CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125513Orig1s000

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type	BLA
Application Number(s)	125513
Priority or Standard	Priority
Submit Date(s)	December 23, 2014
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Division / Office	DGIEP/ODE III
Reviewer Name(s)	Carla Epps, MD, MPH
Review Completion Date	October 20, 2015
Established Name	Asfotase alfa
(Proposed) Trade Name	Strensiq
Therapeutic Class	Enzyme replacement therapy
Applicant	Alexion
Formulation(s)	Subcutaneous injection; 18 mg/0.45 mL, 28 mg/0.7 mL, 40 mg/mL, 80 mg 0.8 /mL
Dosing Regimen	6 mg/kg per week up to 9 mg/kg/week
Indication(s)	Treatment of patients with perinatal/infantile- & juvenile-onset hypophosphatasia (HPP)
Intended Population(s)	Perinatal/infantile- & juvenile-onset HPP patients

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

I recommend an approval action for asfotase alfa for treatment of perinatal/infantile-onset and juvenile-onset hypophosphatasia (HPP). The recommended dosage is 6 mg/kg/week administered subcutaneously in doses of 2 mg/kg 3 times per week or 1 mg/kg 6 times per week. The dosage may be increased up to 9 mg/kg/week for lack of efficacy.

There is sufficient evidence of safety and efficacy based on four phase 2 trials to support this indication and to provide adequate directions for use. Evidence of safety is based on a database of 102 patients with HPP, including 10 adult and 89 pediatric patients with perinatal/infantile- or juvenile-onset HPP.

1.2 Risk Benefit Assessment

Perinatal/infantile-onset and juvenile-onset HPP are pediatric variants of hypophosphatasia, a rare genetic disorder that impairs bone metabolism. It is associated with a high mortality rate in the perinatal/infantile-onset population due to respiratory compromise, seizures, and neurosurgical complications (craniosynostosis). Historically, the survival rate was less than 50% by one year of age. Both perinatal/infantile-onset and juvenile-onset patients suffer from fractures and bone deformities that impede normal growth and development, as well as poor weight gain. Currently, there are no approved therapies for HPP.

The recommendation for approval of BLA 125513 is based upon the results of three pivotal trials: ENB-002-08/ENB-003-08, ENB-010-10, and ENB-006-09/ENB-008-10. ENB-002-08/ENB-003-08 and ENB-010-10 were conducted in perinatal/infantile onset patients younger than 3 years old and 5 years old, respectively. ENB-006-09/ENB-008-10 was conducted in 13 pediatric patients 5 years and older, including 5 perinatal/infantile- and 8 juvenile-onset HPP patients. The efficacy data for the two populations were considered to be supportive of each other (i.e., the two perinatal/infantile-onset trials were supportive of efficacy for the juvenile-onset indication and ENB-006-09/ENB-008-10 was considered to be supportive of the perinatal/infantile-onset indication).

Evidence of efficacy for the perinatal/infantile-onset indication is based on the results of a Kaplan-Meier analysis of pooled overall survival comparing patients enrolled in ENB-002-08/ENB-003-08 and ENB-010-10 (n=68) with a natural history control group (n=48).

Of 70 treated perinatal/infantile-onset patients, 68 patients (97%) were included in survival analyses, based on the patients meeting eligibility criteria for the natural history study ENB-011-10. There was considerable overlap in the eligibility criteria for the natural history study and for ENB-002-08/ENB-003-08, as both were designed to select

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patients with severe HPP disease. Specifically, in addition to a confirmed diagnosis of perinatal/infantile-onset HPP, both protocols required that patients had clinical features such as rachitic chest deformity or seizures associated with severe disease. There were no specific disease severity eligibility criteria for ENB-010-10. However, baseline disease severity in both of the two perinatal/infantile-onset trial populations appeared to be reasonably comparable to the historical control group.

The analysis showed that treatment improved overall survival compared with survival in historical control patients, with 62 out of 68 (91%) treated patients versus 13 out of 48 (27%) historical control patients surviving during the time period evaluated (Week 504 [9.6 years]).
Subgroup analyses and other survival analyses for the same time period yielded similar results. The survival rate for a subgroup of patients who received the proposed dosing regimen of 6 mg/kg/week without dose modifications was 98% (45/46 patients) and the ventilator-free survival rate for the overall pooled population was approximately 80%.

The primary efficacy analysis for the juvenile-onset population compared change in gait in a historical control group (n=6) and treated patients (n=8), as measured by the Tinetti modified Performance Oriented Mobility Assessment-Gait (mPOMA-G) scale. The gait analysis revealed a difference in mean rate of change in MPOMA-G score for treated patients (rate of change was 2.25 per year), primarily due to improvements in step length. The clinical review team did not consider the primary efficacy analysis for the juvenile-onset population- change in gait- to be robust from either a statistical or a clinical perspective. A number of factors limited interpretation of the results, including the post-hoc nature of the analysis, lack of validation of the mPOMA-G instrument in the HPP population, differences in baseline disease severity in the comparator group, and test methodology (re-reading videos filmed for other types of ambulation assessments).

Given the lack of statistical rigor for the data, as per 21 CFR 312.84, the determination of approval for this rare and severely- debilitating disease, rested largely on a medical risk-benefit judgment. At the Agency's request, the applicant had submitted other comparison analyses for the juvenile-onset population, including comparisons of growth and radiographic data for treated juvenile onset patients and a historical control group (n=32). The growth analysis demonstrated improved height and weight growth over time with treatment. For control patients, mean baseline height and weight z-scores were -1.1 (range -4.9 to 2.6) and -1.2 (range -5 to 2.1), respectively; at last assessment, mean height and weight z-scores were -1.1 (range -4.9 to 1.8) and -1 (range -5.7 to 2.1), respectively. For treated patients, mean baseline height and weight z-scores were -1.5 (range -3.8 to 0) and -1.1 (range was -3.5 to 2.3), respectively; at last assessment, mean height and weight z-scores were -0.9 (range -2 to 0) and 0 (range was -1.3 to 2.2), respectively.

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The mean change in height z-score was 0.6 for treated patients compared to zero for control patients. The mean change in weight z-score was 1.1 for treated patients compared to 0.2 for control patients.

At last assessment, all 8 treated juvenile-onset patients maintained normal height and weight z-scores or experienced improvement in abnormal height and weight z-scores. In comparison, approximately 20% of control patients experienced clinically significantly declines in height growth (i.e., decline in height z-scores to <5th percentile for age).

The radiographic analysis also demonstrated improvement with treatment. The key secondary radiographic assessment was change in rickets severity, as assessed by the Radiographic Global Impression of Change (RGI-C) scale. Based on the applicant's responder criterion for substantial healing of rickets (RGI-C score of 2 or higher), at last assessment all 8 juvenile-onset patients were responders, compared to 2/32 control patients (6%).

Data from matched bone biopsy pairs from 12 patients demonstrated treatment effect on bone mineralization, with 4/4 perinatal/infantile-onset patients and 7/8 juvenile-onset patients experienced improvement in bone mineralization indices.

The applicant also analyzed pooled growth and radiographic data for the perinatal/infantile-onset population. Results were consistent with findings for the juvenile-onset population; at last assessment, a majority of perinatal/infantile-onset patients experienced improvements in height (50/71 patients; 70%) and weight (56/72 patients; 78%), and were classified as responders based on RGI-C score (68/75 patients; 90%). The time to response was similar for growth and radiographic findings in both patient populations, with the majority of patients experiencing sustained improvements from Month 6 onward.

The clinical review team concluded that the totality of evidence, including growth, radiographic, and histomorphometric data collected in both populations and survival data collected in the perinatal/infantile-onset population, were sufficient to make a favorable medical risk-benefit determination for approval for the juvenile-onset indication.

Based on the data available for review, asfotase alfa is generally well tolerated in patients with perinatal/infantile- and juvenile-onset HPP. The most commonly reported adverse reactions were injection site reactions, localized lipodystrophy, hypersensitivity reactions, and ectopic calcifications. The 6 times a week dosing schedule was associated with a higher incidence of injection site reactions compared to the 3 times a week dosing schedule.

Ectopic calcifications, including nephrocalcinosis, conjunctival calcifications and band keratopathy are known complications of HPP. Treatment with asfotase alfa raises a

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concern for the potential formation of ectopic calcifications in other tissues as inorganic phosphate released through enzymatic activity binds with calcium to form hydroxyapatite crystals. Of interest, the European Medicines Agency (EMA) recently conducted a review of case reports of corneal calcifications in patients using eye drops containing phosphate buffers. The EMA concluded that there was evidence to suggest that patients with pre-existing corneal damage might develop calcification with exposure to phosphate-containing eye drops.

Based on my review of the available safety data, there was insufficient information to determine whether some of the reported events represented known disease complications or new safety signals. Therefore, I recommend that additional information on ectopic calcification events be collected as a post-marketing requirement (PMR); in addition, data on the long-term impact of immunogenicity on the safety profile of asfotase alfa should be required as a PMR. The applicant has agreed to conduct a post-marketing observational safety study that includes safety monitoring to assess both of these safety issues (see PMR #2949-1).

Finally, asfotase alfa was not evaluated in pregnant or lactating women. This reviewer notes that the applicant has established a HPP disease registry; a pregnancy surveillance program could be included in the registry.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

Routine surveillance for adverse events is recommended. In addition, the applicant has agreed to conduct a post-marketing observational safety study (see PMR 2949-1).

1.4 Recommendations for Postmarket Requirements and Commitments

The following post-marketing requirements (PMRs) and post-marketing commitments (PMCs) were being negotiated with the applicant at the time of this review:

Post-Marketing Requirements

2949-1

A prospective, long-term, observational study in 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.

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Final Protocol Submission: 07/2016
Study Completion: 10/2022
Final Report Submission: 06/2023

2949-2

Develop an assay to directly compare the complement activating capacity of 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.

Final Report Submission: 06/2016

Post-Marketing Commitments

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 Asfotase alfa treatment.

Final Report Submission: 06/2016

2949-4

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

Final Report Submission: 11/2016

2949-5

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

Final Report Submission: 12/2017

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2 Introduction and Regulatory Background

Hypophosphatasia

Hypophosphatasia (HPP) is an inborn error of bone metabolism due to reduced activity of the tissue-nonspecific isoenzyme of alkaline phosphatase (TNSALP) cause by mutations of the ALPL gene. To date, at least 300 mutations have been linked to HPP.[1] The disease 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.[2] Six variants of the disease have been identified:

- Perinatal (lethal) HPP is 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 is characterized by prenatal bone abnormalities and a juvenile 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 is characterized by rickets with an onset between birth and six months of age
- Juvenile HPP characterized by rickets and fractures
- Adult HPP characterized by early dental loss, stress fractures, and pseudofractures of the lower extremities
- Odontohypophosphatasia is 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

The incidence of the severe forms of HPP is approximately 1 per 100,000 births; the prevalence of milder forms of the disease is estimated to be higher.[3] The incidence and severity of HPP varies between ethnic groups, with a high prevalence of the perinatal lethal form reported in the Canadian Mennonite population (1:2500) whereas no cases of HPP have been reported in Africa outside of North Africa.[4] Inheritance of the disease may be autosomal recessive or autosomal dominant. Autosomal dominant forms of the disease are associated with a milder phenotype. In autosomal recessive HPP, carriers may be asymptomatic or have milder disease symptoms. Table 1 summarizes the clinical features of HPP variants.

[1] Mornet E., The Tissue Nonspecific Alkaline Phosphatase Gene Mutations Database, Laboratoire SEPSEP, http://www.sesep.uvsq.fr/03_hypo_mutations.php
[2] Mornet E, Nunes ME, Hypophosphatasia, *GeneReviews* (http://www.ncbi.nlm.nih.gov/books/NBK1150/)
[3] Mornet E, Orphanet J Rare Diseases, 2007; 2:40.
[4] Mornet E, Nunes ME, Hypophosphatasia, *GeneReviews* (http://www.ncbi.nlm.nih.gov/books/NBK1150/)

Table 1: Clinical Features of Hypophosphatasia by Phenotype

Phenotype	Inheritance	Cardinal Features	Dental Features	Clinical Diagnosis
Perinatal (lethal)	AR	Hypomineralization, osteochondral spurs	N/A	Radiographs, prenatal ultrasound examination
Perinatal (benign)	AR or AD	Long-bone bowing, benign postnatal course	±	Prenatal ultrasound examination, clinical course
Infantile	AR	Craniosynostosis, hypomineralization, rachitic ribs, hypercalciuria	Premature loss, deciduous teeth	Clinical course, radiographs, laboratory findings
Juvenile (Childhood)	AR or AD	Short stature, skeletal deformity, bone pain/fractures	Premature loss, deciduous teeth (incisors)	Clinical course, radiographs, laboratory findings
Adult	AR or AD	Stress fractures: metatarsal, tibia; chondrocalcinosis	±	Clinical course, radiographs, laboratory findings
Odontohypophosphatasia	AR or AD	Alveolar bone loss	Exfoliation (incisors), dental caries	Clinical course, dental panorex, laboratory findings

AR= autosomal recessive; AD= autosomal dominant; N/A= not applicable
Source: Mornet E, Nunes ME, Hypophosphatasia, GeneReviews (http://www.ncbi.nlm.nih.gov/books/NBK1150/)

Diagnosis
There are no formal diagnostic criteria for HPP. However, all variants are associated with reduced activity of serum alkaline phosphatase (ALP). The diagnosis may be confirmed by genetic mutation analysis. Biochemical markers of the disease include increased concentrations of pyridoxal-5´-phosphate (PLP), inorganic pyrophosphate (PPi), and phosphoethanolamine (substrates of TNSALP) in serum, tissues, and urine. Other biochemical abnormalities include hypercalcemia (perinatal-onset HPP) and hypercalciuria (infantile-onset HPP).

Clinical course
Perinatal-onset HPP typically is diagnosed on prenatal ultrasound examination which demonstrates unmineralized or hypomineralized bone. As noted earlier, the lethal perinatal form results in stillbirth or early neonatal death secondary to pulmonary insufficiency caused by chest wall deformities (flail chest). Other clinical features may include fever, anemia, failure to thrive, irritability, apnea and bradycardia, intracranial hemorrhage and pyridoxine-dependent seizures. The benign perinatal form clinically resembles other milder forms of HPP.

Infantile-onset HPP presents before age six months of age, with infants developing clinical signs and symptoms of rickets, including growth failure, hypotonia, bowing of long bones, and rachitic changes of the ribs. Other clinical hallmarks are wide fontanels (actually hypomineralized skull bone) and craniosynostosis. Other skull deformities may include hypertelorism and brachycephaly. Infantile-onset HPP patients are at increased risk of pneumonia due to flail chest. Other complications include recurrent vomiting, nephrocalcinosis and renal impairment due to hyperkalemia and hypercalciuria. Bone disease in this population may spontaneously improve or be progressive. Mortality in this subgroup is about 50% by the first year of life.

In juvenile-onset HPP (also termed as childhood HPP), premature loss of the primary teeth (prior to age 5 years) is a major clinical hallmark of disease. Radiographic evidence of dental hypoplasia may precede radiographic evidence of skeletal disease. Patients who develop rickets may have delayed walking, gait abnormalities (waddling gait) and short stature. Other complications include pathologic fractures, most commonly involving the metaphysis, and static myopathy. Patient may also experience bone pain and stiffness. Some patients may improve spontaneously during puberty, with recurrence of skeletal symptoms during adulthood. As in infantile-onset HPP, patients with juvenile-onset HPP may develop nephrocalcinosis. Dental involvement of secondary dentition is generally less severe.

Adult-onset HPP usually presents during middle age, with about 50% of patients having a history of rickets and or premature dental loss during childhood. The chief clinical features of adult-onset HPP are recurrent stress fractures and femoral pseudofractures (areas of osteomalacia). Patients also may experience hip or thigh pain (secondary to femoral pseudofractures) and may develop chondrocalcinosis.

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Treatment

Currently, there are no approved therapies for HPP. There is one case report of an 8-month old infant with severe infantile HPP who was treated with bone marrow transplantation; the patient was reported as have a milder phenotype during childhood.[5] In patients with adult-onset HPP, there are case reports of teriparatide (recombinant human parathyroid hormone fragment) treatment in post-menopausal women resulting in improved bone turnover biomarkers and reduced bone pain following short-term treatment.[6,7] HPP patients have also been treated with serum from patients with Paget's disease as enzyme replacement therapy (ERT) to replace ALP with minimal benefit; presumably because the therapy did not adequately target bone.[8] Animal models have investigated suppression of pc-1 (ENPP1), a gene that antagonizes ALPL gene activity, as a potential therapeutic option for HPP.[9]

Supportive therapies include early dental care to preserve and replace dentition, management of seizures with pyridoxine, pain management with non-steroidal anti-inflammatory drugs (NSAIDs) and orthopedic management of pseudofractures and fractures. Infants with craniosynostosis are referred to a neurosurgeon for monitoring and/ or surgical correction. Some adult patients are treated with calcium supplementation and vitamin D therapy to prevent secondary hyperparathyroidism. Therapies commonly used for other types of bone metabolism disorders, including bisphosphonates and teriparatide are generally contraindicated in HPP because of their safety profile in this population. Bisphosphonates have a similar structure to inorganic pyrophosphate (PPi), which is already elevated in patients with HPP. Teriparatide is contraindicated in children with childhood HPP due to increased risk for osteosarcoma (a pediatric growth plate tumor). Similarly, vitamin D and calcium supplementation are contraindicated in the juvenile-onset variant of HPP, since these parameters are usually normal in this subgroup of patients.

[5] Cahill RA, Wenkert D, et al., Infantile hypophosphatasia: transplantation therapy trial using bone fragments and cultured osteoblasts, *J Clin Endocrinol Metab* 2007; 92(8): 2923-2930.
[6] Whyte MP, Mumm S, Deal C, Adult hypophosphatasia treated with teriparatide *J Clin Endocrinol Metab* 2007; 92(4): 1203-1208. Camacho PM, Painter S, Kadanoff R, Treatment of adult hypophosphatasia with teriparatide, *Endocr Pract* 2008; 14(2): 204-208.
[7] Camacho PM, Painter S, Kadanoff R, Treatment of adult hypophosphatasia with teriparatide, *Endocr Pract* 2008; 14(2): 204-208.
[8] Whyte MP, McAlister WH, et al., Enzyme replacement therapy for infantile hypophosphatasia attempted by intravenous infusions of alkaline phosphatase-rich Paget plasma: results in three additional patients, *J Pediatr* 1984; 105(6): 926-933.
[9] Hessle L, Johnson KA, et al., Tissue-nonspecific alkaline phosphatase and plasma cell membrane glucoprotein-1 are central antagonistic regulators of bone mineralization, *Proc Natl Acad Sci USA* 2002; 99(14): 9445-9449.

2.1 Product Information

Asfotase alfa (human recombinant tissue-nonspecific alkaline phosphatase fusion protein) is a new molecular entity. It is a fusion protein composed of human recombinant TSNALP, an aspartate peptide that targets bone, and human Immunoglubulin G (IgG).

2.2 Tables of Currently Available Treatments for Proposed Indications

N/A

2.3 Availability of Proposed Active Ingredient in the United States

Asfotase alfa is not available in the US.

2.4 Important Safety Issues With Consideration to Related Drugs

All therapeutic protein products present a potential risk for developing anti-drug antibodies (ADA).

2.5 Summary of Presubmission Regulatory Activity Related to Submission

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-001-08, a study in adults, and Protocol ENB-002-08, a compassionate use protocol for patients with infantile HPP.

June 7, 2008: The Division issued a Partial Clinical Hold due to insufficient nonclinical data to support dosing for the 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.

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. The Division noted that a non-concurrent historical control may be appropriate for the perinatal/infantile-onset population because of the high risk of mortality of severe morbidity in this group. However, due to the lower degree of morbidity in the juvenile-onset population, the

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Division emphasized that evidence to support efficacy should be based on adequate and well-controlled trials.

May 31, 2011: The Division held an End-of-Phase 2 meeting with the sponsor. The Division reiterated its concerns about the interpretability of data from open-label trials for the perinatal/infantile- and the juvenile-onset populations.

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. Key issues discussed at the meeting included the lack of agreed-upon efficacy endpoints for HPP and the sponsor's proposed controlled trial design for the juvenile-onset population.

May 21, 2013: Asfotase alfa was granted Breakthrough Therapy Designation 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 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.

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 the BLA for asfotase alfa.

March 27, 2014: The sponsor submitted Wave 1 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 completed submissions for BLA 125513.

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2.6 Other Relevant Background Information

Asfotase alfa was recently approved by Japan (approved July 6, 2015), Canada (approved August 17, 2015) and the EMA (approved September 1, 2015), with the following regional differences in the approved indications:

- treatment for patients with HPP (Japan)
- treatment of patients with confirmed diagnosis of pediatric-onset HPP (Canada)
- long-term enzyme replacement therapy in patients with paediatric-onset HPP to treat the bone manifestations of the disease (EMA)

In Canada, marketing approval was granted as a Notice of Compliance with Conditions (NOC/c) approval; the EMA granted marketing authorization under exceptional circumstances. All approvals were based on review of data from approximately 70 patients collected during the 6-month primary treatment period of three ongoing clinical trials in pediatric patients with perinatal/infantile- and juvenile-onset HPP and data from a retrospective natural history study in pediatric patients with perinatal/infantile-onset HPP (an investigator-sponsored study was also reviewed in Japan).

Reviewer Comments:
Note that authorization by these regulatory authorities was based on review of open-label, short-term efficacy data. Under EMA regulations, an exceptional circumstance is a provisional marketing authorization that is reviewed annually. This regulatory pathway may be used if there are not comprehensive efficacy and safety data for a product under any of the following circumstances:

- *The product is intended for a disease or condition that is so rare that the applicant cannot be expected to provide comprehensive evidence*
- *There is limited scientific knowledge about the disease*
- *There are ethical contraindications to collecting these data.*

In Canada, a NOC/c authorization is granted when the sponsor is required to undertake additional studies to verify the clinical benefit.[10]

The applicant's BLA application submission to the FDA includes a more comprehensive set of data than the data reviewed by the aforementioned regulatory authorities. The application includes efficacy and safety data for 99 perinatal/infantile-onset and juvenile-onset patients up through more than 6 years of treatment (mean duration of treatment for infantile-onset patients and juvenile onset patients was 2 years and 3 years, respectively) as well as data from two retrospective natural history studies (one in perinatal/infantile HPP patients and one in juvenile-onset HPP patients).

[10] http://hc-sc.gc.ca/dhp-mps/prodpharma/notices-avis/conditions/index-eng.php

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3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The overall quality of the data submitted by the applicant was adequate for comprehensive review of the data, and the integrity of the investigators and the conduct of the trials were found to be acceptable by the Office of Scientific Investigations.

Reviewer Comments:
In her Clinical Inspection Summary, Susan Leibenhaut, M.D. of the Division of Clinical Compliance Evaluation noted three data discrepancies for data collected for ENB-006-09/ENB-008-10 that she did not consider to be a compliance issue (see Dr. Leibenhaut's review dated July 30, 2015 for further details):

- *One discrepancy was due to correction of a math error for the 6 Minute Walk Test (6MWT) distance for one patient. The corrected value was lower than the erroneous value.*
- *Derived values for bone biopsy parameters (% of healthy means) reported in the BLA did not match listed values. The difference appears to be because the values for healthy mean listed in the source document and the line listing are rounded off from values in the original reference document (the reference mean for the clinical trials is reported out to the nearest tenth of a fraction whereas the original reference mean is reported out to one hundredth of a fraction).*
- *Patients were usually provided product from two different lots for administration between clinic visits (following an initial observation period at clinic sites, patients were administered asfotase alfa at home). Families were provided drug diaries but the diaries did not have listings for specific lot numbers. Therefore, information on the lot number administered for a specific day was not available.*

Dr. Leibenhaut deferred to the clinical review team as to whether the discrepancies may potentially impact data review. In this reviewer's opinion, none of these data discrepancies adversely impacted the interpretability of the data. The two mathematical discrepancies resulted in minor differences in the values reported. The lack of information of lot numbers had a greater potential for hindering evaluation of treatment effect. However, as discussed later, all of the patients treated in ENB-006-09/ENB-008-10 experienced clinically significant improvements in radiographic and growth parameters. Therefore, there were no apparent issues of disparities in clinical outcomes that might be attributed to differences in drug product administered.

3.2 Compliance with Good Clinical Practices

According to the applicant, these trials were conducted pursuant to the following International Conference on Harmonisation (ICH) guidelines: Good Clinical Practice (ICH E6), Statistical Principles for Clinical Trials (ICH E9), and Choice of Control Group and Related Issues in Clinical Trials (ICH E10).

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3.3 Financial Disclosures

The applicant listed 172 participating investigators at 40 participating sites, including 33 sites that enrolled patients and 7 sites that did not enroll patients.[11] One clinic site (Tawam Hospital, United Arab Emirates) received funding from the applicant but none of the investigators at the site had direct financial arrangements with the applicant. A second hospital (Shriner's Hospital for Children, St. Louis) received funding from the applicant. (b) (6) a second investigator certified that that she had no direct financial arrangements with the applicant but was involved in grant activities funded by the applicant. The remaining clinical sites and investigators had no financial arrangements to disclose.[12] The financial disclosure forms for each clinical trial submitted in the application are reviewed in Section 9.4.

Reviewer Comments:
One investigator who was involved in multiple clinical trials for asfotase alfa received consultant fees for clinical trial development and an educational program on HPP from the applicant. He was granted an exemption of conflict of interest from the Disclosure Review Committee (DRC) at his institution for participation in the clinical trials based on his experience with HPP, with the condition that he file a management plan for conflict of interest for interventional clinical trials (the institution determined that no management plan was necessary for participation in a retrospective natural history study). Because the principal efficacy endpoints for this application were objective measurements (survival and growth), this reviewer does not feel that the disclosed financial arrangements had an adverse impact on the review or interpretability of the data submitted for this application.

[11] Site numbers were specific to the individual trials; therefore, a site that participated in multiple trials had multiple site numbers.
[12] Financial disclosure information was not collected for one investigator at a clinical site that was preliminarily considered for participation in the trial. The applicant stated that the information was not collected because enrollment was already completed before the site was ready for initiation.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

Asfotase alfa Asfotase alfa is a fusion protein expressed in CHO cells. The protein is composed of the soluble catalytic domain of human tissue non-specific alkaline phosphatase (TNSALP), the Fc domain of human IgG1 Fc, and a deca-aspartate peptide (D10) used as a bone targeting domain.

Drug substance

The drug substance for the to-be-marketed drug product is manufactured at a (b) (4) scale. During clinical development, the drug product was (b) (4) The (b) (4) drug products were used in all the clinical studies except for Study ENB-001-08 which used only the (b) (4) product.

Reviewer Comments:
The CMC review team noted that the comparability of the (b) (4) and (b) (4) scales was reviewed as part of the CMC review of the original IND submission for asfotase alfa and that the processes were deemed to be comparable (b) (4)

Drug product

The drug product is supplied as a sterile aqueous solution for SC administration in glass vials containing asfotase alfa; dibasic, sodium phosphate, heptahydrate; monobasic sodium phosphate, monohydrate, and sodium chloride. The solution is provided in two 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 a 0.80 mL volume containing 80 mg of asfotase alfa.

Reviewer Comments:
(b) (4)

Product quality review

Product quality data for this submission was reviewed by Product Quality Reviewers Joslyn Brunelle, Ph.D. (Drug Substance), Mate Tolnay, Ph.D. (Drug Substance), and Gunther Boekhoudt (Drug Product). No deficiencies were identified by the review team that barred approval of the applicant. However, several issues were identified that will

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be addressed through postmarketing commitments (PMCs). The applicant gave the following commitments for post-approval stability testing in the application submission:

- The first three commercial batches shall be placed on stability to confirm expiry.
- No less than one batch of commercial product per year per manufacturing facility in which product is manufactured will be tested according to the post approval stability protocol.
- Results of post-approval stability studies will be reported in the Annual Report (US) or in periodic updates requested by regulatory authorities.
- Any confirmed stability results outside of the approved drug substance specification will be thoroughly investigated for impact to drug substance and drug product lots.

In addition, the CMC review team noted that the applicant had agreed to evaluate the asfotase alfa manufacturing process and develop a control strategy (b) (4) This PMC was developed in response to a PK analysis by the clinical pharmacology review team (b) (4) (b) (4)

Finally, the applicant agreed to evaluate the complement activating capacity of asfotase alfa as a post-marketing commitment.

Reviewer Comments:
There is the potential risk for complement activation through complement binding (C1q) by the IgG Fc region of the asfotase alfa fusion protein. The applicant submitted complement activation testing results that indicated that there was no detectable complement activation with asfotase alfa and also noted that the protein is not targeted towards ligands or cell surface antigens. However, the Agency considered the (b) (4) assay used for testing to be insensitive and advised the applicant to develop an assay to compare the complement activating capacity of asfotase alfa to that of human IgG1 (see Information Request dated May 22, 2015). Product Quality Reviewer Mate Tolnay, Ph.D., noted that the applicant has agreed to evaluate the complement activating capacity of asfotase alfa as a post-marketing commitment and felt that this was acceptable since there did not appear to be any safety signals for events associated with complement activation. I concur with Dr. Tolnay's recommendation.

Facility review/inspection
The Facilities Reviewer was Steven Fong, M.S., Ph.D. The applicant proposed nine sites for asfotase alfa manufacture (see Table 2). The Office of Compliance issued a decision of Official Action Indicated (OAI) for the (b) (4) drug product

release testing site. On September 3, 2015, the applicant withdrew this site from the BLA application.

In a response to an information request submitted on April 30, 2015 (SN0026), the applicant clarified that the Alexion was the primary release testing site and the (b) (4) site is a (b) (4) testing site. The applicant confirmed that all of the drug product release testing included in the submission was performed at Alexion.

Table 2: Proposed Sites for Asfotase alfa Manufacture

Drug Substance Manufacture, Cell Banking and Testing Operations	
Site	**Responsibilities**
(b) (4)	
Alexion Pharmaceuticals, Inc. Smithfield RI	Storage of master & working cell bank
Drug Product Manufacture, Testing, Packaging and Labeling	
Site	**Responsibilities**
(b) (4)	
Alexion Pharmaceuticals Smithfield RI	Drug release and stability testing
(b) (4)	Drug product stability testing
	Drug product release testing
	Drug product release testing

Reviewer Comments:
The CMC review team noted that since all data for the BLA submission were obtained from the Alexion site, withdrawal of the (b) (4) testing site from the license does not compromise the suitability of the CMC information included in the BLA.

Microbiology product quality
Microbiology product quality data were reviewed by Candace Gomez-Broughton, Ph.D. (see her review dated August 21, 2015 for full details). Dr. Gomez-Broughton identified a deficiency in the (b) (4) controls for endotoxin, noting that the (b) (4) results were (b) (4). The applicant agreed to the following post-marketing commitment:

- To re-evaluate the (b) (4) endotoxin limits for the (b) (4) after data from thirty batches is available and (b) (4) to reflect manufacturing process capability

Dr. Gomez-Broughton deemed the sterility assurance and microbiology product quality processes and controls to be adequate for approval of the application with remediation of the (b) (4) endotoxin controls to be addressed as a post-marketing commitment.

Immunogenicity
Immunogenicity data were reviewed by Frederick Mills, Ph.D. Dr. Mills concluded that the immunogenicity assays for anti-product antibodies to asfotase alfa are appropriately validated with adequate sensitivity. Dr. Mills recommended approval of the product since there did not appear to immunogenicity issues that would prevent approval (see Section 4.4.4, Section 6.1.10, and Section 7.4.6 for a discussion of immunogenicity findings for PK, efficacy and safety, respectively). He recommended that the applicant develop an assay for Cross Reactive Immunological Material (CRIM). The applicant agreed to develop the assay as a post-marketing commitment.

Reviewer Comments:
Dr. Mill noted that an assay for CRIM (in this case endogenous TNSALP) will help identify patients without endogenous TNSALP who are most at risk for producing antibodies that may result in loss of asfotase efficacy. I concur with Dr. Mill's recommendation.

CMC Action Recommendation
Approval

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

4.3 Preclinical Pharmacology/Toxicology
The nonclinical data for this submission were reviewed by Dinesh Gautam, Ph.D. (see his review dated August 27, 2015 for further details). The preclinical program included primary pharmacology, safety pharmacology, pharmacokinetics (PK), single and

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repeated dose toxicity studies in juvenile rats and juvenile monkeys, and reproductive and development toxicology studies in rats and rabbits.

In vitro studies showed that asfotase alfa binds with a high affinity (up to 97%) to hydroxyapatite, the primary mineral component of bone and rescued PPI-induced mineralization in mouse osteoblastic cell cells. In studies in a knockout mouse model, mice treated with subcutaneous (SC) doses of asfotase alfa had increased bone mineralization of the feet, rib cage, and pelvic limbs as well as improved body weight gain and survival rate.

In normal rats, intravenous (IV) treatment with asfotase alfa at doses of 30 mg/kg or higher was associated with reduced motor activity, reduced reactivity to stimuli, abnormal gait and reduced mobility, and lower grip strength and a decrease in respiratory rate at all doses tested (3, 30, and 90 mg/kg). Asfotase alfa had no effects on electrocardiogram parameters in juvenile Cynomolgus monkeys when administered as SC doses at dose levels up to 10 mg/kg.

The PK profile 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 species. Distribution studies with radiolabeled asfotase alpha showed that the drug is distributed into peripheral tissues, including bones. The PK profiles following SC dosing indicated slow absorption and elimination of the enzyme; 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 IV and SC 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, 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 (i.e., tissue nonspecific alkaline phosphatase [TNSALP]) animals in both the monkey and rat studies throughout the treatment period. The No Observed Adverse Effect Level (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 doses up to 50 mg/kg/day IV were administered in reproductive and development toxicology studies. Asfotase alfa was not fetotoxic, embryo lethal or teratogenic in rats and rabbits, and had had no effect on fertility or pre- and postnatal development in rats in rats at IV doses up to 50 mg/kg/day IV, the highest dose tested.

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Dr. Gautam deemed the nonclinical program to be adequate to support marketing approval.

Preclinical Pharmacology/Toxicology Action Recommendation
Approval

4.4 Clinical Pharmacology

The clinical pharmacology data for this submission were reviewed by Christine Hon, Ph.D. (Clinical Pharmacology reviewer), Justin Earp Ph.D. (Pharmacometrics reviewer), and Sarah Dorff, Ph.D. (Genomics and Targeted Therapy reviewer). Please refer to the Clinical Pharmacology review (dated August 9, 2015) for further details. The clinical pharmacology review team recommended an approval action for the application.

The data consisted of PK and population PK/PD analyses in HPP patients. The applicant also conducted an open-label PK trial (AA-HV-104) in healthy adults in Canada (n=23) to assess the PK comparability of a different 100 mg/mL formulation with the 100 mg/mL formulation used in clinical trials. AA-HV-104 was terminated due to preliminary PK results that indicated the newer product was not comparable. Top-line preliminary safety data for AA-HV-104 are reviewed in Section 7.4.1.

4.4.1 Mechanism of Action

The rationale for enzyme replacement is that exogenous administration of asfotase alfa (TNSALP) should mitigate the deficiency of endogenous enzyme in hypophosphatasia. The mechanism of action is not fully understood. However, enzymatic activity results in increased concentrations of inorganic phosphate, which subsequently precipitates with calcium to form calcium phosphate which is transformed into hydroxyapatite crystals, which provide the structural matrix for bones and teeth (approximately 75% of the mineral content of bone is hydroxyapatite).

4.4.2 Pharmacodynamics

Multiple pharmacodynamic (PD) were assessed in clinical trials, including biochemical markers, radiographic assessments, survival, growth, and functional assessments. Endpoints used by the applicant to provide the PK/PD rationale for dosing included biomarkers (inorganic pyrophosphate [PPi] and pyridoxal-5'-phosphate [PLP]), radiographic assessments, gross motor functioning, gait and mobility, and survival (see Table 3).

Table 3: Summary of Endpoints Evaluated by Population PK-PD/Efficacy Modeling

Variable	Response Endpoints	Phenotype	PK/PD Findings as Rationale to Support Proposed Dose Regimen
PD (Biochemical)	PPi	Perinatal/infantile-, juvenile-, adult-onset	Show effect on plasma PPi and PLP plateauing out
	PLP	Perinatal/infantile-, juvenile-, adult-onset	
PD (Radiologic)	RGI-C	Perinatal/infantile-, juvenile-onset	Show near maximal change from baseline
	RSS (Knee and Wrist)	Perinatal/infantile-, juvenile-onset	
PD (Functional)	BOT-2	Juvenile-onset	Indicate significant improvement in ambulation
	6MWT	Juvenile-onset	
Efficacy	MPOMA-G	Juvenile-onset	
	Overall survival	Perinatal/infantile-onset	Improve survival

PD, pharmacodynamics; PPi, inorganic pyrophosphate; PLP, pyridoxal-5'-phosphate; RGI-C, Radiographic Global Impression of Change; RSS, Rickets Severity Scale; BOT-2, Bruininks-Oseretsky Test of Motor Proficiency, 2nd Edition; 6MWT, 6 Minute Walk Test; MPOMA-G, modified Performance Oriented Mobility Assessment-Gait score

Source: Clinical Pharmacology Review (dated August 9, 2015), Table 4

Reviewer Comments:
Overall survival and the MPOMA-G endpoint were the primary efficacy endpoints for the perinatal/infantile-onset HPP and juvenile-onset HPP indications, respectively; all other PD endpoints were secondary endpoints in the statistical analyses for efficacy.

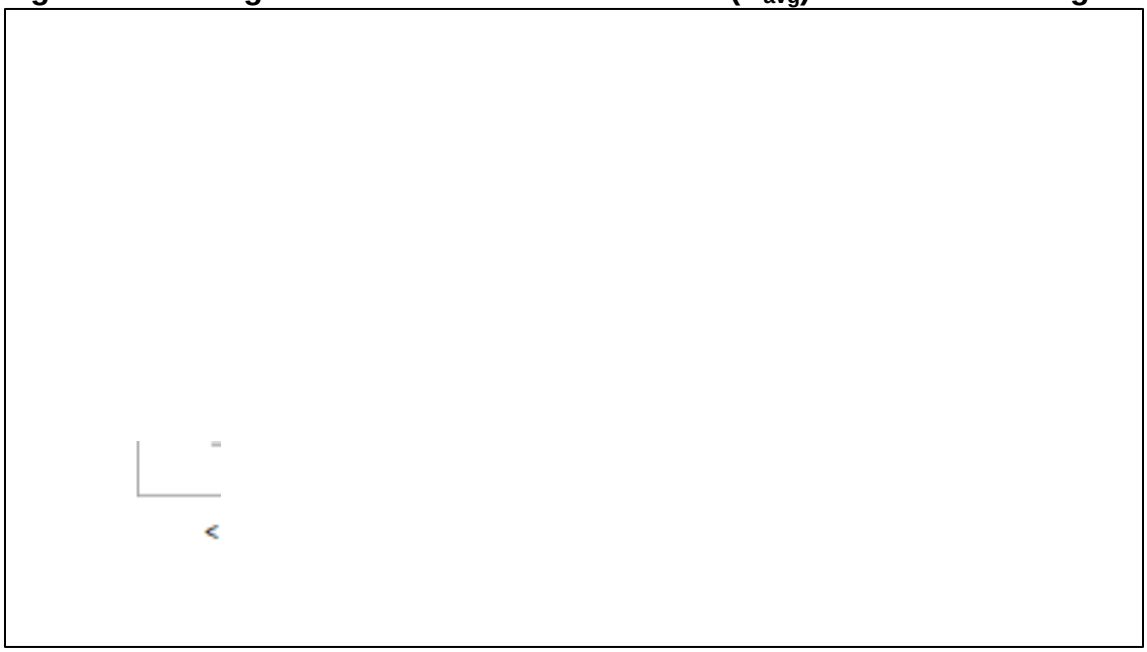
Exposure-Response Relationships

The applicant used PK-PD modeling to evaluate the exposure-response relationship for overall survival in perinatal/infantile-onset patients and for six additional endpoints (BOT-2, 6MWT, RGI-C, RSS, PPi, and PLP) to support the efficacy of asfotase alfa in juvenile-onset patients. The survival analysis showed that asfotase alfa treatment was associated with an increase in overall survival in an exposure-dependent manner. For the other efficacy endpoints, the exposure-response analyses showed a response plateau at asfotase alfa concentrations of 1500- 2000 U/L.

The Pharmacometrics reviewer, Dr. Justin Earp, analyzed the exposure-response relationship for growth (height z-score) in infantile- and juvenile-onset HPP patients. The exposure-response relationship for growth in infantile- and juvenile-onset HPP patients was not apparent, as there was no apparent correlation between individual average concentration over the entire study period (Cavg) and height z-score slope.

Reviewer Comments:
The Clinical Pharmacology review team stated that the proposed dosing regimen of 6 mg/week administered as either 2 mg/kg 3 times weekly or 1 mg/kg 6 times weekly is consistent with the exposure-response relationships for effectiveness of asfotase alfa based on multiple endpoints. The team noted that the proposed regimen resulted in median steady state concentrations of asfotase alfa of >2000 U/L (i.e., within the plateau of exposure-response curves for the efficacy endpoints evaluated) in different patient age groups (see Figure 1).

Figure 1: Average Asfotase Alfa Concentration (C_{avg}) versus Patient Age



Asfotase Alfa Cavg was calculated from the individual post hoc Bayesian estimates of clearance for each individual, and the average dose received over the duration of treatment.

Source: Clinical Pharmacology Review (dated August 9, 2015), Figure 6

As discussed later, there were numerous limitations to interpreting the primary efficacy endpoint (MPOMA-G) results for evaluation of efficacy in juvenile-onset patients. However, asfotase alfa treatment was associated with improvement in growth and radiographic assessments in juvenile-onset patients compared to a historical control group. For this reason, the Pharmacometrics reviewer also analyzed the exposure-response relationship for growth.

4.4.3 Pharmacokinetics

Asfotase alfa PK data after SC administration were available for 38 HPP patients (22 perinatal/infantile onset HPP patients, 14 juvenile-onset HPP patients, one adult-onset HPP patient, and one patient with unknown disease onset status) who received daily doses of 0.3 mg/kg and 0.5 mg/kg or 3 times weekly dosing of 2 mg/kg or 3 mg/kg. The mean patient age was 18 years (range was 1 month to 66 years).

Asfotase alfa PK exhibited dose proportionality across the dose range of 0.3 mg/kg to 3 mg/kg and appeared to be time –independent. Steady state exposure was achieved as early as three weeks following initial dose administration. The elimination half-life following a single IV administration was approximately 5 days. The estimated absolute bioavailability was 62% following SC administration of the (b) (4) 40 mg/mL.

PK data were available for a subset of 21 perinatal/infantile-onset patients who received the proposed labeled dose of 2 mg/kg 3 times a week (see Table 4). The mean time to maximum concentration (t_{max}) ranged from 15 to 20 hours. 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.

Table 4: Summary of Pharmacokinetic Parameters at Week 6 Following Subcutaneous Administration of Asfotase alfa 2 mg/kg Three Times per Week-

	ENB-010-10	ENB-006-09
N	15	6
Age (years)	3.1 ± 2.2	7.8 ± 2.3
Weight at Baseline (kg)	10.6 ± 5.2	21.2 ± 7.9
t_{last} (h)	48.1 ± 0.1	48.0 ± 0.05
t_{max} (h)	15.5 ± 10.3	20.8 ± 10.0
C_{max} (U/L)	1576 ± 720	1781 ± 666
AUC_t (h*U/L)	58743 ± 29580	75985 ± 28122
$C_{max,nor}$ (U/L)/(U/kg)	1.2 ± 0.87	1.0 ± 0.4
$AUC_{t,nor}$ (h*U/L)/(U/kg)	43.6 ± 36.2	41.2 ± 15.6
Accumulation Ratio[a]	2.5	3.8

[a]Ratio values reflect the fold increase of $AUC_{t,nor}$ from Week 1 based on mean $AUC_{t,nor}$ values.
Data are presented as mean ± standard deviation.
t_{last}, time of last concentration; t_{max}, time of maximal concentration; C_{max}, maximal concentration; AUC_t, area under the concentration-time curves over a dosing interval of 48 hours; $C_{max,nor}$, dose normalized C_{max}; $AUC_{t,nor}$, dose normalized AUC_t

Source: Clinical Pharmacology Review (dated August 9, 2015), Table 10

PK Comparability between Products with Different Batch Size and Formulation Strength

The clinical pharmacology review team noted that [redacted] (b) (4) has a significant impact on asfotase alfa exposure, with an estimated [redacted] (b) (4) difference in the Cavg,ss of asfotase alfa between the extremes of the applicant's proposed total [redacted] (b) (4). The team raised the concern that treatment with product lots with [redacted] (b) (4) may potentially result in inadequate systemic asfotase alfa concentrations [redacted] (b) (4) [redacted]. The team recommended that the lower limit of the [redacted] (b) (4) specification be raised to provide more consistent exposure to the patient at concentrations of asfotase alfa expected to be efficacious.

Both the to-be-marketed [redacted] (b) (4) scale product and a [redacted] (b) (4) scale product were used in clinical trials. Based on an intra-subject comparison of PK exposure in four patients who received both products at different study visits, the clinical pharmacology review team noted that a 2-fold lower exposure was observed with the to-be-marketed [redacted] (b) (4) scale product compared with the [redacted] (b) (4) product. The review team attributed the lower exposure to [redacted] (b) (4) [redacted]

In addition, the review team noted that a difference between two formulation strengths used in clinical trials. A 40 mg/mL formulation was used in younger children with lower body weight and a 100 mg/mL formulation was used in older children with higher body weight. The review team stated:

> *"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 Cmax (Cmax,nor) and AUCt,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 after* [redacted] (b) (4) [redacted] *in the products administered. 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 infantile-onset HPP patients to inform its efficacy with respect to overall survival, only the 40 mg/mL formulation strength should be used in pediatric infantile-onset patients."*

Asfotase alfa exposure increased with body weight and clearance increased with formation of antidrug antibodies (ADA); the clearance (CL) value was 11% higher in ADA-positive patients and 21% higher in ADA-positive/neutralizing antibody-positive patients compared to patients who were ADA negative.

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Reviewer Comments:
I concur with the clinical pharmacology review team's recommendations. As discussed earlier, the issue of (b) (4) *will be addressed through a post-marketing commitment. Regarding differences in exposure between formulations, until comparability can be established between the 40 mg/mL and 100 mg/mL formulations, this reviewer recommends that the labeling for asfotase alfa should include instructions that only the 40 mg/mL formulation be used in pediatric patients weighing less than 40 kg for both the juvenile-onset and the perinatal/infantile-onset indication. Because growth retardation may impact adolescents as well as younger pediatric patients in both subgroups, a weight criterion of 40 kg will help ensure that pediatric patients receive a formulation that provides an adequate exposure to support optimal growth and bone development up through puberty. The clinical pharmacology review team also recommending including information about differences in exposure due to the presence of antidrug antibodies. I concur with this labeling recommendation.*

4.4.4 Immunogenicity

Antibody testing results were available for 98/102 patients (96%). Of 98 patients, 76 (78%) patients were anti-drug antibody (ADA)- positive at one or more time points, including 48 (49%) patients who developed persistent antibody titers For the majority of patients(>90%) who were persistently ADA-positive, the time course for developing continuously positive titers was within 48 weeks.[13] Median antibody titers, peak antibody titers, and antibody titers at last assessment were similar in perinatal/infantile-onset patients compared to juvenile-onset patients. Peak titers ranged from 0 to 2048, with a majority of patients (60%) who developed antibodies having titers of 64 or less. The time to development of antibody titers was shorter for perinatal/infantile-onset patients (median time was 23 days) compared to juvenile-onset patients (median time was 79 days). Table 5 summarizes antibody testing results.

[13] The applicant defined continuously ADA-positive as positive results for at least the last 2 available post-baseline assessments, regardless of length of exposure.

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Table 5: Asfotase alfa Antibody Testing Results

	Perinatal /Infantile	Juvenile	Adult	Unknown	All Patients
Patients with Antibody Results- n(%)	75	20	2	1	98
Always Negative- n(%)	19 (25)	2 (10)	0	1 (100)	22 (22)
Ever Positive- n(%)	56 (75)	18 (90)	2 (100)	0	76 (78)
Persistent Positive- n(%)	37 (49)	10 (500	1 (50)	0	48 (49)
Neutralizing Antibody-Positive- n(%)	29(36)	4 (20)	1 (50)	0	34/76 (45)
Titer					
n	56	18	2	0	76
Median	6	24	64	--	12
Min, Max	0, 1024	0, 2048	0, 128	--	0, 2048
Peak Titer- n(%)					
0-64	38 (51)	11 (55)	1	0	50 (51)
128-512	13 (17)	6 (30)	0	0	20 (20)
1024-2048	5 (7)	1 (5)	1	0	6 (6)
Last Titer- n(%)					
0-64	44 (59)	14 (78)	1 (50)	0	59(60)
128-512	10 (13)	3 (17)	1 (50)	0	14 (14)
1024-2048	2 (3)	1(5)	0	0	3 (3)
Time to 1st positive Titer (days)					
n	56	18	2	0	76
Median	23	79	--	--	35
Min, Max	14, 1072	21, 711	251,253	--	14, 1072
Time to Persistent Positive					
< Week 6	19	1	0	0	20
Week 6-Week 12	9	5	0	0	14
Week 24- Week 36	1	1	1	0	2
Week 48 to Week 72	8	2	0	0	10
≥96 Weeks	0	2	0	0	2

Reviewer Comments:
In his Immunology review, Dr. Mills noted that the high incidence of positive antibodies is expected, since asfotase alfa is a fusion protein (i.e., not a native protein). Although development of immunogenicity was associated with lower exposures, as discussed later, there does not appear to be clear patterns for loss of efficacy or safety noted to date with treatment with asfotase alfa. However, given the potential for loss of efficacy and immune-mediated related events with any therapeutic protein and the anticipated need for lifelong-treatment, this reviewer recommends that long-term safety data related to immunogenicity be collected for the product as a post-marketing commitment.

Clinical Pharmacology Action Recommendation

Approval

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5 Sources of Clinical Data

BLA Submission

The applicant submitted the following efficacy and safety data for review:

Natural history study reports

•Final Clinical Study Report for ENB-011-10 (dated January 22, 2014)
•Final Clinical Study Reports for ALX-HPP-502 (dated November 28, 2014) and
• ALX-HPP-502s (sub-study of ALX-HPP-502; dated November 24, 2014)

Phase 2 clinical trial reports

•Interim Clinical Study Report for ENB-002-08/ENB-003-08 (dated April 15, 2015; data analysis cut-off date was October 29, 2014)
•Interim Clinical Study Report for ENB-010-10 (dated April 8, 2015; data analysis cut-off date was November 21, 2014)
•Interim Clinical Study Report for ENB-006-09/ENB-008-10 (dated April 3, 2015; data analysis cut-off date was October 29, 2014)
•Interim Clinical Study Report for ENB-009-10 (dated April 2, 2015; data analysis cut-off date was November 5, 2014)

Integrated Data Analyses

•Integrated Efficacy &Integrated Safety Figures and Tables (dated March 31, 2015)
•120 Day Safety Update (dated April 17, 2015)

The submission also included summary safety and immunogenicity data for ENB-001-08, a Phase 1 dose-escalation trial.[14] Some patients who completed ENB-001-08 enrolled in other asfotase alfa clinical trials and therefore are captured in data analyses for the later trials.

Consults/Literature Review

I also completed a literature review (see Section 9.1) and reviewed the following consult reports:

•Division of Bone, Reproductive and Urologic Products (DBRUP) Consult Review by Marcea Whitaker, M.D. (dated August 29, 2013; DARRTS ID# 3365396)
•Division of Bone, Reproductive and Urologic Products (DBRUP) Consult Review by Stephen Voss, M.D. (dated April 16, 2015; DARRTS ID# 3733103)
•Division of Neurology Products (DNP) Consult Review by Teresa Buracchio M.D. (dated June 24, 2015; DARRTS ID# 3782307)
•Division of Metabolism and Endocrinology Products Consult Review by Marina Zemskova, M.D. (dated January 10, 2014; DARTTS ID# 3434498)

[14] The final clinical study report for ENB-001-08 (dated September 14, 2009) was submitted under IND 100619 on June 26, 2014; a report addendum was submitted with BLA 125513 on December 23, 2015. The applicant also submitted an erratum to the report that included minor laboratory data entry corrections. The revisions did not impact my review of trial results.

5.1 Tables of Studies/Clinical Trials

The clinical development program for asfotase alfa consists of two natural history studies (one each in the perinatal/infantile-onset HPP population and the juvenile-onset HPP population) , one Phase 1 dose-escalation trial (ENB-001-08) and six Phase 2 clinical trials including 3 clinical trials in perinatal/infantile-onset HPP patients (ENB-002-08 and its extension study ENB-003-08, and ENB-010-10) and 3 clinical trials in primarily juvenile-onset HPP patients (ENB-006-09 and its extension study ENB-008-10, and ENB-009-10). Table 6 summarizes clinical trials for asfotase alfa.

Table 6: Clinical Trials and Natural History Studies for Asfotase Alfa

Trial (# Sites) Country	Phase	N	Design	Dosing	Inclusion Criteria ---------- Exclusion Criteria	Duration	Status
Phase 1 trials							
ENB-001-08 (2) Canada US	1	6	OL Safety PK	3 mg/kg IV X 1dose then 1 mg/kg/ SC once a week X 3 doses; 7 mg/kg IV X 1 dose then 2 mg/kg SC once a week X 3 doses	•Adults 18-80 years old with HPP ---------- •Low Ca, Mg, Ph, or Vitamin D levels •Elevated Cr or PTH levels •Prior treatment with bisphosphonates or PTH •Pregnant or lactating women	4 weeks	completed
Phase 2 trials							
ENB-002-08 (10) Canada UAE* UK US (7)	2	11	OL Safety PK	2m/kg IV X 1 dose then 1 mg/kg SC 3 times a week X 1 month, then dose adjustments up to 3 mg/kg SC 3 times a week (9 mg/kg/week; maximum dose 40 mg)	•Infants & children <36 months old with severe perinatal/infantile-onset HPP ---------- •Current or prior clinical significant condition •Investigational therapy within past month or enrollment in another trial •Low Ca, Ph, or Vitamin D levels •Treatable form of rickets •Prior treatment with bisphosphonates	6 months	completed
ENB-003-08 (10) Canada UAE* UK US (7)	2	10	OL Safety /Efficacy	Initial dose same as final dose in ENB-002-08; dose adjustment criteria were same as those for ENB-002-08	• Completion of ENB-002-08 ---------- •Current clinical significant condition •Enrollment in another trial	36 months	ongoing
ENB-010-10 (11) Canada Germany Japan (5) Taiwan Turkey US (2)	2	79	OL Safety /Efficacy PK/PD	6 mg/kg/week (1mg/kg 6 times a week or 2 mg/kg/ 3 times a week) with dose adjustments	•Infants & children <5 years old with infantile-onset HPP ---------- •Current clinically significant condition •Enrollment in another investigational trial •Low Ca, Ph, or Vitamin D levels •Treatable form of rickets •Prior treatment with bisphosphonates	Up to 171 weeks	ongoing

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Table 6: Clinical Trials and Natural History Studies for Asfotase Alfa (cont'd)

Trial (# Sites) Country	Phase	N	Design	Dosing	Inclusion Criteria ---------- Exclusion Criteria	Duration	Status
Phase 2 trials							
ENB-006-09 (2) Canada US	2	13	R, OL Safety /Efficacy PK/PD Parallel dose	2 or 3 mg/kg SC 3 times a week	•Children 5 -12 years old with HPP ---------- • Current clinically significant conditions or congenital abnormalities • Treatment with an investigational drug within past month or enrollment in any other investigational trials for HPP •Low Ca or Ph levels •Treatable form of rickets •Prior treatment with bisphosphonates • Bone fracture or orthopedic surgery within the past 12 months	6 months	completed
ENB-008-10 (2) Canada US	2	12	R, OL Safety /Efficacy	3 mg/kg/week; protocol amended to increase dose to 6 mg/kg/week	•Completion of ENB-006-09 ---------- •Current clinically significant condition •Treatment with investigational drugs or enrollment in another investigational trial •Prior treatment with bisphosphonates	36 months	ongoing
ENB-009-10 (3) Canada US (2)	2	19	R, OL Safety /Efficacy PK/PD	Untreated, 0.3mg/kg SC daily 0.5 mg/kg SC daily Extension: 0.5 mg/kg SC daily, changed to 1 mg/kg SC 6 times a week	•Adolescent & adult patients 13-65 years old with HPP ---------- •Low Ca, Ph, or Vitamin D levels •Elevated Cr or PTH levels •Treatment with bisphosphonates within past 2 years or PTH within past 6 months • Current clinically significant conditions • Treatment with an investigational drug within past month •Orthopedic surgery within past 12 months •Pregnant or lactating women	6 months & extension	ongoing

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Table 6: Clinical Trials and Natural History Studies for Asfotase Alfa (cont'd)

Trial (# Sites) Country	Phase	N	Design	Inclusion Criteria ---------- Exclusion Criteria	Duration	Status
Natural History Studies						
ENB-011-10 (12) Australia Canada Germany Spain Switzerland Taiwan US (6)	N/A	48	Retrospective study	•Patients with severe perinatal- and infantile-onset HPP ---------- •Prior treatment with asfotase alfa •Other clinically significant disease	N/A	completed
ALX-HPP-502 (1) US	N/A	32	Retrospective study Retrospective study	•Patients with juvenile-onset HPP ---------- •Prior treatment with asfotase alfa or other treatments for bone or growth •Other clinically significant disease	N/A	completed
ALX-HP-502s (1) (gait analysis) US	N/A	6				

Ca=calcium; Cr=creatinine; IV=intravenous; OL= open label, Mg=magnesium; N/A= not applicable, PK= pharmacokinetics; PD=pharmacodynamics; Ph=phosphorus; PTH=parathyroid hormone; R=randomized; SC=subcutaneous; UAE= United Arab Emirates; UK= United Kingdom; US= United States

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5.2 Review Strategy

This section discusses trial designs, efficacy endpoints, and patient demographics for the trials reviewed for this submission. Because there are no established endpoints for HPP, the Division engaged other review divisions in discussions with the sponsor about the appropriateness of several endpoints for use in this population prior to submission of the application. These included consultations from the Division of Bone, Reproductive and Urologic Products (DBRUP) regarding bone biopsy data (see the consult review by Dr. Marcea Whitaker dated August 29, 2013)) and the Division of Metabolism and Endocrinology Products (DMEP) regarding the use of height data endpoints in clinical trials (see the consult review by Dr. Marina Zemskova dated January 10, 2014). In addition, the Division requested consultations from DBRUP and the Division of Neurology Products (DNP) during the application review. Dr. Stephen Voss of DBRUP reviewed data for HPP-related bone disease (radiographic and bone biopsy data) and Dr. Teresa Buracchio of DNP reviewed data for HPP-related gait and mobility functioning (see their consult reviews dated April 16, 2015 and June 24, 2015, respectively). I have cited some of their key comments and recommendations in Section 5.2.1 below, which provides an overview of efficacy endpoints evaluated in clinical trials for asfotase alfa, and in the analyses of efficacy data in Section 6.

The full discussion of efficacy analyses is in Section 6 of this review; however, I also provided brief summaries of efficacy results at the end of each trial description in this section. Safety is discussed in Section 7 of this review. Note that all analyses presented in this review were performed in the intent-to-treat (ITT) population, unless otherwise noted.[15]

There were two pivotal trials for the indication of treatment of perinatal/infantile onset HPP: ENB-002-03/ENB-003-08 and ENB-010-10, with ENB-011-10 serving as the retrospective historical control for the primary efficacy analysis. There was one pivotal trial for the indication of treatment of juvenile-onset HPP: ENB-006-08/ENB-008-10, with ALP-HPP-502s serving as the retrospective historical control for the primary efficacy analysis. Supportive studies for the perinatal/infantile onset indication included: ENB-006-08/ENB-008-10 and ENB-009-10. Supportive studies for the juvenile- onset indication included: ENB-002-03/ENB-003-08, ENB-010-10 and ENB-009-10.

Reviewer Comment:
As discussed in Section 6, from a regulatory perspective, because the agreed-upon analyses for the two populations were post-hoc, they are considered to be exploratory. The Statistical Reviewer, Benjamin Vali, M.S., deemed the use of a historical control for the primary efficacy analysis for the perinatal/infantile-onset population to be "reasonable" from a statistical perspective; however, he considered this approach for the juvenile-onset population to not be adequate statistically.

[15] The ITT population was defined as all patients who were randomized to treatment and received at least one dose of asfotase alfa.

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5.2.1 Efficacy Assessments Used in Clinical Trials for Asfotase Alfa

There were different principal efficacy endpoints for the perinatal/infantile-onset and juvenile-onset patient subgroups. Therefore, I reviewed the efficacy data for the patient subgroups separately. However, efficacy data for each subgroup were reviewed as supportive evidence of efficacy for the other subgroup (e.g., survival data for the perinatal/infantile-onset population were evaluated as supportive evidence for the juvenile-onset population and growth data for the juvenile-onset population were evaluated as supportive evidence for the perinatal/ infantile-onset population).

Efficacy parameters specific to the perinatal/infantile-onset subgroup included overall survival and ventilator-free survival. Efficacy parameters specific to the juvenile-onset subgroup included gait performance, 6 Minute Walk Test (6MWT), muscle strength, pain, and disability.

Efficacy parameters evaluated in both subgroups included growth, radiological assessments of HPP-related skeletal abnormalities, bone biopsy, bone mineral density, and age-appropriate measurements of gross motor function.

Table 7 summarizes efficacy assessments used in each clinical trial that were included in formal statistical analyses. Note that some efficacy assessment tools were used in only a single clinical trial. I did not review the data for clinical assessments that were not included in statistical analyses. These included dental films, nutritional assessments, and physical therapy assessments.

