CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

BLA #:	BLA 125513
Drug Name:	STRENSIQ™ (asfotase alfa) 2 mg/kg of body weight administered subcutaneously three times per week or 1 mg/kg of body weight administered subcutaneously six times per week
Indication(s):	Treatment of Patients with Perinatal/Infantile- and Juvenile-onset Hypophosphatasia (HPP)
Applicant:	Alexion Pharmaceuticals, Inc.
Date(s):	Stamp Date: December 23, 2014 PDUFA Goal Date: November 23, 2015
Review Priority:	Original Biologic with Priority Review under the PDUFA V Program (3-month extension due to Major Amendment)
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Medical Division:	Division of Gastroenterology and Inborn Errors Products (DGIEP)
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Keywords: BLA review, Clinical Studies

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1 EXECUTIVE SUMMARY

The applicant submitted the results from the ENB-002-08/ENB-003-08 and ENB-010-10 trials, in addition to the ENB-011-10 natural history study, to support the efficacy claim of STRENSIQ™ (asfotase alfa), (b) (4) for the treatment of perinatal/infantile-onset Hypophosphatasia (HPP). In the agreed upon analyses combining infants from the ENB-002-08/ENB-003-08 and ENB-010-10 studies, asfotase alfa was demonstrated to be superior, although in an exploratory context, to an acceptable historical control group, extracted from retrospective natural history study ENB-011-10, with respect to overall survival and invasive ventilator-free survival. The applicant also submitted the results from the ENB-006-09/ENB-008-10 trial, in addition to the ALX-HPP-502 natural history study, to support the efficacy claim of asfotase alfa for the treatment of juvenile-onset HPP. Product approval for the juvenile-onset HPP patient population will be determined on the totality of descriptive data adjudicated by the clinical review team, with growth being the chief clinical parameter while HPP-related rickets, the 6 Minute Walk Test (6MWT), and gait all being supportive clinical parameters. Overall, the descriptive analysis results of growth presented within this review document suggests that asfotase alfa is providing some desired therapeutic effect.

For perinatal/infantile-onset HPP, there appears to be sufficient evidence in supporting the proposed efficacy claims for asfotase alfa. As noted in the body of this review document, all hypothesis testing should be considered exploratory given that the agreed upon endpoints (i.e., overall survival and invasive ventilator-free survival), planned data integrations, and subsequent historical control comparisons could only be determined during the execution of the relevant perinatal/infantile-onset HPP studies. Consequently, all presented inferential statistics (e.g., p-values) within this review document are considered supportive (i.e., not confirmatory), and therefore no inferential statistics should be presented within the final product labeling. Conversely, the evidence in supporting the proposed efficacy claims for asfotase alfa in the treatment of juvenile-onset HPP is weak from a statistical perspective; hence the clinical review team will determine the sufficiency of this evidence from a clinical perspective.

Given the rare nature of perinatal/infantile-onset HPP, the agreed upon approach/analyses combining infants being administered asfotase alfa from the ENB-002-08/ENB-003-08 and ENB-010-10 studies and subsequently comparing these pooled patients, in regards to overall survival and invasive ventilator-free survival, with baseline matched infants from the ENB-011-10 natural history study (which acted as a historical control group) were ultimately deemed reasonable from a statistical perspective. The design of these individual clinical studies, in addition to the protocol for extracting comparable retrospective natural history data to be utilized as a historical control, was considered acceptable. However, even considering the more rare nature of juvenile-onset HPP, the exploratory analysis pertaining to growth along with all descriptive analyses presented within the clinical review document comparing juvenile patients being administered asfotase alfa from the ENB-006-09/ENB-008-10 study with baseline matched patients from the ALX-HPP-502 natural history study (which acted as a historical control group) were not deemed as the ideal trial design and analysis approach from a statistical perspective. The design of this individual clinical study, in addition to the protocol for extracting comparable

retrospective natural history data to be utilized as a historical control, was considered acceptable. However, relative to an adequate and well-controlled study, which was feasible in this HPP patient population, the use of a historical control presented a weaker level of evidence.

For both HPP populations (i.e., perinatal/infantile- and juvenile-onset), it should be noted that comparisons to a historical control group are not considered to provide results that are as robust or reliable as those from comparisons within a randomized controlled study. Even when there is an observed balance between the non-concurrent groups in regards to identified baseline characteristics/covariates, there may be confounding due to baseline imbalances in latent variables, which can influence outcome to therapy. This potential introduction of bias results from not having a randomization mechanism. In addition, the retrospective nature of both natural history studies introduces the potential for selection bias, i.e., patients ultimately chosen for both historical control groups may be those that result in an overly optimistic estimate of efficacy when comparisons are made to the corresponding treated patients. Both of these issues are further magnified when operating with very small sample sizes, which is the case for both HPP patient populations. Generally speaking, due to the scarcity of this disease population overall, the limitations of the studies, and the post-hoc analysis approaches espoused for both HPP patient populations, the determination of the clinical effectiveness of asfotase alfa will rely more on clinical judgment than on the statistical rigor usually required for larger randomized controlled studies.

2 INTRODUCTION

2.1 Overview

On March 31, 2014, Alexion Pharmaceuticals, Inc. initiated the filing of this Biologics Licensing Application (BLA) for STRENSIQ™ (asfotase alfa) in accordance with Section 351(a) of the Public Health Service Act and Title 21 of the Code of Federal Regulations (CFR), Part 601.2. The active pharmaceutical ingredient (API) of asfotase alfa [2 mg/kg of body weight administered subcutaneously (SC) three times per week, with a maximum injection volume of 1 milliliter (mL), or a dosage regimen of 1 mg/kg of body weight administered six times per week] is human recombinant tissue-nonspecific alkaline phosphatase-Fc-deca-aspartate fusion protein. Effective on July 3, 2008, Enobia Pharmaceuticals, Inc. initiated clinical development of asfotase alfa, under IND 100,619, as a (b) (4) in patients with perinatal/infantile- and juvenile-onset HPP, which is the proposed indication. On February 7, 2012, the Division of Gastroenterology and Inborn Errors Products (DGIEP) was notified by Alexion that they had acquired Enobia to continue the development of asfotase alfa.

HPP is a rare, inherited metabolic serious and life-threatening disease, which is caused by mutations in the gene encoding a specific form of the enzyme alkaline phosphatase called tissue non-specific alkaline phosphatase (TNSALP). Approximately 1 in 100,000 people (hence about 3,200 people total in the United States) is afflicted with this condition worldwide. These genetic mutations lead to the primary biochemical defect in HPP, which is a deficiency of TNSALP enzymatic activity altogether. TNSALP is essential for regulating the phosphate levels in

various metabolites that are critical for normal bone formation, and also for brain and muscle function. The loss of this alkaline phosphatase activity leads to a wide variety of physical ailments which are primarily manifested as bone mineralization defects as well as other systemic defects including inadequate respiratory function, seizures, and muscle weakness.

