increase was due to the presence of the test article in the bloodstream of the animals. The NOAEL dose in juvenile rats in the 6-month IV toxicity study was 13 mg/kg/day, and the NOAEL dose in the 6-month SC toxicology study in juvenile monkeys was 10 mg/kg/day.
- Asfotase alfa was not fetotoxic, embryo lethal or teratogenic in rats and rabbits at up to 50 mg/kg/day IV doses. Asfotase alfa had no effect on fertility in rats at IV doses up to 50 mg/kg/day. It had no adverse effects on pre- and postnatal development in rats at up to 50 mg/kg/day IV doses, the highest dose tested.

The Nonclinical Reviewer recommends an Approval action based on the non-clinical review of the information submitted in the BLA. The Nonclinical Reviewer additionally recommends that the proposed labeling be revised to include the revisions shown below.

4.2 Recommended Label Revisions

The recommended label revisions from the Nonclinical Reviewer are summarized below by section.

A. Section 8.1 of Label (Pregnancy)

Wording in the Pregnancy section should be revised to:

“8.1 Pregnancy

Risk Summary

There are no available human data on STRENSIQ use in pregnant women to inform a drug associated risk. In animal reproduction studies, asfotase alfa administered intravenously to pregnant rats and rabbits during the period of organogenesis showed no evidence of fetotoxicity, embryoletality or teratogenicity at doses causing plasma exposures up to 21 and 24 times, respectively, the exposure at the recommended human dose [see Data].

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

Data

Animal Data

Asfotase alfa administered during the period of organogenesis to rats (from gestation Day 6 to Day 19 post-partum) and rabbits (on gestation days 7 to 19) at intravenous doses up to 50 mg/kg/day, (approximately 21 and 24 times the human AUC of 65486 ng.h/mL at 2 mg/kg dose administered three times weekly for a 50 kg individual, respectively) did not cause any adverse effects on embryofetal development. A pre- and postnatal development study in pregnant rats showed no evidence of adverse effects on pre- and postnatal development at intravenous doses (from Day 6 of gestation to Day 19 postpartum) of asfotase alfa up to 50 mg/kg/day (approximately 21 times the human AUC of 65486 ng.h/mL at 2 mg/kg dose administered three times weekly for a 50 kg individual).

B. Section 13.1 of Label (Carcinogenesis, Mutagenesis, and Impairment of Fertility)

Wording in the Carcinogenesis, Mutagenesis, and Impairment of Fertility section should be revised to:

"13.1 Carcinogenesis, Mutagenesis, and Impairment of Fertility

Long-term studies in animals to evaluate carcinogenic potential or studies to evaluate mutagenic potential have not been performed with asfotase alfa. Asfotase alfa at intravenous doses up to 50 mg/kg/day administered daily in pregnant rats (approximately 21 times the human AUC of 65486 ng.h/mL at 2 mg/kg dose administered three times weekly for a 50 kg individual) was found to have no adverse effect on fertility and reproductive performance of male and female rats."

(b) (4)

4.3 Recommendation

An Approval Action is the recommendation by the Nonclinical Pharmacology/Toxicology discipline provided the labeling revisions described above are made.

5 Clinical Pharmacology/Biopharmaceutics

The reader is referred to the Clinical Pharmacology Review by Christine Yuen-Yi Hon, for complete information. The following is summarized from the Clinical Pharmacology Review.

The Clinical Pharmacology Review focused on the following:

- Pharmacokinetics,
- Exposure-Response Relationships
- PK Comparability between Products with Different Batch Size and Formulation Strength

(b) (4)

- Immunogenicity

Each of these issues and the Clinical Pharmacology Reviewer's conclusion are summarized below.

5.1 Pharmacokinetics

Asfotase alfa PK parameter values after SC administration were available in 38 HPP patients who received a daily dose of 0.3 mg/kg and 0.5 mg/kg or three-times-per-week dosing of 2 mg/kg and 3 mg/kg. Twenty two of these patients had perinatal/infantile-onset HPP, 14 had juvenile-onset HPP, one had adult-onset HPP, and the remaining patient had unknown disease onset status. The mean age of the patients was 18.1, with a range of 1 month to 66 years old. The mean weight at baseline was 34.1 ± 27.9 kg.

After multiple dosing of 2 mg/kg SC 3x/week for 6 weeks, the mean time to maximum concentration (T_{max}) ranged from 15 to 20 hours ($n = 21$). The mean maximum concentration (C_{max}) ranged from 1576 to 1781 U/L, and the mean area under the concentration-time curve over the dosing interval (AUC_t) at Week 6 ranged from 58743 to 75985 h*U/L.

Asfotase alfa PK exhibits dose proportionality across the dose range of 0.3 mg/kg to 3 mg/kg and appears to be time-independent. The C_{max} and AUC_t values after multiple dosing were higher than the values after the first dose, with accumulation ratios ranging from 5 to 6 for daily dosing at 0.3 to 0.5 mg/kg and from 2.5 to 4 for three-times-per-week dosing at 2 to 3 mg/kg, which is consistent with the observed elimination half-life of approximately 130 hours after intravenous (IV) dosing. Steady state exposure was achieved as early as three weeks following initial dose administration. When administered at 2 mg/kg 3x/week, asfotase alfa PK at Week 6 appeared similar between patients in the two age groups (mean age of 3.1 and 7.8 years old).

Asfotase alfa concentration-time profiles following SC administration in HPP patients were well described by a linear, 2-compartment, first-order absorption pharmacokinetic model used for population PK (Pop-PK) analysis. The typical value of clearance (CL) was 12.7 L/day for a subject who has a body weight of 70 kg, is negative for antidrug antibodies (ADA-), (b)(4). The inter-subject variability of CL was 46.5%. The central volume of distribution (V_2) was 4.55 L and the peripheral volume of distribution (V_3) was 44.6 (32.1 – 62.0) L, indicating that asfotase alfa is initially distributed in the intra-vascular space and then distributes to the extra-vascular space. The inter-subject variability for V_2 and V_3 was 85.5% and 42.7%, respectively. The estimated absolute bioavailability was 62% following SC administration of the (b)(4) scale product in 40 mg/mL.

Body weight was a significant covariate for the PK parameters V_2 , V_3 , and CL; asfotase alfa exposure increased with body weight. Immunogenicity was a covariate for CL; formation of antidrug antibodies (ADA) was associated with a higher CL. Compared to in the absence of ADA (ADA-), the CL value was 11% higher in the presence of ADA without neutralizing capability (ADA+/NAb-) and 21% higher in the presence of ADA with neutralizing capability (ADA+/NAb+).

5.2 Exposure-Response Relationships

For the perinatal/infantile-onset HPP patients, asfotase alfa treatment is associated with an increase in overall survival in an exposure-dependent manner.

The E-R for growth in perinatal/infantile- and juvenile-onset HPP patients was not apparent, as there was no apparent correlation between individual average concentration over the entire study period (C_{avg}) and the slope of Z-score for height.

For juvenile-onset HPP patients, an E-R relationship was observed between estimated average asfotase alfa concentration at steady state ($C_{avg,ss}$) and multiple pharmacodynamic (PD) measurements, including the Bruininks-Oseretsky Test of Motor Proficiency, Second Edition (BOT-2) score, 6 Minute Walk Test (6MWT), Radiologic Global Impression of

Change (RGI-C) and Rickets Severity Scale (RSS) scores, and plasma PPI and PLP concentrations. These E-R curves showed that response rapidly improved at low concentrations, followed by a more gradual improvement with increasing concentration until a plateau was reached at a $C_{avg,ss}$ concentration of approximately 1500 - 2000 U/L.

The proposed dosing regimen is 6 mg/kg/week to be administered either as 2 mg/kg SC 3x/week or 1 mg/kg SC 6x/week. The available E-R relationships for effectiveness of asfotase alfa support this proposed regimen. Across patients with different weights, the mean values of the estimated C_{avg} from the proposed dosing regimen were generally above 2000 U/L which was at or above the beginning of the plateau of the E-R relationship for effectiveness. The exposures associated with the proposed 6 mg/kg weekly regimen range from 1430 to 2930 U/L.

5.3 PK Comparability between Products with Different Batch Size and Formulation Strength

In addition to the to-be-marketed products manufactured at (b) (4) scale, a (b) (4) scale product was also used in the clinical trials. The PK of these two products are most likely comparable. Available PK data showed that (b) (4) product had a 2-fold lower exposure than (b) (4) product, based on an intra-subject comparison of the PK exposure in four subjects who received both products at three different study visits. (b) (4)

The clinical development program used two formulation strengths, 40 mg/mL and 100 mg/mL; 40 mg/mL was used in younger children with lower body weight and 100 mg/mL was used in older children with higher body weight. The PK comparability between the 40 mg/mL and 100 mg/mL formulation strength products could not be concluded. Based on the PK data following the first SC dose administration of asfotase alfa in 35 HPP patients, the least-squares mean ratios for normalized C_{max} ($C_{max,nor}$) and $AUC_{t,nor}$ for the 100 mg/mL formulation strength were 89.9 % (90% CI: 64.4% – 126%) and 116 % (90% CI: 84.9% – 158%), respectively, with the 40 mg/mL formulation strength as the reference product. Furthermore, results of Pop-PK analysis indicated that the 100 mg/mL formulation strength achieved a lower exposure with a relative bioavailability of 76.5% compared to the 40 mg/mL formulation strength (b) (4)

Due to the lower exposure with 100 mg/mL formulation strength and the lack of clinical experience with 100 mg/mL strength product in pediatric HPP patients < 40 kg body weight to inform its efficacy with respect to overall survival, only the 40 mg/mL formulation strength should be used in pediatric HPP patients < 40 kg body weight. See Section 5.6 of this CDTL Review.

(b) (4)

(b) (4)

5.5 Immunogenicity

Among 71 subjects with post baseline immunogenicity data, 80% (59) subjects were ADA+. Of these ADA+ patients, 54% remained ADA+ later in the study while 46% had at least one ADA- sample. A few patients had ADA titer values >500 for a prolonged period, but low ADA titers were observed in the majority of the patients. Among the 57 subjects with ADA, 25 (44%) subjects were positive for neutralizing antibodies (NAb+) and 32 (56%) subjects were NAb-.

Immunogenicity had a negative impact on the PK of asfotase alfa. Asfotase alfa exposure in ADA- subjects was approximately 1.5- to 2-fold greater than the exposure in ADA+ subjects, based on a subset of 31 pediatric patients with HPP who have 48-hour AUC data available at Week 6. This difference in the observed exposure data is greater than the exposure difference (< 20%) estimated by the Pop-PK model (11 – 21% higher CL values in ADA+ subjects).

Immunogenicity did not have apparent effect on the pharmacodynamics of asfotase alfa. No apparent trend was observed between asfotase alfa concentration and % inhibition by domain (TNSALP and FcD10).

The impact of immunogenicity on clinical efficacy cannot be evaluated adequately for both the perinatal/infantile-onset HPP patients and the juvenile-onset HPP patients. For the perinatal/infantile-onset subjects, the assessment of the impact of immunogenicity on overall survival was limited by the small number of subjects who died. For the juvenile-onset HPP subjects, no assessment was performed due to the suboptimal quality of the 6MWT video recording for the gait assessment.

Immunogenicity appeared to have an impact on the rate of injection site reactions (ISR) and ectopic calcification; ADA+ subjects had a slightly higher rate of the two adverse events. Because of the small number of subjects and the short duration of the clinical trials, long term immunogenicity and safety assessments are warranted to provide further insight into the impact of immunogenicity on safety.

5.6 Recommendation

An Approval Action is the recommendation by the Clinical Pharmacology discipline pending agreement related to the labeling language. In addition, the Clinical Pharmacology discipline recommends the following:

- The label (Dosage and Administration section) should contain a statement that to ensure adequate systemic exposure, the 80 mg/0.8 mL vial (i.e., the 100 mg/mL formulation) should not be used in pediatric patients weighing < 40 kg; the exposure achieved with the 100 mg/mL formulation was estimated to be 24% lower than the exposure achieved with the 40 mg/mL formulation. See Section 12.3 of this CDTL Review.

(b) (4)

6 Clinical Microbiology

Clinical Microbiology considerations do not apply to this application because asfotase alfa is not an antimicrobial agent.

7 Clinical/Statistical - Efficacy

The reader is referred to the Clinical Review by Carla Epps, and the Statistics Review by Benjamin Vali for complete information.

Proposed Indication

The Applicant proposed the following indication:

"... for [REDACTED] (b) (4) in patients with infantile- and juvenile-onset hypophosphatasia (HPP)."

See discussion about indication wording in Section 12.3 of this CDTL Review.

7.1 Perinatal/Infantile-Onset HPP

This section focuses on the asfotase alfa studies (ENB-002-08/ENB-003-08 and ENB-010-10) and the natural history study (ENB-011-10).

Overview of Studies and Historically-Controlled Analysis:

Efficacy for the perinatal/infantile onset population was based primarily on data from a historical-controlled analysis of the following:

- pooled patients from asfotase alfa studies (ENB-002-08/ENB-003-08 and ENB-010-10) vs.
- a natural history study (ENB-011-10)

An overview of the two asfotase alfa studies and the natural history study is shown in the table below.

Table 3. Overview of Studies (Perinatal/Infantile Onset)

Studies	Design	Age on Entry	Treatment Duration	N
ENB-002-08/ ENB-003-08*	• Open Label, Single Arm	• ≤ 36 months	• 24 weeks; • extension up to 5 years	11 (10 [†])
ENB-010-10	• Open Label, Single Arm	• ≤ 5 years	• 4 years	59
ENB-011-10	• Retrospective Chart Review	• ≤ 5 years	• Not Applicable	48

*ENB-003-08 is an extension study of ENB-002-08

[†]10 patients continued into ENB-003-08

The primary and secondary endpoints of the historically-controlled analysis agreed upon with the sponsor (see Section 2.4 of this CDTL Review) were as follows:

- Primary: Overall Survival
- Secondary: Ventilator-Free Survival

Key Entry Criteria:

The key entry criteria are summarized in the table below.

Table 4. Key Entry Criteria (Perinatal/Infantile Onset)

Entry Criteria	ENB-002-08/ ENB-003-08	ENB-010-10	ENB-011-10 (Natural History Study)
Inclusion	<ul style="list-style-type: none"> ➤ Age ≤ 36 months ➤ Signs of HPP prior to 6 months of age ➤ Documented diagnosis of <u>severe</u> HPP defined as: <ul style="list-style-type: none"> • biochemical abnormalities (ALP 3 SD's below mean for age; PLP 4 X ULN) • radiographic evidence of HPP • ≥ 1 HPP-related findings: <ul style="list-style-type: none"> – Hx fracture/delayed fracture healing – ↑ Ca²⁺ – craniosynostosis – nephrocalcinosis – respiratory compromise • rachitic chest deformity and/or vitamin-B6-dependent seizures • failure to thrive 	<ul style="list-style-type: none"> ➤ Age ≤ 5 years ➤ Signs of HPP prior to 6 months of age ➤ Documented diagnosis of HPP defined as: <ul style="list-style-type: none"> • biochemical abnormalities (ALP below LLN for age; PLP above ULN) • radiographic evidence of HPP • ≥ 2 HPP-related findings: <ul style="list-style-type: none"> – Hx fracture/delayed fracture healing – nephrocalcinosis or ↑ Ca²⁺ – craniosynostosis – respiratory compromise or rachitic chest deformity – vitamin-B6-responsive seizures • failure to thrive 	<ul style="list-style-type: none"> ➤ Age ≤ 5 years ➤ Signs of HPP prior to 6 months of age ➤ Documented diagnosis of HPP defined as ≥1 of following: <ul style="list-style-type: none"> • Documented ALPL gene mutation(s) • ALP below age-adjusted normal range and either PLP or urinary PEA above ULN • ALP below age-adjusted normal range and HPP-related radiographic evidence ➤ One or more of the following clinical features: <ul style="list-style-type: none"> • Respiratory compromise* • Rachitic chest deformity, and/or • Pyridoxine (vitamin B6)-responsive seizures
Exclusion	<ul style="list-style-type: none"> ➤ History of sensitivity to the study drug ➤ Any current or prior clinically significant conditions ➤ Treatment with an investigational drug within one month of study drug administration ➤ Current enrollment in any other investigational trial ➤ Low serum Ca, Ph, or 25(OH) vitamin D ➤ Evidence of a treatable form of rickets ➤ Prior treatment with bisphosphonate 	<ul style="list-style-type: none"> ➤ Other clinically significant disease ➤ Low serum calcium phosphate, or vitamin D levels ➤ Current evidence of treatable form of rickets ➤ Prior treatment with bisphosphonates ➤ Enrollment in any other trial involving an investigational therapy for HPP 	<ul style="list-style-type: none"> ➤ Had received treatment with asfotase alfa or ➤ Had other clinically significant disease

*Respiratory Compromise: defined as respiratory complications (up to and including respiratory failure) that required respiratory support measures and/or medications for symptom(s) management.

