CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125513Orig1s000

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	October 23, 2015
From	Dragos Roman, MD, Acting Associate Division Director /Division of Gastroenterology and Inborn Errors Products
Subject	Division Director Summary Review
BLA #	125513
Applicant Name	Alexion Pharmaceuticals
Date of Submission	December 23, 2014
PDUFA Goal Date	November 23,2015 (extended due to Major Amendment)
Proprietary Name / Established (USAN) Name	Strensiq/asfotase alfa
Dosage Forms / Strength	Single-use vials at concentrations of 40 mg/mL and 100 mg/mL, to be used for subcutaneous injection (18 mg/0.45 mL, 28 mg/0.7 mL, 40 mg/mL, or 80 mg/0.8 mL).
Proposed Indication(s)	(b) (4) in patients with infantile- and juvenile-onset hypophosphatasia (HPP)
Action/Recommended Action for NME:	Approval

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Medical Officer Review	Carla Epps, M.D., Anil Rajpal M.D.
Statistical Review	Benjamin P. Vali, M.S., Yeh-Fong Chen, Ph.D., Mike Welch, Ph.D.
Pharmacology/Toxicology Review	Dinesh Gautam, Ph.D./Sushanta Chakder, Ph.D.,
CMC Review/OBP Review	Joslyn Brunelle Ph.D., Mate Tolnay Ph.D., Gunther Boekhoudt Ph.D., Frederick Mills Ph.D., Gerry Feldman Ph.D., Steven Fong Ph.D., Peter Qiu Ph.D., Gerry Feldman Ph.D., Cristina Ausin-Moreno Ph.D., Michele Dougherty Ph.D.
Microbiology Review	Candace Gomez-Broughton/Patricia Hughes
Clinical Pharmacology Review	Christine Yuen-Yi Hon, Pharm.D., Yow-Ming Wang, Ph.D., Justin Earp, Ph.D., Nitin Mehrotra, Ph.D., Sarah Dorff, Ph.D., Christian Grimstein, Ph.D.
OSI	Susan D. Thompson, M.D., Susan Leibenhaut M.D.
CDTL Review	Anil Rajpal, MD, MPH
OSE/DMEPA	Matthew J Barlow RN, BSN, Kendra Worthy, PharmD
OSE/Division of Epidemiology I	Joel L. Weissfeld, M.D., MPH,

DPMH	Carrie Ceresa, Pharm D, MPH, Tamara Johnson, M.D., M.S., Lynne P. Yao, M.D.
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OND=Office of New Drugs
DDMAC=Division of Drug Marketing, Advertising and Communication
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
OSI=Office of Scientific Investigations
DDRE= Division of Drug Risk Evaluation
DRISK=Division of Risk Management
CDTL=Cross-Discipline Team Leader
DPMH = Division of Pediatric and Maternal Health
DBRUP= Division of Bone, Reproductive and Urologic Products
DMPP=Division of Medical Policy Programs
OPDP= Office of Prescription Drug Promotion
DNP=Division of Neurology Products

1. Introduction

In this application, Alexion Pharmaceuticals proposes to market Strensiq (asfotase alfa) as [redacted] (b) (4) in patients with infantile- and juvenile-onset hypophosphatasia (HPP)". The active ingredient in Strensiq, asfotase alfa, is a novel, previously unapproved biologic that incorporates sequences responsible for the enzymatic function of the tissue non-specific alkaline phosphatase, the enzyme that is missing or deficient in HPP. The Strensiq drug product is formulated as a preservative-free solution intended to be injected subcutaneously at a weekly dose of 6 mg/kg as one of two possible regimens: 2 mg/kg three times per week, or 1 mg/kg six times per week. Since Strensiq is a biologic, it was submitted as a Biologics License Application under Section 351(a) of the Public Health Service Act.

The development program for asfotase alfa started 8 years ago with a pre-IND meeting held in June, 2007, followed by multiple interactions between the Division and the previous sponsor of the IND (Enobia Pharma Inc.) and the current applicant (Alexion Pharmaceuticals) to whom the IND was transferred in 2012. Asfotase alfa received Orphan Drug Designation on September 12, 2008, Fast Track Designation on May 14, 2009, and Breakthrough Designation for the perinatal/infantile and juvenile forms of HPP on May 21, 2013. In March 2015, the Division granted a request for a rolling submission, and the final portion of the application was submitted on December 23, 2014. This BLA was reviewed as a Priority Review; because of a Major Amendment, the PDUFA deadline was extended from August 23, to November 23, 2015.

Major aspects of the asfotase alfa clinical program have been discussed with the applicant and agreed before the submission of the BLA. The Division advised Alexion Pharmaceuticals to establish a natural history cohort to be used as a comparator for efficacy analyses, and agreement was reached that the endpoints of overall survival and ventilator-free survival are acceptable for the perinatal/infantile HPP population. For the juvenile-onset form of HPP, although not formally agreed, a comparison to a natural history group was also seen as potentially acceptable.