Classifications of HPP have generally taken into account the age at onset of the first signs and/or symptoms of the disease, dividing the disease into perinatal, infantile, childhood (juvenile), and adult forms (see the following table).

Disease Form	**Age at Onset of First Signs/Symptoms**
Perinatal	In Utero
Infantile	< 6 months of age
Childhood (Juvenile)	≥ 6 months to ≤ 18 year of age
Adult	> 18 years of age

Disease severity in HPP is generally inversely related to the age of onset while significant morbidity is seen in HPP patients at all ages. In patients with perinatal-onset HPP, signs manifest in utero and the disease is usually lethal. Mortality in newborn patients with perinatal HPP is considered to be 100%. Both aborted fetuses and newborns are grossly abnormal. Radiographic examination may reveal almost total absence of bony structures due to hypomineralization (i.e., little to no mineralization/solidifying of the bones). Patients with perinatal HPP have life threatening disease and death generally results from respiratory insufficiency. Patients with infantile-onset HPP may appear normal at birth but may later present with failure to thrive due to vomiting and/or respiratory failure within the first 6 months of post-natal life. Similar to perinatal HPP, radiographic examination reveals skeletal hypomineralization and rickets (i.e., softening of the bones). Mortality in infantile-onset HPP, usually due to pulmonary complications caused by rib fractures and rachitic deformity (i.e., deformities due to rickets) of the rib cage, is estimated to be as high as 50%. Overall, the perinatal/infantile-onset patient population presents disease symptoms which are homogenous in nature.

Patients with juvenile-onset HPP show signs and symptoms after 6 months of age and up to 18 years of age. These symptoms are heterogeneous in nature and are far less progressive relative to those associated with the perinatal/infantile-onset patient population. Rachitic deformities and enlargement of the wrists, knees, and ankles are common, resulting in short stature in some patients. Typically, patients also have muscle weakness (especially the thighs) and thus walking and other physical milestone acquisitions are frequently delayed. Patients may complain of skeletal pain and stiffness as well as isolated episodes of joint pain and swelling. Patients with adult-onset HPP show signs and symptoms after 18 years of age, and these patients have muscle and skeletal weakness and pain due to rachitic deformities. It should be noted that the applicant did not pursue treatment of the adult-onset patient population within this application.

There are currently no approved treatments for HPP thereby resulting in an unmet medical need. Previous attempts at restoring bone mineralization as a treatment for HPP have had very limited to no success. To date, management of HPP has been essentially symptomatic or orthopedic.

However, these symptomatic treatments are not meant or expected to impact the course of the disease. Asfotase alfa is an ERT designed to address this genetic deficiency by targeting/delivering another form of alkaline phosphatase, known as functional alkaline phosphatase, directly to the affected patient tissues. In this way, asfotase alfa, as hypothesized by the applicant, will counter the genetically defective metabolic process and prevent or reverse the severe and life-threatening consequences of deregulated calcium and phosphate metabolism in patients with HPP. Asfotase alfa is a clear, colorless, aqueous solution supplied in single-use 2 mL glass vials.

The applicant obtained *Orphan Designation* from the Office or Orphan Products Development (OOPD) on September 12, 2008. There is also a pending request for *Rare Pediatric Disease Designation*, which OOPD did approve during this BLA review cycle. Alexion also obtained *Fast Track Designation* from DGIEP on May 14, 2009. Consequently, DGIEP has agreed to receive the BLA on a rolling basis with the final component of the BLA having been submitted on December 23, 2014. *Breakthrough Therapy Designation* was also granted by DGIEP on May 21, 2013. A priority 8-month review cycle was expected under the Prescription Drug User Fee Act (PDUFA) V Program; however, a major amendment due to many additional information requests by multiple scientific review teams increased the review cycle timeline by an additional three months. Consequently the revised PDUFA goal date is November 23, 2015.

For HPP, the regulatory pathway is for full approval under 21 CFR Part 601 utilizing primarily overall survival data in the perinatal/infantile-onset patients and growth in the juvenile-onset patients. There are many small trials in Alexion's asfotase alfa development program that are to be used as the basis for granting full approval. The asfotase alfa clinical development program includes a total of nine ongoing or completed clinical studies consisting of the following:

- One interventional trial (i.e., study ENB-001-08) to assess the safety and tolerability of asfotase alfa;
- Six interventional trials (i.e., studies ENB-002-08/ENB-003-08, ENB-010-10, ENB-006-09/ENB-008-10, and ENB-009-10) conducted to demonstrate the safety and efficacy for perinatal/infantile-onset and juvenile-onset HPP patients;
- Two non-interventional retrospective natural history studies (i.e., studies ENB-011-10 and ALX-HPP-502) separately in patients with perinatal/infantile-onset and juvenile-onset HPP, respectively.

Table 1 below presents information on the seven relevant trials (does not include studies ENB-001-08 and ENB-009-10) contained in this submission.

Table 1
Summary Information for Relevant Clinical Trials

Type of Study; Phase	Study Identifier	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Regimen; Route	Number of Patients	Patient Diagnosis	Duration of Treatment
Safety and Efficacy; Phase 2	ENB-002-08/ ENB-003-08	Efficacy, Safety, Pharmacokinetics (PK)	Multinational, Multicenter, Open-label, Single-arm	Asfotase Alfa; One 2 mg/kg infusion followed by 1 mg/kg/day SC injections 3 times per week with escalation up to 3mg/kg/day; SC injection	Total: 11	Perinatal/Infantile-onset HPP	24 weeks (ENB-002-08) with additional long term extension up to 5 years (ENB-003-08)
Safety and Efficacy; Phase 2	ENB-010-10	Efficacy, Safety, PK	Multinational, Multicenter, Open-label, Single-arm	Asfotase Alfa; 6 mg/kg/week administered as either 1 mg/kg 6 times per week or 2 mg/kg 3 times per week by SC injection; SC injection	Total: 59	Perinatal/Infantile-onset HPP	4 years
Natural History	ENB-011-10	Retrospective chart review of patients with perinatal/infantile-onset HPP	Observational, Natural History, Non-interventional	N/A	Total: 48	Perinatal/Infantile-onset HPP	N/A

Source: Reviewer's Table from applicant's tabular listing of all clinical studies (i.e., Module 5.2 from eCTD sequence 0006).

Summary Information for Relevant Clinical Trials (Continued)

Type of Study; Phase	Study Identifier	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Regimen; Route	Number of Patients	Patient Diagnosis	Duration of Treatment
Safety and Efficacy; Phase 2	ENB-006-09/ ENB-008-10	Efficacy, Safety, PK	Multinational, Multicenter, Open-label, Randomized, Parallel-dose	Asfotase Alfa; 2 or 3 mg/kg SC asfotase alfa 3 times per week (i.e., 6 or 9 mg/kg/week); SC injection	Total: 8	Juvenile-onset HPP	24 weeks (ENB-006-09) with additional long term extension up to 3.5 years (ENB-008-10)
Natural History	ALX-HPP-502	Retrospective chart review of patients with juvenile-onset HPP	Observational, Natural History, Non-interventional	N/A	Total: 32	Juvenile-onset HPP	N/A

Source: Reviewer's Table from applicant's tabular listing of all clinical studies (i.e., Module 5.2 from eCTD sequence 0006).