Table 7: Efficacy Assessments in Asfotase Alfa Clinical Trials

Trial	ENB-011-10	ENB-002-08/ ENB-003-08	ENB-010-10	ALX-HPP-502	ALX-HPP-502s	ENB-006-09/ ENB-008-10	ENB-009-10
Description	Natural History Study	**Pivotal study**	**Pivotal Study**	Natural History Study	Natural History Study	**Pivotal Study**	Supportive Study
Phenotype	Perinatal/ infantile (48)	Perinatal/ infantile (11)	Perinatal/ infantile (59)	Juvenile (32)	Juvenile (6)	Juvenile (8) Perinatal /infantile (5)	Adult (2) Juvenile (12) Perinatal/Infantile (4) Unknown (1)
Efficacy Assessments							
Overall Survival	X	X	X				
Ventilator-free survival	X	X	X				
Growth		X	X	X		X	X*
mPOMA-G					X	X	
6MWT				X		X	X
RGI-C		X	X	X		X	X*
RSS		X	X	X		X	X*
DEXA scan						X	X
Bone biopsy						X	X
Fractures		X	X			X	X
BSID-III		X	X				
PDMS-2		X	X				
BOT-2		X	X			X	
HHD						X	X
LEFS							X
PODCI						X	
CHAQ						X	
BPI-SF							X

* Pediatric patients only
mPOMA-G=modified Performance Oriented Mobility Assessment-Gait; 6MWT=6 Minute Walk Test; RGI-C=Radiographic Global Impression of Change; RSS=Rickets Severity Scale; DEXA=Dual Energy Absorptiometry; BSID-III= Bayley Scale of Infant and Toddler Development, 3rd Edition; PDMS-2= Peabody Developmental Motor Scales, 2nd Edition; BOT-2=Bruininks-Oseretsky Test of Motor Proficiency , 2nd Edition; HHD= Hand Held Dynamometry; LEFS= Lower Extremity Function Scale; PODCI= Pediatric Outcomes Data Collection Instrument; CHAQ= Child Health Assessment Questionnaire; BPI-SF= Brief Pain Inventory- Short Form

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Survival Assessments

- **Overall Survival**

Overall survival was defined as 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.

- **Ventilator-Free Survival**

Ventilator-free survival was defined as 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).

Growth Assessments

Growth assessments in clinical trials included recumbent length /height, weight, head and chest circumference (for infants), arm span, and body mass index (BMI). Length and height measurements in clinical trials were obtained using a stadiometer. No information on growth measurement methodology was available for the natural history studies. Results were expressed as z-scores calculated using the Centers for Disease Control (CDC) growth charts and methodology.[16]

Reviewer Comments:
I focused my review on the height and weight data because there are established z-scores for the entire pediatric age span for these two growth parameters. All patients enrolled in trials for the juvenile-onset indication were from the United States and Canada; patients enrolled in the trials for the perinatal/infantile-onset indication were from a number of geographic regions. CDC growth charts are widely used in other countries and are similar to the World Health Organization (WHO) pediatric growth charts for length and height at all ages and for weight for infants 12 months old and older. The two growth curves have different weight cut-offs for identifying underweight and overweight infants up through one year of age due to differences in breastfeeding rates between the US and other countries, and the exclusion of overweight infants in the development of the WHO growth charts.[17] Given that the majority of perinatal/infantile-onset patients had growth measurements beyond 12 months of age, use of the CDC growth references for both US and international patients was acceptable for analysis of growth patterns in the clinical trials.
DGIEP discussed height as a potential clinical endpoint to support an efficacy claim for the juvenile-onset population during a post-Breakthrough Therapy Designation meeting held with the applicant in January 2014. Prior to the meeting, Dr. Marina Zemskova of

[16] http://www.cdc.gov/growthcharts/percentile_data_files.htm.
[17] de Onis M, Onyango AW, et al., Comparison of the World Health Organization (WHO) child growth standards and the National Center for Health Statistics/WHO international growth reference: implications for child health programs, *Public Health Nutrition* 2006; 9(7): 942-947.

the Division of Metabolism and Endocrinology Products (DMEP) provided consultation on height evaluation in the juvenile HPP program. In her consult, Dr. Zemskova noted the need for consistent, standardized methodology of height measurements to ensure data quality.

The applicant appears to have used consistent methodology for height measurements (a wall-mounted stadiometer) in clinical trials that enrolled older pediatric patients, including ENB-006-09/ENB-008-10 and ENB-009-10.

It is not clear if a consistent methodology was used across trials for the perinatal/infantile-onset population. The statistical analysis plan (SAP) and Study Operations Manual (SOM) for ENB-002-08/ENB-003-08 stipulated that growth measurements were to be measured 3 times at each time point and must be within 1% of each other; the mean value was to be recorded in the electronic case report form. However, the SOM for ENB-010-10 was not available for review and the SAP for the protocol did not include a description of the growth measurement methodology. As noted earlier, no information was available on methodology for growth measurements used in the natural history studies. However, the height data appear to be grossly reliable; specifically, I did not uncover any decreases in raw height measurements.

In addition to non-standardized methods of growth measurement, Dr. Zemskova identified other challenges to analyzing growth data for the juvenile-onset population, including the small sample size and the lower incidence of growth retardation in juvenile-onset patients. Dr. Zemskova noted that one analytic approach might be a descriptive analysis of individual height standard deviation scores (i.e., z-scores) in patients enrolled in Study ENB- 006-09/ENB -008-10 accompanied by a graphic display of the height trajectory (see her review dated January 10,2014 for further details). I analyzed both individual height trajectories and changes in mean height z-scores to assess treatment effect in both the perinatal-infantile-onset and the juvenile-onset populations.

Ambulation Assessments

- **Modified Performance Oriented Mobility Assessment- Gait (m-POMA-G)**

The Performance Oriented Mobility Assessment (POMA) was originally developed as a screening tool to assess the risk of falls in the elderly.[18] The scale consists of two subscales that assess qualitative measures of balance (POMA-B) and gait (POMA-G). The POMA-G gait parameters include initiation of gait, step length and height, step symmetry, step continuity, path (deviation), trunk (instability), and walk stance. There are 16 items (9 items for balance and 7 items for gait) and each item is scored as 0-2

[18] Tinetti M, Performance-Oriented Assessment of Mobility Problems in Elderly Patients, *JAGS* 1986; 34: 119-126.

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points with a maximum score of 28. A higher score indicates better performance. The modified Performance Oriented Mobility Assessment-Gait (mPOMA-G) scale used for the juvenile-onset population did not include initiation of gait and path subscales.

Gait videos were read by three trained physical therapists who did not participate in the clinical care of enrolled patients and who were blinded to patient identifiers and dates of video recording.

Reviewer Comments:
In her consult review, Dr. Teresa noted that the mPOMA-G is not commonly used in the pediatric community and that no minimum clinically important change in gait score has been established in the juvenile-onset HPP population. As discussed later, lack of validation of gait measurement for this population was one of the factors limiting the interpretability of the gait analysis results.

- **6 Minute Walk Test (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.

Reviewer Comments:
In general, there are limitations to use of the 6MWT as an endpoint in clinical trials because it is performance dependent. Pediatric patients especially may lack the understanding or willingness to perform the test. Multiple articles in the published literature point out that there are no uniform 6MWT reference standards for healthy children, with differences both between and within geographic regions, and racial or ethnic groups. Differences in daily physical level may also results in lower 6MWT values. In a recently published study by Klepper and Muir, the authors reported lower 6MWT values of a group of inner-city US children aged 7-11 years. The authors attributed the lower values to both a higher proportion of obese children in their sample and due to a lower physical activity level due to scarce opportunities for physical activity or organized sports in the children's neighborhood.[19] *The applicant used the published reference equations for predicted distance walked developed by Geiger et al. in a population of healthy children in Austria.*[20] *Of note, Klepper et al. reported that, on average, children in their study walked 82% of the distance predicted by the Geiger reference equation.*

[19] Klepper SE, Muir N, Reference values on the 6-minute walk test for children living in the United States, *Pediatr Phys Ther* 2011; 23: 32-40.
[20] Geiger R, Strasak A, Treml B et al., Six-minute walk test in children and adolescents, *J Pediatr* 2007; 150: 395-399.

As noted above, the 6MWT was developed to assess exercise capacity. A recent review article by Bartels et al. noted that evidence of the appropriateness of the 6MWT as a functional outcome measurement tool varies among chronic pediatric populations.[21] *The 6MWT is currently being used as an outcome measure in clinical trials in Duchenne muscular dystrophy. However, to date, the 6MWT has not been used as the basis of approval of a neuromuscular or musculoskeletal indication.*

Radiographic Assessments

- **Radiographic Global Impression of Change (RGI-C)**

The applicant developed the RGI-C scale to assess changes from baseline in skeletal abnormalities and rickets associated with HPP. The scale is a 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). Radiographs for all clinical trials were evaluated and scored independently by a central panel of three pediatric radiologists and an average RGI-C score was calculated. Scoring was based on assessment of radiographs of the chest, bilateral wrists and bilateral knees.

RGI-C Scoring Scale
+3= very much better (i.e., complete or near complete healing of rickets)
+2= much better (i.e., substantial healing)
+1= minimally getter (i.e., minimal healing)
0= unchanged
-1= minimally worse (i.e., minimally worse (i.e., minimal worsening of rickets)
-2= much worse (i.e., moderate worsening)
-3= very much worse (i.e., severe worsening)

The applicant performed responder analyses of changes in RGI-C scores over time, with a responder defined as a patient achieving a RGI-C score of 2 or higher (classified as “substantial” healing of HPP-associated rickets).

[21] Bartels B, de Groot JF, Terwee CB, The six-minute walk test in chronic pediatric conditions: A systematic review of measurement properties, *Phys Ther* 2013; 93(4): 529-541.

- **Rickets Severity Scale (RSS)**

The RSS was 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).[22] The scale is a 10-point scale, with a score of 0 representing absence of rickets and a score of 10 representing severe rickets. Radiographs for all clinical trials were evaluated and scored independently by a single independent rater. RSS 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).

Reviewer Comments:
The RGI-C assesses changes over time while the RSS assesses the degree of abnormality. Neither scale has been validated for use in the HPP population. There is some overlap between radiographic abnormalities assessed by the RGI-C and the RSS; the RGI-C incorporated a wider array of skeletal assessments. As discussed later, some HPP patients did not have some of the hallmark radiographic findings associated with nutritional rickets and therefore had low RSS scores. They did have other radiographic abnormalities characteristic for HPP that are not captured by the RSS.

Bone Assessments

- **Bone Biopsy**

Bone biopsies were performed as histomorphometric assessments of bone mineralization. Changes in osteomalacia were evaluated through measurements of osteoid thickness and volume, and mineralization lag time and were reported as change from baseline and change in percent of healthy mean.

Reviewer Comments:
Osteoid thickness and volume, and mineralization lag time are standard histomorphometric criteria used to diagnose osteomalacia and to assess for treatment response. [23] *The key analyses for these parameters were change from baseline.*

- **Dual Energy X-ray Absorptiometry (DEXA)**

DEXA scans were performed as radiologic assessments of bone mineral density (BMD) and bone mineral content (BMC). Pediatric normative values (BMD z-scores) have been established for DEXA measurements, with a z-score of $\leq$- 2 indicating low BMD.

[22] Thacher TD, Fischer PR, et al., Radiographic scoring method for the assessment of the severity of nutritional rickets, *J Trop Pediatr* 2000; 137(3): 367-373.
[23] Parfitt AM, Wiu S, Rao DS, The mineralization index- A new approach to the histomorphometric appraisal of osteomalacia, *Bone* 2004; 35(320-325).

Reviewer Comments:
DEXA is the recommended densitometry method for assessment of BMD in children and adolescent both due to its low patient risk, precision and availability of pediatric normative data.[24]

Motor Function Assessments

- **Bayley Scale for Infant and Toddler Development- Edition 3 (BSID-III)**

The BSID was developed (normed and validated) in a population of US children for use in impaired and healthy children between 1 and 42 months of age. The scale includes 5 domains: cognition, receptive communication, expressive communication, fine motor, and gross motor. The applicant reported raw, scaled, composite, percentile rank, and age-equivalent BSID scores. Patients ages 43 months or older were assessed using the PDMS-2 or the BOT-2. Investigators were allowed to continue to use the BSID-III scale for assess patients 43 months or older who had severe developmental delays. Scaled indicate a patient's performance relative to healthy peers of the same age; scoring ranges from 1 to 19, with a normal mean of 10 and a standard deviation (SD) of 3.

- **Peabody Developmental Motor Scales, Second Edition (PDMS-2)**

The PMDS-2 was developed (normed and validated) in a population of healthy US and Canadian children for use in children between 43 and 71 months of age. The scale includes 5 subtests, including 2 subtests for fine motor function (grasping, and visual-motor integration) and 3 subtests for gross motor function (reflexes [ages birth to 11 months only], stationary, locomotion, and object manipulation [ages $\geq$12 month only]). The gross motor subtests were administered in clinical trials. The applicant reported composite gross motor scores and raw, standard, age-equivalent, and percentile scores for each subtest. The mean score (SD) for the standardized score for each subtest is 10(3).

- **Bruininks-Oseretsky Test of Motor Proficiency - Second Edition (BOT-2)**

The BOT-2 was developed (normed and validated) in a US population for use in children and young adults from 4 to 21 years of age with normal motor functioning and mild to moderate motor deficit. The gross motor component of the scale includes subtests for running speed and agility, balance, bilateral coordination, and strength. The running speed/agility, strength, and balance subtests were administered to patients aged 72 months or older in clinical trial. The applicant reported total, scale, and age-equivalent scores for each subtest and a composite score (standard score and percentile rank) for the speed/agility and strength subtests. The mean score (SD) for the standardized score for each subtest is 15(5).

[24] Estrada A, Ramnitz MS, Gafni RI, Bone densitometry in children and adolescents, *Curr Opin Obstet Gynecol* 2014; 26:339-346.

Reviewer Comments:
There were a number of factors that limited the interpretability of developmental assessment findings in clinical trials. One key limitation was the ability of the scales to assess changes over time. The developmental assessment literature discusses criteria for selecting assessment tools for evaluating developmental status. One key factor in selecting a tool is whether the tool is intended to be discriminative (used for screening or diagnosis) or evaluative (used to assess change over time or response to an intervention). All of the developmental assessment scales used in clinical trials for asfotase alfa were designed for use as discriminative assessment tools. In a review of standardized neurodevelopmental tools for preschool children, Tieman et al. noted that discriminative measures generally are not appropriate for use as outcome measures for children with identified developmental delays.[25] However, the authors stated that the PDMS-2 may be appropriate for children with motor delays. The BOT-2 has also been used as both a discriminative and evaluative tool.[26]

Second, because the assessments were age-specific, a single tool was not used to assess changes over time, presenting an issue of concurrent validity across tests.[27]

A further limitation was that some of the scales have only been validated in populations of healthy children (i.e., the PDMS-2) or populations that included mild to moderately impaired children (i.e., the BOT-2). Note that the majority of patients in clinical trials had some degree of motor function impairment at trial entry. Other limitations included the lack of a control group, lack of baseline assessments for a large proportion of patients, and potential differences in norm scales across cultures.[28] For example, a recently published Dutch study noted differences in norm values between Dutch and US children on the BSID-III.[29]

The BSID-III is a recently released version of the BSID. As a result, there are limited data on its use. In addition, scale scores for the BSID-III are not comparable to the prior version (BSID-II) and some published reports have raised the concern that the BSID-III may underestimate developmental delays.[30]

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[25] Tieman BL, Palisano RJ, Sutlive AC, Assessment of motor development and function in preschool children, Ment Retard Dev Disabil Res Rev 2005; 11(3): 189-196.
[26] Deitz JC, Kartin D, Kopp K, Review of the Bruininks-Oseretsky Test of Motor Proficiency, Second Edition (BOT-2), *Phys Occup Ther Pediatr* 20078; 27(4): 87-102.
[27] Concurrent validity refers to the extent to which the results of a particular test or measurement correspond to those of a previously established measurement for the same construct.
[28] The applicant noted that the PDMS-2 Locomotion subset was chosen for use in clinical trials because it had the greatest concurrent validity with the BSID-III.
[29] Steenis LJP, Verhoeven M, et al., Performance of Dutch children on the Bayley III: a comparison study of US and Dutch norms, *PLOS One* 10(8): e0132871. Published August 12, 2015.
[30] Anderson PJ, De Luca CR, et al., Underestimation of developmental delay by the new Bayley-III scale, *Arch Pediatr Adolesc Med* 2010; 164(4): 352-356.

I briefly described trial findings for developmental assessments. However, I did not consider the data to be of sufficient quality to evaluate for clinically meaningful changes in motor development. As discussed later, although some patients achieved small improvements in standardized test scores on the BSID-III, PDMS-2 and BOT-2 subtests, scores generally remained within the same range of standard deviation from the mean. For example, a change in standardized score from 1 to 3 still represented a test score that was more than two standard deviations from the mean, indicating a functioning score below the 3rd percentile for age peers.

Muscle Strength Assessments

- **Hand Held Dynamometry**

Hand held dynamometry is a quantitative measure of muscle strength measured through a device placed between the hand of the examiner and the patient's tested body part. Muscle strength was assessed by hand held dynamometry in the following muscle groups: grip, knee flexors and extensors, and hip flexors, extensors and abduction. Results were reported as ranking by age and gender based norms.

Reviewer Comments:
HHD is commonly used in clinical practice. However, there are limited data on the reliability and validity of the HHD when compared to isokinetic muscle strength testing, which is considered to be the "gold standard" muscle strength assessment.[31]

Disability and Pain Assessments

- **Child Health Assessment Questionnaire (CHAQ)**

The Child Health Assessment Questionnaire (CHAQ) was originally developed to measure function in childhood rheumatic disease but is currently used in other childhood arthritis conditions.[32] The scale includes patient self-report instruments for older children and parent-report instruments. Disability scores range from 0 (no disability) to 3 (severe disability); pain (discomfort index) scores range from 0 (no pain) to 100 (highest level of pain) based on a visual analog scale.

Reviewer Comments:
No minimum clinically important difference (MCID) in change in CHAQ score has been established for the HPP population.

[31] Stark T, Walker B, et al. , Hand-held dynamometry correlation with the gold standard isokinetic dynamometry: a systemic review, *PM R* 2011; 3(5): 472-479.
[32] Groen W, Nørgaard, et al., Comparing different revisions of the Childhood Health Assessment Questionnaire to reduce the ceiling effect and improve score distribution: Data from a multi-center European cohort study of children with JIA, *Pediatr Rheumatol Online J*; 8:16

- **Pediatric Outcomes Data Collection Instrument (PODCI)**

The PODCI was developed and validated in a US population of healthy children to measure functional status and includes 5 domains (Transfers and Basic Mobility, Upper Extremity and Physical Function, Sports and Physical Function, Pain/Comfort, and Happiness) as well as a Global Function that is the average of the first 4 domains. Standardized scores range from 0 (worst health) to 100 (best health); with a normative mean (SD) score of 50(10). Self-report questionnaires are available for patients ages 11 to 18; parent-report questionnaires are available for both adolescents (patients ages 11 to 18 years) and children (patients ages 10 years or younger).[33]

- **Lower Extremity Functional Scale (LEFS**)

The LEFS is a self-report measure designed to assess functional disability in the lower extremities. Scoring ranges from 0 to 80 points, with higher scores corresponding to better functioning. The minimal clinically important difference for the scale is 9 scale points.

- **Brief Pain Inventory (BPI-SF)**

The Brief Pain Inventory-Short Form (BPI-SF) questionnaire provides information on pain severity and the degree to which pain interferes with functioning. The scale for each subtest ranges from 0 to 10, with higher scores indicating more severe pain.

5.2.2 Study Drug Dosing in Clinical Trials for Asfotase Alfa

Drug dosing and dosing scheduled varied across clinical trials, with doses ranging from 2.1 mg/kg/week to 9 mg/kg/week and dosing frequency ranging from daily dosing to dosing 3 times weekly. Note that only patients in ENB-010-10 received the proposed labeled dose of 6 mg/kg/week as the starting dose for treatment.

[33] http://www.aaos.org/research/outcomes/outcomes_peds.asp

5.3 Discussion of Individual Studies/Clinical Trials

5.3.1 ENB-011-10 (Infantile-onset HPP Natural History Study)

This was an international, multicenter, retrospective natural history study of patients with severe perinatal- and infantile-onset HPP. The objective of the study was to characterize the natural history of patients with severe perinatal- and infantile-onset HPP. This study served as the non-concurrent historical control group for the pooled efficacy analyses for infantile-onset patients enrolled in ENB-002-08/ENB-003-08 and ENB-010-10.

Patients were eligible for ENB-011-10 if they had a documented diagnosis of HPP disease (i.e., genetic, biochemical, or radiographic evidence of HPP), signs of HPP prior to 6 months of age and had one or more of the following clinical features:

- Respiratory compromise
- Rachitic chest deformity, and/or
- Pyridoxine (vitamin B6)-responsive seizures

Respiratory compromise was defined as respiratory complications (up to and including respiratory failure) that required respiratory support measures and/or medications for symptom(s) management. Patients who had received treatment with asfotase alfa or who had other clinically significant disease were excluded from the study.

The primary outcome measure for the study was overall survival; invasive ventilator-free survival time was the secondary outcome measure.

A total of 48 patients were enrolled from 12 sites in 7 countries, including the US (6 sites), Germany, Australia, Canada, Spain, Switzerland, and Taiwan (1 site each). Data was abstracted from medical records for patients with information available from birth to 5 years of age. Data collection included demographic information, diagnostic history, disease history, developmental history, hospitalization history, medications and therapies, and laboratory data. The data collection period was from September 2012 through April 2013.

Statistical Methods

All available data were used for analysis. For the primary analysis, 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. Survival times were derived using the most complete information available, with highest preference given to complete date, then age, and finally partial date. For missing dates, the day was imputed as 15 and the missing month was imputed as June.

Because the period of diagnosis for enrolled patients spanned several decades, the applicant provided analyses stratified by 3 diagnosis periods (prior to 1990, 1990 through 1999, and 2000 and later) as well as analyses for the overall enrolled population.

Reference ID: 3836304

Study Results

Patient Demographics and Medical History

Table 8 summarizes patient demographics. Of 127 patients identified as potential candidates for participation, 60 patients were pre-screen failures. Of the remaining 67 patients, duplicate records were identified for 2 patients and subsequently 65 patients were screened and 48 patients were enrolled. Seventeen patients were screening failures due to lack of adequate documentation of diagnostic and clinical data needed to confirm eligibility.

Table 8: ENB-011-10- Patient Demographics

Characteristic	Enrolled Patients N=48
Gestational age at Birth (weeks)	
N	36
Mean (SD)	37.9 (2.6)
Median	39.0
Min Max	30, 41
Age at Data Abstraction if Alive (weeks)	
N	13
Mean (SD)	507 (319)
Median	401
Min Max	81, 1030
Sex- n(%)	
Male	26 (54)
Female	22 (46)
Race- n (%)	
American Indian or Alaska Native	1 (2)
Asian	2 (2)
Black or African American	3 (6)
White	40 (83)
Other	2 (4)
Region of Birth- n (%)	
Middle East	1 (2)
North America	33 (69)
Europe	8 (17)
Asia	1 (2)
Australia	2 (4)
Unknown	3 (6)

Diagnostic History

Table 9 summarizes the diagnostic history for enrolled patients.

All but one enrolled patient had at least one of the clinical criteria for study entry (i.e., respiratory compromise, rachitic chest, and/or vitamin B6-responsive seizures); one stillborn patient was included in the study based on clinical findings of pulmonary hypoplasia, radiographic findings, and abnormal ALP levels. Eight of 48 patients (17%) had documentation of all three clinical criteria for HPP.

Reference ID: 3836304

The mean age of onset of symptoms of HPP was at approximately one month old and mean age at time of HPP diagnosis was approximately 5.5 months old (22.5 weeks). Approximately one-third of patients (29%) had signs of HPP in utero. The majority of patients were diagnosed by serum ALP levels (85%) and radiological findings (79%).

Table 9: ENB-011-10- Patient Diagnostic History

Diagnostic History	Enrolled Patients
Age at Onset of HPP (Days)	
N	47
Mean (SD)	32 (51)
Median	1
Min, Max	0, 179
Signs of HPP in utero- n(%)	
Yes	14 (29)
No	15 (31)
Unknown	19 (40)
Age at HPP Diagnosis (Weeks)	
N	47
Mean (SD)	22.5 (40.5)
Median	8.6
Min, Max	0, 178
Diagnosis Confirmation- n (%)	
Serum ALP	41 (85)
Radiological Findings	38 (79)
Sign/Symptoms	25 (52)
Other Diagnostic Testing	
TNSALP Gene Mutation Analysis	17 (35)
Plasma PLP	13 (27)
Urinary PEA	12 (25)
Other	3 (6)

ALP=alkaline phosphatase; PLP= pyridoxal-5'-phosphate; PEA= phosphoethanolamine

Patients enrolled in the study were born between 1970 and 2011. Slightly more than half of enrolled patients were diagnosed with HPP prior to 2000 (27 patients; 56%). As noted earlier, the applicant provided data stratified by the following diagnosis periods; prior to 1990, 1990 through 1999, and 2000 and later. The proportion of patients with respiratory compromise (range across periods was 81% to 86%) and rachitic chest (range across periods was 62% to 93%) was generally similar across diagnosis periods. A lower proportion of patients documented with vitamin B6-responsive seizures was reported for 1990-1999 (0/14 patients) compared to the other two diagnosis periods (range was 23% to 29%).

Disease History

Table 10 summarizes the most common disease histories for enroll patients by age interval from birth to 5 years of age. The most commonly documented disease symptoms were chest deformity, respiratory distress, respiratory failure, failure to thrive, and elevated calcium levels. Almost half of patients had documented respiratory failure prior to age 6 months.

Table 10: ENB-011-10- Patient Disease History

Disease History	Enrolled Patients n=48			
	Birth to 5 Years n=48	<6 months of age n=48	6 months to 3 years of age n=27	>3 to 5 years of age n=13
	n (%)			
Chest deformity	39/43 (91)	28/35 (80)	22/23 (96)	10/12 (83)
Respiratory distress	30/39 (77)	25/39 (64)	10/20 (50	2/11 (18)
Failure to thrive	28/37 (76)	24/36 (67)	19/21 (91)	7/11 (64)
Respiratory failure	26/36 (72)	18/38 (47)	8/19 (42)	0/11 (0)
Elevated serum or urine calcium	28/39 (72)	26/38 (68)	14/19 (74)	2/11 (18)
Respiratory tract infections	21/33 (64)	13/31 (42)	15/19 (79)	5/11 (46)
Craniosynostosis	19/31 (61)	15/30 (50)	14/19 (74)	7/11 (64)
Nephrocalcinosis	16/31 (52)	11/31 (36)	10/16 (63)	4/10 (40)
Early tooth loss	10/23 (44)	0/24 (0)	10/14 (71)	7/9 (78)
Pneumonia	15/36 (42)	6/34 (18)	10/20 (50)	2/11 (18)
Vitamin B6-responsive seizures	7/35 (20)	6/36 (17)	3/21 (14)	0/11 (0)
Low serum phosphate	5/25 (20)	2/29 (7)	3/17 (18)	0/10 (0)
Delayed fracture healing	5/28 (18)	2/26 (8)	4/15 (27)	1/11 (9)

Source: ENB-011-10 Final Clinical Study Report (dated January 22, 2014), Table 8

The applicant noted some shifts in disease history over time, with greater proportions of patients diagnosed with respiratory failure prior to 1990 (>90% of patients) compared to 1990 and later (63%-67% of patients). Conversely, greater proportions of patients were diagnosed with failure to thrive (88% vs. 45% of patients) early tooth loss (50%-64% vs. 0% of patients), nephrocalcinosis (44%-69% vs. 33% of patients), and pneumonia (45%-50% vs. 27% of patients) from 1990 onward compared to prior to 1990. Some diagnosis history trends were stable across diagnosis periods, including craniosynostosis (50%- 69% of patients) and tachypnea and respiratory distress (between 60% and 70% of patients) The applicant noted that the observed shifts may be due to a number of factors, including earlier mortality or differences in record-keeping in the pre-1990 diagnosis period compared with later periods.

Reviewer Comments:
As discussed later, the survival rate in the natural history population increased over time. This appears to be due to improved standard of care, rather than differences in disease severity between the three diagnosis periods. Note that the proportion of patients with non-acute disease features (e.g., failure to thrive) or disease features that manifest later in the disease course (e.g., early tooth loss) increased over time, concurrent with the rise in survival across the three diagnosis periods. Table 11 summarizes disease history stratified by patient status (alive or dead) and diagnosis

period. Note that the proportions of patients with a particular disease history were generally similar for the diagnosis periods from 1990 and later. For example, equal proportions of deceased patients had failure to thrive (80%); similar numbers of patients still living had early tooth loss (75% vs. 100%). Respiratory failure and the presence of vitamin B6–responsive seizures appear to be predictors for a worse prognosis. Note that no surviving patients had a disease history of respiratory failure or vitamin B6–responsive seizures.

Table 11: ENB-011-10- Common Disease Histories (Documented for >5 patients in Either Group) Among Deceased and Alive Patients

	Enrolled Pts					
	Deceased n=35			Alive N=13		
Disease History	**Prior to 1990 n=13**	**1990 through 1999 n=10**	**From 2000 n=12**	**Prior to 1990 n=0**	**1990 through 1999 n=4**	**From 2000 n=9**
	n (%)					
Respiratory failure	10/11 (91)	6/6 (100)	10/10 (100)	0/0	0/3(0)	0/6 (0)
Respiratory distress	10/12 (83)	7/7 (100)	9/10 (90)	0/0 (0)	2/4 (50)	2/6 (33)
Chest deformity	7/11 (64)	9/9 (100)	10/10 (100)	0/0 (0)	4/4 (100)	9/9 (100)
Craniosynostosis	5/10 (50)	3/4 (75)	2/5 (40)	0/0 (0)	2/4 (50)	7/8 (88)
Failure to thrive	5/11 (46)	4/5 (80)	8/10 (80)	0/0 (0)	4/4 (100)	7/7 (100)
Respiratory tract infection	5/12 (42)	5/6 (83)	3/5 (60)	0/0 (0)	3/4 (75)	5/6 (83)
Nephrocalcinosis	3/9 (33)	3/5 (60)	5/7 (71)	0/0 (0)	1/4 (25)	4/6 (67)
Vitamin B6-responsive seizures	2/11 (18)	0/5 (0)	5/9 (56)	0/0 (0)	0/4 (0)	0/6 (0)
Early tooth loss	0/6 (0)	0/2 (0)	0/4 (0)	0/0 (0)	3/4 (75)	7/7 (100)

Source: ENB-011-10 Final Clinical Study Report (dated January 22, 2014), Table 11

Respiratory Support

Requirements for respiratory support differed between deceased and surviving patients (see Table 12). A majority of deceased patients (81%) required respiratory support, primarily invasive ventilation (approximately two-thirds of all deceased patients who received respiratory support required invasive ventilation). In contrast, only about one quarter of surviving patients required any form of respiratory support, primarily non-invasive forms of support (two-thirds of surviving patients received supplemental oxygen).

Table 12: ENB-011-10- Requirements for Respiratory Support of Enrolled Patients Up to 5 Years of Age

Category	Enrolled Patients n=48		
	All Patients n=48	Patients Deceased n=35	Patients Alive n=13
Patients requiring respiratory support- n(%)	29/45 (64)	26/32 (81)	3/13 (23)
Maximum respiratory support required			
•Invasive ventilation- n(%)	19/29 (66)	18/26 (69)	1/3 (33)
•Supplemental O2- n(%)	9/29 (31)	7/26 (27)	2/3 (67)
•CPAP- n(%)	1 (3)	1 (4)	0
•BiPAP- n(%)	0	0	0

The mean age for first support (SD) was 13 weeks (18 weeks), with a median of zero weeks and range of 0-59 weeks. Mean ages for maximum and last support were 16 (20 weeks) and 26 (40) weeks, respectively. The majority of patients (57%) required first support within the first week of life and approximately half of patients (48%) were started on maximum support within the first week of life. The applicant noted that all 13 patients who were alive at the time of data abstraction were reported to have no current requirements for any form of respiratory support. Figure 2 summarizes patient age at the first occurrence of respiratory support.

Figure 2: ENB-011-10- Age at Occurrence of Respiratory Support

Source: ENB-011-10 Final Clinical Study Report (dated January 22, 2014), Figure 2

Radiological Findings

Radiological data were available for 20 to 37 patients, depending on the finding. The most frequently reported bone abnormalities present at the time of diagnosis were osteopenia and rachitic chest deformity (>85%), metaphyseal abnormalities (>60%), physeal widening (55%), and long bone bowing (48%). Table 13 summarizes radiological finding at the time of diagnosis.

Table 13: ENB-011-10- Radiological Findings

Radiological Findings	Enrolled Patients n=48
Osteopenia- n(%)	33/37 (89)
Rachitic chest/deformed ribs n(%)	32/37 (87)
Metaphyseal fraying- n(%)	19/28 (68)
Metaphyseal flaring- n(%)	20/30 (67)
Metaphyseal radiolucencies ("tongues")- n(%)	15/24 (63)
Physeal widening- n(%)	12/22 (55)
Long bone bowing- n(%)	14/29 (48)
Thin gracile bones- n(%)	12/27 (44)
Sclerosis- n(%)	6/20 (30)
Bony spurs- n(%)	6/23 (26)
Facture (non-union)- n(%)	7/30 (23)
Absence of some/all bones- n(%)	7/30 (23)

Source: ENB-011-10 Final Clinical Study Report (dated January 22, 2014), Table 13

Hospitalization

A majority of deceased (77%) and surviving patients (92%) required hospitalization for disease-related complications, most commonly respiratory conditions and craniosynostosis (see Table 14).

Table 14: ENB-011-10- Hospitalizations

Hospitalizations	Enrolled Patients N=48			
	All Patients		Deceased (n=35)	Alive (n=13)
Reasons	Events	Patients n(%)	Patients n(%)	Patients n(%)
Any reason	133	39 (81)	27 (77)	12 (92)
All respiratory compromise	46	22 (46)	18 (51)	4 (31)
Respiratory failure	5	2 (4)	2 (6)	0
Respiratory distress	21	12 (25)	11 (31)	1 (8)
Others	20	11 (23)	7 (20)	4 (31)
Seizure-related	8	7 (15)	6 (7)	1 (8)
Craniosynostosis	16	9 (19)	4 (11)	5 (39)
Renal-related	3	2 (4)	1 (3)	1 (8)
Others	62	28 (58)	16 (46)	12 (92)

Medications and Other Therapies
Approximately two-thirds of patients (31/48; 65%) used medications or other therapies for treatment of HPP-related disease. Medication classes and therapies used by 5 or more patients included adrenergic inhalants, antiepileptics, nonsteroidal anti-inflammatory agents, systemic corticosteroids, diuretics, and vitamin preparations (pyridoxine).

TNSALP Gene Mutation Analysis
Nineteen of 48 patients (40%) had an identified TNSALP gene mutation.

Developmental History
Data on motor development were available for 27/48 patients (57%). Of these patients, 24/27 (89%) had delayed motor development up to 5 years of age, including 23 patients with gross motor delays and 2 patients with fine motor delays.
Data on cognitive development were available for 19/48 patients (40%), with cognitive delays being reported in 3 patients during development up to 5 years of age.

5.3.2 ENB-002-08 & Extension Study ENB-003-08 (Infantile-Onset HPP Pivotal Trial)

ENB-002-08 was a 6-month, Phase 2, multicenter, open-label trial to evaluate the safety, tolerability, and pharmacology of asfotase alfa in patients <36 months of age with infantile-onset HPP (defined as onset of first signs or symptoms in utero or before 6 months of age). Ten of 11 patients enrolled in ENB-002-08 completed the trial. The trial was conducted at 10 sites in Canada, United Arab Emirates, United Kingdom (2 sites), and the United States (6 sites). The trial period was from October 2008 to May 2010.

ENB-003-08 is an ongoing extension study for ENB-002-08 to evaluate the long-term safety and efficacy of treatment with asfotase alfa for up to 60 months. The interim clinical study report for ENB-003-08 included efficacy and safety data up through the data analysis cut-off date of October 29, 2014. At the time of the data analysis cut-off date, nine patients had received at least 48 months of treatment with asfotase alfa and were continuing treatment in ENB-003-08. The analysis populations included patients who withdrew from the trials or died (2 patients).

Eligibility criteria included diagnosis of severe HPP defined as:

- biochemical abnormalities (decreased ALP and increased PLP)
- radiographic evidence of HPP
- rachitic chest deformity and/or vitamin-B6-dependent seizures,
- one or more HPP-related findings (e.g., craniosynostosis)
- failure to thrive

Exclusion criteria for ENB-002-08 included the following:

- 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(0H) vitamin D
- Evident of a treatable form of rickets
- Prior treatment with bisphosphonate

Patients were excluded from continuing treatment in ENB-003-08 if they had a history of sensitivity to asfotase alfa, had a clinically significant disease precluding trial participation, or if they had enrolled in any other investigational trial for treatment of HPP (e.g., bone marrow transplantation).

The primary objectives of ENB-002-08 were to assess the efficacy, safety, and tolerability of single and multiple doses of asfotase alfa in patients with infantile-onset

HPP. The primary objectives of ENB-003-08 were to assess the long-term tolerability and efficacy of asfotase alfa in treating rickets in patients with infantile-onset HPP. Other objectives of ENB-002-08 were to assess the PK, bioavailability, and pharmacodynamics (PD) of asfotase alfa and to assess its effect on mortality, growth and development, and other clinical signs and symptoms of HPP. Other objectives of ENG-003-08 were to assess long-term PK and PD of asfotase alfa and to assess its effect on mortality, growth and development, and other clinical signs and symptoms of HPP.

ENB-002-08 Protocol Amendments

No region-specific protocols were written for the trials. There were 5 protocol amendments to ENB-002-08 (Amendments 1, 1.A, 1.B., 1.C, and 2) implemented between September 22, 2008 and Jun 12, 2009. Key changes to the trial protocol included raising the age criterion to ≤36 months (original age criterion was ≤18 months) and increasing patient enrollment (original enrollment target was 6 patients) and study sites, addition of efficacy and safety assessments, and adjustments to dosing and the dose escalation schedule.

Changes to efficacy assessments included use of the BSID-III in place of the Alberta Infant Motor scale for motor assessment, and addition of assessments of historical skeletal x-rays and physical therapy assessments. Additional safety assessment included closer monitoring during drug administration, renal ultrasounds, parathyroid hormone and urinary calcium assessments, and inclusion of guidelines for home treatment and management of injection- and infusion-associated reactions, and modification of the infusion rate to minimize infusion-associated reactions.

Protocol amendments to drug dosing and administration included changing the dosing schedule from every other day to 3 times per week and allowing for a dose adjustment if a patient experienced clinical decline (Amendment 1 dated September 22, 2008) and a revision of the dose escalation schedule to allow dose escalation after an interim safety/PK review (Amendment 1.A dated November 20, 2008).

A region-specific amendment for Canada increased subcutaneous doses from 1 mg/kg to 3 mg/kg administered 3 times per week based on a PK data review (Amendment 2 dated November 10, 2008).

ENB-003-08 Protocol Amendments

There were 9 protocol amendments to ENB-003-08 implemented between March 12, 2009 and June 11, 2014. Amendment 2 (dated June 15, 2009) amended the protocol to align with protocol changes made in ENB-002-08, including increase in patient enrollment and study sites. Administrative changes included changing to use of a central laboratory for laboratory assessments (Amendment 3 dated February 1, 2010). The trial duration was also extended to up to 84 months or until regulatory approval

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(Amendment 7 dated December, 2013 and Amendment 8 [UK-specific] dated February 10, 2014). Other key changes to the trial protocol included additions to and modifications of efficacy and safety assessments, and adjustments to the dose escalation schedule.

Additional efficacy assessments included the PDMS-2, ventilator support assessments (Amendment 4 dated February 4, 2011), and BOT-2 (Amendment 6 dated February 21, 2012). In addition, the RGI-C scoring system was changed from a 5-point to a 7-point scale (Amendment 4 dated February 15, 2011). Key changes to safety assessments included the replacement of fundoscopic examinations with more comprehensive ophthalmologic examinations (Amendment 7 dated December 5, 2013). The applicant noted that, as per the suggestion of Health Canada (and FDA concurrence), provisions for dose increases for lack of efficacy were included in the protocol.

Changes in the Statistical Analysis Plan (SAP)

After acquiring sponsorship of asfotase alfa, the applicant developed a combined statistical analysis plan (SAP) for ENB-002-08 and ENB-003-08, with change in RGI-C as the primary efficacy endpoint and overall survival as an additional analysis (SAP Version 2.0 dated February 7, 2013). In addition, PK analyses were removed from the SAP to be performed by the applicant's Clinical Pharmacology Group. Following post-Breakthrough Designation meeting discussions with the Division in 2013, the applicant changed the primary efficacy endpoint for the infantile-onset population to overall survival, performing a pooled analysis of survival data from ENB-002-08/ENB-003-08 and ENB-010-10 (see Section 6 for pooled analysis results). Ventilator-free survival was evaluated as a secondary endpoint. This change in statistical analysis was implemented in SAP Version 5.0 (dated July 29, 2014). SAP Version 5.0 also addressed changes in statistical analyses for the juvenile-onset population.

Treatment

- **Dosing**

In ENB-002-08, patients received a single IV infusion of 2 mg/kg of asfotase alfa. The purpose of the initial IV infusion was to calculate the bioavailability of asfotase alfa when delivered subcutaneously. After a washout period of 7 days, patients were administered SC injections of 1 mg/kg asfotase alfa 3 times per week (total 3 mg/kg per week) up to a maximum of 40 mg per SC injection. The initial SC dose was based on a NOAEL in rats of 30 mg/kg/week IV.

Dose adjustments were allowed for changes in weight and/or for safety concerns or for lack of efficacy, with a maximum allowed dose per SC injection of 40 mg. Lack of efficacy was defined by three outcomes: no radiographic improvement in rickets, deterioration of pulmonary function, and worsening failure to thrive. Dosing adjustments could be made as follows:

- After 1 month of treatment, the dose could be increased to 1.5 mg/kg (later changed to 2 mg/kg) 3 times per week if at least 2 of the 3 outcomes were evident
- After 3 months of treatment, the dose could be increased to 2 mg/kg 3 times per week if a patient failed to improve in only one of the outcomes
- After 3 months of treatment, the dose could be increased to 3 mg/kg 3 times per week if a patient failed to improve in 2 of the 3 outcomes

The initial dose in ENB-003-08 was the same as the final dose being administered in ENB-002-08.

Assessments

- **ENB-002-008**

All initial trial treatments and assessments were performed in-hospital at the trial site. After a screening visit to assess eligibility, baseline evaluations were performed and treatment was initiated. Patients remained in the hospital for at least 1.5 to 2 weeks of SC injections. Once discharged, patients received injections in a medical facility until at least Week 12. After Week 12, if there were no safety concerns, the patient's parents/guardians were trained on SC injections and administered the injections at home for the remainder of the trials. Initial home injections were performed under medical supervision.

- **ENB-003-08**

The final visit of Study ENB-002-08 was allowed to serve as the baseline visit for ENB-003-08. Subsequent visits were scheduled every 3 months for the first 12 months of ENB-003-8 and then every 6 months. Patients who were not receiving injections at home at the time of enrollment into ENB-003-08 continued to received infections at a medical facility or at home under medical supervision for the first 3 months of the trial. At the Month 3 visit, the investigator could allow unsupervised injections at home if the patient had not had recurrent injection-associated reactions (IARs) or had not had one or more severe IARs within the first 3 months of ENB-003-08.

Efficacy assessments in both trials included radiographic assessments for rickets (RGI-C and Rickets Severity Scale [RSS]), growth measurements (height/length, weight, head circumference, and chest circumference), and gross motor function (BSID-III). ENB-300-08 also included the PDMS-2 and BOT-2 assessments, dental assessments, nutritional assessments, and physical therapy assessments (as needed based upon the individual needs of the patient).

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Pharmacodynamic assessments included plasma PPi and PLP, urinary calcium:creatinine ratio, and parathyroid hormone. Overnight urinary PPi was also assessed in ENB-002-08.

Safety assessment included adverse events (AEs), infusion-/injection-associated reactions (IARs), vital signs, physical examinations, laboratory tests, antibody testing, and concomitant medications and therapies. Fundoscopic examinations and renal ultrasound were also performed to monitor for ectopic calcifications in small blood vessels of the eye and in the kidney. As noted earlier, full ophthalmologic examinations replaced fundoscopic examinations as assessments for ectopic calcifications of the eye. An independent DSMB was established for the trials to perform ongoing and ad hoc safety data reviews.

Radiographic findings were reviewed by central radiologists. Laboratories evaluations were initially performed at local laboratories but were later performed centrally.

See Table 56 and Table 57 in the Appendix for summaries of the assessments schedules for ENB-002-08 and ENB-003-08, respectively.

- **Patient Disposition**

Patient Disposition

Nine patients were continuing treatment in ENB-003-08 as of the October 29, 2014 analysis cutoff date for the interim clinical study report. Ten of 11 patients enrolled in ENB-002-08 completed the trial and continued participation in ENB-003-08. One patient (Patient 002-03-01) withdrew from ENB-002-08 after the initial IV infusion due to a hypersensitivity reaction characterized by fever, chills, and irritability. One patient (Patient 002-08-01) died of sepsis while enrolled in ENB-003-08 after about 30 weeks of treatment. Table 15 summarizes patient disposition for ENB-002-08/ENB-003-08.

Table 15: ENB-002-08/ENB-003-08- Patient Disposition

Disposition	All patients (n=11)
Enrolled- n (%)	11 (100)
Treated- n (%)	11 (100)
Discontinued from ENB-002-08- n (%) • AE	1 (9)
Completed ENB-002-08- n (%)	10 (91)
Discontinued from ENB-003-08- n (%) • Death	1 (9)
Ongoing in ENB-003-08- n (%)	9 (82)

Source: ENB-002-08/ENB-003-08 Interim Clinical Study Report (dated April 15, 2015), Table 10

Demographics

The age range of patients was 3 to 158 weeks (mean age was 59 weeks) when they first received study drug. The majority of patients were white (10/11; 91%) and more than half were female (7/11; 64%). At baseline, all but one patient had some degree of respiratory compromise and about half of the patients (5/11; 46%) required respiratory support. Eight of 11 patients (73%) had nephrocalcinosis at baseline. Baseline mean z-scores for length/height and weight were well below the 3rd percentile for age (z-scores were at 0 percentile for both parameters). Three patients did not meet one of the biochemical or clinical eligibility criteria. Three patients had ALP levels that were not below the protocol specified level of >3 standard deviations below lower limits of normal and one neonatal patient did not meet the protocol definition of failure to thrive. However, all 11 patients had confirmed genetic mutations of the TNSALP gene, including 10 patients with compound heterozygote mutations and one patient with a homozygote mutation.

Table 16 and Table 17 summarize baseline patient demographics and clinical findings for patients at entry into ENB-002-08.

Table 16: ENB-002-08/ENB-003-08- Baseline Patient Demographics

Characteristic	Asfotase Alfa (n=11)
Age (weeks)	
Mean (SD)	59 (59)
Min, Max	3, 158
Sex- n(%)	
Male	4 (36)
Female	7 (64)
Ethnicity- n(%)	
Hispanic or Latino	1 (9)
Not Hispanic or Latino	10 (91)
Race- n(%)	
White	10 (991)
Other	1 (9)
Ventilation Status- n(%)	
No support	6 (55)
CPAP	1 (9)
Mechanical Ventilation	3 (27)
Other	1 (9)
RSS Score (n=10)	
Mean (SD)	8.3 (1.7)
Min, Max	5.5, 10
Scale: 0 (normal) to 10 (severe rickets)	
Length Z-score	
Mean (SD)	-4.1 (2.2)
Min, Max	-9.2, -0.7
Weight Z-score	
Mean (SD)	-3.4 (1.5)
Min, Max	-5.4, -0.5
Genetic Mutation Analysis	
Yes	11(100)
No	0
Plasma PPI (μM) (n=8)	
Mean (SD)	5.59 (2.26
Min, Max	2.91, 10.48
(Reference range: 1.33 to 5.71 μM)	
PLP (ng/mL) (n=9)	
Mean (SD)	380.0 (256.65)
Min, Max	100, 880
(Reference range: 11.76 to 68.37 ng/mL)	

Table 17: ENB-002-08/ENB-003-08- Baseline Patient Clinical Findings

Parameter	Asfotase Alfa n=11
Abnormally shaped chest- n(%)	
Yes	6 (55)
No	5 (45)
History of respiratory compromise- n(%)	
Yes	10 (91)
No	1 (9)
Seizures- n(%)	
Yes	1 (9)
No	10 (91)
Difficulty gaining weight, failure to thrive, and/or difficulty eating swallowing- n(%)	
Yes	10 (91)
No	1 (9)
High/abnormal serum calcium - n(%)	
Yes	8 (73)
No	3 (27)
Nephrocalcinosis- n(%)	
Yes	8 (73)
No	3 (27)
Fractures- n(%)	
Yes	6 (55)
No	5 (45)
Craniosynostosis- n(%)	
Yes	3 (27)
No	8 (73)

Reviewer Comments:
I compared disease history for ENB-002-08/ENB-003-08 patients with the disease history of all patients (i.e. alive and deceased patients; n=21) in the most recent historical control cohort (patients diagnosed with HPP from 2000 and later). Generally, the level of disease severity was similar between the two groups. In both groups, almost all patients (>90%) had a history of respiratory complications and failure to thrive. Similar proportions of patients had a history of nephrocalcinosis (approximately 70% of patients in both groups). However, a smaller proportion of patients in ENB-002-08/ENB-003-08 had a history of craniosynostosis and vitamin B6-responsive seizures compared to the 2000 and later historical cohort. Approximately one quarter of ENB-002-08/ENB-003-08 had a history of craniosynostosis compared to almost 50% of historical controls. Fewer than 10% of ENB-002-08/ENB-003-08 patients had a history of vitamin B6-responsive seizures compared to about one quarter of the historical controls.

Although only 5/11 ENB-002-08/ENB-003-08 patients (45%) required respiratory support at trial entry, 9/11 patients (81%) had required some level of respiratory support in the past.

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Concomitant Medications and Therapies

Concomitant medications were summarized by WHO ATC Class. All 11 patients received concomitant medications during the trial. The most commonly used medications were analgesics/antipyretics (100%), beta-lactam antibacterials (91%), systemic antihistamines, antibacterial penicillins, and vaccines (82 % each). Table 18 summarizes concomitant medications used by 50% or more patients enrolled in the trial.

Table 18: ENB-002-08/ENB-003-08- Concomitant Medications

Medication	n(%)
Analgesics/antipyretics	11 (100)
Beta-lactam antibacterials/penicillins	10 (91)
Bacterial vaccines	9 (82)
Antihistamines for systemic use	9 (82)
Hypnotics & sedatives	9 (82)
Viral vaccines	9 (82)
Antithrombotic agents	8 (73)
IV solutions	8 (73)
Drugs for peptic ulcer and GERD	7 (64)
Emollients	7 (64)
General anesthetics	7 (64)
Inhalants, adrenergics	7 (64)
Oxygen	7 (64)
Opioids	7 (64)
Antipruritics	6 (55)
Blood and related products	6 (55)
Combined bacterial and viral vaccines	6 (55)
Decongestants	6 (55)
Iron preparations	6 (55)
Laxatives	6 (55)
Multivitamin combinations	6 (55)
Systemic corticosteroids	7 (64)

Ten of 11 patients underwent non-medication interventions for HPP-related complications during the trial, such as feeding tube and central line placement, orthopedic casting and bracing, surgery for craniosynostosis, and tracheostomy. Six of 11 patients (55%) also required physical, speech, and/or occupational therapy.

Protocol Deviations

Twenty-five major protocol deviations were reported for 8 patients.[34] The most frequent types of major deviations were nonconformance with the informed consent procedure (5

[34] The applicant used a standard definition of major deviations across clinical trials, defining major deviations as deviations "that could potentially impact the rights, welfare, or safety of the patient and/or the integrity of the study data."

patients), nonconformance with AE recording/reporting (3 patients), and eligibility criteria not met (3 patients). Minor protocol deviations were reported for all 11 patients. The majority of minor deviations (216/248 deviations; 87%) were due to missing an assessment/procedure (144 deviations reported for 11 patients) or an assessment/ procedure that was done outside of the specified time window (72 deviations reported for 10 patients).

Overall, compliance with treatment was high. Seven patients missed drug doses during the trial. Four patients missed a total of 3 to 4 doses intermittently. Two patients missed 9 consecutive doses due to hospitalization or problems with drug shipment; one patient missed at least 10 doses intermittently. Table 19 summarizes information for patients who missed drug doses.

Table 19: ENB-0002-08/ENB-003-08- Missed Doses

Patient ID	Visit Window of Missed Dose	Total # of Missed Doses
002-01-01	Month 18 to Month 24 Month 24 to Month 30 Month 30 to Month 36	1 1 1
002-02-01	Baseline to Month 3 Month 6 to Month 9 Month 20 to 27 Month 30 Month 42 to Month 48 Month 54 to Month 60 Month 60 to month 66	2 or 3 (no doses over 5 days) 1 Unknown- parents did not complete dosing diary 3 doses- patient was hospitalized 1 2 1
002-04-01	Month 6 to Month 9	9- delayed drug shipment
002-04-02	Month 6 to Month 9	4- delayed drug shipment
002-05-01	Month 12 to Month 15 Month 15 to Month 18	1 3
002-06-01	Month 24 to Month 30 Month 30 to Month 36 Month 42 to Month 48 Month 48 to Month 54	1 1 1 1
002-08-01	Month 8	9- patient was hospitalized, died

Source: ENB-002-08/ENB-003-08 Interim Clinical Study Report (dated April 15, 2015), Listing 16.2.5.1.3.0

Reviewer Comments:
Based on my review of the data, the reported protocol deviations did not appear to affect the efficacy and safety analyses.

Dose Adjustment
Following an intravenous dose of 2mg/kg, the starting dose of asfotase alfa was 3 mg/kg/week administered as 1 mg/kg 3 times per week.[35] All ten patients completing ENB-0002-08 received dose increases during the extension phase, including 3 patients due to a dosing error or shortage of study drug (the patients had initially received decreased doses), 4 patients due to weight increase, and 6 patients due to lack of efficacy. Of the 6 patients whose doses were increased due to lack of efficacy, 4 patients received dose increases of 6 mg/kg/week, one patient (Patient 002-02-01) received a dose increase of 9 mg/kg/week, and one patient (Patient 002-09-02) received a dose increase of 12 mg/kg/week.

Reviewer Comments:
As discussed in Section, all but one ENB-002-08/ENB-003-08 patient (Patient 002-09-02) experienced improvement in one or more clinical parameters (respiratory status, RGI-C score, height and/or weight z-score) after dosing was increased to doses of 6 mg/kg/week or higher.

Efficacy Summary
Trial findings for ENB-002-08/ENB-003-08 provide supportive evidence of an efficacy claim of an efficacy claim for asfotase alfa for treatment of perinatal/infantile-onset HPP at doses of 6 mg/kg/week to 9 mg/kg/week. Nine of 11 patients enrolled in the trial were alive and continuing on treatment at the time of data analysis cutoff; one patient discontinued due to a hypersensitivity reaction during her initial treatment and one patient died of sepsis after about 30 weeks of treatment. Ten of 11 patients had a prior history of respiratory support or required respiratory support at some point in the trial; all 9 patients continuing treatment required no respiratory support at last assessment.

A majority of patients experienced clinically significant improvements in growth, most notably in weight gain. Nine of 10 patients who entered the extension study had severe growth retardation, with baseline height and weight z-scores below the 3rd percentile for age. A majority of patients experienced improvements in both height and weight-scores. All 7 patients who experienced improvements in weight z-scores had weights within the normal range for age at last assessment. Six patients experienced improvement in height z-scores, including 3 patients who also achieved heights within the normal range for age at last assessment.

[35] One patient (Patient 002-10-01) did not receive an intravenous dose of asfotase alfa because she was being treated with pyridoxine for seizures. Because pyridoxine raises plasma PLP levels (PLP is a form of vitamin B6 that crosses the blood-brain barrier), there was a concern that an acute rise in alkaline phosphatase activity following intravenous dosing could result in vitamin B6 central nervous system toxicity (see Section 7.5.5 for a further discussion of drug-drug interactions).

All nine patients continuing on treatment achieved and sustained RGI-C scores of 2 or higher, meeting the applicant's responder criterion for substantial improvement of rickets; the patient who died during the trial also was a RGI-C responder. RSS scores also improved for all 9 patients over time, with 8 patients achieving RSS scores <1.5 at last assessment, indicating mild rickets.

The time to response was similar for growth and radiographic findings, with the majority of patients experiencing sustained improvements from Month 6 onward.

Gross motor function assessment trends also generally indicated improvement from baseline. However, the interpretability of these assessments was limited due to the small number of patients, and the lack of baseline assessments for a majority of patients.

The starting dose of asfotase alfa for all patients was 3 mg/kg/week. All but one patient experienced improvement in one or more clinical parameters (respiratory status, RGI-C score, and/or growth parameters) after dosing was increased to doses of 6 mg/kg/week or higher.

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5.3.3 ENB-010-10 (Infantile-onset HPP Pivotal Trial)

This is an ongoing international, multicenter, open-label trial of the safety, efficacy, and PK of asfotase alfa in infants and children <5 years old with HPP. Patients <5 years old are eligible for ENB-010-10 if they had a documented diagnosis of HPP and onset of symptoms prior to 6 months of age. Patients are excluded from the trial if they meet any of the following exclusion criteria:

- other clinically significant disease
- low serum calcium phosphate, or vitamin D levels[36]
- current evidence of treatable form of rickets
- prior treatment with bisphosphonates
- enrollment in any other trial involving an investigational therapy for HPP

The primary objectives of ENB-010-10 are to determine the effect of asfotase alfa treatment on skeletal manifestations of HPP and to determine the safety and tolerability of repeated SC injections of asfotase alfa. Other objectives of ENB-010-10 are to evaluate the effects of asfotase alfa treatment on respiratory function, growth, and development, PK, and disease biomarkers.

ENB-010-10 Protocol Amendments

There are regional-specific protocols for ENB-010-10 for the following 4 regions: US/Canada/Taiwan/Turkey, European Union, non-European Union countries (except for Japan), and Japan. Regional-specific protocols shared common eligibility criteria and study objectives and study assessments but had minor differences in assessments. In addition, the initial protocol for Japan did not allow for home administration of injections. There was one major amendment made to the protocol used at sites in the US, Canada, Taiwan and Turkey.

Amendment 1 (dated October 13, 2011)

- Extended the duration of the trial to 24 months or until regulatory approval was obtained
- Added BOT-2 assessments
- Removed the maximum age criterion (<9 months of age) for inclusion in analysis of survival and the related requirement to enroll a minimum of 15 patients <9 months of age
- Add a requirement that critically affected patients < 6 months of age remain at the trial site for the first 24 weeks of the trial
- Allowed enrollment of patients with elevated PLP if they were receiving pyridoxine for treatment of seizures
- Revised dosing language to allow for flexibility in dosing frequency and maximum dose allowed for dose adjustments

[36] Patients with low vitamin D levels are eligible for enrollment after correction of levels with vitamin D supplements.

- Allowed optional continued use of the BSID-III beyond the age cut-off (42 months) for patients with severe developmental delay
- Removed use of patient diaries for recording dosing information between visits

The protocol was also amended to increase enrollment to 60 patients and to allow enrollment outside of the EU (specifically, Australia, Germany, Italy, Saudi Arabia, Spain, and the UK) and to extend the duration of treatment to 48 months or until the product became commercially available (Amendment 5, Version 8.0 dated January 24, 2013).

Two additional amendments were approved prior to the data analysis cut-off date for the submission but were not implemented until after the cut-off date (Amendment 8 dated June 2, 2014 and Amendment 9 dated September 15, 2014). The amendments further expanded patient enrollment to 80 patients, study sites to 25 sites and study duration to 72 months (48 months in the UK). Amendment 8 created one global protocol for all regions except Japan. The amendments also implemented the following changes to efficacy and safety assessments:

Amendment 8 (dated June 2, 2014)

- Updated wording regarding dose adjustments for efficacy or safety reasons
- Added full ophthalmology examinations to better characterize ectopic calcifications
- Created a new DMC charter (no longer required ad hoc review and stopping rules by DMC)
- Some x-ray assessments were made optional, depending on level of patient improvement

Amendment 9 (dated September 15, 2014)

- Clarified exclusion criterion for use of bisphosphonates (chronic use within 2 years of study entry was prohibited)
- Added plans for PK and PD analyses
- Added more assessments to evaluate for injection-associated reactions

In addition, there were region-specific amendments for Germany, Japan, and France. The initial German protocol was identical to Amendment 1 for the US/Canada/Taiwan/ Turkey protocol. The German protocol was further amended four times. Changes to the protocol included extending treatment duration to 48 months or until the product became commercially available. The protocol was also amended to establish a maximum treatment dose of 9 mg/kg/week.

The initial Japanese protocol did not include a home injection procedure and required hospitalization of all patients for the first week of treatment. The protocol was

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subsequently amended to allow home injections. The protocol was also amended to increase patient enrollment numbers and allow vitamin D levels obtained within 3 months of the screening visit to be used to determine eligibility.

A France-specific amendment established a maximum treatment dose of 9 mg/kg/week.

Changes to Planned Analyses
The original statistical analysis plan included an analysis of change in RGI-C from baseline to week 24 as the primary analysis. The SAP was changed to include analyses of overall survival and ventilator-free survival time in a pooled analysis of ENB-002-08/ENB-003-08 and ENB-010-10 data as the primary efficacy analysis for the FDA. At the request of the EMA, the applicant also added an analysis of change in RGI-C from baseline to Week 48. Other changes included the addition of RSS analyses. An analysis of infusion- associated reactions was dropped due to incomplete dosing information and change in methodology for identifying infusion- associated reactions. PK analyses were reported in a separate report.