2. Background

Hypophosphatasia (HPP) is a rare metabolic bone disease caused by inactivating mutations - approximately 300 loss-of-function mutations have been identified to date - in the gene encoding the tissue-nonspecific alkaline phosphatase (TNSALP). This enzyme plays a significant role in bone mineralization. It acts on several substrates, among them inorganic pyrophosphate (PPi), from which it releases inorganic phosphate, a precursor of calcium phosphate. The latter precipitates as hydroxyapatite crystals in the bone matrix, giving strength and rigidity to the bones. Biochemically, the loss of TNSALP function seen in HPP is associated with accumulation of substrates such as PPI (which also acts as an inhibitor of mineralization) and pyridoxal 5'-phosphate (PLP), the main circulating form of vitamin B_6.

The clinical manifestations of HPP are primarily skeletal. The defective bone mineralization leads to rickets and osteomalacia, with subsequent deformities and fractures of the long bones, and abnormalities of the thoracic cage resulting in respiratory dysfunction and insufficiency. Non-skeletal manifestations include pyridoxine-responsive seizures (in absence of TNSALP, pyridoxal 5'-phosphate cannot cross the blood-brain barrier), hypercalcemia, hypercalciuria (including nephrocalcinosis), myopathy (contributing to delayed or abnormal gait), and dental manifestations.

These clinical manifestations of HPP have different degrees of severity. They vary from death in utero or during the neonatal period (with almost no skeletal mineralization) to clinical forms that have mostly dental manifestations or minimal bone findings. Several phenotypes have been described based on the age of onset: perinatal/infantile, juvenile, and adult. In general, the severity of HPP is inversely related to age, with the neonatal form being the most severe. In this BLA, Alexion Pharmaceuticals is seeking an indication for the perinatal/infantile and juvenile phenotypes. Of note, there are no approved treatments in the US for HPP, and no effective therapies. Strensiq has been recently approved in Europe and Japan.

The drug substance in Strensiq is asfotase alfa, a soluble glycoprotein composed of two identical polypeptide chains, each 726 amino acids in length (theoretical mass of 161 kd per chain). Each polypeptide chain is a fusion of three components: the catalytic domain of human tissue non-specific alkaline phosphatase, the Fc domain of the human immunoglobulin G1, and a bone targeting domain (a deca-aspartate peptide). The two polypeptide chains are covalently linked by two disulfide bonds, (b) (4). A

graphic representation of the asfotase alfa structure is shown below. Asfotase alfa is engineered and expressed in a Chinese hamster ovary cell line.

This BLA submission includes the results of seven ongoing or completed clinical studies of asfotase alfa, but critical to the determination of safety and effectiveness of Strensiq are two clinical trials in patients with perinatal/infantile form of HPP (both single-arm, open-label, totaling 68 subjects) and a clinical trial in the juvenile form of HPP (also single-arm, open label; enrolled 8 patients). The efficacy of both the perinatal/infantile HPP program and the juvenile HPP programs is supported by comparisons of data obtained from the above-mentioned clinical trials with data collected retrospectively from two natural history cohorts (one for the perinatal/infantile and one for the juvenile-onset HPP). Therefore, these efficacy analyses will be the focus of the efficacy section of this memorandum (as they are in both the statistical and clinical reviews). An additional issue of importance is the potential immunogenicity of Strensiq, since asfotase alfa is different in structure from the native sequence of TNSALP. Specific questions related to immunogenicity are whether immunogenicity was adequately characterized, if the immunogenicity assays were adequate, if there were any clinical safety signals related to immunogenicity and, if present, do such safety findings preclude approval, or can they be managed through labeling or other forms of risk minimization. As with any other biologic, the ability of manufacturing a consistent drug product is also critical to approvability, and will be addressed in this memorandum.

3. CMC/Device

I am in agreement with the OPQ's recommendation for Strensiq's approval from a product quality perspective. The manufacture of Strensiq was found to be "well controlled", leading to a product that is "pure and potent". Manufacturing facilities have been deemed acceptable (one of the two drug product release testing site was deficient, but it was withdrawn by the applicant). .

The OPDQ review recommends 2 PMR's and 2 PMCs. The PMRs include:

- A requirement that the applicant develop an assay to directly compare the complement activating capacity of asfotase alfa to that of human IgG1 (the reason for this requirement is that asfotase alfa contains an intact Fc region and can potentially activate the complement system). This concern is theoretic at this time because no adverse events suggestive of complement activation have been identified in the safety review of the BLA, and should not preclude approval of Strensiq.
- A requirement that the applicant develop a validated cross-reactive immunologic material (CRIM) assay for patients with hypophosphatasia. The purpose of this request is to expand and improve the understanding of the immunogenicity of Strensiq, and attempt to correlate antibody response to different types of mutations that may result in different enzyme activity levels.