The perinatal/infantile onset population will be assessed through the following studies: ENB-002-08/ENB-003-08 and ENB-010-10. Analyses combining infants (i.e., 68 in total) being administered asfotase alfa from the aforementioned studies will compare these pooled patients, in regards to overall survival and invasive ventilator-free survival, with baseline matched infants from a historical control group (i.e., natural history data for 48 total patients collected retrospectively from chart reviews though natural history study ENB-011-10). The juvenile onset population will be assessed through the ENB-006-09/ENB-008-10 study. Analyses will compare these patients (i.e., eight in total), in regards to growth, with baseline matched juveniles from a historical control group (i.e., natural history data for 32 total patients collected retrospectively from chart reviews though natural history study ALX-HPP-502).

2.2 Data Sources

This BLA was submitted electronically in eCTD format via the FDA Electronic Submissions Gateway (ESG). The content, including the electronic data sets and labeling information, is located in the Center for Drug Evaluation and Research (CDER) electronic document room (EDR) at the location: \\CDSESUB1\evsprod\BLA125513\0006. Sequences 0016, 0019, 0020, 0021, 0024, and 0028 contain all the contents relevant for this review.

The clinical study report (CSR), clinical datasets and analysis datasets were reviewed separately (along with applicable integrations) for the ENB-002-08/ENB-003-08, ENB-010-10, ENB-011-10, ENB-006-09/ENB-008-10, and ALX-HPP-502 studies. For each of these studies (along with the applicable integrations), the clinical/tabulation datasets were compliant to the CDISC/SDTM v.3.1.3 implementation guide standard. The analysis datasets for these studies (along with the applicable integrations) were compliant to the CDISC/ADaM v.1.0 implementation guide standard. Adequate data definition files (in define.xml and define.pdf formats), a study data and analysis data reviewer's guide and software code (in .txt, format) were also submitted for all of these studies and applicable integrations.

Please note that Table 8 in the Appendix summarizes the specific Information Requests (IRs) and teleconferences (TCs) that involved the primary statistical reviewer's major participation and contribution. The primary statistical reviewer continued to assist the clinical review team as needed during the review cycle.

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

3.1.1 ENB-002-08/ENB-003-08 and ENB-010-10 vs. ENB-011-10

The ENB-002-08/ENB-003-08 and ENB-010-10 studies utilized an electronic case report form (eCRF) within an electronic data capture (EDC) system while the ENB-011-10 study utilized patient charts collected retrospectively from appropriately identified study sites. The submitted data quality for all studies appeared to be adequate. It was possible to reproduce the integrated

primary analysis dataset (along with the integrated results presented within the ISE report), specifically both survival endpoint values, from the original data source. All ENB-002-08/ENB-003-08 and ENB-010-10 trial data presented in this written review reflects the updated November 2014 study data cutoff.

3.1.2 ENB-006-09/ENB-008-10 vs. ALX-HPP-502

The ENB-006-09/ENB-008-10 study utilized an eCRF within an EDC system while the ALX-HPP-502 study utilized patient charts collected retrospectively from appropriately identified study sites. The submitted data quality for both studies appeared to be adequate. It was possible to reproduce the integrated primary analysis dataset (along with the integrated results presented within the ISE report), specifically the growth variable values, from the original data source. All ENB-006-09/ENB-008-10 trial data presented in this written review reflects the updated November 2014 study data cutoff.

3.2 Evaluation of Efficacy

3.2.1 ENB-002-08/ENB-003-08 and ENB-010-10 vs. ENB-011-10

The pre-specified primary objectives of the ENB-002-08/ENB-003-08 study were to determine the efficacy (along with safety, long-term tolerability and PK) of asfotase alfa in treating the skeletal manifestations of patients having perinatal/infantile-onset HPP. This was a phase 2, multinational, multicenter, open-label, single-arm, 24-week study (ENB-002-08) with additional long-term extension up to five years (ENB-003-08). Patients were administered one 2 mg/kg infusion followed by SC injections of 1 mg/kg/day three times per week (with escalation up to 3mg/kg/day three times per week). The pre-specified primary objectives of the ENB-010-10 study were also to determine the efficacy (along with safety, tolerability and PK) of asfotase alfa in treating the skeletal manifestations of patients having perinatal/infantile-onset HPP. This was a phase 2, multinational, multicenter, open-label, single-arm, 4-year study. Patients were administered 6 mg/kg/week as either SC injections of 1 mg/kg six times per week or 2 mg/kg three times per week. For the ENB-011-10 study, specified demographic and clinical data from eligible perinatal/infantile-onset HPP patients (i.e., comparable to the cohort from the ENB-002-08/ENB-003-08 study) were extracted through retrospective clinical chart reviews. For any patient alive as of the last chart record reviewed, their physician was contacted to determine the patient's survival status. There was no planned enrollment for any of these studies given the paucity of this patient population; all efforts were made to enroll/extract as many patients as possible. As can be seen below, ultimately 11 and 59 patients were enrolled, treated, and available for analysis for the ENB-002-08/ENB-003-08 and ENB-010-10 studies, respectively. A total of 48 patients were extracted for the ENB-011-10 natural history study.

To determine the efficacy profile of asfotase alfa therapy in perinatal/infantile-onset HPP patients, analyses combining infants being administered asfotase alfa from the aforementioned clinical trials compared these pooled patients, in regards to overall survival and ventilator-free survival, with baseline matched infants from the aforementioned natural history study, which acted as a historical control group. Patients from the ENB-002-08/ENB-003-08 and ENB-010-

10 studies would only be qualified for pooling, and subsequent comparisons, if they met the entry/extraction criteria for natural history study ENB-011-10.

This integrated historical-controlled analysis plan and the following analysis endpoints were agreed upon after negotiations between the applicant and DGIEP during formal face-to-face meetings under IND 100,619 (i.e., Type C meeting on April 16, 2013 and Type B meeting on September 3, 2013).

Primary Endpoint: Time to Death from Birth up to Point of Last Contact (i.e., overall survival)

Secondary Endpoint: Time to Start of Invasive Ventilator Use or Death from Birth up to Point of Last Contact (i.e., invasive ventilator-free survival)

The analysis set used for these integrated efficacy analyses was the set of all qualified enrolled/extracted patients. Adjusting for multiplicity was not applicable given that these integrated analyses and endpoints were determined well into the execution of these studies. From a strict regulatory perspective, these analyses are designated as post-hoc, and hence all hypothesis testing is considered exploratory in nature.