Reviewer Comments;
The study protocol for ENB-010-10 was consistent across regions in terms of eligibility criteria, study drug dosing and study assessments. The minor variations in the schedule of assessments consisted primarily of additional safety assessment s implemented at some sites (Germany and Japan). Thus, there did not appear to be any significant differences in study implementation across study sites or study regions. As noted earlier, the changes in the statistical analysis plan for the primary efficacy analyses of overall survival and ventilator-free survival were agreed upon with the Division.

The applicant included analyses of infusion- and injection-associated reactions in the integrated safety summary (ISS) submitted for the application.

Treatment
Dosing
In ENB-010-10, patients received 6 mg/kg/week of asfotase alfa, administered as either 1 mg/kg 6 times per week or 2 mg/kg 3 times per week.

As noted earlier, the maximum allowed dose per the German and French protocols was 9 mg/kg/week. Dose adjustments were allowed for changes in weight and/or for safety concerns, tolerability issues, or for lack of efficacy. Indications of lack of efficacy included (but were not specifically limited to):

- 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)

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- Acute decline in respiratory status indicated by intubation with difficulty weaning from mechanical ventilation within 30 days

Reviewer Comments:
As noted earlier, patients in ENB-010-10 were the only patients in clinical trials who received the proposed labeled dose of asfotase 6 mg/kg/week as their starting dose for treatment.

Assessments
Efficacy, safety, PK and PD assessments for ENB-010-10 were the same as those for ENB-002-08/ENB-003-08. An independent DSMB performed regularly scheduled and ad hoc safety reviews.

All initial trial treatments and assessments were performed in-hospital at the trial site. After a screening visit to assess eligibility, baseline evaluations were performed and treatment was initiated. Patients younger than 6 months of age who were critically ill due to respiratory compromise and/or seizures remained at the site for the first 24 weeks of treatment. Otherwise, patients received injections at study visits or at home. Home injections were administered under the guidance of a home are nurse for at least the first 4 weeks of treatment.

Patients treated under the Japanese protocol were hospitalized for the first week of the trial, regardless of disease severity and home injections initially were not allowed.

See Table 58 in the Appendix for a summary of the assessments schedule for ENB-010-10.

Statistical Analysis
The primary efficacy analysis for the infant-onset population was overall survival and ventilator-free survival, based on a pooled analysis of data from ENB-002-08/ENB-003-10 and ENB-010-10. Statistical analysis methods and results for pooled efficacy analyses are discussed in Section 6.

Patient Disposition
Fifty-nine patients had been enrolled in the trial as of the data analysis cut-off date of November 12, 2014 (see Table 20). Six patients died after starting treatment with asfotase alfa, including one patient(Patient 010-16-03) who withdrew from the trial and subsequently died about one week later. The remaining 53 patients (90%) are continuing in the trial.

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Table 20: ENB-010-10- Patient Disposition

Disposition	Asfotase alfa (n=59)
Enrolled- n (%)	59 (100)
Treated- n (%)	59 (100)
Completed - n (%)	0
Discontinued- n (%) • Death • Withdrawal*	6 (10) 5(9) 1 (2)
Ongoing - n (%)	53 (90)

*Patient died one week after trial withdrawal.

Source: ENB-010-10 Interim Clinical Study Report (dated April 8, 2015), Table 8

Demographics

The age range of patients was 1 day to 312 weeks (mean age was 118 weeks) at screening. The majority of patients were white (46/59; 78%) and approximately half were female (32/59; 54%). At baseline, approximately two-thirds of patients (37/59; 63%) had some degree of respiratory compromise and approximately one-third of patients (19/59; 32%) required respiratory support. Thirty-four of 59 patients (58%) had nephrocalcinosis at baseline. Baseline mean z-scores for length/height and weight were well below the 3rd percentile for age (mean z-scores were at 0 percentile for both parameters). Six patients did not meet one of the biochemical or clinical eligibility criteria. Five patients had ALP levels or Vitamin D levels that did not meet eligibility criteria or that were obtained after initial drug dosing. One patient who was diagnosed in utero also had respiratory failure and therefore did not meet the inclusion criterion to be medically stable. One patient received two doses of a bisphosphonate one month prior to study entry and therefore failed the inclusion criterion of no prior bisphosphonate treatment. However, all six patients had a genetically confirmed diagnosis of HPP. Of the 59 patients enrolled in the trial, 45 patients (76%) had confirmed genetic mutations of the TNSALP gene.

Table 21 and Table 22 summarize baseline patient demographics and clinical findings for patients in ENB-010-10, respectively.

Table 21: ENB-010-10- Baseline Patient Demographics

Characteristic	Asfotase Alfa (n=59)
Age (weeks)	
Mean (SD)	118 (111)
Median	69
Min, Max	0.1, 312
Sex- n(%)	
Male	27 (46)
Female	2 (54)
Race- n(%)	
White	46 (78)
Asian	7 (12)
Multiple	1 (2)
Unknown	5 (9)
Ventilation Status- n(%)	
No support	40 (68)
Supplemental Oxygen	5 (9)
CPAP	2 (3)
Mechanical Ventilation	11 (19)
Other	1 (2)
RSS Score (n=58)	
Mean (SD)	
Median	4.8 (3.1)
Min, Max	4.3
Scale: 0 (normal) to 10 (severe rickets)	0, 10
Length Z-score (n=58)	
Mean (SD)	-3.1 (2.1)
Min, Max	-10.1, 0.9
Weight Z-score (n=59)	
Mean (SD)	-3.2 (3.5)
Min, Max	-23.8, 0
Plasma PPI (μM) (n=56)	
Mean (SD)	6.48 (2.04)
Min, Max	2.72, 12.38
(Reference range: 1.33 to 5.71 μM)	
PLP (ng/mL) (n=53)	
Mean (SD)	2711.3 (5287.35)
Min, Max	48, 24600
(Reference range: 11.76 to 68.37 ng/mL)	

Table 22: ENB-010-10- Baseline Patient Clinical Findings

Parameter	Asfotase Alfa N=59
Abnormally shaped chest- n(%)	49 (86)
History of respiratory compromise- n(%)	37 (63)
Seizures- n(%)	13 (22)
Difficulty gaining weight, failure to thrive, and/or difficulty eating swallowing- n(%)	51 (86)
High/abnormal serum calcium - n(%)	55 (93)
Nephrocalcinosis- n(%)	34 (58)
Fractures- n(%)	19 (32)
Craniosynostosis- n(%)	8 (14)

Reviewer Comments:
I compared disease history for ENB-010-10 patients with the disease history of all patients (i.e. alive and deceased patients; n=21) in the most recent historical control cohort (patients diagnosed with HPP from 2000 and later). Generally, the level of disease severity was similar between the two groups.

The proportion of patients with a history of failure to thrive was similar for ENB-010-10 patients (86%) and historical control patients (>90%). A smaller proportion of ENB-010-10 patients (63%)) had a history of respiratory complications compared to the historical controls (>90%). Similar proportions of patients had a history of seizures (approximately 25%) and nephrocalcinosis (60% to 70%). However, a smaller proportion of ENB-010-10 patients (14%) had a history of craniosynostosis compared historical controls (approximately 50%).

Concomitant Medications
Fifty-seven of 59 patients (97%) received concomitant medications during the course of the trial. The most commonly used medications (used by >50% of patients) were: analgesics/antipyretics (75%), and nonsteroidal anti-inflammatory medications (54%).

Other medications used by >20% of patients included beta-lactam antibacterials, general anesthetics, penicillins, hypnotics and sedatives, adrenergic inhalants, opioids, vitamin supplements, iron, laxatives, diuretics, viral and bacterial vaccines, antipruritics, and emollients.

Fifty-two of 59 patients (97%) underwent non-medication interventions for HPP-related complications during the trial, such as feeding tube and central line placement, orthopedic casting and bracing, surgery for craniosynostosis, and tracheostomy. Twelve of 59 patients (20%) also required physical, speech, and/or occupational therapy.

Treatment Compliance
Fourteen patients missed doses, including 10 patients who missed 3 doses or less, and 3 patients who missed 4 to 7 doses. One patient (Patient 010-16-01) missed approximately 21 consecutive doses over a 2-month period due to an extended hospitalization for pneumonia.

Protocol Deviations
Table 23 summarizes protocol deviations for ENB-010-10. Ninety-one major protocol deviations were reported for 26 patients (44%) and 322 minor deviations were reported for 49 patients (83%). The most commonly reported major deviations were assessment/procedure not done, study drug administered incorrectly, assessment/procedure done incorrectly and eligibility criteria not met (6 patients; 10%). The most commonly reported minor deviations were assessment/procedure done incorrectly (73%), and assessment/procedure not done (37%) or done outside of window (31%).

Table 23: ENB-010-10- Protocol Deviations

Protocol Deviations	Events, n	Patients, n (%)
Major Deviations	**91**	**26 (44)**
Assessment/procedure not done	47	16 (27)
Study drug administered incorrectly	12	8 (14)
Assessment/procedure done incorrectly	10	7 (12)
Eligibility criteria not met	6	6 (10)
Non-compliance with informed consent procedure	4	4 (7)
Assessment/procedure done outside of window	3	3 (5)
Non-compliance with AE recording/reporting procedures	3	2 (3)
SAE reporting	4	2 (3)
Study drug not administered	2	2 (3)
Minor Deviations	**322**	**49 (83)**
Assessment/procedure done incorrectly	211	43 (73)
Assessment/procedure not done	45	22 (37)
Assessment/procedure done outside of window	39	18 (31)
Study drug not administered	18	10 (17)
Study drug administered incorrectly	6	4 (7)
Non-compliance with informed consent procedure	1	1 (2)
SAE reporting	2	1 (2)

Source: ENB-010-10 Interim Clinical Study Report (dated April 8, 2015), Table 9

Reviewer Comments:
This reviewer notes that the applicant's classification of protocol deviations was inconsistent. For example, some incidents of failure to obtain blood pressure readings were classified as major deviations while others were classified as minor deviations, even when the reason for not doing the reading was the same (child crying or uncooperative). Similarly, some missed fundoscopic examinations were classified as major deviations while others were classified as minor deviations. However, based on my review of the protocol deviations listings and data analysis dataset, for ENB-010-10, the reported deviations did not impact the review of this application.

The most commonly reported deviations of assessment/procedure not done appeared to be missed vital sign assessments and PK assessments. The most common reason for study drug not being administered correctly was calculation of the dose based on a weight value obtained at a previous visit. I did not uncover any significant errors in the dose administered.

Efficacy Summary

Trial findings for ENB-010-10 provide supportive evidence of an efficacy claim for asfotase alfa for treatment of perinatal/infantile-onset HPP at doses of 6 mg/kg/week to 9 mg/kg/week. Enrollment is ongoing and therefore only baseline data were available for recently enrolled patients. Of 59 patients enrolled in the trial, 6 patients died after starting treatment with asfotase alfa and 53 patients (90%) were alive and continuing on treatment at the time of data analysis cutoff.

As observed in ENB-002-08/ENB-003-08, a majority of ENB-010-10 patients demonstrated improvement in growth and radiographic findings. The time to response was similar for growth and radiographic findings, with the majority of patients experiencing sustained improvements from Month 6 onward with optimal dosing.

A majority of ENB-010-10 patients had severe growth retardation at baseline, with approximately 80% of patients (46/59 patients) having baseline height z-scores below the 3rd percentile for age and 60% of patients (34/59 patients) having baseline weight z-scores below the 3rd percentile for age. Of 41 patients with available post-baseline data, approximately 75% have experienced improvements in height and weight z-scores.

Of 54 patients with available post-baseline RGI-C data, 36 patients (67%) achieved and sustained RGI-C scores of 2 or higher over time, meeting the applicant's responder criterion for substantial improvement of rickets. Approximately one-third of patients (18/54 patients) were non-responders, including 5 patients who experienced no change or a decline in RGI-C scores. Similar patterns were observed for RSS scores, with 32/42 patients (75%) with available post-baseline data experiencing improved RSS

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scores, including 15 patients who achieved RSS scores of zero, indicating complete healing of rickets.

Gross motor function assessment trends also generally indicated improvement from baseline. However, the interpretability of these assessments was limited due to the small number of patients, and the lack of baseline assessments for a majority of patients.

Fourteen patients experienced no change or a decline in clinical status (death, lack of improvement in height or weight, and/or RGI-C non-responder), most commonly no improvement in height gain (9 patients). There were no consistent patterns observed in lack of response. For example, 5/6 patients who died experienced improvement in weight-z-scores and were RGI-C responders. There were no clear differences in terms of baseline disease severity or antibody status between patients who improved and patient who had a lack of response.

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. These findings indicate that 6 mg/kg/week dosing may be suboptimal dose for some perinatal/infantile onset patients.

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5.3.4 ALX-HPP-502 (Juvenile-onset HPP Natural History Study) & ALX-HPP-502s (Gait Analysis Sub-study)

This was an international, multicenter, retrospective natural history study of patients with juvenile-onset HPP. The objective of the study was to characterize the natural history of patients with juvenile-onset HPP during childhood and early adolescence, including skeletal manifestations and growth. The evaluation period for the study was defined as the time period in which a patient was 5 to 15 years of age, inclusive, at Tanner stage ≤2. A patient was assumed to be of Tanner state ≤2 until a Tanner stage of 3 or more was reported. The study served as the non-concurrent control group for juvenile-onset patients enrolled in ENB-006-09/ENB-00810.

Patients were eligible for ALX-HPP-502 if they had a documented diagnosis of HPP (confirmed by genetic or biochemical analysis) with onset of signs or symptoms between > 6 months and <18 years of age, and had the following data available from medical records:

- At least 1 set of paired x-rays of the knees or hands/wrists taken at least 6 months but no more than 3 years apart
- At least 2 documented height measurement taken at least 3 years apart

Patients were excluded if they had previously received asfotase alfa or other treatments that targeted bone formation or growth, or if they had any other clinically significant disease during the evaluation period for the study (i.e., between 5 and 15 years of age).

Patients eligible for consideration for study enrollment included deceased patients. In addition, historical data for patients enrolled in ENB-006-09 could be considered for use in the natural history study.

The original primary outcome measures for the study were radiographic change in skeletal manifestations of HPP as measured by RGI-C score and height (change in height z-scores); the original secondary outcome measure was weight (change in weight z-scores). Following post-Breakthrough Therapy Designation discussions with the Agency, the applicant changed the primary efficacy analysis to a comparison of change in gait (as measured by mPOMA-G) between treated patients and a subgroup of historical control patients.

A total of 32 patients were enrolled from 9 sites in 6 countries, including the US (3 sites), United Kingdom (2 sites), Australia, Canada, The Netherlands, and Turkey (1 site each). Data was abstracted from medical records for patients from birth to 15 years of age. Data collection included demographic information, diagnostic history, disease history, developmental history, hospitalization history, medications and therapies, and laboratory data. A sub-group of 6 patients had archived videos filmed as part of other clinical assessments that were deemed adequate for re-reading to evaluate for changes in gait. The data collection period was from June 2014 through September 2014.

ALX-HPP-502 Protocol Amendments
Two amendments to the protocol were written to broaden eligibility criteria but were not implemented. Rules for selecting the baseline x-ray set for scoring radiographic findings were set in place after the study protocol and the SAP were finalized.

Changes in the Statistical Analysis Plan
As noted earlier, the SAP was changed to include an analysis of change in gait. For analyses of RGI-C and growth, the earliest available data points were defined as the baseline point. The original SAP also included overall survival analyses and analyses of some parameters by survival status. However, these analyses were not performed since all patients were alive at the end of the assessment period for the study.

Study Results
Patient Disposition
Of 54 patients screened for the study, 32 patients were enrolled. The most common reasons for screening failure was a lack of paired x-ray sets (14 patients). Other reasons for screening failure included lack of adequate documentation of diagnostic and medical history data needed to confirm eligibility (5 patients) and no informed consent (2 patients). All enrolled patients were alive at the time of data abstraction.

Protocol Deviations
Noncompliance with the informed consent procedure was reported for one patient; the study site began data abstraction based on verbal consent and obtained written consent at a later date.

Patient Demographics and Medical History
Table 24 summarizes patient demographics. The median age of enrolled patients was 18.9 years (range was 7.7 to 31.6 years). All but one patient were white and approximately two-thirds of the patients were males (69%). Patients who were screening failures were similar demographically to enrolled patients. The median age was 17.9 years and patients were predominantly white, non-Hispanic males from North America.

Mean age at onset of first signs/symptoms was 17.5 months (range was 7 to 41 months) and mean age at time of diagnosis was 47 months (range was 12 to 157 months). All enrolled patients were eligible for the study based on biochemical diagnosis of HPP (low serum alkaline phosphatase levels); genetic confirmation of disease was available for 25/32 patients (78%).

Table 24: ALX-HPP-502- Baseline Patient Demographics

Variable	Enrolled Patients n=32
Age- years	
n	32
Mean (SD)	19.3 (6.6)
Median	18.9
Min, Max	7.7, 31.6
Gender- n(%)	
Male	22 (69)
Female	10 (31)
Race- n(%)	
White	31 (97)
Other	3 (3)
Ethnicity- n(%)	
Hispanic	4 (13)
Not Hispanic	28 (87)
Region of birth- n(%)	
North America	25 (78)
Europe	5 (16)
Australia	2 (6)
Age at Onset of Signs/Symptoms - Months	
n	32
Mean (SD)	17.5 (9.2)
Median	14.5
Min, Max	7, 41
Age at Time of Diagnosis - Months	
n	31
Mean (SD)	47 (32.2)
Median	39
Min, Max	12, 157
HPP diagnosis confirmation- n(%)	
•Low ALP levels	32 (100)
•Genetic mutation analysis	25 (78)

The chart review for the study included collection of information on a pre-specified list of HPP-specific clinical conditions. The most commonly reported HPP- specific clinical signs and symptoms in medical records were tooth and musculoskeletal and connective tissue disorders (31/32 patients; 97%). Premature tooth loss was reported in all but one patient and primarily occurred prior to 5 years of age (31/32 patients). Other dental disorders included dental caries (31%) and tooth development disorder (25%). Musculoskeletal and connective tissue disorders were reported in all but one patient; arthralgia, bone deformity (long-bone bowing), and gait disturbance were the most commonly reported disorders (20 patients each; 63%). Other musculoskeletal-related conditions included bone pain (53%), myalgia (44%), myopathy, fractures (31% each), and scoliosis (22%). Although 25% of patients had a history of pneumonia, no patient had a history of requiring respiratory support. Other conditions reported in >10% of

patients included deafness (19%), other bone deformities such as rachitic chest (13% to16%), and delayed union of fractures (13%).

Other medical history (not pre-specified) included motor delay (defined as starting to walk at > 15 months of age; 22% of patients) and difficulty gaining weight (25% of patients).

Table 25 summarizes clinical findings for the study population stratified by age interval.

Table 25: HPP-Specific Conditions Reported in >20% of Juvenile-Onset Patients

HPP-Specific Disorders	Birth to <5 years old n(%)	>5 to 15 years 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)

Reviewer Comments:
Although, juvenile-onset patients generally do not experience severe respiratory compromise, there is considerable overlap in the chief clinical features of disease between the juvenile-onset and perinatal/infantile-onset population. One key clinical issue pertinent to the review of this application is the adverse impact of HPP disease on both bone and growth in both disease sub-groups. As discussed later, the observed treatment effect of asfotase alfa on both skeletal disease and growth in both patient sub-groups provides strong evidence of efficacy in the juvenile-onset patient population.

5.3.5 ENB-006-09/ENB-008-10 (Juvenile-Onset HPP Pivotal Trial)

ENB-006-09 was a 6-month, Phase 2, multicenter, open-label, dose-ranging, historical control trial to evaluate the safety, efficacy, PK and PD of asfotase alfa in pediatric patients ages 5 to 12 years old with perinatal/infantile-onset or juvenile-onset HPP. Patients with a documented diagnosis of HPP and open growth plates at the time of entry into the trial were eligible for participation. Exclusion criteria included the following:

- History of sensitivity to the study drug
- Any other clinically significant conditions or congenital abnormalities
- Treatment an investigational drug within 1 month of study entry or enrollment in any other investigational trials for HPP
- Low serum calcium or phosphorus levels
- Treatable form of rickets
- Prior treatment with bisphosphonates
- Bone fracture or orthopedic surgery within the past 12 months

ENB-006-09 was conducted at 2 sites in Canada and the United States. The trial period was from September 2009 to July 2010.

ENB-008-10 is an ongoing extension study for ENB-006-09 to evaluate the long-term safety and efficacy of treatment with asfotase alfa for up to 60 months. Patient were excluded from continuing on treatment if they had any other clinically significant disease, were treated with any other investigational drugs or were enrolled in any other investigational trials for HPP, or had previously been treated with bisphosphonates. Twelve of 13 patients randomized into ENB-006-09 completed the trial and entered the extension study ENB-008-10. The interim clinical study report for ENB-006-09/ENB-008-10 included efficacy and safety data for patients who had completed up to 168 weeks (>3 years) of treatment on or before the analysis cut-off date of October 29, 2014.

The primary objectives of ENB-006-09 were to assess the efficacy, safety, and tolerability of asfotase alfa in children ages 5 to 12 years of age with HPP. The primary objectives of ENB-008-10 were to assess the long-term tolerability and efficacy of asfotase alfa in this study population. Other objectives of ENG-003-08 were to assess long-term PK and PD of asfotase alfa and to assess its effect on growth, ambulation, gross motor function, and other clinical signs and symptoms of HPP.

ENB-006-09 Protocol Amendments

There were no amendments made to the protocol.

ENB-008-10 Protocol Amendments

There were four amendments made to the protocol implemented from May 19, 2010 to February 1, 2011. Major amendments included addition of injection-site reactions as safety assessments (Amendment 1 dated May 19, 2010) and increased frequency of

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functional assessments (Amendment 2 dated August 5, 2010 and Amendment 3 dated October 13, 2010). The most recent amendment (Amendment 4 dated February 1, 2011) eliminated some efficacy assessments (bone biopsy, PFT, dental films) and safety assessments (skull films and urine calcium creatinine ratios). The amendment also changed the dosing regimen (dose increased from 3 mg/kg/week to 6 mg/kg/week) and allowed safety-related dose adjustments to be made at any time during the trial.

Other changes included a change in the statistical methodology for radiographic analyses (Amendment 2 deleted a requirement to adjudicate differences in RGI-C scores for statistical analysis of change from baseline in RGI-C) and extension of the study duration to at least 42 months (Amendment 4).

Changes in the Statistical Analysis Plan
As noted earlier, as agreed upon with the Agency, the applicant changed the primary efficacy analysis for the juvenile-onset population to change in gait, using a retrospective historical control group. The original primary efficacy analysis for ENB-006-09 was change in rickets severity, as measured by change in RGI-C and RSS scores. In the original SAP, a 5-point system was used for RGI-C scoring; subsequently, a 7-point system was used for RGI-C scoring. The original SAP also included an interim analysis of the 24-week data from ENB-006-09 that served as the basis for the dose change made for patients continuing in the extension trial.

Reviewer Comments:
As noted earlier, the Statistical Reviewer did not consider the revised statistical analyses to be adequate from a statistical perspective. Regarding the change in the scoring system for RGI-C, it appears that all RGI-C scores submitted in the data analysis datasets used the 7-point scoring system. Therefore, this change did not impact an analysis of the RGI-C results.

Determination of Sample Size
The sample size for the trial was determined for the original statistical analysis.

Treatment
Dosing
The doses selected for ENB-006-09 were selected based on the results of ENB-001-08 and interim results for ENB-002-08. In ENB-006-09, patients received SC injections of 2mg/kg or 3 mg/kg of asfotase alfa administered 3 times per week (a total of 6 or 9 mg/kg/week) for 24 weeks.

Dose adjustments were allowed for lack of efficacy or due to safety-related concerns.

In ENB-008-10, patients initially received asfotase alfa 3 mg/kg/week administered as 1 mg/kg 3 times per week. The total weekly dose was increased to 6 mg/kg/week after a study-wide dose adjustment implemented under Protocol Amendment 4. Dosing

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frequency is 3 to 6 times per week (i.e. 2 mg/kg administered 3 times per week or 1 mg/kg administered 6 times per week). Treatment duration will be for at least 42 months or until the drug is commercially available.

During scheduled visits, study drug was administered at the trial site. Barring safety concerns or issues with drug administration or compliance, all other injections were administered without medical supervision at home. If any concerns arose, patients received medically supervised injections. Patients were monitored by home healthcare staff for at least the first 4 weeks of study drug administration.

Assessments
Efficacy assessments for ENB-006-09/ENB-008-10 included radiographic assessments and bone mineral density assessments, functional assessments (6MWT, BOT-2, HHD, and PFT), and disease severity assessments (CHAQ and PODCI). Safety assessments for ENB-006-09/ENB-008-10 were the same as the safety assessments used for the perinatal/infantile clinical trials.

- **ENB-006-09**

Screening assessments included physical examination, Tanner stage, growth parameters (height and weight), vital signs, skeletal x-rays, safety laboratory assessments (chemistry hematology, and urinalysis), vitamin D level, and functional assessments (6MWT, BOT-2, HHD, and PFT).

Baseline assessments included gene mutation analysis (if not already documented), physical examination, growth parameters, vital signs, dual energy X-ray absorptiometry (DEXA) scan, functional assessments, disease severity assessments (CHAQ, PODCI), disease biomarkers (PPi and PLP), parathyroid hormone (PTH) levels, safety laboratory assessments, 24-hour urine, renal ultrasound, dental x-rays, antibody testing, and PK sampling. During ENB-06-09, skeletal x-rays and disease biomarkers were assessed at Weeks 6 and 12, and at the end of the trial (Week 24). Functional assessments, vitamin D levels, and renal ultrasound were performed at Weeks 12 and 24. Height and head circumference were assessed at 12 and 24 weeks. Tanner staging, DEXA scan, dental x-rays, and bone biopsies were repeated at Week 24. PK sampling and all other trial assessments were performed at Weeks 6, 12, 18, and 24.

- **ENB-008-10**

The final visit of ENB-006-09 (Week 24) served as the baseline visit for ENB-008-10. In ENB-008-10, fundoscopic examinations, arm span, nutritional assessments, and urine calcium:creatinine ratio were added as baseline assessments. The following assessments were performed every 6 months: Tanner staging, fundoscopic examination, height, arm span, DEXA scan, PODCI, and renal ultrasound. All other efficacy and safety assessments were performed at Months 3, 6, and 9, and then every 6 months.

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Adverse events and concomitant medications and therapies were monitored continuously ENB-006-09 and ENB-008-10 beginning with the screening period.

Radiographic findings were reviewed by central radiologists. Screening bone biopsy samples were originally analyzed by (b) (4) and subsequently re-analyzed at (b) (4) All clinical laboratory testing was performed by a central laboratory.

See Table 59 and Table 60 in the Appendix for the schedule of assessments for ENB-006-09 and ENB-008-10, respectively.

- **Patient Disposition**

Patients Disposition

Twelve of 13 patients enrolled in ENB-006-09 completed the trial and continued participation in ENB-008-10 (see Table 26). One perinatal/infantile-onset patient withdrew from ENB-006-09 after completion of Week 4 for previously scheduled elective surgery (scoliosis repair). Twelve patients were participating in ENB-008-10 as of the analysis cut-off date for the interim clinical study report.

Table 26: ENB-006-09/ENB-008-10- Patient Disposition

Disposition	Historical Control Group n(%)	Asfotase Alfa 2 mg/kg n(%)	Asfotase Alfa 3 mg/kg n(%)	Asfotase Alfa Combined n(%)
Enrolled	16	6 (100)	7 (100)	13
Treated		6 (100)	7 (100)	13
Discontinued from ENB-006-09		0	1 (14)	1 (8)
AE		0	0	0
Completed ENB-006-09		6 (100)	6 (86)	12 (92)
Ongoing in ENB-008-10		6 (100)	6 (86)	12 (92)

Source: ENB-006-09/ENB-008-10 Interim Clinical Study Report, Table 8

Demographics

The age range of treated patients was 6 to 12 years (mean age was 8.8 years) at baseline. All patients but one were white and non-Hispanic or Latino (12/13; 92%) and the majority of patients were male (11/13; 85%). Five patients had infantile-onset HPP and 8 patients had juvenile-onset HPP. The median age of onset of HPP symptoms was 12 months (range was 1 to 22 months).

At baseline, all patients had a history of unusual gait and premature tooth loss. A majority of patients also had delayed walking (85%), muscle weakness (62%), and high phosphorus levels (54%). Mean baseline height and weight z-scores were -1.94 (less than 3rd percentile) and -1.64 (~5th percentile), respectively.

All 13 patients underwent gene mutation analysis. The majority of patients (11/13) were compound heterozygotes. One patient was heterozygous for a presumably dominant mutation and one patient (Patient 006-02-03) had no detectable disease-causing mutation. Four patients had genetic confirmation of disease but did not meet one of the biochemical or clinical eligibility criteria; 3 patients had vitamin D levels below the protocol-specified minimum level and one patient had an excluded comorbidity (Asperger's syndrome).

Table 27 and Table 28 summarize baseline patient characteristics and baseline patient clinical findings for ENB-010-10, respectively.

Table 27: ENB-006-09/ENB-008-10- Baseline Patient Characteristics

Characteristic	Asfotase Alfa 2 mg/kg (n=6)	Asfotase Alfa 3 mg/kg (n=7)	Asfotase Alfa Combined (n=13)
Age at Enrollment (years)			
n	6	7	13
Mean (SD)	8.4 (2.2)	9.1 (2.3)	8.8 (2.2)
Median	8.1	10.0	8.6
Min, Max	6, 12	6, 12	6, 12
Sex- n(%)			
Male	5 (83)	6 (86)	11 (85)
Female	1 (17)	1 (14)	2 (15)
Ethnicity- n(%)			
Hispanic or Latino	1 (17)	0	1 (8)
Not Hispanic or Latino	5 (83)	7 (100)	12 (92)
Race- n(%)			
White	6 (100)	6 (86)	12 (92)
Other	0	1 (14)	1 (8%)
HPP Phenotype- n(%)			
Perinatal/Infantile-onset	3 (50)	2 (29)	5 (39)
Juvenile -onset	3 (50)	5 (71)	8 (62)
Age at Onset of HPP Symptoms (months)			
n	6	7	13
Mean (SD)	10.8 (8.7)	10.3 (6.0)	10.5 (7.0)
Median	8.5	12.0	12.0
Min, Max	1, 22	1, 17	1, 22
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

Table 27: ENB-006-09/ENB-008-10- Baseline Patient Characteristics- cont'd

Characteristic	Asfotase Alfa 2 mg/kg (n=6)	Asfotase Alfa 3 mg/kg (n=7)	Asfotase Alfa Combined (n=13)
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 28: ENB-006-09/ENB-008-10- Baseline Patient Clinical Findings

Parameter	Asfotase Alfa 2 mg/kg (n=6)	Asfotase Alfa 3 mg/kg (n=7)	Asfotase Alfa Combined (n=13)
	n(%)		
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)

Concomitant Medications and Therapies
Concomitant medications were summarized by WHO ATC Class. All 11 patients received concomitant medications during the trial. The most commonly used medications (used by >50% of patients) were analgesics/antipyretics (85%), local anesthetics (69%), antihistamines (69%), antipruritics (62 %), beta-lactam antibacterials (54%), and opioids for pain management (54%).

Protocol Deviations
13 major protocol deviations were reported for 7 patients (54%) and 216 minor protocol deviations were reported for all 13 patients. The most frequent types of major deviations were eligibility criteria not met (4 patients), nonconformance with informed consent procedure, and study drug administered incorrectly (2 patients each).

Minor deviation reported in ten or more patients included assessment/procedure done incorrectly (12 patients) or done outside of window (11 patients) and study drug not administered (10 patients).

Compliance was assessed by medical supervision of injections and review of drug administration and drug accountability records. Compliance was 99% during the 24-week primary treatment period; data on compliance during the extension phase were not available for review.

Reviewer Comments:
Regarding patients with major protocol deviations, as in the other clinical trials for asfotase alfa, some patients were considered ineligible based on a biochemical diagnostic criterion. However, all of the patients had genetic confirmation of disease. One juvenile-onset patient who had an exclusion criterion violation (the patient had a comorbidity of Asperger's syndrome that prevented him from reliably performing functional assessments) was uncooperative during his baseline 6MWT. Since the focus of my efficacy review for juvenile-onset patients was objective endpoints (growth and radiographic assessments, the reported deviations did not impact my review of efficacy results. In addition, there did not appear to be any deviations that impacted my safety review.

Dose Adjustments
As noted earlier, the ENB-008-10 protocol was amended to increase patient dosing from 3 mg/kg/day to 6 mg/kg/day. No patients received further dose increases during the extension trial.

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Efficacy Summary

Trial findings for the 8 patients enrolled in ENB-006-09/ENB-008-10 provide supportive evidence of efficacy for asfotase alfa for treatment of juvenile-onset HPP at doses of 6 mg/kg/week.

The primary efficacy analysis compared change in gait in a historical control group (n=6) and treated patients. A difference in mean rate of change in MPOMA-G score was observed for treated patients (rate of change was 2.25 per year), primarily due to improvements in step length. Six of 8 treated (75%) patients showed at least a 1 point improvement in step length in either foot compared to 1/6 (17%) historical control patients who showed any improvement with either foot. No substantial difference in gait scores was observed for the control group (rate of change per year was 0.37).

The gait assessment findings suggest treatment benefit; however, 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 these limitations, the gait assessment analysis was not sufficient as the sole evidence to support an efficacy claim for the juvenile-onset population. However, the totality of evidence, including exploratory analyses of growth and radiographic assessments in the juvenile-onset population, and survival analyses in the perinatal/infantile-onset population provide compelling evidence that treatment with asfotase alfa provides clinical benefit in the juvenile-onset population.

Based on comparison with a historical control group (n=32), treated juvenile-onset patients had improved height and weight growth over time. For control patients, mean baseline height and weight z-scores were -1.1 (range -4.9 to 2.6) and -1.2 (range -5 to 2.1), respectively; at last assessment, mean height and weight z-scores were -1.1 (range -4.9 to 1.8) and -1 (range -5.7 to 2.1), respectively. For treated patients, mean baseline height and weight z-scores were -1.5 (range -3.8 to 0) and -1.1 (range was -3.5 to 2.3), respectively; at last assessment, mean height and weight z-scores were -0.9 (range -2 to 0) and 0 (range was -1.3 to 2.2), respectively.

The mean change in height z-score was 0.6 for treated patients compared to zero for control patients. The mean change in weight z-score was 1.1 for treated patients compared to 0.2 for control patients.

At last assessment, all 8 treated juvenile-onset patients maintained normal height and weight z-scores or experienced improvement in abnormal height and weight z-scores. In comparison, approximately 20% of control patients experienced clinically significantly declines in height growth (i.e., decline in height z-scores to <5th percentile for age).

A comparison of radiographic assessments in control patients and treated patients also demonstrated improvement with treatment. All 8 juvenile-onset patients sustained RGI-

C scores of 2 higher at their last assessment, meeting the applicant's responder criterion for substantial improvement of rickets. Two of 32 control patients (6%) had RGI-C scores of 2 or higher at last assessment. A majority of control patients (28/32 patients) had RGI-C scores <1 at all time points, indicating that there is minimal change of radiographic findings over time in untreated patients. Median change in RSS from baseline to last assessment also was greater in treated patients (median change was 2.5) compared to control patients (median change was 0). Median baseline RSS were lower in control patients (median score was 1) compared with treated patients (median score was 2.4); 25% of control patients had baseline RSS scores of zero. Because treated patients had more severe rickets disease at baseline than historical control patients, the applicant performed analyses of RGI-C scores adjusted for baseline RSS. These analyses also demonstrated a treatment effect for asfotase alfa.

Functional assessments were supportive of efficacy. Results for the 6MWT demonstrated improvement in the distance waked with treatment. The applicant defined normal walking distances as values ≥ 84% percent predicted distance walked for sex and age, based on reference values for healthy children published by Geiger et al.[37] At baseline, none of the 13 patients enrolled in ENB-006-09/ENB-008-10 had percent predicted distance walked values ≥84% (mean value for the overall population was 59%). At last assessment, 5/11 patients with post-treatment values had percent predicted values above 84%, including 2 juvenile-onset and 3 perinatal/infantile-onset patients; 9/11 patients had percent predicted values above 80%, including 5 juvenile-onset patients and 4 perinatal/infantile-onset patients (mean value for the overall population was 85%).

Other functional assessment trends (gross motor function and muscle strength) also generally indicated improvement from baseline. However, the interpretability of these assessments was limited due to the small number of patients, and the lack of baseline assessments for many patients.

The time to response was similar for growth and radiographic findings, with the majority of patients experiencing sustained improvements from Month 6 onward.

37 Geiger R, Strasak A, Treml B, et al., Six-minute walk test in children and adolescents, *J Pediatr* 2007; 150:395-399, e1-e2.

5.3.6 Other Asfotase alfa Clinical Trials

ENB-009-10 (Mixed HPP Population Phase 2 Clinical Trial)

ENB-009-10 is an ongoing Phase 2, multicenter, open-label trial to evaluate the efficacy, safety, and pharmacology of asfotase alfa in patients aged 13 to 65 years with infantile-, juvenile-, or adult-onset HPP. Nineteen patients were enrolled in three sites in Canada (1 site) and the United States (2 sites), including four patients who were previously enrolled in and completed ENB-001-08. The trial began in June 2010. The analysis cut-off data for the interim clinical study report for ENB-009-10 was November 5, 2014. The applicant submitted additional efficacy as part of the 120 Day Safety Update.

Eligibility criteria included a pre-established diagnosis of HPP and bone biopsy evidence of osteomalacia. Clinical criteria use to establish a diagnosis of HPP included:

- biochemical abnormalities (decreased ALP and increased PLP)
- radiographic evidence of HPP
- rachitic chest deformity and/or vitamin-B6-dependent seizures,
- one or more HPP-related findings (e.g., craniosynostosis)
- failure to thrive

Exclusion criteria for ENB-002-08 included the following:

- History of sensitivity to the study drug
- Pregnant or lactating women
- History of sensitivity to tetracycline
- Serum calcium, creatinine, PTH or phosphorus levels below normal range
- Serum 25(OH) vitamin D below 20 ng/mL
- Medical condition or other issues that may have interfered with study compliance
- Treatment with bisphosphonates within past 2 years or for more than 2 years at any time point; patients with a prior history of bisphosphonate use were required to have normal or elevated bone resorption markers
- Orthopedic surgery within past 12 months that may have interfered with ability to perform functional assessments
- Treatment with PTH within past 6 months
- Participation in an interventional or investigational study within past 30 days.

The primary analyses for the trial are change from baseline in PPi and PLP. Other efficacy analyses include change in bone mineral density as measured by DEXA scan and change in walking ability as measured by the 6MWT.

ENB-009-10 Protocol Amendments
There have been 5 amendments to the protocol implemented from May 4, 2010 to October 20, 2011. Key changes included clarification and modification of eligibility criteria for bone biopsy findings and bisphosphonate use, and adjustment of study dosing (dosing was increased to 1 mg/kg/day administered 6 times weekly during the extension phase of the trial).

Reviewer Comments:
The changes to the bone biopsy and bisphosphonate use criterion likely did not impair the interpretability of efficacy data. The applicant noted that the bone biopsy criterion was changed to osteoid thickness and mineralization lag time rather than osteoid surface z-score. Increased osteoid thickness and prolonged mineralization lag time are considered the preferred histomorphometric criteria for osteomalacia. Regarding use of bisphosphonates, the original criterion appeared to be designed to exclude patients on long-term bisphosphonate therapy due to the potential risk of suppressed bone formation associated within prolonged bisphosphonate use. However, the revised criterion required that patients had normal (or elevated) bone resorption, indicating that patients did not have bisphosphonate-induced abnormal bone function. Thus, both changes likely did not introduce significant selection bias.

There were multiple per protocol changes to dosing, with the starting dose for the trial being significantly lower (about one-third to one-half of the proposed dose of 6 mg/kg/week). These changes placed the greatest limitation in interpreting efficacy results.

None of the protocol changes impaired my review of safety.

Treatment
Dosing
Patients assigned to the control group did not receive treatment until the extension period. During the 24-week primary treatment period, patients assigned to treatment received a dose of 0.3 mg/kg/ or 0.5 mg/kg administered 7 times per week (2.1 mg/kg/week or 3.5 mg/kg/week). During the extension period, all patients received a dose of 3.5 mg/kg/week for approximately 24 to 48 weeks. The dose was then changed to 6mg/kg/week (administered as 1 mg/kg 6 times per week), with a maximum daily dose of 80 mg. Dose adjustments were allowed for weight. Dose reductions during the 24-week primary treatment period could only be made for safety reasons; changes in dosing or dosing regimen could be made during the extension period.

Reviewer Comments:
The applicant noted that ENB-009-10 was initiated before dosing data were available from ENB-001-08 and ENB-002-08. The dose increase to 6 mg/kg/week was implemented after a review of ENB-002-08 data that indicated efficacy at this dose level.

Reference ID: 3836304

Assessments
Efficacy assessments for ENB-009-10 included skeletal radiographs (in patients <18 years old), DEXA bone scan, 6MWT, BOT-2, LEFS, HHD, BPI-SF, PFTs, and functional disability (HOST). Dental assessments and nutritional assessments were also performed but were not included in formal analyses.

Bone biopsies were performed at screening in all patients, at Week 24 in control patients, and at Week 48 in patients randomized to asfotase alfa, respectively. Patients who underwent the screening bone biopsy in ENB-001-08 were exempt from the screening bone biopsy in this trial. Screening bone biopsy samples were originally analyzed by the (b) (4) and were reanalyzed at (b) (4)

Pharmacodynamic assessments included plasma PPi and PLP, parathyroid hormone, and urinary calcium:creatinine ratio.

Safety assessments for ENB-009-10 were the same as for ENB-002-08/ENB-003-08 and ENB-006-08/ENB-008-10 as well as the following assessments: electrocardiograms and pregnancy testing.

See Tables 61-63 in the Appendix for the schedule of assessments for ENB-009-10.

Results
Demographics
The mean age at trial entry was 41 years (range was 12 to 66 years). The study population included 4 patients with perinatal/infantile-onset HPP, 12 patients with juvenile-onset HPP, 2 patients with adult-onset HPP and 1 patient with an unknown phenotype. Six of 19 patients were adolescents (3 patients each with perinatal/infantile-onset HPP and juvenile-onset HPP). The Tanner stage of two adolescents was unknown; one patient was Tanner stage 1 and 3 patients were Tanner stage 4. All patients had a genetically confirmed diagnosis of HPP.

Table 29 summarizes patient demographics for ENB-009-10.

Table 29: ENB-009-10- Patient Demographics

Characteristic	Asfotase Alfa (n=19)
Age (years) Mean (SD) Median Min, Max	 41 (20) 53 13, 66
Phenotype- n(%) Perinatal/infantile-onset Juvenile-onset Adult-onset Unknown	 4 (21) 12 (63) 2 (11) 1 (5)
Sex- n(%) Male Female	 7 (37) 12(63)
Ethnicity- n(%) Hispanic or Latino Not Hispanic or Latino	 0 (0) 19 (100)
Race- n(%) White Other	 18 (95) 1 (5)
6MWT % Predicted- n(%) >25% to < 75% >75%	(n=15) 7(37) 8 (42)
Genetic Mutation Analysis Yes No	 19 (100) 0
Plasma PPI (µM) Mean (SD) Median Min, Max Reference ranges: 13-18 years(<0.75- 4.78 µM); >18 years (1.00-5.82 µM)	(n=19) 5.78 (2.13) 5.23 2.15, 1012.10
PLP (ng/mL) Mean (SD) Median Min, Max Reference ranges: 5-18 years (5.74-61.15 ng/mL); >18 years (2.81-26.70 ng/mL)	(n=19) 423 (427) 267 29, 1590

Disposition

Four patients formerly enrolled in ENB-001-08 enrolled in ENB-009-10 (see Table 30). Three patients discontinued from ENB-009-10, including 2 patients who experienced AEs (injection site reaction and lipohypertrophy) and one patient who was noncompliant with treatment. One patient transferred from a Canadian site to a US site during the course of treatment.

Table 30: ENB-009-10- Patient Disposition

Disposition	Asfotase alfa (n=19)
Enrolled- n (%)	19 (100)
Treated- n (%)	19 (100)
Discontinued from ENB-009-10 - n (%) •AE •Noncompliance	3 (16) 2 (11) 1 (5)
Ongoing in ENB-003-08- n (%)	16 (84)

Source: ENB-002-08/ENB-003-08 Interim Clinical Study Report (dated April 15, 2015), Table 10

Concomitant Medications
All 19 patients received concomitant medications during the course of the trial. The most commonly used medications (used by >50% of patients) were nonsteroidal anti-inflammatory medications and other analgesics/antipyretics.

Concomitant non-medication therapies included surgical procedures for fracture repairs, orthotics and dental procedures.

Protocol deviations
Fifteen of 19 patients (79%) had 30 major deviations and all 19 patients had minor deviations (268 events). The most frequently reported major deviation was eligibility criteria not met (12 patients; 63%), including 10 patients who did not meet the initial protocol criterion for presence of osteomalacia on bone biopsy, and 3 patients who had a history of bisphosphonate use prior to trial entry.

The most frequently reported minor deviations were assessment/procedure done outside of the specified time window (18/19 patients; 95%) and assessment/procedure not done (17/19 patients; 90%).

Reviewer Comments:
As noted earlier, all of the patients in ENB-009-10 had genetically confirmed HPP disease. Therefore, inclusion of these patients in the trial likely would not impact the interpretability of PK and safety data, which were the primary analyses for the trial.

Treatment Compliance
Treatment compliance initially was tracked by patient diaries and subsequently was monitored by collecting empty medication vials at study visits. Fourteen of 19 patients missed doses that were classified as protocol deviations, including three patients who missed 3 doses or less and three patients who missed fewer 10 doses or less.

Two of three patients who missed 10 doses or more were adolescents. One adolescent missed 16 doses over an unspecified period of time and one adolescent (Patient 009-01-09) missed 168 doses prior to withdrawing from the trial after Week 120. One adult

patient missed dosing over two 4- month periods, missing 8 doses during one period due to drug shortage and 20 doses during the second period (reason not specified).

Dose adjustments
As discussed earlier, all patients experienced per protocol changes in dosing. Patient 009-10-01-08 received a dose reduction (0.5 mg 3 times a week instead of 0.5 mg 7 times a week) due to AEs (injection site reaction and injection site atrophy). One patient received a reduced dose (0.4 mg/kg/week instead of 1 mg/kg/week) for about 2 months due to a dose calculation error. Two patients requested changes in dosing frequency from 6 times to 3 times a week.

Efficacy Summary
Results for biomarkers, the primary efficacy analysis for the trial, were consistent with other trial findings, with sustained decreased in biomarker levels observed with treatment in all treatment groups.

Radiographic findings demonstrated improvement in RGI-C and RSS scores for the 6 adolescent patients enrolled in the trial; albeit of a smaller degree than changes noted in other trials.

Bone assessments included bone biopsies and DEXA scans. Most patients had baseline mineralization indices consistent with osteomalacia on bone biopsies. Median change in osteoid thickness and volume were similar between treatment and control groups; baseline and changes in mineralization lag time were variable. DEXA assessments revealed no consistent trends in bone mineral density z-scores for adolescent patients.

Four of 6 adolescent patients had severe growth retardation at baseline (height z-scores below the 3rd percentile for age); one patient was also severely underweight. No patients experienced improvement in height z-scores. Three patient experienced decreases in height or weight z-scores, including 2 patients whose weights declined to below the 3rd percentile for age.

Functional and disability assessments were supportive of efficacy. Results for the 6MWT demonstrated improvement with treatment, with increased median values for percent predicted distance over time reported for all treatment groups. A majority of patients (14/18 patients) had increased LEFS scores at last assessment, including 8/18 patients (44%) who reported a 9 point or more increase in score, indicating a clinically important improvement in function.

The observed variable findings for treatment response on bone mineralization and growth in adolescent patients likely reflect inadequate exposure, as ENB-009-10 patients received lower doses than the proposed marketing dose of 6 mg/kg/week.

Reference ID: 3836304

ENB-001-08 (Phase 1 Trial- Unknown HPP Phenotype Dose-Escalation Trial)
This was an 8-week, Phase 1, multicenter, open-label, dose-escalating trial to evaluate the safety, tolerability, and pharmacology of asfotase alfa in adult patients with a history of onset of signs and symptoms of HPP during childhood. Patients 28 to 80 years of age with a clinical diagnosis of HPP (defined as low serum ALP, radiologic evidence of osteopenia or osteomalacia, and medical history of HPP-related findings such as dental loss and rickets) were eligible for the trial. The trial was conducted at two sites in Canada and the United States. The trial period was from August 2008 to January 2009

The primary objective of the trial was to assess the safety and tolerability of asfotase alfa. Other objectives were to assess the PK, bioavailability, and pharmacodynamics of asfotase alfa and to assess its effect on clinical signs and symptoms of HPP after repeated dosing. The primary endpoint of the trial was safety. PK parameters were evaluated as secondary endpoints. PD parameters (including PPi, PLP, and biomarkers of bone turnover) and efficacy parameters (bone pain, bone mineral density, fractures, and radiographic assessments of bone abnormalities) were exploratory endpoints. In addition, baseline bone biopsies were performed in one dose cohort (n=3).

Six patients enrolled and completed the study. The patient age range was 24 to 58 years old. All patients were white. All patients had a history of fractures, osteopenia, and premature dental loss and had genetic confirmation of HPP disease; no data were provided on HPP phenotype.

Patients were treated at Week 1 with a single intravenous (IV) dose of asfotase alfa followed by weekly SC injections for weeks 2 through 4. The first cohort of patients (n=3) received asfotase alfa 3 mg/kg IV followed by weekly SC doses of 1 mg/kg. The second cohort (n=3) received asfotase alfa 3 mg/kg IV followed by weekly SC doses of 2mg/kg/week.[38] See Table 64 in the Appendix for the schedule of assessments for ENB-001-08.

Efficacy Summary

The applicant noted that variability in PK characteristics (bioavailability, C_{max}, clearance and half-life) was observed between cohorts and between individual patients. At week 3, plasma PLP levels declined in 5/6 patients (levels could not be fully quantified in the sixth patient); plasma PPi levels were unchanged in the lower dose cohort but declined in the higher dose cohort. The applicant concluded that the sample size was too small to evaluate for dose effect. No consistent changes were noted in other PD or efficacy endpoints.

[38] Dose levels in the original protocol were 0.4 mg/kg daily and 1 mg/kg daily. Based on PK modeling, dose levels were changed to 1 mg/kg/week and 2 mg/kg/ week.

6 Review of Efficacy

Efficacy Summary

The Statistical Reviewer, Behrang Vali, MS, deemed the design of the individual clinical trials for the perinatal/infantile-onset population and the protocol for the retrospective natural history study to be acceptable from a statistical perspective. However, Mr. Vali deemed that the analysis for the juvenile-onset population was not robust from a statistical perspective because the analysis was selected post-hoc and was based on historical control data collected retrospectively after results for clinical trials were already known (please refer to his review dated September 19, 2015 for further details). Mr. Vali concluded that "the determination of the clinical effectiveness of asfotase alfa will rely more on clinical judgment that on the statistical rigor usually required for larger randomized controlled studies." This reviewer agrees with Mr. Vali's assessment.

As discussed below, the primary efficacy analysis for the perinatal/infantile-onset population provides robust evidence to support an efficacy claim for this population. 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 totality of evidence, including growth, radiographic, and histomorphometric data, is compelling and was deemed sufficient to support an efficacy claim for the juvenile-onset population.

In addition, efficacy analyses for the two populations were deemed to support efficacy for each other.

Perinatal/Infantile-onset HPP Indication

The BLA submission contained data from two open-label clinical trials (ENB-002-08/ENB-003-08 and ENB-010-10) to support the perinatal/infantile-onset HPP indication. The primary efficacy outcome measure was overall survival. Ventilator-free survival was the key secondary endpoint.

The applicant performed a Kaplan-Meier analysis of pooled overall survival patients enrolled in ENB-002-08/ENB-003-08 and ENB-010-10 (n=68) who met the entry criteria for the natural history study. The results of the survival analysis showed that treatment improved overall survival compared with survival in historical control patients, with 62 out of 68 (91%) treated patients versus 13 out of 48 (27%) historical control patients surviving at Week 504 (approximately 10 years). A subgroup analysis of patients who received the proposed dosing regimen of 6 mg/kg/week for $\geq$1 week without dose modifications yielded similar results, with 45/46 patients surviving at Week 504. Ventilator-free survival results for the pooled treated patient group were similar to the overall survival results; at Week 504, the Kaplan-Meier estimate of ventilator-free survival rate for the overall pooled population was approximately 80%.

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Some data analyses for the juvenile-onset population also were considered to be supportive of efficacy for the perinatal/infantile-onset, including comparative analyses of growth and radiographic assessment data from treated juvenile-onset patients and a historical control group.

The applicant's analyses of pooled growth and radiographic data for the perinatal/infantile-onset population produced results that were consistent with findings for the juvenile-onset population. A majority of perinatal/infantile-onset patients experienced improvements in height (50/71 patients; 70%) and weight (56/72 patients; 78%), and were classified as RGI-C responders at last assessment (68/75 patients; 90%).

Juvenile-onset HPP Indication

The applicant submitted data from one open-label trial (ENB-006-09/ENB-008-10) to support the juvenile-onset indication. The primary efficacy analysis compared change in gait in a historical control group (n=6) and treated patients (n=8), as measured by the Tinetti modified Performance Oriented Mobility Assessment-Gait (mPOMA-G) scale. The predominant clinical feature of juvenile-onset disease is bone disease, which manifests as impaired gait, bone pain, and muscle weakness. Thus gait represents a clinically relevant endpoint for this disease population. However, the gait analysis was deemed not to be robust from a statistical perspective because the analysis was selected post-hoc and was based on historical control data collected retrospectively after results for clinical trials were already known.

The gait analysis revealed a difference in mean rate of change in MPOMA-G score for treated patients (rate of change was 2.25 per year), primarily due to improvements in step length. Six of 8 treated (75%) patients showed at least a 1 point improvement in step length in either foot compared to 1/6 (17%) historical control patients who showed any improvement with either foot. No substantial difference in gait scores was observed for the control group (rate of change per year was 0.37).

The gait assessment findings suggested treatment benefit; however, a number of factors limited interpretation of the results. Limiting factors included the post-hoc nature of the analysis, lack of validation of the mPOMA-G instrument in the HPP population, differences in baseline disease severity, and test methodology (re-reading videos filmed for other types of ambulation assessments). Given these limitations, the gait assessment analysis was deemed to be insufficient from a clinical perspective to serve as the sole evidence to support an efficacy claim for the juvenile-onset population.

However, the totality of evidence, including exploratory analyses of growth and radiographic assessments in the juvenile-onset population, and survival analyses in the perinatal/infantile-onset population provide substantial evidence of treatment benefit in the juvenile-onset population. Specifically, natural history data demonstrated that

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untreated patients typically experienced no improvement or worsening of radiographic and growth parameters over time. In comparison, all eight treated patients maintained normal height and weight z-scores or experienced improvements in abnormal height and weight z-scores; all treated patients were also classified as RGIC-responders.

As per the Agency's request, the applicant performed comparative analyses of change in growth parameters (height and weight z-scores) and radiographic assessments over time for treated juvenile-onset patients compared to a historical control group (n=32). The growth analysis demonstrated improved height and weight growth over time with treatment. For control patients, mean baseline height and weight z-scores were -1.1 (range -4.9 to 2.6) and -1.2 (range -5 to 2.1), respectively; at last assessment, mean height and weight z-scores were -1.1 (range -4.9 to 1.8) and -1 (range -5.7 to 2.1), respectively. For treated patients, mean baseline height and weight z-scores were -1.5 (range -3.8 to 0) and -1.1 (range was -3.5 to 2.3), respectively; at last assessment, mean height and weight z-scores were -0.9 (range -2 to 0) and 0 (range was -1.3 to 2.2), respectively.

The mean change in height z-score was 0.6 for treated patients compared to zero for control patients. The mean change in weight z-score was 1.1 for treated patients compared to 0.2 for control patients.

At last assessment, all 8 treated juvenile-onset patients maintained normal height and weight z-scores or experienced improvement in abnormal height and weight z-scores. In comparison, approximately 20% of control patients experienced clinically significantly declines in height growth (i.e., decline in height z-scores to <5th percentile for age).

The radiographic analysis also demonstrated improvement with treatment. The key secondary radiographic assessment was change in rickets severity, as assessed by the Radiographic Global Impression of Change (RGI-C) scale. Based on the applicant's responder criterion for substantial healing of rickets (RGI-C score of 2 or higher), at last assessment all 8 juvenile-onset patients were responders, compared to 2/32 control patients (6%).

Data from matched bone biopsy pairs from 12 patients demonstrated treatment effect on bone mineralization, with 4/4 perinatal/infantile-onset patients and 7/8 juvenile-onset patients experiencing improvement in bone mineralization indices.

The time to response was similar for growth and radiographic findings in both the juvenile-onset and perinatal/infantile-onset populations, with the majority of patients experiencing sustained improvements from Month 6 onward. Other functional assessment trends (gross motor function and muscle strength) also generally indicated improvement with treatment.

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6.1 Indication

The applicant proposes the following indication:

[redacted] (b) (4)

Reviewer Comments:
This reviewer does not agree with the term [redacted] (b) (4) *for the indicated population* [redacted] (b) (4) [redacted] *I reviewed the literature to see what terms were used to describe the various HPP subgroups; juvenile-onset HPP was sometimes also termed "childhood HPP" but I did not encounter the term* [redacted] (b) (4) *HPP to describe any group of HPP patients. This reviewer recommends that the indication be revised to describe each patient subgroup included in the indication. Therefore, this reviewer recommends that the indication be revised as follows:*

> *"STRENSIQ is indicated for the treatment of patients with perinatal/infantile- and juvenile-onset hypophosphatasia (HPP)."*

For a final version of the indication for STRENSIQ, please see final product labeling.

6.1.1 Methods

Historical control data were available for overall survival and ventilator-free survival for the perinatal/infantile-onset population and for gait, growth, and radiographic assessments for the juvenile-onset population. All other efficacy data were open-label. The applicant pooled efficacy data for the primary efficacy analyses for the perinatal/infantile-onset population (overall survival and ventilator-free survival) and the juvenile-onset population (gait), comparing data from clinical trials to historical comparator groups for the two populations. As per the Agency's request, the applicant also compared pooled efficacy data for radiographic assessments (RGI-C and RSS) for both patient populations. In addition, the applicant performed an analysis of pooled growth (height and weight z-scores) for both populations, including a comparison of change in growth parameters over time for treated juvenile-onset patients compared to a historical control group.

6.1.2 Demographics

Overall, patient demographics and baseline disease characteristics for the historical control groups for the perinatal/infantile-onset population and the juvenile-onset population were similar to those of patients in clinical trials. The majority of patients in the overall population and in the two patient subgroups were white and from North America, with approximately equal numbers of male and female. See Section 5 for a summary of patient demographics and baseline disease characteristics for individual clinical trials.

Perinatal/infantile population
The mean age at time of diagnosis in the historical control group was 23 weeks. The majority of historical control patients had biochemical confirmation of disease (85%); approximately one-third also had genetic confirmation of disease.

At trial entry, the mean age of ENB-002-0/ENB-003-08 patients and ENB-010-10 patients was 59 weeks (14.8 months) and 118 weeks (29.5 months), respectively. All patients enrolled in ENB-002-03/ENB-003-08 and 76% of patients enrolled in ENB-00-10 had genetic confirmation of disease.

Generally, the level of disease severity was similar between patients in clinical trials and the most proximate historical control cohort (patients diagnosed with HPP from 2000 and later). The proportion of patients in the historical control groups with a history of respiratory complications and failure was similar compared to patients in ENB-002-08/ENB-003-08 (~90%) but higher compared to patients in ENB-010-10 (~60%). Patients in ENB-010-10, the larger of the two perinatal/infantile-onset HPP trials, closely matched the historical control group in the proportion of patients with failure to thrive (85 to 90%), nephrocalcinosis (70), and vitamin B6-responsive seizures (25%). 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 (50%).

Juvenile-onset population
The mean age of patients in the historical control was 19 years compared to a mean age of 9 years for ENB-006-09/ENB-008-10 patients. Approximately 78% of historical control patients had genetic confirmation of disease compared to 100% of ENB-006-09/ENB-008-10 patients.

ENB-006-09/ENB-008-10 patients appeared to have more severe baseline disease compared to the historical control group. All trial patients had gait disturbance and muscle weakness at baseline compared to approximately half of control patients. In addition, a higher proportion of trial patients (50%) had a history of poor growth or difficulty gaining weight compared to control patients (25%).

6.1.3 Subject Disposition
Of 102 HPP patients enrolled in clinical trials, 90 patients (88%) were continuing treatment as of the data analysis cutoff dates for each trial. Three patients discontinued treatment due to adverse events (hypersensitivity reactions and injection site reactions) and two patients withdrew consent. Seven perinatal/infantile patients died, including 1 patient who died prior to starting treatment. All juvenile-onset patients in the historical control group and in clinical trials were alive at the time of data analysis cut-off.

Reference ID: 3836304

6.1.4 Analysis of Primary Endpoint(s)

Three trial populations were reviewed in the data analyses:

- Intent-to-Treat (ITT): patients who received at least one dose of asfotase alfa
- Per Protocol (PP): all ITT patients who had no major protocol violations.
- Safety population: patients who received at least one dose of trial medication.

The Applicant performed all efficacy analyses using the ITT; some analyses were also performed using the PP population.

Reviewer Comments:
The applicant excluded nine perinatal/infantile-onset patients from PP analyses (3 patients in ENB-002-08/ENB-003-08 and 6 patients in ENB-010-10) because they did not meet all of the biochemical eligibility criteria for enrollment. Similarly, one juvenile-onset patient with Asperger syndrome (comorbid conditions were an exclusion criterion for ENB-006-09/ENB-008-10) was excluded from a PP analysis of 6MWT results. However, all of these patients had genetic confirmation of HPP. Unless otherwise noted, all efficacy results for both the perinatal/infantile- and juvenile-onset indications in this review pertain to the ITT populations.