The PMCs include:

- A commitment to develop a control strategy (b) (4) (b) (4) .
- A commitment to (b) (4) the (b) (4) limits for endotoxin content after data from thirty batches become available (b) (4)

The clinical studies conducted in the Strensiq program used drug product (b) (4) (b) (4) (b) (4) higher order structure, specific activity of the drug substance, and other critical attributes for both drug substance and drug product were evaluated and found to adequate. The proposed specifications were found to be acceptable for approval. Product and (b) (4) related impurities were either characterized and found to be of no concern, or were in extremely low concentrations that are not expected to pose a risk to humans. Review of the leachable data did not identify any significant risk to the patients either. The drug substance container closure was found to be acceptable. Stability data support a storage time of (b) (4) months.

4. Nonclinical Pharmacology/Toxicology

I concur with the determination reached by the pharmacology/toxicology review team who concludes that there are no pharmacology/toxicology issues that could preclude approval. There are no recommendations for additional pre-clinical studies.

The review indicates that "in support of the nonclinical safety, the applicant has submitted adequate nonclinical studies (pharmacology, pharmacokinetic, toxicology and reproductive and developmental toxicology) of asfotase alfa". The NOAELs of 13 mg/kg/day (rats) and 10 mg/kg/day (juvenile monkeys) provide 6 and 5 times margins of safety for the to-be-labeled human dose of 6 mg/kg/week, based on AUC comparisons. This NOEL was established on the basis of the highest dose that was evaluated and not on actual demonstrable toxicity. Therefore, it is possible that the margins of safety for the to-be-marketed human dose may be even higher.

In vitro data and animal studies provide proof of the expected biological activity of the asfotase alfa construct, and support the rationale for using asfotase alfa therapeutically in humans. Specifically, radiolabeled tagging of asfotase alfa confirms that is distributed to peripheral tissues including bone in animals. In a mouse model of HPP (Akp2-/-) generated by genetic inactivation of TNSALP, treatment with asfotase alfa intravenously and subcutaneously resulted in a reduction of inorganic pyrophosphate (a TNSALP substrate), and improved bone mineralization and survival rate.

(b) (4) product-related impurities were within the acceptable limits and were all considered qualified. In addition, the levels of all potential leachables from the container closure system were within the recommended safety limit. Carcinogenicity studies of asfotase alfa were not conducted. The nonclinical reviewers comment that because asfotase alfa is a large protein and has no known anabolic effects, it is not expected to be carcinogenic.

5. Clinical Pharmacology/Biopharmaceutics

I concur with the clinical pharmacology review team which concludes that "from a clinical pharmacology perspective, the information submitted in this BLA is acceptable to support the approval of asfotase alfa for the proposed indication." The clinical pharmacology reviewers have two recommendations:

- To restrict the use of the higher concentration (100 mg/mL) formulation strength to older children (>40 kg in the currently proposed label) because in infants and young children it was associated with a 24% lower exposure than that achieved with the lower concentration (40 mg/ml) formulation strength.
- (b) (4)

[redacted] (b) (4)

These two recommendations and the observations that triggered them will be discussed further in this memorandum, along with a brief summary of the drug's pharmacokinetics, exposure-response (E-R) relationship, and impact of immunogenicity on PK drug characteristics.

PK information was obtained in patients with both forms of HPP (perinatal/infantile and juvenile) for a variety of doses and dose regimens, across ages ranging from neonates to adults. The estimated absolute bioavailability was 62% following subcutaneous administration. The mean T_{max} ranged from 15 to 20 hours. The elimination half-life following subcutaneous administration was approximately 5 days, and steady state exposure was achieved after three weeks of administration. Dose proportionality was observed across the dose range of 0.3 mg/kg to 3 mg/kg. Generally, PK seemed similar between patients with perinatal/infantile and juvenile HPP. Some degree of drug accumulation was seen, but it was not associated with evidence of toxicity. Covariates that influenced the PK characteristics were body weight and immunogenicity (presence of anti-drug antibodies was associated with a higher clearance). The proposed dosing (on a mg/kg basis) addresses the need for adjustments based on weight.

No formal QT/QTc studies were performed for asfotase alfa. The clinical pharmacology review notes that because the drug is a therapeutic protein, the risk for prolongation of QT/QTc interval is minimal. Not requesting a dedicated QT/QTc study at this point seems reasonable given also the fact that ECG monitoring in animals (6-month monkey study) did not identify a cardiovascular safety signal, and limited testing in human studies (reviewed by the clinical reviewer) did not raise any concern of clinically relevant QT prolongation.