Table above summarized from the Clinical Review.

See additional details of entry criteria in the Clinical Review.

Dosing

Dosing in each of the asfotase alfa studies is summarized in the table below.

Table 5. Dosing in the Asfotase Alfa Studies (Perinatal/Infantile Onset)

	ENB-002-08/ENB-003-08	ENB-010-10
Dosing	<p>ENB-002-08:</p> <ul style="list-style-type: none"> ➤ Day 1: 2 mg/kg IV X 1 ➤ Day 7: 3 mg/kg/wk SC (as 1 mg/kg TIW) ➤ After 1 mo: up to 4.5 mg/kg/wk SC (as 2 mg/kg TIW) later changed to 6 mg/kg/wk SC (as 2 mg/kg TIW) if ≥ 2 outcomes (see below) ➤ After 3 mo: up to 6 mg/kg/wk SC (as 2 mg/kg TIW) if 1 outcome (see below) ➤ After 3 mo: up to 9 mg/kg/wk SC (as 3 mg/kg TIW) if 2 outcomes (see below) <p>ENB-003-08:</p> <ul style="list-style-type: none"> ➤ Final dose of ENB-002-08 is initial dose of ENB-003-08 	<ul style="list-style-type: none"> ➤ 6 mg/kg/wk SC (as 2 mg/kg TIW) X 4 yrs; or ➤ 6 mg/kg/wk SC (as 1 mg/kg 6 x per wk) X 4 yrs ➤ Dose Escalation was allowed (see below)
Dose Adjustment Rules	<p>ENB-002-08 and ENB-003-08:</p> <ul style="list-style-type: none"> ➤ Dose adjustment allowed for changes in weight and/or for safety concerns or for lack of efficacy <p>ENB-002-08:</p> <ul style="list-style-type: none"> ➤ Lack of efficacy was defined by three outcomes: <ul style="list-style-type: none"> • No radiographic improvement in rickets, • Deterioration of pulmonary function, and • Worsening failure to thrive <p>ENB-003-08:</p> <ul style="list-style-type: none"> ➤ Lack of efficacy included (but was not specifically limited to): <ul style="list-style-type: none"> ▪ Lack of improvement after 3 months of consistent dosing based on x-ray and laboratory data (PLP, PPi, calcium, phosphorus, and urinary calcium:creatinine ratio) ▪ Acute decline in respiratory status indicated by intubation with difficulty weaning from mechanical ventilation within 30 days 	<ul style="list-style-type: none"> ➤ Dose adjustments allowed for changes in weight and/or for safety concerns, tolerability issues, or for lack of efficacy. ➤ Lack of efficacy included (but was not specifically limited to): <ul style="list-style-type: none"> • Lack of improvement after 3 months of consistent dosing based on x-ray and laboratory data (PLP, PPi, calcium, phosphorus, and urinary calcium:creatinine ratio) • Acute decline in respiratory status indicated by intubation with difficulty weaning from mechanical ventilation within 30 days ➤ Note the maximum allowed dose per the German and French protocols was 9 mg/kg/wk SC.

Table above summarized from the Clinical Review.

See additional details of dosing in the Clinical Review.

Efficacy Endpoints and Other Efficacy Assessments:

The endpoints of the historically-controlled analysis (pooled patients from ENB-002-08/ENB-003-08 and ENB-010-10 vs. ENB-011-10) agreed upon with the sponsor (see Section 2.4 of this CDTL Review) are shown in the table below.

Table 6. Efficacy Endpoints of the Historically-Controlled Analysis*

Endpoint	Definition
Primary:	<u>Overall Survival</u> : time from birth to death. Patients that had not died were censored at the date of data abstraction; patients whose status was unknown at the time of data abstraction were censored at the time of last known contact.
Secondary:	<u>Ventilator-free survival</u> : time from birth to death or first day of beginning ventilator support (including continuous positive airway pressure [CPAP], bi-level positive airway pressure [BiPAP], and mechanical ventilation via intubation or tracheostomy).

*Pooled patients from ENB-002-08/ENB-003-08 and ENB-010-10 vs. ENB-011-10
Table above summarized from the Clinical Review

Other efficacy assessments in the asfotase alfa studies included those shown in the table below.

Table 7. Other Efficacy Assessments in the Asfotase Alfa Studies*

Assessment	Description
Growth	<ul style="list-style-type: none"> ➤ Growth assessments in clinical trials included recumbent length /height, weight, head and chest circumference (for infants), arm span, body mass index (BMI).[#] <ul style="list-style-type: none"> • Length and height measurements in clinical trials were obtained using a stadiometer. • Results were expressed as z-scores calculated using the Centers for Disease Control (CDC) growth charts and methodology.²
RSS	<ul style="list-style-type: none"> ➤ Scale developed to assess the severity of nutritional rickets and response to therapy based on assessments of rickets changes (metaphyseal fraying and cupping and growth plate changes) (see Appendix 1) <ul style="list-style-type: none"> • 10-point scale, with a score of 0 representing absence of rickets and a score of 10 representing severe rickets • Scoring is based on assessment of radiographs of the wrists and knees (maximum possible score of 4 points for the wrists and 6 points for the knees). ➤ Radiographs for the clinical trials were evaluated and scored independently by a single independent rater.
RGI-C	<ul style="list-style-type: none"> ➤ Applicant-developed scale to assess changes from baseline in skeletal abnormalities and rickets associated with HPP (see Appendix 1). <ul style="list-style-type: none"> • 7-point scale, ranging from a score of -3 (severe worsening of HPP-associated rickets) to 3 (complete or near complete healing of HPP-associated rickets); a RGI-C score of zero (0) signified no change from baseline (see below). • Scoring is based on assessment of radiographs of the chest, bilateral wrists and bilateral knees. ➤ Radiographs for the clinical trials were evaluated and scored independently by a central panel of three pediatric radiologists and an average RGI-C score was calculated.

RSS=Rickets Severity Scale; RGI-C=Radiographic Global Impression of Change

*These assessments are in the asfotase alfa studies (ENB-002-08/ENB-003-08 and ENB-010-10) but not the natural history study (ENB-011-10)

[#]No information on growth measurement methodology was available for the natural history study.

Table above summarized from the Clinical Review

² http://www.cdc.gov/growthcharts/percentile_data_files.htm.

See additional discussion of the above efficacy assessments and other efficacy assessments in the Clinical Review.

Demographic and Baseline Characteristics:

Demographic and baseline characteristics are summarized in tables in Appendix 3 of this CDTL Review.

The overall conclusion and comments regarding demographic and baseline characteristics are summarized below.

Overall Conclusion: This reviewer agrees with the Clinical Reviewer's conclusion that overall, patient demographics and baseline disease characteristics for the historical control group (ENB-011-10) were similar to those of patients in clinical trials (ENB-002-08/ENB-003-08 and ENB-010-10).

Geographic Region/Race/Gender: The Clinical Reviewer noted that the majority of perinatal/infantile-onset patients were white and from North America, with approximately equal numbers of male and female. The Statistics Reviewer noted that there was an imbalance between the non-concurrent groups regarding geographic region (i.e., North America region of 51.5% in clinical trials vs. 77.1% in historical control group), but this variable was not considered as critical as the other variables in influencing outcome to therapy.

Age on Entry: The Clinical Reviewer commented that the mean age on entry was 59 weeks in ENB-002-08/ENB-003-08 versus 118 weeks in ENB-010-10.

Craniosynostosis: The Clinical Reviewer also noted that both clinical trial populations had a smaller proportion of patients with a history of craniosynostosis (25% of ENB-002-08/ENB-003-08 patients and 14 % of ENB-010-10 patients) compared to the historical control group (61%).

Chest Deformity/Abnormally Shaped Chest: This reviewer notes that the proportion of patients with abnormally shaped chest in ENB-010-10 (86%) was higher than that in ENB-002-08/ENB-003-08 (55%) but similar to the proportion of patients with chest deformity in the historical control ENB-011-10 (91%).

Respiratory Compromise/Failure/Distress: This reviewer notes that the respiratory compromise/failure/distress history of the historical control group (history of respiratory distress 77%, and history of respiratory failure 72%) appeared to be more similar to that of ENB-002-08/ENB-003-08 (history of respiratory compromise 91%) than ENB-010-10 (history of respiratory compromise 63%).

Seizures: The Clinical Reviewer noted that history of seizures of the historical control group (20%) appeared to be more similar to that of ENB-010-10 (22%) than ENB-002-08/ENB-003-08 (9%).

PLP: This reviewer notes that PLP varied across the trials. In ENB-010-10, mean PLP was 2711 ng/mL; in ENB-002-08/ENB-003-08, mean PLP was 380 ng/mL. As discussed in the Clinical Review, PLP did not correlate with clinical outcomes. See Section 12.3 of this CDTL Review.

Disposition:

ENB-002-08/ ENB-003-08: Of the 11 patients that enrolled in ENB-002-08, 10 completed the study; there was one discontinuation due to a hypersensitivity reaction characterized by fever, chills, and irritability after the initial IV infusion of asfotase alfa. Of the 10 patients that entered Study ENB-003-08, nine completed the study; there was one death due to sepsis during Study ENB-003-08 after about 30 weeks of treatment.

ENB-010-10: Of the 59 patients that enrolled in this study, six died after starting treatment with asfotase alfa, including one patient who withdrew from the trial and subsequently died about one week later. The remaining 53 patients (90%) are continuing in this study.

Dose Increases Due to Lack of Efficacy:

See earlier section "Dosing" for dose adjustment rules.

ENB-002-08/ENB-003-08: Six patients had dose increases due to lack of efficacy. Dose increases were to 6 mg/kg/wk (four patients), 9 mg/kg/wk (one patient), and 12 mg/kg/wk (one patient). The Clinical Reviewer noted that of the six patients, five (the patients with dose increases to 6 mg/kg/wk and 9 mg/kg/wk) had improvement in one or more clinical parameters (respiratory status, RGI-C score, height z-score, and/or weight z-score) after the dose increase.

ENB-010-10: Ten patients received doses higher than 6 mg/kg/week due to lack of efficacy (based on PK exposure data or lack of RGI-C response), including 3 patients who died. Of the seven surviving patients, all 7 patients were RGI-C responders and 5 patients achieved improvement in both height and weight.

The Clinical Reviewer concluded that the above findings indicate that 6 mg/kg/week dosing may be a suboptimal dose for some perinatal/infantile onset patients.

Overall Survival:

Overall survival results are summarized in the table below; the Kaplan-Meier figure plotting these data is presented in the figure that follows.

Table 8. Overall Survival – ENB-002-08/ENB-003-08 and ENB-010-10 vs. ENB-011-10 (All Qualified Enrolled/Extracted)

	ENB-002-08/ENB-003-08 and ENB-010-10 Asfotase Alfa (N = 68)	ENB-011-10 Historical Control (N = 48)
Alive at Point of Last Contact		
n (%)	62 (91.2%)	13 (27.1%)
Corresponding 95% CI [1]	(81.4%, 97.3%)	(15.3%, 41.9%)
Time to Death from Birth (in Days)		
n	68	48
Mean (SD)	1397.3 (949.06)	1113.1 (1891.23)
Median	1353.0	270.5
Min, Max	73, 3487*	1, 7211*
Hazard Ratio (Asfotase Alfa / Historical Control)		
Point Estimate	0.089	
Corresponding 95% CI	(0.039, 0.202)	
Log-Rank test p-value [2]	<0.0001	

Table above is modified from the Statistics Review. Source: Statistics Reviewer's Table generated from ISE ADTTE dataset.

Note: Denominators for percentages are N. * denotes censoring.

[1]: Using the Clopper-Pearson method.

[2]: Considered exploratory.

Figure 2. Overall Survival – ENB-002-08/ENB-003-08 and ENB-010-10 vs. ENB-011-10 (All Qualified Enrolled/Extracted)

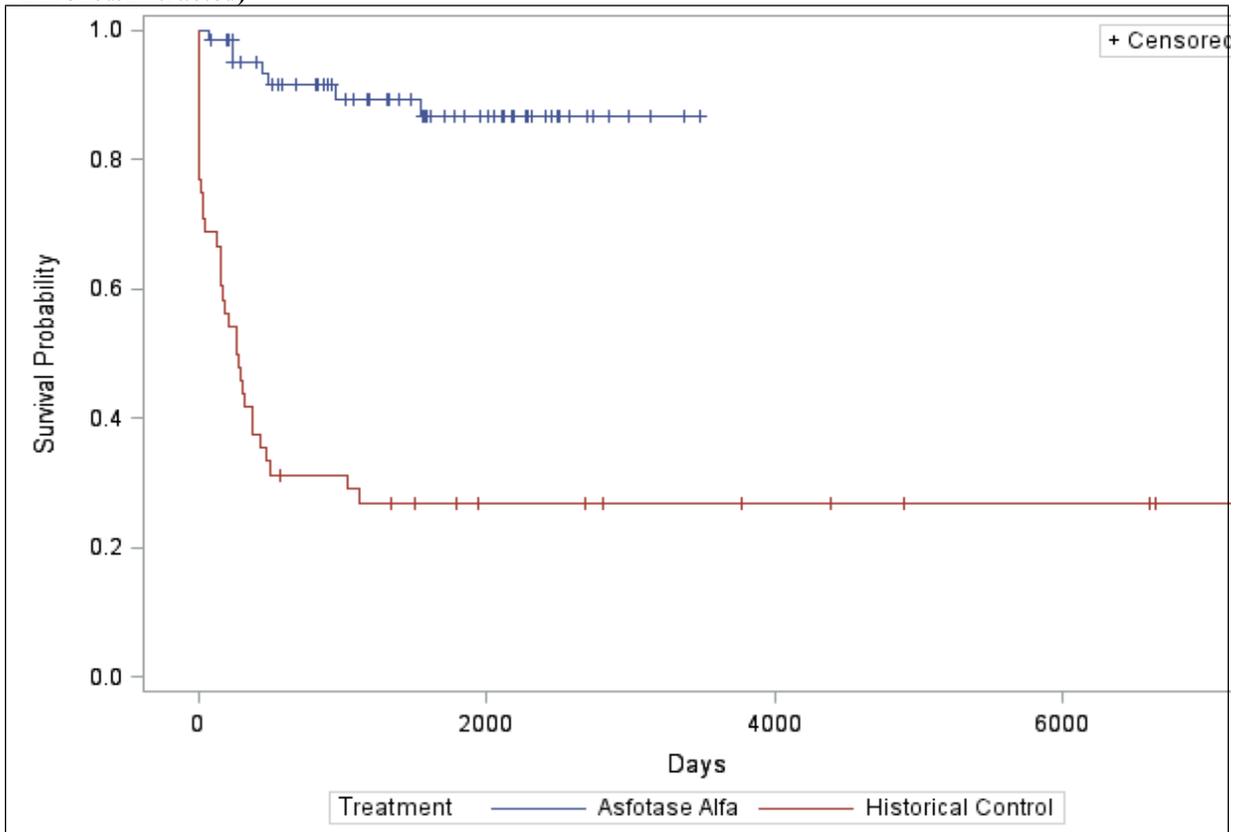


Figure above is taken from the Statistics Review. Source: Statistics Reviewer’s Figure using SAS generated from ISE ADTTE dataset.