A. Perinatal/Infantile-onset Population

The primary efficacy analysis for the perinatal/infantile-onset population was overall survival.

Statistical Analysis Plan
The Statistical Reviewer, Behrang Vali, MS, deemed the design of the individual clinical trials for the perinatal/infantile-onset population and the protocol for the retrospective natural history study to be acceptable from a statistical perspective. However, he recommended that no inferential statistics be included in labeling, since all analyses were exploratory.

Determination of Sample Size
Samples sizes for clinical trials were based on the original statistical analyses for the open-label trials for the perinatal/infantile-onset populations, which was change in RGI-C from baseline to 24 weeks.

Additional Analyses
As per the Agency's request, the applicant also performed an analysis of ventilator-free survival and subgroup analyses of overall survival and ventilator-free survival by geographic region.

Reference ID: 3836304

Analysis of Primary Endpoint
As noted earlier in the overview of the natural history of HPP, perinatal/infantile-onset disease is associated by early mortality, primarily due to respiratory complications. Additionally, growth is typically severely affected in this subgroup of patients.

The use of a historical control comparator group meets the regulatory requirements for adequate and well-controlled trials as delineated in 21 CFR 314.126. The design provides a reasonable assessment of treatment benefit because of the known natural history of high mortality rate in infancy in perinatal/infantile onset patients.

Of 70 treated perinatal/infantile-onset patients, 68 patients (97%) were included in survival analyses, based on the patients meeting eligibility criteria for the natural history study ENB-011-10. There was considerable overlap in the eligibility criteria for the natural history study and for ENB-002-08/ENB-003-08, as both were designed to select patients with severe HPP disease. Specifically, in addition to a confirmed diagnosis of perinatal/infantile-onset HPP, both protocols required that patients had clinical features such as rachitic chest deformity or seizures associated with severe disease.[39] There were no specific disease severity eligibility criteria for ENB-010-10. However, as noted earlier, baseline disease severity in both of the two perinatal/infantile-onset trial populations appeared to be reasonably comparable to the historical control group.[40]

Overall Survival- Treated Patients vs. Historical Controls
The applicant performed a Kaplan-Meier analysis of overall survival for treated patients enrolled in ENB-002-08/ENB-003-08 and ENB-010-10 (n=68) who met the entry criteria for the natural history study. The results of the survival analysis in patients with infantile-onset HPP showed that treatment improved overall survival compared with survival in historical control patients, with 62 out of 68 (91%) treated patients versus 13 out of 48 (27%) historical control patients surviving at Week 504 (9.6 years). A subgroup analysis of patients who received the proposed dosing regimen of 6 mg/kg/week for ≥1 week without dose modifications yielded similar results for the same time period, with 45/46 patients surviving.

Figure 3 presents a Kaplan Meier plot of overall survival for treated perinatal/infantile-onset patients compared with the historical control group. For the historical control group, median survival time from birth to death was approximately 9 months (271 days; 95% CI 115, 428); the median survival was not estimable for treated patients since more than half of these patients survived beyond the data cutoff.

[39] In all clinical trials for asfotase alfa, diagnostic confirmation could be established by genetic, biochemical, and/or radiographic evidence of HPP disease.
[40] Based on my review, all patients enrolled in ENB-002-08/ENB-003-08 appeared to meet the entry criteria for the natural history study. ENB-010-10 had the lowest proportion of patients with respiratory compromise (one of the clinical disease eligibility criteria for the natural history study) and therefore, the two patients excluded from the survival analyses likely were enrollees in this trial. However, the applicant did not specify which patients were excluded from the survival analyses.

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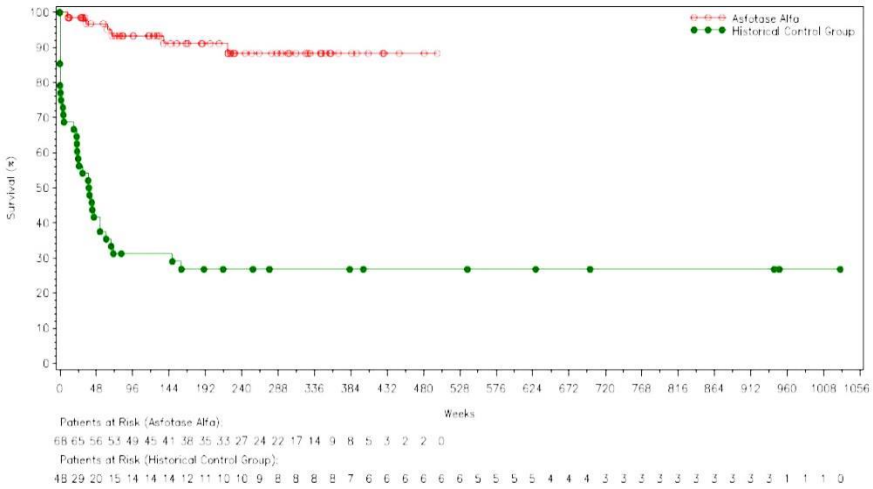
Figure 3: Kaplan Meier Plot of Overall Survival Treated vs. Historical Controls



Source: Figures for Integrated Efficacy Analysis (dated March 30, 2015), Figure 2.2.1.1.1.1.

Subgroup analyses by geographic regions also showed improved survival for treated patients compared to controls for North American (US and Canada) and for other regions. For North America, survival rates were 89% (31/35 patients) for treated patients compared to16% (6/37 patients) for controls; for non- North American regions, survival rates were 94% (31/33 patients) for treated patients compared to 64% (7/11 patients) for controls.

Survival rates for the individual trials were similar to the overall survival rate. One patient enrolled in ENB-002-08/ENB-003-08 died at approximately Month 8 of treatment after developing septic shock. The remaining ten patients were alive at the time of the data analysis cut-off date of October 29, 2014. Six of 59 patients enrolled in ENB-010-10 died following initiation of study drug deaths. Survival out to 200 weeks (~3.8 years) was approximate 83%. See Section 7.3.1 for narratives for patient deaths.

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. The lowest survival rate was observed in patients diagnosed prior to 1990; there were no survivors at 168 weeks (age 3.5 years). Five-year survival rates were similar for patients diagnosed from 2000-2004 (0.40; 95% confidence interval 0.052, 0.753) and for patients diagnosed from 2005 onward (0.43; 95% confidence interval 0.188, 0.651).

Figure 4 presents a Kaplan Meier plot of overall survival stratified by diagnosis period.

Figure 4: Kaplan-Meier Analysis of Overall Survival for the Historical Control Group by Diagnosis Period

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

Reviewer Comments:
One potential bias associated with the use of a non-concurrent historical control is the impact of changes in standard of care on the natural course of a disease. Note that there was a decrease in mortality in early infancy over time, with more infants surviving to 24 week of age who were diagnosed with HPP after 2000 compared to patients from earlier diagnosis periods. 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. However, 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.

Most noteworthy is the survival rate for trial 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.

Therefore, this reviewer considers the pooled analysis for overall survival to be robust evidence to support efficacy of asfotase alfa in perinatal/infantile onset patients.

Ventilator-Free Survival and Respiratory Support-Free Survival- Historical Control vs. Treated Patients

Invasive ventilation was defined as mechanical ventilation via intubation or tracheostomy. The median time from birth to invasive ventilation or death for the historical control group was approximately 8 months (236 days, 95% CI 78, 300). As with overall survival, the ventilator-free survival rate decreased rapidly within the first year of life and was constant after 48 months. Results for invasive ventilation-free survival were similar, with the median age to event being less than 1 year of age.

Ventilator-free survival results for the pooled treated patient group was similar to the overall survival results, with a ventilator-free survival rate of approximately 80% for the overall pooled population as well as the two geographic regions at Week 504 (9.6 years).

Figure 5 presents a Kaplan Meier plot of ventilator-free survival for treated patients compared with the historical control group.

Figure 5: Kaplan Meier Analysis of Ventilator-Free Survival Treated vs. Historical Controls

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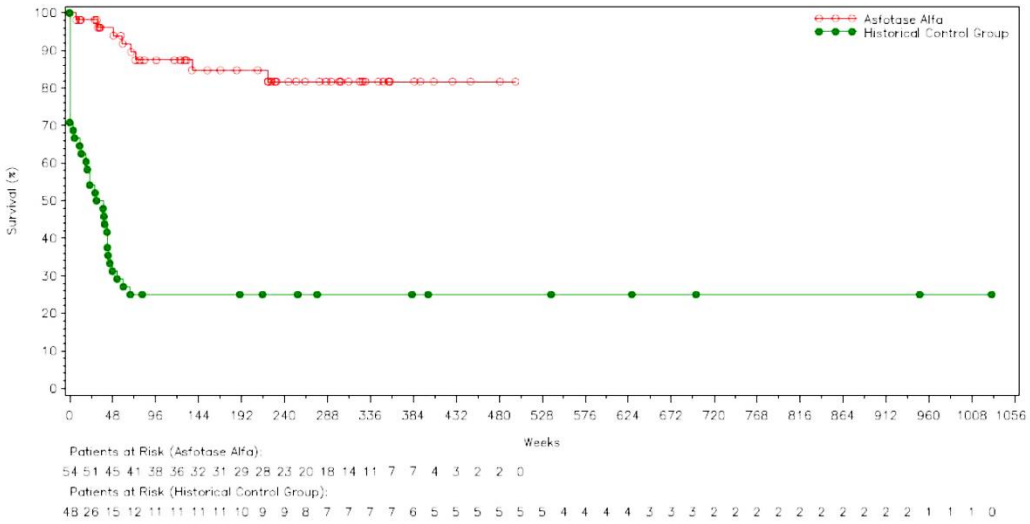


Source: Figures for Integrated Efficacy Analysis (dated March 30, 2015), Figure 2.2.1.2.1.1

Respiratory Support

The applicant also performed analyses of levels of respiratory support as a secondary efficacy analysis. In the historical control group, requirements for respiratory support differed between deceased and surviving patients (see Table 31). A majority of deceased patients (26/32 patients; 81%) required respiratory support, primarily invasive

ventilation (approximately two-thirds of all deceased patients who received respiratory support required invasive ventilation). In contrast, about one quarter of surviving patients (3/13 patients; 23%) required any form of respiratory support, primarily non-invasive forms of support (two-thirds of surviving patients received supplemental oxygen). The applicant noted that all 13 patients who were alive at the time of data abstraction were reported to have no current requirements for any form of respiratory support.

Table 31: Historical Control Group- Requirements for Respiratory Support

Category	Enrolled Patients n=48		
	All Patients n=48	Patients Deceased n=35	Patients Alive n=13
Patients requiring respiratory support- n(%)	29/45 (64)	26/32 (81)	3/13 (23)
Maximum respiratory support required- n(%)			
•Invasive ventilation	19/29 (66)	18/26 (69)	1/3 (33)
•Supplemental O2	9/29 (31)	7/26 (27)	2/3 (67)
•CPAP	1 (3)	1 (4)	0
•BiPAP	0	0	0

A majority of patients (57%) required first support within the first week of life and approximately half of patients (48%) were started on maximum support within the first week of life. Figure 6 summarizes patient age at the first occurrence of respiratory support.

Figure 6: Historical Control Group - Age at Occurrence of Respiratory Support

Source: ENB-011-10 Final Clinical Study Report (dated January 22, 2014), Figure 2

Prior to entry into ENB-002-08, 9/11 patients (82%) required some form of respiratory support, including 3 patients (Patients 002-02-01, 002-03-01, and 002-08-01) with a history of dependence on invasive mechanical ventilation. Two patients on invasive mechanical ventilation discontinued from the trial (one patient died and one patient discontinued due to an AE); the remaining patient was on no respiratory support as of the data analysis cut-off date.

Ten of 11 patients required some form of respiratory support during the trial as of the analysis cut-off date; one patient (Patient 002-04-01) needed no respiratory support prior to or at any time during the trial as of the analysis cut-off date. Starting at approximately Week 192 (Month 48) through Week 240 (approximately Month 60), all of the nine patients continuing treatment required no respiratory support.

No information was provided on past history of respiratory support for ENB-010-10 patients. Forty patients (68%) were not on respiratory support at baseline and 47 patients (80%) were not on respiratory support at last assessment. Five of 40 patients (13%) not on respiratory support at baseline required support during the course of treatment; including two patients who required transient respiratory support and three patients who required invasive ventilator support. One patient (Patient 010-25-01) required invasive ventilator support from Week 24 to Week 48, his last available assessment prior to data analysis cutoff date. Two patients required invasive ventilator support until their deaths (Patients 010-13-01 and Patient 010-19-01).

Eleven of 19 patients (58%) who required respiratory support at baseline no longer required support or achieved a reduced level of support at their last available assessment. Four of 11 patients (36%) who required invasive ventilator support at baseline no longer required support or achieved a reduced level of support at their last available assessment; 3 patients were on no support and one patient received supplemental oxygen. Two of 3 patients on CPAP at baseline were weaned to no support and all 5 patients on supplemental oxygen at baseline were weaned to no support during the course of treatment.

Table 32 summarizes levels of respiratory support at baseline and last assessment for treated patients.

Table 32: ENB-002-08/ENB-003-08- Shifts in Level of Respiratory Support from Baseline to Last Patient Assessment

	ENB-002-08/ENB-003-08			ENB-010-10		
Level of Respiratory Support	**Past History n=11**	**Baseline n=11**	**Last Assessment n=11**	**Past History n=59**	**Baseline n=59**	**Last Assessment n=59**
No support- n (%)	2 (18)	6 (55)	8 (89)	--	40 (68)	47 (80)
Supplemental O_2- n(%)	4 (36)	1 (9)	1 (11)	--	6 (10)	1 (2)
CPAP/BiPAP- n (%)	2 (18)	1 (9)	0	--	2 (3)	1 (2)
Invasive mechanical ventilation- n (%)	3 (27)	3 (27)	2	--	11 (11)	10 (17)

0_2=oxygen; CPAP= continuous positive airway pressure; BiPAP= biphasic positive airway pressure

Reviewer Comments:
Overall, the results demonstrated that patients at all levels of respiratory support improved with treatment, including patients requiring invasive ventilator support at trial entry. Few patients required a higher level of respiratory support during treatment compared to historical or baseline levels of support. Three ENB-002-08/ENB-003-08 patients and 2 ENB-010-10 patients transiently required a higher level of respiratory support compared to his/her historical or baseline levels of support due to intercurrent respiratory infections or respiratory distress; none of these patients were on respiratory support at the time of their last assessments. Three ENB-010-10 patients required higher levels of respiratory support at last assessment compared to baseline; all three patients required invasive ventilation (two patients died and one patient continued on invasive ventilation at the time of data analysis cutoff).

B. Juvenile-Onset Population

The primary efficacy endpoint was change from baseline in gait.

Statistical Analysis Plan

The Statistical Reviewer, Behrang Vali, MS, deemed that both the post-hoc analysis for the primary endpoint and use of a nonconcurrent historical control group for the juvenile-onset population were not adequate statistical approaches, noting that it was feasible to conduct an adequate and well-controlled in this population. He recommended that no inferential statistics be included in labeling, since all analyses were exploratory.

Determination of Sample Size

Sample size for ENB-006-09 was based on the original planned analyses for the trials which were change in RGI-C from baseline to 24 weeks.

Additional Analyses

As per the Agency's request, the applicant also provided analyses of correlation between the mPOMA-G and the 6MWT.

Analysis of Primary Endpoint
As noted earlier in the overview of the natural history of HPP, the predominant clinical feature of juvenile-onset disease is bone disease, which manifests as impaired gait, bone pain and muscle weakness. Thus gait represents a clinically relevant endpoint for this disease population. However, as pointed out by the Statistical Reviewer, Benjamin Vali, M.S., the level of evidence presented from the gait analysis is not robust from a statistical perspective because it was determined post-hoc and was based on historical control data collected retrospectively after results for the clinical trials were already known. The Statistical Reviewer pointed out that, in contrast to the perinatal/infantile-onset population, it was feasible to conduct a prospective, randomized, controlled trial in the juvenile-onset population. This reviewer agrees with the Statistical Reviewer's assessment of the statistical validity of the gait analysis.

In addition, the sponsor did not provide adequate clinical justification of the appropriateness of the gait measurement used for the analysis. The applicant performed a post-hoc analysis of gait as measured by the modified Performance Oriented Mobility Assessment-Gait (mPOMA-G) as the primary endpoint for the juvenile-onset HPP population. The initial primary endpoint for ENB-006-08 was change in rickets severity (as measured by the RGI-C scale) in treated patients compared to a historical control group. However, the Agency determined that a clinical endpoint was needed to support full approval for the juvenile-onset population and the applicant subsequently proposed change in gait as the primary efficacy endpoint. The Agency agreed that change in gait was an appropriate clinical endpoint but noted that applicant would need to describe what degree of change in gait would be considered clinically meaningful in this population (see pre-BLA meeting minutes dated July 2, 2014). In this reviewer's opinion, the applicant did not provide sufficient information to determine the suitability of the mPOMA-G as a tool to measure gait in the juvenile-onset HPP population. In addition, as noted later, the applicant did not provide a rationale for what constitutes a minimal clinically important change in gait for this population. Therefore, from a clinical perspective, this reviewer considers the gait analysis to be inadequate as the sole evidence to support of an efficacy claim for the juvenile-onset indication.

mPOMA-G- Treated Patients vs. Historical Controls
Gait videos were read by three trained physical therapists who did not participate in the clinical care of enrolled patients and who were blinded to patient identifiers and dates of video recording. Videos obtained for the 6MWT for ENB-006-09/ENB-008-10 patients were re-evaluated and scored for gait. Gait videos obtained as part of routine clinical evaluation were available for a historical group of patients followed at Shriners Hospitals for Children (St. Louis, MO).

Dr. Teresa Buracchio reviewed the gait videos and gait data and evaluated the relationship of the gait data to 6MWT and strength assessments. Gait assessment data for 8 treated patients enrolled in ENB-006-09/ENB-008-10 were compared with gait assessment data for 6 historical control patients. The median (range) rate of change

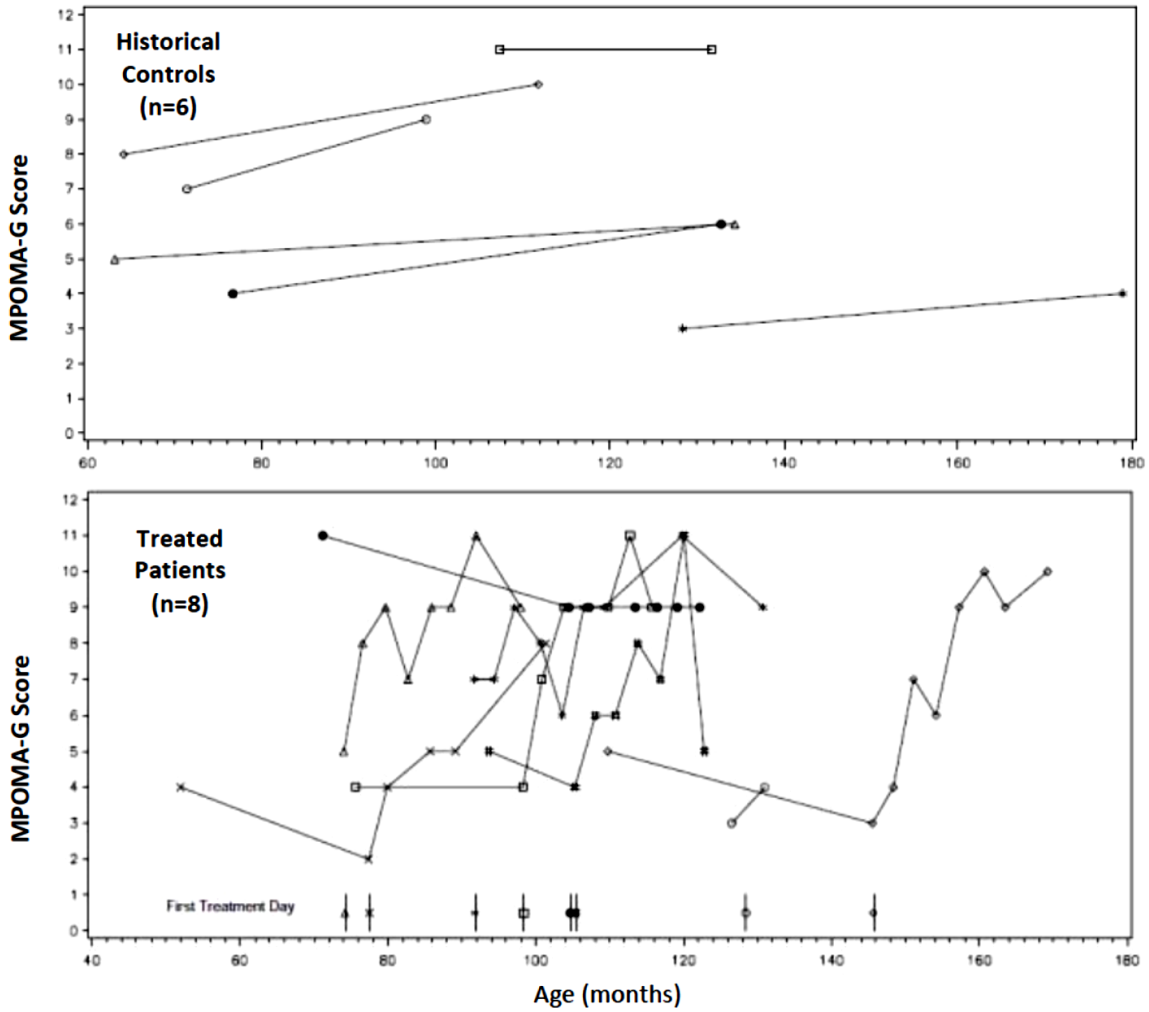
Reference ID: 3836304

per year was 2.51/year (0.0, 4.6) in asfotase alfa-treated patients compared with 0.33/year (0.0, 0.9) for untreated historical controls (p=0.0303, Wilcoxon rank-sum test).

Due to varying durations of treatment for patients, the applicant also performed a secondary analysis of the absolute change in mPOMA-G scores from baseline to last Assessment; the analysis showed a median increase of 3.0 (0, 7) for asfotase alfa-treated patients, compared with a median increase of 1.5 (0, 2) for historical controls (p=0.2561, Wilcoxon rank-sum test). Dr. Buracchio noted that the greatest improvement in scoring components for gait assessment was seen in step length. Six of 8 treated patients (75%) showed at least a 1 point improvement in step length in either foot compared to 1/6 historical control patients (17%) who showed any improvement with either foot.

Figure 7 presents gait assessment results for historical controls and treated patients.

Figure 7: MPOMA-G Results for Historical Controls vs. Treated Patients



Source: Figures for Integrated Efficacy Analysis (dated December 5, 2014), Figures 3.2.1.6.1.3 and 3.2.1.6.1.4.

The sponsor has reported a high correlation between the mPOMA-G and 6MWT. The 6MWT (expressed as distance walked in meters) and mPOMA-G, for Baseline and the last mPOMA-G assessment, showed a strong correlation (Pearson's Correlation Coefficient of 0.8574) that was statistically significant ($p<0.001$).

Reviewer Comments:
There are a number of limitations to the interpretability of these results including the fact that the assessment was performed post-hoc, lack of validation of the mPOMA-G in the HPP population, differences in baseline disease severity, and the methodology used.

Regarding the validation of the test, Dr. Buracchio commented:

> *"The POMA-G uses qualitative assessments of common gait abnormalities in the elderly that may predispose individuals to falls. Although the POMA-G measures some commonly assessed gait parameters such as step or stride length and step symmetry, it should be noted that there is no established uniform set of gait parameters used in assessment of gait. The scale has been used clinically and in research studies in the elderly population as a risk assessment tool for falls. It has also been used to assess risk for falls in diseases common in the elderly such as dementia, stroke, and Parkinson's disease. It is not commonly used in the pediatric community but the sponsor has provided one literature reference of its use in children with hearing impairment.*[41]
>
> *The POMA scale was developed for use as a screening tool to assess risk for falls with a cut-off score and it was not originally intended to be used as a continuous measure of gait change; however some observational longitudinal research studies have attempted to analyze it this way. The scale was also originally validated with combined administration of both gait and balance subscales and the subscales have not been independently validated. Although researchers have used the POMA subscales independently and as continuous measures, a clinically meaningful change on the total scale or on the gait subscale has not been established."*

Regarding baseline disease severity, note that baseline mPOMA-G scores were generally lower in treated patients compared to historical controls. All patients in both groups had a history of gait disturbance; however, a higher proportion of treated patients reported musculoskeletal symptoms that likely would impede gait. All 8 treated patients reported a history of bone deformity, arthralgia/joint pain, bone pain, and muscle weakness compared to 3/6 historical control patients. Dr. Buracchio also noted that step length may increase with age and that therefore patient age (or change in height) should be considered in reviewing the results.

Regarding the methodology for the gait assessments, Dr. Buracchio noted that there were several potential sources of bias or variability in the methods used, including lack of a uniform method for administering the assessments, and differences in the format of the videos and the clinical assessments recorded between the treatment groups. In addition, Dr. Buracchio pointed out that it was unclear whether the physical therapists scoring the videos were specifically trained on the mPOMA-G scale and whether there was adequate inter-rater reliability.

Dr. Buracchio also discussed the limitations to interpretation of the correlation between the 6MWT and the mPOMA-G:

[41] de Souza Melo R, da Silva P, Tassitano R, Macky C, daSilva L. Balance and gait evaluation: comparative study between deaf and hearing students. *Rev Paul Pediatr.* 2012; 30(3):385-91.

> *"I could find no previously reported correlations between the two measures for comparison. It is expected that there will be some correlation between the 6MWT and the mPOMA-G as certain measures such as step length captured on the mPOMA-G will clearly influence the distance that is walked. However, the correlation reported by the sponsor may be inflated since the mPOMA-G was assessed by a video taken as a part of the 6MWT. For a more accurate correlation, the two measures should be obtained independently."*

Given the multiple limitations to interpretation of the gait assessment findings, although the findings suggest treatment benefit, I consider the gait assessment results to be inconclusive for efficacy in the juvenile-onset population. However, as discussed later, the totality of evidence demonstrates efficacy in the juvenile-onset population.

6.1.5 Analysis of Secondary Endpoints(s)

Endpoints treated as secondary endpoints in the applicant's pooled analyses for the submission are discussed in this section. However, as noted earlier, all statistical analyses were developed post-hoc and therefore are exploratory.

A. Radiographic Assessments

Radiographic findings in all trials demonstrated an improvement in both radiographic assessments of skeletal abnormalities over time. Radiographic evidence of response was documented by Week 24 across trials and HPP phenotypes, with a majority of patients (51/83 patients; 61%) being classified as responders (RGI-C score of 2 or higher) by Week 48 of treatment.

The applicant performed pooled analyses that demonstrated that 68/75 perinatal/infantile-onset patients were RGI-C responders at last assessment. All 8 juvenile-onset patients were RGI-C responders at last assessment. The applicant performed correlation analyses that showed that both RGI-C and RSS correlated well with height, an important measure of bone health in children (Pearson correlations of 0.418 and -0.693, respectively).

Radiographs from 8 juvenile-onset patients were compared to radiographs for 32 historical controls to assess the treatment effect of asfotase alfa on HPP-related rickets. All treated patients were rated as responders by Month 54 of treatment. Two of 32 historical control patients (6%) were rated as responders at last assessment. A majority of historical control patients (28/32) patients had RGIC scores between -1 and <1 at all time points), indicating that there is minimal change of radiographic findings over time in untreated patients. Treated patients had more severe rickets at baseline based on baseline RSS score; analyses of RGI-C scores adjusted for baseline RSS also demonstrated a positive treatment effect.

Due to differences in treatment duration and dosing regimens between trials, results for the individual trials are also presented below.

Perinatal/infantile Onset Population

- **ENB-002-08/ENB-003-08**

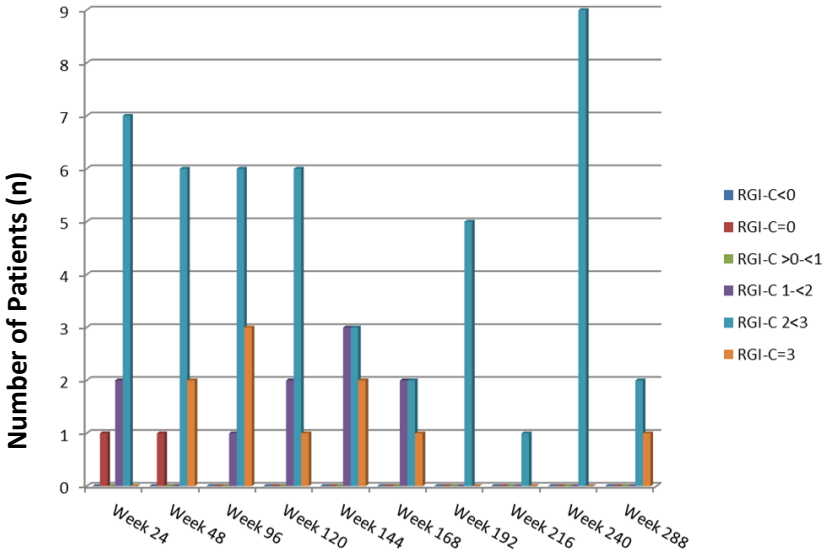
RGIC

RGI-C data were available were available for 9/11 patients (82%) up through Week 240 (one patient had no post-baseline data available and one patient died at Week 30). All nine patients achieved and sustained RGI-C scores of 2 or higher.

Reviewer Comments:
One patient (Patient 002-02-01) had no change in RGI-C or RSS score up through Week 48. Following a dose increase from 6 mg/kg/week to 9 mg/kg/week at Week 80, the patient achieved and sustained RGI-C scores of 2 from Week 120 up through her last assessment at Week 288. Her RSS score decreased to and remained at 6 from Week 240 up through her last assessment at Week 288.

Figure 8 presents the proportion of patients in each RGI-C score category over time.

Figure 8: ENB-002-08/ENB-003-08- RGI-C Scores Distribution over Time

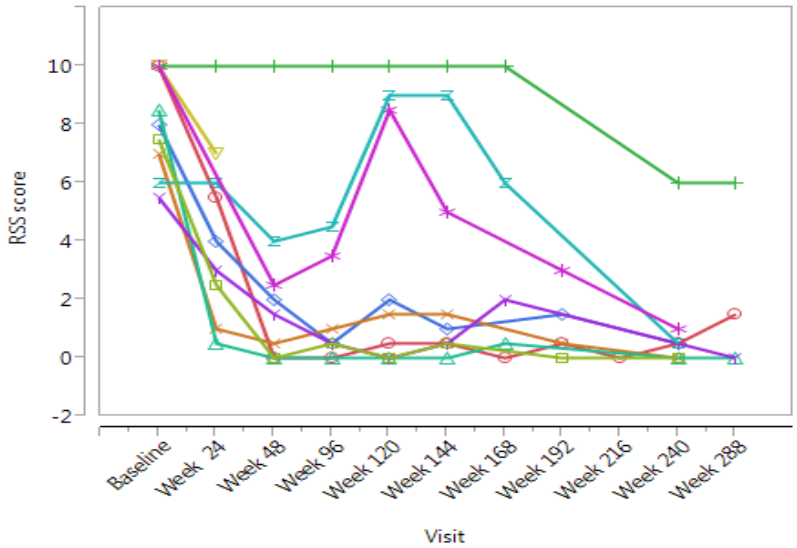


RSS

RSS data were available for 9/11 patients (82%) up through Week 240 (one patient had no post-baseline data available and one patient died at Week 30). Baseline RSS scores ranged from 6 to10. RSS scores improved (scores decreased) for all patients, with 8 patients achieving RSS scores ≤1.5, indicating mild rickets severity.

Figure 9 presents the change in individual patient RSS scores over time.

Figure 9: ENB-002-08/ENB-003-08- Individual Patient RSS Scores over Time



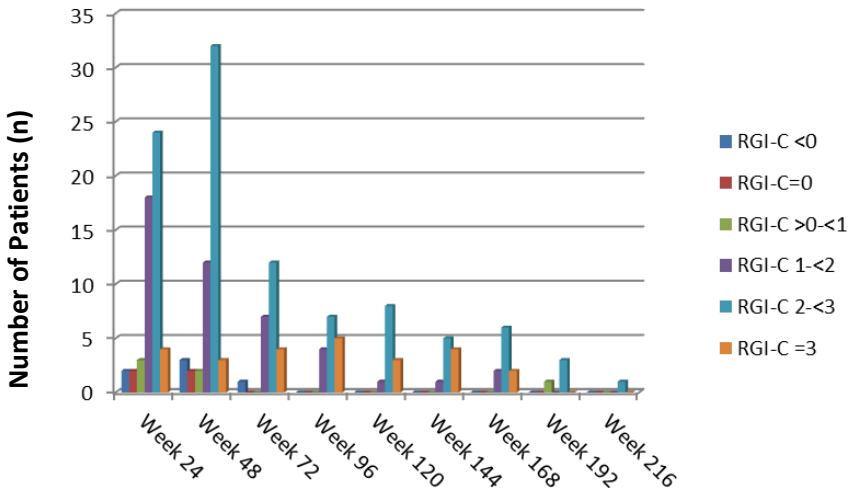
- **ENB-010-10**

RGIC

RGI-C scores were available for 54/59 patients (92%). Twenty-eight patients had data available for up to their Week 48 assessment; 24 patients had data available up to Week 72 or later. Of the 54 patients for whom RGI-C data were available, 36 patients (67%) achieved and sustained RGI-C scores of 2 or higher over time.

Figure 10 presents individual patient RGI-C scores over time for ENG-010-10.

Figure 10: ENB-010-10- Individual Patient RGI-C Scores Over Time



Of the 18 patients who were non-responders, five patients experienced no change (RGI-C score of 0) or a decline in RGI-C scores; 2 patients achieved RGI-C scores of ≥2 at least once but had RGI-C scores <2 at their last available assessment.

Nine patients had their doses increased to greater than 6 mg/kg/week (doses ranged from 7.5 mg/kg/week to 28 mg/kg/week), with 7 patients achieving and sustaining RGI-C scores of ≥2 following the dose increase (the remaining two patients achieved a RGI-C score of ≥2 at least once but had RGI-C scores <2 at their last available assessment). Twelve of the 18 patients who were non-responders had been treated for 48 weeks; the remaining 6 patients had been treated for 72 weeks or longer.

One patient had a RGI-C score of 0 at Week 24. The patient's dose had been decreased from 9 mg/kg/week to 3 mg/kg/week due to an AE of pneumonia assessed as possibly treatment-related.

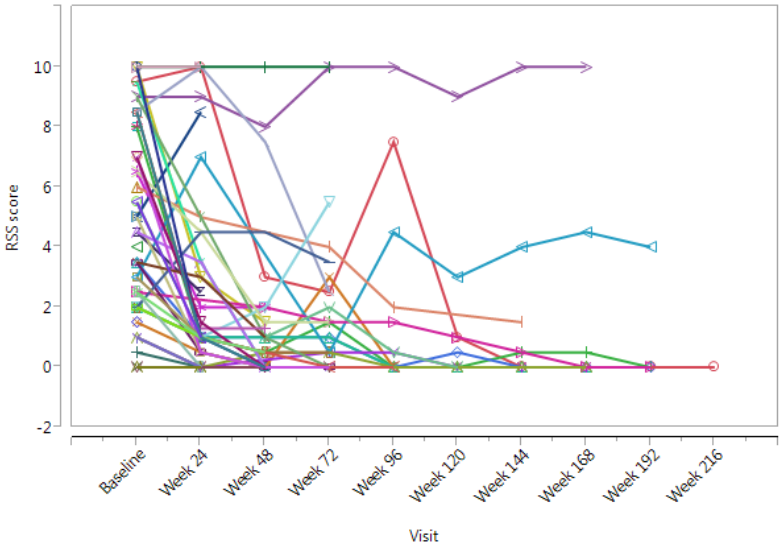
Reviewer Comments:
One patient had no response in RGI-C score died of cardiorespiratory arrest after approximately 28 weeks of treatment. Based on my review of the information provided, there did not appear to be any clear causal relationship between treatment and the reported AE of pneumonia (see patient narrative for Patient 010-10-19-01 in Section 7.3.1 for further details.)

EMA-Specified Primary Efficacy Analysis (Change in RGIC at Week 48)
The applicant performed an analysis of change in RGI-C from baseline to Week 48 as the EMA-specified primary efficacy analysis for ENB-10-10. Patients treated less than 48 weeks were excluded from the analysis. Median RGI-C scores for the ITT population were 2.0, with 23/33 patients (70%) achieving RGI-C scores of 2 or higher.

RSS
Baseline RSS scores were available for 58/59 (98%) patients. Median RSS score at baseline was 4 (range was 0 to 10).
Thirty-two of 43 patients (74%) with available RSS data at Week 24 or later experienced improvements in RSS scores, with15/34 patients (44%) achieving RSS scores of zero. Seven of 43 patients (16%) experienced worsening scores or no improvement. For the 43 patients with available RSS data at Week 24 or later, the median RSS score at last assessment was 0 (range was 0 to 10).

Figure 11 presents individual patient RSS scores over time for ENB-010-10.

Figure 11: ENB-010-10-Individual Patient RSS Scores over Time



<u>Juvenile-onset Population</u>

- **ALX-HPP-502 (Juvenile-Onset Historical Control Group)**

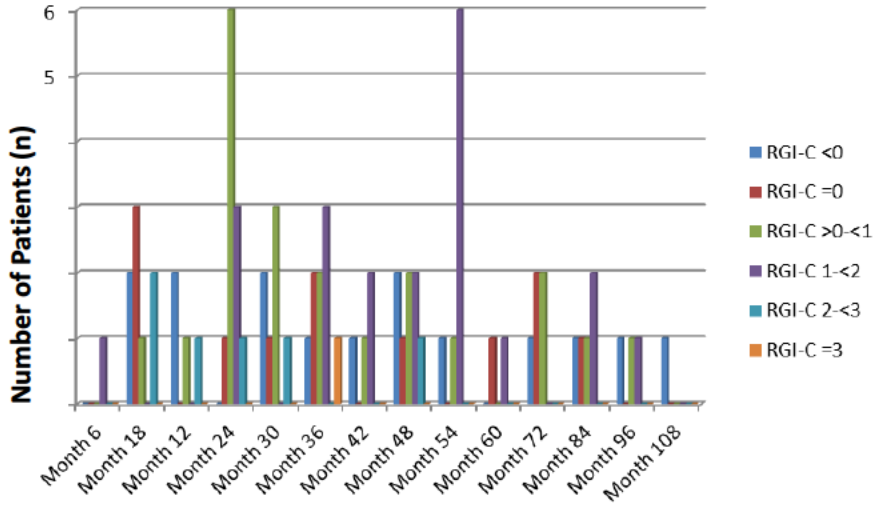
Twenty-eight of 32 patients had evaluable paired x-ray films. The mean time interval between x-ray evaluations was 42 months (range was 4.5 months to 95 months). The majority of patients (75%) had paired films obtained 4 years or more apart; one patient had paired x-ray films obtained less than 24 months apart.

The most commonly observed radiographic skeletal abnormalities at baseline were osteopenia, irregular provisional zone of calcification, metadiaphyseal sclerosis, apparent physeal widening, and irregular zone of calcification.

RGIC

The median change in RGI-C score at last assessment was 0.3 (range was -2.3 to 2.3). As last assessment, 18/ 32 patients (56%) had improved RGI-C scores and 14/ 32 patients (44%) had worsening or no change in RGI-C. Figure 12 summarizes changes in RGI-C score category over time.

Figure 12: Historical Controls- Indivdidual Patient RGI-C Scores Over Time



Reviewer comment:
The majority of patients (28/32) patients had RGIC scores between -1 and <1 at all time points), indicating that there is minimal change of radiographic findings over time in untreated patients. In his consult review, Dr. Voss pointed out that treated patients had more severe rickets at baseline (based on baseline RSS score) than the control group, and therefore had greater potential for improvement. He noted that the applicant analyzed RGI-C scores with adjustment for baseline RSS and reported that the adjustment analysis also demonstrated a positive treatment effect.

RSS

Twenty-seven of 32 patients had baseline radiograph eligible for RSS scoring. Eight of 32 patients (25%) had no evidence of rickets as measured by the RSS scale (i.e., no growth plate abnormalities); all 8 patients had documented evidence of other HPP-related skeletal abnormalities based on the RGI-C scale The median RSS score at baseline was 1 (range was 0 to 3.5). No significant changes in RSS scores were observed over time (see Table 33). At last assessment, the median change in score of 0 (range was -2 to 1.5; n=26).

Reviewer Comment:
The historical group RSS findings highlight the limitations of using the RSS to assess disease progress or treatment response in HPP patients. Because the RSS only assesses growth plate involvement, it is not designed to capture some bone findings of HPP-related rickets that involve bone areas away from the growth plates, such as rib abnormalities (findings also seen with nutritional rickets) or metaphyseal areas of sclerosis or lucency (findings unique to HPP-related rickets).

Table 33: Historical Controls- RSS Scores over Time (n=32)

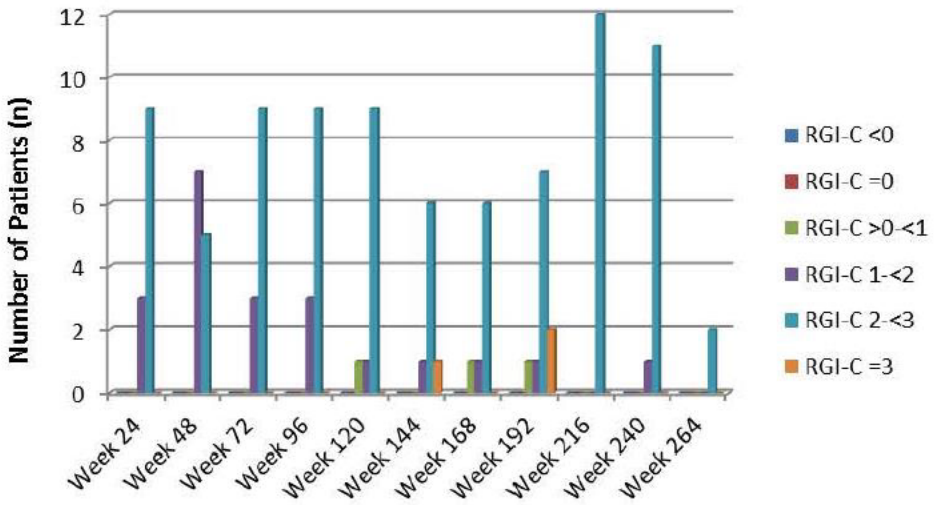
Statistic	Baseline	Month 12	Month 24	Month 36	Month 48	Month 72	Last Assessment
n	27	6	9	7	10	6	27
Mean (SD)	1.1 (1.1)	1.1 (1.4)	0.5 (0.6)	0.9 (1.1)	1.2 (0.7)	0.8 (0.6)	1.3 (0.9)
Median	1	0.5	0.5	0.5	1	0.5	1.4 1
Min, Max	0,1.5	0, 1.5	0, 1.5	0, 3	0.5, 3	0.5, 2	1.5 0, 3.5

- **ENB-006-09/ENB-008-10**

RGI-C

Twelve of 13 patients were responders at the time of their last assessment (Week 216 to Week 264); one perinatal/infantile onset patient had no post-baseline x-rays (see Figure 13).

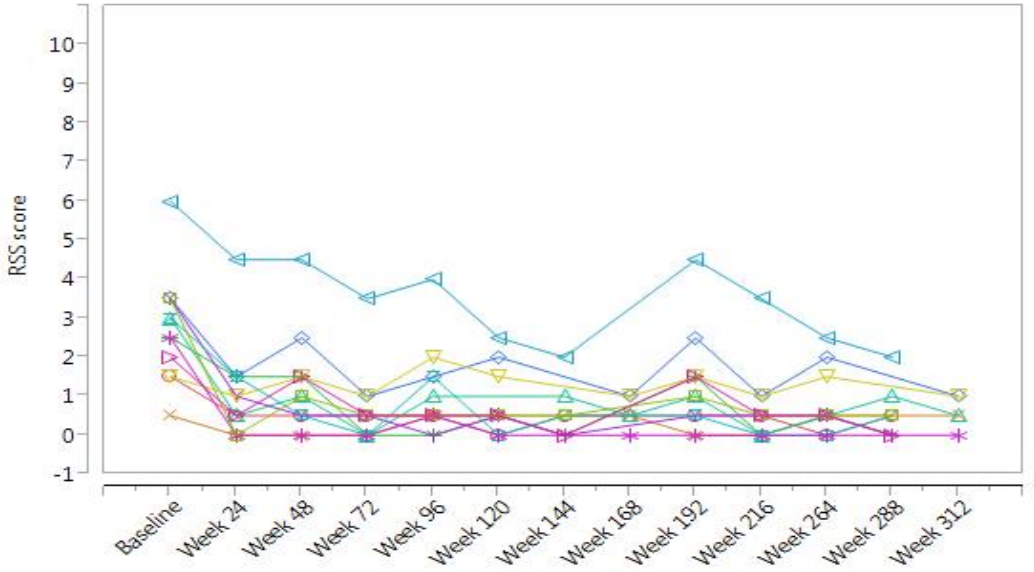
Figure 13: ENB-006-09/ENB-008-10- RGI-C Scores over Time



RSS

RSS scores were available for 12/13 patients (see Figure 14). At last assessment, RSS scores decreased in 11/12 patients from baseline to last assessment; one perinatal/infantile-onset patient's score remained stable at 0.5. Median RSS scores at baseline and last assessment were 2.8 (range was 0.5 to 6) and 0.5 (range was 0 to 2), respectively.

Figure 14: ENB-006-09/ENB-008-10- Individual Patient RSS Scores over Time



- **ENB-009-10**

RGIC

RGIC measurements were obtained for the six pediatric patients enrolled in ENB-009-10, including 3 patients randomized to the control group and 3 patients randomized to treatment during the primary treatment phase of the trial. All 6 patients experienced improvements in RGI-C scores, with RGI-C scores ranging from 0.33 to 2.3 at last assessment. Two patients (both randomized to the control group) were RGIC-responders at their last assessment at 192 weeks.

RSS

RSS scores were available for 3/6 adolescent patients. All three patients experienced decreases in RSS scores (change in RSS scores ranged from -2 to -6).

Reviewer Comments:
The time course to response was similar for adolescent patients compared to younger pediatric patients, with most patients showing improvements in radiographic assessments by Week 24. However, the magnitude of change was smaller in the earlier part of treatment. For example, the patients who were RGI-C responders did not become responders until Week 168 and Week 192 of treatment. As noted earlier, patients received lower doses than the proposed labeled dose of 6 mg/kg/week for a large portion of their treatment course. Thus, these findings are likely due to patients' receiving a suboptimal dose of asfotase alfa for a portion of their treatment course.

B. Growth

Perinatal/infantile-onset Population

No control group data for growth were available for the perinatal/infantile onset population. Growth trends were similar to the trends observed for RGI-C, with a majority of patients who achieved improved height z-scores also having sustained improvement in height and weight growth from Month 6 onward.

A majority of patients in ENB-002-08/ENB-003-08 and ENB-010-10 had severe growth retardation at baseline, with 53/70 patients (76%) having height z-scores and 51/70 patients (73%) having weight z-scores below the 3rd percentile for age.[42] Mean baseline height and weight z-scores for patients in these trials were -3.3 and -3.2, respectively. At last assessment, the mean height and weight z-scores were -2.9 and -2.4, respectively. The mean time interval between baseline and last assessment was 21 months (range was 1 month to 72 months).

In ENB-006-09/ENB-008-10 and ENB-009-10, 3/8 perinatal/infantile-onset patients had baseline height z-scores below the 3rd percentile for age and 2/8 patients had weight z-scores below the 3rd percentile for age. Mean baseline height and weight z-scores were -2.6 and -2.5, respectively. The mean time between baseline and last assessment was 56 months (range was 53 to 60 months).

In the overall perinatal/infantile-onset population (n=78), weight z-scores improved in 56/72 patients (78%) and height z-scores improved in 50/71 patients (70%). Mean change in weight z-score from baseline to the last assessment was 0.9 (range was -4.2 to 5.3). Mean change in height z-score from baseline to last assessment was 0.5 (range was -4.4 to 4.9).

As discussed below, the results indicate that there is a range of dose response for growth, with some patients appearing to benefit from doses of asfotase alfa higher than 6 mg/kg/week. Some critically ill perinatal/infantile-onset patients were treated with doses higher than the 9 mg/kg/dose increase allowed in trial protocols. For the majority of patients, changes in height and weight followed similar trends (i.e., patients experienced improvement or deterioration in both parameters).

- **ENB-002-08/ENB-003-08**

Height

Ten of 11 patients (91%) enrolled in ENB-002-08/ENB-003-08 had baseline height z-scores below the 3rd percentile for age. Of the 10 patients who entered ENB-003-08, 6 patients (60%) had improved z-scores at their last assessment, including three patients who achieved normal for age height z-scores. For patients whose height z-scores

[42] Two patients only had post-baseline height data; both had height z-scores well below the 3rd percentile for age.

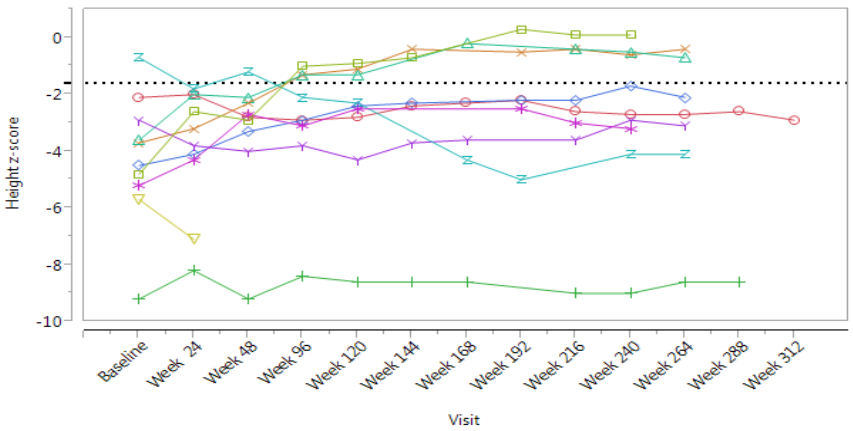
improved, changes in z-scores ranged from 0.6 to 4.9. Figure 15 presents the shift in height z-scores over time for ENB-002-08/ENB-003-08.

Figure 15: ENB-002-08/ENB-003-08- Height Z-scores Distribution over Time

Baselin

Four patients (40%) had worsening height z-scores over time; including two patients who also experienced a decline in weight z-score. The sole patient who had a normal baseline height z-score experienced the largest score decline (her height z-score declined from -0.7 at baseline to -4.1 at Week 264, a change of -3.4). For patients whose height z-scores declined, changes in z-scores ranged from -0.2 to -3.4. Figure 16 presents individual patient height z-scores over time.

Figure 16: ENB-02-008/ENB-03-008- Individual Patient Height Z-scores over Time



NB: Values at or above the dotted line represent scores within normal range for age (i.e., z-scores $\geq 5^{th}$ percentile for age)

Weight

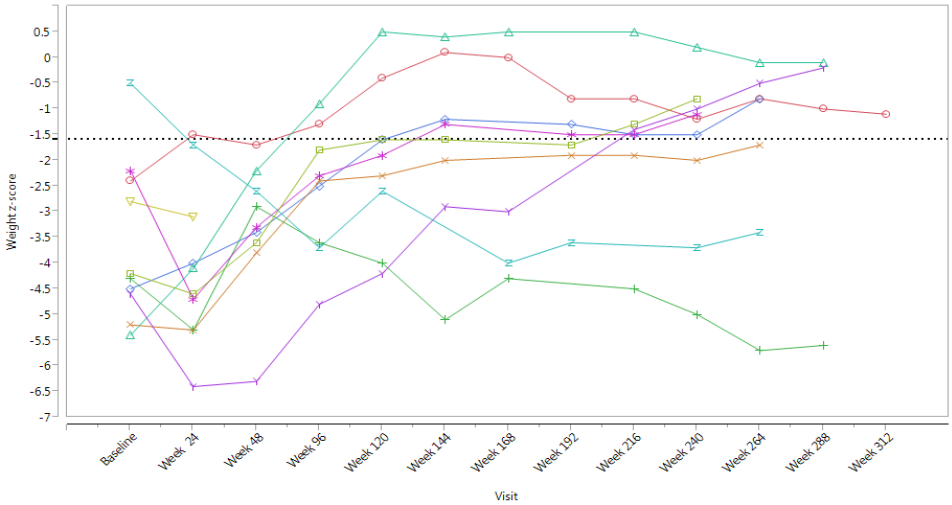
Nine of the 11 patients (82%) enrolled in ENB-002-08/ENB-003-08 had baseline weight z-scores below the 3rd percentile for age. Of the 10 patients who entered ENB-003-08, 7 patients (70%) achieved and sustained normal for age weight z-scores. For patients whose weight z-scores improved, increases in z-scores ranged from 1.1 to 5.3. Figure 17 presents the shift in weight z-scores over time for ENB-002-08/ENB-003-08.

Figure 17: ENB-02-008/ENB-03-008- Weight Z-scores Distribution over Time

Baselir

Three patients (30%) had worsening weight z-scores over time, including two patients who also experienced worsening height scores. The sole patient who had a normal baseline weight z-score experienced the largest decline in score (her weight z-score declined from -0.5 at baseline to -3.4 at Week 264, a change of -2.9). For patients whose weight z-scores declined, decreases in z-scores ranged from -0.3 to -2.9. Figure 18 presents individual patient weight z-scores over time.

Figure 18: ENB-02-008/ENB-03-008- Individual Patient Weight Z-scores over Time



NB: Values at or above the dotted line represent scores within normal range for age (i.e., z-scores $\geq$5th percentile for age)

Reviewer Comments:
I reviewed the dosing data for the five patients who did not experience an improvement in height and/or weight at last assessment. As noted earlier, all patients in the trial had their doses increased from 3 mg/kg/week to 6 mg/kg/week, with the majority of dose increases implemented at Week 12 of treatment. The data indicate that dosing at higher than 6 mg/kg/week may be necessary in some patients for optimal growth.

Three patient received doses higher than 6 mg/kg/week for some portion of their treatment courses. These included two patients (Patient 002-01-01 and Patient 002-02-01) whose doses were increased to 9 mg/kg/week, based on PK results that revealed exposures below the target range. Patient 002-01-01's height z-score was stable on the 9 mg/kg/week dose regimen and then worsened when her dose was reduced back to 6 mg/kg/week (the dose reduction was based on repeat PK results that revealed an exposure exceeding the target range). Patient 002-02-01's height z-score but not weight z-score improved on the 9 mg/kg/week dosing regimen; she remained on the 9 mg/kg/week regime. The third patient (Patient 002-09-02), had a dose adjustment from 6 mg/kg/week to12 mg/kg/week based on a decline in his alkaline phosphatase level; he continued to experience declines in height and weight z-scores up through his last assessment.

The remaining two patients who experienced a decline in growth (Patient 002-06-01 and Patient 002-08-01) received dose increases of 6 mg/kg/week early on in treatment but received no further dose increases. Patient 002-06-01 initially experienced a worsening z-score; however, at last assessment, his height z-score had essentially returned to baseline (baseline z-score was -2.9 and last assessment score was-3.1). Patient 002-

08-01 experienced declines in both height and weight z-scores, including one patient who died of sepsis at approximately Week 30 of treatment.

Immunogenicity did not appear to factor into the difference in growth response. The two patients who experienced worsening of both height and weight growth were antibody-negative throughout their treatment course. The other three patients were ADA-positive but had transiently positive neutralizing antibodies.

- **ENB-010-10**

Height

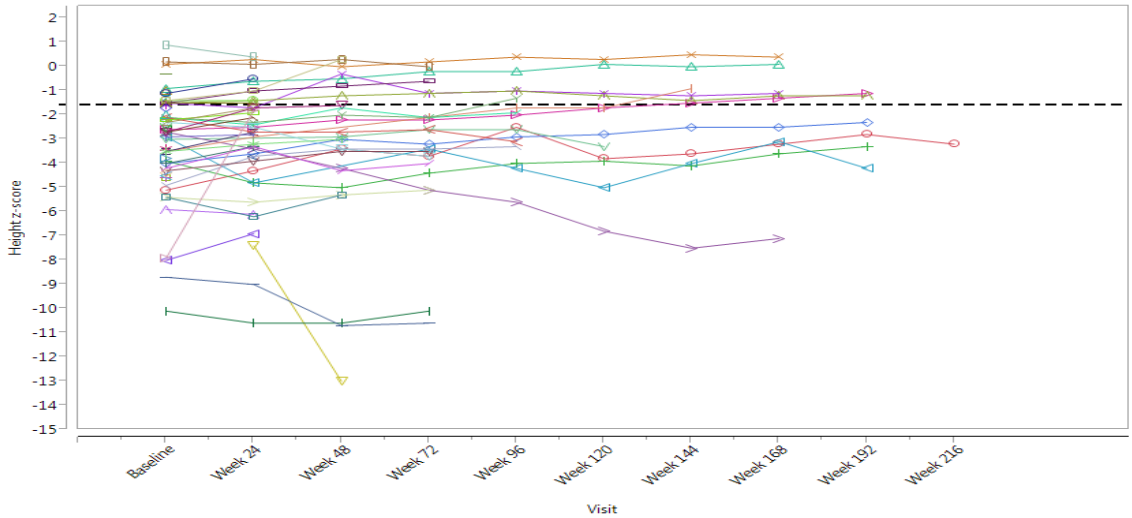
Forty-six of the 59 patients (78%) enrolled in ENB-010-10 had baseline height z-scores below the 3rd percentile for age. Thirty of 41 patients (75%) with baseline and post-baseline height measurements achieved improved height z-scores, including four patients who achieved normal for age height z-scores. For patients whose height z-scores improved, changes in z-scores ranged from 0.1 to 6.1.

Three patients experienced no change in height z-score, including two patients with normal for age baseline z-scores and one patient with severe growth failure at baseline (baseline z-score was -10.1)

Eight of 41 patients (20%) had worsening height z-scores over time. For patients whose height z-scores declined, changes in z-scores ranged from -0.2 to -4.4.

Figure 19 presents individual patient height z-scores over time.

Figure 19: ENB-010-10- Individual Patient Height Z-scores over Time



NB: Values at or above the dotted line represent scores within normal range for age (i.e., z-scores ≥5th percentile for age)

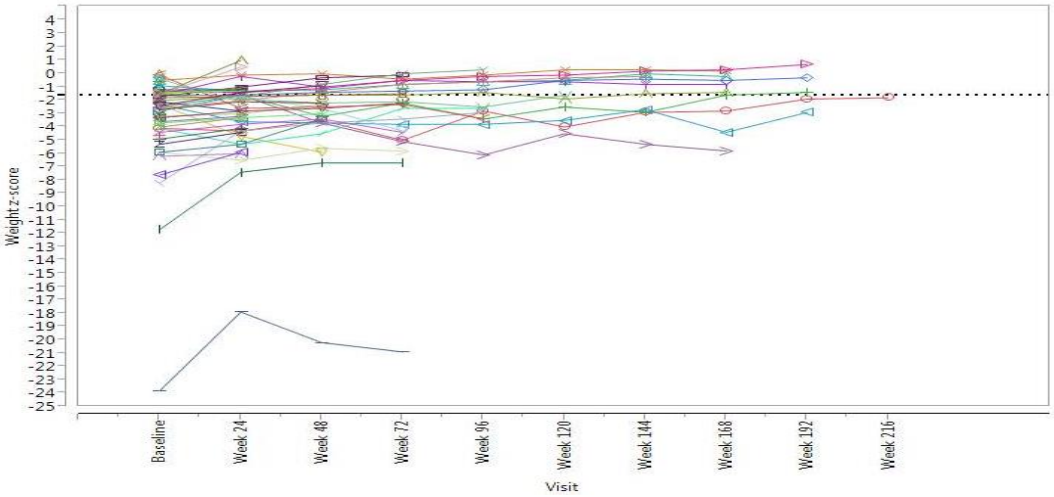
Weight

Thirty-four of the 59 patients (58%) who entered ENB-010-10 had baseline weight z-scores <-2 (<3rd percentile for age). Thirty-three of 43 patients (77%) with baseline and post-baseline weight measurements achieved improved weight z-scores, including seven patients who achieved normal for age weight z-scores. For patients whose weight z-scores improved, changes in z-scores ranged from 0.1 to 5.3. Three patients experienced no change in weight z-score.

Seven of 43 patients (20%) had worsening weight z-scores over time. For patients whose weight z-scores declined, changes in z-scores ranged from -0.6 to -4.2.

Figure 20 presents individual patient weight z-scores over time.

Figure 20: ENB-010-10- Individual Patient Weight Z-scores over Time



NB: Values at or above the dotted line represent scores within normal range for age (i.e., z-scores $\geq 5^{th}$ percentile for age)

Reviewer Comments:
Growth trends were similar to the trends observed for RGI-C, with the majority of patients who achieved improved height z-scores and weight z-scores having sustained improvement in growth from Month 6 onward. As observed in ENB-002-08/ENB-003-08, some patients appeared to benefit from a dose increase. Ten patients received dose increases (doses ranged from 7.5 mg/kg/week to 28 mg/kg/week), with five patients achieving improvement in both height and weight z-scores following the dose increase.

I reviewed the treatment duration and dosing regimens for the 10 patients who had unchanged or worsening growth scores. Four of 10 patients had been treated for 48 weeks or less:

- *Patient 010-01-07 received a non-protocol dose of 14 mg/kg/week and continued to have worsening height and weight z-scores up through Week 48*
- *Patient 010-13-05 was receiving 6 mg/kg/week and had worsening weight z-scores up through Week 48*
- *Patient 010-19-01 received a dose increase of 9 mg/kg/week due to lack of efficacy. At week 24, the patient missed multiple doses following by a dose reduction to 3 mg/kg/week due to an AE of pneumonia assessed as possibly treatment related. The patient had a decline in height z-score but improvement weight z-score at the week 24 assessment. He died 2 weeks later of cardiopulmonary arrest.*

The remaining seven patients without improvement in growth parameters included 4 patients who did not receive dose adjustments and 3 patients who received dose increases of 9 mg/kg/week (2 patients) and 12 mg/kg/week (one patient). One patient (Patient 010-13-04) who received a dose increase of 9 mg/kg/week stabilized his weight z-score but continued to have worsening height z-scores.