In patients with juvenile-onset HPP, an exposure-response relationship was observed between the estimated average asfotase alfa concentration at steady state (Cavg,ss) and multiple pharmacodynamic, radiological and clinical assessments (the Bruininks-Oseretsky Test of Motor Proficiency score, 6 Minute Walk Test, Radiologic Global Impression of Change and Rickets Severity Scale scores, and plasma PPi and PLP concentrations). These E-R curves showed that response rapidly improved at low drug concentrations, followed by a more gradual improvement with increasing drug concentration until a plateau was reached at a Cavg,ss concentration of approximately 1500 - 2000 U/L. The clinical pharmacology team indicates that for the proposed dosing regimen of 6 mg/kg/week the mean values of the estimated Cavg were generally above 2000 U/L which was at or above the beginning of the plateau of the E-R relationship for effectiveness (the range of values for the 6 mg/kg/week regimen was 1430 to 2930 U/L). This information supports the proposed to-be-marketed dose regimen.

The clinical pharmacology review makes the observation that the [redacted] (b) (4) in the Strensiq drug substance impacted patient exposure to asfotase alfa. Specifically, it was estimated that there is approximately a [redacted] (b) (4) in the average plasma drug concentration at steady state (Cavg,ss) of asfotase alfa between the extremes of the proposed [redacted] (b) (4). Based on this observation, the

clinical pharmacology team recommends (b) (4) The drug exposure observed for asfotase alfa that contains (b) (4) is expected to be close to the maximum response on the E-R curves. This recommendation is reasonable and has been the basis of a Post Marketing Commitment request already accepted by the applicant.

Two drug product strengths (40 mg/mL and 100 mg/mL) were used in the asfotase alfa clinical program to accommodate the range of doses needed to be administered for different body weights across age groups. The 40 mg/mL strength was used in younger children (who had lower body weights), while the more concentrated formulation of 100 mg/mL was used in older children. The clinical pharmacology review concluded that the 40 mg/mL and 100 mg/mL formulations do not have comparable PK, and in fact the 100 mg/mL formulation resulted in lower serum exposures to the drug (24% less). This observation (possibly due to differences in bioavailability between the two dosage strengths), combined with the lack of clinical experience with 100 mg/mL strength product in the perinatal/infantile HPP patients, is the basis for the recommendation that only the 40 mg/mL formulation strength should be used in this subgroup of patients for now. I agree with this recommendation.

6. Microbiology

Not applicable (Strensiq is not an antimicrobial product).

7. Clinical/Statistical-Efficacy

7.1 Perinatal/infantile HPP

Perinatal/infantile HPP was evaluated in two open-label, single-arm, interventional clinical trials:

- Study ENB-002-08 was a multinational, multicenter, open-label, single-arm, 24-week clinical trial conducted in 11 patients, followed by an extension trial for up to 5 years (Study ENB-003-08). Study ENB-002-08 and Study ENB-003-08 will be referred to as Study ENB-002-08/ENB-003-08 in this memorandum because they are a continuum. Patients were given one 2 mg/kg infusion followed by subcutaneous injections of 1 mg/kg/day three times per week (3 mg/kg/week) with escalation up to 3 mg/kg/day three times per week (9 mg/kg/week).
- Study ENB-010-10 was a multinational, multicenter, open-label, single-arm, 4-year study conducted in 59 patients who received 6 mg/kg/week subcutaneously as either 1 mg/kg six times per week or 2 mg/kg three times per week.

The comparator for the efficacy analyses of these studies was the natural history study ENB-011-10, which included 48 patients who were selected from retrospective clinical chart reviews. Patients in this study were enrolled on the basis of inclusion criteria that overlapped

considerably with those of the above-listed Strensiq intervention studies. Of note, the clinical trials preceded the natural history study. For the latter, data were collected after reviewing clinical charts of patients with HPP, and patients were "enrolled" in the natural study if they met general characteristics of disease severity as those of patients enrolled in studies ENB-002-08/ENB-003-08 and ENB-010-10 (i.e. patients were not matched one to one). Thus, for any patient alive as of the last chart note reviewed, their physician was contacted to determine the patient's survival status. Efforts were made to identify as many patients as possible, and in the end 48 such patients were identified.

For the purpose of analysis, patients from the ENB-002-08/ENB-003-08 and ENB-010-10 studies were pooled for comparisons of overall survival and ventilator-free survival via-a-vis the natural history cohort. This approach was found acceptable, and was agreed by the Division in pre-submission meetings, and was specified in the Statistical Analysis Plan. The limitations to this approach - using retrospective data as a historical control - are highlighted in the statistical review and briefly summarized here. They relate to the fact that a comparison to a historical control group is not as robust methodologically as a comparison made in the context of a randomized study, and that potential confounding by unidentified variables may influence the outcome. In addition, the retrospective nature of the natural history study may introduce selection bias and may result in an overly optimistic estimate of efficacy. All these issues have been discussed internally and with the applicant in previous meetings. I am in agreement with the comments made by the statistical team indicating that due to the statistical limitations imposed by the design of the studies (ultimately driven by the scarcity of patients with this condition) we will have to rely not strictly and exclusively on statistical comparisons as demonstration of efficacy, but on the integration of the overall efficacy data. I am also in agreement with the recommendation made by the statistical team that the efficacy data be presented in the label descriptively and without inferential statistics.