Both time-to-event endpoints were assessed for patients within the combined trials and historical control group. The survival and invasive ventilator-free survival rates (i.e., the percentage of patients who did not experience the event of interest in either context) were assessed for both groups separately. A 95% Confidence Interval (CI), using the Clopper-Pearson method, for each group's survival and invasive ventilator-free survival rates were also calculated by the statistical reviewer.

For each time-to-event endpoint, the analytical methodology compared the median time to event between the patient groups through a standard Kaplan-Meier approach with hypothesis testing utilizing the log-rank test. In addition, a hazard ratio along with a corresponding 95% CI was presented. The proportional hazards assumption was checked by graphically observing log(-log(estimated survival probability) versus log(time in days) for each group. An additional sensitivity analysis, for small sample size purposes, was conducted by the statistical reviewer utilizing the Nelson-Aalen approach in lieu of Kaplan-Meier. To further assess the sensitivity of the results to censored data, the statistical reviewer espoused a "worst-case" imputation strategy for the analyses by designating censored patients at the point of last contact as "failures", i.e., having experienced the event of interest at that censoring time point.

One final sensitivity analysis was conducted by the statistical reviewer pertaining to dosing. Of the qualified pooled patients included in these survival analyses, those patients in studies ENB-002-08/ENB-003-08 and ENB-010-10 who received the proposed labeling dosing regimen of 6 mg/kg/week (i.e., 1 mg/kg/day six times per week or 2 mg/kg/day three times per week) for greater than or equal to one week without dose modifications were separately analyzed in a subsequent subgroup analysis. For this subgroup/sensitivity analysis, patients were excluded from the survival population due to a dosing regimen that was different from the proposed regimen (i.e., 6 mg/kg/week) either through the initial dosing period of the trial or through dose adjustments that were made during trial treatment with asfotase alfa. It should be noted that all

11 patients from the ENB-002-08/ENB-003-08 trial were excluded as this study had an initial dosing regimen of a single 2 mg/kg IV dose followed by 1 mg/kg SC administered three times per week. An additional 11 patients from the ENB-010-10 trial were also excluded for dose adjustments due to an insufficient clinical response, an adverse event, or an initial dosing regimen different from 6 mg/kg/week.

The relevant demographics and baseline characteristics for all pertinent/qualified patients are presented in Table 2 below.

Table 2
Demographic and Baseline Characteristics – ENB-002-08/ENB-003-08 and ENB-010-10 vs. ENB-011-10
(All Qualified Enrolled/Extracted)

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

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

It can be seen from the presented demographic and baseline characteristics that there was an imbalance between the non-concurrent groups regarding geographic region. However, this variable was not considered as critical as the other variables in influencing outcome to therapy.

It should be noted that all the following analysis results presented within this section were generated by the statistical reviewer.

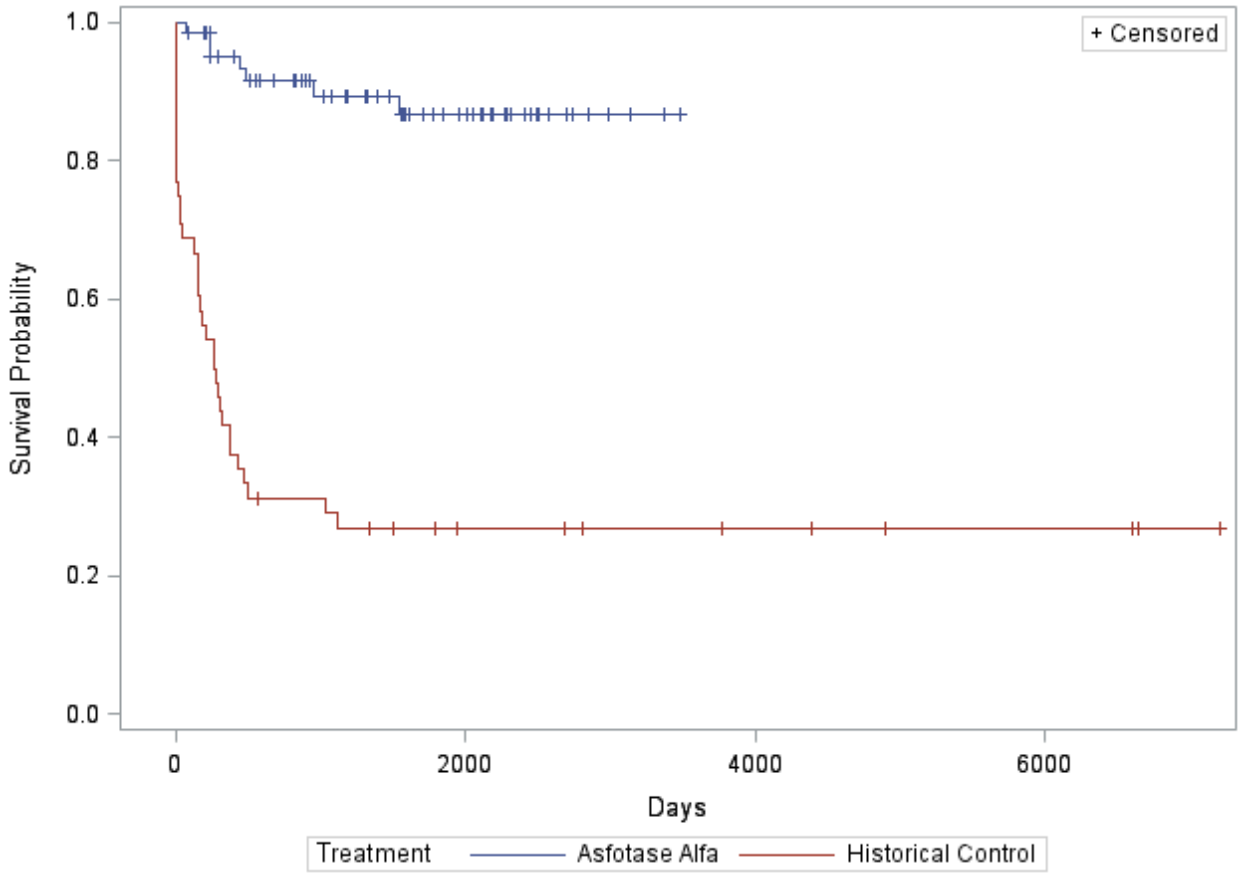
Table 3
Overall Survival – ENB-002-08/ENB-003-08 and ENB-010-10 vs. ENB-011-10
(All Qualified Enrolled/Extracted)

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

Source: Reviewer's Table generated from ISE ADTTE dataset.
Note: Denominators for percentages are N. * denotes censoring.
[1]: Using the Clopper-Pearson method.
[2]: Considered exploratory.