The Statistics Reviewer noted that asfotase alfa showed superiority, in an exploratory context, in the time to death from birth up to the point of last contact when compared to the historical control group.

Stratified Analysis of Overall Survival by Diagnosis Period

Because the natural history data were collected over a period of several decades, the applicant performed a stratified analysis of overall survival by diagnosis period:

- Prior to 1990
- 1990-1999
- 2000 onward

See the figure below.

Table 9. Kaplan-Meier Analysis of Overall Survival for the Historical Control Group by Diagnosis Period

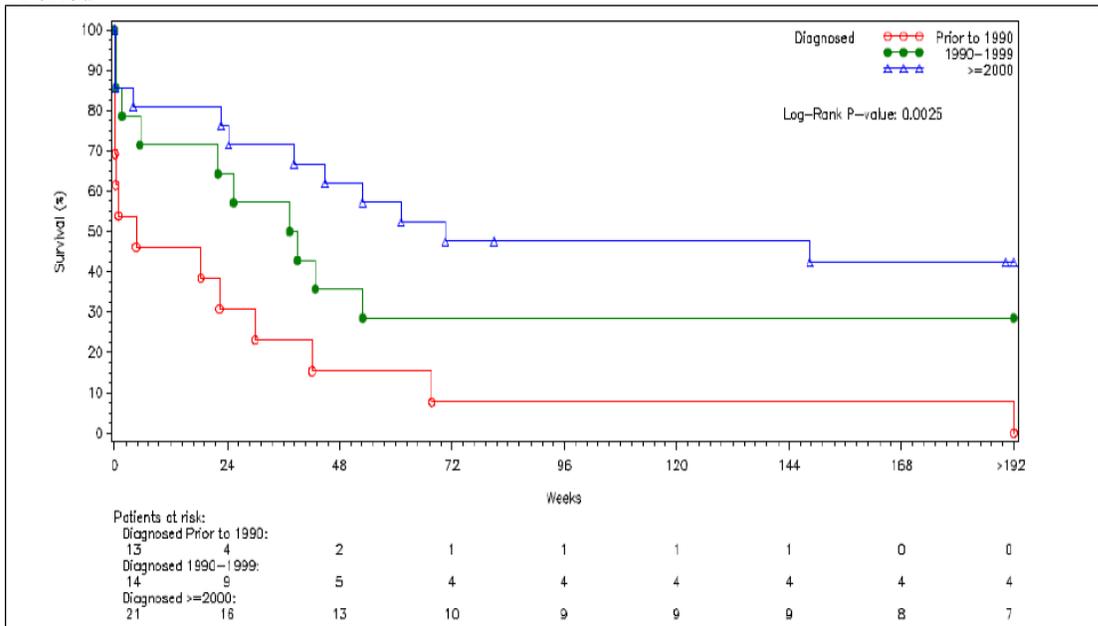


Figure above taken from the Clinical Review.

Source: ENB-011-10 Final Clinical Study Report (dated January 22, 2014), Figure 7

The survival rate observed was highest in patients diagnosed in 2000 onward, and lowest in patients diagnosed prior to 1990. The Clinical Reviewer noted that this shift likely reflects improvements in supportive care over time, as patient disease history (i.e., severity of disease) was similar across diagnosis period patient cohorts. The Clinical Reviewer noted that survival rates declined to less than 50% by age 72 weeks even in the cohort of patients diagnosed after 2000, a cohort of patients approximately contemporary with treated patients.

KM analysis of five-year survival rates were also provided for the following diagnosis periods:

- 2000-2004
- 2005 onward

See the table below.

Table 10. Five-Year Survival Rates for 2000-2004 and 2005-onward

Diagnosis Period	Five-Year Survival Rate
2000-2004	0.40 (95% CI: 0.052, 0.753)
2005 onward	0.43 (95% CI: 0.188, 0.651)

Table above summarized from the Clinical Review

Five-year survival rates were similar for patients diagnosed from 2000-2004 and for patients diagnosed from 2005 onward. The applicant concluded that the above analysis suggests that the trend of increasing survival rates with later diagnosis period did not continue.

The Clinical Reviewer commented on the survival rate for trial patients and historical control patients with the most severe clinical disease.

"For ENB-0002-08/ENB-003-08, all 4 patients with a history of respiratory failure (3 patients) or seizures (1 patient) were alive at the time of the data analysis cut-off date. For ENB-010-10, 10/ 13 patients (77%) with a history of seizures were alive at the time of the data analysis cut-off date. In contrast, none of the historical control patients with a history of respiratory failure or vitamin B6-responsive seizures survived."

The Clinical Reviewer concluded that the pooled analysis for overall survival constituted robust evidence to support efficacy of asfotase alfa in perinatal/infantile onset patients.

Ventilator-Free Survival:

Ventilator-free survival results are summarized in the table below; the Kaplan-Meier figure plotting these data is presented in the figure that follows.

Table 11. Invasive Ventilator-Free Survival – ENB-002-08/ENB-003-08 and ENB-010-10 vs. ENB-011-10 (All Qualified Enrolled/Extracted)

	ENB-002-08/ENB-003-08 and ENB-010-10 Asfotase Alfa (N = 68)	ENB-011-10 Historical Control (N = 48)
No Ventilator Use and Alive at Point of Last Contact		
n (%)	45 (66.2%)	12 (25.0%)
Corresponding 95% CI [1]	(54.6%, 78.2%)	(13.6%, 39.6%)
Time to Start of Ventilator-Use or Death from Birth (in Days)		
n	68	48
Mean (SD)	1234.8 (989.95)	930.6 (1725.85)
Median	1078.0	236.0
Min, Max	21, 3487*	1, 7211*
Hazard Ratio (Asfotase Alfa / Historical Control)		
Point Estimate	0.278	
Corresponding 95% CI	(0.162, 0.478)	
Log-Rank test p-value [2]	<0.0001	

Table above modified from the Statistics Review. Source: Statistics Reviewer’s Table generated from ISE ADTTE dataset.

Note: Denominators for percentages are N. * denotes censoring.

[1]: Using the Clopper-Pearson method.

[2]: Considered exploratory.

Figure 3. Invasive Ventilator-Free Survival – ENB-002-08/ENB-003-08 and ENB-010-10 vs. ENB-011-10 (All Qualified Enrolled/Extracted)

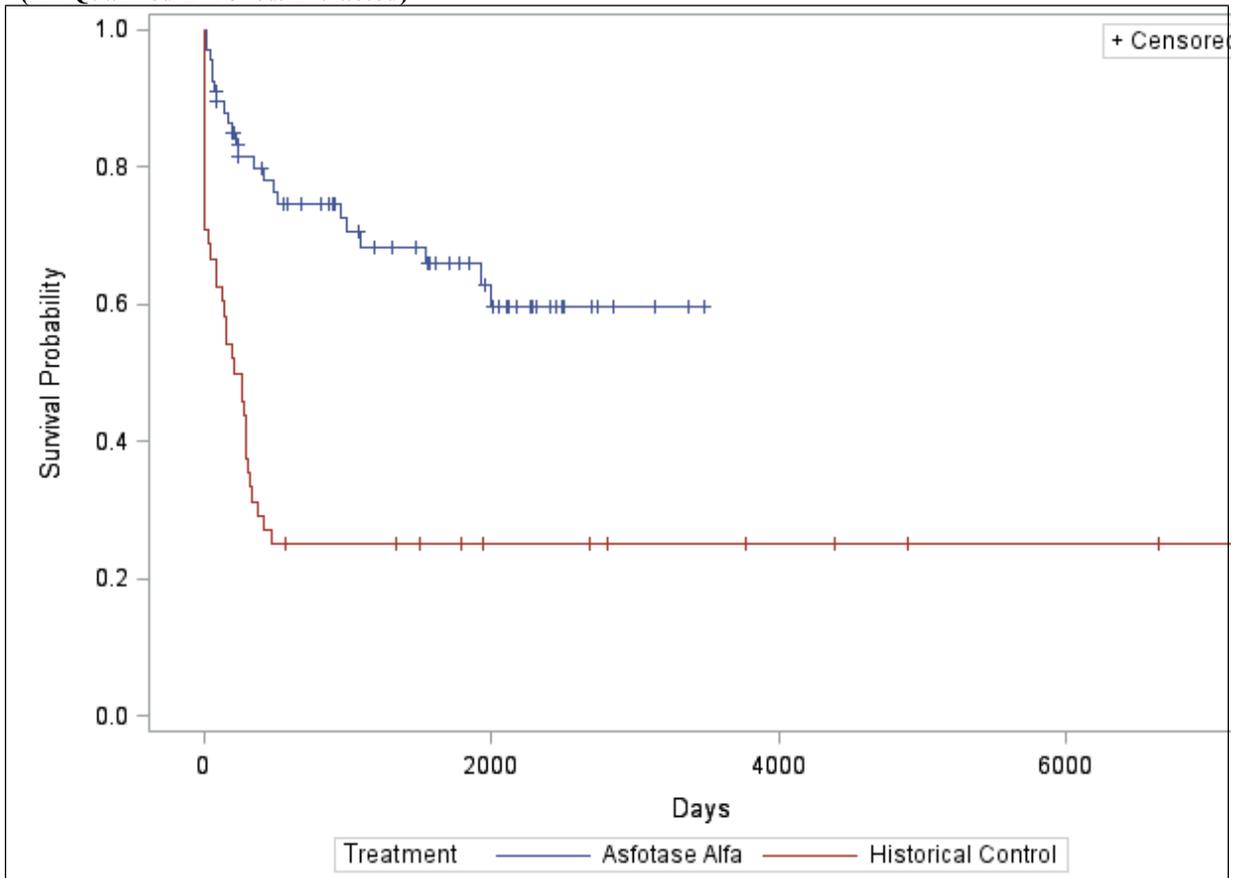


Figure above is taken from the Statistics Review. Source: Statistics Reviewer’s Figure using SAS generated from ISE ADTTE dataset.

The Statistics Reviewer noted that asfotase alfa showed superiority, in an exploratory context, in the time to start of invasive ventilator use or death from birth up to the point of last contact when compared to the historical control group.

Shifts in Level of Respiratory Support from Baseline to Last Patient Assessment

An additional analysis of the levels of respiratory support at baseline and last assessment for treated patients in each of the studies was provided. See the following table.

Table 12. Shifts in Level of Respiratory Support from Baseline to Last Patient Assessment

Level of Respiratory Support	ENB-002-08/ENB-003-08		ENB-010-10	
	Baseline n=11	Last Assessment n=11	Baseline n=59	Last Assessment n=59
No support- n (%)	6 (55)	8 (89)	40 (68)	47 (80)
Supplemental O ₂ - n(%)	1 (9)	1 (11)	6 (10)	1 (2)
CPAP/BiPAP- n (%)	1 (9)	0	2 (3)	1 (2)
Invasive mechanical ventilation- n (%)	3 (27)	2	11 (11)	10 (17)

The Clinical Reviewer concluded that the results demonstrated that patients at all levels of respiratory support improved with treatment, including patients requiring invasive ventilator support at trial entry

Other Efficacy Assessments:

Results for growth and RGI-C are discussed below. The Clinical Review includes discussion of other efficacy assessments.

Growth

Height and weight measurements (as measured by z-scores) were available post-treatment for the 68 perinatal-/infantile-onset patients enrolled in Studies ENB-002-08/003-08 and ENB-010-10; additionally, height and weight z-scores were available post-treatment for 4 perinatal-/infantile-onset patients enrolled in Study ENB-006-09/ENB-008-10 (described in Section 7.2 of this CDTL Review).

For Studies ENB-002-08/003-08 and ENB-010-10, the mean time interval between baseline and last assessment was 21 months (range was 1 month to 72 months). For Study ENB-006-09/ENB-008-10, the mean time between baseline and last assessment was 56 months (range was 53 months to 60 months).

Height and weight z-scores at baseline and at the last assessment are shown in the table below.

Table 13. Height and Weight Z-Scores at Baseline and at Last Assessment

	Height Z-score				Weight Z-score			
	Baseline		Last Assessment		Baseline		Last Assessment	
	Mean	Min, Max	Mean	Min, Max	Mean	Min, Max	Mean	Min, Max
Studies ENB-002-08/003-08 and ENB-010-10* (N=68)	-3.3	-10.1, 0.9	-2.9	-10.6, 0.4	-3.2	-23.8, 0	-2.4	-20.9, 1.1
Study ENB-006-09/ENB-008-10 (N=4)**	-2.6	-6.6, -0.7	-1.5	-5.8, 0.4	-2.5	-8.2, -1.0	-1.5	-5.4, 0.5

*The mean time interval between baseline and last assessment was 21 months (range was 1 month to 72 months).

**The mean time between baseline and last assessment was 56 months (range was 53 months to 60 months).

RGI-C

Radiographs from a total of 68 perinatal-/infantile-onset patients were examined to assess the treatment effect of asfotase alfa on HPP-related rickets. These included 64 perinatal-/infantile-onset patients enrolled in Studies ENB-002-08/003-08 and ENB-010-10, and 4 perinatal-/infantile-onset patients enrolled in Study ENB-006-09/ENB-008-10 (described in Section 7.2 of this CDTL Review). See discussion of RGI-C in Appendix 1. Patients who achieved a RGI-C score of ≥ 2 (corresponding to substantial healing of rickets) were classified as being responders to treatment.

The mean time interval between the baseline and last RGI-C assessment was 24 months (range was 1 month to 67 months).

Radiologic improvements could be seen by Month 24; at last assessment, 50/68 [74%] treated patients were rated as RGI-C responders.

No comparative data were available from historical controls.

7.2 Juvenile-Onset HPP

This section focuses on the asfotase alfa studies (ENB-006-09/ENB-008-10) and the natural history study (ALX-HPP-502).

Overview of Studies and Historically-Controlled Analysis:

Efficacy for the juvenile onset population was based primarily on data from historical-controlled analyses of the following:

- Juvenile-onset patients from asfotase alfa studies (ENB-006-09/ENB-008-10) vs.
- a natural history study (ALX-HPP-502)

An overview of the asfotase alfa studies and the natural history study is shown in the table below.

Table 14. Overview of Studies (Juvenile Onset)

Studies	Design	Age on Entry	Treatment Duration	N
ENB-006-09/ ENB-008-10*	• Open Label, Single Arm	• 5 to 12 yrs	• 24 weeks; • extension up to 60 months	8†
ALX-HPP-502 (ALX-HPP-502s#)	• Retrospective Chart Review	• 5 to 15 yrs	• Not Applicable	32 (6#)

*ENB-008-10 is an extension study of ENB-006-09

#ALX-HPP-502s is a sub-study of ALX-HPP-502 patients with 2 or more video recordings capturing basic mobility

†13 overall (8 juvenile- and 5 perinatal/infantile-onset pts) entered ENB-006-09; 12 overall (8 juvenile- and 4 perinatal/infantile-onset pts) continued into ENB-008-10

The primary endpoint of the historically-controlled analysis agreed upon with the sponsor (see Section 2.4 of this CDTL Review) was:

- Primary: Gait (change from baseline)

Key Entry Criteria:

The key entry criteria are summarized in the table below.