Although studies ENB-002-08/ENB-003-08 and ENB-010-10 were conducted separately, pooling the efficacy data from these studies seems appropriate because they had very similar designs (both were single-arm, open-label, multicenter, multinational clinical trials). The inclusion criteria (see summary in Table 4 of the CDTL review) were very similar and aimed at capturing the same patient population: children with perinatal/infantile HPP. This turned out to be indeed the case, since the baseline patient characteristics were similar.

The agreed primary efficacy endpoint was overall survival measured as time to death from birth up to point of last contact; an important, clinically relevant, and related endpoint was ventilator-free survival measured as time to start of invasive ventilator use (or occurrence of death) from birth up to point of last contact. The results of the overall survival analysis are reproduced below from the Statistical Review. In this analysis Strensiq showed superiority to the untreated group: a larger percentage of patients survived at the last point of contact (91.2% vs. 27.1%) and the median time to death from birth was also longer in the Strensiq cohort (1353 days vs. 270.5 days). The statistical reviewer conducted multiple sensitivity analyses including a "worse-case" imputation strategy, as well as an analysis of a subgroup of 46 patients who received the to-be-labeled dose of 6 mg/kg/week, and confirmed the results of the primary efficacy analysis.

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.

The secondary analysis of time to start of invasive ventilator use or death from birth up to point of last contact was consistent with the primary endpoint analysis. For this comparison, sensitivity analyses under a "worse-case" scenario or including only patients treated at the to-be-marketed dose were consistent and confirmed the results.

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.

The statistical reviewers conclude that:

> 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.

Additional efficacy analyses are summarized in the CDTL and clinical reviews. They include changes in radiological assessments (Radiographic Global Impression of Change score or RGI-C) and growth endpoints (weight and length/height), and provide results that are consistent with the pharmacologic effect of Strensiq described above. RGI-C was developed for patients with HPP and was used to compare change from baseline in appearance of knees, hands/wrists, chest radiographs for younger children. This radiological score has not been formally validated, and the results can only be seen as supportive of the main efficacy analyses. While no control group was available in assessing height, the data were presented as height Z-scores, which methodologically incorporate in its calculation a historical comparator (normal height population from CDC growth charts).

7.2 Juvenile HPP

The juvenile HPP program was limited to data obtained in only 8 patients who were enrolled in a single, multinational, multicenter, open-label, randomized, parallel-dose, 24-week study (ENB-006-09), followed by a long-term extension up to 3.5 years (ENB-008-10). In this study, which will be referred to as study ENB-006-09/ENB-008-10, patients were randomized to receive either 2 mg/kg or 3 mg/kg of asfotase alfa subcutaneously three times per week (6 mg/kg or 9 mg/kg for the entire week).

Similar to the perinatal/infantile program, the efficacy data from this clinical trial were compared to retrospective data collected from patients with juvenile-onset HPP. The retrospective cohort (Study ALX-HPP-502) included patients with disease-specific characteristics comparable to the population enrolled in study ENB-006-09/ENB-008-10. In Study ALX-HPP-502, information regarding efficacy assessments was collected from medical charts. Efforts were made to enroll/extract as many patients as possible, and in the end the whole cohort included a total of 32 patients. The design of the individual clinical studies and the protocol for Study ALX-HPP-502 were considered acceptable by the statistical reviewers.

This historical control approach, not unlike the one used in the perinatal/infantile population, was agreed between the applicant and the Division. I am acknowledging the statistical limitations of this approach, which are highlighted in the statistical review. Within the limitations of a comparison to a historical cohort, asfotase alfa treatment showed improvements in 1) radiological scores (all 8 asfotase alfa-treated patients were rated as responders by Month 54 of treatment; a responder was defined as an RGI-C score ≥ 2); 2) mobility, which was measured by the 6 Minute Walk Test (6/7 patients or 86% improved postbaseline); and 3) growth and height. Mean height Z-score changed from -1.5 at baseline to -0.9 on treatment while it remained relatively unchanged in the historical control group (mean of -1.1 at both baseline and last assessment). Similarly, mean weight Z-score stayed about the same in the control group (-1.2 at baseline and -1 at last assessment) while improvement was noted in the Strensiq group (mean of -1.5 at baseline and 0 at last assessment). Within group improvement in height Z-score is important even in the absence of a comparator group because height data are calculated based on CDC growth standards (i.e. it incorporates a comparison to normally growing children for a specific age and gender). In addition, as illustrated in Tables 6 and 7 of the statistical review a greater percentage of patients in the Strensiq cohort showed a Z-score improvement of > 0.5 (relative to baseline) than in the control group, indicating an effect on linear growth. Corroborated with evidence of biochemical improvement (mean reductions in substrates such as PPi and PLP), favorable changes in radiological assessments (RGI-C score), and improvement in mobility (6 Minute Walk Test), the linear growth data support a determination of efficacy in the juvenile HPP cohort. This observation is consistent with the evidence of efficacy noted in the neonatal/infantile form of HPP. The totality of evidence within phenotype, across phenotypes, and for similar endpoints across phenotypes (biochemical, radiological and growth-related) provides a reassuring degree of consistency.