Seven of 10 patients (70%) who did not experience improvement in growth parameters were ADA-positive, including 5 patients who had neutralizing antibodies (50%), which was similar to the proportion of patients who were ADA-positive (71%) and neutralizing antibody-positive(51%) in the overall ENB-010-10 population.

Juvenile-onset Population

Growth (as measured by height and weight z-scores) in treated patients was compared growth in historical control patients. Height and weight data for historical patients 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 5 years for treated patients.

A majority of patients in both groups had baseline height and weight measurements within the normal range for age. A higher proportion of treated patients compared to historical controls had improved height and weight growth over time. Height z-scores improved in 7/ 8 (88%) treated patients compared to 14/ 32 (44%) patients in the control group. Weight z-scores improved in 7/ 8 (88%) treated patients compared to 18/32 (56%) patients in the control group.

No treated patients experienced clinically significant declines in height or weight growth (one patient's height z-score decreased by -0.5 but remained within the normal range for age). In the control group, 18/32 patients (56%) had decreased height z-scores,

including 6/32 patients (19%) whose height z-scores declined to below the 5th percentile for age; 13/32 patients (43%) had declines in weight z-scores, including 3/32 (9%) patients whose weight z-scores declined to below the 5th percentile for age. One patient in the control group had no change in weight z-score.

For treated patients, the mean changes in height and weight z-scores from baseline to the last assessment were 0.6 (range was -0.5 to 1.8) and 1.2 (range was -0.1 to 2.3), respectively. For historical control patients, the mean changes in height and weight z-scores from baseline to the last assessment were 0 (range was -1.5 to 1.1) and 0.2 (range was -1.1 to 1.9), respectively.

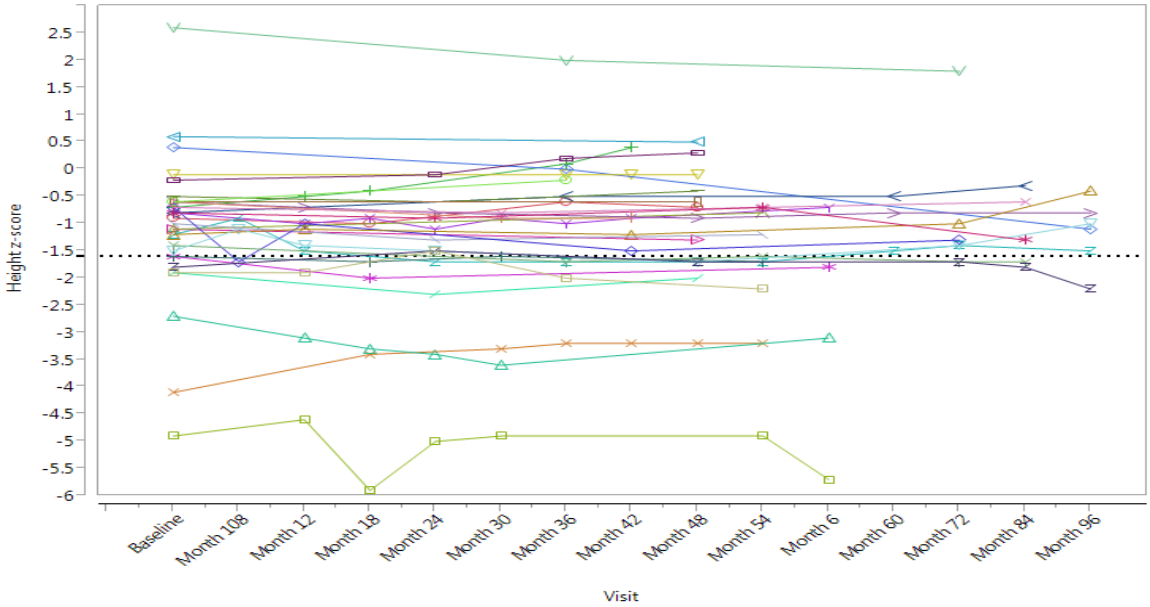
- **ALX-HPP-502 (Historical Control Group)**

Height

At baseline, the majority of patients had height z-scores (23/32 patients; 72%) within the normal range for age. Eighteen of 32 patients (56%) had decreased height z-scores, including 6/32 patients (19%) whose height z-scores declined to below the 5th percentile for age. The mean change in height z-scores from baseline to the last assessment was 0 (range was -1.5 to 1.1)

Figure 21 presents individual patient height z-scores for ALX-HPP-502.

Figure 21: Historical Controls Height Z-Scores over Time



NB: Values at or above the dotted line represent scores within normal range for age (i.e., z-scores $\geq 5^{th}$ percentile for age)

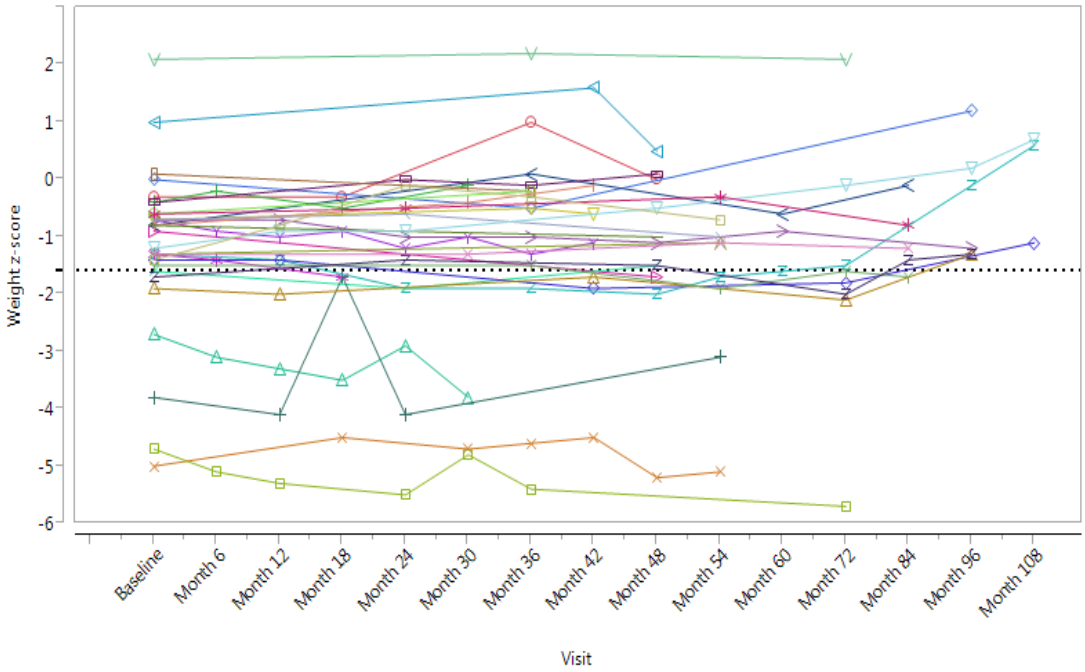
Weight
At baseline, the majority of patients had weight z-scores (25/32 patients; 78%) within the normal range for age. At last assessment, 13/32 patients (43%) had declines in weight z-scores, including 3/32 (9%) patients whose weight z-scores declined to below the 5th percentile for age. One patient had no change in weight z-score.

The mean change in weight z-score from baseline to last assessment was 0.2 (range was -1.1 to 1.9), respectively.

Eleven patients had weight z-score increases of 0.5 or greater (range was 0.5 to 1.9). The two patients with abnormal baseline weight z-scores had increases of 0.5 or greater but both patients' scores remained below normal for age.

Figure 22 presents individual patient weight z-scores for ALX-HPP-502.

Figure 22: Historical Controls Weight Z-scores over Time



NB: Values at or above the dotted line represent scores within normal range for age (i.e., z-scores $\geq 5^{th}$ percentile for age)

- **ENB-006-09/ENB-008-10**

Height

Mean baseline height z-scores for perinatal/infantile-onset patients and juvenile-onset patients were -2.6 (range was -6.6 to -0.7) and -1.5 (range was -3.8 to 0), respectively.

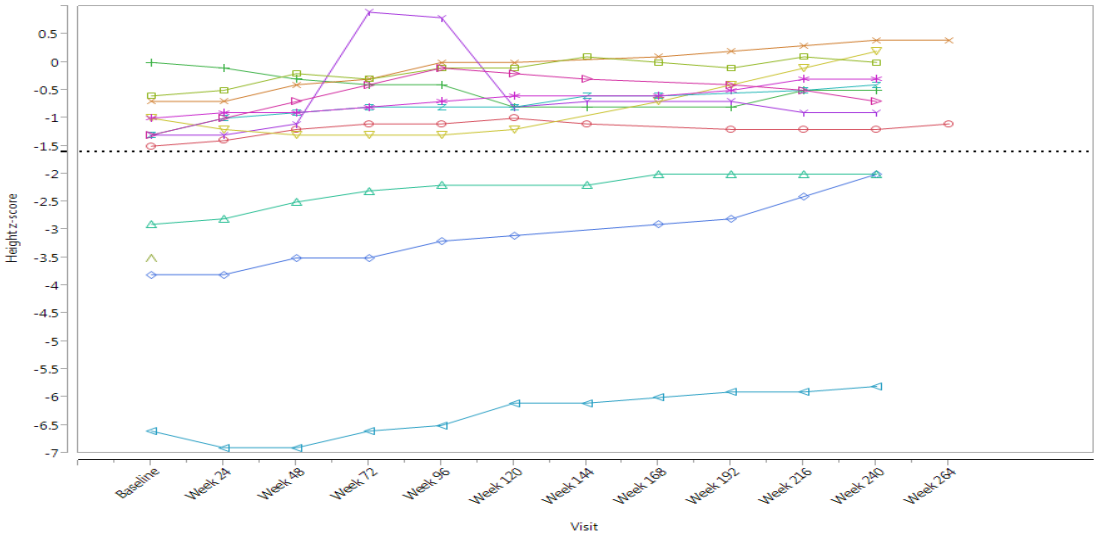
Nine of thirteen patients had baseline height z-scores that were within normal range for age, including 3 perinatal/infantile-onset patients and 6 juvenile-onset patients. All 9 patients maintained normal height z-scores.

Four patients (2 perinatal/infantile-onset patients and 2 juvenile-onset patients) had baseline height z-scores below the 3rd percentile for age. Height z-scores increased for three patients; one infantile-onset patient only had a baseline height measurement.

At last assessment, mean height z-scores for perinatal/infantile-onset patients and juvenile-onset patients were -1.5 (range was -5.8 to 0.4) and -0.9 (range was -2 to 0), respectively. Increases in height z-scores for perinatal/infantile-onset patients and juvenile-onset patients ranged from 0.6 to 1.2 and 0.4 to 1.8, respectively.

Figure 23 presents individual patient height z-scores for ENB-006-09/ENB-008-10.

Figure 23: ENB-006-09/ENB-008-10- Individual Patient Height Z-Scores over Time



NB: Values at or above the dotted line represent scores within normal range for age (i.e., z-scores ≥5th percentile for age)

Weight

Mean baseline weight z-scores for perinatal/infantile-onset patients and juvenile-onset patients were -2.5 (range was -8.2 to -1) and 0 (range was -1.3 to 2.2), respectively.

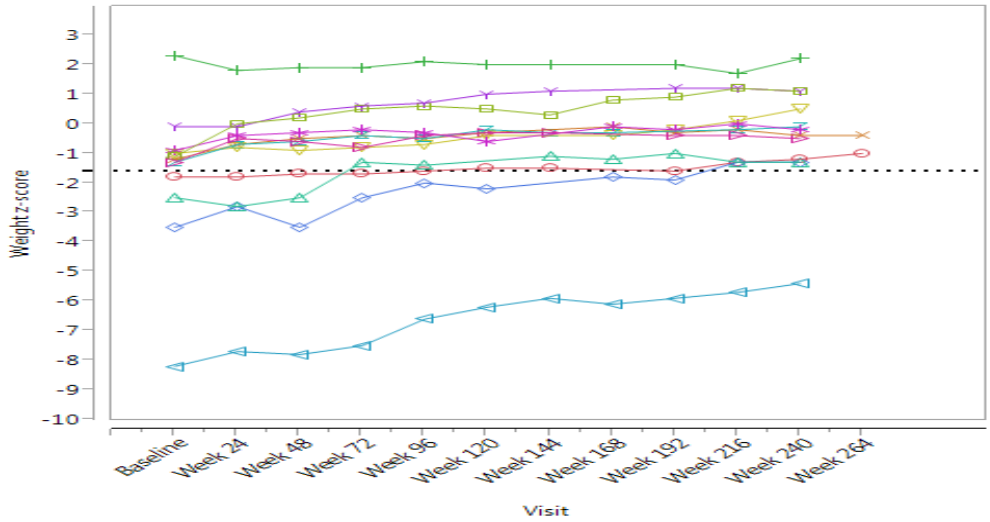
Eight of 13 patients (4 juvenile-onset patients and 4 perinatal/infantile-onset patients) had baseline weight z-scores within normal limits for age. All eight patients maintained or increased their baseline weight z-scores.

Four patients had baseline weight z-scores below the 3rd percentile for age, including 3 juvenile-onset patients and one perinatal/infantile-onset patient). All four patients experienced increased weight z-scores, with the three juvenile-onset patients achieving weight z-scores within normal limits for age.

At last assessment, mean weight z-scores for perinatal/infantile-onset patients and juvenile-onset patients were -1.5 (range was -5.4 to 0.5) and -0.9 (range was -2 to 0), respectively. Increases in weight z-scores for perinatal/infantile-onset patients and juvenile-onset patients ranged from 0.8 to 2.8 and 0.7 to 2.2, respectively. One obese juvenile-onset patient experienced a slight decrease in weight z-score (z-score change was -0.1).

Figure 24 presents individual patient weight z-scores over time.

Figure 24: ENB-006-09/ENB-008-10- Individual Patient Weight Z-scores over Time



NB: Values at or above the dotted line represent scores within normal range for age (i.e., z-scores ≥5th percentile for age)

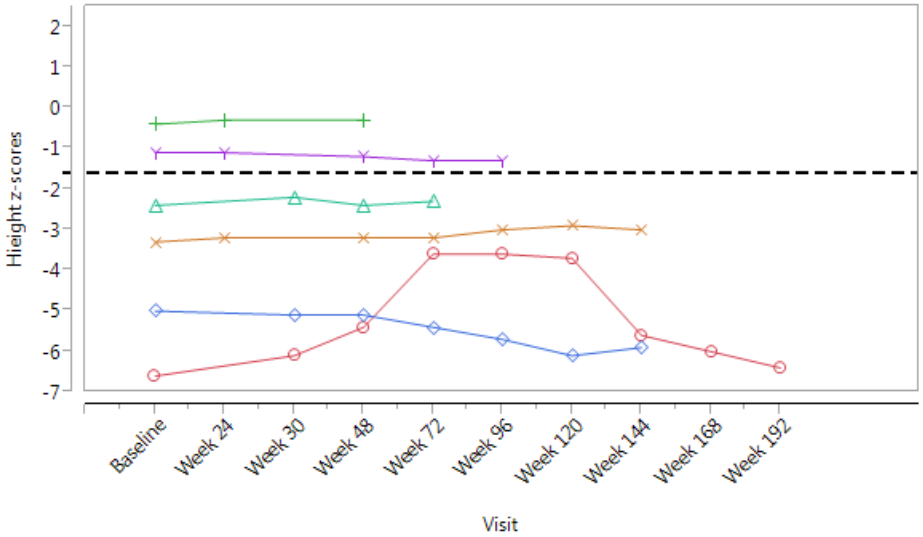
- **ENB-009-10**

Height and weight z-scores were available for the six adolescent patients (3 infantile-onset and 3 juvenile-onset patients) for measurements obtained prior to patients reaching 18 years of age (see Figure 25 and Figure 26).

Height

At baseline, 4/6 patients had height z-scores below the 3rd percentile for age and 2 patients had normal height z-scores (one infantile-onset patient and one juvenile-onset patient). At last assessment, height z-scores were essentially unchanged for 5/6 patients (one infantile-onset patient with an abnormal baseline height z-score experienced a transient increase in her score) and one juvenile-onset patient with an abnormal baseline z-score experienced a height z-score decrease of -0.9. The mean change in height z-score was -0.2 (range was -0.9 to 0.1).

Figure 25: ENB-009-10- Individual Patient Height Scores over Time



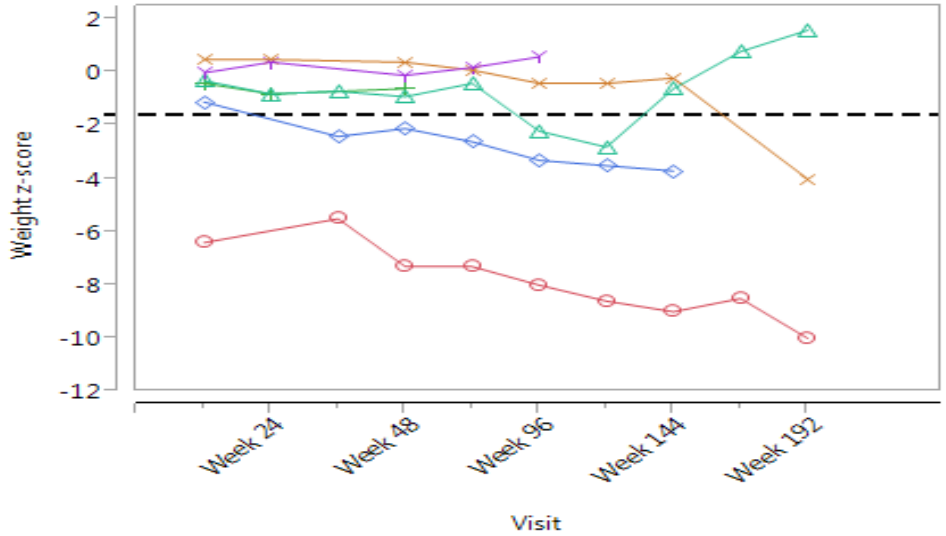
NB: Values at or above the dotted line represent scores within normal range for age (i.e., z-scores ≥5th percentile for age)

Weight

At baseline, one infantile-onset patient had an abnormal baseline weight z-score; the remaining five patients weight z-scores within the normal range for age. At last assessment, three patients maintained normal weight z-scores; three patients had abnormal weight z-scores, including two patients (one infantile-onset patient and one juvenile onset patient) who had normal baseline weight z-scores. The mean change in weight z-score was -1.4 (range was -4.5 to 1.9).

Reference ID: 3836304

Figure 26: ENB-009-10- Individual Patient Weight Scores over Time



NB: Values at or above the dotted line represent scores within normal range for age (i.e., z-scores ≥5th percentile for age)

Reviewer Comments:
Interpretation of the height data is limited due to lack of information on the Tanner stage. At least 3 of the patients were Tanner stage 4 and therefore had limited potential for height growth. However, the weight data are consistent with findings in the other trials, demonstrating that some patients had a poor weight response with asfotase dosing less than 6 mg/kg/week.

C. Six Minute Walk Test (6MWT)

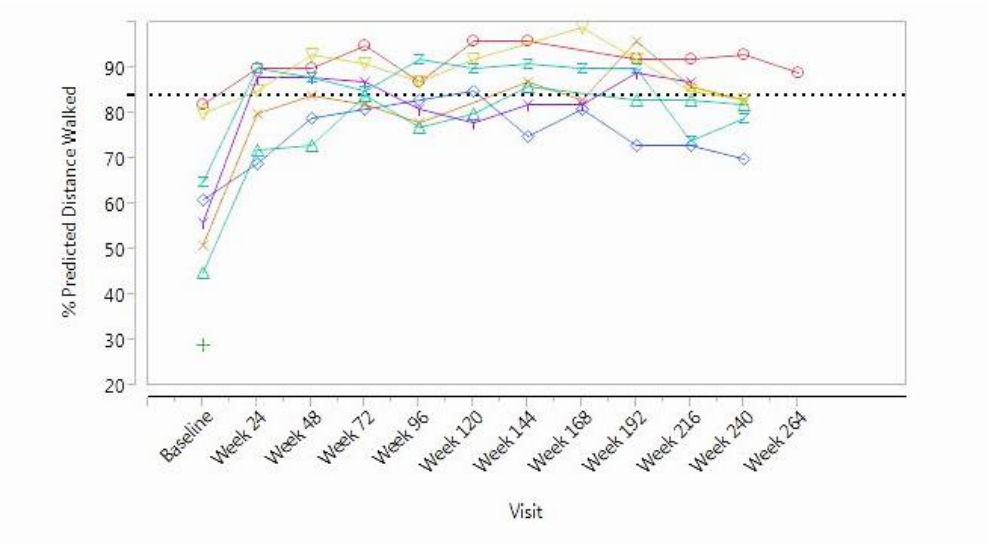
The 6MWT was performed in patients in ENB-006-09/ENB-008-10 and ENB-009-10. Patients in both trials demonstrated improvement in distance walked and percent predicted distance walked, with a majority of patients in both trials achieving percent predicted distance values within normal range for age.

- **ENB-006-09/ENB-008-10**

Eleven of 13 patients had baseline and post-baseline 6MWT data available. At baseline, 9/11 patients had percent predicted distance walked below the normal range for age (<84%). At baseline, none of the 13 patients enrolled in ENB-006-09/ENB-008-10 had percent predicted distance walked values ≥84% (mean value for the overall population was 59%). At last assessment, 5/11 patients with post-treatment values had percent predicted values above 84%, including 2 juvenile-onset and 3 perinatal/infantile-onset patients; 9/11 patients had percent predicted values above 80%, including 5 juvenile-onset patients and 4 perinatal/infantile-onset patients (mean value for the overall population was 85%).

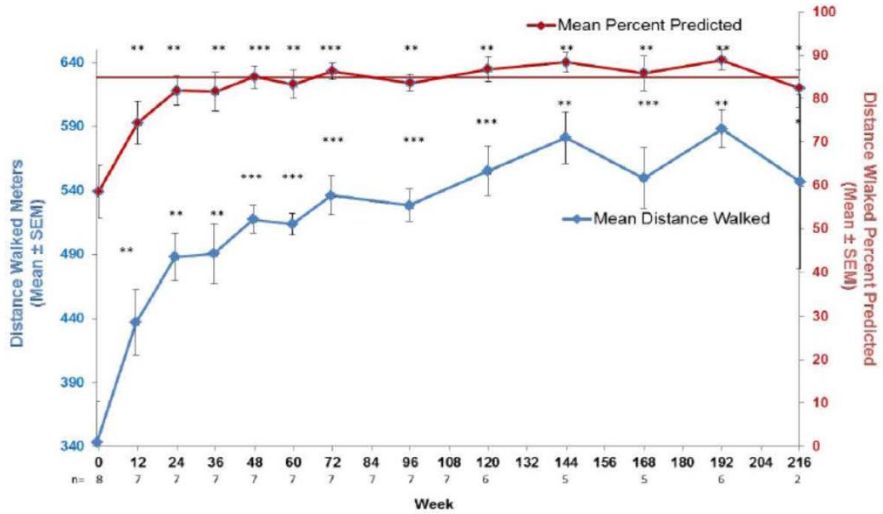
Figure 27 presents individual patient 6MWT % predicted values for juvenile-onset patients in ENB-006-09/ENB-008-10. Figure 28 presents the applicant's analysis of mean change in 6MWT distance and mean percent predicted value for juvenile-onset patients in ENB-006-09/ENB-008-10.

Figure 27: ENB-006-09/ENB-008-10- 6MWT Results over Time- Juvenile-Onset HPP Population



NB: The dotted line represents the lower threshold for normal percent predicted distance walked for age

Figure 28: ENB-006-09/ENB-008-10- 6MWT Results over Time- Juvenile-Onset HPP Population



NB: The dotted line represents the lower threshold for normal percent predicted distance walked for age

Source: Applicant's submission, Module 2.5 (Clinical Overview), Figure 8b

- **ENB-009-10**

Sixteen of 19 patients (84%) had baseline and post baseline 6MWT values available, including all patients randomized to treatment and 3/6 patients in the control group. Two patients did not complete the baseline 6MWT due to physical limitations and one adolescent patient with Asperger syndrome was uncooperative during the assessment.

Baseline median values for distance walked as percent predicted were below normal (<84%) in all treatment groups. Mean and median percent predicted distance values improved over time in all treatment groups. At last assessment, median percent predicted distance walked scores increased to >90% in the control and the asfotase alfa 0.5 mg/kg treatment groups and approached normal (median percent predicted value was 81%) in the asfotase alfa 0.3 mg/kg treatment group.

Reviewer Comments:
6MWT results were consistent in younger pediatric patients, adolescents and adults in demonstrating improvement in ambulation. The published literature notes that there are statistical challenges to using the 6MWT in pediatric patients with chronic conditions, including defining measurement error (i.e., minimal detectable change [MDC]) and defining clinically important changes (i.e., minimal clinically important difference [MCID] from the patient's perspective).[43] *As noted earlier, the applicant used normative values for the 6MWT developed in a European population which are in fact higher than normative values from studies in US children. In my review of individual patient results, there were wide performance swings for some patients, highlighting the challenge of identifying true differences between repeated measures of walking distance. However, there were consistent intra- and inter-patient trends of improvement in distance walked. Moreover, patients who had abnormal baseline functioning not only experienced improved functioning but achieved and sustained normal or near normal values. In this reviewer's opinion, these findings represent a more than minimal clinically important difference in functioning.*

D. Motor Assessments

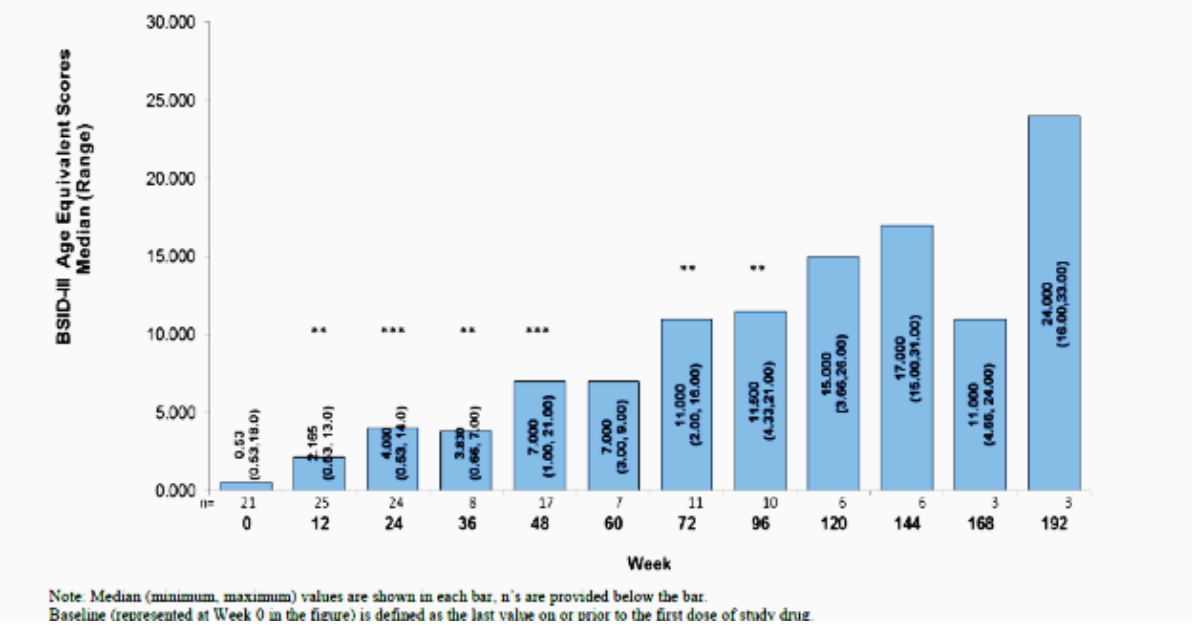
The applicant provided pooled analyses of motor function assessment results by patient phenotype. Patients in ENB-002-08/ENB-003-08 and ENB-010-10 were administered the BSID-III, PDMS-2 and BOT-2 assessments. Patients in ENB-006-09 were administered the BOT-2. Results for the BSID-III were reported as age equivalent scores while results for the other motor function tools were reported as standardized scores based on the normal mean for age.

[43] Bartels B, de Groot JF, Terwee CB, The six-minute walk test in chronic pediatric conditions: A systematic review of measurement properties, *Phys Ther* 2013; 93 (4): 529-541.

BSID-III

The applicant noted that age equivalent scores for the BSID-III increased over time, indicating a treatment effect. Figure 29 presents BSID-III Age equivalent scores for 39 perinatal/infantile onset patients with available baseline and post-baseline BSID-III values.

Figure 29: BSID-III Results- Perinatal/infantile-onset HPP Patients



Source: Applicant's submission, Module 2.5 (Clinical Overview), Figure 9

Reviewer Comments:

The applicant's age-equivalent analysis is difficult to interpret because it does not give a clear picture of the rate or degree of change in motor function compared to what would be expected for age for the study population. For example, an age equivalent score of 6 months is normal for a 6 month old baby but not a 2 year old child. In addition, the applicant included all patients who had repeat assessments in the analysis, including 6 ENB-002-08/ENB-003-08 patients whose initial assessments were completed after starting treatment.

Therefore, I also analyzed shifts in standardized scores for BSID-III to compare patient scores to normed scores (see Table 34) for 32 patients who had true baseline assessments. Overall, although numerical scores improved over time, patients generally stayed within the same functional range when compared to the mean for age. For example, an increase in score from 2 to 3 still represented a score more than two standard deviations below the mean for age (<3rd percentile for age). There was a

trend toward improvement in scores, with 7/32 patients with baseline and post-baseline assessments experiencing a shift in BSID-III scores to within 2 standard deviations from the mean.

Table 34: Perinatal/infantile-onset Patients- Shifts in BSID-III Gross Motor Subtest Scores

		Last Assessment		
		Score > 2 SD below mean	Score ≤ 2 SD to 1 SD below	Score < 1 SD below mean
Baseline/ Initial Assessment	Score > 2 SD below mean	**18**	**8**	**3**
	Score ≤ 2 SD to 1 SD below mean	**6**	**1**	**0**
	Score < 1 SD below mean	**2**	**0**	**2**

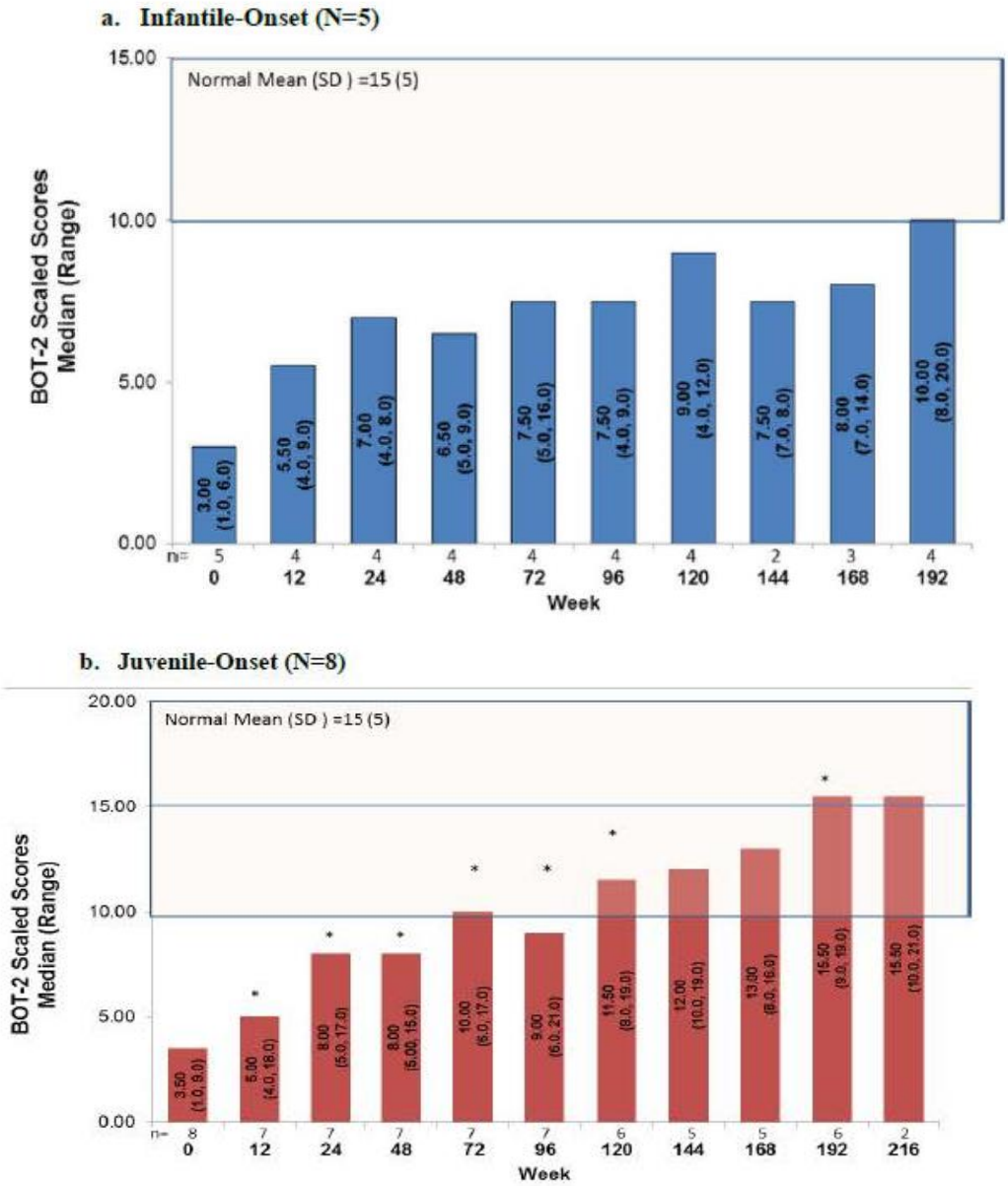
PDMS-2

Due to their age at trial entry, no patients enrolled in ENB-002-08/ENB-003-08 or ENB-010-10 patients had baseline PDMS-2 assessments. Sixteen of 22 patients (6 ENB-002-08/ENB-003-08 patients and 16 ENB-010-10 patients) with available serial PDMS-2 data had initial assessment scores below the 3rd percentile for age. At last assessment, the distribution of score shifted with 10 patients having scores above the 3rd percentile for age; twelve patients had stable rank score percentiles.

BOT-2

Baseline and post-baseline BOT-2 scores were available for 11/13 patients enrolled in ENB-006-09/ENB-008-10. BOT-2 scores improved in both perinatal/infantile- onset and juvenile-onset patients as well as the overall group, with mean scores for both sub-groups approaching the mean for age (see Figure 30). The applicant noted that the mean composite score increased from <3rd percentile for age at baseline (n=13) to approach the 50th percentile (percentile rank was 44) at Week 144 (n=11).

Figure 30: BOT-2 Results ENB-006-09/ENB-008-10



Source: Applicant's BLA 125513 submission dated December 23, 2014, Module 2.5, Figure 10

Baseline and post-baseline BOT-2 scores were available for 2/6 adolescent patients enrolled in ENB-009-10. Scores were reported as age level equivalents. One patient maintained normal scores for age from baseline up through Week 96. One 14 year patient had a baseline score equivalent to motor function for a 4 year old; at Week 192, her score was equivalent to motor function for an 8 year-old.

Reviewer Comments:
The trends in PDMS-2 and BOT-2 scores suggest that some patients experienced some degree of catch-up in motor skills compared to their age peers. Note that the test interval for most patients with no change in PDMS-2 rank score percentiles was 6 months or less, suggesting that the duration of treatment may not have been long enough to evaluate for a treatment effect.

6.1.6 Other Endpoints

Dr. Marcea Whitaker of DBRUP reviewed preliminary bone biopsy data (see her review dated August 29, 2013 for further details). Dr. Stephen Voss reviewed additional biopsy analyses and other bone disease data submitted with the BLA submission (see his review dated April 16, 2015 for further details). In his review, Dr. Voss concluded that the data demonstrated improvement in bone-related endpoints for pediatric patients with perinatal/infantile- and juvenile-onset 12 years old or younger, with moderate correlations of radiographic findings (RSS but not RGIC) with bone biopsy data. He noted that the DEXA data were inconclusive. Dr. Voss considered bone-related data for adolescent patients and adult patients to be less consistent, citing small sample size and differences in dosing as factors that limited the interpretability of results in these patients.

E. Bone Assessments

Bone Biopsy
Bone biopsies were performed in patients enrolled in ENB-006-09/ENB-008-10 and ENB-009-10.

ENB-006-09/ENB-008-10
Twelve of 13 ENB-006-08/ENB-008-10 had paired (pre- and post-treatment) bone biopsies obtained at baseline and Week 24 (one perinatal/infantile-onset patient who discontinued from the trial only had a baseline biopsy). Bone biopsy results were reported as change from baseline and percent of the healthy mean based on reference values published by Glorieux et al.[44] All four of the perinatal/infantile-onset patients and 7/8 of the juvenile-onset patients experienced reductions in osteoid thickness and volume indices (see Table 35 and Table 36). Three of four perinatal/infantile-onset patients experienced declines in mineralization lag times (MLT); changes in MLT were variable in juvenile-onset patients.

[44] Glorieux FH, Travers R, Taylor A, et al., Normative data for iliac bone histomorphometry in growing children, Bone 2000; 26(2): 103-109.

Table 35: ENB-006/09/008-10- Mineralization Indices in Infantile-Onset HPP Patients Treated with Asfotase alfa

	Osteoid thickness (µm)			Osteoid volume (%)			Mineralization lag time (d)		
Patient #	BL	Wk 24	**Change**	BL	Wk 24	**Change**	BL	Wk 24	**Change**
01-04	7.7	6.4	**-1.3**	7.3	5.0	**-2.3**	89	39	**-50**
01-07	7.7	7.0	**-0.7**	5.6	5.3	**-0.3**	43	23	**-20**
02-02	14.0	6.4	**-7.6**	14.7	4.8	**-9.9**	126	48	**-78**
02-03	13.6	8.2	**-5.4**	11.0	8.0	**-3.0**	39	57	**+18**
02-04	16.3	-	**-**	31.0	-	**-**	954	-	**-**
Median	**13.6**	**6.7**	**-6.9**	**11.0**	**5.2**	**-5.8**	**89**	**44**	**-45**
Source: ADBONE									

Source: DBRUP Consult Review by Dr. Stephen Voss (dated April 16, 2015; DARRTS ID #3733103

Table 36: ENB-006-09/008-10- Mineralization Indices in Juvenile-Onset HPP Patients Treated with Asfotase alfa

	Osteoid thickness (µm)			Osteoid volume (%)			Mineralization lag time (d)		
Pt #	BL	Wk 24	**Change**	BL	Wk 24	**Change**	BL	Wk 24	**Change**
01-01	14.6	13.0	**-1.6**	15.0	11.5	**-3.5**	125	114	**-11**
01-02	11.5	5.8	**-5.7**	7.2	3.0	**-4.2**	30	33	**+3**
01-03	18.5	9.3	**-9.2**	23.7	8.2	**-15.5**	225	58	**-167**
01-05	11.4	5.9	**-5.5**	7.4	4.5	**-2.9**	77	17	**-61**
01-06	16.5	10.6	**-5.9**	14.6	6.2	**-8.4**	33	35	**+2**
01-08	15.3	22.4	**+7.1**	13.9	28.1	**+14.2**	87	750	**+663**
01-09	11.9	7.2	**-4.7**	17.5	4.2	**-13.3**	25	37	**+12**
02-01	15.0	9.2	**-5.8**	9.9	8.3	**-1.6**	103	37	**-65**
Median	**14.8**	**9.2**	**-5.6**	**14.3**	**7.2**	**-7.1**	**82**	**37**	**-45**
Source: ADBONE									

Source: DBRUP Consult Review by Dr. Stephen Voss (dated April 16, 2015; DARRTS ID #3733103

ENB-009-10

Paired bone biopsies were performed in all 19 patients. Patients randomized to the control group had repeat biopsies at Week 24 and patients randomized to asfotase alfa had repeat biopsies at week 48. Most patients had baseline mineralization indices consistent with osteomalacia (defined in this trial as a MLT z-score $\geq$2). Dr. Voss noted that median changes in osteoid thickness and volume values were similar between treatment and control groups and that baseline MLT and change in MLT values were variable. Only two adolescent patients received treatment; post-treatment changes for both patients show no change to worsening of osteoid indices. Table 37 summarizes bone biopsy results for ENB-009-10.

Table 37: ENB-009-10-Mineralization Indices in Adolescent/Adult Patients

	Osteoid thickness (µm)			Osteoid volume (%)			Mineralization lag time (d)		
Pt #	BL	Wk 24/48	**Change**	BL	Wk 24/48	**Change**	BL	Wk 24/48	**Change**
Control group									
01-04	10.9	9.6	**-1.3**	13.9	12.9	**-1.0**	-	63.9	**-**
01-05*	14.8	25.4	**+10.6**	18.7	26.6	**+7.9**	31.5	266.2	**+234.7**
01-09*	14.3	9.4	**-3.9**	12.5	10.3	**-2.2**	92.6	158.1	**+65.5**
02-02*	13.4	7.4	**-6.0**	10.8	5.7	**-5.1**	95.5	56.4	**-39.1**
03-04	11.9	7.4	**-4.5**	7.5	5.3	**-2.2**	271.2	527.3	**+256.1**
05-05	10.8	10.0	**-0.8**	6.2	10.0	**+3.8**	640.1	515.2	**-124.9**
Median	**12.6**	**9.5**	**-2.6**	**11.7**	**10.1**	**-1.6**	**95.5**	**212.1**	**+65.5**
Asfotase alfa 2.1 mg/kg/wk									
01-03	9.4	4.4	**-5.0**	2.6	1.1	**-1.5**	-	-	**-**
01-08*	6.4	-	**-**	2.6	-	**-**	44.4	-	**-**
01-10	4.7	4.3	**-0.4**	2.4	5.5	**+3.1**	96.9	170.7	**+73.8**
02-01*	7.3	14.1	**+6.8**	5.3	12.3	**+7.0**	240.6	142.4	**-98.2**
03-03	18.3	18.6	**+0.3**	13.9	13.7	**-0.2**	-	-	**-**
03-06	8.7	7.4	**-1.3**	7.6	6.6	**-1.0**	3277	485	**-2792**
03-07	9.8	8.3	**-1.6**	11.2	11.2	**0.0**	1333	517	**-816**
Median	**8.4**	**7.9**	**-0.8**	**5.3**	**8.9**	**-0.1**	**240.6**	**329.7**	**-457.1**
Asfotase alfa 3.5 mg/kg/wk									
01-01	18.4	13.5	**-4.9**	12.7	6.5	**-6.2**	-	1444	**-**
01-06	4.8	5.6	**+0.8**	4.0	3.1	**-0.9**	174.5	34.7	**-139.8**
01-11	10.1	7.3	**-2.8**	4.9	2.8	**-2.1**	457.5	96.0	**-361.5**
02-03*	8.1	9.1	**+1.0**	6.3	6.1	**-0.2**	114.8	45.6	**-69.2**
03-01	8.4	5.8	**-2.6**	8.2	3.0	**-5.2**	364.3	379.4	**+15.1**
03-02	4.4	3.8	**-0.6**	3.1	0.8	**-2.3**	177.8	98.4	**-79.4**
Median	**8.2**	**6.5**	**-1.6**	**5.6**	**3.0**	**-2.2**	**177.8**	**97.2**	**-79.4**

*indicates adolescent patient; respective ages are 13 yr (pt #01-05);14 yr (#01-09); 16 yr (#02-02); 16 yr (#01-08); 14 yr (#02-01); 15 yr (#02-03); the remaining patients were adults (≥ 18 y/o)
Source: ENB-009-10 CSR Listing 16.2.6.2.1

Source: DBRUP Consult Review by Dr. Stephen Voss (dated April 16, 2015; DARRTS ID #3733103

Reviewer Comments;
Dr. Voss provided the following comments:

> *"These biopsy data (from 8 juvenile-onset HPP patients, and the 5 infantile-onset patients discussed above) were previously reviewed by Dr. Marcea Whitaker (DBRUP consult, DARRTS 8/29/13) and considered to represent a positive effect of asfotase alfa on osteomalacia at 6 months, in both infantile- and juvenile-onset HPP. Although there are no biopsy data on untreated patients, osteoid reduction as seen in 11/12 HPP patients does not in general occur spontaneously in untreated osteomalacic patients."*

Dr. Voss noted that the 24-week interval between baseline and repeat biopsies was likely too short to demonstrate an effect on mineralization lag time, accounting for the variability in findings for this parameter. He noted that the bone biopsy data for younger pediatric patients but not adolescent and adult patients were supportive of efficacy, qualifying that the doses used in ENB-009-10 were lower than doses used in ENB-006-09/ENB-008-10 and were lower than the intended marketing dose of 6 mg/kg/week. This reviewer agrees that the data were for the older patients were inconclusive and may reflect inadequate exposure for a treatment response.

Dual Energy X-ray Absorptiometry (DEXA)
Bone mineral content and bone mineral density (BMD) were assessed by DEXA in patients in ENB-006-09/ENB-008-10 and ENB-009-10.

ENB-006-09/ENB-008-10
In EINB-006-09/ENB-008-10, BMD-z-scores were only available for a subset of the BMD assessments (lumbar spine but not hip and whole body) , thus limiting the interpretability of DEXA findings. Mean baseline lumbar spine BMD z-scores were -2.4 in both perinatal/infantile- and juvenile-onset patients and increased over time in both subgroups (see Table 38 and Table 39). Dr. Voss noted that z-scores improved even in one juvenile-onset patient who had apparent worsening mineralization indices on bone biopsy.

Table 38: ENB-006/09/008-10- Lumbar Spine BMD Z-Scores (DEXA) in Infantile-Onset HPP Treated with Asfotase alfa

		Z-score change from baseline	
	n	Mean	Range
Week 24	4	0.5	0.1, 0.8
Week 72	4	0.4	-0.5, 1.5
Week 96	4	0.0	-0.6, 0.6
Week 120	4	-0.2	-1.2, 0.5
Week 144	2	1.9	1.4, 2.3
Week 168	3	0.3	-1, 1.3
Week 192	4	0.9	-0.7, 2.4
Source: ADBONE			

Source: DBRUP Consult Review by Dr. Stephen Voss (dated April 16, 2015; DARRTS ID #3733103

Table 39: ENB-006/09/008-10- Lumbar Spine BMD Z-Scores (DEXA) in Juvenile-Onset HPP Treated with Asfotase alfa

		Z-score change from baseline	
	n	Mean	Range
Week 24	8	0.8	-0.6, 1.6
Week 72	8	1.0	-0.6, 1.7
Week 96	8	0.8	-0.5, 1.3
Week 120	6	0.9	-0.8, 1.8
Week 144	6	0.4	-0.8, 1.6
Week 168	4	0.8	-0.8, 1.8
Week 192	7	0.9	-0.8, 1.9
Week 216	2	1.3	0.9, 1.7
Source: ADBONE			

Source: DBRUP Consult Review by Dr. Stephen Voss (dated April 16, 2015; DARRTS ID #3733103)

ENB-009-10

Total hip and lumbar spine BMD z-scores were available for the 6 adolescent patients in ENB-009-10. However, some patients had surgical hardware that interfered with readings for whole body BMD. No consistent trends in z-scores were noted in the adolescent patients (see Table 40). Based on his review, Dr. Voss noted that most of the adult patients showed small increases in hip and spine BMD.

Table 40: ENB-009-10- BMD & Z-Score Assessed Using DEXA in Adolescent Patients.

Patient Number	009-01-05	009-01-09	009-02-02	009-02-01	009-01-08	009-02-03
Dose Group [a]	Control[b]	Control	Control	0.3 mg/kg	0.3 mg/kg	0.5 mg/kg
Total Hip BMD, g/cm^2 (Z-score)						
Baseline	NA	0.461 (NA)	0.622 (-3.3)	0.685 (-2.4)	0.986 (NA)	0.823 (-1.6)
Week 24	NA	0.464 (NA)	0.658 (-2.9)	0.694 (-2.3)	1.145 (NA)	0.870 (-1.3)
Week 48	0.133 (NA)	0.412 (NA)	0.727 (-2.3)	0.704 (-2.2)	NA	0.847 (-1.4)
Week 72	0.200 (-6.1)	0.493 (NA)	0.714 (-2.4)	0.675 (-2.4)	NA	0.912 (-0.9)
Week 96	0.286 (-5.4)	0.536 (-4.0)	1.748[c] (4.9)	0.685 (-2.3)	0.986 (NA)	0.973 (-0.4)
Week 120	0.246 (-5.7)	0.569 (-3.6)	0.680 (-2.5)	0.715 (-2.0)	NA	0.953 (-0.6)
Week 144	0.286 (-5.4)	--[d]	0.679 (-2.4)	0.742 (-1.7)	--[d]	1.006 (-0.2)
Week 168	0.244 (-5.8)	--[d]	0.710 (-2.2)	0.713(-2.0)	--[d]	1.011 (-0.2)
Week 192	0.338 (-5.1)	--[d]	0.693 (-2.2)	--[d]	--[d]	1.045 (0.1)
Lumbar Spine BMD, g/cm^2 (Z-score)						
Baseline	NA	0.682 (-2.4)	0.673 (-2.3)	0.640 (-3.2)	0.974 (-0.3)	0.767 (-1.5)
Week 24	NA	0.692 (-2.5)	0.658 (-2.6)	0.683 (-2.9)	1.012 (-0.0)	0.800 (-1.4)
Week 48	NA	0.708 (-2.6)	0.730 (-2.2)	0.688 (-3.0)	NA	0.826 (-1.4)
Week 72	NA	0.846 (-1.5)	0.803 (-2.0)	0.669 (-3.5)	NA	0.874 (-1.2)
Week 96	NA	0.864 (-1.0)	0.843 (-1.8)	0.704 (-3.2)	1.032 (0.1)	0.882 (-1.2)
Week 120	NA	0.868 (-1.2)	0.852 (-1.8)	0.705 (-3.3)	NA	0.893 (-1.2)
Week 144	NA	--[d]	0.843 (-2.0)	0.692 (-3.6)	--[d]	0.908 (-1.2)
Week 168	NA	--[d]	0.835 (-2.2)	0.682 (-3.8)	--[d]	0.904 (-1.4)
Week 192	NA	--[d]	0.815 (-2.5)	--[d]	--[d]	0.898 (-1.6)

BMD = Bone mineral density; NA = not available.
[a] Dose group is the treatment assignment at randomization.
[b] This patient did not have DEXA assessments; a waiver was granted because the patient was multidrug-resistant staphylococcus aureus positive (Listing 16.2.6.2.3)
[c] There is no record of this patient having hardware installed in the femur between visit Weeks 72 and 96; it is possible that is an erroneous value.
[d] Patient had withdrawn from study and was not on treatment at this visit.

Source: ENB-009-10 Interim Study Report (dated April 2, 2015), Table 40

Fractures

The applicant collected data on prior history of fractures in all trials and also performed post-hoc reviews of the incidence of on-study fractures (a post-hoc review was not conducted for patients in ENB-001-08), including the number of patients with new-onset of fractures. ENB-009-10 had the highest reported proportion of patients with a prior fracture history (95%)) and with on-study fractures (75%). The proportion of patients with new onset of fractures during clinical trials ranged from 0% to 20%. Fracture locations were similar across clinical trials, and included upper and lower extremities and vertebrae; rib fractures and clavicle fracture were also reported in patients in the two perinatal/infantile onset trials. Table 41 summarizes fracture findings for clinical trials.

Table 41: Fracture History for Patients in Clinical Trials

Trial	Prior fracture history	On-study fractures	New-onset fractures
	n (%)	n (%)	n (%)
ENB-002-08/ENB-003-08 (n=11)	6/11 (55)	6/10 (60)	2/10 (20)
ENB-010-10 (n=59)	19/59 (32)	9/59 (15)	4/59 (7)
ENB-006-09/ENB-008-10 (n=13)	3/13 (23)	2/13 (15)	2/13 (15)
ENB-009-10 (n=19)	18/19 (95)	14/19 (74)	0/19 (0)
Total	**46/102 (45)**	**31/101 (31)**	**8/101 (8)**

Reviewer Comment:
Fractures are a significant clinical feature in all HPP phenotypes. There was insufficient information to assess the impact of asfotase alfa on fractures.

F. Biochemical Markers

Baseline PPi and PLP levels varied across trials. At baseline, approximately half of ENB-002-08/ENB-003-08 patients (n=4) had normal PPi values and mean PPi for ENB-006-09/ENB-008-10 patients also was within the normal range. Baseline PPi and PLP levels were variable in ENB-009-10 patients. Biomarker levels decreased by Week 6 to Week 12 of treatment with asfotase alfa in all trials, with reductions sustained over time. Most patients normalized both PPi and PLP values over time; some fluctuation in PLP values was observed in all trials.

Reviewer Comments:
The biomarker results demonstrate that all patients had a pharmacodynamic response to treatment, with the majority of patients achieving normal values. However, these biomarkers do not appear to correlate with clinical status or clinical response. Note that although all ENB-002-08/ENB-003-08 patients had severe HPP disease as per protocol eligibility criteria, approximately half of the patients had normal baseline PPi values. Similarly, although all patients experienced reductions in biomarker values or achieved normalized values, some perinatal-infantile-onset patients demonstrated a poor clinical response in terms of growth or radiographic assessments. A lack of correlation was also noted in adolescent and adult patients.

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G. Muscle Strength

Hand Held Dynamometry (HHD)

HHD assessments were conducted in ENB-006-09/ENB-008-10 and ENB-009-10 and included hip extensor and hip abductor muscle strength measurements. At baseline, median percent predicted strength was <50% of predicted values based on a normative sample in both trial populations. Treatment with asfotase alfa resulted in increased strength in both muscle groups that was sustained over time as measured by percent predicted values in the overall ENB-006-09/ENB-008-10 population as well as the juvenile-onset subgroup. Smaller increases were observed in ENB-009-10 patients, with minimal improvement in hip abduction strength noted at last assessment. Table 42 and Table 43 summarize HHD results for the two trials.

Table 42: ENB-006-09/ENB-008-10- HHD Percent Predictive Values at Baseline and Last Assessment- Juvenile-Onset ITT Population

	Median (min, max)
	p-value [b]

[a] The right side w
[b] p-value based on
Source: Table 3.2

Source: DNP Consult Review by Dr. Teresa Buracchio (dated June 24, 2015; DARRTS ID# 3782307)

Table 43: ENB-009-10- HHD Percent Predictive Values at Baseline and Last Assessment- ITT Population

Muscle Group Test Statistic	Percent Predicted Actual Value (n=19)		Patients with improved scores- n (%)
	Baseline	Last Assessment	
Hip Extension (Dominant Side)			
n	18	14	14
Median Min, Max	42 11, 111	45 20, 99	11/14 (79)
Hip abduction (Dominant Side)			
n	18	13	13
Median Min, Max	48 9, 126	50 31, 100	11/13 (85)

Reviewer Comment:
The smaller increment of improvement observed in ENB-009-10 patients may have been due to the lower asfotase alfa doses used in this population.

H. Pain and disability

Pain and disability were evaluated as exploratory endpoints in ENB-006-08/ENB-008-10 and ENB-009-10. Assessments generally demonstrated improvement from baseline with asfotase alfa treatment.

Child Health Assessment Questionnaire (CHAQ)

The Child Health Assessment Questionnaire (CHAQ) was administered in ENB-006-08/ENB-008-10. Baseline and post-baseline scores were available for 12/13 patients (92%). Baseline disability scores ranged from 0 to 2.25 and baseline pain scores ranged from 0 to 60. At last assessment, all patients reported disability scores of 0 and 9/12 (75%) patients reported pain scores of 0. Two patients experienced increases in pain scores at last assessment.

Reviewer Comments:
Interpretation of these findings is limited due to the lack of control group and use of parent-reported data for some patients. In addition, no MCID has been established for the HPP population. However, the shift in the proportion of patients with scores of 0 on both subscales suggests a response to treatment with asfotase alfa.

Pediatric Outcomes Data Collection Instrument (PODCI)

Baseline and post-baseline PODCI assessments were available for 12/13 patients. At baseline 9/13 patients (69%) had Global Function scores more than one standard deviation below the mean (median score was 27) and 5/13 patients (38%) had Transfers and Basic Mobility scores more than one standard deviation below the mean (median score was 41). At last assessment, 9/12 (75%) patients had Global Function

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scores within one standard deviation of the mean and all 12 patients had Transfers and Basic Mobility scores above the mean (median scores for both domains was 52).

Reviewer Comments:
The observed shift in scores for both Global Function and Transfers and Basic Mobility are consistent with other functional assessment findings in the trial and are consistent with improvement with treatment with asfotase alfa. As with the CHAQ, interpretability was limited by the lack of a control group and the potential bias introduced by reliance on parent-reports for a majority of patients. Based on my review of the PODCI data, scoring was very similar between self-report and parent-report scores for patients who had both scores.

ENB-009-10
Lower Extremity Functional Scale (LEFS)
Baseline and post-baseline LEFS scores were available for 18/19 patients. Median LEFS scores increased from 35 at baseline (range was 17 to 78) to 52 at last assessment (range was 23 to 80). At last assessment, 14/18 (78%) patients experienced an increase in LEFS score; 8/18 (44%) patients experienced a 9 point or more increase in score at last assessment. At last assessment, four patients (22%) experienced a decrease or no change in LEFS score, no patients experienced a 9 point or more decrease in score.

Pain (BPI-SF)
Minimal to no decreases in pain interference and pain severity scores were observed from baseline to last assessment in all treatment groups (see Table 44).

Table 44: ENB-009-10- BPI-SF Scores at Baseline and Last Assessment

Visit	Control N=6	Asfotase 0.3 mg/kg N=7	Asfotase 0.5 mg/kg N=6
Pain Interference			
Baseline			
n	6	7	6
Mean (SD)	**2.8** (2.5)	**4.1** (3.4)	**3.8** (2.4)
Median	2.5	5	4
Min, Max	0, 6	0, 9	0, 7
Week 24			
n	4	7	6
Mean (SD)	**3** (2.3)	**2** (3.1)	**2**.5 (1.6)
Median	3	0	3
Min, Max	1.5	0, 8	0, 4
Last Assessment			
n	6	7	6
Mean (SD)	**1.7** (1.8)	**2.7** (3.0)	**3.8** (2.9)
Median	1.5	3	35
Min, Max	0, 4	0, 8	0, 9
Pain Severity			
Baseline			
n	6	7	6
Mean (SD)	**3.2** (1.7)	**2.3** (2.8)	**4.7** (2.0)
Median	3	2	5.5
Min, Max	1, 6	0, 8	1, 6
Week 24			
n	4	7	6
Mean (SD)	**2.8** (1.7)	**1.6** (1.7)	**4** (2.3)
Median	2.5	1	4
Min, Max	1, 5	0, 5	1, 7
Last Assessment			
n	6	7	6
Mean (SD)	**1.8** (1.7)	**2.4** (2.5)	**3.8** (1.8)
Median	2	2	3.5
Min, Max	0, 4	0, 7	2, 6

Reviewer Comments:
It is difficult to evaluate the pain data due to the mild severity of pain at baseline (especially in the control group) and the small sample size and. In addition, no clinically minimally important difference in pain has been established for the HPP population.

I. Pulmonary Function Tests

Pulmonary function testing (forced vital capacity [(FVC best effort and FVC percent of predicted]) was performed in patients enrolled in ENB-006-09/ENB-008-10 and ENB-009-10. Mean values were within normal range at baseline and remained stable over time in both trials.

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6.1.7 Subpopulations

There were no apparent differences in efficacy by gender or geographic region. There were insufficient numbers to assess for differences by race or age (i.e., adult compared to pediatric patients).

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

As discussed earlier, the trends in growth noted in the infantile-onset population suggest that asfotase alfa doses > 6mg/kg/week are needed to for optimal growth in some infantile-onset patients. Per protocol dosing in clinical trials allowed for dose increases up to 9 mg/kg/week. The Clinical Pharmacology review team's analysis of the exposure-response relationship of asfotase alfa to height growth supported the proposed dosing of 6 mg/kg/week. Some dose increases reported in the trials were based on exposure data that indicated lower than targeted exposure with the 6 mg/kg/week dosing regimen. However, other dose adjustments were based on lack of clinical response. Table 45 summarizes information for 13 patients who experienced dose adjustments based on PK and/or clinical response and their clinical status at last assessment. Eight of 13 patients who received dose increases survived and experienced improvement in at least 2 of 3 clinical parameters (height, weight, and/or RGI-C). The majority of patients who did not have a complete clinical response following a dose increase had no improvement in height z-score (7/8 patients).

Table 45: Clinical Status at Last Assessment for Patients with Dose Adjustments Based on PK and/or Clinical Evidence of Lack of Efficacy

Pt ID	Age	Height z-score decline	Weight z-score decline	RGI-C Non-responder	Date of dose adjustment	Dose (mg/kg/wk)
ENB-002-08/ENB-003-08 patients						
002-08-01-01	7 mon	X			Week 24	9→6
002-08-02-01	32 mon		X		Week 96	9→6
002-08-09-02	0 mon	X	X		Week 120	6→12
ENB-010-10 patients						
010-01-01	4 mon				1st increase was at Month 2 to 9 mg/kg/week	Multiple doses- max dose was 28; final dose was 6
010-01-07*	0 mon	X	X		Baseline	14
010-13-01*	4 mon	X			Month 2	6→12
010-13-04	2 mon	X			Month 6	6→9
010-16-01	3 mon	X	X		Month 4	6→9
010-16-04	5 mon				Month 3	6→9
010-16-05	16 mon				Week 6	6→9
010-19-01*	8 mon	X		X	Month 5	9→3
010-27-01	1 mon				Month 2	6→9
010-38-02	71 mon (5.9 yrs)				Month 5	6→7.5

*patients who died during trials

Reviewer Comments:
As discussed earlier, there was no indication of significant differences in standard of care received by patients who had persistent growth delay with treatment. Some of the observed variability in response may be due to genetic differences. Based on the documented improved clinical responses in 8/13 of patients who received asfotase alfa doses > 6 mg/kg/week, this reviewer recommends 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.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

There did not appear to be any waning of efficacy over time in patients who demonstrated a response to treatment.