Table 15. Key Entry Criteria (Juvenile Onset)

Entry Criteria	ENB-006-09/ ENB-008-10*	ALX-HPP-502/ ALX-HPP-502s
Inclusion	<ul style="list-style-type: none"> ➤ Age 5 to 12 years ➤ Documented diagnosis of HPP ➤ Open growth plates at time of enrollment 	<p><u>ALX-HPP-502</u></p> <ul style="list-style-type: none"> ➤ Age 5 to 15 years ➤ Documented diagnosis of HPP ➤ Signs of HPP at ≥ 6 months to < 18 years of age ➤ Following data available in patient's medical records when the patient was age 5 - 15 years. <ul style="list-style-type: none"> ▪ At least 1 set of paired x-rays of the knees or hands/wrists taken at least 6 months but no more than 5 years apart ▪ At least 2 documented height measurement taken at least 3 years apart <p><u>ALX-HPP-502s</u></p> <ul style="list-style-type: none"> ➤ In addition to above, had at least 2 video recordings capturing basic mobility at 2 different routine clinic visits
Exclusion	<ul style="list-style-type: none"> ➤ History of sensitivity to the study drug ➤ Any current or prior clinically significant conditions ➤ Treatment with an investigational drug within one month of study drug administration ➤ Current enrollment in any other investigational trial ➤ Low serum Ca, Ph, or 25(OH) vitamin D ➤ Evidence of a treatable form of rickets ➤ Prior treatment with bisphosphonate 	<ul style="list-style-type: none"> ➤ Had received treatment with asfotase alfa or ➤ Had other clinically significant disease

*Note that ENB-006-09/ENB-008-10 does not specify signs of HPP at ≥ 6 months to < 18 years of age; thus, perinatal/infantile-onset HPP patients were also included.
Table above summarized from the Clinical Review.

See additional details of entry criteria in the Clinical Review.

Dosing

Dosing in each of the asfotase alfa studies is summarized in the table below.

Table 16. Dosing in the Asfotase Alfa Studies (Juvenile Onset)

ENB-006-09/ENB-008-10	
Dosing	ENB-006-09: <ul style="list-style-type: none"> ➤ 6 mg/kg/wk SC (administered as 2 mg/kg SC TIW); or ➤ 9 mg/kg/wk SC (administered as 3 mg/kg SC TIW) ENB-008-10: <ul style="list-style-type: none"> ➤ 3 mg/kg initially; was increased to 6 mg/kg/wk*
Dose Adjustment Rules	<ul style="list-style-type: none"> ➤ Dose adjustments for change in body weight ➤ Dose adjustments allowed for lack of efficacy or due to safety-related concerns based on Investigator's/Sponsor's review/consideration of study drug tolerability, X-ray, substrate, and PK data.

*Dose was 6 mg/kg/wk in amended protocol; dose was 3 mg/kg in original protocol.

Table above summarized from the Clinical Review.

See additional details of dosing in the Clinical Review.

Efficacy Endpoints and Other Efficacy Assessments:

The endpoints of the historically-controlled analyses (juvenile-onset patients from ENB-006-09/ENB-008-10 vs. ALX-HPP-502) agreed upon with the sponsor (see Section 2.4 of this CDTL Review) are shown in the table below.

Table 17. Efficacy Endpoints of the Historically-Controlled Analyses*

Endpoint	Definition
Primary:	<u>Change from Baseline in Gait</u> : measured by modified Performance Oriented Mobility Assessment-Gait (mPOMA-G) (see Appendix 2).
Secondary:	<u>Growth</u> : measured by height and weight z-scores
	<u>RGI-C</u> : Proportion of patients with RGI-C ≥ 2 (see Appendix 1)

*Juvenile-onset patients from ENB-006-09/ENB-008-10 vs. ALX-HPP-502

Table above summarized from the Clinical Review

Other efficacy assessments in the asfotase alfa studies included those shown in the table below.

Table 18. Other Efficacy Assessments in the Asfotase Alfa Studies*

Assessment	Description
6MWT	The 6 Minute Walk Test (6MWT) was developed to assess functional exercise capacity in adults with cardiopulmonary disease. The test is self-paced, with individuals being instructed to cover the furthest possible distance in 6 minutes without running. Reference values have been established for healthy children from Europe, Asia, Africa, and North America. The applicant reported 6MWT results as total distance walked (meters) and percent of predicted distance walked for age. Percent predicted distance walk values above 80% for age were defined as normal.

Table above summarized from the Clinical Review

See additional discussion of the above efficacy assessments and other efficacy assessments in the Clinical Review.

Demographic and Baseline Characteristics:

Demographic and baseline characteristics are summarized in tables in Appendix 4 of this CDTL Review.

The overall conclusion and comments regarding demographic and baseline characteristics are summarized below.

Overall Conclusion: This reviewer agrees with the Clinical Reviewer's conclusion that overall, patient demographics and baseline disease characteristics for the historical control group (ALX-HPP-502) were similar to those of patients in clinical trials (ENB-006-09/ENB-008-10).

Gait: The Clinical Reviewer noted that at baseline, all patients in ENB-006-09/ENB-008-10 had a history of unusual gait. For the similar item (gait disturbance) in the historical control group (ALX-HPP-502), the percentage of patients was 63%.

Growth: The Clinical Reviewer noted that mean baseline height and weight z-scores in ENB-006-09/ENB-008-10 were -1.94 (less than 3rd percentile) and -1.64 (~5th percentile), respectively. For the historical control group (ALX-HPP-502), the baseline height and weight z-scores were -1.07 (~14th percentile) and -1.15 (less than 13th percentile), respectively.

Disposition:

ENB-006-09/ENB-008-10: ENB-006-09 included 8 patients with juvenile-onset HPP. All 8 patients continued into the extension study (ENB-008-10) and were treated for at least 48 months.

Dose Adjustments:

See earlier section "Dosing" for dose adjustment rules.

ENB-006-09/ENB-008-10: Two patients received dose reductions during the primary treatment period, including one patient who experienced a decrease in vitamin B6 levels and one patient who experienced recurrent injection site reactions. During the extension phase, the dosing regimen for all patients was initially changed to 3 mg/kg per week. Dosing was subsequently increased to 6 mg/kg per week, with no patients requiring doses higher than 6 mg/kg per week.

mPOMA-G and 6MWT:

mPOMA-G:

Videos from 8 asfotase alfa-treated patients (ENB-006-09/ENB-008-10) and 6 historical controls (ALX-HPP-502) were compared to assess gait performance using the mPOMA-G scale (see Appendix 2).

The observed mean rate of change in mPOMA-G score for asfotase alfa-treated patients (ENB-006-09/ENB-008-10) was 2.25 per year; no substantial difference in gait scores was observed for the historical control group (the mean rate of change was 0.37 per year).

Improvement in mPOMA-G scores for asfotase alfa-treated patients was primarily due to improvements in step length, with 6/8 treated (75%) patients showing at least a 1 point improvement in step length in either foot. In comparison, one of 6 (17%) historical control patients showed any improvement in step length.

The Clinical Reviewer noted that although the mPOMA-G gait assessment findings suggest treatment benefit, there were a number of limitations to the interpretability of these results including:

- use of a post-hoc analysis,
- lack of validation of the mPOMA-G in the HPP population,
- differences in baseline disease severity, and
- test methodology (re-reading videos filmed for other types of ambulation assessments).

Given the above limitations, the Clinical Reviewer concluded the following:

- The gait assessment analysis (mPOMA-G) was not sufficient as the sole evidence to support an efficacy claim for the juvenile-onset population.

6MWT:

Asfotase alfa-treated patients (ENB-006-09/ENB-008-10) demonstrated improvements in mobility as measured by the 6 Minute Walk Test (6MWT) (absolute distance and percent predicted distance walked).

At baseline, none of the 8 treated patients had 6MWT percent predicted values within the normal range for age, sex, and height-matched peers.

By Month 48, 6/7 patients (86%) with post-baseline assessments had 6MWT percent predicted values within the normal range for age, sex, and height-matched peers.

Overall Conclusion (mPOMA-G and 6MWT):

The Clinical Reviewer concluded that improvements noted in both of these components of ambulation (gait as measured by the mPOMA-G and mobility as measured by the 6MWT) are supportive of the efficacy of asfotase alfa in the treatment of patients with juvenile-onset HPP.

Growth:

Height and weight measurements (as measured by z-scores) in 8 asfotase alfa-treated patients (ENB-006-09/ENB-008-10) were compared with a historical cohort of 32 untreated patients (ALX-HPP-502). Height and weight data for historical control patients (ALX-HPP-502)

were collected from medical records. The interval from first to last growth assessment ranged from 19 to 109 months for patients in the historical control group and up to 60 months for asfotase alfa-treated patients.

Height and weight z-scores at baseline and at the last assessment are shown in the table below.

Table 19. Height and Weight Z-Scores at Baseline and at Last Assessment

	Height Z-score				Weight Z-score			
	Baseline		Last Assessment		Baseline		Last Assessment	
	Mean	Min, Max	Mean	Min, Max	Mean	Min, Max	Mean	Min, Max
Asfotase Alfa (n=8)*	-1.5	-3.8, 0	-0.9	-2, 0	-1.1	-3.5, 2.3	0	-1.3, 2.2
Historical Control (n=32)*	-1.1	-4.9, 2.6	-1.1	-4.9, 1.8	-1.2	-5, 2.1	-1	-5.7, 2.1

*The time interval from baseline and last assessment ranged from 19 to 109 months for patients in the historical control group and up to 60 months for treated patients.

Asfotase alfa-treated patients (n=8) from ENB-006-09/ENB-008-10; historical control patients (n=32) from ALX-HPP-502

RGI-C:

Radiographs from 8 asfotase alfa-treated patients (ENB-006-09/ENB-008-10) and 32 historical controls (ALX-HPP-502) were compared to assess HPP-related rickets using the 7-point RGI-C scale (see Appendix 1). Patients who achieved a RGI-C score of ≥ 2 (corresponding to substantial healing of rickets) were classified as being responders to treatment.

All 8 asfotase alfa-treated patients were rated as responders (i.e., RGI-C score ≥ 2) by Month 54 of treatment.

The mean duration between the baseline and last RGI-C assessments for historical control patients was 56 months (range was 8 to 95 months). At last assessment, 2/32 (6%) of historical control patients were rated as responders.

Other Efficacy Assessments:

6MWT results were described above. Other efficacy assessments are discussed in the Clinical Review.

7.3 Discussion

Perinatal/Infantile-onset HPP

Both the Clinical and Statistics Reviewers concluded that there is sufficient evidence for supporting the proposed efficacy claims for asfotase alfa in the treatment of perinatal/infantile-onset HPP. This Reviewer agrees with the conclusions of the Clinical and Statistics Reviewers. This Reviewer notes that each of the criteria for a historically controlled analysis to be persuasive was met. Patients in the trials and historical control group are adequately matched (based on entry criteria and baseline characteristics), the study endpoints (pertaining to survival) are objective, and the outcome on treatment is markedly

different from that of the historical control (KM estimate of overall survival: 97% vs. 42%). This Reviewer notes further that the Clinical Pharmacology Reviewer concluded that for perinatal/infantile-onset HPP patients, asfotase alfa treatment is associated with an increase in overall survival in an exposure-dependent manner, thus providing further supportive evidence of efficacy (see Section 5.2 of this CDTL Review).

The Statistics Reviewer emphasized that all hypothesis testing was considered exploratory given that the agreed upon endpoints (i.e., overall survival and ventilator-free survival), planned data integrations, and subsequent historical control comparisons were all determined well into the execution of the relevant perinatal/infantile-onset HPP studies. Consequently, the Statistics Reviewer concluded that no inferential statistics should be presented within the final product labeling (see Section 12.3 of this CDTL Review).

The Clinical Reviewer recommended, based on the documented improved clinical responses in perinatal/infantile-onset patients who received doses > 6 mg/kg/week, that the labeling include recommendations and criteria for dose increases up to 9 mg/kg/week, the highest per protocol dose used in clinical trials, for perinatal/infantile-onset patients.

Juvenile-onset HPP

The Statistics Reviewer concluded that the evidence in supporting the proposed efficacy claims for asfotase alfa in the treatment of juvenile-onset HPP is weak from a statistical perspective; hence the clinical review team will determine the sufficiency of this evidence from a clinical perspective. The Clinical Reviewer agreed with the Statistics Reviewer. The Clinical Reviewer commented that the primary efficacy analysis for the juvenile-onset population was flawed from a statistical and clinical perspective and therefore was insufficient as stand-alone evidence to support efficacy. However, the Clinical Reviewer concluded that the totality of evidence, including growth, RGI-C, and the 6MWT, is compelling and was deemed sufficient to support an efficacy claim for the juvenile-onset population. In addition, the Clinical Reviewer commented that efficacy analyses for the perinatal/infantile-onset population are supportive evidence of efficacy for the juvenile-onset population, and vice versa. This Reviewer agrees with the Clinical Reviewer on each of the above points. This Reviewer further notes that the Clinical Pharmacology Reviewer concluded that for juvenile-onset HPP patients, an E-R relationship was observed between estimated average asfotase alfa concentration at steady state ($C_{avg,ss}$) and multiple PD measurements, including the 6MWT and the RGI-C, thus providing further supportive evidence of efficacy (see Section 5.2 of this CDTL Review).

7.4 Recommendation

An Approval Action is the final recommendation from a Clinical/Statistical standpoint. See Section 7.3 Discussion above.

See Section 12.3 of this CDTL Review for a summary of the main revisions to the Applicant's proposed Dosage and Administration, and Clinical Studies sections of the label.

8 Safety

The reader is referred to the Clinical Review by Carla Epps for complete information.

8.1 Overview of Data Evaluated for Safety

The primary safety information for the clinical review included data for 102 patients with HPP submitted in the 120-Day Safety Update Report (dated April 11, 2015).

Clinical Trials: These 102 patients received asfotase alfa in the following clinical trials:

- ENB-002-08/ENB-003-08 (data analysis cutoff date October 29, 2014),
- ENB-006-09/ENB-008-10 (data analysis cutoff date November 5, 2014),
- ENB-009-10 (data analysis cutoff date November 5, 2014), and
- ENB-010-10 (data analysis cutoff date November 12, 2014).

Phenotype: These 102 patients were by phenotype:

- Perinatal/infantile-onset HPP: n=79
- Juvenile-onset HPP: n=20
- Adult-onset HPP: n=2
- Unknown phenotype: n=1

8.2 Exposure

Duration of exposure is summarized in the tables below by phenotype and overall.

Table 20. Duration of Exposure [weeks]

Descriptive Statistics	Duration of Exposure [weeks]				
	Perinatal/ Infantile Onset (n=79)	Juvenile-Onset (n=20)	Adult-Onset (n=2)	Unknown Onset (n=1)	All Patients (n=102)
Mean (SD)	102 (94)	193 (46)	192 (0)	215	123 (93)
Median (Min, Max)	71 (0.1, 312)	192 (96, 260)	192 (192, 192)	--	99 (0.1, 312)

Table modified from Clinical Review. Source is 120 Day Safety Update Report (dated April 11, 2015), Table 7

Table 21. Number (%) of Patients by Duration of Exposure

Duration of Exposure	Number (%) of Patients				
	Perinatal/ Infantile Onset (n=79)	Juvenile-Onset (n=20)	Adult-Onset (n=2)	Unknown Onset (n=1)	All Patients (n=102)
< 6 months	20 (25%)	0	0	0	20 (20)
6 months to <1 year	13 (17%)	0	0	0	13 (13%)
1 to <1.5 years	7 (9%)	0	0	0	7 (7)
18 months to <2 years	7 (9%)	1 (5%)	0	0	8 (8%)
2 years to < 2.5 years	3 (4%)	1 (5%)	0	0	4 (4%)
2.5 years to < 3 years	2 (3%)	1 (5%)	0	0	3 (3%)
3 years to <3.5 years	3 (4%)	2 (10%)	0	0	5 (5%)
3.5 years to < 4 years	6 (8%)	2 (10%)	1 (50%)	0	9 (9%)
4 years to <4.5 years	4 (5%)	5 (25%)	1 (50%)	1 (100%)	11 (11%)
4.5 years to < 5 years	6 (8%)	6 (30%)	0	0	12 (12%)
5 to < 6 years	6 (8%)	2 (10%)	0	0	8 (8%)
>6 years	2 (3%)	0	0	0	2 (2%)

Table modified from Clinical Review. Source is 120 Day Safety Update Report (dated April 11, 2015), Table 7

8.3 Dosing

The initial dose differed across trials (see Section 7 of this CDTL Review). The total dose ranged from 0.9 to 28 mg/kg/wk.