Finally, the applicant provided biopsy data from 8 juvenile-onset HPP patients, and 5 infantile-onset patients who were treated with asfotase alfa. These limited but important assessments indicated a positive effect of asfotase alfa on osteomalacia at 6 months in both

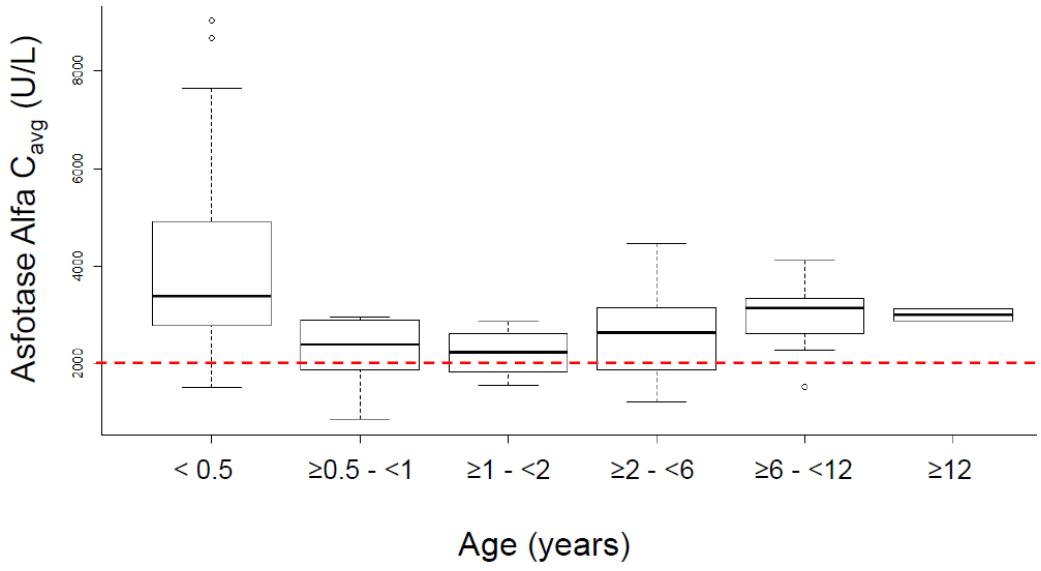
perinatal/infantile and juvenile HPP, at to-be-marketed doses. The consultant who reviewed these data notes that "although there are no biopsy data on untreated patients, osteoid reduction as seen in 11/12 HPP patients does not in general occur spontaneously in untreated osteomalacic patients." These are limited observations in an uncontrolled setting, but add direct end-organ histological confirmation of the other observed effects of Strensiq (i.e. biochemical, radiological and clinical).

7.3 Dose comments

The doses and dose regimens proposed by the applicant were found to be acceptable by all reviewers, across disciplines. As already indicated, the nonclinical review concluded that the to-be-labeled and marketed 6 mg/kg/week dose had 5-6 fold margins of safety relative to animal toxicology data based on comparative exposure (AUC); because this NOEL was established on the basis of the highest dose that was evaluated, and not on actual demonstrable toxicity, it is conceivable that the margins of safety for the 6 mg/kg/week may be even higher.

Exposure-response analyses summarized in the joint clinical pharmacology/pharmacometrics review support the selection of a 6 mg/kg/week dosing regimen. Figure 1 of the pharmacometrics review (reproduced below) illustrates that exposures across all pediatric age groups tend to be around or above the asfotase alfa Cavg,ss of 2000 U/L at which maximum response is reached (exposures associated with the proposed 6 mg/kg weekly regimen range from 1430 to 2930 U/L) . Dosing by body weight seems acceptable because it produces similar exposures across the range of ages for which approval and labeling are sought. The clinical pharmacology review indicates that the available exposure-response data support also the frequency of administration (three vs. six times a week).

Figure 1. Average Asfotase Alfa Concentration versus 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.



The clinical review team recommends that patients who do not respond to the 6 mg/kg/week regimen should have their doses increased to 9 mg/kg/week (in both perinatal/infantile and

juvenile HPP trials there were observations of patients who failed to respond to the 6 mg/kg regimen but showed radiological and clinical response once the dose was further increased to 9 mg/kg). The pharmacometrics reviewers agree that the option to increase the dose in patients who are not responding to the 6 mg/kg/week dose is acceptable and supported by exposure-response analyses. Based on the combined clinical and pharmacometrics observations and analyses, I agree that the option to increase the weekly dosing regimen is acceptable as long as patients tolerate the dose.