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6.1.10 Additional Efficacy Issues/Analyses

Immunogenicity
In reviewing individual patient outcomes, the immunogenicity profile for the group of patients who died or who did not experience improvement in growth parameters or RGI-C was similar to the overall population, with 13/19 patients (68%) that developed antibodies and 9/19 patients (47%) that developed neutralizing antibodies (including patients who were tolerized at last assessment). Table 46 summarizes antibodies status for all 19 patients who had a sub-optimal clinical response to treatment (i.e., death, decline in height or weight z-score, or RGIC- non-responder). The table includes information on patients who developed neutralizing antibodies but self-tolerized. I did not include ENB-009-10 patients in this analysis because they received lower doses and therefore suboptimal clinical responses may be due to underdosing.

Reviewer Comments:
Although there was no clear signal of loss of efficacy related to immunogenicity in clinical trials, the long-term impact of immunogenicity for this drug remains unknown. As discussed earlier, I recommend that long-term data on the immunogenicity of asfotase alfa be collected as a post-marketing requirement.

Table 46: Antibody Status of Patients with Clinical Deterioration and/or RGI-C Non-responders

Pt ID	Age	Antibody Status	Height	Weight	RGI-C	Dose Change / Date Dose Changed	Dose (mg/kg/wk)
	ENB-002-08/ENB-003-08 patients						
002-01-01	7 mon	PP NAB+/T	X			Decrease Week 24	9→6
002-02-01	32 mon	PP NAB+/T		X		Decrease Week 96	9→6
002-06-01	35 mon	Positive NAB+ X1	X				6
002-08-01*	0 mon	Negative	X	X			6
002-09-02	0 mon	Negative	X	X		Increase Week 120	6→12
	ENB-010-10 patients						
010-01-07*	0 mon	Negative	X	X		Baseline	14
010-13-01*	4 mon	PP NAB+	X			Increase Month 2	6→12
010-13-04	2 mon	Negative	X	No change		Increase Month 6	6→9
010-13-05	5 mon	Negative		X			6
010-16-01	3 mon	PP NAB+	X	X		Increase Month 4	6→9
010-18-02	1 mon	PP NAB+	X	X	X		6
010-19-01*	8 mon	PP NAB+	X		No change	Decrease Month 5-6	9→3
010-20-01	4 mon	Positive	X	X			6
010-22-01	33 mon	PP NAB+	No change		X		6
010-23-01	60 mon	PP	X				6
010-38-06	1 mon	PP	NA	NA	X		6
010-16-03*	6 wks	Negative					6
010-18-03*	22 mon	PP NAB+/T					6
010-18-04*	6 mon	PP NAB+					6

PP=persistent positive antibodies; NAB+= neutralizing antibody-positive; NAB+/T=neutralizing antibody-positive/ tolerized; NA= not available
*patients who died during trials

7 Review of Safety

Safety Summary

Asfotase alfa is generally well tolerated in patients with perinatal/infantile- and juvenile-onset HPP. Ten deaths have been reported in clinical trials and compassionate use programs; all deaths were attributed to HPP-related disease complications.

A total of 274 serious adverse events (SAEs) were reported in 48 patients, the majority of whom (42 patients) were perinatal/infantile onset patients. Eight patients experienced SAEs that the investigator assessed as treatment-related, including injection site reactions, hypersensitivity reactions, craniosynostosis (2 patients each), conductive deafness, chronic hepatitis, and a drug dosing error (1 patient each).[45]

The most common AEs (>20%) reported among all patients were injection site reactions, upper respiratory infections/nasopharyngitis, fever/pyrexia, vomiting, extremity pain, gastroenteritis/gastrointestinal infection, fractures, headaches, and constipation. The applicant reported that 79/102 (77%) of patients experienced events considered to be related to the use of asfotase alfa; the majority of treatment-related events were injection site reactions. A higher proportion of patients on a 6 times per week dosing schedule reported injection site reactions compared to patients on a 3 times per week dosing schedule.

Other adverse reactions considered related to the use of asfotase alfa as reported by the applicant include lipohypertrophy, hypersensitivity reactions, and ectopic calcifications. Lipodystrophy has been associated with the injection of other drug products including steroids, insulin, and growth hormone. Hypersensitivity reactions are a known risk of treatment with therapeutic protein products. Ectopic calcifications, including nephrocalcinosis, conjunctival calcifications and band keratopathy are known complications of HPP. Treatment with asfotase alfa raises a concern for the potential formation of ectopic calcifications in other tissues as inorganic phosphate released through enzymatic activity binds with calcium to form hydroxyapatite crystals. Based on my review of the available safety data, there was insufficient information to determine whether some of the reported events represented known disease complications (i.e., band keratopathy) or new safety signals (i.e., calcifications involving deeper layers of the cornea or other ophthalmic structures). Of interest, the EMA recently conducted a review of case reports of corneal calcifications in patients using eye drops containing phosphate buffers. The EMA concluded that there was evidence to suggest that patients with pre-existing corneal damage might develop calcifications with exposure to phosphate-containing eye drops and recommended that product information for these

[45] *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 and conductive deafness, known complications of HPP disease, may be increased with asfotase alfa treatment. Based on my review of the information provided, there was no clear safety signal for these two events.*

medicines contain a warning about the risk of development of corneal calcifications. Given the mechanistic plausibility of development of ectopic calcifications with treatment with asfotase alfa, and multiple limitations in the interpretation of the data for ectopic calcifications (small sample sizes, 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.]), additional information on ectopic calcification events is needed. The applicant will be required to collect this information as a post-marketing requirement.

Based on my independent analysis of reported adverse events, 1/102 (1%) patients in the safety database experienced an anaphylactic reaction. Of 98 patients with evaluable antibody testing results, 76 patients (78%) treated in clinical trials thus far have developed ADA titers to asfotase alfa; 48 patients (49%) have developed neutralizing antibodies. Overall safety results did not appear to be different for these patients. However, information is needed on the long-term impact of immunogenicity on the safety profile of this product. Long-term immunogenicity data, including incidence rates of anaphylaxis and severe allergic reactions, and assessment for signals of systemic immune complex-mediated reactions, will be required as a post-marketing requirement.

Based on review of the available safety data, my independent safety analysis did not uncover major discrepancies compared with the applicant's analysis. I reclassified some events as lipodystrophy or hypersensitivity that the applicant had classified as injection site reactions (e.g., injection site atrophy was reclassified as lipodystrophy and some events of erythema were reclassified as hypersensitivity reaction). However, the reclassifications did not significantly alter event incidence.

Asfotase alfa was not evaluated in pregnant or lactating women. This reviewer notes that a pregnancy surveillance program could be included in the applicant's HPP registry.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The primary safety information for this clinical review includes data submitted in the 120 Day Safety Update Report (dated April 17, 2015) for 102 patients with HPP who received asfotase alfa in the following clinical trials: ENB-002-08/ENB-003-08 (data analysis cut-off date October 29, 2014), ENB-006-09/ENB-008-10 (data analysis cut-off date November 5, 2014), ENB-009-10 (data analysis cut-off date November 5, 2014) , and ENB-010-10 (data analysis cut-off date November 12, 2014).

The safety update also included preliminary top-line safety results from clinical trial AA-HV-104 (see Section 4.4 for further details on trial AA-HV-014) and cumulative safety

data for 16 patients treated under compassionate use programs. The data analysis cut-off date for the compassionate use programs was November 30, 2014.

I also reviewed safety data reported in the final clinical study report for ENB-001-08 (dated September 14, 2009, which included patients who subsequently enrolled in ENB-009-10 (see Section 7.1.3 below for information on data pooling).

7.1.2 Categorization of Adverse Events

The applicant coded AEs by System Organ Class (SOC) and AE preferred terms using the Medical Dictionary for Regulatory Activities (MedDRA; Versions 16.1 and 17.1). I revised AE preferred terms and SOC terms so that AE terms were clustered together to allow for a more meaningful description of the AE profile of Strensiq. For example, lipohypertrophy and lipoatrophy were grouped together as lipodystrophy.

Reporting of adverse events included information such as classification of relationship to study medication, classification of severity of AE, and date of onset and resolution of AE. These appear to be adequate to assess the safety profile of Strensiq.

Reviewer Comments:
Note that the version of MedDRA used to code events changed during the course of the clinical trials. The applicant stated that the change in coding dictionary did not have an impact on overall interpretation of the safety data. This reviewer concurs with the applicant's assessment.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

Safety data were pooled for the following clinical trials: ENB-002-08/ENB-003-08, ENB-006-09/ENB-008-10, ENB-009-10, and ENB-010-10.

Safety data from ENB-001-08 were not included in the integrated safety analysis due to differences in trial designs. Four of 6 patients who participated in Study ENB-001-08 were subsequently enrolled in Study ENB-009-10 and are included in the integrated safety analyses under that study.

7.2 Adequacy of Safety Assessments

Safety parameters for the clinical trials reviewed included physical examination, vital signs, hypersensitivity reactions ("infusion/injection-associated reactions"), injection site reactions, chemistry, hematology, and urinalysis, pregnancy screening (in female patients of childbearing potential), antibody testing, concomitant medications and therapies, and adverse events.[46] Adverse events of special interest included ectopic calcifications. Specific assessments to monitor for ectopic calcifications included renal

[46] Electrocardiograms were also included in safety assessments for ENB-001-08 and ENB-009-10.

ultrasounds and ophthalmology examinations. These safety parameters appear to be adequate to assess the safety profile of asfotase alfa.

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

Exposure

Through the analysis cut-off dates for the integrated analyses, 102 patients were exposed to asfotase alfa (see Table 47). Ninety patients were continuing treatment in ongoing studies, including 79 patients with infantile-onset HPP, 20 patients with juvenile-onset HPP, 2 patients with adult-onset HPP, and one patient whose HPP phenotype is unknown.

Duration of exposure ranged from one day to 6.5 years (312 weeks). A majority of patients (n=54) received at least 2 years of treatment, with 42 patients receiving 3.5 years (168 weeks) or more of treatment. Mean duration of treatment for infantile-onset patients and juvenile onset patients was 2 years and 3 years, respectively. The applicant noted that the shorter duration of exposure in infantile-onset patients is attributable to the 31 more recently enrolled patients in Study ENB-010-10.

Table 47: Asfotase alfa Duration of Exposure by Phenotype

Treatment Duration (months)	Perinatal/ Infantile Onset (n-79)	Juvenile-Onset (n=20)	Adult-Onset (n=2)	Unknown Onset (n=1)	All Patients (n=102)
Treatment Duration (weeks) n Mean (SD) Median Min, Max	79 102 (94) 71 0.1, 312	20 193 (46) 192 96, 260	2 192 (0) 192 192, 192	1 215 - -	102 123 (93) 99 0.1, 312
< 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 (70
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)

Source: 120 Day Safety Update Report (dated April 17, 2015), Table 7

As discussed in Section 5, initial asfotase alfa dosing differed across clinical trials. Total weekly asfotase alfa dosing in patients with HPP ranged from 0.9 mg/kg/week to 28 mg/kg/week, with the majority of patients either starting on or achieving a dose of 6 mg/kg/week within the first 24 weeks of treatment. Twenty-four patients received a maximum asfotase alfa dose greater than 6 mg/kg/week, including 19/79 (24%) perinatal/infantile onset patients and 5/20 (25%) juvenile-onset patients.

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 (see Section 7.3.3). Twelve 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). One patient increased the dosing schedule due to adverse events (injection site reactions) experienced with a 3 times per week dosing schedule. Table 48 summarizes dosing regimens in clinical trials by HPP phenotype.

Table 48: Cumulative Asfotase alfa Dosing by HPP Phenotype

Dosing Cumulative	Perinatal/ Infantile (n-79)	Juvenile (n=20)	Adult (n=2)	Unknown (n=1)	All Patients* (n=102)
Schedule					
3x per week	67 (85)	2 (10)	0	0	69 (68)
6x per week	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 2)

* One patient who was discontinued after initial dosing due to a hypersensitivity reaction is not included in exposure analyses.
Source: 120 Day Safety Update Report (dated April 17, 2015), Tables 2.3.8.2.1, 33.8.2.1 ((maximum daily dose), 2.3.8.7.1, and 3.3.8.7.1 (changes in dosing).

Demographics

The majority of patients in all trials were white and non-Hispanic or Latino (>90%) and approximately half of patients were female. The median age of patients with perinatal/infantile-onset HPP was 1.9 years and the median age of patients with juvenile-set HPP was 16.9 years. The youngest perinatal/infantile-onset patient was one day old. No patients with the perinatal/infantile-onset or juvenile-onset phenotype were >65 years old. As per protocol design, patient ages varied across studies.

By geographic region, two-thirds of the patients in the pooled safety analysis set were enrolled in the US or Canada, 25% of patients were enrolled in Europe, and the remaining 8% of patients were enrolled in Asia (Japan) or other regions. Table 49 summarizes patient demographics by HPP phenotype.

Table 49: Summary of Patient Demographics by HPP Phenotype- Asfotase alfa Safety Set

Patient Baseline Characteristics	Perinatal/Infantile (n=79)	Juvenile (n=20)	Adult (n=2)	Unknown (n=1)	All Patients (n=102)
Age at First Dose (years)					
Mean (SD)	3.8 (7)	29.3 (22.3)	55.6 (15.6)	64.2	10.4 (17.6)
Median	1.9	16.9	55.8	--	3.5
Min, Max	0. 56	6.2, 59.3	44.7, 66.8	--	0. 66.8
Sex					
Male	38 (48)	10 (50)	0	1 (100)	49 (48)
Female	41 (52)	10 (50)	2 (100)	0	53 (52)
Race					
Asian	7 (9)	0	0	0	7 (7)
White	64 (81)	19 (95)	2 (100)	1 (100)	86 (84)
Other	3 (4)	1 (5)	0	0	4 (4)
Unknown	5 (6)	0	0	0	5 (4)
Ethnicity					
Hispanic or Latino	2 (3)	1 (5)	0	0	3 (3)
Not Hispanic	72 (91)	19 (95)	2(100)	1(100)	94 (92)
Unknown	5 (6)	0	0	0	5 (5)
Geographic Region					
USA/Canada	45 (57)	20 (100)	2 (100)	1 (100)	68 (67)
Europe	26 (33)	0	0	0	26 (25)
Asia	5 (6)	0	0	0	5 (5)
Other regions	3 (4)	0	0	0	3 (3)

Source: 120 Day Safety Update Report (dated April 17, 2015), Tables 1.1.1.1.1 and 1.1.2.1.3

7.2.2 Explorations for Dose Response

Relationship between dose and response was evaluated in all trials. There was no clear dose response relationship in terms of safety signals seen. See Section 4.4 and Section 7.5.1 for evaluation of AEs and dose dependency for asfotase alfa, respectively.

7.2.3 Special Animal and/or In Vitro Testing

None.

7.2.4 Routine Clinical Testing

Routine safety laboratory studies were performed for all asfotase alfa trials. Laboratory assessments for all clinical trials were analyzed at central laboratory sites (local laboratories were used at trial start for ENB-002-08 and then transitioned to central laboratory sites). Laboratory results are discussed in Section 7.4.2.

7.2.5 Metabolic, Clearance, and Interaction Workup

See Section 4.4 for information on metabolic, clearance, and interaction properties of the drug.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

The trials were adequately designed to allow for safety analyses for immunogenicity, a known adverse effect related to treatment with enzyme replacement therapy products and other therapeutic protein products.

The trials also included monitoring for ectopic calcifications, specifically renal ultrasounds and eye examinations.

Reviewer Comments:
As discussed later, more data are needed regarding the potential risk for development of ectopic calcifications with asfotase alfa treatment. Some of the patients did not have baseline eye or renal ultrasound examinations. In addition, a less comprehensive ophthalmologic examination was required in earlier versions of the trial protocols. The small number of patients with findings of tissue calcifications in clinical trials and the lack of baseline information for some of these patients limit the ability to evaluate for a potential safety signal.

7.3 Major Safety Results

The major safety results reviewed in this section are from clinical trials ENB-002-08/ENB-003-08, ENB-006-09/ENB-008-10, ENB-009-10, and ENB-010-10.

A total of 274 nonfatal SAEs were reported for 48 patients (47%), including 16 SAEs in 8 patients (8%) that were assessed as treatment related.

No deaths, SAEs, severe AEs, or discontinuations due to AEs were reported for ENB-001-08 or AA-HV-104.

7.3.1 Deaths

The applicant reported 10 deaths in patients treated with asfotase alfa, including 7 patients enrolled in clinical trials and 3 patients treated in compassionate use programs. In addition, one patient died after trial enrollment but prior to receiving study drug. All reported deaths were attributed to HPP-related disease complications. Patient narratives for patients who received study drug are provided below (I did not include a narrative for the patient who died prior to treatment):

Patient Deaths in Clinical Trials

- **Patient 002-08-08-01 (Perinatal/infantile-onset HPP)- Cause of Death: Septic Shock**
  Sex: Male Age at Study Entry: 2.9 weeks

The patient's medical history was significant for premature gestation, rickets, leg fractures, craniosynostosis, respiratory compromise (patient was ventilator dependent since birth), pneumonia, nephrocalcinosis, and hypercalciuria. He was treated with a single IV dose of asfotase alfa for PK analysis on February 16, 2009, followed by a trial regimen of 1 mg/kg administered SC 3 times per week. His dose was increased on April 6, 2009 (Week 7) to 2 mg/kg SC 3 times per week due to lack of efficacy (based on PK data). The patient's clinical course was complicated by multiple SAEs of systemic infections following initiation of asfotase alfa treatment, including a central line infection, 2 episodes of pneumonia, and tracheitis. On (b) (6), the patient presented with respiratory distress, fever, tachycardia and hypotension, and was diagnosed with septic shock. Study drug was interrupted and the patient was treated with antibiotics, vasopressors, and blood products. The patient developed asystole and died at age 34 weeks on (b) (6) No resuscitative efforts were conducted due to the patient having a Do Not Resuscitate Order.

The applicant assessed the event of septic shock as unrelated to treatment.

The patient's clinical course was also significant for SAEs of craniosynostosis and severe conductive hearing loss (see narrative for Patient 002-08-08-01 in Section 7.3.2)

Reviewer Comment:
This reviewer agrees with the investigator's and applicant's assessments.

- **Patient 010-10-01-07 (Perinatal/infantile-onset HPP)- Cause of death: Cardiopulmonary arrest**
  Sex: Male Age at Trial Entry: 1 day

The patient's medical history was significant for lung hypoplasia and respiratory compromise requiring mechanical ventilation at birth. He was started on asfotase alfa 2 mg/kg 7 times per week on December 21, 2011. At approximately 5 weeks of age, he was reported to have severe arrhythmia that resolved after 30 minutes without intervention. His clinical course was complicated by multiple events of lung collapse and respiratory failure between (b) (6) and (b) (6). On (b) (6) he developed severe progressive respiratory failure and severe pulmonary hypertension. On (b) (6) he experienced the first of multiple episodes of cardiopulmonary arrest. Following his family's decision to discontinue

resuscitation efforts, he subsequently died of cardiac arrest at age 62 weeks on (b) (6)

The investigator and applicant attributed the fatal event of cardiopulmonary arrest to underlying disease.

Reviewer Comment:
This reviewer agrees with the investigator's and applicant's assessments.

- **Patient 010-10-13-01 (Perinatal/infantile-onset HPP)-Cause of death: Brain herniation**
  Sex: Male Age at Trial Entry: 21 weeks

The patient's medical history was significant for seizures, failure to thrive, high blood calcium levels, nephrocalcinosis, respiratory compromise, gastroesophageal reflux, anemia, and developmental delay. He was started on asfotase alfa 2 mg/kg 3 times per week on October 29, 2010. The patient experienced multiple SAEs due to disease-related complications, including events of worsening respiratory compromise, lower respiratory tract infections, feeding tube complications, electrolyte abnormalities, and abnormal hepatic function. On June 27, 2011 (Week 34 of treatment), the patient's dose of asfotase alfa was increased to 4 mg/kg 3 times per week due to a SAE of pulmonary edema. The patient was also noted to have persistent elevated urine PLP levels at that time. The patient remained on treatment with asfotase alfa until his death.

At approximately 4 months of age, the patient was diagnosed with craniosynostosis by head CT scan. The patient experienced a number of neurological SAEs related to the craniosynostosis and seizures, including convulsions, increased intracranial pressure, hydrocephalus, and brain edema. The patient was reported to have increasing seizure activity in the 2 to 3 weeks preceding his death. He was hospitalized on (b) (6) for a history of multiple seizures for several days for further evaluation and management. He was noted to have respiratory compromise en route to the hospital and was febrile upon arrival to the hospital. His admission examination was significant for intermittent screaming spells associated with dilated pupils, slurred speech, severe tachycardia, and diaphoresis. Head CT scans and an electroencephalogram were normal at the time of admission. The patient was treated with antibiotics for presumed central line infection and meningitis or encephalitis. The patient was admitted to the pediatric intensive care unit due to worsening respiratory distress noted in the emergency department. In the intensive care unit, the patient's respiratory status continued to deteriorate and he required intubation for pulmonary edema and respiratory failure. He also experienced hyperkalemic cardiac arrest and was resuscitated and placed on vasopressors. On (b) (6) the patient also developed liver dysfunction, with elevated transaminases and coagulopathy. The following day, the patient was noted to have a fixed and

dilated right pupil. A head CT scan revealed elevated intracranial pressure, cerebral edema, hydrocephalus, and impending herniation, which was treated by emergent placement of a ventriculoperitoneal shunt. The patient's intracranial hypertension continued to worsen and was refractory to medical management. After being advised that the patient likely was progressing to brain death, the patient's mother requested removal of life support on (b) (6) and the patient died within an hour after life support was withdrawn. The patient was 4 years 3 months old at the time of death.

The investigator and applicant attributed the fatal event of brain herniation to underlying disease.

Reviewer's Comment:
This reviewer agrees with the investigator's and applicant's assessments.

- **Patient 010-10-16-03 (Perinatal/infantile- onset HPP)-Cause of death: Respiratory failure**
  Sex: Male Age at Trial Entry: 6 weeks

The patient's medical history included refractory vitamin B6- dependent seizures, anemia, and mechanical ventilator support for respiratory compromise. The patient was started on asfotase alfa 2 mg/kg 3 times per week on October 5, 2011. The patient was noted to have normal head ultrasound examinations one week prior to study entry and on Day 1 of treatment. A repeat head ultrasound obtained 5 days after starting treatment reveals changes consistent with hypoxic-ischemic encephalopathy. A brain MRI obtained 2 weeks after starting treatment revealed progression of hypoxic-ischemic changes in the brain. Based on these findings and the patient's prognosis, the family elected to withdraw the patient from the trial on (b) (6). The patient subsequently died of respiratory failure and brain death at age 10 weeks on (b) (6)

The investigator and applicant attributed the fatal event of respiratory failure to underlying disease.

Reviewer's Comment:
This reviewer agrees with the investigator's and applicant's assessments.

- **Patient 010-10-18-03 (Perinatal/infantile- onset HPP)-Cause of death: Respiratory failure**
  Sex: Female Age at Trial Entry: 20 months

The patient's medical history included atrial septal defect, gastroesophageal reflux, short stature, kyphosis, delayed gross motor development, and intermittent urinary tract infections. The patient was noted to have craniosynostosis at her baseline physical examination. She was started on asfotase alfa 2 mg/kg 3 times per week on May 13, 2013. She underwent surgical repair of the craniosynostosis at age 22 months without postoperative complications. On (b) (6), the patient developed a respiratory illness that progressed to pneumonia with respiratory failure. She died of severe respiratory failure at 2 years 7 months on (b) (6).

The investigator and applicant attributed the fatal event of respiratory failure to underlying disease.

Reviewer's Comment:
This reviewer agrees with the investigator's and applicant's assessments.

- **Patient 010-10-18-04 (Perinatal/infantile- onset HPP)-Cause of death: Complications of HPP**
  Sex: Female Age at Trial Entry: 7 months

The patient's medical history included rachitic rib deformities, abnormally shaped head, poor weight gain, dysphagia, developmental delay, bowing and deformities of the extremities, muscle weakness, intermittent anemia, hypercalcemia, and urinary tract infection. The patient was started on asfotase alfa 2 mg/kg 3 times per week on October 23, 2013 and received only 3 doses of study drug.

Approximately one month prior to trial entry, the patient had imaging and ophthalmology evaluations due to her abnormal head shape, including a skull x-ray that revealed wide cranial suture and bone demineralization, and normal head ultrasound and ophthalmology examinations. On (b) (6), she was noted to have a bulging fontanel with normal neurologic, head ultrasound and ophthalmologic evaluations. On (b) (6) the patient had a persisting bulging fontanel with no signs of increased intracranial pressure on physical examination. On (b) (6) the patient was found unresponsive in her car seat while the family was driving to her Week 6 study visit. Resuscitation effects were unsuccessful. An autopsy report noted that the patient had multiple rib fractures, edema of the lungs, and cerebral swelling.

The investigator and applicant attributed the fatal event to complications of HPP.

Reviewer's Comment:
This reviewer agrees with the investigator's and applicant's assessments.

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- **Patient 010-10-19-01 (Perinatal/infantile- onset HPP)-Cause of death: Severe pneumonia**
  Sex: Male Age at Trial Entry: 39 weeks

The patient's medical history included exophthalmos, bulging fontanel, growth retardation, kyphosis, poor weight gain, seizures, hypercalcemia, and nephrocalcinosis. He had no prior history of respiratory support. The patient was started on asfotase alfa 2 mg/kg 3 times per week on November 6, 2012. His asfotase alfa dose was changed twice during the course of treatment, first increased to 3 mg/kg 3 times per week at Week 5 due to insufficient improvement.

On (b) (6) (approximately Week 13 of treatment), the patient was hospitalized for pneumonia and gastroenteritis and treated with antibiotics. The gastroenteritis resolved but the patient's respiratory status deteriorated over the course of 2 weeks and the patient was intubated on (b) (6) after experiencing respiratory arrest. He was also started on intravenous steroid medication. The investigator noted that the patient had elevated eosinophil count following asfotase alfa injections and lower counts just prior to dosing. As a result, study drug was temporarily held starting on (b) (6) and the patient's steroid dose was increased and antibiotic treatment was adjusted. The patient was extubated and placed on nasal CPAP in early (b) (6) The patient was re-challenged with asfotase alfa and appeared to do well without antibiotics. In addition, his eosinophil count was within the normal range. However, the patient was not able to wean off of CPAP. The patient missed a total of 21 doses of study drug between (b) (6).

On (b) (6) (approximately Week 26 of treatment), the patient had increased respiratory difficulty, vomiting and weight loss. His steroid dose was decreased and the patient was stated to been in good condition upon discharge on (b) (6). On (b) (6), the patient was observed in hospital for several hours due to complaints of agitation and constipation, which resolved after a bowel clean out. The following day, the patient's mother contacted the hospital to report that his CPAP apparatus was broken. The patient arrived at the hospital in cardiac arrest and was resuscitated but died following a second cardiac arrest at age 15 months. No autopsy was performed.

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. The applicant stated that a causal relationship to treatment could not be ruled out but considered equipment failure in the midst of an ongoing respiratory process to be a contributing factor.

Reviewer's Comment:
This reviewer agrees with the applicant that equipment failure contributed to the patient's progression to cardiopulmonary arrest. There was not sufficient

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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. However, the patient's eosinophil levels returned to and remained within normal limits following drug re-challenge. Furthermore, elevated eosinophil counts have also been reported in other patients but do not appear to be associated with increased incidence of treatment-related AEs (see Section 7.4.2).

Patients in Compassionate Use Programs

Japan (Perinatal/infantile- onset HPP)-Cause of death: Complications of HPP
Sex: Female Age at Trial Entry: 14 months
The patient's medical history was significant for hyperammonemia, pulmonary hypoplasia, pulmonary hypertension, multiple bullae, chronic lung disease and tracheostomy. The patient was treated with asfotase alfa 2 mg/kg 3 times per week. The patient is reported to have improvement of her skeletal condition and pulmonary hypertension but her overall pulmonary condition deteriorated, requiring long-term ventilator support. After approximately 7 weeks of asfotase alfa treatment, the patient developed cardiac tamponade from a tension pneumothorax (due to expansion of the lung bullae) and resuscitation was unsuccessful. The cause of death was reported to be lung bullae and chronic lung disease and was assessed as unrelated to treatment.

The Netherlands (Perinatal/infantile- onset HPP)-Cause of death: Respiratory insufficiency
Sex: Male Age at Trial Entry: 7 months
The patient's medical history was significant for ventilator dependency since birth. He was started on treatment with asfotase alfa 2 mg/kg 3 times per week at age 1 month. The dose was increased to 3 mg/kg 3 times per week at an unspecified time and then 4 mg/kg 7 times per week at age 6 months due the patient's clinical condition not improving. The patient's respiratory insufficiency continued to worsen and the patient died at age 7 months. The event of respiratory insufficiency was assessed as unrelated to treatment.

South Africa (Perinatal/infantile- onset HPP)-Cause of death: Complications of HPP
Sex: Male Age at Trial Entry: 4 months
The patient's medical history was significant for ventilator dependency and tracheostomy. He was treated with asfotase alfa 2 mg/kg 3 times per week. After approximately 8 weeks of treatment, he experienced severe hypoxic brain injury secondary to a vomiting episode. The family decided to remove the patient from ventilator support. The patient was reported to have shown improvement in skeletal

mineralization and respiratory function prior to the vomiting episode. The treating physician assessed the fatal event as unrelated to treatment.

Reviewer Comments:
The applicant noted that 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) and that half of the patients had received asfotase alfa doses > 6 mg/kg/week. There did not appear to be any differences in exposure between patients who survived and patients who died. Based on my review of available PK data for ENB-002-08/ENB-003-08 and ENB-010-10, patients had exposures approaching or within the exposure plateau range for survival (see Section 4.4.2). In addition, 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 care. I also reviewed antibody status for the seven patients treated in clinical trials who died (see Section 6.1.10). There were no clear patterns in antibody status relative to other clinical responses (i.e., growth or radiographic assessments) or time to death. These 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. However, more information is needed on the long-term impact of immunogenicity on clinical outcomes, including survival.

7.3.2 Nonfatal Serious Adverse Events

A total of 274 nonfatal SAEs 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 274 SAEs, 258 SAES were assessed as unrelated to treatment. The majority of patients experiencing nonfatal SAEs (42/48 patients; 88%) were patients with perinatal/infantile-onset HPP. The most commonly reported SAEs (reported in 3 or more patients) were craniosynostosis (12 patients), pneumonia (7 patients), convulsions, respiratory disorders, respiratory distress, decreased oxygen saturation (4 patients each), increased intracranial pressure, apnea, hypoxia, upper respiratory tract infection, feeding disorder, food intolerance, pyrexia, and bradycardia (3 patients each).

Table 50 summarizes information for the 8 patients who experienced nonfatal SAEs assessed by the investigator and applicant as treatment- related.

Table 50: Summary of Nonfatal SAEs Assessed as Treatment-related

Patient ID	Dose	Phenotype	Day	SAE	Severity	Status
002-08-05-01	2 mg/kg/ 3 times a week	Perinatal/ Infantile	Day 765	Chronic hepatitis	severe	Resolved
002-08-08-01	2 mg/kg/ 3 times a week	Perinatal/ Infantile	Day 128 Day 198	Craniosynostosis Conductive deafness	severe	Resolved- (surgically repaired); Ongoing at time of death
009-10-01-04	1 mg/kg 6 times a week	Juvenile	Day 806 Day 830	Oral hypoesthesia/ extremity pain Chills (3 events) Headache (2 events)	moderate	Resolved
010-10-16-11	2 mg/kg/ 3 times a week	Perinatal/ Infantile	Day 7	Injection site reaction (2 events)	moderate	Dose interruption-resolved
010-10-18-05	2 mg/kg/ 3 times a week	Perinatal/ Infantile	Day 56	Craniosynostosis	moderate	Resolved (surgically repaired)
010-10-22-01	2 mg/kg/ 3 times a week	Perinatal/ Infantile	Day 122	Chills/pyrexia	moderate	Resolved
01010-10-27-01	3 mg/kg/ 3 times a week	Perinatal/ Infantile	Day 129	Injection site abscess	mild	Resolved
010-10-38-03	2.5 mg/kg 3 times a week	Perinatal/ Infantile	Day 237	Dosing error- patient given double dose X1 due to calculation error	moderate	Dose was corrected; one dose was suspended

Narratives for the reported SAEs:

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. Therefore, I have not included detailed patient narratives for these events in my review. In addition, the medication error clearly is treatment-related.

Regarding the events of chronic hepatitis, craniosynostosis, and conductive deafness, assessment of causality is problematic. Mechanistically, there is a theoretical risk for all of these events with treatment with asfotase alfa. However, craniosynostosis and conductive deafness are known complications of HPP. 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. However, in this reviewer's opinion, there was insufficient information to evaluate for a relationship between treatment and development of craniosynostosis or deafness. Patient narratives are provided below for the SAES of chronic hepatitis, craniosynostosis, and conductive deafness.

Reference ID: 3836304

- **Patient 002-08-05-01**

SAE: chronic hepatitis

The patient is a female with perinatal/infantile-onset HPP age 28 weeks at trial entry. Her medical history was significant for respiratory insufficiency and was negative for hepatobiliary problems. She received an initial IV dose of asfotase alfa on December 3, 2008 and then was started on asfotase alfa SC 2 mg/kg 3 times per week on December 10, 2008. The patient experienced persistent elevation of her hepatic enzymes (ALT and AST) beginning in February 2010. The patient underwent a comprehensive evaluation for liver disease, including ultrasound examinations of the liver, gallbladder, and pancreas, negative viral serology and immunology studies, and a liver biopsy. Biopsy results revealed a mild nonspecific hepatitis, possibly drug-induced. One of the patient's concomitant medications- montelukast- was suspected to be the etiology of the hepatitis (there are case reports of drug-induced hepatitis associated with montelukast) and was discontinued in October 2010. The patient continued to have elevated enzymes in May 2012; the event was subsequently reported as resolved in June 2014. The patient remained on asfotase alfa treatment without interruption.

The investigator and applicant assessed the event as possibly related to treatment.

Reviewer Comments:

The applicant reviewed 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 Section 7.4.2). The liver is a target organ for asfotase alfa and therefore, it is mechanistically plausible that treatment with asfotase alfa contributed to the reported event of hepatitis. According to the 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. In this reviewer's opinion, there is sufficient evidence to warrant inclusion of this event in labeling.

- **Patient 002-08-08-01**

The patient was a 2.9 week old male with perinatal/infantile-onset HPP at trial entry. The patient's medical history was significant for premature gestation, rickets, leg fractures, craniosynostosis, respiratory compromise (patient was ventilator dependent since birth), pneumonia, nephrocalcinosis, and hypercalciuria. The patient was treated with a single IV dose of asfotase alfa for PK analysis on February 16, 2009, followed by a trial regimen of 1 mg/kg administered SC 3 times

per week. The patient's dose was increased on April 6, 2009 (Week 7) to 2 mg/kg SC 3 times per week due to lack of efficacy (unspecified); the patient's asfotase alfa activity values increased to within the target range (650-1000 U/L)following the dose increase. The patient's clinical course was complicated by multiple episodes of systemic infections and the patient died of septic shock at age 34 weeks (see narrative for Patient 002-08-01 in Section 7.3.1)

SAE: craniosynostosis
On June 23, 2009, the patient was diagnosed with craniosynostosis. Reconstructive surgery was planned based on a CT scan that showed near complete closure of coronal and lambdoid sutures. However, the patient died prior to the surgery being scheduled.

Reviewer Comment:
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 this patient to assess for causality.

SAE: conductive deafness
Results of the patient's newborn hearing screening examination were inconclusive due to environmental noise in the examination location. Severe conductive hearing loss in both ears noted on an auditory brainstem Response (ABR) evaluation in (b) (6); these findings were confirmed on repeat evaluation in (b) (6) An otoscopic examination performed under anesthesia in (b) (6) had revealed "slit-like soft tissue stenosis" of the auditory canals.

The investigator assessed the event as possibly treatment-related, with the hearing loss being secondary to study drug affecting the auditory bones. The applicant concurred with the investigator's assessment based insufficient information to definitively rule out the theoretical possibility of a drug effect on auditory bone structure.

Reviewer Comments:
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 this reviewer's opinion, an adverse effect on auditory bone structure remains a theoretical risk.

Reference ID: 3836304

- **Patient 010-10-18-05**

SAE: craniosynostosis

The patient is a 47 week old male with perinatal/infantile-onset HPP. Medical history was significant for kyphosis, difficulty eating/swallowing and gaining weight, muscle weakness, gross motor delay, hypercalcemia, and low alkaline phosphatase. He was started on asfotase alfa 2 mg/kg 3 times per week on October 9, 2013. On (b) (6), the patient was hospitalized for surgical repair of the craniosynostosis and was treated post-operatively with antibiotics for fever. He was discharged home on an unspecified date.

The investigator assessed the event of craniosynostosis as possibly related to treatment.

Reviewer Comment:
There is insufficient information to assess for causality.

7.3.3 Dropouts and/or Discontinuations

Five patients experienced AEs that led to discontinuation of treatment or study withdrawal, including 4 patients with perinatal/infantile-onset HPP and one patient with juvenile-onset HPP (see Table 51). Two patients withdrew consent, including one patient with perinatal/infantile-onset HPP who experienced a hypersensitivity reaction during her initial infusion of asfotase alfa and one patient with juvenile-onset HPP who experienced multiple injection site reactions. Three patients with perinatal/infantile-onset HPP discontinued treatment due to death from disease-related complications.

Table 51: Dropouts and Discontinuations in Clinical Trials

Patient ID	Age*/Sex	Dose	AE	Action Taken	Comment
002-08-03-01	20 months Female	2 mg/kg IV X 1 dose	Hypersensitivity reaction	Discontinued treatment	
002-08-08-01	3 weeks Male	1 mg/kg 3 times per week; increased to 2 mg/kg 3 times per week	Septic shock	Discontinued treatment	Pt died (see patient narrative)
010-10-01-07	1 day Male	2 mg/kg 3 times per week	Cardiopulmonary arrest	Discontinued treatment	Pt died (see patient narrative)
010-10-18-04	23 weeks Female	2 mg/kg/ 3 times per week X 3 doses	HPP-related complications	Discontinued treatment	Pt died (see patient narrative)
009-10-01-08	16 years Female	3.5 mg/kg/week; decreased to 1.5 mg/kg/week	Injection site reaction (2 events) Injection site atrophy	Patient withdrew consent	

*Age at trial entry

Eight patients experienced AEs that lead to an interruption of study drug dosing. Two patients had drug dosing interruptions due to an adverse reaction (injection site reaction); 5 patients had drug dosing interruptions due to intercurrent illness and one patient had dosing interrupted for a possible positive pregnancy test (repeat pregnancy test was negative). Table 52 summarizes information for patients who experienced study drug interruptions.

Table 52: Patients Who Experienced Drug Dosing Interruptions in Clinical Trials

Patient ID	Phenotype	Age*	Dose (mg/kg/wk)	Date of AE	AE	Treatment-related
002-08-09-02	Perinatal/ infantile	Newborn	6	96 days	Severe pneumonia	No
009-10-02-01	Perinatal/ infantile	14 years		16 days	Lab error (borderline pregnancy test result)	No
010-10-16-01	Perinatal/ infantile	3 months	9	296 days 307 days	Changed neurological status	No
010-10-16-05	Perinatal/ infantile	15 months	9	Day 64 Day 65 Day 74 Day 77	Hematuria Increased hepatic enzymes/pancreatitis Respiratory disorder Food intolerance	No
010-10-16-11	Perinatal/ infantile	38 months	6	Day 6	Injection site reaction	Yes
010-10-29-01	Perinatal/ infantile	61 months	6	Day 115	Arthralgia	No
010-10-31-01	Perinatal/ infantile	71 months	6	Day 89	Rhinitis	No
010-10-33-01	Perinatal/ infantile	51 months	6	Days 3,5,7,9, 11	Injection site reaction	Yes

*Age at trial entry

Patients with dose modifications due to AEs

Eight patients had dose modifications due to AEs, including two patients whose doses were increased due to disease-related AEs, 5 patients whose doses were reduced due to AEs assessed as treatment-related, and one patient whose dose was decreased to correct a dose calculation error (see Table 53). In addition, two patients required an adjustment of their initial IV infusion rate due to AEs.

Table 53: Patients Who Experienced Dose Modifications in Clinical Trials

Patient ID	Phenotype	Age*	Dose Modification	Date of AE	AE	Treatment-related
002-08-01-01	Perinatal/ Infantile	7 months	Dose increased from 3 mg/kg/wk to 9 mg/kg/wk	Day 17	Respiratory distress	No
002-08-04-014	Perinatal/ Infantile	30 months	IV infusion interrupted	Day 1	Pyrexia, stomatitis, tachycardia, tachypnea, vomiting	Yes
002-08-09-02	Perinatal/ Infantile	Newborn	IV infusion rate reduced	Day 1	Vomiting	Yes
			Dose increased from 6 mg/kg/wk to 12 mg/kg/wk	Day 702 Day 830 Day 842	Decreased mobility Rib & tibia fracture Abnormal ALP level	No
010-10-19-01	Perinatal/ Infantile	9 months	Dose (9 mg/kg/wk) suspended for one month, then reduced to 3 mg/kg/wk		Severe pneumonia	Yes
006-09-01-02	Juvenile	10 years	Dose decreased from 9 mg//kg/wk to 6 mg/kg/wk	Day 34	Vitamin B6 decreased	Yes
006-09-01-06	Juvenile	12 years	Dose reduced from 9 mg/kg/wk to 4.5 mg/kg/wk	Day 13 Day 104	Injection site reaction Injection site reaction	Yes
			Dose reduced to 3 mg/kg/wk per ENB-008-10 protocol; dose increased to 6 mg/kg/wk	Day 194 Day 213 Day 227	Fatigue Muscular weakness Gait disturbance	No
009-10-01-08	Juvenile	16 years	Dose decreased from 3.5 mg/kg/wk to 1.5 mg/kg/wk Pt subsequently withdrew consent	Day 235 Day 288 Day 336 Day 343	Injection site reaction Injection site atrophy Injection site reaction Injection site reaction & atrophy	Yes
010-10-38-03	Perinatal/ Infantile	4 weeks	Dose calculation error	Day 237	Incorrect dose administered	Yes

*Age at trial entry
ALP=alkaline phosphatase

7.3.4 Significant Adverse Events

Severe AEs
There were 197 severe AEs reported in 38 patients in clinical trials ENB-002-08/ENB-003-08, ENB-010-10, ENB-006-09/ENB-008-10, and ENB-009-10. The majority of severe AEs were reported in perinatal/infantile-onset patients (33/38 patients; 87%). The most commonly reported severe AEs (reported in more than two patients) were craniosynostosis (12 patients), pneumonia (7 patients), respiratory disorder, respiratory distress, decreased oxygen saturation, convulsions(4 patients each), increased intracranial pressure, apnea, hypoxia, upper respiratory infection, feeding disorder, food intolerance, pyrexia and bradycardia (3 patients each).

Six patients experienced severe AEs assessed as treatment-related. Five perinatal/infantile-onset patients experienced events of pneumonia and respiratory arrest (Patient 010-10-19-01), craniosynostosis and conductive deafness (Patient 02-08-08-01, kyphosis (Patient 010-10-13-01), chronic hepatitis (Patient 002-08-05-01), and injection site atrophy (Patient 006-09-02-03). One juvenile-onset patient experienced an event of injection site discoloration (Patient 009-10-01-08). The events of pneumonia, craniosynostosis, chronic hepatitis, conductive deafness were also assessed as SAEs (see patient narratives in Section 7.3.2 for further details).

No severe AEs were reported for ENB-001-08 or AA-HV-104.

Reviewer Comments:
This reviewer agrees that the reported events of injection site reactions and chronic hepatitis were treatment-related. However, the remaining reported severe AEs are consistent with known complications of HPP. This reviewer notes that the three patients who experienced the events of pneumonia/respiratory arrest, craniosynostosis and conductive deafness, and kyphosis all had severe HPP disease and died during the course of treatment (see patient narratives in Section 7.3.1). Although the onset of these events was following the start of treatment, there was no additional information (e.g., autopsy results) available in patient narratives that indicated a potential relationship to treatment.

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;

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

Reviewer Comments:
Injection site lipodystrophy has been reported for other medications including steroids, insulin, growth hormone, and vaccines. This reviewer recommends including information on lipodystrophy in the labeling for asfotase alfa, including information on minimizing risk of developing lipodystrophy (e.g., rotation of injection sites).

7.3.5 Submission Specific Primary Safety Concerns

Submission specific primary safety concerns with this application include hypersensitivity reactions and ectopic calcifications.

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 120 Day Safety Update included a report for one patient who experienced a SAE of hypersensitivity reaction that met the National Institute of Allergy and Infectious Diseases/Food Allergy and Anaphylaxis Network criteria for anaphylaxis:[47]

- **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 (b) (6) approximately (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

[47] 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

premedication. At the time of the last investigator report (date not provided), the patient had not had recurrence of an allergic reaction.

Ectopic Calcifications

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 applicant reviewed potential events of interest for ectopic calcification, specifically nephrocalcinosis, conjunctival, corneal, and eye deposits, and breast calcifications. Of note, baseline fundoscopic evaluations were not required for Study ENB-006-09. Twenty-five patients had ophthalmic ectopic calcification findings at one of more time points, including 4 patients who had findings at baseline. Patients were reported to be asymptomatic and without changes in visual acuity. Forty-two of 95 (44%) of patients with baseline renal ultrasound evaluations had findings consistent with nephrocalcinosis at baseline, including two patients who had renal failure at baseline; all patients with baseline renal ultrasound evaluations were in the perinatal/infantile-onset HPP group.

Twenty five patients experienced 29 potential events of interest, including 12 perinatal/infantile-onset patients, 11 juvenile-onset patients, and two adult-onset patients. A total of 14 patients experienced events of ectopic calcification assessed by the investigator as treatment-related, including 3/12 (25%) perinatal/infantile-onset patients with events of conjunctival calcifications (2 patients) and corneal deposits (1 patient) and 11 juvenile-onset patients with events of eye deposits (6 patients), conjunctival deposits (4 patients), corneal deposits and nephrocalcinosis (1 patient each). The event of nephrocalcinosis was reported in a patient who had nephrocalcinosis at baseline that worsened over the course of treatment. Two adult patients (1 juvenile-onset patient and one adult-onset patient) experienced events of breast calcifications that were not considered to be treatment-related. Table 54 summarizes ectopic calcification AEs assessed by the investigator and applicant as treatment-related.

Table 54: 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 (n=7)	0	6/6	0	0/1
Conjunctival deposits (n=7)	2/3	4/4	0	0
Corneal deposits (n=4)	1/3	1/1	0	0
Nephrocalcinosis (n=7)	0/6	1/1	0	0
Breast calcifications (n=2)	0	0/1	0/1	0

Note that total number of patients=26; one patient had both ophthalmic and renal calcifications.

Reference ID: 3836304

Reviewer Comments:
Ectopic calcifications, including nephrocalcinosis, conjunctival calcifications and band keratopathy are known complications of HPP that have been reported in the literature.[48] *Conjunctival calcifications and band keratopathy are recognized ocular manifestations of hypercalcemia and observed in other conditions that cause hypercalcemia (e.g., sarcoidosis and hyperparathyroidism).*[49] *Band keratopathy is characterized by the appearance of a band across the central cornea formed by calcium deposition in the superficial cornea.*

The applicant noted that 52% of patients in the perinatal/infantile-onset natural history study developed nephrocalcinosis by age 5 years; nephrocalcinosis was documented in 6% of patients in the juvenile-onset natural history study. The prevalence of nephrocalcinosis in clinical trial patients was similar as per the integrated analyses performed by the applicant, with 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%). There did not appear to be standardized criteria for assessing causality for events of nephrocalcinosis. As noted earlier, the sole event of nephrocalcinosis that was assessed as treatment-related was based on worsening of the patient's nephrocalcinosis over time. The applicant noted that some patients had documented improvement in renal ultrasound findings over the course of treatment.

No data were available on the prevalence of conjunctival calcifications or band keratopathy from the natural history study or the literature. Based on my review of the datasets and patient narratives, there was insufficient information for AEs described as ectopic calcifications of the eye or cornea to determine whether the calcifications represent known disease complications (i.e., band keratopathy) or new safety signals (i.e., calcifications involving deeper layers of the cornea or other ophthalmic structures).

Of note, the issue of the potential risk of corneal calcifications with exposure to phosphate-containing products was the subject of a recent review conducted by the EMA. The EMA reviewed case reports of corneal calcifications in patients using eye drops containing phosphate buffers. The EMA concluded that there was evidence to suggest that patients with pre-existing corneal damage might develop calcification with exposure to phosphate-containing eye drops and recommended that product information for these medicines contained a warning about the risk of development of corneal calcifications.[50, 51]

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[48] Brenner RL, Smith JL, et al., Eye Signs of Hypophosphatasia, *Arch Ophthal* 1969; 81(15): 614-617
[49] Lessell S, Norton EW, Band keratopathy and conjunctival calcification in hypophosphatasia, *Arch Ophthal* 1964; 714): 497-499.
[50] http://www.ema.europa.eu/docs/en_GB/document_library/Medicine_QA/2012/12/WC500136247.pdf
[51] http://online.liebertpub.com/doi/pdf/10.1089/jop.2014.0054
Popiela MZ, Hawksworth N, Corneal calcification and phosphates: do you need to prescribe phosphate free?, *J Ocul Pharmacol Ther* 2014; 30(10): 800-2 dio: 10.1089/jop.2014.0054

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.) This reviewer recommends that additional information on ectopic calcification events be collected as a post-marketing requirement.

7.4 Supportive Safety Results

The major safety results reviewed in this section are from clinical trials ENB-002-08/ENB-003-08, ENB-006-09/ENB-008-10, ENB-009-10, and ENB-010-10.

7.4.1 Common Adverse Events

All 102 patients experienced at least one treatment-emergent adverse event (TEAE), with 3676 TEAEs reported through the analysis cut-off dates for the trials. The majority of TEAEs (2542/3676 events reported in 101/102 patients [99%]) were assessed by the investigator as not related to treatment. The majority of TEAEs (2758/3676 events reported in 100/102 patients [98%]) were mild in intensity; 197/3676 events in 38 patients (37%) were severe in intensity.

The most commonly reported TEAEs in the overall HPP population were injection site reactions (62%), with injection site erythema, discoloration, and pain being the most commonly reported types of injection site reactions. Other AEs reported in 20% or more of HPP patients included upper respiratory infection/nasopharyngitis (51%), fever/pyrexia (40%), vomiting (35%), extremity pain (27%), gastroenteritis/ gastrointestinal infection (25%), fractures (25%), ectopic calcifications (25%), headaches (22%), and constipation (21%). Table 55 adverse events reported in 10% or more of the overall HPP population.

A total of 1134 AEs in 79 (77%) patients were assessed as treatment-related; the majority of treatment-related events (1026/1134 events; 90%) were injection-site reactions. The most commonly reported treatment-related AEs in the overall HPP population were injection site reactions (62%), lipodystrophy (15%), ectopic calcifications (14%), and hypersensitivity reactions (12%).

Table 55: Most Commonly Reported Treatment-Emergent Events (≥10% of Patients) by HPP Phenotype

Preferred Term	Perinatal/ Infantile N=79	Juvenile N=20	Adult N=2	Unknown N=1	All Patients N=102
Injection site reactions	41	19 (	2 (100)	1 (100)	63 (62)
Erythema	32 (41)	15 (75)	1 (50)	1 (100)	49 (48)
Discoloration	12 (15)	8 (40)	0	0	20 (20)
Pain	11 (14)	8 (40)	0	0	20 (20)
Pruritus	10 (13)	7 (35)	0	9(100)	18 (18)
Swelling	8 (10)	6 (30)	0	0	14 (14)
Induration	10 (13)	3 (15)	0	0	23 (13)
Bruising	6 (8)	4 (20)	2 (100)	0	12 (12)
Unspecified reaction	5 (6)	4 (20)	1 (50)	0	12 (12)
Macule	4 (5)	7 (35)	0	0	11 (11)
Upper respiratory infection/ Nasopharyngitis	39	12	1	0	52
Pyrexia/fever	40 (51)	1 (5)	0	0	41 (40)
Vomiting	31 (39)	5 (25)	0	0	36 (35)
Pain in extremity	16 (20)	10 (50)	0	1 (100)	27 (27)
Gastroenteritis/gastrointestinal infection	22 (28)	4 (20)	0	0	26 (25)
Fracture	18 (23)	7 (35)	1 (100)	0	26 (25)
Tooth loss	26 (33)	0	0	0	26 (25)
Ectopic calcifications	12 (15)	11 (55)	2 (100)	0	25 (25)
Headache	14 (18)	7 (35)	0	1 (100)	22 (22)
Constipation	20 (25	1 (5)	0	0	21 (21)
Cough	10 (13)	7 (35)	1 (50	0	18 (18)
Otitis media/ear infection	14 (18)	4 (20)	0	0	18 (18)
Arthralgia	8 (10)	9 (450	0	1 (100)	18 (18)
Pneumonia	15 (19)	2 (10)	0	0	17 (17)
Diarrhea	15 (19)	2 (10)	0	0	17 (17)
Procedural pain	10 (13)	7 (35)	0	0	17 (17)
Contusion	11 (14)	5 (25)	0	0	16 (16)
Craniosynostosis	16 (20)	0	0	0	16 (16)
Lipodystrophy	7 (9)	8 (40)	0	0	15 (15)
Hypersensitivity reactions*	10 (13)	2 (10)	0	0	12 (12)
Back pain	5 (6)	6 (300	0	1 (100)	12 (12)
Dental caries	10 (13)	2 (10)	0	0	12 (12)
Conjunctivitis	9 (11)	2 (10)	0	0	11 (11)
Fall	9 (11)	1 (50	0	1 (100)	11 (11)
Oropharyngeal pain	6 (8)	5 (25)	0	0	11 (11)
Erythema	7 (9)	3 (15)	0	1 (100)	11 (11)
Rash	10 (13)	1 (5)	0	0	11 (11)
Respiratory tract infection	10 (13)	0	0	0	10 (10)

*Hypersensitivity reactions included erythema, emesis/vomiting, extremity pain, rib pain, flushing, lip numbness, pain, nausea, fussiness/irritability, fever, chills/shivering, headache, and anaphylaxis.

ENB-001-08
All 6 patients experienced at least one TEAE. The most commonly reported TEAEs (reported in 2 or more patients) were headache (4 patients), nausea (3 patients), chills, flushing, and drowsiness (2 patients each). Adverse events assessed as treatment-related included headache, rigors/chills, nausea, decrease in blood pressure, warm/flushed feeling, and tingling; all of these events were reported within one day of receiving the initial infusion. Other TEAEs assessed as treatment-related were reported at later time points during the trial (during Weeks 1-4) and included administration site (IV site) pain/discomfort and drowsiness.

AA-HV-104
Twelve of 23 individuals (52%) experienced 37 TEAEs. The most commonly reported events were injection site erythema, headaches (3 individuals each), injection site swelling, and back pain (2 individuals each). Six of 23 individuals (26%) experienced 19 events assessed as treatment-related. The most commonly reported events (14/19 events) were injection site reactions. Other treatment-related events included headache, myalgia, and increased alanine aminotransferase.

7.4.2 Laboratory Findings

Hematology
Hematology parameters assessed in clinical trials included: basophils, eosinophils, mean corpuscular hemoglobin, mean corpuscular volume (MCV), and mean corpuscular hemoglobin concentration, erythrocytes, hematocrit, leukocytes, lymphocytes, monocytes, neutrophils, and reticulocytes.

For most hematology parameters, the majority of patients in the pooled asfotase alfa safety set remained in the same category (low, normal, or high) over the course of treatment. There was a shift in eosinophil values. Approximately one-third of patients had elevated eosinophil counts at baseline that persisted over the course of treatment. In addition, one third of patients (33/94 patients) had normal eosinophils counts that shifted to high values at the time of their last assessment; 27/94 patients had shifts from normal to high values within the first 24 weeks of treatment.

Chemistry
Chemistry parameters assessed included: metabolic panel, liver enzymes (alanine aminotransferase [ALT], aspartate aminotransferase [AST], gamma-glutamyl transaminase [GGT]), vitamin D, vitamin B6, parathyroid hormone (PTH), urinalysis, and urine calcium:creatinine ratio. For most clinical chemistry parameters, the majority of patients remained in the same category (low, normal, or high) over the course of treatment. No potential Hy's Law cases were identified.[52]

[52] Hy's Law Case was defined as ALT or AST > 3X upper limit of normal (ULN) while Total Bilirubin > 2X ULN (within 30 days) and ALP < 2X ULN (within 14 days).

Seventy-three laboratory AEs were reported in 32 patients (26 perinatal/infantile-onset patients and 6 juvenile-onset patients). The most commonly reported laboratory AEs (reported in 2 or more patients) were low vitamin D level (8 patients), decreased hemoglobin (7 patients); elevated alanine aminotransaminase level (5 patients), elevated parathyroid hormone (PTH) level (4 patients), increased Vitamin D level (3 patients), high blood cell count, elevated leukocyte esterase in urine, elevated liver enzymes, low potassium, and increased urine calcium/creatinine ratio (2 patients each).

Four laboratory AEs were assessed as treatment-related, including decreased vitamin B6 level, increased urine calcium/creatinine ratio, elevated PTH, and low bicarbonate.

Asfotase alfa dosing was decreased from 9 mg/kg/week to 6 mg/kg/week for the patient who experienced a decreased vitamin B6 level.

No laboratory AEs were reported for ENB-001-08.

Reviewer Comments:
No other patients experienced dose reductions due to laboratory AEs. Asfotase alfa dosing was interrupted for one patient who experienced elevated liver enzymes. The patient presented with fever and vomiting and underwent a diagnostic work-up that was significant for elevated liver enzymes and an abnormal gallbladder ultrasound. The patient was hospitalized for treatment of acute pancreatitis; asfotase alfa treatment was suspended during her hospitalization. Both the events of elevated liver enzymes and acute pancreatitis were assessed as unrelated to treatment.

7.4.3 Vital Signs

There were no consistent changes from baseline in vital signs over the course of asfotase alfa treatment. Vital signs AEs reported in 2 or more patients included decreased oxygen saturation (42/102 patients; 41 %) and increased CSF pressure (2 patients; 2%).

No vital signs AEs were reported for ENB-001-08.

Reviewer Comment:
The reported vital signs AEs are consistent with HPP-related complications (respiratory compromise and increased intracranial pressure secondary to craniosynostosis).

7.4.4 Electrocardiograms (ECGs)

Electrocardiogram (ECG) assessments were performed in ENB-001-08 and ENB-009-10. ECGs were read locally.

No ECG AEs were reported for ENB-01-008.

In ENB-009-10, 5/13 patients with baseline ECGs had abnormal baseline findings, none of which were considered to be clinically significant. There were no clear patterns of abnormalities noted on baseline assessments.

Seven patients with normal baseline ECGs had one or more post-baseline abnormal ECGs (5 juvenile-onset patients, 1 infantile-onset patient, and one adult-onset patient). Abnormalities included QTcB interval >450 msec and/or change from baseline in QTc interval > 30 msec; no QTcB intervals were >500 msec and no patients experienced changes from baseline in QTc >60msec. No ECG abnormalities were considered to be clinically significant.

7.4.5 Special Safety Studies/Clinical Trials

None.

7.4.6 Immunogenicity

There were no consistent patterns observed for AEs assessed as treatment-related in perinatal/infantile-and juvenile-onset patients by patient ADA status. A higher incidence of lipodystrophy was reported in patients who were ever ADA-positive (17/74 patients; 23%) compared to patients who were ADA-negative (zero patients).

Conversely, the incidence of injection site reactions, hypersensitivity reactions, and ectopic calcifications was higher in patients who were ADA-negative compared to patients who were ever ADA-positive. Injection site reactions were reported in 18/24 patients (75%) who were ADA-negative compared to 36/74 patients (49%) who were ever ADA-positive. In ADA-negative patients, the incidence of hypersensitivity reactions and ectopic calcifications was 25% and 21%, respectively. In ADA-positive patients, the incidence of hypersensitivity reactions, and ectopic calcifications was 9% and 5%, respectively.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

Dose level

There were no consistent patterns in the incidence of TEAEs by dose level. A larger proportion of patients (58/80 patients; 73%) receiving doses lower than 6 mg/kg/week experienced injection site reactions compared to patients (12/21patients; 57%) receiving doses of 6 mg/kg/week or higher. A larger proportion of patients (24/80 patients; 30%) receiving doses lower than 6 mg/kg/week experienced events of lipohypertrophy compared to patients receiving doses of 6 mg/kg/week or higher (1/21 patients; 5%). A

larger proportion of patients receiving doses of 6 mg/kg/week or higher (7/21; 33%) experienced hypersensitivity reactions compared to patients receiving doses lower than 6 mg/kg/week (8/80 patients; 10%). Similar proportions of patients in the two dose levels experienced events of ectopic calcifications.

Dose frequency
The overall incidence of treatment-related AEs was higher in patients on a 6 times per week dosing schedule (28/32 patients; 88 %) compared to patients on a 3 times per week dosing schedule (50/69 patients; 73 %). Approximately half of patients receiving asfotase alfa 6 times per week experienced events of lipohypertrophy and ectopic calcifications compared to 13% of patients who received asfotase alfa 3 times per week. Eighty-four percent of patients on a 6 times per week dosing scheduled experienced injection site reactions compared to 62% of patients on a 3 times per week dosing schedule.

The incidence of hypersensitivity reactions was higher in patients (12/69 patients; 19%) on a 3 times weekly dose schedule compared to patients on a 6 times per week dose schedule (2/32 patients; 6 %).