The Clinical Reviewer noted that the majority of patients either started on or achieved a dose of 6 mg/kg/wk within the first 24 weeks of treatment. The proportion of patients receiving > 6 mg/kg/wk was the following: (1) Perinatal/Infantile Onset: 19/79 (24%); (2) Juvenile-Onset: 5/20 (25%); and (3) Overall: 24/102 (24%).

The table below summarizes dosing by phenotype and overall.

The Clinical Reviewer noted the following regarding dose changes (see table below):

- The majority of changes in dose amount were per protocol.
- Of 38 patients who experienced a decrease in dose amount, six patients (16%) had their doses decreased due to AEs assessed as treatment-related.
- 12 patients experienced an increase in dosing frequency, primarily due to a change in the protocol schedule or to limit the volume of each injection (maximum allowed volume per injection was 1 mL); 1 patient increased the dosing schedule due to AE's (injection site reactions) experienced with a 3 times weekly schedule.

Table 22. Number (%) of Patients by Dosing Schedule, Maximum Dose, and Dose Changes

Dosing Characteristic	Perinatal/ Infantile Onset (n=79)	Juvenile- Onset (n=20)	Adult- Onset (n=2)	Unknown Onset (n=1)	All Patients* (n=102)
Dosing Schedule					
3x Weekly	67 (85%)	2 (10%)	0	0	69 (68%)
6x Weekly	11 (14%)	18 (90%)	2 (100%)	1(100%)	32 (31%)
Maximum Dose					
≤1 mg/kg/day	6 (8%)	12 (60%)	2 (100%)	1 (100%)	21 (21%)
>1 to 2 mg/kg/day	53 (67%)	3 (15%)	0	0	56 (55%)
>2 mg/kg/day	19 (24%)	5 (25%)	0	0	24 (24%)
Dose Changes					
Dose Increased	27 (34%)	12 (60%)	2 (100%)	1(100%)	42 (41%)
Dose Decreased	29 (37%)	9 (45%)	0	0	38 (37%)
Dose Frequency Increased	5 (6%)	7 (35%)	0	0	12 (12%)

*One patient who was discontinued after initial dosing due to a hypersensitivity reaction is not included in exposure analyses.

Table modified from Clinical Review. Source: 120 Day Safety Update Report (dated April 11, 2015), 2.3.8.2.1, 3.3.8.2.1 (maximum daily dose); 2.3.8.7.1, 3.3.8.7.1 (changes in dosing).

8.4 Safety Findings

Deaths:

The deaths are summarized in the tables below. Note that all were perinatal/infantile HPP patients.

Table 23. Deaths in Clinical Trials

Patient #	Age at Study Entry/Sex	Dose (mg/kg) Frequency at Event Onset	Days from First Dose to Event Onset (to Death)	AE (Preferred Term)	Relationship to Asfotase Alfa ^a
002-08-08-01	2.9 wk/M	2 mg/kg TIW	214 d (222 d)	Septic shock	Unrelated
010-10-01-07	0.1 wk/M	2 mg/kg 7×/wk	436 d (436 d)	Cardio-respiratory arrest	Unrelated
010-10-13-01	20.9 wk/M	4 mg/kg TIW	1400 d (1403 d)	Coagulopathy	Unlikely
			1400 d (1403 d)	Hepatic function abnormal	Unlikely
			1401 d (1403 d)	Brain oedema	Unrelated
			1401 d (1403 d)	Hydrocephalus	Unrelated
			1401 d (1403 d)	Intracranial pressure increased	Unrelated
			1401 d (1403 d)	Brain herniation	Unrelated
010-10-15-01 ^b	33.4 wk/M	NA	Not dosed	Respiratory failure/	Unrelated
010-10-16-03	6.6 wk/M	2 mg/kg TIW	7 d (22 d)	Neurological examination abnormal	Unlikely
010-10-18-03	89.0 wk/F	2 mg/kg TIW	316 d (329 d)	Respiratory failure/	Unrelated
010-10-18-04	22.7 wk/F	2 mg/kg TIW	42 d (42 d)	Hypophosphatasia	Unrelated
010-10-19-01	38.9 wk/M	3 mg/kg TIW	94 d (204 d)	Pneumonia	Possible

D = day; F = female; M = male; a As assessed by the Investigator; b Patient 010-10-15-01 died 2 days after study enrollment, prior to initiating asfotase alfa treatment. This patient had been considered a screen failure Table above modified from a table found in the Safety Update Report dated April 11, 2015

Regarding the event for which relationship to asfotase alfa was assessed as "Possible", the Clinical Reviewer noted that the investigator initially assessed the event of pneumonia as unrelated to treatment but later changed the assessment as possibly treatment-related with the

impression the patient had a steroid-dependent respiratory condition. Additionally, the Clinical Reviewer commented that there was not sufficient information (e.g., autopsy findings) provided to determine the etiology or nature of pulmonary changes that resulted in respiratory deterioration and the final fatal event. The history of elevated eosinophil counts in this patient raises a question of a possible inflammatory response as an etiology for pulmonary injury.

Table 24. Deaths in Compassionate Use Programs

Country	Age at Start of Treatment/Sex	Dose (mg/kg) Frequency at Event Onset	Days from First Dose to Death	Cause of Death	Relationship to Asfotase Alfa ^a
Japan	14 mo/F	2 mg/kg TIW	~ 7 wks	Complications of HPP	Unrelated
The Netherlands	1 mo/M	4 mg/kg 7x/wk	~ 6 mos	Respiratory Insufficiency	Unrelated
South Africa	4 mo/M	2 mg/kg TIW	~ 8 wks	Complications of HPP	Unrelated

^a As assessed by the treating physician.

Table above is summarized from the Clinical Review.

See detailed narratives of the deaths in the Clinical Review.

CDTL Comment: This Reviewer agrees with the assessment of the Clinical Reviewer and Applicant that all of the deaths described above were due to the underlying disease.

Discussion of Reported Deaths: The Clinical Reviewer noted the following:

- All patient deaths occurred in patients with infantile onset HPP who had clinical features of HPP associated with poor prognosis (i.e., rachitic chest deformity, respiratory compromise, and/or vitamin B6-responsive seizures). This was also noted by the Applicant.
- There did not appear to be any differences in exposure between patients who survived and patients who died.
- Based on the information provided in the patient narratives, patients received comparable levels of critical care for events such as respiratory failure and increased intracranial pressure.
- Based on review of antibody status for the 7 patients treated in clinical trials who died (no information on antibody status was available for patients in compassionate use programs), 3 patients were ADA-negative, and 4 patients were ADA positive (including 3 patients who had persistently positive antibodies and 2 patients who developed neutralizing antibodies); the Clinical Reviewer commented that there were no clear patterns in antibody status to other clinical responses (i.e., growth or radiographic assessments) or time to death.

CDTL Comment: This Reviewer agrees with the Clinical Reviewer's conclusion that the above findings suggest that the lack of response in terms of survival for some patients may be due to genetic differences in response to treatment rather than differences in drug exposure, immunogenicity, and/or standard of care, but more information is needed on the long-term impact of immunogenicity on clinical outcomes, including survival.

Serious Adverse Events:

Reported SAE's: A total of 274 nonfatal SAE's were reported in 48 patients; including 42 patients with perinatal/infantile-onset HPP, 5 patients with juvenile-onset HPP, and one patient with adult-onset HPP. Of the 274 SAE's, 258 SAE's were assessed as unrelated to treatment by the Investigator. The 16 nonfatal SAEs assessed as treatment-related occurred in 8 patients, and are summarized in the table below.

Table 25. Information for the 8 patients who experienced nonfatal SAEs assessed as treatment related*

Patient ID	Dose	Phenotype	Day	SAE	Severity	Outcome
002-08-05-01	2 mg/kg TIW	Infantile	765	• Chronic hepatitis	severe	Resolved
002-08-08-01	2 mg/kg TIW	infantile	128 198	• Craniosynostosis • Conductive deafness	severe	Resolved- (surgically repaired); Ongoing at time of death
009-10-01-04	1 mg/kg 6 x/wk	Juvenile	806 830	• Oral hypoesthesia • Extremity pain • Chills (3 events) • Headache	moderate	Resolved
010-10-16-11	2 mg/kg TIW	Infantile	7	• Injection site reaction (2 events)	moderate	Dose interruption-resolved
010-10-18-05	2 mg/kg TIW	Infantile	56	• Craniosynostosis	moderate	Resolved (surgically repaired)
010-10-22-	2 mg/kg TIW	Infantile	122	• Chills • Pyrexia	moderate	
01010-10-27-01	3 mg/kg TIW	Infantile	129	• Injection site abscess	mild	Resolved
010-10-38-03	2.5 mg/kg TIW	Infantile	237	• Dosing error (dose too high due to calculation error)	moderate	Dose was corrected

*assessed by the Investigator. Table above modified from the Clinical Review.

Discussion of Injection Site Reactions, Hypersensitivity Reactions, and Dosing Error: The events of injection site reactions and the events consistent with hypersensitivity reactions (chills, pyrexia, headache, etc.) are known adverse effects with drugs administered subcutaneously and with therapeutic proteins, respectively. The medication error was clearly treatment-related. Therefore, the Clinical Reviewer did not include detailed patient narratives for these events.

Discussion of Chronic Hepatitis, Craniosynostosis, and Conductive Deafness: The Clinical Reviewer described the events of chronic hepatitis, craniosynostosis, and conductive deafness in patient narratives (see the Clinical Review). The Clinical Reviewer commented that mechanistically, there is a theoretical risk for all three of these events with treatment with asfotase alfa; however, craniosynostosis and conductive deafness are known complications of HPP. Each of these AE's are summarized below.

- Chronic Hepatitis:

- Chronic Hepatitis Event Narrative: According to the chronic hepatitis event narrative, the patient was started on montelukast about 6 months prior to the event, which suggests that montelukast may indeed have played a role in the patient developing hepatitis. Conversely, there is also evidence suggesting that asfotase alfa played a role, including the negative work-up for other etiologies and the persistence

- of the hepatitis for at least 18 months after montelukast was discontinued (no data were available for the interval between May 2012 and June 2014).
- Query for Other Hepatic Events: The applicant conducted a query for other hepatic events and identified one report of a patient with AEs of acute pancreatitis and increased hepatic enzymes that were assessed as unrelated to treatment (see Clinical Review).
 - *CDTL Comment*: *This Reviewer agrees with the Clinical Reviewer's conclusion that based on the information provided in the submission, there appears to be sufficient evidence of a causal link between treatment and the reported case of chronic hepatitis; there is sufficient evidence to warrant inclusion of this event in labeling (see Section 12.3 of this CDTL Review).*
 - Craniosynostosis:
 - Discussion of Craniosynostosis Cases: One of the potential risks with asfotase alfa treatment is abnormal deposition of calcium, not only in the form of ectopic calcifications but also as excessive calcium deposition in areas of active bone formation. This is the basis for a concern that the risk for craniosynostosis may be increased with asfotase alfa treatment. However, there is insufficient information for the two patients that experienced this event to assess for causality.
 - *CDTL Comment*: *This Reviewer agrees with the Clinical Reviewer's conclusion that there was insufficient information to evaluate for a relationship between treatment and development of craniosynostosis in the two patients that experienced this SAE.*
 - Conductive Deafness:
 - Discussion of Conductive Deafness Case: Deafness is a known complication of perinatal/infantile- onset HPP and may have a conductive and sensorineural component. Given the lack of a baseline auditory evaluation and/or imaging evaluation and the clinical findings of soft-tissue stenosis on examination, in the Clinical Reviewer's opinion, an adverse effect on auditory bone structure remains a theoretical risk.
 - *CDTL Comment*: *This Reviewer agrees with the Clinical Reviewer's conclusion that there was insufficient information to evaluate for a relationship between treatment and development of deafness.*

Common Adverse Events:

Overall, the most common adverse reactions reported were injection site reactions (63%). Other common adverse reactions included lipodystrophy (28%), ectopic calcifications (22%), and hypersensitivity reactions (76%), including pyrexia, vomiting, pain in extremity, headache, erythema, irritability, chills, hypoesthesia oral, flushing and nausea.

The table below shows the most common AE's (reported in $\geq 10\%$) in clinical trials following subcutaneous injection of asfotase alfa, by patient population and asfotase alfa dosage regimen.

The frequency of injection site reactions, lipodystrophy and ectopic calcification were higher in patients with juvenile-onset HPP as compared to perinatal/infantile-onset HPP patients. Within the perinatal/infantile-onset HPP patients, the frequency of these types of reactions

(except for ectopic calcification) was higher in patients treated with less than or equal to 6 mg/kg per week than those who received more than 6 mg/kg per week.

The majority of injection site reactions resolved within a week. Two patients experienced injection site reactions that led to reductions of their asfotase alfa dose. One patient switched from six times per week dosing to 3 times per week dosing as a result of injection site reactions. One other patient experienced a severe injection site reaction of injection site discoloration and withdrew from the trial.

Table 26. Most Commonly Reported Treatment-Emergent Adverse Events (>10% of Patients) by HPP Phenotype and Dose

Adverse Reaction Category or Term	Perinatal/ Infantile-onset HPP			Juvenile- onset HPP
	≤ 6 mg/kg/wk (N=66) n (%)	> 6 mg/kg/wk (N=13) n (%)	Total (N=79) n (%)	(N=20) n (%)
Injection site reactions	38 (58)	6 (46)	44 (56)	18 (90)
Erythema	29 (43.9)	3 (23.1)	32 (40.5)	15 (75.0)
Discoloration/ Hypopigmentation	11 (16.7)	1 (7.7)	12 (15.2)	8 (40.0)
Pain/ Tenderness	10 (15.2)	1 (7.7)	11 (13.9)	8 (40.0)
Pruritus/ Itching	10 (15.2)	0 (0.0)	10 (12.7)	7 (35.0)
Swelling	8 (12.1)	0 (0.0)	8 (10.1)	6 (30.0)
Induration	9 (13.6)	1 (7.7)	10 (12.7)	3 (15.0)
Macule	4 (6.1)	0 (0.0)	4 (5.1)	7 (35.0)
Reaction, not otherwise specified	6 (9.1)	1 (7.7)	7 (8.9)	4 (20.0)
Bruising	6 (9.1)	0 (0.0)	6 (7.6)	4 (20.0)
Nodule	2 (3.0)	0 (0.0)	2 (2.5)	2 (10.0)
Other injection site reactions*	10 (15.2)	3 (23.1)	13 (16.5)	4 (20.0)
Ectopic calcifications	6 (9.1)	5 (38.5)	11 (13.9)	11 (55.0)
Lipodystrophy	12 (18.2)	2 (15.4)	14 (17.7)	14 (70.0)
Injection site atrophy	4 (6.1)	2 (15.4)	6 (7.6)	8 (40.0)
Injection site hypertrophy	5 (7.6)	0 (0.0)	5 (6.3)	6 (30.0)
Hypersensitivity reactions	47 (71.2)	11 (84.6)	58 (73.4)	17 (85.0)
Pyrexia/fever	31 (47.0)	9 (69.2)	40 (50.6)	1 (5.0)
Vomiting/emesis	23 (34.8)	8 (61.5)	31 (39.2)	5 (25.0)
Pain in extremity	13 (19.7)	3 (23.1)	16 (20.3)	10 (50.0)
Headache	12 (18.2)	2 (15.4)	14 (17.7)	7 (35.0)
Erythema/redness	5 (7.6)	2 (15.4)	7 (8.9)	3 (15.0)
Irritability	3 (4.5)	5 (38.5)	8 (10.1)	1 (5.0)
Nausea	1 (1.5)	1 (7.7)	2 (2.5)	3 (15.0)
Other hypersensitivity reactions**	3 (4.5)	0 (0.0)	3 (3.8)	1 (5.0)

* Other injection site reactions include injection site rash, inflammation, papule, hemorrhage, hematoma, urticaria, warmth, calcification, mass, scar and cellulitis

** Other hypersensitivity reactions include rigor/chills, hypoesthesia oral, flushing and anaphylaxis

Other Significant Adverse Events:

Hypersensitivity Reactions

Hypersensitivity reactions were reported for 12 patients, including 10 perinatal/infantile-onset patients and two juvenile-onset patients. The most commonly reported hypersensitivity reactions (reported in 2 or more patients) were erythema/redness (6 patients), extremity pain (3 patients), emesis/vomiting, fever, chills, and headache (2 patients each).