It can be observed from Table 3 above that asfotase alfa showed superiority, in an exploratory context, in the time to death from birth up to the point of last contact when compared to the historical control group. The "worse-case" imputation strategy did not impact the study conclusions. It should be noted that the proportional hazards assumption was deemed appropriate by graphically observing that the log(-log(estimated survival probability) versus log(days) for each group were reasonably parallel to one another. The additional sensitivity analysis conducted by the statistical reviewer utilizing the Nelson-Aalen approach also did not impact the study conclusions. The final sensitivity analysis conducted by the statistical reviewer, which included 46 patients (of the 68 total qualified patients from the original analysis) that received the proposed dosing regimen of 6 mg/kg/week (i.e., 1 mg/kg/day six times per week or 2 mg/kg/day three times per week) without dose modifications, was also consistent with the overall study conclusions. The Kaplan-Meier figure plotting the aforementioned overall data is presented below in Figure 1. These analyses repeated for the time to start of invasive ventilator use or death from birth up to point of last contact follow immediately thereafter.

Figure 1
Overall Survival – ENB-002-08/ENB-003-08 and ENB-010-10 vs. ENB-011-10
(All Qualified Enrolled/Extracted)



Source: Reviewer's Figure using SAS generated from ISE ADTTE dataset.

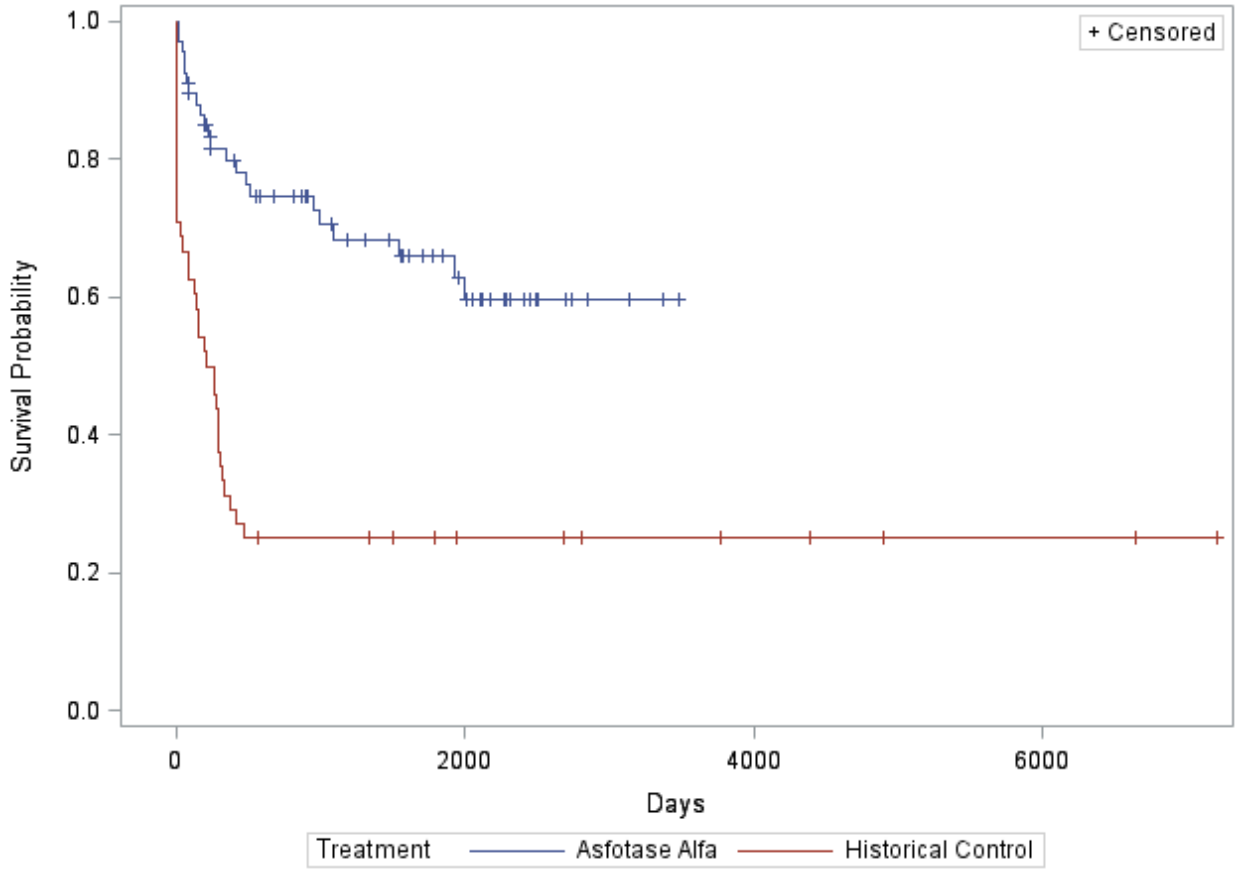
Table 4
Invasive Ventilator-Free Survival – ENB-002-08/ENB-003-08 and ENB-010-10 vs. ENB-011-10
(All Qualified Enrolled/Extracted)

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

Source: Reviewer's Table generated from ISE ADTTE dataset.
Note: Denominators for percentages are N. * denotes censoring.
[1]: Using the Clopper-Pearson method.
[2]: Considered exploratory.

It can be observed from Table 4 above that asfotase alfa showed superiority, in an exploratory context, in the time to start of invasive ventilator use or death from birth up to the point of last contact when compared to the historical control group. The "worse-case" imputation strategy did not impact the study conclusions. It should be noted that the proportional hazards assumption was deemed appropriate by graphically observing that the log(-log(estimated survival probability) versus log(days) for each group were reasonably parallel to one another. The additional sensitivity analysis conducted by the statistical reviewer utilizing the Nelson-Aalen approach also did not impact the study conclusions. The final sensitivity analysis conducted by the statistical reviewer, which included 46 patients (of the 68 total qualified patients from the original analysis) that received the proposed dosing regimen of 6 mg/kg/week (i.e., 1 mg/kg/day six times per week or 2 mg/kg/day three times per week) without dose modifications, was also consistent with the overall study conclusions. The Kaplan-Meier figure plotting the aforementioned overall data is presented below in Figure 2.

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



Source: Reviewer's Figure using SAS generated from ISE ADTTE dataset.

Statistical Reviewer Comments:
Given the rare nature of perinatal/infantile-onset HPP, the agreed upon analyses combining infants being administered asfotase alfa from the ENB-002-08/ENB-003-08 and ENB-010-10 studies and subsequently comparing these pooled patients, in regards to overall survival and invasive ventilator-free survival, with baseline matched infants from the ENB-011-10 natural history study (which acted as a historical control group) were ultimately deemed reasonable from a statistical perspective. The design of these individual clinical studies, in addition to the protocol for extracting comparable retrospective natural history data to be utilized as a historical control, was considered acceptable. It should be emphasized that all hypothesis testing was considered exploratory given that these agreed upon endpoints, planned data integrations, and subsequent historical control comparisons were all determined well into the execution of these relevant studies. Consequently, all previously presented inferential statistics (e.g., p-values) are considered supportive and not confirmatory, and no inferential statistics should be presented within the final product labeling.