7.5.2 Time Dependency for Adverse Events

A majority of perinatal/infantile- and juvenile-onset patients who reported injection site reactions and hypersensitivity reactions experienced their first reaction within the first 4 months of treatment; 48/65 patients (74%) with injection site reactions experienced their first reaction within the first month of treatment and 11/15 patients (73%) with hypersensitivity reactions experienced their first reaction within the first 4 months of treatment. There was no apparent time relationship for lipodystrophy and ectopic calcification events. Figures 31-33 present the time to first events of injection site reactions, lipodystrophy and ectopic calcifications for perinatal/infantile- and juvenile-onset patients.[53]

[53] NB: The applicant included events of lipoatrophy in the Kaplan Meier plot for injection site reactions. However, based on my review, the distribution of events of lipoatrophy were similar to the distribution of events of lipohypertrophy.

Figure 31: Injection Site Reactions- Kaplan Meier Plot of Time to First Event

Source: Primary Figures for Safety Summary (dated March 27, 2015); Figure 5.3.1.8.2

Figure 32: Lipodystrophy- Kaplan Meier Plot of Time to First Event

Source: Primary Figures for Safety Summary (dated March 27, 2015); Figure 5.3.1.10.2

Figure 33: Ectopic Calcifications- Kaplan Meier Plot of Time to First Event

Source: Primary Figures for Safety Summary (dated March 27, 2015); Figure 5.3.1.14.5

7.5.3 Drug-Demographic Interactions

There were insufficient numbers to evaluate for differences by race or age since the vast majority of patients were white (>90%) and <18 years of age (86%). There were no apparent differences in overall adverse events or adverse reactions by gender.

The majority of adverse reactions reported for all geographic regions were injection site reactions. There were no regional differences in the overall incidence of adverse events; there was a slightly higher incidence of adverse events reported as treatment related in patients from the USA/Canada region (82%) compared to patients from all other regions (68%).

7.5.4 Drug-Disease Interactions

Safety monitoring included monitoring for ectopic calcifications, a submission-specific safety concern (see Section 7.3.5).

7.5.5 Drug-Drug Interactions

Safety monitoring during clinical trials included monitoring for signs and symptoms of peripheral neuropathy. Peripheral neuropathy is a known complication of vitamin B6 (pyridoxine) that is generally associated with prolonged usage at high doses.[54] The applicant noted that peripheral neuropathy secondary to vitamin B6 toxicity was a

[54] Potter MC, Wozniak KM, et al., Glutamate carboxypeptidase II inhibition behaviorally and physiologically improves pyridoxine-induced neuropathy in rats, PLOS One 2014; 9(9): e102936.

potential concern with treatment with asfotase alfa due to increased levels of pyridoxal (the primary form of vitamin 6 found in the central nervous system) formed with the metabolism of PLP. The applicant noted that no evidence of peripheral toxicity was observed in nonclinical studies even at very high doses of asfotase alfa. However, there are no nonclinical data on the concomitant use of vitamin B6 and asfotase alfa. As noted earlier, one patient being treated with pyridoxine for HPP-related seizures did not receive an initial intravenous dose of asfotase alfa out of concern of that the patient would be exposed acutely to a critical level of pyridoxal. No events of peripheral neuropathy were reported in clinical trials.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

There was no evidence of human carcinogenicity in the safety evaluation.

7.6.2 Human Reproduction and Pregnancy Data

Asfotase alfa was not evaluated in pregnant or lactating women. This reviewer notes that the applicant has established a HPP disease registry; a pregnancy surveillance program could be included in the registry.

7.6.3 Pediatrics and Assessment of Effects on Growth

As discussed earlier, treatment with asfotase alfa demonstrated efficacy on growth for both patients with perinatal/infantile-onset HPP and patients with juvenile-onset HPP. See Section 6.1.5 for further discussion of clinical trial growth data.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

There were no reported events of accidental overdose. One perinatal/infantile-onset patient was treated with doses of asfotase alfa that exceeded the protocol-specified dose due to lack of clinical response at doses of 6 to 9 mg/kg/week; maximum dosing was 28 mg/kg/week. The patient demonstrated improvements in radiographic assessments and asfotase alfa was incrementally decreased to 6 mg/kg/week. At the time of the patient's last assessment before the analysis cutoff date, the patient was reported to be clinically stable on the 6 mg/kg/week dose regimen. No treatment-related AEs were reported for the patient.

Asfotase alfa is unlikely to have drug abuse potential given the mechanism of action and because treatment is monitored by trained medical personnel.

7.7 Additional Submissions / Safety Issues

None.

8 Postmarket Experience

None.

9 Appendices

9.1 Literature Review/References

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9.2 Labeling Recommendations

The labeling will be in PLR format. Content and formatting were reviewed to meet the latest best-practices. The final labeling contains all of the labeling revisions negotiated with the applicant.

As noted in Section 6.1, I recommend that Strensiq is specifically indicated for perinatal/infantile- and juvenile-onset patients. I do not agree with the applicant's proposal to use the term (b) (4) for the indicated population (b) (4) In addition, I recommend the following edits to the applicant's proposed labeling for Strensiq:

- **Section 2 (Dosage and Administration)**

Recommendation:
The applicant proposes a dose of 6 mg/kg/week administered as 2 mg/kg 3 times a week or 1 mg/kg administered 6 times a week. However, some perinatal/infantile-onset patients appeared to require 9 mg/kg/week, the maximum per protocol dose in clinical trials, to achieve improved growth. Therefore, I recommend that the labeled dosing range for (b) (4) should be 6 mg/kg/week up to 9 mg/kg/week.

I agree with the clinical pharmacology review team's recommendation to include a caution regarding the use of the 80 mg/0.8 mL formulation in pediatric patients due to the lower exposure achieved with that formulation. Specifically, I recommend that labeling caution against use of the 80 mg/0.8 mL formulation in pediatric patients weighing less than 40 kg.

In addition, dosing should be adjusted for weight increases and dosing information should be provided in a weight-based table of doses for each dose level and dosing frequency for both of the two drug concentrations (40 mg/0.4 mL and 80 mg/0.8 mL).

- **Section 5 (Warnings and Precautions)**

Recommendation:
The applicant's proposed labeling does not clearly characterize hypersensitivity reactions observed in clinical trials. The labeling should be revised to clearly describe hypersensitivity reactions (including anaphylaxis). Section 5 should also include information on lipodystrophy and ectopic calcifications.

- **Section 6 (Clinical Trials Experience)**

Recommendation:
The applicant's proposed labeling does not clearly 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). The labeling should be revised to clearly identify injection site reactions and hypersensitivity reactions (including anaphylaxis). The labeling should also include information on the incidence of lipodystrophy and ectopic calcifications.

- **Section 12 (Dosage and Administration)**

Recommendation:
This reviewer agrees with the applicant's proposal to include information on bone biopsy data in Section 12.2 (Pharmacodynamics). However, the applicant's proposed labeling also includes (b) (4) . This information should be removed from the label. In addition, the label should clarify that the disease biomarkers PPi and PLP do not correlate with clinical outcomes

- **Section 14 (Clinical Studies)**

Recommendation:
The applicant's proposed labeling focuses on (b) (4) The labeling should be revised to focus on the efficacy data for which there is a historical comparator group, including survival and ventilator-free survival data for the perinatal/infantile-onset population and growth, radiographic, and gait data for the juvenile-onset population.

9.3 Advisory Committee Meeting
No advisory committee was held for this submission.

9.4 Financial Disclosure Review Templates
See forms on the following page.

14 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

9.5 Schedules of Assessments for Asfotase alfa Clinical Trials

Table 56 **ENB-002-08 Schedule of Assessments**

Table 57 **ENB-003-08 Schedule of Assessments**

Table 58 **ENB-010-10 Schedule of Assessments**

Table 59 **ENB-006-09 Schedule of Assessments**

Table 60 **ENB-008-10 Schedule of Assessments**

Table 61 **ENB-009-10 Schedule of Assessments- Screening to Week 12- All Patients**

Table 62 **ENB-009-10 Schedule of Assessments- Week 24 to End of Study- Asfotase alfa Treatment Groups for Primary Treatment Period**

Table 63 **ENB-009-10 Schedule of Assessments- Week 24 to End of Study- Control Group for Primary Treatment Period**

Table 64 **ENB-001-08 Schedule of Assessments**

Table 56: ENB-002-08 Schedule of Assessments

Assessment	Screening	Baseline	Main Treatment Period														
Day/Week:	-2W to -2D	-2D to -1D	D1	D2	D3	D4	D5	D8	D9	D10	D11	W3	W4	W8	W12	W18	W24
Medical History	X																
Physical examination	X	X					X				X		X	X	X	X	X
Fundoscopic examination		X					X						X		X		X
Growth	X	X													X		X
Vital signs	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X	X
Skeletal films	X	X											X		X		X
TNSALP gene mutation analysis			X														
Safety labs*	X		X	X		X					X		X	X	X	X	X
PK analysis			X	X	X		X	X	X	X	X	X	X		X	X	X
Ca & Phos	X		X	X	X	X		X	X	X	X		X	X	X	X	X
Urinary Ca:Cr ratio	X		X					X			X		X		X	X	X
PPi			X					X						X	X	X	
Overnight Urinary PPi		X	X										X		X		X
Osteopontin			X												X	X	X
PLP	X														X		X
PTH	X		X					X				X	X		X	X	X
25(OH) Vit D	X														X		X
Renal ultrasound		X													X		X
Antibody testing			X										X	X	X	X	X
BSID-III		X													X		X
Respiratory support		X											X		X		X

*Safety labs included chemistry, hematology, and urinalysis
TNSALP= tissue nonspecific alkaline phosphatase; PK= pharmacokinetics; Ca=calcium; Phos= phosphorus; Cr= creatinine; PPI- inorganic phosphate; PLP= pyridoxal-5'-phosphate; PTH= parathyroid hormone; BSID-III= Bayley Scale of Infant & Toddler Development, 3rd Edition

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Table 56: ENB-002-08 Schedule of Assessments (cont'd)

Assessment	Screening	Baseline	Main Treatment Period														
Day/Week:	-2W to -2D	-2D to -1D	D1	D2	D3	D4	D5	D8	D9	D10	D11	W3	W4	W8	W12	W18	W24
Study drug administration			X					X		X		X	X	X	X	X	X
Concomitant medications and therapies	↔																
Adverse events	↔																

*Safety labs included chemistry, hematology, and urinalysis
TNSALP= tissue nonspecific alkaline phosphatase; PK= pharmacokinetics; Ca=calcium; Phos= phosphorus; Cr= creatinine; PPI- inorganic phosphate; PLP= pyridoxal-5'-phosphate; PTH= parathyroid hormone; BSID-III= Bayley Scale of Infant & Toddler Development, 3rd Edition

Table 57: ENB-003-08 Schedule of Assessments

Assessment	Baseline	Treatment Period																			
Week:		**3**	**6**	**9**	**12**	**15**	**18**	**21**	**24**	**27**	**30**	**33**	**36**	**39**	**42**	**45**	**48**	**51**	**54**	**57**	**60**
Medical History	X																				
Physical examination	X	X	X		X		X		X		X		X		X		X		X		X
Fundoscopic examination	X		X		X		X		X		X		X		X		X		X		X
Vital signs	X	X	X	X	X		X		X		X		X		X		X		X		X
Skeletal films	X	X	X	X	X		X		X		X		X				X				X
Renal ultrasound	X		X		X		X		X		X		X		X		X		X		X
Safety labs*	X	X	X	X	X		X		X		X		X		X		X		X		X
PPi	X	X	X	X	X		X		X		X		X		X		X		X		X
PLP	X	X	X	X	X		X		X		X		X		X		X		X		X
Urinary Ca:Cr ratio	X	X	X	X	X		X		X		X		X		X		X		X		X
25(OH) Vit D	X		X		X				X		X		X		X		X		X		X
PTH	X	X	X	X	X		X		X		X		X		X		X		X		X
Antibody testing	X	X	X	X	X		X		X		X		X		X		X		X		X
BSID-III/BOT-2	X		X		X		X		X		X		X		X		X		X		X
Physical therapy assessment	X	X	X		X		X		X		X		X		X		X		X		X
Respiratory support assessment	X	X	X	X	X		X		X		X		X		X		X		X		X
Dental assessment	X	X	X	X	X		X		X		X		X		X		X		X		X
Nutritional assessment	X		X		X		X		X		X		X		X		X		X		X
In-office study drug administration	X	X	X	X	X		X		X		X		X		X		X		X		X
Safety follow-up communication						X		X		X		X		X		X		X		x	

*Safety labs included chemistry, hematology, and urinalysis
TNSALP= tissue nonspecific alkaline phosphatase; PK= pharmacokinetics; Ca=calcium; Phos= phosphorus; Cr= creatinine; PPI- inorganic phosphate; PLP= pyridoxal-5'-phosphate; PTH= parathyroid hormone; BSID-III= Bayley Scale of Infant & Toddler Development, 3rd Edition; BOT-2= Bruininks-Oseretsky Test of Motor Proficiency, 2nd Edition

Table 57: ENB-003-08 Schedule of Assessments (cont'd)

Assessment	Baseline	Treatment Period																			
Week:		**3**	**6**	**9**	**12**	**15**	**18**	**21**	**24**	**27**	**30**	**33**	**36**	**39**	**42**	**45**	**48**	**51**	**54**	**57**	**60**
Concomitant medication/therapy assessments		↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
Adverse events		↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔

*Safety labs included chemistry, hematology, and urinalysis
TNSALP= tissue nonspecific alkaline phosphatase; PK= pharmacokinetics; Ca=calcium; Phos= phosphorus; Cr= creatinine; PPI- inorganic phosphate; PLP= pyridoxal-5'-phosphate; PTH= parathyroid hormone; BSID-III= Bayley Scale of Infant & Toddler Development, 3rd Edition; BOT-2= Bruininks-Oseretsky Test of Motor Proficiency, 2nd Edition

Table 58: ENB-010-10 Schedule of Assessments

Assessment	Screening	Baseline				Treatment Period										
Week/Month:	**-4W to -2D**					**W3**	**W6**	**W6**	**W6**	**M3**	**M6**	**M9**	**M12**	**M15**	**M18**	**M24 then Q6m**
Day:		**-1D**	**D1**	**D2**	**D3**	**D1**	**D1**	**D2**	**D3**	**D1**	**D1**	**D1**	**D1**	**D1**	**D1**	
Medical History	X															
Physical examination	X	X				X	X			X	X	X	X	X	X	X
Fundoscopic examination	X										X		X		X	X
Growth	X	X				X	X			X	X	X	X	X	X	X
Vital signs	X	X	X			X	X			X	X	X	X	X	X	X
Skeletal films	X									X	X	X	X	X	X	X
TNSALP gene mutation analysis			X													
Safety labs*	X		X			X	X			X	X	X	X	X	X	X
PK analysis			X	X	X		X	X	X	X	X	X	X	X	X	X
Ca & Phos																
Urinary Ca:Cr ratio			X			X	X			X	X	X	X	X	X	X
PPi			X				X			X	X	X	X	X	X	X
PLP	X		X				X			X	X	X	X	X	X	X
PTH			X				X			X	X	X	X	X	X	X
25(OH) Vit D	X										X		X		X	X
Renal ultrasound	X										X		X		X	X
Antibody testing			X			X	X			X	X	X	X	X	X	X
BSID-III		X								X	X	X	X	X	X	X
Respiratory support	X	X	X			X	X			X	X	X	X	X	X	X

*Safety labs included chemistry, hematology, and urinalysis
TNSALP= tissue nonspecific alkaline phosphatase; PK= pharmacokinetics; Ca=calcium; Phos= phosphorus; Cr= creatinine; PPI- inorganic pyrophosphate; PLP= pyridoxal-5'-phosphate; PTH= parathyroid hormone; BSID-III= Bayley Scale of Infant & Toddler Development, 3rd Edition; PDMS= Peabody Developmental Motor Scales, 2nd Edition; BOT-2= Bruininks-Oseretsky Test of Motor Proficiency, 2nd Edition

Table 58: ENB-010-10 Schedule of Assessments (cont'd)

Assessment	Screening	Baseline				Treatment Period										
Week / Month:	**-4W to -2D**					**W3**	**W6**	**W6**	**W6**	**M3**	**M6**	**M9**	**M12**	**M15**	**M18**	**M24 then Q6m**
Day:		**-1D**	**D1**	**D2**	**D3**	**D1**	**D1**	**D2**	**D3**	**D1**	**D1**	**D1**	**D1**	**D1**	**D1**	
PDMS		X								X	X	X	X	X	X	X
BOT-2		X								X	X	X	X	X	X	X
Gross Motor Milestone Checklist		X								X	X	X	X	X	X	X
Dental assessment		X					X			X	X	X	X	X	X	X
Nutritional assessment		X									X		X	X	X	X
Concomitant medication/therapy	↔															
Adverse events	↔															

*Safety labs included chemistry, hematology, and urinalysis
TNSALP= tissue nonspecific alkaline phosphatase; PK= pharmacokinetics; Ca=calcium; Phos= phosphorus; Cr= creatinine; PPI- inorganic pyrophosphate; PLP= pyridoxal-5'-phosphate; PTH= parathyroid hormone; BSID-III= Bayley Scale of Infant & Toddler Development, 3rd Edition; PDMS= Peabody Developmental Motor Scales, 2nd Edition; BOT-2= Bruininks-Oseretsky Test of Motor Proficiency, 2nd Edition

Table 59: ENB-006-09 Schedule of Assessments

	Screening	Baseline		Treatment												
Week:	**-3**			**1**			**6**				**12**		**18**		**24**	
Day:	**1**	**-2**	**-1**	**1**	**2**	**3**	**-1**	**1**	**2**	**3**	**-1**	**1**	**-1**	**1**	**-1**	**1**
Assessment																
Informed consent, enrollment, randomization	X															
ALP gene mutation analysis			X													
Medical history	X															
Physical examination	X	X					X				X		X		X	
Tanner staging	X														X	
Height	X	X									X				X	
Weight	X	X					X				X		X		X	
Head circumference	X	X									X				X	
Vital signs	X	X		X			X	X			X	X	X	X	X	X
Skeletal x-rays	X						X				X				X	
DEXA		X													X	
Bone biopsy			X													X
Panorex		X													X	
6MWT	X	X									X				X	
HHD	X	X									X				X	
PFT	X	X									X				X	
BOT-2	X	X									X				X	
CHAQ		X									X				X	
PODCI		X									X				X	
PPi			X				X				X					X
PLP			X				X				X					X
PTH			X				X				X			X		X
Safety labs*	X		X				X				X			X		X
25(OH) Vitamin D	X										X					X
24 hr urine			X	X			X				X		X		X	
Renal ultrasound		X										X			X	
Antibody testing			X				X				X			X		X

Table 59: ENB-006-09 Schedule of Assessments (cont'd)

	Screening	Baseline		Treatment												
Week:	-3			1			6				12		18		24	
Day:	1	-2	-1	1	2	3	-1	1	2	3	-1	1	-1	1	-1	1
Assessment																
PK sampling				X	X	X		X	X	X		X		X		X
Concomitant medications/therapy	←															→
Adverse events	←															→

*Safety labs included chemistry, hematology, and urinalysis
TNSALP= tissue nonspecific alkaline phosphatase; DEXA=Dual Energy X-ray Absorptiometry; 6MWT=6 Minute Walk Test; HHD= Hand Held Dynamometry; PFT= Pulmonary Function Tests; BOT-2=Bruininks-Oseretsky Test of Motor Proficiency, 2nd Edition; PODCI= Pediatric Outcomes Data Collection Instrument; PPI- inorganic pyrophosphate; PLP= pyridoxal-5'-phosphate; PTH= parathyroid hormone; PK= pharmacokinetics

Table 60: ENB-008-10 Schedule of Assessments

Assessment	Baseline	Treatment Period			
Week:	**-3**	**Month 3**	**Month 6**	**Month 9**	**Every 6 months**
Day:	**1**	**-2**	**-1**	**1**	**2**
Informed consent, enrollment, randomization	X				
TNSALP gene mutation analysis	X				
Medical history	X				
Physical examination	X	X	X	X	X
Tanner staging	X		X		X
Fundoscopic examination					X
Height	X		X		X
Weight	X	X	X	X	X
Arm span	X		X		X
Vital signs	X	X	X	X	X
Skeletal x-rays	X	X	X	X	X
DEXA	X				X
6MWT	X	X	X	X	X
BOT-2	X	X	X	X	X
HHD	X	X	X	X	X
PODCI	X		X		X
CHAQ	X	X	X	X	X
PPi	X	X	X	X	X
PLP	X	X	X	X	X
PTH	X	X	X	X	X
25(OH) Vitamin D	X		X		X
Urine Ca:Cr ratio	X	X	X	X	X
Renal ultrasound	X		X		X
Safety labs*		X	X	X	X
Antibody testing	X	X	X	X	X
PK sampling	X	X	X	X	X
Nutritional assessment		X	X		X
Concomitant medications/therapies	↔				
Adverse events	↔				

*Safety labs included chemistry, hematology, and urinalysis
TNSALP= tissue nonspecific alkaline phosphatase; DEXA=dual energy x-ray absorptiometry; 6MWT=6-Minute Walk Test; BOT-2= Bruininks-Oseretsky Test of Motor Proficiency, 2nd Edition; HHD= Hand Held Dynamometry; PODCI= Pediatric Outcomes Data Collection Instrument; CHAQ= Child Health Assessment Questionnaire; PPI- inorganic pyrophosphate; PLP= pyridoxal-5'-phosphate; PTH= parathyroid hormone; Ca=calcium; Cr= creatinine; PK= pharmacokinetics

Reference ID: 3836304

Table 61: ENB-009-10 Schedule of Assessments- Screening to Week 12- All Patients

	Screening		Baseline	Primary Treatment Period			
Week:	**-7**	**-4**	**Baseline**	**3**	**5**	**6**	**12**
Day:	**-49**	**-28**	**-1 to 2**				
Assessment							
Informed consent,	X						
TNSALP gene mutation analysis			X				
Bone resorption markers	X						
Medical history	X						
Physical examination	X	X	X			X	X
Height	X	X	X			X	X
Weight	X	X	X			X	X
Vital signs	X		X	X		X	X
Tanner staging			X				
Bone biopsy		X					
Skeletal x-rays	X						
DEXA			X				X
6MWT	X		X				X
BOT-2	X		X				X
LEFS			X				X
HHD	X		X				X
BPI-SF				X			X
HOST	X						
PFT	X						
PPi			X			X	X
PLP	X		X			X	X
PTH	X		X			X	X
25(OH) Vitamin D	X						X
Urine Ca:Cr ratio			X	X		X	X
Renal ultrasound			X				
Fundoscopy			X				
Safety labs*	X		X	X		X	X
ECG			X				
Pregnancy testing	X	X	X	X		X	X
Antibody testing			X	X		X	X
PK sampling			X	X		X	X
Nutritional assessment							
Concomitant medications/therapies			←	—	—	—	→
Adverse Events			←	—	—	—	→

*Safety labs included chemistry, hematology, and urinalysis
TNSALP= tissue nonspecific alkaline phosphatase; DEXA=dual energy x-ray absorptiometry; 6MWT=6-Minute Walk Test; BOT-2= Bruininks-Oseretsky Test of Motor Proficiency, 2nd Edition; LEFS= Lower Extremity Function Scale; HHD= Hand Held Dynamometry; BPI-SF= Brief Pain Inventory- Short Form; HOST= Hypophosphatasia Outcomes Study Telephone Survey; PFT= Pulmonary Function Tests; PPI-inorganic pyrophosphate; PLP= pyridoxal-5'-phosphate; PTH= parathyroid hormone; Ca=calcium; Cr= creatinine; PK= pharmacokinetics

Reference ID: 3836304

Table 62: ENB-009-10 Schedule of Assessments- Week 24 to End of Study- Asfotase alfa Treatment Groups for Primary Treatment Period

	Primary Treatment Period	Extended Treatment Period		
Week:	**24**	**36**	**48**	**Every 6 months**
Assessment				
Physical examination	X	X	X	X
Height	X	X	X	X
Weight	X	X	X	X
Vital signs	X	X	X	X
Tanner staging	X		X	X
Bone biopsy	X		X	
Skeletal x-rays	X		X	X
DEXA	X			X
6MWT	X		X	X
BOT-2	X		X	X
LEFS	X		X	X
HHD	X		X	X
BPI-SF	X		X	X
PFT	X		X	X
PPi	X	X	X	X
PLP	X	X	X	X
PTH	X	X	X	X
25(OH) Vitamin D	X	X	X	X
Urine Ca:Cr ratio	X	X	X	X
Renal ultrasound	X		X	X
Fundoscopic examination	X		X	X
Safety labs*	X	X	X	X
ECG	X		X	X
Pregnancy testing	X		X	X
Antibody testing	X	X	X	X
PK sampling	X		X	X
Nutritional assessment	X		X	X
Concomitant medications/therapies	X	←	—	→
Adverse Events	X	←	—	→

*Safety labs included chemistry, hematology, and urinalysis
DEXA=dual energy x-ray absorptiometry; 6MWT=6-Minute Walk Test; BOT-2= Bruininks-Oseretsky Test of Motor Proficiency, 2nd Edition; LEFS= Lower Extremity Function Scale; HHD= Hand Held Dynamometry; BPI-SF= Brief Pain Inventory- Short Form; PFT= Pulmonary Function Tests; PPI- inorganic pyrophosphate; PLP= pyridoxal-5'-phosphate; PTH= parathyroid hormone; Ca=calcium; Cr= creatinine; ECG= electrocardiogram; PK= pharmacokinetics

Reference ID: 3836304

Table 63: ENB-009-10 Schedule of Assessments- Week 24 to End of Study- Control Group for Primary Treatment Period

	Primary Treatment Period	Extended Treatment Period				
Week:	**24**	**27**	**30**	**36**	**48**	**Every 6 months**
Assessment						
Physical examination	X		X	X	X	X
Height	X		X	X	X	X
Weight	X		X	X	X	X
Vital signs	X	X	X	X	X	X
Tanner staging	X				X	X
Bone biopsy	X					
Skeletal x-rays	X				X	X
DEXA	X					X
6MWT	X				X	X
BOT-2	X				X	X
LEFS	X				X	X
HHD	X				X	X
BPI-SF	X				X	X
PFT	X				X	X
PPi	X		X	X	X	X
PLP	X		X	X	X	X
PTH	X		X	X	X	X
25(OH) Vitamin D	X			X	X	X
Urine Ca:Cr ratio	X		X	X	X	X
Renal ultrasound	X					X
Fundoscopy	X					X
Safety labs*	X		X	X	X	X
ECG	X					X
Pregnancy testing	X		X		X	X
Antibody testing	X		X	X	X	X
PK sampling	X				X	X
Nutritional assessment	X				X	X
Concomitant medications/therapies	X	←	—	—	—	→
Adverse events		←	—	—	—	→

*Safety labs included chemistry, hematology, and urinalysis

DEXA=dual energy x-ray absorptiometry; 6MWT=6-Minute Walk Test; BOT-2= Bruininks-Oseretsky Test of Motor Proficiency, 2nd Edition; LEFS= Lower Extremity Function Scale; HHD= Hand Held Dynamometry; BPI-SF= Brief Pain Inventory- Short Form; PFT= Pulmonary Function Tests; PPI- inorganic pyrophosphate; PLP= pyridoxal-5'-phosphate; PTH= parathyroid hormone; Ca=calcium; Cr= creatinine; ECG= electrocardiogram; PK= pharmacokinetics

Table 64: ENB-001-08 Schedule of Assessments

Assessment	Screening	Baseline	IV Treatment				SC Treatment												DATA SAFETY MONITORING BOARD	Study End
Week:			1				2					3		4						8
Day:		-2 to 1	1	2	3	4	7	8	9	10	11	14	15	21	22	23	24	25		
Medical History	X																			
TNSALP gene mutation analysis	X																			
Physical examination	X	X					X					X		X						X
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X
Pregnancy test	X	X					X					X		X						X
ECG	X		X															X		
DEXA		X																X		
Bone scan		X																X		
Skeletal films	X	X																X		
Bone biopsy		X																X		
Pain (VAS)		X																		
Renal ultrasound																				
Safety labs*	X	X		X			X			X		X	X	X		X		X		X
Ca & Phos	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X		X		X
PPi		X	X	X				X					X		X			X		
Urinary PPi		X	X																	
PLP	X	X																X		
25(OH) Vitamin D	X																	X		
Osteopontin		X	X	X				X					X		X			X		
Osteocalcin		X																X		
CTX		X																X		
NTX		X	X												X					
Deoxypyridinoline		X	X												X					
Antibody testing			X															X		X
PK sampling			X	X	X	X	X	X	X	X	X		X		X	X	X	X		X
Concomitant medications/therapies	←																	→		
Adverse events	←																	→		

*Safety labs included chemistry, hematology, and urinalysis

Table 64: ENB-001-08 Schedule of Assessments (cont'd)

IV=intravenous; SC=subcutaneous; TNSALP= tissue nonspecific alkaline phosphatase; ECG= electrocardiogram; DEXA=dual energy x-ray absorptiometry; VAS=visual analog scale; Ca=calcium; Phos= phosphorus; Cr= creatinine; PPI- inorganic pyrophosphate; PLP= pyridoxal-5'-phosphate; CTX= c-telopeptide crosslinks; NTX= n-telopeptide crosslinks.

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/s/

CARLA L EPPS
10/21/2015

ANIL K RAJPAL
10/21/2015

DRAGOS G ROMAN
10/21/2015

3.3 Financial Disclosures

The applicant listed 172 participating investigators at 40 participating sites, including 33 sites that enrolled patients and 7 sites that did not enroll patients.[11] One clinic site (Tawam Hospital, United Arab Emirates) received funding from the applicant but none of the investigators at the site had direct financial arrangements with the applicant. A second hospital (Shriner's Hospital for Children, St. Louis) received funding from the applicant. (b) (6) a second investigator certified that that she had no direct financial arrangements with the applicant but was involved in grant activities funded by the applicant. The remaining clinical sites and investigators had no financial arrangements to disclose.[12] The financial disclosure forms for each clinical trial submitted in the application are reviewed in Section 9.4.

Reviewer Comments:
One investigator who was involved in multiple clinical trials for asfotase alfa received consultant fees for clinical trial development and an educational program on HPP from the applicant. He was granted an exemption of conflict of interest from the Disclosure Review Committee (DRC) at his institution for participation in the clinical trials based on his experience with HPP, with the condition that he file a management plan for conflict of interest for interventional clinical trials (the institution determined that no management plan was necessary for participation in a retrospective natural history study). Because the principal efficacy endpoints for this application were objective measurements (survival and growth), this reviewer does not feel that the disclosed financial arrangements had an adverse impact on the review or interpretability of the data submitted for this application.

[11] Site numbers were specific to the individual trials; therefore, a site that participated in multiple trials had multiple site numbers.
[12] Financial disclosure information was not collected for one investigator at a clinical site that was preliminarily considered for participation in the trial. The applicant stated that the information was not collected because enrollment was already completed before the site was ready for initiation.

Medical Officer Review: Breakthrough Therapy Designation Request
Division of Gastroenterology & Inborn Errors Products

IND / SD #: IND 100619
Sponsor: Alexion
Drug: Asfotase alfa
Drug Class: Enzyme replacement therapy
Dose and Form: Subcutaneous injection
Proposed Indication: Hypophosphatasia
Date Received: March 22, 2013
Medical Policy Council Review Date: May 15, 2013
Date Review Completed: May 9, 2013
Clinical Reviewer: Juli Tomaino, MD
Team Leader: Jessica J. Lee, MD

Synopsis and Recommended Regulatory Action

A breakthrough therapy designation request was received on March 25, 2013 for asfotase alfa for the treatment of hypophosphatasia (HPP). The preliminary clinical data from Phase 1 and 2 trials demonstrated an improvement in bone mineralization and respiratory status in perinatal- and infantile-onset HPP patients and an improvement in bone mineralization in juvenile-onset HPP patients. Additional data were submitted for juvenile-onset HPP patients that showed an overall trend toward improvement in multiple clinical signs and symptoms, including neurological development, gross motor function (strength, endurance), pain, and growth. Reductions in biomarkers (inorganic pyrophosphate and pyridoxal 5'-phosphate) were seen in all ages of HPP patients. The sponsor also provided narrative descriptions of infantile- and juvenile-onset patients who have demonstrated improvement in motor function. The Division believes that the sponsor has submitted data that provides sufficient "evidence that the drug may demonstrate substantial improvement on 1 or more clinically significant endpoints."

Division's Recommended Regulatory Action: Grant breakthrough designation request for perinatal-, infantile-, and juvenile-onset HPP patients.

Background

Hypophosphatasia is a rare, genetic disorder with high morbidity and mortality that affects all age groups with an incidence of 1/100,000 live births worldwide.[1] Asfotase alfa is an enzyme

[1] Mornet, E. Hypophosphatasia. Orphanet J Rare Dis. 2007; 2:40

Reference ID: 3309199

replacement therapy, human recombinant tissue-nonspecific alkaline phosphatase (TNSALP), for the treatment of patients with HPP. HPP results from a deficiency of the enzyme tissue-nonspecific alkaline phosphatase (TNSALP). TNSALP enables bone mineralization and vitamin B_6 delivery to the brain. The two major substrates of TNSALP are inorganic pyrophosphate (PPi) and pyridoxal 5'-phosphate (PLP), the major circulating form of vitamin B_6. TNSALP hydrolyzes PPi to inorganic phosphate (Pi), which precipitates with calcium to form calcium phosphate. Calcium phosphate is then converted to hydroxyapatite crystals that interweave with collage to strengthen bone. The absence of TNSALP leads to increased levels of PPi, an inhibitor of bone mineralization, B_6 deficiency, and seizures. [2]

Asfotase alfa has two important structural domains: a catalytic domain that restores the deficient enzyme activity of TNSALP in HPP patients, and a bone targeting domain for preferential accumulation in bone. There have not been reports of extra-osseous calcifications in patients treated with asfotase alfa. However, the sponsor is monitoring for signs suggestive of extra-osseous activity.

There are four main phenotypes of HPP that are categorized based on age of onset: perinatal, infantile, juvenile, and adult. The severity of the disease is inversely proportional to age of onset, and clinical manifestations depend on the phenotype. Decreased bone mineralization is common to all phenotypes. Patients with perinatal-onset disease usually die within minutes to weeks of birth and quickly decline due to complications related to seizures and respiratory failure from pulmonary hypoplasia or chest wall deformities. Infantile-onset patients present with symptoms before 6 months of age, and their usual clinical manifestations include failure to thrive, vitamin B_6-responsive seizures, craniosynostosis, nephrocalcinosis, and respiratory distress. Juvenile-onset patients present between 6 months and 18 years of age, and their symptoms include rachitic deformities, short stature, delayed motor milestones, premature loss of teeth, and pain. Many adults with HPP experience mild symptoms during childhood, but suffer from osteomalacia, recurrent poorly healing fractures, and pain during adulthood.[2]

There are no approved treatments for HPP. Treatment is mainly symptomatic through pain control and orthopedic procedures to repair fractures and stabilize weakened bone.
The previously attempted treatments have not been successful. Four infants have been treated with serum from patients with Paget's disease, and all died of respiratory complications. 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. Two infants underwent experimental bone marrow transplant for HPP. All patients had initial improvement but continued to have disease progression. One

[2] Whyte, MP. Physiological role of alkaline phosphatase explored in hypophosphatasia. Ann N Y Acad Sci. 2010; 1192:190-200

Reference ID: 3309199

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.

Asfotase alfa was granted an Orphan designation on September 12, 2008 and a Fast Track designation on May 14, 2009. As of February 8, 2013, seven clinical trials have been completed or are ongoing, and one trial is being planned. Sixty-three HPP patients have been treated with asfotase alfa, including 31 patients with perinatal- or infantile-onset disease, 21 with juvenile-onset disease, 8 with adult-onset disease, and 3 patients with unknown age of onset.

Clinical Evidence Submitted in Breakthrough Therapy Designation Request

An overview of the multi-center, multi-national, open label clinical trials is summarized in Table 1. The ages of treated patients ranged from one day to 66 years old, and there were four main HPP phenotypes: perinatal-, infantile-, juvenile-, and adult-onset HPP. The sponsor reported that they are planning to submit the clinical study reports (CSR) of the completed clinical trials to the Agency in the next few months.

Table 1: Overview of Clinical Development Plan

Study Number	Phase/ Patient Population	Study Design	Number Enrolled/ Completed	Mean Age at Entry (range)	Gender
ENB-001-08	Phase 1 Adults	Multi-center, multinational, open-label, dose-escalating [a], safety/efficacy, PK, PD	6 enrolled 6 completed	44.8 years (24-58)	2 M 4 F
ENB-002-08	Phase 2 Infants and young children	Multicenter, multinational, open-label, single group assignment, safety/efficacy	11 enrolled 10 completed [b]	12.7 months (0.5-35)	4 M 7 F
ENB-003-08	Phase 2 Infants and young children, Extension of ENB-002-08	Multicenter, multinational, open-label, single group assignment, safety/efficacy	10 enrolled 9 receiving treatment [c]	18 months (6-41)	4 M 6 F

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ENB-006-09	Phase 2 Children and early adolescents	Multicenter, multinational, open-label, dose comparison, parallel assignment, historical control, safety/ efficacy, PK, PD	13 enrolled [d]	100.6 months (60-144)	11 M 2 F
ENB-008-10	Phase 2 Children and early adolescents, Extension of ENB-006-09	Multicenter, multinational, open-label, dose comparison, parallel assignment, safety/ efficacy, PK, PD	12 enrolled and receiving treatment	105.0 months (72-144)	10 M 2 F
ENB-009-10	Phase 2 Adolescents and Adults	Randomized, open-label, multicenter, multinational, dose- ranging [a], concurrent control, safety/ efficacy, PK	19 enrolled and receiving treatment	491.4 months (156-792)	7 M 12 F
ENB-010-10	Phase 2 Infants and Children ≤ 5 years of age	Open-label, multicenter, multinational, safety/efficacy, PK	13 enrolled, 12 receiving treatment [e]	37.9 months (1-69)[f]	6 M 5 F [f]

F = female; M = male; PD = pharmacodynamics; PK=pharmacokinetics;

[a] For all clinical studies except ENB-001-08 and ENB-009-10, dose adjustments were allowed for lack of efficacy or safety-related concerns.

[b] Patient 002-03-01 discontinued after the IV dose and before SC study drug administration due to a moderate infusion-associated reaction.

[c] Patient 003-08-01 died on (b) (6), after approximately (b) (6) on treatment in this extension study (after approximately (b) (6) of ENB-0040 treatment) from SAE of septic shock which was considered unrelated to study drug.

[d] Patient 006-02-04 in the 3 mg/kg group discontinued to undergo a pre-planned scoliosis surgery.

[e] Patient 010-16-03, with prior history of vitamin B_6-responsive seizures and hypoxia, was found to have abnormal neurological findings and subsequently died. In the opinion of the Investigator, the event was unlikely related to study drug.

[f] Gender was unavailable for 2 patients. Descriptive statistics for age are included for the 9 patients for whom data were reported in the clinical listings for the study.

(Source: Adapted from the sponsor's Breakthrough Therapy Designation Request, dated March 19, 2013, page 38/81 of Investigator Brochure)

The sponsor provided descriptive summaries of the preliminary results from the completed and ongoing trials to support a Breakthrough Therapy Designation. Table 2 lists the status of the completed, ongoing, and planned clinical trials.

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Table 2: Status of Clinical Trials for the Treatment of HPP with Asfotase alfa

Clinical Study	Status
ENB-001-08 - *A Phase 1 Multi-center, Open-Label, Dose-Escalating Study in Adults with HPP*	Completed
ENB-002-08 - *A Phase 2 Open-Label Study of the Safety, Tolerability and Pharmacology of Asfotase Alfa in Severely Affected Patients with Infantile HPP*	CSR will include ongoing extension study.
ENB-003-08 - *Extension of Study ENB-002-08 in Severely Affected Infants and Young Children with HPP*	
ENB-010-10 - *A Phase 2 Open-Label, Multicenter Study of the Safety, Efficacy and PK of Asfotase Alfa in Pediatric Patients 5 Years of Age or Younger with HPP*	Ongoing
ENB-011-10 - *A Retrospective, Non-Interventional Epidemiologic Study of the Natural History of Patients with Severe Perinatal and Infantile HPP*	Ongoing
ENB-006-09 - *A Phase 2 Open-Label, Randomized, Dose-Ranging, Historical Control Study in Children*	CSR will include ongoing extension study.
ENB-008-10 - *Extension Study of Protocol ENB-006-09 Evaluating the Long-Term Safety and Efficacy of asfotase alfa in Children with HPP*	
ENB-009-10 - *A Randomized, Dose Response, Observational Control Study in Adolescents and Adults with HPP*	Ongoing

(b) (4)

(Source: Replicated from the Sponsor's Breakthrough Therapy Designation Request dated March 19, 2012, page 16/26)

Perinatal/Infantile-Onset HPP Patients

ENB-002-08 was a 6-month, international, multicenter, open-label study to assess the safety, tolerability, and PK of asfotase alfa in severely affected patients less than 3 years of age with infantile-onset HPP. Eleven patients were enrolled with one patient withdrawing from the study on Day 1 due to an infusion reaction. The remaining 10 patients completed 24 weeks of treatment and continued into the extension trial, ENB-003-08. Efficacy measurements for both ENB-002-08 and ENB-003-08 included improvement in bone mineralization as measured by skeletal radiograph, respiratory status, growth, cognitive and motor development scores. Perinatal-onset disease is usually fatal within weeks to months of birth,[3] and onset of seizures

[3] Leung, EC, et al. Outcome of Perinatal Hypophosphatasia in Manitoba Mennonites: A Retrospective Cohort Analysis. JIMD Rep. 2013 Apr 12. [Epub ahead of print]

Reference ID: 3309199

has been associated with 100% mortality by 18 months of age.[4] Historically, approximately 50% of infantile-onset patients have died from respiratory failure or infection.[2,5] Table 3 shows the results for skeletal mineralization as measured by radiographic assessment, growth parameters, and biomarkers after 24 weeks of treatment.

Table 3: Efficacy Results at 24 weeks: Perinatal/Infantile-Onset HPP (ENB-002-08)

Efficacy Outcome Parameter	Baseline	Week 24	*P* value[a] or 95% CI
Radiographic Assessments (Primary Efficacy Outcome)			
RGI-C (n=11) (n [%] of radiographic responders)	---	9 (82)	95% CI: [48,98]
Median total RGI-C	---	2.0[b]	0.021
Median total RSS	10[c]	6	0.0039
Growth Parameters			
Median length-for-age z-score	-3.775	-3.530	0.34
Median weight-for-age z-score	-3.835	-4.279	0.75
Median head circumference-for-age z-score	-0.991	-2.089	0.34
TNSALP Substrates			
Median plasma PPi (μM)	5.17	1.05[d]	0.063
Median PLP (ng/mL)	261.5	45.9	0.0039

CI=confidence interval; PPi=inorganic pyrophosphate; PLP=pyridoxal-5´-phosphate; RGI-C = Radiographic Global Impression of Change; RSS=rickets severity scale; TNSALP = tissue-nonspecific alkaline phosphatase.
[a] Unless otherwise specified, *P* values were determined by the sign test. The sign test tests the null hypothesis that the median change from Baseline to Week 24 is 0 (i.e., no change).
[b] For Patient 002-03-01, who discontinued from the trial without any post-Baseline assessments, the ITT analysis used an RGI-C score of 0 (i.e., no change).
[c] For Patient 002-02-01, who had no visible bones on X-ray for scoring, and Patient 002-03-01, who discontinued from the trial without any post-Baseline assessments, the ITT analysis used a Thacher score of 10 and a change in Thacher score of 0 (i.e., no change).
[d] Only 5 patients had valid post-Baseline results for plasma PPi; in the remaining patients, samples were compromised, as asfotase alfa was not sufficiently inhibited with levamisole.
(Source: Replicated from the sponsor's submission for Breakthrough Therapy Designation request, dated March 19, 2013, page 45/81 of the Investigator brochure)

Nine of 11 (82%) patients were categorized as radiographic responders, defined as improvement in bone mineralization as measured by the radiographic global impression of change (RGI-C)

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[4] Baumgartner-Sigl S. Pyridoxine-responsive seizures as the first symptom of infantile hypophosphatasia caused by two novel missense mutations (c.677T>C, p.M226T; c.1112C>T, p.T371I) of the tissue-nonspecific alkaline phosphatase gene. Bone. 2007; 40(6):1655-61

[5] Caswell AM, Whyte MP, Russell RG. Hypophosphatasia and the extracellular metabolism of inorganic pyrophosphate: clinical and laboratory aspects. Crit Rev Clin Lab Sci. 1991; 28(3):175-232

Reference ID: 3309199

score. RGI-C is a 7-point ordinal scale assessed by 3 central pediatric radiologists experienced in the evaluation of skeletal dysplasia. Severe worsening of rickets was defined as a change of -3 from baseline to Week 24, a score of 0 reflected no change in rickets, and +3 reflected a complete or near complete healing of rickets. A responder was defined as a mean RGI-C score of +2 or more. All responders demonstrated improvements in metaphyseal radiolucencies, thin gracile bones, and fractures. One non-responder had no visible bones at baseline and was the most severely affected patient, which may have limited the ability to achieve treatment response with asfotase alfa. One patient, who withdrew from the study on Day 1, was considered a non-responder in the results analysis.

There were no consistent trends observed in growth parameters. Ten patients had a history of failure to thrive and nine patients had a history of feeding tube requirement. Seven of ten patients showed an improvement in length-for-age z-scores. The patients who did not show improvement in weight or head circumference, remained at their baseline measurements and did not show a decline. Longer-term data are needed to evaluate further the growth outcomes in infantile-onset patients with HPP after treatment with asfotase alfa.

It is important to note that RGI-C scores are not validated in this disease population. The sponsor plans to submit a formal analysis of all collected data, including ventilator-free survival outcomes in infantile-onset patients enrolled in ENB-002-08/ENB-003-08. The sponsor submitted longer-term data describing improvements in respiratory status after 36 months as part of the Breakthrough Therapy Designation request and results are shown in Table 4 below.

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Table 4: Respiratory Status at 36 months for Perinatal/Infantile onset HPP (ENB-002-08/ENB-003-08)

Patient	Baseline respiratory support	Other significant baseline characteristics	Progression during early treatment period	Respiratory support at month 36 of treatment	Duration of Treatment at last observed visit
002-01-01	CPAP	Use of accessory muscles	Respiratory distress CPAP, BiPAP	None	48 mo.
002-02-01	Invasive Ventilation			Invasive ventilation[a]	42 mo.
002-03-01	Invasive Ventilation			N/A[b]	Day 1
002-04-01	None	Chest deformity		None	36 mo.
002-04-0	None	Chest deformity	Oxygen	None	36 mo.
002-05-01	CPAP	Respiratory compromise	Pneumonia Resp. failure	Supplemental Oxygen	42 mo.
002-06-01	Nasal Oxygen	Chest deformity	Upper resp. tract infection X2	None	42 mo.
002-08-01	Invasive Ventilation	Coarse breath sounds, chest deformity		N/A[b]	W7
002-09-02	Oxygen	Chest deformity	Oxygen desaturation	None	36 mo.
002-10-01	None	Restrictive pulmonary disease. Vitamin B_6 responsive seizures.	Oxygen Restrictive pulmonary disease	None	36 mo.
002-10-02	None	Subcostal retractions	Oxygen O_2 desaturation	None	36 mo.

[a] Patient was weaned of invasive ventilation at month 42
[b] Patients did not reach visit at month 30

(Source: Replicated from the sponsor's submission for Breakthrough Therapy Designation request, dated March 19, 2013, page 19/26)

At baseline, four patients required no respiratory support, two patients required CPAP, two patients required oxygen, and three patients were invasively ventilated. Three of the four patients on room air at baseline experienced disease progression early in the treatment phase and required supplemental oxygen. At 36 months of treatment, 7/11 (64%) required no respiratory support, one patient required invasive ventilation but was weaned from the ventilator at 42 months, and one patient continued to require supplemental oxygen. Two ventilated patients did not reach the 36 month follow up; one patient withdrew from the study on Day 1 after an infusion reaction, and one patient died after seven months of treatment during the extension phase. This patient was a 33-week premature infant with respiratory failure, craniosynostosis, conductive hearing loss, and pneumonia who eventually died from septic shock and respiratory failure. The death was deemed likely related to disease progression and complications related to HPP, and probably unrelated to treatment with asfotase alfa.

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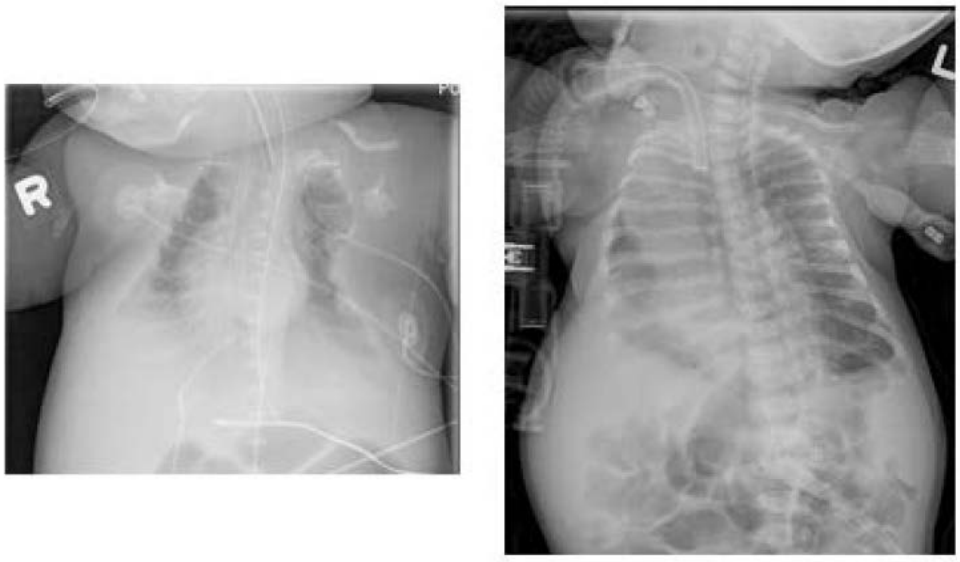
ENB-10-10 is an ongoing, open-label, multicenter, multinational study of the safety, efficacy, and PK of asfotase alfa in infants and children ≤ 5 years of age with HPP. No formal results were provided. As of February 8, 2013, 18 patients were enrolled and preliminary data from 9 of the 18 patients were available. The sponsor stated that rapid skeletal improvement was demonstrated on X-ray. Figure 1 below was provided as preliminary evidence of radiographic skeletal improvement in a patient with perinatal-onset HPP. Given the differences in quality and position on the X-ray below, it is difficult to make conclusions from these images without additional clinical information.

Figure 1: Skeletal Improvement as Measured by X-ray for a Patient with Perinatal-onset HPP



Baseline (day 1 of life) 9 months of treatment

In addition to the completed or ongoing clinical trials in perinatal- and infantile-onset HPP, the sponsor is conducting an ongoing natural history study in this patient population. A comprehensive natural history study of the perinatal- and infantile-onset phenotype has not been previously described. The results of this study will be submitted to the Agency and will provide a valuable comparison cohort of untreated historical controls.

Juvenile-Onset HPP Patients

Improvements in bone mineralization on X-ray as measured by the RGI-C score, rickets severity scale (RSS), and DEXA were reported in juvenile-onset HPP patients during Studies ENB-006-09 and ENB-008-10. More importantly, improvements in mineralization defect were

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demonstrated by bone biopsy. Table 5 shows the Week 24 results from the clinical trial in juvenile-onset HPP patients.

Table 5: Preliminary Efficacy Results Demonstrating Improvement in Bone Mineralization by X-ray, DEXA, and Bone Biopsy in Juvenile-Onset HPP Patients (ENB-006-09)

Efficacy Outcome Parameter	Baseline	Week 24	*P* value[a]
Radiographic Assessments (Primary Efficacy Outcome)			
RGI-C treated patients (n=13) (n [%] of radiographic responders)	---	9 (69%)	0.002[b]
RGI-C controls (n=17) (n [%] of radiographic responders)	---	2 (12%)	
Total RSS treated patients (mean difference from Baseline)	---	-1.81	0.0013[c]
Total RSS controls (mean difference from Baseline)	---	-0.59	
DEXA			
Median hip BMC (g)	6.61	9.30	0.0063
Median hip BMD (g/cm^2)	0.396	0.520	0.0063
Median lumbar spine BMC (g)	13.84	16.53	0.0063
Median lumbar spine BMD (g/cm^2)	0.421	0.492	0.0063
Median lumbar spine z-score	-2.2	-1.3	0.0063
Median whole body BMC (g)	555.65	624.44	0.0005
Median whole body BMD (g/cm^2)	0.725	0.739	0.39
Trans-iliac Crest Bone Biopsy			
Quantitative histomorphometric parameters[d]	Variable	Variable	0.13-1.00
Qualitative assessment of mineralization defect (n [%] patients)	10 (83%)	0 (0%)	0.0020[e]

BMC = bone mineral content; BMD = bone mineral density; RGI-C = Radiographic Global Impression of Change; RSS = rickets severity scale

[a] Unless otherwise specified, statistical significance was determined by the sign test. The sign test tests the null hypothesis that the median change from Baseline to Week 24 is 0 (i.e., no change).

[b] The *P* value for the radiographic responder analysis was determined by the Fisher exact test.

[c] The *P* value for the RSS analysis was determined by the permutation test.

[d] Raw and z-scores, where available, for the following histomorphometric parameters were analyzed: O.Th (or width), MLT, cortical width, cancellous bone volume, osteoid volume, osteoid surface, osteoblast-osteoid interface, eroded surface/bone surface, mineralizing surface/bone surface, osteoclast number (length based), osteoclast number (surface based), single-label surface, double-label surface, mineralization apposition rate, bone formation rate (surface based), bone formation rate (volume based), and adjusted apposition rate. The median varied for each parameter.

[e] The *P* value for mineralization defect on bone biopsy was determined by the exact McNemar test of pairwise change from Baseline.

(Source: Adapted from the sponsor's Breakthrough Therapy Designation Request, dated March 19, 2013, page 21/26)

In juvenile-onset HPP patients aged 5 -12 years old, bone mineralization improved in majority of patients, 9/13 (69%) compared to 2/17 (12%) in historical controls, based on radiographic scores. It should be noted that the historical controls were non-concurrent controls. The data for the control comparison group was obtained from a longitudinal natural history database on children

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who did not meet the inclusion criteria or were unable to participate in the trial. The patients selected for the control group were required to have a diagnosis of HPP with low serum ALP, elevated plasma PLP, normal serum calcium and phosphate, and no prior treatment with bisphosphonates or bone marrow transplant. X-rays from these patients were required to have been performed at least 6 months apart but no more than 26 months apart. Non-concurrent historical controls are suitable comparisons as long as the matching criteria are appropriate. The sponsor plans to provide the Agency with the specific matching criteria used for the juvenile-onset control group in the next few months.

The primary efficacy endpoint was bone mineralization as measured by X-ray. X-rays are not sensitive or specific to measure disease activity in HPP. Bone mineralization changes as measured by radiographic scores (radiographic global impression of change or rickets severity score) would not be acceptable to demonstrate efficacy of a drug in the absence of evidence correlating the X-ray findings with acceptable measures of HPP disease improvement or decline, such as bone mineralization changes as seen on bone biopsy. Nevertheless, the sponsor performed paired bone biopsies that showed an improvement of bone mineralization defect in all patients with baseline mineralization defects.

Based on bone biopsy data in juvenile-onset HPP patients, 10 of 12 (83%) patients had bone mineralization defects at baseline and 0/10 (0%) patients showed evidence of bone mineralization defects at 24 weeks after treatment with asfotase alfa. Evaluation of bone mineralization using bone biopsy is a clinically meaningful endpoint in HPP, since deficient TNSALP is responsible for impaired bone mineralization and subsequent clinical manifestations of the disease (e.g., fractures, pain, impaired growth and motor development, and respiratory failure).

In addition, DEXA scores trended toward improvement in all measures except whole body BMD. The sponsor also conducted multiple functional assessments to measure clinical improvement, including age appropriate scoring systems for cognitive, gross, and fine motor skills, developmental milestones, growth, muscle strength, and pain. Overall, these measures showed a consistent trend toward improvement, and potentially reflect a clinically meaningful effect on the underlying disease.

Adult HPP Patients

ENB-001-08 was a 1-month, open-label, dose escalation phase 1 trial in adult patients with HPP. This phase 1 trial enrolled adult patients with HPP based on current age and not age of disease onset. Some adult patients in this trial may actually have juvenile-onset disease and remain symptomatic as adults. The sponsor reported that asfotase alfa was safe and well tolerated, and the trial demonstrated a dose-dependent treatment effect and an overall decreasing trend in biomarkers (PPi and PLP). The most common adverse reactions include infusion-related adverse

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reactions, headache, and nausea. Hypocalcemia and B_6 toxicity were not reported. In this one-month, phase 1 trial, no anti-asfotase alfa antibodies were detected; however, patients treated during trials of longer duration have developed anti-asfotase alfa antibodies. There were no consistent changes in bone mineral density, pain, or bone imaging. It is important to note that this was a short term (i.e., one month), dose-finding trial in a limited number of adult patients with HPP. Therefore, changes in clinical endpoints or immunogenicity may not have been detected.

Adult-Onset HPP Patients

ENB-009-10 is an ongoing, randomized, open-label, multicenter, multinational, dose-ranging, concurrent-control study of the safety, efficacy, and PK of asfotase alfa in adolescents and adults with HPP. Nineteen patients are enrolled and receiving treatment at this time. The sponsor stated that after 24 weeks of treatment with asfotase alfa, preliminary data suggests significant decreases in biomarkers (PPi and PLP) and an improvement in the 6-Minute-Walk-Test (6MWT) in treated patients compared to controls. The sponsor did not provide specific numbers or percentages of patients who improved with treatment. The 6MWT has limitations with respect to reproducibility and was developed to reflect functional capacity based on cardiopulmonary reserve, not musculoskeletal strength. Therefore, an improvement in 6MWT may not necessarily reflect a clinical benefit in the adult HPP population since these patients do not have cardiopulmonary disease manifestations. However, it is possible that adult HPP patients with decreased bone mineralization will also benefit from treatment with asfotase alfa based on the current knowledge of the pathophysiology of the disease, although there are limited data at this time to directly support a treatment benefit in adult HPP patients. During a recent Type C meeting held on April 16, 2013, the sponsor agreed that there is an unmet need in the adult HPP patients. Although adult HPP patients were not initially included in the clinical development plan, the sponsor agreed during the meeting to include the adult patients in the future clinical development plans.

Safety and Immunogenicity

Based on the available data, asfotase alfa appears safe with no unexpected safety signals. Most frequently reported adverse reactions are local injection site reactions. One infant developed chronic hepatitis that was categorized as a rare, serious adverse reaction, possibly related to asfotase alfa. The sponsor is continuing to monitor for other occurrences of hepatitis. Three deaths occurred in infantile-onset HPP patients due to disease-related complications. One patient died from progressive respiratory failure (compassionate use in the Netherlands), one patient died from septic shock after 7 months of treatment during ENB-003-08 ("Extension of Study ENB-002-08 in Severely Affected Infants and Young Children with HPP"), and one patient with a complex medical history, including seizures and abnormal neurologic findings, died of respiratory failure after withdrawing from ENB-010-10 (A Phase 2 Open-Label, Multicenter

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Study of the Safety, Efficacy, and PK of Asfotase alfa in Pediatric Patients 5 years of Age or Younger with HPP”).

In general, immunogenicity is a concern with ERT, and patients have developed antibodies to asfotase alfa during the clinical trials. The sponsor is currently developing an assay to detect neutralizing antibodies to asfotase alfa. Additional data are being collected to gain a better understanding of the immunogenicity profile of asfotase alfa.

(b) (4)

Conclusion

Based on the preliminary clinical data provided, the Division concludes that a Breakthrough Therapy Designation should be granted for asfotase alfa to treat patients with perinatal-, infantile-, and juvenile-onset hypophosphatasia. Asfotase alfa is intended to treat a serious or life-threatening disease or condition, and preliminary clinical data indicate that the drug may demonstrate substantial improvement over existing therapies on ventilator-free survival in perinatal- and infantile-onset HPP patients and improvements in bone mineralization in juvenile-onset HPP patients.

Division’s Recommended Regulatory Action

Grant breakthrough designation request for perinatal-, infantile-, and juvenile-onset HPP patients

Questions for the Medical Policy Council

Reference ID: 3309199

1. The Division believes that asfotase alfa meets the criteria for a breakthrough therapy designation based on preliminary clinical data demonstrating improvement in bone mineralization and ventilator-free survival in patients with HPP. Does the Council agree?

2. Although the skeletal manifestations are similar across the HPP phenotypes, data are limited at this time in adults with HPP. The Division believes that a breakthrough designation applies to perinatal-, infantile-, and juvenile-onset HPP phenotypes at this time. Does the Council agree?

A meeting with the Medical Policy Council was held on May 15, 2013. The Medical Policy Council concurred with the Division's conclusion to grant breakthrough therapy designation for asfotase alfa for perinatal-, infantile-, and juvenile-onset HPP patients.

Attachments:

1. Meeting minutes from Type C meeting (April 16, 2013)

Type C meeting minutes April 1...

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/s/

JULI A TOMAINO
05/15/2013

JESSICA J LEE
05/15/2013

Clinical Consultation

From: Stephen Voss MD, Medical Officer DBRUP
Through: Theresa Kehoe MD, Medical Team Leader DBRUP
Hylton Joffe MD, MMSc, Division Director DBRUP
To: Carla Epps MD, Medical Officer DGIEP
Kevin Bugin, MS, RAC, SRPM, DGIEP
Subject: **New BLA 125513 for Strensiq (asfotase alfa), (b) (4) for hypophosphatasia (IND 100619)**
DBRUP Tracking # 95
Date of consult: April 17, 2015

Overview: Hypophosphatasia (HPP) is a rare genetic disorder marked by deficiency of tissue-non-specific alkaline phosphatase (TNSALP), with clinical manifestations including rickets and osteomalacia. Asfotase alfa has been developed (b) (4) for HPP. The previous (Enobia) and current (Alexion) sponsors have conducted open label clinical studies, primarily in infants and children with HPP, supported by studies in untreated HPP historical controls.