The Clinical Reviewer identified a patient that experienced signs and symptoms consistent with anaphylaxis, including difficulty breathing, nausea, periorbital edema, and dizziness. The Clinical Reviewer noted that the event met the National Institute of Allergy and Infectious Diseases/Food Allergy and Anaphylaxis Network criteria for anaphylaxis:³

The Clinical Reviewer summarized the case as follows:

"Patient 010-10-01-04 (Perinatal/infantile-onset HPP)

The patient was a 4.9 year old female at study entry. She started treatment with asfotase alfa at a dosing regimen of 2 mg/kg (2 injections per dose) 3 times per week on April 13, 2011. The patient experienced multiple injection site reactions, including pain, erythema, and lipoatrophy, prior to the reported event. On [REDACTED] (b) (6) approximately [REDACTED] (b) (6) [REDACTED] (b) (6) after starting asfotase alfa treatment, she experienced a reaction within minutes of receiving an injection that was characterized by flushing, swollen eyes, difficulty breathing, coughing, nausea, dizziness, trembling, headache, and feeling cold. The patient was evaluated by paramedics within several minutes of the onset of symptoms and was noted to have a normal blood pressure and temperature and no problems breathing. The patient was monitored for 30 minutes in hospital and did not require any intervention. The patient was pretreated with diphenhydramine and monitored in hospital for administration of her next injection. The patient's vital signs were stable and she was asymptomatic following the injection. She received premedication for injections for an unspecified period of time and subsequently received injections without premedication. At the time of the last investigator report (date not provided), the patient had not had recurrence of an allergic reaction."

Lipodystrophy

Lipodystrophy, an abnormal redistribution of fat, may manifest as areas of fat loss (lipoatrophy) or fat accumulation (lipohypertrophy). Thirty events of lipoatrophy were reported in 14 patients and 35 events of lipohypertrophy were reported in 11 patients. Events of lipodystrophy occurred more frequently in juvenile-onset patients (30% to 40%) compared to perinatal/infantile onset patients (6% to 8%).

All events of lipodystrophy except one were reported as mild or moderate in severity. Some patients were advised to rotate injection sites to avoid events of lipodystrophy; one patient's

³ Sampson HA, Muñoz-Furlong A, et al., Symposium on the definition and management of anaphylaxis: Summary report, *J Allergy Clin Immunol* 2005; 115(3): 584-591

asfotase alfa dose was reduced due to lipoatrophy. The majority of events were ongoing at the time of last site contact with the patient.

The Clinical Reviewer commented that injection site lipodystrophy has been reported for other medications including steroids, insulin, growth hormone, and vaccines. The Clinical Reviewer recommended including information on lipodystrophy in the labeling for asfotase alfa, including information on minimizing risk of developing lipodystrophy (e.g., rotation of injection sites).

Ectopic Calcifications

The Clinical Reviewer noted that treatment with asfotase alfa raises a concern for the potential formation of ectopic calcifications in tissues as inorganic phosphate released through enzymatic activity binds with calcium to form hydroxyapatite crystals.

The table below summarizes ectopic calcification AEs assessed by the investigator and applicant as treatment-related.

Table 27: Patients with Ectopic Calcifications AEs Assessed as Treatment-related

Preferred Term	Perinatal/infantile n=79	Juvenile n=20	Adult n=2	Unknown n=1
Eye deposits		6/6	0	0/1
Conjunctival deposits	2/3	4/4	0	0
Corneal deposits	1/3	1/1	0	0
Nephrocalcinosis	0/6	1/1	0	0
Breast calcifications	0	0/1	0/1	0/1

The Clinical Reviewer commented that ectopic calcifications, including the following are known complications of HPP that have been reported in the literature:⁴

- nephrocalcinosis,
- conjunctival calcifications
- band keratopathy

However, the Clinical Reviewer further noted that the following are recognized ocular manifestations of hypercalcemia and observed in other conditions that cause hypercalcemia (e.g., sarcoidosis and hyperparathyroidism):⁵

- conjunctival calcifications
- band keratopathy

Band keratopathy is characterized by the appearance of a band across the central cornea formed by calcium deposition in the superficial cornea.

No data were available on the prevalence of conjunctival calcifications or band keratopathy from the natural history study or the literature. The Clinical Reviewer commented that based on her review of the datasets and patient narratives, there was insufficient information for

⁴ Brenner RL, Smith JL, et al., Eye Signs of Hypophosphatasia, *Arch Ophthalmol* 1969; 81(15): 614-617

⁵ Lessell S, Norton EW, Band keratopathy and conjunctival calcification in hypophosphatasia, *Arch Ophthalmol* 1964; 71(4): 497-499.

AEs described as ectopic calcifications of the eye or cornea to determine whether the calcifications represent:

- (a) known disease complications (i.e., band keratopathy); or
- (b) new safety signals (i.e., calcifications involving deeper layers of the cornea or other ophthalmic structures).

The Clinical Reviewer noted that the sole event of nephrocalcinosis that was assessed as treatment-related was based on worsening of the patient's nephrocalcinosis over time. The Clinical Reviewer noted that nephrocalcinosis reported in the medical history of 37/90 patients (41%), including 35/67 perinatal/infantile-onset patients (52%) and 2/20 juvenile onset patients (10%), and that there did not appear to be standardized criteria for assessing causality for events of nephrocalcinosis.

The Clinical Reviewer commented that there were multiple limitations in the interpretation of the data for ectopic calcifications, including the small sample sizes (particularly for the juvenile-onset population), lack of baseline data for a large proportion of patients, and lack of detailed information for the clinical findings (e.g., number or size of renal calcifications, location of cornea calcifications etc.) The Clinical Reviewer recommends that additional information on ectopic calcification events is collected as a post-marketing requirement (see Section 8.5 of this CDTL Review).

8.5 Recommendation

An Approval Action is the final recommendation from a Safety standpoint.

A PMR is recommended for a post-marketing, observational epidemiologic study of specific risks, including severe hypersensitivity reactions (including anaphylaxis), systemic immune complex-mediated reactions and ectopic calcification events. See PMR wording below and in Section 13.5 of this CDTL Review. See also the DEPI Review.

PMR: Conduct a 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. The purpose of the study is to assess the long term safety of treatment with STRENSIQ (asfotase alfa) with respect to incidence rates of severe hypersensitivity reactions (including anaphylaxis), systemic immune complex-mediated reactions and ectopic calcification events. Specify case definitions and validation methods and procedures for all outcomes. Enroll adequate number of patients, including both infantile-onset and juvenile-onset-patients, and follow for a minimum of 5 years from the time of enrollment, or until death, whichever comes first.

The DRISK Reviewer concluded that risk mitigation measures beyond professional labeling are not warranted for asfotase alfa at this time. The DRISK Reviewer noted that the benefit-risk profile for asfotase alfa is acceptable and the risks can be mitigated through professional labeling. (See DRISK Review.)

9 Advisory Committee Meeting

This application was not presented to an Advisory Committee.

10 Pediatrics

PeRC and PREA

Asfotase alfa was granted an orphan product designation on September 12, 2008. Therefore, the regulations that pertain to the Pediatric Equity in Research Act (PREA) do not apply to asfotase alfa. The submission was not presented to the Pediatric Review Committee (PeRC).

DPMH Consult

The Division consulted the Division of Pediatric and Maternal Health (DPMH) to aid in the review of the labeling. The reader is referred to the DPMH consultation review by Dr. E. Hausman (Pediatrics); the DPMH recommendations have been incorporated into final labeling.

11 Other Relevant Regulatory Issues

11.1 Financial Disclosures

The Clinical Reviewer indicated in the Clinical Review that the Applicant adequately disclosed financial arrangements with the clinical investigators, and that these arrangements did not raise concern over the integrity of the data. The reader is referred to the Clinical Investigator Financial Disclosure Form included in the Clinical Review.

11.2 Office of Scientific Investigations (OSI) Audits

The reader is referred to the OSI Clinical Inspection Summary (CIS) by Susan Leibenhaut for complete information.

Overview of Inspections and Final Classifications:

An overview of the investigators / sites inspected and final classifications are presented in the table below. These investigators / sites were chosen because of high enrollment. A focused sponsor inspection was also conducted because the product is a new molecular entity.

Table 28. Overview of Investigators / Sites Inspected and Final Classifications

Investigator / Location	Study	Site No.	No. Pts [§]	Final Classification
Michael P. Whyte St. Louis, MO	ENB-006-09 / ENB-008-10 [#]	1	9	VAI
	ENB-011-10	7	12	
	ALX-HPP-502	257	22	
	ALX-HPP-502s*	*	6	
Cheryl Rockman-Greenberg Winnipeg, Manitoba, Canada	ENB-006-09 / ENB-008-10 [#]	2	4	NAI
	ENB-002-08 / ENB-008-10 [#]	1	1	
Sponsor (Alexion) Cheshire, CT	All studies [†]	N/A	N/A	NAI [‡]

[§]No. pts enrolled

[#]Extension study

*only site was the Whyte site

[†]Each of the studies noted in the table, and extension study 003-08

[‡]this was Pending NAI in the OSI CIS, but was NAI in the Sponsor Monitor NAI Letter dated August 14, 2015

Inspector's Key Findings:

The Inspector's key findings are summarized below by Clinical Investigator (CI) and for the sponsor inspection.

Michael P. Whyte:

- A discrepancy between the line listing and the source document for the Week 120 6MWT was noted for one subject in Study ENB-008-10. The value was noted to be incorrectly calculated on the source worksheet as 920 (13 hash marks X 40m=520) and incorrectly reported on the line listings as 920, but correctly entered as 520 in the CRF. This is discussed further in the sponsor inspection below.
- A Form FDA 483 was issued citing the following two violations (discussion in the CIS of each violation is included):
 - (1) Failure to properly dispose of unused investigational drugs. Specifically, when subjects returned unused temperature sensitive study drug, the site returned it back into the general drug inventory and re-dispensed it to study subjects.
 - ❖ The CIS noted that it was determined (based on discussion with the product reviewers for this BLA) that the drug was stable under the conditions of storage and handling at the site so that refrigeration would have been ideal, but not required for product stability.
 - (2) CI did not ensure study personnel were delegated to perform study related activities. The pharmacist who is employed by Shriners Hospital was not on the delegation log. There was no delegation to a physical therapist of certain duties required in the protocol to be conducted by a physical therapist.
 - ❖ The CIS noted that this observation is not a protocol violation. The protocol required a licensed physical therapist, and this individual was supplied by the sponsor. In addition, the study was conducted in an unblinded fashion, so whether employed by the sponsor or the clinical site, bias could be introduced. The finding is discussed further in the sponsor inspection section below.

The OSI Reviewer noted that the observations noted on the Form FDA 483 are not considered serious violations. The OSI Reviewer concluded that the data generated by this site appear acceptable in supportive of the respective indication.

Cheryl Rockman-Greenberg:

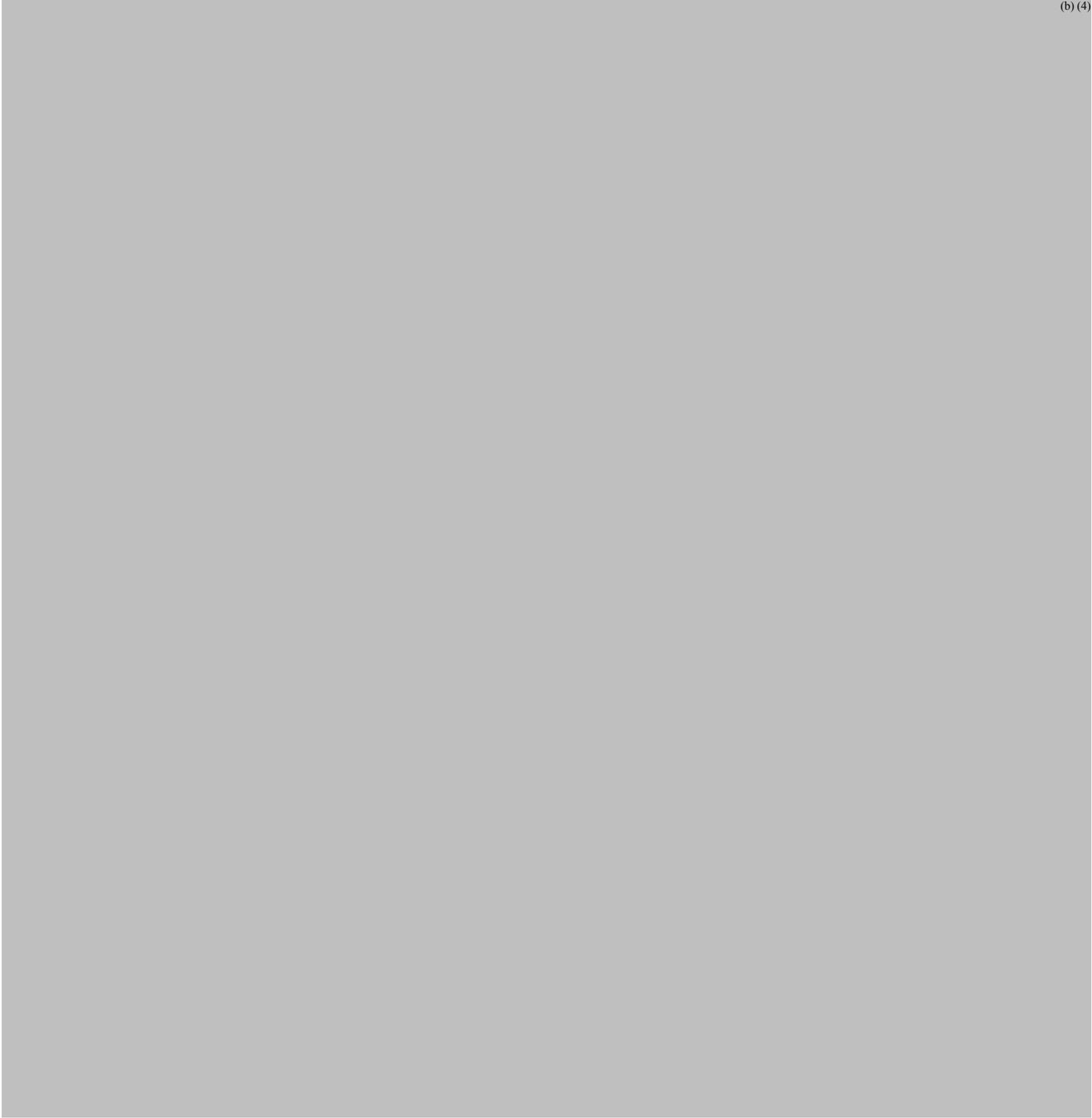
(b) (4)

The Clinical Reviewer and the DBRUP Consult Reviewer concluded that this is not a significant issue. This CDTL Reviewer agrees with the determination of the Clinical Reviewer and the DBRUP Consult Reviewer.