8. Safety

The asfotase alfa clinical program studied a total of 102 patents with HPP, including 79 patients with perinatal/infantile form and 20 patients with juvenile HPP. While the duration of exposure ranged from one day to 6.5 years, more than half of patients received asfotase alfa for longer than 2 years. Doses as low as 0.9 mg/kg/week and as high as 28 mg/kg/week were explored, but the vast majority of patients were exposed to the to-be-marketed doses of 6 mg/kg/week and 9 mg/kg/week.

Asfotase alfa was generally well tolerated by both patients with perinatal/infantile HPP and by patients with juvenile-onset HPP. Not surprisingly, given the severity of the disease, 10 deaths were reported across the clinical program, which included also compassionate use protocols (all deaths were in the most severe form of the disease, the perinatal/infantile form). Dr. Epps reviewed in detail the narrative for all these events and concluded that all deaths were attributed to HPP-related disease complications.

The most common adverse events reported were injection site reactions, which were seen in as many as 63% of patients. Given the absence of a concurrent control group, the adverse events recorded in the main clinical trials reviewed in this memorandum can be classified as 1) adverse events clearly due to the drug administration (such as injection site reactions and localized lipodystrophy); 2) adverse events which likely represent background events related to the disease itself (fractures for instance); 3) adverse events likely due to intercurrent infections or conditions frequently seen in childhood (e.g., upper respiratory infections, nasopharyngitis, vomiting, etc.).

Dr. Epps singles out three adverse events of significance for labeling: hypersensitivity reactions (including anaphylaxis, which was seen in one patient), lipodystrophy, and ectopic calcifications. Hypersensitivity reactions are a known risk associated with the administration of therapeutic protein products, and do not represent an obstacle to approvability, particularly in a patient population with no therapeutic options. The risk can be communicated appropriately if they are labeled as a warning/precaution rather than a contraindication. Given the need for therapy and the availability of treatments for hypersensitivity, it should be left at the discretion of the practitioner whether to continue or discontinue Strensiq treatment in case of an observed allergic reaction.

Lipodystrophy has been observed with other injectable protein products, and may be prevented, or at least minimized, with proper administration (rotation of the injection sites).

Ectopic calcifications, on the other hand, pose a difficult dilemma because ocular calcifications and nephrocalcinosis have been described in HPP. In her review, Dr. Epps proposed a possible mechanism of action for drug-induced tissue calcification, and expresses concern that an additional risk for such calcifications cannot be confirmed or ruled out in this relatively limited dataset. As such, she proposes that the adverse event of ectopic calcifications, which occurred in 14% of patients, should be elevated to a warning/precaution. Although the evidence of Strensiq-induced calcifications is limited, it seems prudent to take this approach and inform practitioners, even if the risk is hypothetical at this stage. The proposed labeling language acknowledges that there is insufficient information to determine whether or not the reported events were consistent with the course of the disease or due to Strensiq treatment, and recommends that patients should not miss their routine ophtalmological and renal evaluations.

Immunogenicity is a potential safety concern with any protein therapeutic. Asfotase alfa is not an exact copy of the native TNSALP, and therefore has an intrinsic risk for development of anti-drug antibodies (ADA). Immunogenicity information was obtained from samples collected from 7 clinical trials submitted in this BLA, which included patients across all age groups. The sampling was judged to be appropriate, and the approach to evaluating immunogenicity was consistent with FDA requirements. It included successively a screening step, a confirmatory step (including measuring ADA titers), followed by the characterization of the specificity of the ADAs to different domains of the asfotase alfa (targeting signal, enzymatic domain, Fc domain), and assessment of neutralizing activity. Of the 98 patients with HPP who had post-baseline antibody data, 76 (78%) developed anti-drug antibodies at some time point after receiving Strensiq treatment. Generally, ADA titers were low. The median time to first ADA positive result was 37.0 days (range of 14 to 1072 days). Not all patients who tested positive for ADAs post-baseline remained consistently positive throughout treatment. A little less than half (45%) of the ADA positive patients were identified as having neutralizing antibodies. Formation of anti-drug antibodies resulted in a reduced systemic exposure of asfotase alfa due to a higher clearance, but no other identifiable clinical effects. Evaluation of the long term risk of immunogenicity of the drug, along with safety of Strensiq in general, will continue postmarketing (see Post Marketing Requirement Recommendations Section).

9. Advisory Committee Meeting

There were no Advisory Committee Meetings regarding this application. The applicant and the FDA had multiple communications at different stages of the Strensiq development program, and the major constituents of the clinical program have been discussed and found to be acceptable prior to submission of the BLA.

10. Pediatrics

Because asfotase alfa has received orphan designation, the Pediatric Research and Equity Act (PREA) requirements do not apply to this application.

The Applicant has submitted a request for a Rare Pediatric Disease Priority Review Voucher along with data to support such a request. The Office of Orphan Products Development (OOPD) has reviewed this request and concluded that HPP meets the FDASIA definition of a rare pediatric disease, and is eligible for a voucher. A priority review voucher is expected to be issued at the time of marketing approval.