In general, utilization of a historical control can be valid if the course of the untreated disease within a patient population is well understood to be uniform with outcomes that can be predicted reliably. In addition, a valid historical control from a natural history study must have the same eligibility requirements, medical workup, and clinical evaluations as the clinical trial, i.e., patients from the natural history study must be adequately matched to patients from the clinical trial in terms of inclusion/exclusion criteria (and thus closely resembling the trial group in all known relevant baseline and observational variables) while also having comparable clinical evaluations in each group. Using a historical control is most likely to be persuasive when the study endpoint is objective and when the outcome on treatment is markedly different from that of the historical control (including a high level of statistical significance in the treatment vs. historical control comparison). Given that perinatal/infantile-onset HPP is homogeneous in its phenotype and expectedly fatal within the first year of life, the acceptable similarity between both patient cohorts in terms of baseline characteristics, the fact that the endpoints pertain to survival (which DGIEP had recommended during asfotase alfa's clinical development program), and the significant difference between the non-concurrent groups for both endpoints, it was deemed by both the clinical and statistical review teams that the historical control group from the ENB-011-10 study was reasonable for comparison to the combined ENB-002-08/ENB-003-08 and ENB-010-10 patient cohort.

It should be noted, however, that comparisons to a historical control group are not considered to provide results that are as robust or reliable as those from comparisons within a randomized controlled study. Even when there is an observed balance between the non-concurrent groups in regards to identified baseline characteristics/covariates, there may be confounding due to baseline imbalances in latent variables, which can unknowingly influence outcome to therapy. This potential introduction of bias results from not having a randomization mechanism. In addition, the retrospective nature of the ENB-011-10 study introduces the potential for selection bias, i.e., patients ultimately chosen for the historical control group may be those that result in an overly optimistic estimate of efficacy when comparisons are made to the treated patients. Both of these issues can be further magnified when operating with very small sample sizes, which is the case for perinatal/infantile-onset HPP. Nevertheless, it was adjudicated that the applicant's due diligence in acquiring all available, and properly comparable, data was sufficient thereby mitigating the aforementioned potential issues.

3.2.2 ENB-006-09/ENB-008-10 vs. ALX-HPP-502

The pre-specified primary objectives of the ENB-006-09/ENB-008-10 study were to determine the efficacy (along with safety, long-term tolerability and PK) of asfotase alfa in treating HPP-related rickets, using an ordinal Radiographic Global Impression of Change (RGI-C) scale score, in patients having juvenile-onset HPP. This was a phase 2, multinational, multicenter, open-label, randomized, parallel-dose, 24-week study (ENB-006-09) with additional long-term extension up to 3.5 years (ENB-008-10). Patients were randomized to receive either 2 mg/kg or 3 mg/kg of asfotase alfa three times per week (i.e., 6 or 9 mg/kg/week) though SC injections. For the ALX-HPP-502 study, specified demographic and clinical data from eligible juvenile-onset HPP patients (i.e., those comparable to the cohort from the ENB-006-09/ENB-008-10 study) were extracted through retrospective clinical chart reviews. There was no planned enrollment for any of these studies given the extreme paucity of this patient population; all

efforts were made to enroll/extract as many patients as possible. As can be seen below, ultimately eight patients were enrolled, treated, and available for analysis for the ENB-006-09/ENB-008-10 study, and a total of 32 patients were extracted for the ALX-HPP-502 natural history study.

To determine the efficacy profile of asfotase alfa therapy in juvenile-onset HPP patients, post-hoc exploratory descriptive analyses were conducted comparing ENB-006-09/ENB-008-10 study patients, in regards to growth and HPP-related rickets, to baseline matched juveniles from the aforementioned natural history study, which acted as a historical control group. This approach was espoused after negotiations between the applicant and DGIEP during formal face-to-face meetings under IND 100,619 (i.e., Type C meeting on April 16, 2013 and Type B meeting on September 3, 2013). The applicant had suggested, and was willing to conduct, clinical trial ENB-014-12, which was designed as a phase 3, multinational, multicenter, randomized, double-blind, placebo-controlled, two-arm, 24-week study of the safety and efficacy of asfotase alfa (at a 6 mg/kg/week dosing regimen) in pediatric patients with juvenile-onset HPP targeting 30 total patients (15 randomized into each arm). Alexion had planned to finalize the design of this trial protocol following the Type B meeting on September 3, 2013, and this study was to be ongoing at BLA filing. However, DGIEP gave the applicant the option to utilize this historical control approach in its stead, suggesting that it could be sufficient for determining clinical benefit in this patient population; Alexion expectedly took this less burdensome option.

The only relevant clinical parameters that were comparable between the ENB-006-09/ENB-008-10 trial (using all eight enrolled/treated patients) and the ALX-HPP-502 natural history study (using all 32 extracted patients) were growth and HPP-related rickets. As stated previously, all comparisons were descriptive and exploratory in nature. One approach for adjudicating growth was to analyze the shift in change from baseline in height z-scores using referenced growth charts from the Centers for Disease Control (CDC) from the year 2000 that were normalized by age and gender; this approach is presented within this review document (note: other descriptive growth analyses using height and weight are presented within the clinical review document). HPP-related rickets were adjudicated using the RGI-C score. Since RGI-C scores are not validated in this disease population, this exploratory comparison will not be presented within this review document. Please see the clinical review document for the HPP-related rickets descriptive analysis along with descriptive analyses pertaining to the 6MWT, gait, and other exploratory clinical parameters presented by the clinical reviewer.

The relevant demographics and baseline characteristics for all pertinent patients are presented in Table 5 below. It can be seen that these non-concurrent patient cohorts were reasonably balanced for these baseline variables.

Table 5
Demographic and Baseline Characteristics – ENB-006-09/ENB-008-10 vs. ALX-HPP-502 (All Enrolled/Extracted)

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

Source: Reviewer's Table generated from ISE ADSL dataset.
Note: Denominators for percentages are N.

It should be noted that all the following analysis results presented within this section were presented by the applicant. Tables 6 and 7 below present the shift in change from baseline in height z-scores for the ENB-006-09/ENB-008-10 patient cohort and ALX-HPP-502 patient cohort, respectively, broken up into three categories: change from baseline < -0.5, -0.5 ≤ change from baseline ≤ +0.5, change from baseline > +0.5. The z-score cut-point of 0.5 was chosen due to it being considered clinically meaningful by the clinical review team. The basic descriptive statistics for baseline height z-scores for the ENB-006-09/ENB-008-10 patient cohort is as follows: mean = -1.5; median = -1.1; standard deviation = 1.26; minimum = -3.8; maximum = 0.0. The basic descriptive statistics for baseline height z-scores for the ALX-HPP-502 patient cohort is as follows: mean = -1.1; median = -0.9; standard deviation = 1.29; minimum = -4.9; maximum = 2.6.