The OSI Reviewer concluded that the data generated for the studies conducted at this site are considered reliable, and noted that the determinations of the significance of the issues noted above are deferred to the review team.

Sponsor Inspection:

(b) (4)



Final Conclusion:

OSI concluded that the studies appear to have been conducted adequately, and the data generated by each of the two sites and by the sponsor may be used in support of the respective indication.

11.3 Rare Pediatric Disease Priority Review Voucher Program

The Rare Pediatric Disease Priority Review Voucher (RPDPRV) Program, established under the Food and Drug Administration Safety and Innovations Act (FDASIA), entitles the sponsor of a qualifying rare pediatric disease product application to receive a voucher for 'priority review' of any subsequent human drug application upon marketing approval of the product. The Applicant has submitted data to support that HPP is a rare pediatric disease based on the criteria specified in Section 529 of the Federal Food, Drug, and Cosmetic Act. The Office of Orphan Products Development (OOPD) has accepted that the prevalence of HPP in the U.S. is less than 200,000, and that more than 50% of HPP patients are 18 years of age or younger. Therefore, the OOPD has determined that HPP meets the FDASIA definition of a rare pediatric disease to be eligible for a voucher. The reader is referred to the OOPD consultation review by Karen Russell, dated May 21, 2015, for complete information. A priority review voucher will be issued at the time of marketing approval.

12 Labeling

12.1 Proprietary Name

For complete information, see the DMEPA Proprietary Name Review by Matthew Barlow, dated April 13, 2015. DMEPA concluded that the proprietary name of "Strensiq" was acceptable. This was communicated to the Applicant in the Proprietary Name Request Conditionally Acceptable Letter dated April 13, 2015.

12.2 Office of Prescription Drug Promotion (OPDP) Comments

The Office of Prescription Drug Promotion (OPDP) determined that the proposed name (Strensiq) is acceptable from a promotional perspective. This is documented in the Proprietary Name Review by Matthew Barlow, dated April 13, 2015.

12.3 Physician Labeling / Medication Guide / Carton and Container Labeling

The main revisions to the Applicant's proposed Physician Labeling are summarized below:

➤ Indications and Usage (Section 1 of Label):

The Applicant had initially proposed " [REDACTED] (b) (4)

- Replacement of [REDACTED] (b) (4) with "treatment of": The wording [REDACTED] (b) (4) was replaced with "treatment of" because of current labeling practice and regulations. [REDACTED] (b) (4)

(b) (4)

- Replacement of (b) (4) with "perinatal/infantile-": The term "(b) (4)" was replaced with "perinatal/infantile-".

Thus, the final indication wording is the following:

"...for the treatment of patients with perinatal/infantile- and juvenile-onset hypophosphatasia (HPP)".

➤ Dosage and Administration (Section 2 of Label):

- Statement Cautioning Patients < 40 kg Not to Use the 80 mg/0.8 mL Vial: Based on the finding from the Clinical Pharmacology review that the exposure achieved with the 100 mg/mL formulation (i.e., 80 mg/0.8 mL vial) was estimated to be 24% lower than the exposure achieved with the 40 mg/mL formulation, the following statement was added:

"Caution: Do not use the 80 mg/0.8 mL vial of STRENSIQ in pediatric patients weighing less than 40 kg because the systemic exposure of asfotase alfa achieved with the 80 mg/0.8 mL vial (higher concentration) is lower than that achieved with the other strength vials (lower concentration). A lower exposure may not be adequate for this subgroup of patients [see *Dosage Forms and Strengths (3), Clinical Pharmacology (12.3)*]."

(b) (4)

- Recommendation for Dose Escalation (Perinatal/Infantile-Onset): The Clinical Reviewer noted that some perinatal/infantile-onset patients appeared to require 9 mg/kg/week, the maximum per protocol dose in clinical trials, to achieve improved growth. Thus, for the Perinatal/Infantile-Onset HPP population, the following recommendation for dose escalation was included:
"The dose of STRENSIQ may be increased for lack of efficacy up to 9 mg/kg per week administered subcutaneously as 3 mg/kg three times per week."
- Statement about Tolerability of the Six Times Per Week Regimen: Although the six times per week regimen (i.e., 1 mg/kg six times per week) was included as an option for administration of the 6 mg/kg/wk dose, the following statement was included:
"Injection site reactions may limit the tolerability of the six times per week regimen."

➤ Warnings and Precautions (Section 5 of Label):

- Hypersensitivity Reactions: Although the originally proposed labeling from the Applicant included hypersensitivity as a warning and precaution and appropriately included recommendations for the prescriber to mitigate the risk, it did not appropriately summarize the adverse reaction and risk (b) (4). This warning and precaution was revised to include the following:
 - a summary of the observed case consistent with anaphylaxis
 - a description of other reported signs/symptoms consistent with hypersensitivity reactions
- Lipodystrophy: This warning and precaution was not included in the originally proposed labeling from the Applicant. This warning and precaution was added to include a description of the risk as well as recommendations for minimizing the risk (e.g., rotation of injection sites).
- Ectopic Calcifications: This warning and precaution was not included in the originally proposed labeling from the Applicant. This warning and precaution was added to include a description of the risk as well as recommendations for monitoring for the risk (e.g., ophthalmology examinations and renal ultrasounds to monitor for signs and symptoms of ophthalmic and renal ectopic calcifications).

➤ Adverse Reactions - Clinical Trials Experience (Section 6.1 of Label):

- Delineating Injection Site Reactions and Hypersensitivity Reactions: The Applicant's originally proposed labeling did not delineate between injection site reactions (i.e., reactions secondary to trauma or inflammation due to introduction of a material to the subcutaneous space) and hypersensitivity reactions (i.e., reactions representing an allergic response to asfotase alfa). In the revised labeling, these are clearly delineated in the table of adverse reactions as well as in the text of this section.
- Chronic Hepatitis: Chronic hepatitis was included in Section 6.1 (Clinical Trials Experience) as a less common adverse reaction that occurred at a rate less than 1%.

➤ Clinical Pharmacology - Pharmacodynamics (Section 12.2 of Label):

- Bone Mineralization Indices: The Applicant's proposal to include bone mineralization indices data was accepted. The following was included:

"Bone biopsy data from perinatal/infantile-onset and juvenile-onset HPP patients treated with STRENSIQ demonstrated decreases in osteoid volume and thickness indicating improved bone mineralization."
- Inorganic Pyrophosphate (PPi) and Pyridoxal-5'-Phosphate (PLP): The Applicant's proposal to include a statement that perinatal/infantile-onset and juvenile-onset HPP patients treated with STRENSIQ had reductions in PPi and PLP was accepted. A

statement was added to clarify that reductions in PPi and PLP do not correlate with clinical outcomes.

➤ Clinical Studies (Section 14 of Label):

- Perinatal/Infantile-Onset HPP: The applicant's proposed labeling focused on (b) (4) he labeling was revised to focus on the efficacy data for which there is a historical comparator group, including survival and ventilator-free survival data. It should be noted that for these analyses, inferential statistics (e.g., p values) were not presented as all hypothesis testing was considered exploratory given that the agreed upon endpoints, planned data integrations, and subsequent historical control comparisons were all determined well into the execution of the relevant perinatal/infantile-onset HPP studies; however, presentation of the hazard ratio (asfotase alfa / historical control) and its corresponding 95% Confidence Interval was considered an acceptable alternative. In addition, RGI-C and growth data were included because these data were considered supportive evidence of efficacy for perinatal/infantile-onset HPP.
- Juvenile-Onset HPP: The applicant's proposed labeling focused on (b) (4) The labeling was revised to focus on the efficacy data for which there is a historical comparator group, including growth, RGI-C, and gait (MPOMA-G) data. Mobility (6MWT) data were also included.

A statement was added for each of the populations (perinatal/infantile-onset and juvenile-onset) that there were insufficient data to assess the effect of asfotase alfa on fractures.

In addition to these revisions, additional revisions are currently being negotiated with the Applicant. Many of these revisions are based on recommendations from the Review of Patient Labeling (DMPP and OPDP) and the Review of PI, PPI, and Carton/Container Labeling (OPDP).

The Division of Medication Error Prevention and Analysis (DMEPA) reviewed the carton and container labels. They made a number of recommendations that were communicated to the Applicant (see DMEPA Label, Labeling and Packaging Review).

13 Recommendations/Risk Benefit Assessment

13.1 Recommended Regulatory Action

All of the review disciplines recommended an Approval action. This Reviewer concurs with the recommendations from each of the disciplines.

13.2 Risk Benefit Assessment

The benefit of asfotase alfa for perinatal/infantile- and juvenile-onset hypophosphatasia (HPP) has been established in the clinical trials. The safety profile was acceptable based on what was found in the clinical trials. The benefit-risk profile for asfotase alfa is favorable and the risks can be mitigated through professional labeling (see Section 12.3 of this CDTL Review) and a required postmarketing observational study (see Section 13.5 of this CDTL Review).

13.3 Recommendation for Postmarketing Risk Evaluation and Mitigation Strategy Requirements (REMS)

No special postmarketing risk management activities are recommended for this Application.

13.4 Recommendation for Postmarketing Required Pediatric Studies

No postmarketing required pediatric studies are recommended.

13.5 Recommendation for other Postmarketing Study Requirements (PMRs)

The following other postmarketing required studies are recommended for the current application, with the following language for the Approval Letter.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (FDCA) authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to assess a known serious risk of severe hypersensitivity reactions (including anaphylaxis), to assess a signal of a serious risk of ectopic calcification events and to identify an unexpected serious risk of systemic immune complex-mediated reactions.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA will not be sufficient to assess these serious risk(s).

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

- 2949-1 Conduct a 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. The purpose of the study is to assess the long term safety of treatment with STRENSIQ (asfotase alfa) with respect to incidence rates of severe hypersensitivity reactions (including anaphylaxis), systemic immune complex-mediated reactions and ectopic calcification events. Specify case definitions and validation methods and procedures for all outcomes. Enroll adequate number of patients, including both infantile-onset and juvenile-onset-patients, and follow for a minimum of 5 years from the time of enrollment, or until death, whichever comes first.

The timetable you submitted on October 6, 2015, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	07/2016
Study Completion:	10/2023
Final Report Submission:	04/2024

- 2949-2 Develop an assay to directly compare the complement activating capacity of STRENSIQ (asfotase alfa) to that of human IgG1. The assay should be set up under conditions to readily detect complement activation by IgG1. A dose response curve to demonstrate the sensitivity of the assay is recommended.

The timetable you submitted on October 6, 2015, states that you will conduct this study according to the following schedule:

Final Report Submission:	06/2016
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Submit the protocol(s) to your IND 100619, with a cross-reference letter to this BLA. Submit all final report(s) to your BLA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate: **“Required Postmarketing Protocol Under 505(o),” “Required Postmarketing Final Report Under 505(o),” “Required Postmarketing Correspondence Under 505(o).”**

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 601.70 requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 601.70 to satisfy the periodic reporting requirement under section

505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 601.70. We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

13.6 Recommendation for Postmarketing Study Commitments (PMCs)

The following postmarketing commitments are recommended for the current application, with the following language for the Approval Letter.

POSTMARKETING COMMITMENTS SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B

2949-3 Develop a validated cross-reactive immunologic material (CRIM) assay for patients with hypophosphatasia (HPP) and test patient samples in a cohort of untreated patients. Results should be correlated with antibody response (binding and neutralizing), genetic mutations, enzyme activity level and clinical outcome in patients who are receiving STRENSIQ (asfotase alfa) treatment. (b) (4)

The timetable you submitted on October 6, 2015, states that you will conduct this study according to the following schedule:

Final Report Submission: 06/2016

2949-4 Evaluate the STRENSIQ (asfotase alfa) manufacturing process and develop a control strategy (b) (4)
Provide detailed summaries of all data utilized to propose the revised control strategy (b) (4)

The timetable you submitted on October 6, 2015, states that you will conduct this study according to the following schedule:

Final Report Submission: 11/2016

2949-5 Re-evaluate the (b) (4) endotoxin limits for the (b) (4) after data from thirty batches is available and (b) (4) (b) (4) limits to reflect manufacturing process capability.

The timetable you submitted on October 6, 2015, states that you will conduct this study according to the following schedule:

Final Report Submission: 12/2017

Submit clinical protocols to your IND 100619 for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all postmarketing final reports to this BLA. In addition, under 21 CFR 601.70 you should include a status summary of each commitment in your annual progress report of postmarketing studies to this BLA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies/trials, number of patients entered into each study/trial. All submissions, including supplements, relating to these postmarketing commitments should be prominently labeled “**Postmarketing Commitment Protocol,**” “**Postmarketing Commitment Final Report,**” or “**Postmarketing Commitment Correspondence.**”

13.7 Recommended Comments to Applicant

None.

APPENDIX 1: Radiographic Rickets Severity Scale (RSS) and Radiographic Global Impression of Change (RGI-C)

Radiographic Rickets Severity Scale (RSS)

The following is taken from the Consult Review by Stephen Voss, M.D. (DBRUP).

"The radiographic Rickets Severity Scale (RSS) was developed for nutritional rickets, as a means to quantify bone changes and monitor response to therapy, and has demonstrated good reliability and reproducibility (Thacher 2000). This system grades growth plate and metaphyseal changes of distal radius and ulna (max. 2 points each) and distal femur/proximal tibia (max. 3 points each), for a maximum (i.e. worst) score of 10."

Radiographic Global Impression of Change (RGI-C)

The following is taken from the Consult Review by Stephen Voss, M.D. (DBRUP).

"The Radiographic Global Impression of Change (RGI-C) was developed specifically for HPP in order to encompass all the radiographic features, not just those measured by the RSS. The sponsor considers these two scales to be complementary. There are no published studies validating either of these methods for HPP. A reader using the RGI-C evaluates paired X-rays (baseline and any postbaseline point) of knees, hands/wrists, and for younger children also chest. Changes from baseline are assessed for the following manifestations:

Infantile-onset HPP patients ≤ 5 years old:

- Metadiaphyseal patchy focal sclerosis
- Apparent physeal widening
- Irregularity of the provisional zone of calcification
- Metaphyseal radiolucencies (tongues or rounded areas)
- Metaphyseal flaring
- Metaphyseal fraying
- Thin gracile bones
- Apparent absence of some or all bones
- Thin ribs
- Chest deformity
- Evidence of recent fractures

Older infantile- and juvenile-onset patients:

- Metadiaphyseal sclerosis
- Apparent physeal widening
- Irregularity of the provisional zone of calcification
- "Popcorn" calcifications of metadiaphyses (rounded lucencies and patchy sclerosis)

- Transverse subphyseal band of lucency
- Osteopenia of short tubular bones (evaluated for hands/wrists)
- Osteopenia (evaluated for knees)
- Metaphyseal radiolucencies (tongues of rounded areas) (evaluated for hands/wrists)
- Tongues of radiolucency (evaluated for knees)
- Metaphyseal fraying (evaluated for hands/wrists)
- Physeal corner defects (evaluated for knees)
- Demineralization of the distal metaphyses (evaluated for hands/wrists)"

In the Consult Review, Dr. Voss included the following comment:

"A potential disadvantage of this scale is that some of these criteria are subjective or susceptible to variations in technique, particularly the identification of osteopenia by X-ray, which is generally considered unreliable."

The following is taken from the Consult Review by Stephen Voss, M.D. (DBRUP).

"Based on these factors the patient is assigned at each timepoint an overall score for the change from baseline on the following 7-point scale. Thus, RGI-C scores indicate not the degree of abnormality (as in the RSS), but changes over time.