11. Other Relevant Regulatory Issues

DSI audits were completed. No serious violations were identified at the two sites that were inspected, and the data generated at these sites were found to be acceptable.

Financial Disclosure documents have been reviewed by Dr. Epps and found to be satisfactory.

12. Labeling

Labeling negotiations have been completed at the time of this memorandum (the labeling will include physician labeling, Instructions for Use, and carton and container labeling). In summary:

- Strensiq will be labeled for two indications, reflecting the two phenotypes that have been studied: perinatal/infantile HPP and juvenile HPP.
- The dose regimen to be labeled is 6 mg/kg/week as either three subcutaneous injections of 2 mg/kg or six injections of 1 mg/kg, with an option to increase the dose to 9 mg/kg given as three 3 mg/kg injections.
- No contraindications have been identified.
- The labeled Warnings and Precautions are hypersensitivity reactions, lipodystrophy, and ectopic calcifications.
- The Dosing and Administration section cautions against using the 80 mg/0.8 mL vial in pediatric patients weighing less than 40 kg because of the lower exposure observed with this dosage strength (the 40 kg threshold was selected because all patients with perinatal/infantile HPP enrolled in the trials were below this weight).

The proprietary name (Strensiq) has been reviewed by the Division of Medication Error Prevention and Analysis (DMEPA) and found to be acceptable. This decision has already been communicated to the applicant. The Office of Prescription Drug Promotion (OPDP) determined that the proposed name is acceptable from a promotional perspective.

Recommendations regarding the Pregnancy and Lactation sections of the Strensiq label, provided via a consult by the Division of Pediatric and Maternal Health, have been incorporated in the label.

13. Decision/Action/Risk Benefit Assessment

- Regulatory Action

Approval.

- Risk Benefit Assessment

In this BLA Alexion Pharmaceuticals has provided evidence of effectiveness for Strensiq (asfotase alfa) in the treatment of two pediatric hypophosphatasia phenotypes: perinatal/infantile and juvenile-onset. Strensiq will be the first approved therapy for the indication of perinatal/infantile and juvenile-onset HPP, a devastating childhood condition for which there is no effective treatment. The active ingredient in Strensiq (asfotase alfa) contains the catalytic site of the enzyme that has been identified to be deficient in HPP (tissue non-specific alkaline phosphatase). Strensiq treatment in HPP aims at replacing the missing or deficient endogenous enzyme.

The demonstration of effectiveness of Strensiq in the treatment of HPP comes from several lines of evidence:

- histological (bone biopsy in a subgroup of patients with perinatal/infantile and juvenile HPP)
- biochemical (reduction and normalization of serum substrates, PI and PPI, in perinatal/infantile and juvenile HPP)
- radiological (improvement in radiological scores for both perinatal/infantile and juvenile forms of HPP)
- clinical
    - overall survival and ventilator-free survival (for the perinatal/infantile form of the disease)
    - growth (for both perinatal/infantile and juvenile HPP)
    - mobility (juvenile HPP).

Among the above listed benefits, improvement in overall survival and ventilator-free survival in the perinatal/infantile phenotype is the clearest benefit. Improvements in growth and mobility are also of clinically significance.

The risks associated with Strensiq treatment, as understood from the current safety dataset, appear manageable. Among them, allergic reactions seem to be the most significant, but should not preclude approval as they are not an unusual occurrence for enzyme replacement therapies (and for protein therapeutics in general). The immunogenicity observed in the Strensiq program is another concern but the long-term significance, if any, cannot be assessed at this time; the current assessment is that it does not interfere with efficacy in a meaningful way even in the presence of neutralizing antibodies, and systemic complications have not been identified. All other potential risks are manageable (lipodystrophy at the injection site) or still largely theoretical (ectopic calcifications). Many of these potential risks will be further evaluated in postmarketing reporting and in a series of PMRs and PMCs (see below).

I concur with all other clinical reviewers that the risk benefit of Strensiq in children with HPP is overall favorable if used as labeled.

- Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies

None. The potential safety risks identified to date can be communicated effectively by labeling, and a REMS is not necessary at this point.

- Recommendation for other Postmarketing Requirements and Commitments

The following PMRs and PMC have been recommended and agreed across review teams:

PMR 2949-1
A prospective, long-term, observational study in STRENSIQ (asfotase alfa) treated patients with perinatal/infantile-onset and juvenile-onset hypophosphatasia (HPP) from ages birth and older. The purpose of the study is to assess the long term safety of treatment with STRENSIQ 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.

Final Protocol Submission:	07/2016
Study Completion:	10/20223
Final Report Submission:	064/20234

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

Final Report Submission: 06/2016

PMC 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 ASTRENSIQ (asfotase alfa) treatment. (b) (4)

Final Report Submission: 06/2016

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

Final Report Submission: 11/2016

PMC 2949-5
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.

Final Report Submission: 12/2017

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/s/

DRAGOS G ROMAN
10/23/2015