Table 6
Shift in Change from Baseline in Height Z-Scores – ENB-006-09/ENB-008-10
(All Enrolled)

	(N=8)		
Visit – Statistic	$\Delta < -0.5$	$-0.5 \leq \Delta \leq +0.5$	$\Delta > +0.5$
Week 24 – n/N (%)	0/8	8/8 (100%)	0/8
Week 48 – n/N (%)	0/8	8/8 (100%)	0/8
Week 96 – n/N (%)	0/8	5/8 (62.5%)	3/8 (37.5%)
Week 120 – n/N (%)	1/7 (14.3%)	4/7 (57.1%)	2/7 (28.6%)
Week 144 – n/N (%)	1/6 (16.7%)	2/6 (33.3%)	3/6 (50.0%)
Week 168 – n/N (%)	0/5	2/5 (40.0%)	3/5 (60.0%)
Week 192 – n/N (%)	1/7 (14.3%)	2/7 (28.6%)	4/7 (57.1%)
Week 216 – n/N (%)	0/2	1/2 (50.0%)	1/2 (50.0%)

Source: Reviewer's Table presenting data from Table 3.2.6.1.2 from Response to Information Request on May 22, 2015 (eCTD sequence 0028).
Note: Δ denotes change from baseline. Percentages are out of the number of patients with height z-score change from baseline data at the particular visit (displayed as N for each visit).

Table 7
Shift in Change from Baseline in Height Z-Scores – ALX-HPP-502
(All Extracted)

	(N=32)		
Visit – Statistic	$\Delta < -0.5$	$-0.5 \leq \Delta \leq +0.5$	$\Delta > +0.5$
Week 24 – n/N (%)	1/4 (25.0%)	3/4 (75.0%)	0/4
Week 48 – n/N (%)	0/11	11/11 (100%)	0/11
Week 96 – n/N (%)	2/14 (14.3%)	12/14 (85.7%)	0/14
Week 120 – n/N (%)	1/6 (16.7%)	4/6 (66.7%)	1/6 (16.7%)
Week 144 – n/N (%)	1/15 (6.7%)	12/15 (80.0%)	2/15 (13.3%)
Week 168 – n/N (%)	1/7 (14.3%)	4/7 (57.1%)	2/7 (28.6%)
Week 192 – n/N (%)	1/11 (9/1%)	9/11 (81.8%)	1/11 (9.1%)
Week 216 – n/N (%)	0/10	9/10 (90.0%)	1/10 (10.0%)

Source: Reviewer's Table presenting data from Table 3.2.6.1.6 from Response to Information Request on May 22, 2015 (eCTD sequence 0028).
Note: Δ denotes change from baseline. Percentages are out of the number of patients with height z-score change from baseline data at the particular visit (displayed as N for each visit).

It can be observed from Table 6 and Table 7 that only a few patients in each study cohort actually got worse in terms of change from baseline in height z-scores over time (i.e., change from baseline < -0.5). The majority of patients within each cohort were within the stable change from baseline range over time (i.e., $-0.5 \leq$ change from baseline $\leq +0.5$). However, of those patients that actually improved over time (i.e., change from baseline > +0.5), a greater percentage of them were in the ENB-006-09/ENB-008-10 group than in the ALX-HPP-502 group. This suggests that asfotase alfa is providing some desired therapeutic effect regarding growth.

Statistical Reviewer Comments:

Even considering the extremely rare nature of juvenile-onset HPP, the exploratory analysis pertaining to growth presented above along with all descriptive analyses presented within the clinical review document comparing juvenile patients being administered asfotase alfa from the ENB-006-09/ENB-008-10 study with baseline matched juvenile patients from the ALX-HPP-502 natural history study (which acted as a historical control group) were not deemed as the ideal trial design and analysis approach from a statistical perspective as a basis for marketing approval.

The design of this individual clinical study, in addition to the protocol for extracting comparable retrospective natural history data to be utilized as a historical control, was considered acceptable. However, relative to an adequate and well-controlled study, the use of a historical control presented a weaker level of evidence, which is being based on the totality of descriptive data adjudicated by the clinical review team, with growth being the chief clinical parameter while HPP-related rickets, the 6MWT, and gait all being supportive clinical parameters. Consequently, the determination of the clinical effectiveness of asfotase alfa in juvenile-onset HPP patients will rely exclusively on clinical judgment alone, much of it being informed by individual graphical patient profiles for each patient, than on the statistical rigor usually required for larger randomized controlled studies. This reviewer disagrees with DGIEP giving the applicant the option for this path forward in lieu of conducting study ENB-014-12, and believes that the division should have pushed for this clinical trial, which Alexion was willing to conduct. Comparisons to a historical control group are not considered to provide results that are as robust or reliable as those from comparisons within a randomized controlled study. Even when there is an observed balance between the non-concurrent groups in regards to identified baseline characteristics/covariates (which was the case here), there may be confounding due to baseline imbalances in latent variables, which can unknowingly influence outcome to therapy. This potential introduction of bias results from not having a randomization mechanism.

As stated above for perinatal/infantile-onset HPP patients, the utilization of a historical control can generally be valid if the course of the untreated disease within a patient population is well understood to be uniform with outcomes that can be predicted reliably. In addition, a valid historical control from a natural history study must have the same eligibility requirements, medical workup, and clinical evaluations as the clinical trial, i.e., patients from the natural history study must be adequately matched to patients from the clinical trial in terms of inclusion/exclusion criteria (and thus closely resembling the trial group in all known relevant baseline and observational variables) while also having comparable clinical evaluations in each group. Using a historical control is most likely to be persuasive when the study endpoint is objective and when the outcome on treatment is markedly different from that of the historical control (including a high level of statistical significance in the treatment vs. historical control comparison). Given that juvenile-onset HPP is heterogeneous in its phenotype and much less fulminant than in perinatal/infantile onset patients, the fact that there are a battery of clinical parameters being analyzed (with many not assured to be clinically meaningful), and the anecdotal nature of the descriptive comparisons between the non-concurrent groups for only a few clinical parameters (i.e., growth and HPP-related rickets), it was deemed by this reviewer that the historical control group from the ALX-HPP-502 study was only weakly convincing as an appropriate comparator to the ENB-006-09/ENB-008-10 study even considering the acceptable

similarity between both patient cohorts in terms of baseline characteristics. In addition, the retrospective nature of the ALX-HPP-502 study introduces the potential for selection bias, i.e., patients ultimately chosen for the historical control group may be those that result in an overly optimistic estimate of efficacy when comparisons are made to the treated patients. This issue, along with the potential for confounding due to baseline imbalances in latent variable as previously described, can be further magnified when operating with very small sample sizes, which is the case for juvenile-onset HPP. It was adjudicated that the applicant's due diligence in acquiring all available, and properly comparable, data was reasonably sufficient thereby mitigating these potential issues. Nonetheless, other potential issues may still be prevalent.