- +3 = very much better, i.e. complete or near complete healing of rickets
- +2 = much better i.e. substantial healing
- +1 = minimally better i.e. minimal healing
- 0 = unchanged
- -1 = minimally worse, i.e. minimal worsening of rickets
- -2 = much worse, i.e. moderate worsening
- -3 = very much worse i.e. severe worsening"

APPENDIX 2: Performance Oriented Mobility Assessment-Gait (POMA-G) and Modified POMA-G Scales

POMA-G Scale

The POMA-G Scale is shown below.

Table 29. POMA-G Scale

Assessment	Observation	Score	
1	Initiation of gait	Any hesitancy or multiple attempts	= 0
		No hesitancy	= 1
2	Step length and height	Does not pass the left stance foot with step	= 0
		Passes the left stance foot	= 1
	a) Right swing foot	Does not clear floor completely with step	= 0
		Right foot completely clears floor	= 1
	b) Right foot clear	Does not pass the right stance foot with step	= 0
		Passes the right stance foot	= 1
	c) Left swing foot	Does not clear floor completely with step	= 0
		Left foot completely clears floor	= 1
d) Left foot clear	Right and left step length not equal	= 0	
	Left foot completely clears floor	= 1	
3	Step symmetry	Stopping or discontinuity between steps	= 0
4	Step continuity	Steps appear continuous	= 1
		Marked deviation	= 0
5	Path	Mild/moderate deviation or uses walking aid	= 1
		Straight without walking aid	= 2
		Marked sway or uses walking aid	= 0
6	Trunk	No sway but flexion of knees or back or spreads arms out while walking	= 1
		No sway, no flexion, no use of arms, and no walking aid	= 2
7	Walk stance	Heels apart	= 0
		Heels almost touching while walking	= 1
Gait score		/12	

Abbreviations: POMA-G = Performance-Oriented Mobility Assessment, Gait subtest.

The table above is taken from the Division of Neurology Products Consult Review.

Modified POMA-G Scale

The Modified POMA-G Scale is shown below.

Table 30. Modified POMA-G Scale

Assessment	Observation	Score	
1	Step length and height		
	a) Right swing foot	Does not pass the left stance foot with step	= 0
		Right heel passes the left stance foot	= 1
		Right foot passes the left stance foot by at least the length of individual's foot between the stance toe and swing heel	= 2
	b) Right foot clear	Right foot does not clear floor completely with step or raises foot by more than 1 - 2 inches	= 0
		Right foot completely clears floor	= 1
	c) Left swing foot	Does not pass the right stance foot with step	= 0
		Left heel passes the right stance foot	= 1
		Left foot passes the right stance foot by at least the length of individual's foot between the stance toe and swing heel	= 2
	d) Left foot clear	Left foot does not clear floor completely with step or raises foot by more than 1 - 2 inches	= 0
		Left foot completely clears floor	= 1
	2	Step symmetry	
		Right and left step length not equal (estimate) = 0 Right and left step appear equal = 1	
3	Step continuity	Stopping or discontinuity between steps	= 0
		Steps appear continuous unilaterally (observe raising heel of 1 foot as heel of other foot touches the floor, unilaterally) or flat foot contact on stance limb when heel of other foot touches the floor bilaterally, no breaks or stops in stride	= 1
		Steps appear continuous bilaterally (observe raising heel of 1 foot as heel of other foot touches the floor, bilaterally), no breaks or stops in stride, step lengths equal	= 2
4	Trunk	Marked sway or uses walking aid. Marked sway = moderate lateral flexion as the result of instability bilateral or unilateral	= 0
		No marked sway but compensatory patterns such as trunk flexion, knee flexion, arm abduction or retraction to increase postural stability while walking	= 1
		No sway, no flexion, no use of arms, and no walking aid	= 2
5	Walk stance	Heels always apart, wide base of support utilized to increase postural stability	= 0
		Heels intermittently apart	= 1
Gait score		/12	

Abbreviations: MPOMA-G = Modified Performance-Oriented Mobility Assessment, Gait subtest.

The table above is taken from the Division of Neurology Products Consult Review.

APPENDIX 3: Demographic and Baseline Characteristics - Perinatal/Infantile-Onset HPP (ENB-002-08/ENB-003-08, ENB-010-10, and ENB-011-10)

Demographic and baseline characteristics are summarized in the tables below.

ENB-002-08/ENB-003-08 and ENB-010-10 vs. Historical Control

Table 31. Selected Demographic and Baseline Characteristics (ENB-002-08/ENB-003-08 and ENB-010-10 vs. ENB-011-10)

	ENB-002-08/ENB-003-08 and ENB-010-10 (N = 68)	ENB-011-10 Historical Control (N = 48)
Age at Symptom Onset (months)		
N	68	48
Mean (SD)	1.6 (1.69)	1.1 (1.67)
Median	1.0	0.03
Min, Max	0, 6	0, 6
Gender – n (%)		
Female	37 (54.4%)	22 (45.8%)
Male	31 (45.6%)	26 (54.2%)
Race – n (%)		
American Indian or Alaskan Native	0	1 (2.1%)
Asian	7 (10.3%)	2 (4.2%)
Black or African American	0	3 (6.3%)
Native Hawaiian or Other Pacific Islander	0	0
Other	2 (2.9%)	2 (4.2%)
White	54 (79.4%)	40 (83.3%)
Unknown	5 (7.4%)	0
Geographical Region – n (%)		
Europe	27 (39.7%)	8 (16.7%)
North America	35 (51.5%)	37 (77.1%)
Other	6 (8.8%)	3 (6.3%)

Table above is modified from the Statistics Review. Source: Statistics Reviewer's Table generated from ISE ADSL dataset.

Note: Denominators for percentages are N. Two patients (i.e., ENB-010-10-01-04 and ENB-010-10-19-02) from the overall 70-patient ENB-002-08/ENB-003-08 and ENB-010-10 pooled cohort did not qualify for the analysis due to not meeting the entry/extraction criteria for natural history study ENB-011-10. Race was not reported by the site for the five patients treated in France, in compliance with local regulations.

ENB-002-08/ENB-003-08 vs. ENB-010-10**Table 32. Selected Demographic Characteristics (ENB-002-08/ENB-003-08 vs. ENB-010-10)**

Characteristic	ENB-002-08/ENB-003-08 (n=11)	ENB-010-10 (n=59)
Age (weeks)		
Mean (SD)	59 (59)	118 (111)
Min, Max	3, 158	0.1, 312
Sex- n(%)		
Male	4 (36)	27 (46)
Female	7 (64)	2 (54)
Race- n(%)		
White	10 (91)	46 (78)
Asian		7 (12)
Multiple		1 (2)
Unknown		5 (9)
Other	1 (9)	

Table above summarized from the Clinical Review

Table 33. Selected Baseline Disease Characteristics (ENB-002-08/ENB-003-08 vs. ENB-010-10)

Characteristic	ENB-002-08/ENB-003-08 (n=11)	ENB-010-10 (n=59)
Ventilation Status- n(%)		
No support	6 (55)	40 (68)
Supplemental Oxygen	0	5 (9)
CPAP	1 (9)	2 (3)
Mechanical Ventilation	3 (27)	11 (19)
Other	1 (9)	1 (2)
RSS Score	(n=10)	(n=58)
Mean (SD)	8.3 (1.7)	4.8 (3.1)
Min, Max	5.5, 10	4.3
Scale: 0 (normal) to 10 (severe rickets)		
Length Z-score		(n=58)
Mean (SD)	-4.1 (2.2)	-3.1 (2.1)
Min, Max	-9.2, -0.7	-10.1, 0.9
Weight Z-score		
Mean (SD)	-3.4 (1.5)	-3.2 (3.5)
Min, Max	-5.4, -0.5	-23.8, 0
Genetic Mutation Analysis		
Yes	11(100)	45 (76)
Plasma PPI (µM)	(n=8)	(n=56)
Mean (SD)	5.59 (2.26)	6.48 (2.04)
Min, Max	2.91, 10.48	2.72, 12.38
(Reference range: 1.33 to 5.71 µM)		
PLP (ng/mL)	(n=9)	(n=53)
Mean (SD)	380.0 (256.65)	2711.3 (5287.35)
Min, Max	100, 880	48, 24600
(Reference range: 11.76 to 68.37 ng/mL)		

Table above modified from the Clinical Review.

Table 34. Selected Baseline Disease Characteristics (ENB-002-08/ENB-003-08 vs. ENB-010-10)

Characteristic	ENB-002-08/ ENB-003-08 (n=11)	ENB-010-10 (n=59)
Abnormally shaped chest- n(%)	6 (55)	49 (86)
History of respiratory compromise- n(%)	10 (91)	37 (63)
Seizures- n(%)	1 (9)	13 (22)
Difficulty gaining weight, failure to thrive, and/or difficulty eating/swallowing- n (%)	10 (91)	51 (86)
High/abnormal serum calcium - n(%)	8 (73)	55 (93)
Nephrocalcinosis- n(%)	8 (73)	34 (58)
Fractures- n(%)	6 (55)	19 (32)
Craniosynostosis- n(%)	3 (27)	8 (14)

Table above modified from the Clinical Review.

Historical Control

Table 35. Selected Baseline Disease Characteristics (ENB-011-10)

Disease History	ENB-011-10 Natural History Study n=48
Chest deformity	39/43 (91)
Respiratory distress	30/39 (77)
Failure to thrive	28/37 (76)
Respiratory failure	26/36 (72)
Elevated serum or urine calcium	28/39 (72)
Respiratory tract infections	21/33 (64)
Craniosynostosis	19/31 (61)
Nephrocalcinosis	16/31 (52)
Early tooth loss	10/23 (44)
Pneumonia	15/36 (42)
Vitamin B6-responsive seizures	7/35 (20)
Low serum phosphate	5/25 (20)
Delayed fracture healing	5/28 (18)

Table above modified from the Clinical Review.

APPENDIX 4: Demographic and Baseline Characteristics - Juvenile-Onset HPP (ENB-006-09/ENB-008-10 and ALX-HPP-502)

Demographic and baseline characteristics are summarized in the tables below.

ENB-006-09/ENB-008-10 vs. Historical Control

Table 36. Selected Demographic and Baseline Characteristics (ENB-006-09/ENB-008-10 vs. ALX-HPP-502)

Characteristic	ENB-006-09/ENB-008-10 (N=8)	ALX-HPP-502 Historical Control (N = 32)
Age at Symptom Onset (months)		
N	8	32
Mean (SD)	15.3 (4.03)	17.5 (9.21)
Median	13.5	14.5
Min, Max	12, 22	7, 41
Gender – n (%)		
Female	2 (25.0%)	10 (31.3%)
Male	6 (75.0%)	22 (68.8%)
Race – n (%)		
American Indian or Alaskan Native	0	0
Asian	0	0
Black or African American	0	0
Native Hawaiian or Other Pacific Islander	0	1 (3.1%)
Other	0	1 (3.1%)
White	8 (100%)	30 (93.8%)
Unknown	0	0
Geographical Region – n (%)		
Europe	0	5 (15.6%)
North America	8 (100%)	25 (78.1%)
Other	0	2 (6.3%)

Table above is modified from the Statistics Review. Source: Statistics Reviewer's Table generated from ISE ADSL dataset.

Note: Denominators for percentages are N.

ENB-006-09/ENB-008-10**Table 37. Selected Baseline Patient Characteristics (ENB-006-09/ENB-008-10)**

Characteristic	Asfotase Alfa 2 mg/kg TIW (n=6)	Asfotase Alfa 3 mg/kg TIW (n=7)	Asfotase Alfa Combined (n=13)
Height Z-score			
n	6	7	13
Mean (SD)	-2.2 (2.3)	-1.7 (1.4)	-1.94 (1.8)
Median	-1.3	-1.3	-1.3
Min, Max	-6.2, -0.6	-3.8, 0	-6.6, 0
Weight Z-score			
n	6	7	13
Mean (SD)	-2.6 (2.8)	-0.8 (1.7)	-1.64 (2.34)
Median	-1.5	-1.0	-1.21
Min, Max	-8.2, -1	-3.5, 2.3	-8.2, 2.3
RSS Score			
n	6	7	13
Mean (SD)	2.7 (2.0)	2.9 (0.6)	2.8 (1.3)
Median	2.3	3.0	3
Min, Max	0.5, 6	2, 3.5	0.5, 6
Baseline Distance Walked- Percent of Predicted- n%			
<25%	0	0	0
>25% to <75 %	5 (83%)	6 (86%)	11 (85%)
>75%	1 (17%)	1 (14%)	2 (15%)
Plasma PPI (µM)			
n	6	7	13
Mean (SD)	4.57 (0.67)	5.39 (1.08)	5.01 (0.97)
Min, Max	4.59	5.45	4.86
Reference range: <0.75 to 5.71 µM (varies by age)	3.74, 5.48	4.13, 6.96	3.74, 6.96
PLP (ng/mL)			
n	6	7	13
Mean (SD)	217 (164)	212 (98)	214 (127)
Min, Max	185	245	218
Reference range: 5.74 to 61.15 ng/mL	75, 527	84, 333	76, 527

Table above modified from the Clinical Review

Table 38. ENB-006-09/ENB-008-10 Baseline Patient Clinical Findings

Parameter	Asfotase Alfa 2 mg/kg TIW (n=6)	Asfotase Alfa 3 mg/kg TIW (n=7)	Asfotase Alfa Combined (n=13)
Unusual gait	6 (100%)	7 (100%)	13 (100%)
Premature tooth loss	6 (100%)	7 (100%)	13 (100%)
Delayed walking	5 (83%)	6 (86%)	11 (85%)
Muscle weakness	5 (83%)	3 (43%)	8 (62%)
High serum phosphorus	3 (50%)	4 (57%)	7 (54%)
Difficulty gaining weight	3 (50%)	3 (43%)	6 (46%)
Joint hypermobility	3 (50%)	3 (43%)	6 (46%)
Joint pain	4 (67%)	2 (29%)	6 (46%)
Muscle pain	3 (50%)	3 (43%)	6 (46%)
Bone pain limiting activities	3 (50%)	3 (43%)	6 (46%)
Abnormally shaped chest	3 (50%)	3 (43%)	6 (46%)

Table above from the Clinical Review.

Historical Control

Table 39. Height and Weight Z-score at Baseline (Historical Control; ALX-HPP-502)

Characteristic	ALX-HPP-502 Historical Control (N = 32)
Height Z-score	
Mean (SD)	-1.07 (1.29)
Median (Min, Max)	-0.86 (-4.9, 2.6)
Weight Z-score	
Mean (SD)	-1.15 (1.41)
Median (Min, Max)	-0.86 (-5.0, 2.1)

Table above generated from Pages 61-62 of the ALX-HPP-502 Study Report.

Table 40. HPP-Specific Conditions Reported in >20% of Juvenile-Onset Patients (ALX-HPP-502) (stratified by age interval)

HPP-Specific Disorders	Birth to <5 yrs old n(%)	>5 to 15 yrs old n(%)	Birth to 15 years old n(%)
Tooth loss	31 (97)	2 (6)	31 (97)
Arthralgia	12 (38)	17 (53)	20 (63)
Gait disturbance	16 (50)	19 (59)	20 (63)
Bone deformity	15 (47)	19 (59)	17 (53)
Muscular weakness	14 (44)	15 (47)	17 (53)
Dental caries	6 (19)	9 (28)	10 (31)
Myopathy	8 (25)	10 (31)	19 (31)
Craniosynostosis	7 (22)	8 (25)	10 (31)
Fractures	2 (6)	10 (31)	10 (31)
Tooth development disorder	5 (16)	6 (19)	8 (25)
Pneumonia	5 (16)	3 (9)	8 (25)
Scoliosis	3 (9)	7 (22)	7 (22)

Table above from the Clinical Review.

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/s/

ANIL K RAJPAL
10/23/2015