The sponsor received breakthrough therapy designation on 5/21/13. Dr. Marcea Whitaker (DBRUP) consulted previously regarding bone-specific endpoints. The BLA was submitted on 12/23/14. DBRUP is asked to comment on the significance of the sponsor's efficacy data analyses of HPP-related bone disease (bone biopsy and radiographic data).

Background: Hypophosphatasia is a rare disease in which the activity of TNSALP, the predominant circulating form of ALP, is reduced due to inactivating mutations. Lack of TNSALP enzyme activity leads to accumulation of certain substrates including inorganic pyrophosphate (PP_i), an inhibitor of skeletal mineralization, causing osteomalacia and rickets of long bones and ribs. (Accumulation of another substrate, PLP, indicates vitamin B6 deficiency in the CNS which may lead to seizures.)

HPP patients are classified by age of onset of signs/symptoms. “Perinatal onset” (developing in utero, evident at birth) and “infantile onset” (<6 months of age) HPP often feature rachitic chest deformities with high mortality due to respiratory insufficiency, and failure to thrive. In “juvenile (or childhood) onset” (onset at ≥ 6 months to ≤18 years of age), the predominant clinical feature of HPP is generally bone disease, similar to vitamin-D deficiency and other forms of rickets: bowed legs and other deformities; impaired growth; fractures; bone pain; muscle weakness; and impaired gait. Other manifestations may include impaired teeth mineralization and nephrocalcinosis. Less commonly, patients may initially present in adulthood, with fractures due to osteomalacia. There is no specific treatment.

Radiographic changes of rickets are best seen at the most active growth plates, therefore are usually assessed by AP knee and PA hand/wrist X-rays. The earliest finding is loss of the distinct line (zone of provisional calcification) at the end of the metaphysis (“fraying”). Subsequently, the lucent growth plate widens axially and the adjacent

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metaphysis widens transversely ("flaring" or "splaying"). Periosteal bone formation is relatively spared so the end of the metaphysis may become concave ("cupping"). Costochondral junctions may show similar features. Other common findings include bending of femur and/or tibia with genu varum or valgum, osteopenia and fractures. In addition to these typical features of rickets, HPP may exhibit unique abnormalities. In particular, metaphyseal involvement is often more patchy in HPP, with characteristic "punched out" lucencies, sometimes adjacent to areas of increased density (osteosclerosis).

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.

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:

<u>Infantile-onset HPP patients ≤5 years old:</u>

- 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

<u>Older infantile- and juvenile-onset patients:</u>

- 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)

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Reviewer 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.*

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

In the HPP trials (see below), both RSS and RGI-C were used to score all skeletal X-rays for pediatric patients (< 18 y/o) with open growth plates, including children treated in the open label studies and untreated controls. A single radiologist, blinded to assessment time point and other patient information, rated each set of films according to the RSS. For the RGI-C, which was designated as the primary radiographic endpoint, 3 radiologists independently scored each set of post-baseline films (blinded to the timepoint and other patient data) in comparison to baseline. The average of the RGI-C scores from the 3 readers at each timepoint was used for analysis. Patients with RGI-C mean scores of +2 or greater at a given point were defined as "responders". There was good inter-rater agreement according to two statistical analyses which are presented in the Summary of Clinical Efficacy Appendix D (p. 228). There was also good concordance of RGI-C with RSS (n=135 patients, Pearson correlation −0.664, $p<0.0001$).

Asfotase alfa (ENB-0040), a human (IgG_1) recombinant fusion protein of TNSALP, is intended as long-term enzyme replacement therapy for patients with perinatal, infantile and juvenile onset HPP. Asfotase alfa has a catalytic domain that restores the enzyme activity and a bone targeting domain which leads to preferential accumulation in bone. The proposed dose of asfotase alfa is 2 mg/kg 3x/week or 1 mg/kg 6x/week as a SQ injection.

<u>Infantile-onset HPP patients</u>

Children with HPP of infantile onset (prior to 6 months of age) are treated primarily in the following open label studies:

- Studies ENB-002-08 and extension ENB-003-08 (age 0-3 y/o at enrollment) (n=11)
- Study ENB-010-10 (age 0-5 y/o at enrollment) (n=28)
- Study ENB-006-09 and extension ENB-008-10 (age 5-12 y/o at enrollment) (n=5)

Study ENB-010-10 is currently still enrolling, and the extension studies are ongoing. <u>Enrollment criteria</u> for these studies included perinatal or infantile onset HPP; subnormal serum ALP; elevated PLP; radiographic evidence of HPP (flared and frayed metaphyses;

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severe, generalized osteopenia and widened growth plates); rachitic chest deformity and/or vitamin B_6-responsive seizures; failure to thrive; and 1 or more HPP-related findings e.g. non-traumatic fractures, delayed fracture healing, craniosynostosis, hypercalcemia, nephrocalcinosis or respiratory compromise.

Dosing regimens of these studies varied. In ENB-002-08/003-08, patients received 3 mg/kg/wk of asfotase alfa and in ENB-010-10 they received 6 mg/kg/wk, but dose adjustments were permitted for efficacy or safety issues. In ENB-006-09/008-10, patients were randomized to receive either 6 mg/kg/wk or 9 mg/kg/wk for the first 24 weeks, followed by 3 mg/kg/wk for 3-9 months, then increased to 6 mg/kg/wk (dose adjustments allowed). For all 44 infantile-onset HPP patients in these studies, the average weekly dose was 6.6 mg/kg/wk and average treatment duration was over 2 years.

Patient Disposition: Of the 44 infantile onset children, 38 were continuing to receive asfotase alfa at the analysis cutoff data, 4 had died and 2 others had discontinued (details in footnotes to RGI-C results table below).

Demographics/ Baseline Characteristics: mean age at onset of symptoms was 1.6 months (range 0-5.5 mos), and mean age at enrollment was 33 months (range 0-12.4 yr). There were 21 boys/23 girls; 35 white/ 6 Asian/ 3 "other" race/ 0 black. Patients exhibited major growth delays: mean baseline height and weight Z-scores were -3.4 and -3.6. The mean (SD) baseline RSS score was 5.7 (3.4) indicating moderately severe rickets overall (though variable, with range 0-10) and there were high rates of HPP-related morbidities at baseline:

Table 14: HPP-Specific Medical History – All Treated Infantile-Onset Patients ≤12 Years of Age (N=44)

Parameter	Infantile-Onset Patients ≤12 Years of Age (N=44)
Abnormally shaped chest	33 (75.0%)
History of respiratory compromise (up to and including respiratory failure)	31 (70.4%)
Seizures	14 (31.8%)
Difficulty gaining weight, failure to thrive, and/or difficulty eating/swallowing	39 (88.6%)
Fractures (including vertebral) and/or delayed fracture dealing	15 (34.1%)
Bone/joint pain [a]	16 (48.5%)
Delayed walking (first walked at ≥15 months of age) [b]	26 (59.1%)
Muscle weakness	34 (77.3%)
Nephrocalcinosis/kidney stones	26 (59.1%)

Source: Summary of clinical efficacy m2.7.3, p. 64

Radiographic Outcomes

RGI-C: Virtually all asfotase alfa-treated children with infantile onset HPP showed some evidence of radiographic improvement (RGI-C >0, table below), and improvements were generally maintained. Median score was ≥ +2 (the "substantial healing" level) at every timepoint beginning at week 24. Median was significantly different from 0 (by Wilcoxon signed rank test) at $p<0.005$ for every timepoint except weeks 216 and 240 (where n's were small). For the designated primary radiographic endpoint of RGI-C at week 24, improvements were statistically significant for each of the 3 studies individually as well

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as pooled. Of the 30 children treated for ≥48 weeks, 27 achieved a score of ≥ +2 at least once, and each of the other 3 reached a score of +1.7.

RGI-C scores in infantile-onset HPP patients treated with asfotase alfa

Pt #	Age* Sex	Wk 12	Wk 24	Wk 36	Wk 48	Wk 60	Wk 72	Wk 96	Wk 120	Wk 144	Wk 168	Wk 192	Wk 216	Wk 240
Study 002-08 /003-08 (n=11)														
01-01	0F	1.3	2	2.3	2.7	2.7	2.7	2.7	2.7	2.7	2.7	2.7	2.7	2
02-01	2F	0	0	1	1.3	1	1.7	2	2	2	2	-	-	2
03-01	1F	(a)	-	-	-	-	-	-	-	-	-	-	-	-
04-01	2M	1	1.7	2	2.7	-	2	2	2.3	1.7	-	2	-	-
04-02	0F	0.7	2.3	2.7	3	2.7	3	3	2.7	3	-	2.7	-	-
05-01	0F	2	2.3	3	3	3	2.7	2.7	3	3	3	-	-	2.7
06-01	3F	1.3	1.7	2	2	2	2	2	2.7	2.3	1.7	-	-	2
08-01	0M	1.7	2	(b)	-	-	-	-	-	-	-	-	-	-
09-02	0M	-1	2	2	2	1.7	1.7	2	2	-	1.3	-	-	-
10-01	0F	0	2	1.7	2	2	2	2	1.7	1.7	-	2	-	-
10-02	0M	1.3	2.3	2.7	3	3	2.7	3	3	3	-	2.7	-	-
Study ENB-010-10 (n=28)														
01-01	0F	2	-0.3	2	2	2	2	1.7	2	2	2	-	-	-
01-02	0M	2	2.3	2.3	2.7	-	2.3	2.7	3	3	-	-	-	-
01-03	5F	1.7	2	2.3	2.3	-	1.3	2.3	2.7	2.7	-	-	-	-
01-04	4F	3	3	3	3	-	3	3	2.3	-	-	-	-	-
01-05	4M	2.3	3	3	3	-	3	3	2.7	-	-	-	-	-
01-06	3F	3	2.3	3	2	-	3	3	3	-	-	-	-	-
01-07	0M	2	2	2	2	(c)	-	-	-	-	-	-	-	-
13-01	0M	-0.7	0.7	-	-	-	2.7	1.7	2	1.3	-	-	-	-
13-02	5M	1	1	2	2	-	1.7	3	2	2	-	-	-	-
13-03	3F	3	3	2.7	3	-	2.3	3	3	-	-	-	-	-
13-04	0M	-1.7	-	1.3	2	-	1	-	-	-	-	-	-	-
16-01	0M	0	2	2	2	-	2	2	1.7	-	-	-	-	-
16-02	3F	1.3	1.7	1.7	-	-	1.7	1.7	-	-	-	-	-	-
16-03	0M	(d)	-	-	-	-	-	-	-	-	-	-	-	-
16-04	0F	0	2	2.3	2	-	-	-	-	-	-	-	-	-
16-05	1F	-1	1.7	1.7	1.7	-	-	-	-	-	-	-	-	-
16-06	5M	3	2.3	-	-	-	-	-	-	-	-	-	-	-
16-07	4F	1.7	1.7	-	-	-	-	-	-	-	-	-	-	-
18-01	0F	0.7	1.7	2	2	-	-	-	-	-	-	-	-	-
18-02	0F	1	1.3	-	-	-	-	-	-	-	-	-	-	-
18-03	1F	1	2	-	-	-	-	-	-	-	-	-	-	-
19-01	0M	0.3	0	(e)	-	-	-	-	-	-	-	-	-	-
19-02	1F	1	1.3	-	-	-	-	-	-	-	-	-	-	-
20-01	0F	1.7	2	2.7	2.3	-	-	-	-	-	-	-	-	-
21-01	5F	0.7	1	-	-	-	-	-	-	-	-	-	-	-
22-01	2F	0.7	0.7	-	-	-	-	-	-	-	-	-	-	-
23-01	5M	0.7	0.7	0.7	-	-	-	-	-	-	-	-	-	-
24-01	0M	2	3	-	-	-	-	-	-	-	-	-	-	-
Study 006-09/ 008-10 (n=5)														
01-04	5M	2	2	1.7	1.7	2	2	1	2	-	1.7	2	-	-
01-07	12M	0.3	1	1.3	1.7	0.7	1	1	0.7	-	0.7	0.7	-	-
02-02	7M	0.7	2	2	1.3	2	2	2	2	2	2	2	-	-
02-03	10M	2	2	1.7	1.7	1.7	1.7	2.3	2.3	3	3	-	-	-
02-04	10M	(f)	-	-	-	-	-	-	-	-	-	-	-	-

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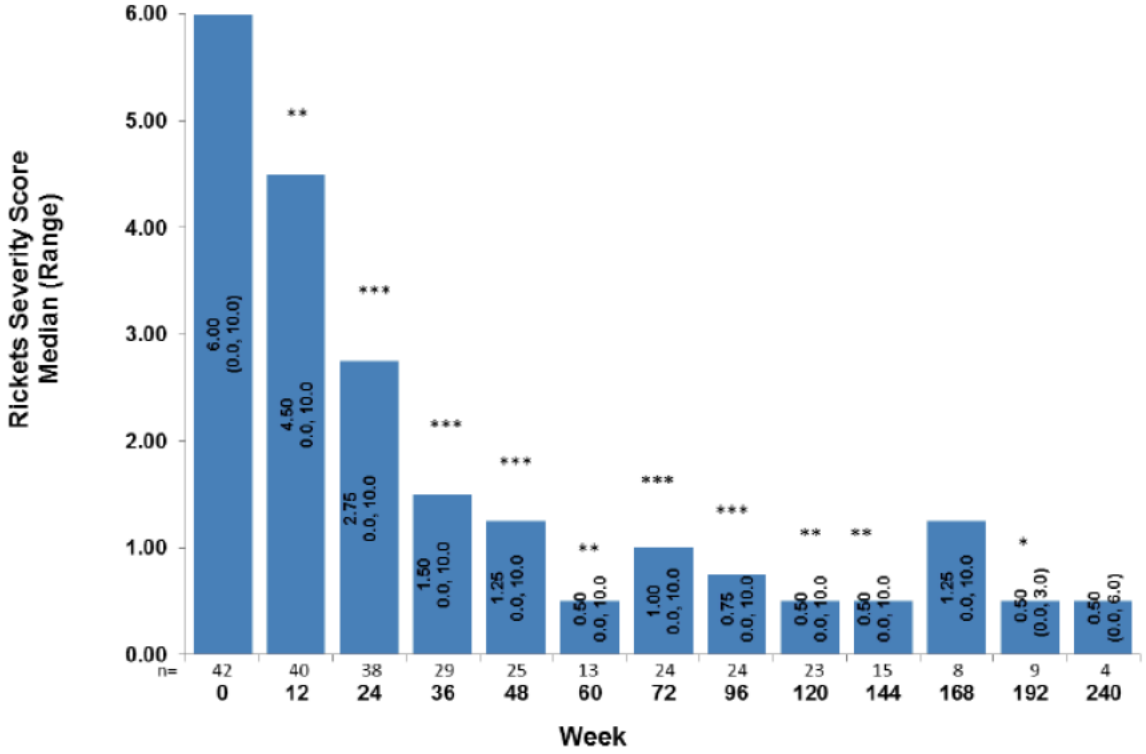
Median RGI-C score and range														
Median		**1.0**	**2.0**	**2.0**	**2.0**	**2.0**	**2.0**	**2.17**	**2.33**	**2.33**	**2.0**	**2.0**	**2.7**	**2.0**
Low		-1.7	-0.3	0.7	1.3	0.7	1.0	1.0	0.7	1.3	0.7	0.7	2.7	2.0
High		3.0	3.0	3.0	3.0	3.0	3.0	3.0	3.0	3.0	3.0	3.0	2.7	2.7

Source: ADRADIO, observed data (not LOCF)
* Age (years) at enrollment
a) discontinued following reaction to initial IV infusion
b) died of sepsis at week 30
c) cardiopulmonary arrest at day 436, later died
d) discontinued after 2 doses because of encephalopathy, died within 1 week
e) drug held because of pneumonia at day 94, later died
f) discontinued at day 31 to undergo scoliosis surgery

RSS scores declined with treatment (figure below). There were 4/44 patients who had an increase from baseline RSS >1 at any point (002-08-09-02; 010-10-13-01; 010-10-16-01; 010-10-23-01). In some of these instances, RGI-C scores remained neutral or positive because of changes outside the growth plates, e.g. improvements in ribs or in metaphyseal areas of sclerosis.

Figure 5: Effect of Asfotase Alfa on Rickets (RSS) – All Treated Infantile-Onset HPP Patients ≤12 Years of Age (N=44)



Abbreviations: RSS = Rickets Severity Scale.
Note: Median (minimum, maximum) values are shown in each bar, ns are provided below the bar.
Note: The RSS is a 10-point rating scale, with a maximum score of 4 points for the wrists and 6 points for the knees, in which a score of 10 represents severe rickets and 0 represents an absence of rickets.
P-values based on Wilcoxon signed rank test evaluating whether median change from Baseline is significantly different from 0 * p< 0.005 ** p< 0.001 ***<0.0001
Source: Summary of Clinical Efficacy p. 71

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Reviewer comment: *A retrospective study of historical controls with infantile-onset HPP (ENB-011-10) was conducted but did not include systematic review of radiographs, therefore there are no untreated control RGI-C or RSS data in this population, as there are for juvenile-onset HPP patients (see below).*

Growth: Mean changes in height Z-scores were >0 for all time points, but significant at p<.05 only at weeks 144 and 216. Mean weight Z-scores also increased.

Bone biopsies (transiliac) were performed in patients who were ≥ 5 y/o at treatment initiation in study ENB-006-09 (and not in any of the younger children because of perceived increased risk). These data were previously reviewed by DBRUP (see below).

In ENB-006-09, 4 infantile-onset HPP children had paired biopsies at baseline and week 24 of treatment; the other (pt #02-04) dropped out after 1 month so only had a baseline biopsy. At baseline, biopsies in 3/5 children met the usual criteria for osteomalacia (osteoid thickness >9 µm and mineralization lag time >25 days), and median osteoid volume of 11% (relative to bone volume) was well above the usual value of 2.4% in healthy children. Following 24 weeks of treatment with asfotase alfa, 4/4 children had reductions in osteoid thickness and volume indices, and 3/4 had decline in mineralization lag time (table below).

Mineralization indices in infantile-onset HPP patients treated with asfotase alfa (ENB-006/09/008-10)

	Osteoid thickness (µm)			**Osteoid volume (%)**			**Mineralization lag time (d)**		
Patient #	BL	Wk 24	**Change**	BL	Wk 24	**Change**	BL	Wk 24	**Change**
01-04	7.7	6.4	**-1.3**	7.3	5.0	**-2.3**	89	39	**-50**
01-07	7.7	7.0	**-0.7**	5.6	5.3	**-0.3**	43	23	**-20**
02-02	14.0	6.4	**-7.6**	14.7	4.8	**-9.9**	126	48	**-78**
02-03	13.6	8.2	**-5.4**	11.0	8.0	**-3.0**	39	57	**+18**
02-04	16.3	-	**-**	31.0	-	**-**	954	-	**-**
Median	**13.6**	**6.7**	**-6.9**	**11.0**	**5.2**	**-5.8**	**89**	**44**	**-45**
Source: ADBONE									

Reference ID: 3733103

DXA of whole body, lumbar spine and hip was conducted in studies ENB-006/008-10 as another means to evaluate bone mineralization in patients ≥5 y/o at start of treatment. Whole body mean BMC and BMD in the 5 infantile onset patients at baseline were 698 g and 0.697 g/cm^2 respectively, and increased during treatment:

Whole body BMC and BMD (DXA) in infantile onset HPP treated with asfotase alfa (ENB-006/09/008-10)

	BMC Mean change from baseline (range)	**BMC Mean percent change** (range)	**BMD Mean change from baseline** (range)	**BMD Mean percent change** (range)
Week 24 n=4	**78** (43, 106)	**12.7** (5.3, 19.3)	**0.049** (-0.011, 0.161)	**8.3** (-1.4, 27.9)
Week 72 n=4	**207** (-19, 293)	**25.7** (-5.6, 47.7)	**0.116** (0.036, 0.252)	**19.3** (4.2, 43.6)
Week 96 n=4	**270** (-24, 448)	**33.4** (-7.1, 55.4)	**0.148** (0.052, 0.312)	**24.4** (6.0, 54.0)
Week 120 n=4	**378** (47, 529)	**51.2** (13.7, 87.5)	**0.124** (-0.012, 0.311)	**21.0** (-1.5, 53.8)
Week 144 n=2	**418** (197, 639)	**67.9** (57.2, 78.5)	**0.164** (0.029, 0.298)	**28.4** (5.2, 51.6)
Week 168 n=3	**440** (214, 562)	**69.5** (48.0, 98.5)	**0.040** (0.031, 0.054)	**5.4** (4.3, 6.3)
Week 192 n=4	**593** (200, 794)	**83.4** (57.9, 114.2)	**0.125** (0.010, 0.328)	**19.5** (1.8, 56.8)
Source: ISE Table 2.2.13.1.1, ADBONE				

Reviewer comment: *Whole body BMD Z-scores were not provided for data prior to week 120 for most patients, rather, whole body peak reference (%) was provided. This was also the case for hip BMD. Without Z-scores, these data are difficult to interpret, because robust increases over time in BMD and BMC are expected in children. For lumbar spine BMD however, Z-scores were provided: mean Z-score at baseline was -2.4 SD which increased moderately during treatment:*

Lumbar spine BMD Z-scores (DXA) in infantile onset HPP treated with asfotase alfa (ENB-006/09/008-10)

		Z-score change from baseline	
	n	Mean	Range
Week 24	4	0.5	0.1, 0.8
Week 72	4	0.4	-0.5, 1.5
Week 96	4	0.0	-0.6, 0.6
Week 120	4	-0.2	-1.2, 0.5
Week 144	2	1.9	1.4, 2.3
Week 168	3	0.3	-1, 1.3
Week 192	4	0.9	-0.7, 2.4
Source: ADBONE			

Reference ID: 3733103

Juvenile-onset HPP patients

Children with HPP of juvenile onset (6 mos to 18 yrs of age) were treated in open label study ENB-006-09 and extension ENB-008-10 (age 5-12 y/o at enrollment) (n=8). (These studies also enrolled 5 infantile onset HPP patients, who were included in the analyses discussed above.) For comparison, a retrospective historical control study (ALX-HPP-502) of untreated juvenile onset HPP patients was conducted (n=32).

Enrollment criteria: for patients in the treatment study, age 5-12 yr with open growth plates; prepubescent (Tanner stage 1 or 2); rachitic X-ray changes; serum ALP <LLN; plasma PLP ≥2x ULN; and serum 25-OH-vit D ≥20 ng/mL. Among the exclusion criteria were hypocalcemia or hypophosphatemia; evidence of a treatable form of rickets; prior treatment with bisphosphonates; or S/P bone marrow transplantation.

Entry criteria for historical control patients (ALX-HPP-502) specified that patients must have documentation of juvenile-onset HPP with low serum ALP and/or TNSALP gene mutation, HPP-related skeletal abnormalities and at least 2 sets of wrist or knee X-rays taken between the ages of 5 and 15 years at Tanner stage ≤2, at least 6 months apart, available for review. Patients who had received during that time any bone- or growth-related treatment (e.g. asfotase alfa, bisphosphonates, growth hormone, bone marrow transplant) were excluded.

Dosing regimen: In ENB-006-09/008-10, patients were randomized to receive either 6 mg/kg/wk or 9 mg/kg/wk for the first 24 weeks, following which they received 3 mg/kg/wk for 3-9 months, then increased to 6 mg/kg/wk (dose adjustments allowed for efficacy or safety issues).

Patient Disposition: There were 8 patients enrolled in Study ENB-006-09 with juvenile-onset HPP, and all were continuing on treatment at the BLA cutoff date, with an average weekly dose of 5.7 mg/kg and mean treatment duration of 3.6 years.

Reference ID: 3733103

Demographics and Baseline Characteristics: In the 8 asfotase alfa-treated patients, mean age of onset of HPP symptoms was 15 months (range 12-22 months). Age at enrollment was 6-12 y/o (median 8.4 yr); there were 2 girls and 6 boys; all were white. Compared to the infantile onset patients there were fewer patients with history of respiratory compromise (25% vs. 70%), and none with history of seizures or nephrocalcinosis:

Table 29: HPP-Specific Medical History - All Treated Juvenile-Onset Patients 5-12 Years of Age (N=8)

Parameter	Juvenile-Onset Patients 5-12 Years of Age (N=8)
Abnormally shaped chest	6 (75.0%)
History of respiratory compromise (up to and including respiratory failure)	2 (25.0%)
Vitamin B_6-responsive Seizures	0 (0.0%)
Difficulty gaining weight, failure to thrive, and/or difficulty eating/swallowing	5 (62.5%)
Fractures (including vertebral) and/or delayed fracture dealing	2 (25.0%)
Bone/joint Pain	4 (50.0%)
Delayed Walking (first walked at ≥15 months of age)	6 (75.0%)
Muscle weakness	5 (62.5%)
Nephrocalcinosis/kidney stones	0 (0.0%)

Source: Summary of clinical efficacy m2.7.3, p. 101

Growth delays were less pronounced than the infantile onset patients, with mean baseline height and weight Z-scores of -1.5 and -1.1. Rickets was also somewhat less severe, with mean (SD) baseline RSS score of 2.88 (0.694) (range 1.5-3.5).

For 32 untreated historical controls (ALX-HPP-502) with juvenile onset HPP, mean age at onset of symptoms was 17.5 months (range 7-41 months). There were 10 girls and 22 boys, all except 2 white. At baseline (earliest measurements available between age 5-15 y/o, median was at 6 y/o), mean height- and weight Z-scores were -1.1 and -1.2. Symptoms experienced between age 5-15 y/o included bowing of long bones (59%), gait disturbance (59%), muscle weakness (47%), joint pain (53%) bone pain (50%), fractures (31%), rachitic chest (13%). All patients had baseline X-ray findings characteristic of HPP, but skeletal findings were less severe than treated pts, with median RSS score of 1.0 (range 0-3.5); there were 8/32 who had baseline RSS scores of 0.

Reference ID: 3733103

Radiographic Outcomes: RGI-C

All 8 asfotase alfa-treated children with juvenile onset HPP showed evidence of radiographic improvement during treatment (RGI-C >0, table below). Median score was ≥ +2 (the "substantial healing" level) at every timepoint beginning at week 24. Median was significantly different from 0 (by Wilcoxon signed rank test) at $p<0.05$ for every timepoint except weeks 168 and 216 (where n's were small). The last score recorded was ≥ +2 for each of the 8 children.

RGI-C scores in juvenile-onset HPP patients treated with asfotase alfa (studies ENB-006-09/008-10)

Pt #	Age* Sex	Wk 12	Wk 24	Wk 36	Wk 48	Wk 60	Wk 72	Wk 96	Wk 120	Wk 144	Wk 168	Wk 192	Wk 216
01-01	8F	1.3	1.7	1.7	1.3	1.7	1.7	1.3	1.3	1.3	-	1.7	2
01-02	10M	0.7	2	1.3	1.7	2	2.3	2	2	2	-	2.7	-
01-03	8M	2	1.7	2	1.7	2	2	2	2	-	2	2.3	2.3
01-05	8M	1.7	2.3	2	2	2.3	2.7	2	-	2	2.7	2.7	-
01-06	12M	2.3	2.3	2	2	2	2	2	2	2.3	-	3	-
01-08	6M	1.7	2	2	2	2	2.3	2	2	2.7	2.7	-	-
01-09	6F	2	2	2.3	2.3	3	2	2.3	2.3	-	2.7	2.3	-
02-01	7M	2	2.3	2	2	2	2.7	2	2.7	2	2.3	2.7	-
Median RGI-C score and range													
Median		**1.8**	**2.0**	**2.0**	**2.0**	**2.0**	**2.2**	**2.0**	**2.0**	**2.0**	**2.7**	**2.7**	**2.2**
Low		0.7	1.7	1.3	1.3	1.7	1.7	1.3	1.3	1.3	2.0	1.7	2.0
High		2.3	2.3	2.3	2.3	3.0	2.7	2.3	2.7	2.7	2.7	3.0	2.3

Source: ADRADIO, observed data (not LOCF)
Last entry for each patient is their last RGI-C measurement
* Age (years) at enrollment

For comparison, X-rays from the 32 untreated controls in study ALX-HPP-502 were read alongside those from the treated patients, by radiologists who were blinded to treatment status. For controls, the earliest available hand/wrist or knee films taken at age ≥5 y/o became the baseline (median 6.0 years = younger than baseline for treated pts), for comparison to subsequent films taken until the patient reached Tanner stage >2 or age 15 y/o. The time interval between baseline and paired postbaseline films varied from 5-95 months. For analysis the sponsor chose to assign postbaseline films to the categories of "week 24", "week 48" and "week 96" but in reality the timelines were much longer, with median postbaseline intervals of approx. 111, 116 and 132 weeks respectively for these categories. The median interval for the last assessment in control patients was 222 weeks, longer than the median for the treated patients which was 182 weeks. Thus the sponsor observes that the control patients "had a longer window of opportunity to demonstrate spontaneous healing". As shown in the table below, only 3/32 untreated controls attained an RGI-C score ≥ +2 at any point, and several had negative readings. Median scores for controls were +0.3 to +0.5, significantly lower than median scores for asfotase alfa-treated patients (see Figure 35 below). Separate scores for wrists and knee X-rays showed similar treatment group differences.

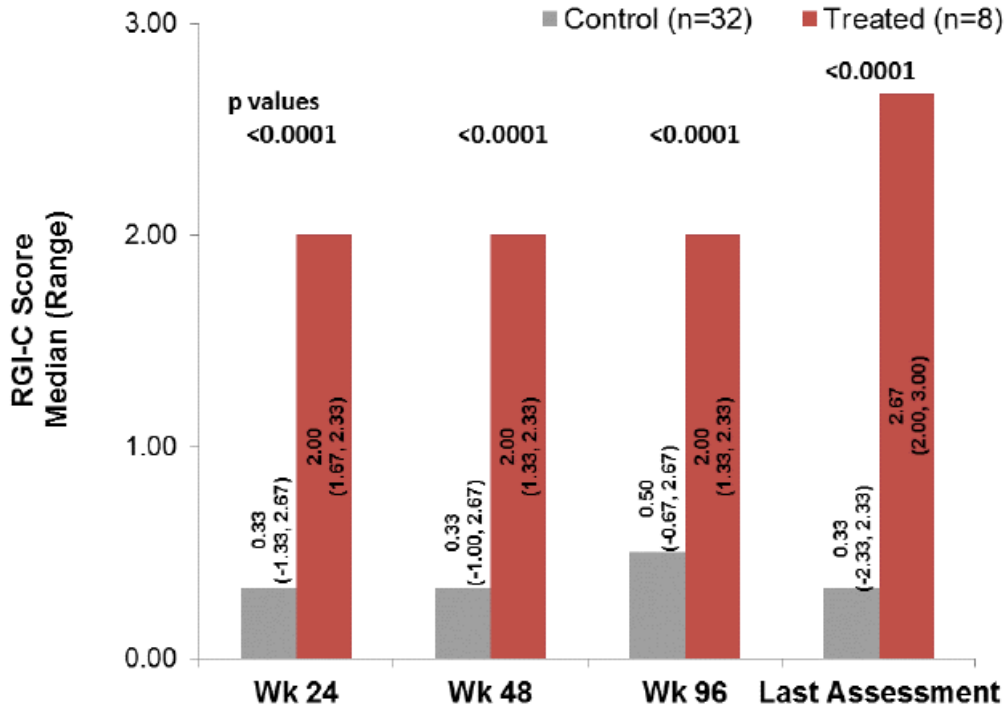
Reference ID: 3733103

RGI-C scores in juvenile-onset HPP untreated controls (study ALX-HPP-502)

Pt #	Age* Sex	"Wk 24"	"Wk 48"	"Wk 96"	Last
0182-001A	5M	-1	-1	-0.7	-0.3
0182-002A	13M	2.3	2.3	2.3	2.3
0189-001A	7F	1.3	1.3	1.3	1.3
0192-001A	5F	-0.7	-0.7	-0.3	-0.3
0193-001A	10M	-0.3	-0.3	-	-0.3
0193-003A	6F	2.7	2.7	2.7	2
0195-002A	9F	0.3	0.3	0	0
0200-001A	10M	0	0	0	0
0204-001A	6M	1.3	2	1.7	1.3
0257-003A	5F	0.3	0.3	0.3	0.3
0257-006A	6M	0	0	0	0
0257-007A	5M	0	0	0	0
0257-008A	6M	0	0	0	0
0257-009A	5M	0.3	0.3	0.3	0.3
0257-010A	5M	0.7	1	1	1
0257-012A	11M	0.3	0.3	0.3	0.3
0257-014A	7F	0.7	0.7	0.7	1
0257-015A	5F	0.7	0.7	0.7	-0.3
0257-017A	6F	-0.7	-0.7	0.3	0.3
0257-019A	6M	0.3	0.3	0.3	0.7
0257-022A	5M	1.3	1.3	1.3	1.3
0257-023A	5F	0.3	0.3	0.3	0.3
0257-024A	5M	0	0	0.7	1
0257-001A	5M	-0.3	-0.7	-0.7	-1
0257-021A	5M	0.7	0.7	0.7	1.3
0257-013A	5M	0	0	1	0.3
0257-005A	5M	1.3	1.3	1.3	-1
0257-026A	5M	0	0	0.3	-1.7
0257-027A	5M	0.7	0.7	0.7	0
0183-001A	10M	-1.3	-	-	-2.3
0257-025A	5F	1.3	1.3	1.3	1.3
0257-004A	8M	0.3	0.3	1.3	1.7
Median RGI-C score and range					
Median		**0.3**	**0.3**	**0.5**	**0.3**
Low		-1.3	-1.0	-0.7	-2.3
High		2.7	2.7	2.7	2.3
Source: ADRADIO, observed data (not LOCF) * Age (years) at baseline X-rays					

Reference ID: 3733103

Figure 35: RGI-C Scores at Weeks 24, 48, 96, and Last Assessment for Asfotase Alfa-Treated and Historical control Patients with Juvenile-Onset Hypophosphatasia

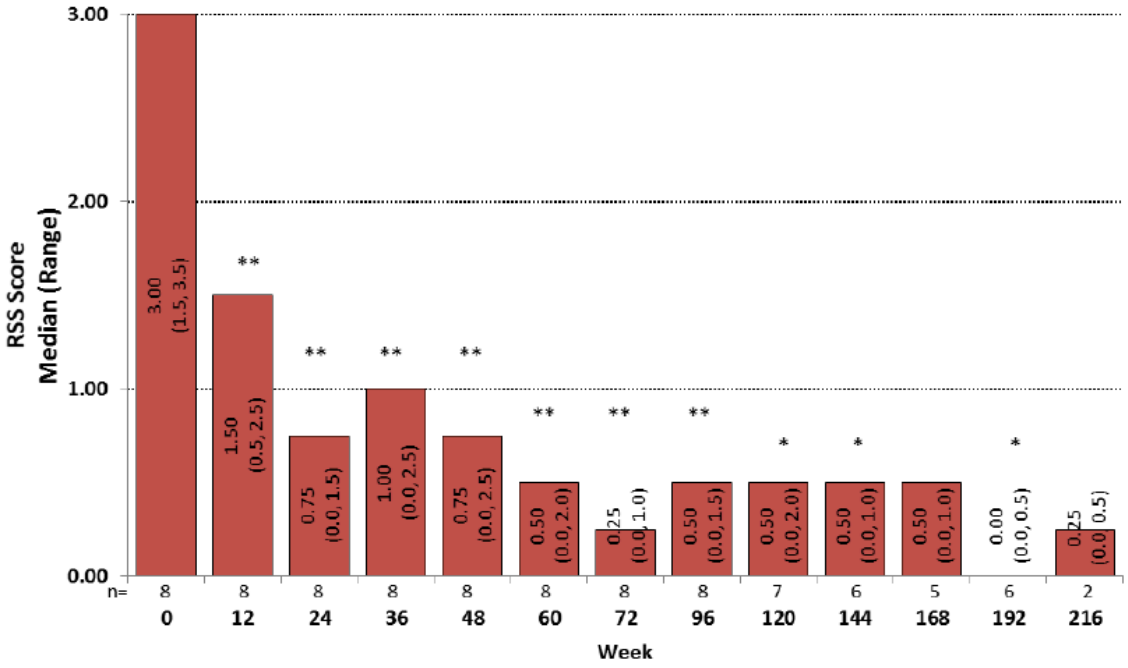


Note: Median (minimum, maximum) RGI-C values are in each bar.
Median difference (days) between Baseline and Week 24 RGI-C X-ray pairs in the historical control group = 778.5.
Median difference (days) between Baseline and Week 48 RGI-C X-ray pairs in the historical control group = 813.0.
Median difference (days) between Baseline and Week 96 RGI-C X-ray pairs in the historical control group = 924.5.
Median difference (days) between Baseline and Last Assessment RGI-C X-ray pairs in the historical control group = 1551.5.
p-value based on Wilcoxon rank sum test (exact method) comparing the median RGI-C scores for asfotase-alfa treated patients and historical controls.
Source: Summary of Clinical Efficacy p. 143

RSS Scores declined in the 8 treated patients from the median baseline of 3.0 (on 0-10 scale, see Figure 22 below). In control patients, median baseline RSS was lower (1.0), and median change from baseline was 0.0 at each timepoint and at last assessment. None of the 8 treated patients had an increase from baseline RSS score at any point, compared to 11/32 untreated controls.

Reference ID: 3733103

Figure 22: Effect of Asfotase Alfa on Rickets (RSS) - All Treated Juvenile-Onset HPP Patients ≤12 Years of Age (N=8)



Abbreviations: RSS = Rickets Severity Scale.
Note: median (min, max) values are shown in the bar; n's are shown below the bar.
Note: The RSS is a 10-point rating scale, with a maximum score of 4 points for the wrists and 6 points for the knees, in which a score of 10 represents severe rickets and 0 represents an absence of rickets.
p-values based on Wilcoxon signed-rank test testing whether the median change from Baseline equals 0.
* $p<0.05$, ** $p<0.001$.
Source: Summary of Clinical Efficacy p. 108

Reviewer comment: *Asfotase-alfa-treated patients with juvenile onset HPP clearly exhibited greater improvement radiographically than untreated controls. However, treated patients had more severe rickets at baseline (mean baseline RSS 2.88, vs.1.06 controls), therefore greater potential for improvement. The sponsor analyzed RGI-C scores with adjustment for baseline RSS, and reports that this did not negate the positive treatment effect (Summary of Clinical Efficacy p. 143).*

Growth

In study 006-09/008-10, mean height Z-scores in the 8 juvenile onset patients were numerically increased from baseline starting at week 24, and in general were progressively higher at later timepoints.

In untreated juvenile onset HPP controls (ALX-HPP-502), there were minimal changes from baseline in mean height Z-scores, ranging from -0.22 to +0.06 at various timepoints and -0.03 at last assessment.

Reference ID: 3733103

Bone biopsy

Biopsies were conducted at baseline and after 24 weeks of treatment in study 006-09/008-10. Similar to the infantile-onset HPP children in this study (see above), juvenile-onset patients had baseline histomorphometry generally consistent with osteomalacia (osteoid thickness > 9 µm, mineralization lag time >25 days) (table below). Following treatment, 7/8 patients had declines in osteoid thickness and volume, and variable changes in mineralization lag time from +12 to -167. The one exception (patient #01-08) had increases (potential worsening) of all 3 parameters, despite a good radiographic response (initial RSS 3 declining to 0-0.5; RGI-C scores 2 to 2.7), and improvement in height Z-scores.

Mineralization indices in juvenile-onset HPP patients treated with asfotase alfa (ENB-006-09/008-10)

	Osteoid thickness (µm)			**Osteoid volume (%)**			**Mineralization lag time (d)**		
Pt #	BL	Wk 24	**Change**	BL	Wk 24	**Change**	BL	Wk 24	**Change**
01-01	14.6	13.0	**-1.6**	15.0	11.5	**-3.5**	125	114	**-11**
01-02	11.5	5.8	**-5.7**	7.2	3.0	**-4.2**	30	33	**+3**
01-03	18.5	9.3	**-9.2**	23.7	8.2	**-15.5**	225	58	**-167**
01-05	11.4	5.9	**-5.5**	7.4	4.5	**-2.9**	77	17	**-61**
01-06	16.5	10.6	**-5.9**	14.6	6.2	**-8.4**	33	35	**+2**
01-08	15.3	22.4	**+7.1**	13.9	28.1	**+14.2**	87	750	**+663**
01-09	11.9	7.2	**-4.7**	17.5	4.2	**-13.3**	25	37	**+12**
02-01	15.0	9.2	**-5.8**	9.9	8.3	**-1.6**	103	37	**-65**
Median	**14.8**	**9.2**	**-5.6**	**14.3**	**7.2**	**-7.1**	**82**	**37**	**-45**
Source: ADBONE									

Reviewer comment: *These biopsy data (from 8 juvenile-onset HPP patients, and the 5 infantile-onset patients discussed above) were previously reviewed by Dr. Marcea Whitaker (DBRUP consult, DARRTS 8/29/13) and considered to represent a positive effect of asfotase alfa on osteomalacia at 6 months, in both infantile- and juvenile-onset HPP. Although there are no biopsy data on untreated patients, osteoid reduction as seen in 11/12 HPP patients does not in general occur spontaneously in untreated osteomalacic patients. Significance of the one patient who had apparent worsening on biopsy is unclear in light of his radiographic and clinical improvement. Regarding the lack of improvement in dynamic parameters of mineralization such as mineralization lag time and mineralizing surface/ bone surface (MS/BS), it was concluded that 24 weeks was likely too short a time period to demonstrate such effects.*

Reference ID: 3733103

DXA of whole body, lumbar spine and hip was conducted in studies ENB-006-09/008-10. (No DXA data on the untreated controls are available.) Whole body mean BMC and BMD in the 8 juvenile onset patients were 610 g and 0.712 g/cm^2 respectively at baseline, and increased during treatment:

Whole body BMC and BMD (DXA) in juvenile onset HPP treated with asfotase alfa (ENB-006/09/008-10)

	BMC Mean change from baseline (range)	**BMC Mean percent change** (range)	**BMD Mean change from baseline** (range)	**BMD Mean percent change** (range)
Week 24 n=8	**84** (42, 168)	**14.1** (5.3, 22.5)	**0.012** (-0.010, 0.031)	**1.7** (-1.3, 5.0)
Week 72 n=8	**232** (87, 569)	**39.2** (11,4, 70.9)	**0.070** (0.010, 0.172)	**10.2** (1.3, 27.6)
Week 96 n=8	**312** (185, 700)	**52.8** (24.2, 87.2)	**0.071** (-0.004, 0.187)	**10.3** (-0.6, 30.0)
Week 120 n=6	**456** (277, 838)	**78.0** (31.0, 104.4)	**0.042** (-0.044, 0.150)	**5.7** (-5.9, 19.7)
Week 144 n=6	**501** (286, 1000)	**77.6** (37.4, 124.6)	**0.106** (0.007, 0.218)	**15.2** (1.0, 35.0)
Week 168 n=5	**454** (361, 611)	**88.7** (47.2, 109.5)	**0.061** (-0.045, 0.192)	**9.3** (-6.1, 30.8)
Week 192 n=7	**565** (368, 1117)	**95.7** (48.1, 139.1)	**0.103** (-0.003, 0.239)	**14.7** (-0.4, 31.4)
Week 216 n=1	**497** (497, 497)	**112.3** (112.3, 112.3)	**0.029** (0.029, 0.029)	**3.9** (3.9, 3.9)
Source: ISE Table 2.2.13.1.1, ADBONE				

Reviewer comment: *As noted above, Z-scores were not reported for most of the whole body or hip BMD data, which makes the findings difficult to interpret. Lumbar spine Z-scores were reported: mean Z-score at baseline was -2.4 SD and changes from baseline were all >0 for 6/8 patients, including patient #01-08 who, despite the unfavorable histomorphometric changes related to mineralization, actually had increase in spine Z-score >1 at most points.*

Lumbar spine BMD Z-scores (DXA) in juvenile onset HPP treated with asfotase alfa (ENB-006/09/008-10)

		Z-score change from baseline	
	n	Mean	Range
Week 24	8	0.8	-0.6, 1.6
Week 72	8	1.0	-0.6, 1.7
Week 96	8	0.8	-0.5, 1.3
Week 120	6	0.9	-0.8, 1.8
Week 144	6	0.4	-0.8, 1.6
Week 168	4	0.8	-0.8, 1.8
Week 192	7	0.9	-0.8, 1.9
Week 216	2	1.3	0.9, 1.7
Source: ADBONE			

Reference ID: 3733103

Analyses of correlation of the various bone related endpoints was previously provided by the sponsor (tables below). The radiographic indices (RGI-C and RSS) correlate significantly with each other and with height, weight and functional measures. Osteoid thickness and volume correlated moderately with RSS but not well with RGI-C or height. The sponsor cites the positive correlations to support their use of RSS and RGI-C as efficacy endpoints.

Correlation of Rickets Scoring Methods (RSS and RGI-C) With Other Disease Variables

	Pearson Correlation Coefficient/P value					
	RSS (baseline+post)			RGI-C (all post)*		
Parameter	N	Pearson Correlation/ P value	Figure	N	Pearson Correlation/ P value	Figure
Osteoid Volume/Bone Volume % healthy mean	24	0.418/P=0.0423	14	12	-0.015/P=0.9643	15b
Osteoid thickness % healthy mean	24	0.429/P=0.0364	3	12	-0.217/P=0.4971	12b
Height z-score	119	-0.729/P<0.0001	18	108	0.261/P=0.0065	16c
Weight z-score	132	-0.693/P<0.0001	29	121	0.418/P<0.0001	27c
6MWT	109	-0.661/P<0.0001	7	100	0.284/P=0.0043	42c
BOT-2 shuttle run	110	0.666/P<0.0001	9	99	-0.441/P<0.0001	43c
PODCI Parent Normative Global Functioning Scale	96	-0.750/P<0.0001	48b	84	0.595/P<0.0001	45c
CHAQ Disability Index	96	0.654/P<0.0001	49b	84	-0.589/P<0.0001	46c

*Correlations with RGI-C are based on change from baseline.
6MWT = Six Minute Walk Test; BOT-2 = Bruininks-Oseretsky Test of Motor Proficiency, Second Edition; CHAQ = Childhood Health Assessment Questionnaire; PODCI = Pediatric Outcomes Data Collection Instrument; RGI-G = Radiographic Global Impression of Change; RSS = Rickets Severity Scale.

Correlation of Height with Bone Mineralization, 6MWT, BOT-2, PODCI, and CHAQ (Studies ENB-006-09/ENB-008-10)

	Pearson Correlation Coefficient/P value		
	Height z-score (baseline+post)		
Parameter	N	Pearson Correlation/ P value	Appendix 2 Figure
Osteoid Volume/Bone Volume % healthy mean	24	-0.188/ P=0.3786	22
Osteoid thickness % healthy mean	24	-0.063/ P=0.7686	20
6MWT	111	0.522/P<0.0001	24
BOT-2 shuttle run	109	-0.320/P=0.0007	26
PODCI Parent Normative Global Functioning Scale	96	0.399/P<0.0001	51b
CHAQ Disability Index	96	-0.491/P<0.0001	52b

6MWT = Six Minute Walk Test; BOT-2 = Bruininks-Oseretsky Test of Motor Proficiency, Second Edition; CHAQ = Childhood Health Assessment Questionnaire; PODCI = Pediatric Outcomes Data Collection Instrument.

Source: IND 100619, meeting package dated 10/31/13, pp. 86 and 41 respectively

Reviewer comment: *Among the efficacy variables, the biopsy-based measures correlated the least well with the others; there are several possible reasons for this. Osteoid indices had relatively few datapoints, particularly for RGI-C (n=12) because it measures changes over time. Histomorphometric data are less reproducible than other measures such as height and weight; in a study of 8 healthy children with paired biopsies from adjacent bone locations, the precision errors (% CV) of osteoid thickness and osteoid volume (OV/BV) were 11.5% and 20.6% respectively.*[1] *It is also possible that HPP-related osteomalacia (measured by osteoid thickness and volume) and rickets (represented by radiographic findings, growth, and possibly the functional endpoints)*

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may respond differently to treatment. This is plausible because mineralization of osteoid (bone modeling or remodeling), and of physeal cartilage (endochondral ossification) are different processes. As an example, early treatments for children with X-linked hypophosphatemia using phosphate supplements and pharmacologic doses of vitamin D were effective in reversing radiographic signs of rickets, but did not heal the coexistent osteomalacia, and did not appear to prevent recurrent fractures or abnormal bone healing after surgery.[2,3]

HPP patients >12 y/o at enrollment

Study ENB-009-10 has enrolled 19 adolescent (>12 y/o) and adult patients with HPP, regardless of age at onset. The sponsor considers this a supportive study and did not incorporate the data with those from the other studies described above, in part because the patients were more heterogeneous and the asfotase alfa doses used were lower. The sponsor is not seeking an indication for adult onset HPP.

Enrollment criteria: Adolescent (>12 y/o) and adult patients with HPP (at any age of symptom onset), "evidence of osteopenia or osteomalacia on skeletal radiographs", osteomalacia on biopsy (Mlt Z-score of ≥ +2), and no bisphosphonate use within 2 years.

Dosing regimens: During the initial 24-week period, patients are randomized to one of two asfotase alfa regimens (2.1 mg/kg/wk or 3.5 mg/kg/wk) or no treatment. After week 24 all patients are eligible for the extension phase with asfotase alfa (3.5 mg/kg/wk for ~24 wk then 6 mg/kg/wk). Thus, doses in the asfotase alfa groups for the first 48 weeks were lower than in the other studies with younger patients. All assignments/ treatments were open label.

Demographics and Baseline Characteristics: Mean age of the 19 patients was 40.9 y/o (range 13-66 y/o). Most patients were white (18/19), female (12/19), and were adults ≥18 y/o (13/19). Among the 6 adolescents, 3 were Tanner stage 4, 1 was Tanner stage 1, and 2 were Tanner stage unknown. Age at symptom onset ranged from 0-36 years with a mean of 4.9 years. By age at HPP symptom onset they are classified as infantile onset (n=4), juvenile onset (n=12), adult onset (n=2) and undetermined (age of onset unknown, n=1). The adolescent patients were equally split between infantile and juvenile onset (n=3 each). At baseline, 18/19 patients had experienced bone pain severe enough to limit activity; 18/19 had a history of fractures; 16/19 required analgesics for severe bone pain; 15/19 had unusual gait; 10/19 had pseudofractures; 9/19 had knock-knees; 8/19 had bowing of the legs; 8/19 had an abnormally shaped head.

Disposition: As of the analysis cutoff date, all 19 patients had completed at least 48 weeks of treatment.

Bone Biopsies were performed at baseline and week 48 for patients randomized to asfotase alfa, and at baseline and week 24 for patients randomized to untreated control in the initial 24-week period. At baseline, most adolescent and adult patients had increased osteoid and prolonged mineralization lag time consistent with osteomalacia (see table below). Following treatment, median change in osteoid thickness and volume % were

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similar between treatment and control groups. . Mineralization lag time (Mlt), and changes thereof, were highly variable; most asfotase-treated patients showed declines (i.e. improvement), but one patient with no baseline had an Mlt of 1444 at week 48 of treatment. Of the 6 adolescent patients, only 2 were treated with asfotase alfa and had a post-baseline biopsy (#02-01 and 02-03); these patients showed no change to worsening of osteoid indices, though perhaps improvement in Mlt.

Mineralization indices in adolescent/adult patients (Study ENB-009-10)

	Osteoid thickness (µm)			**Osteoid volume (%)**			**Mineralization lag time (d)**		
Pt #	BL	Wk 24/48*	**Change**	BL	Wk 24/48*	**Change**	BL	Wk 24/48*	**Change**
Control group									
01-04	10.9	9.6	**-1.3**	13.9	12.9	**-1.0**	-	63.9	**-**
01-05**	14.8	25.4	**+10.6**	18.7	26.6	**+7.9**	31.5	266.2	**+234.7**
01-09**	14.3	9.4	**-3.9**	12.5	10.3	**-2.2**	92.6	158.1	**+65.5**
02-02**	13.4	7.4	**-6.0**	10.8	5.7	**-5.1**	95.5	56.4	**-39.1**
03-04	11.9	7.4	**-4.5**	7.5	5.3	**-2.2**	271.2	527.3	**+256.1**
05-05	10.8	10.0	**-0.8**	6.2	10.0	**+3.8**	640.1	515.2	**-124.9**
Median	**12.6**	**9.5**	**-2.6**	**11.7**	**10.1**	**-1.6**	**95.5**	**212.1**	**+65.5**
Asfotase alfa 2.1 mg/kg/wk									
01-03	9.4	4.4	**-5.0**	2.6	1.1	**-1.5**	-	-	**-**
01-08**	6.4	-	**-**	2.6	-	**-**	44.4	-	**-**
01-10	4.7	4.3	**-0.4**	2.4	5.5	**+3.1**	96.9	170.7	**+73.8**
02-01**	7.3	14.1	**+6.8**	5.3	12.3	**+7.0**	240.6	142.4	**-98.2**
03-03	18.3	18.6	**+0.3**	13.9	13.7	**-0.2**	-	-	**-**
03-06	8.7	7.4	**-1.3**	7.6	6.6	**-1.0**	3277	485	**-2792**
03-07	9.8	8.3	**-1.6**	11.2	11.2	**0.0**	1333	517	**-816**
Median	**8.4**	**7.9**	**-0.8**	**5.3**	**8.9**	**-0.1**	**240.6**	**329.7**	**-457.1**
Asfotase alfa 3.5 mg/kg/wk									
01-01	18.4	13.5	**-4.9**	12.7	6.5	**-6.2**	-	1444	**-**
01-06	4.8	5.6	**+0.8**	4.0	3.1	**-0.9**	174.5	34.7	**-139.8**
01-11	10.1	7.3	**-2.8**	4.9	2.8	**-2.1**	457.5	96.0	**-361.5**
02-03**	8.1	9.1	**+1.0**	6.3	6.1	**-0.2**	114.8	45.6	**-69.2**
03-01	8.4	5.8	**-2.6**	8.2	3.0	**-5.2**	364.3	379.4	**+15.1**
03-02	4.4	3.8	**-0.6**	3.1	0.8	**-2.3**	177.8	98.4	**-79.4**
Median	**8.2**	**6.5**	**-1.6**	**5.6**	**3.0**	**-2.2**	**177.8**	**97.2**	**-79.4**

*Week 24 for control group; week 48 for asfotase alfa groups
**indicates adolescent patient; respective ages are 13 yr (pt #01-05);14 yr (#01-09); 16 yr (#02-02); 16 yr (#01-08); 14 yr (#02-01); 15 yr (#02-03); the remaining patients were adults (≥ 18 y/o)
Source: ENB-009-10 CSR Listing 16.2.6.2.1

Reviewer comment: *Unlike biopsy results from children with HPP (study 006-09, see above), these results do little to support efficacy of asfotase alfa in treating osteomalacia. However, most of the patients were adults, therefore not directly relevant to the indication sought; data from the two treated adolescents were inconclusive. Also as noted by the sponsor, the doses used in this study (2.1-3.5 mg/kg/wk) were lower than doses prior to the week-24 biopsy in the other study (6-9 mg/kg/wk), and lower than the intended marketing dose (6 mg/kg/wk).*

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DXA: Whole body BMD was confounded by the presence of fracture fixation hardware in many patients. Total hip and lumbar spine BMD mostly increased during treatment in the 6 adolescent patients, with no consistent trend in Z-scores (table below). Most of the adult patients showed small increases in hip and spine BMD (not shown).

Table 40: Bone Mineral Density and z-score Assessed Using DEXA in Adolescent Patients

Patient Number	009-01-05	009-01-09	009-02-02	009-02-01	009-01-08	009-02-03
Dose Group [a]	**Control[b]**	**Control**	**Control**	**0.3 mg/kg**	**0.3 mg/kg**	**0.5 mg/kg**
Total Hip BMD, g/cm^2 (z-score)						
Baseline	NA	0.461 (NA)	0.622 (NA)	0.685 (NA)	0.986 (NA)	0.823 (NA)
Week 24	NA	0.464 (NA)	0.658 (NA)	0.694 (NA)	1.145 (NA)	0.870 (NA)
Week 48	NA	0.412 (NA)	0.727 (NA)	0.704 (NA)	NA	0.847 (NA)
Week 72	0.200 (-6.1)	0.493 (NA)	0.714 (-2.4)	0.675 (-2.4)	NA	0.912 (-0.9)
Week 96	0.206 (-5.4)	0.536 (-4.0)	1.748[c] (4.9)	0.685 (-2.3)	0.986 (NA)	0.973 (-0.4)
Lumbar Spine BMD, g/cm^2 (z-score)						
Baseline	NA	682[d] (-2.4)	0.673 (-2.3)	0.640 (-2.8)	0.974 (-0.3)	0.767 (-1.3)
Week 24	NA	0.692 (-2.5)	0.658 (-2.6)	0.683 (-2.5)	1.012 (-0.0)	0.800 (-1.2)
Week 48	NA	0.708 (-2.6)	0.730 (-2.2)	0.688 (-2.6)	NA	0.826 (-1.2)
Week 72	NA	0.846 (-1.5)	0.803 (-2.0)	0.669 (-3.5)	NA	0.874 (-1.2)
Week 96	NA	0.864 (-1.0)	0.843 (-1.8)	0.704 (-3.2)	1.032 (0.1)	0.882 (-1.2)
Week 120	NA	NA	NA	NA	NA	NA

BMD = Bone mineral density; NA = not available.

[a] Dose group is the treatment assignment at randomization.

[b] This patient did not have DEXA assessments; a waiver was granted because the patient was multidrug-resistant staphylococcus aureus positive (Listing 16.2.6.2.3)

[c] There is no record of this patient having hardware installed in the femur between visit Weeks 72 and 96; it is possible that is an erroneous value.

[d] "682" was the value recorded in Listing 16.2.6.2.3 and was a data error; 0.682 g/cm^2 is the correct value. This error will be corrected in the final CSR.

Source: Listing 16.2.6.2.3

Source: ENB-009-10 CSR

Radiographic: The 6 adolescent patients in the study underwent radiographic assessments of rickets. Patients 01-08 and 02-01 had closed growth plates so were ineligible for RSS, and patient 02-03 had RSS=0 at baseline which was not reassessed at later points, therefore the only RSS data are on the 3 control patients in table 44 below, who began asfotase treatment at week 24 and showed minimal declines in RSS. RGI-C scores (table 45 below) showed slight improvements on treatment.

Table 44: By-patient Listing of Rickets Severity Scale (RSS) Findings in Adolescent Patients by Study Visit – Full Analysis Set

Patient Number	Baseline/ PTP	Week 24/ PTP	Week 48/ ETP	Week 72/ ETP	Week 96/ ETP
009-01-05	8.50	7.50	6.50	6.00	6.00
009-01-09	5.50	5.50	4.50	4.50	5.00
009-02-02	3.00	1.50	1.00	1.50	NA

ETP = extension treatment period; NA = not available; PTP = primary treatment period.

Note: RSS scores at Week 24 are prior to study drug administration; Week 48 represents 24 weeks of asfotase alfa treatment; Week 72 represents 48 weeks of asfotase alfa treatment; Week 96 represents 72 weeks of asfotase alfa treatment

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Table 45: Radiographic Global Impression of Change (RGI-C) by Study Visit – Average Reader Scores in Adolescent Patients – Full Analysis Set

Patient Number	Week 24	Week 48	Week 72	Week 96
Control Group				
009-01-05	1.00	0.67	1.00	1.00
009-01-09	1.00	0.33	0.33	1.67
009-02-02	1.00	1.33	1.33	1.67
Asfotase Alfa 0.3 mg/kg				
009-01-08	0.33	0.33	0.33	0.33
009-02-01	0	0	0	0.33
Asfotase Alfa 0.5 mg/kg				
009-02-03	0.33	1.00	0.33	0.67

Note: For patients in the control group, RGI-C scores at Week 24 are prior to study drug administration; Week 48 represents 24 weeks of asfotase alfa treatment; Week 72 represents 48 weeks of asfotase alfa treatment; Week 96 represents 72 weeks of asfotase alfa treatment

Note – Values represent the average reader score based upon 3 individual radiologists assessments

Source: Study ENB-009-10 CSR pp. 127-8

Summary and conclusions

Children with infantile- and juvenile-onset HPP, treated with asfotase alfa starting at age ≤ 12 y/o, exhibited improvement in bone-related endpoints. Paired bone biopsies showed decreases at 24 weeks in osteoid thickness and volume in 11/12 children. Although there were no biopsy data from untreated controls for comparison, clinical experience is that such changes do not generally occur spontaneously in patients with untreated mineralization disorders. Radiographic indices of rickets (RGI-C and RSS) indicated improvements in nearly all children (both infantile- or juvenile-onset), which exceeded improvements in all but a few untreated control patients (with caveats that radiographic controls were age ≥5 y/o and had somewhat milder severity of rickets). Radiographic findings (RSS but not RGI-C) correlated moderately with the limited quantity of biopsy data, and both RSS and RGI-C correlated well with height, an important measure of bone health in children. In the long term, these changes would be expected to continue to improve growth and decrease deformities and disability. BMD and BMC are not generally used to evaluate osteomalacia and rickets, and the limited DXA data were inconclusive.

Compared to younger children, the number of treated adolescents is smaller, and the bone related data less consistent: paired biopsies in 2 treated adolescents did not show improvement in osteomalacia, and radiographic indices in 6 adolescents showed minimal positive changes during treatment, less than in younger children. Biopsies in adults (who mostly had juvenile onset HPP) also showed no clear evidence of improvement. The adolescent/adult study used small, possibly suboptimal doses. Thus, it is uncertain whether there is significant skeletal benefit (reduced osteomalacia and fracture risk) to patients from continuing (or initiating) treatment with asfotase alfa beyond epiphyseal closure.

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