3.3 Evaluation of Safety

This evaluation is beyond the scope of this review. Please see Section 7 of the clinical review document for full details regarding the safety profile of asfotase alfa in perinatal/infantile- and juvenile-onset HPP patients.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

Subgroup analyses of overall survival and invasive ventilator-free survival for gender, race, and geographic region were conducted for the perinatal/infantile-onset HPP patients (i.e., the ENB-002-08/ENB-003-08 and ENB-010-10 vs. ENB-011-10 studies). The results of these subgroup analyses were all consistent with the whole group analysis results presented above in Section 3.2.1, hence these subgroup analysis results are not presented. The limited number of patients from the juvenile-onset HPP population (i.e., the ENB-006-09/ENB-008-10 vs. ALX-HPP-502 studies) precluded any meaningful subgroup analysis in this patient population.

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

Given the rare nature of perinatal/infantile-onset HPP, the agreed upon approach/analyses combining infants being administered asfotase alfa from the ENB-002-08/ENB-003-08 and ENB-010-10 studies and subsequently comparing these pooled patients, in regards to overall survival and invasive ventilator-free survival, with baseline matched infants from the ENB-011-10 natural history study (which acted as a historical control group) were ultimately deemed reasonable from a statistical perspective. The design of these individual clinical studies, in addition to the protocol for extracting comparable retrospective natural history data to be utilized as a historical control, was considered acceptable. However, even considering the more rare nature of juvenile-onset HPP, the exploratory analysis pertaining to growth along with all descriptive analyses presented within the clinical review document comparing juvenile patients being administered asfotase alfa from the ENB-006-09/ENB-008-10 study with baseline matched patients from the ALX-HPP-502 natural history study (which acted as a historical control group)

were ultimately deemed as not adequate from a statistical perspective. The design of this individual clinical study, in addition to the protocol for extracting comparable retrospective natural history data to be utilized as a historical control, was considered acceptable. However, relative to an adequate and well-controlled study, which was feasible in this HPP patient population, this approach typically presents a weaker level of evidence.

For both HPP populations (i.e., perinatal/infantile- and juvenile-onset), it should be noted that comparisons to a historical control group are not considered to provide results that are as robust or reliable as those from comparisons within a randomized controlled study. Even when there is an observed balance between the non-concurrent groups in regards to identified baseline characteristics/covariates, there may be confounding due to baseline imbalances in latent variables, which can influence outcome to therapy. This potential introduction of bias results from not having a randomization mechanism. In addition, the retrospective nature of both natural history studies introduces the potential for selection bias, i.e., patients ultimately chosen for both historical control groups may be those that result in an overly optimistic estimate of efficacy when comparisons are made to the corresponding treated patients. Both of these issues are further magnified when operating with very small sample sizes, which is the case for both HPP patient populations. Generally speaking, due to the scarcity of this disease population overall, the previously discussed limitations of the studies, and the post-hoc analysis approaches espoused for both HPP patient populations, the determination of the clinical effectiveness of asfotase alfa will rely more on clinical judgment than on the statistical rigor usually required for larger randomized controlled studies.

5.2 Collective Evidence

The applicant submitted the results from the ENB-002-08/ENB-003-08 and ENB-010-10 trials, in addition to the ENB-011-10 natural history study, to support the efficacy claim of asfotase alfa for the treatment of perinatal/infantile-onset HPP. In the agreed upon analyses combining infants from the ENB-002-08/ENB-003-08 and ENB-010-10 studies, asfotase alfa was demonstrated to be superior, in an exploratory context, to an acceptable historical control group, extracted from retrospective natural history study ENB-011-10, with respect to overall survival and invasive ventilator-free survival.

The applicant submitted the results from the ENB-006-09/ENB-008-10 trial, in addition to the ALX-HPP-502 natural history study, to support the efficacy claim of asfotase alfa for the treatment of juvenile-onset HPP. Product approval for this HPP patient population will be based on the totality of descriptive data adjudicated by the clinical review team, with growth being the chief clinical parameter while HPP-related rickets, the 6MWT, and gait all being supportive clinical parameters. The descriptive analysis results of growth presented within this review document suggests that asfotase alfa is providing some desired therapeutic effect.

5.3 Conclusions and Recommendations

There appears to be sufficient evidence in supporting the proposed efficacy claims for asfotase alfa in the treatment of perinatal/infantile-onset HPP. The claims reflected within the applicant's submitted product labeling are supported by the results presented in this review. It should be

emphasized that all hypothesis testing was considered exploratory given that the agreed upon endpoints (i.e., overall survival and ventilator-free survival), planned data integrations, and subsequent historical control comparisons were all determined well into the execution of the relevant perinatal/infantile-onset HPP studies. Consequently, all previously presented inferential statistics (e.g., p-values) within this review document are considered supportive and not confirmatory, and no inferential statistics should be presented within the final product labeling. Conversely, the evidence in supporting the proposed efficacy claims for asfotase alfa in the treatment of juvenile-onset HPP is weak from a statistical perspective; hence the clinical review team will determine the sufficiency of this evidence from a clinical perspective.

6 APPENDIX

As stated in Section 2.2 above, Table 8 below summarizes the specific IRs and TCs that involved the primary statistical reviewer's major participation and contribution.

Table 8
Primary Statistical Reviewer's Major Participation and Contribution

IR / TC	IR Send Date / Response Receipt Date (eCTD sequence) Or Date of TC	Contribution
IR (with follow-up TC with the applicant) regarding resubmitting all studies (i.e., CSRs) with the most up-to-date data available, which ended up being through November 2014	March 5, 2015 (IR and TC) / March 23, 2015 (0016), April 15, 2015 (0019), April 16, 2015 (0021)	Identified that each relevant submitted study had an analysis cutoff date that was two years prior to the BLA stamp date (December 23, 2014). Helped the clinical review team write the language for the IR, which included graphical patient profiles.
IR regarding resubmitting the integrated summary of efficacy (ISE) and integrated summary of safety (ISS) with the most up-to-date data available (i.e., November 2014)	March 10, 2015 / April 16, 2015 (0020)	Helped the clinical review team write the language for the IR.
IR for multiple analyses for clinical review	April 9, 2015 / April 28, 2015 (0024)	Helped the clinical review team write the language for the IR.
IR for analyses of height (i.e., the shift in change from baseline in z-score categories) for infantile- and juvenile-onset patients	May 11, 2015 and May 15, 2015 / May 22, 2015 (0028)	Wrote the language for the IR.
Internal meetings exclusively with the clinical review team	April 2, 2015; May 7, 2015; June 12, 2015; September 2, 2015	Helped the clinical review team analyze and interpret the juvenile-onset data (height data most importantly).
IR for multiple analyses for clinical review	July 16, 2015 / July 24, 2015 (0033)	Statistical Team Leader helped the clinical review team write the language for the IR.

Source: Reviewer's Table.

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/s/

BENJAMIN P VALI
09/18/2015

YEH FONG CHEN
09/18/2015

MICHAEL E WELCH
09/19/2015