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APPLICATION NUMBER:

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OFFICE DIRECTOR MEMO

Office Deputy Director Decisional Memo

Date	October 23, 2015
From	Amy G. Egan, MD, MPH
Subject	Office Deputy Director Decisional Memo
NDA/BLA #	BLA 125513
Applicant Name	Alexion Pharmaceuticals, Inc.
Date of Submission	December 23, 2014
PDUFA Goal Date	August 23, 2015 (extended to November 23, 2015 due to major amendment)
Proprietary Name / Established (USAN) Name	Strensiq/ asfotase alfa
Dosage Forms / Strength	Solution for subcutaneous injection/single use vials at concentrations of 40 mg/mL and 100 mg/mL
Applicant Proposed Indication(s)	For (b) (4) in patients with infantile- and juvenile-onset hypophosphatasia (HPP).
Action:	Approval
Approved Indication(s)/Populations	For the treatment of patients with perinatal/infantile- and juvenile-onset hypophosphatasia (HPP).

Material Reviewed/Consulted	Names of discipline reviewers
Medical Officer Review	Carla Epps, MD
Statistical Review	Benjamin Vali, MS
Pharmacology Toxicology Review	Dinesh Gautam, PhD
OBP Review	Cristina Ausin-Moreno, PhD
Microbiology Review	Candace Gomez-Broughton, PhD
Clinical Pharmacology Review	Christine Hon, PharmD
DPMH	Carrie Ceresa, PharmD, MPH (maternal health)/Ethan Hausman, MD (pediatric)
DMPP	Shawna Hutchins, MPH, BSN, RN
OPDP	Adewale Adeleye, PharmD, MBA
OSI	Susan Leibenhaut, MD
CDTL Review	Anil Rajpal, MD
DD Summary Review	Dragos Roman, MD
OSE/DMEPA	Matthew Barlow, RN, BSN
OSE/DRISK	Jasminder Kumar, PharmD
OSE/DEPI	Joel L. Weissfeld, MD, MPH

CMC=Chemistry Manufacturing and Controls

OBP=Office of Biotechnology Products

DPMH=Division of Pediatric and Maternal Health

DMPP=Division of Medical Policy Programs

OPDP=Office of Prescription Drug Promotion

OSI=Office of Scientific Investigations

CDTL=Cross-Discipline Team Leader

OSE= Office of Surveillance and Epidemiology

DMEPA=Division of Medication Error Prevention and Analysis

DRISK=Division of Risk Management

DEPI=Division of Epidemiology

Benefit-Risk Summary and Assessment

Strensiq (asfotase alfa) is a subcutaneously administered tissue non-specific alkaline phosphatase (TNSALP) developed for the treatment of hypophosphatasia (HPP), a rare inherited disorder caused by inactivating mutations in the alkaline phosphatase liver-type (ALPL) gene, which encodes the TNSALP enzyme. Lack of TNSALP enzyme activity leads to accumulation of certain substrates including inorganic pyrophosphate (PPi), causing osteomalacia and rickets of long bones and ribs, and pyridoxal-5'-phosphate (PLP), a co-factor form of vitamin B6. The goal of therapy is to reduce the accumulated substrates, PPi and PLP, caused by the defective enzyme and restore normal skeletal integrity. This memo documents my concurrence with the Division of Gastroenterology and Inborn Errors Products' approval recommendation for BLA 125513 for Strensiq (asfotase alfa) injection for the treatment of patients with perinatal/infantile- and juvenile-onset HPP.

Efficacy was assessed in the perinatal/infantile-onset HPP population in two open-label, single-arm studies (Studies 1 and 2) in 68 subjects receiving Strensiq compared to an historical control cohort of 48 untreated patients with similar clinical features of the disease. The primary efficacy endpoint was overall survival. The key secondary endpoint was invasive ventilation-free survival. Efficacy was clearly and robustly demonstrated on both endpoints. Further supportive evidence was provided by radiologic findings which demonstrated clinically meaningful improvement in HPP-associated rickets, and by improvements in height and weight z-scores. Additionally, population pharmacokinetic analyses demonstrated that there was an exposure-response relationship with survival in the perinatal -/infantile-onset HPP population, and in Study 1, improvement in one or more clinical parameters (respiratory status, radiographic findings, and/or growth) occurred in patients after dosing was increased from 3 mg/kg/week to doses of 6 mg/kg/week or higher.

Efficacy was assessed in the juvenile-onset HPP population in one open-label, single-arm study (Study 3) in 8 subjects receiving Strensiq compared to an historical control cohort of 32 untreated juvenile-onset HPP patients. The primary efficacy endpoint was change in gait as measured by the modified Performance Oriented Mobility Assessment-Gait (mPOMA-G) scale, a qualitative measure of gait. Secondary endpoints included growth and radiographic assessments. While improvement in gait was observed in Strensiq-treated subjects relative to the historical controls, methodologic issues with the test precluded reliance on this result as the basis for establishing efficacy. However, supportive data demonstrated improvements in the 6 Minute Walk Test (6MWT); improvements in height and weight z-scores; improvement in radiographic findings of HPP-associated rickets over time; improvement in bone mineralization indices from matched bone biopsy pairs; and

demonstration of an exposure-response relationship between asfotase alfa concentration at steady state and improvements in the 6MWT and the radiographic assessments, as well as reductions in the substrates inorganic pyrophosphate and pyridoxal-5'-phosphate.

The safety of Strensiq was assessed in 99 subjects with perinatal/infantile- or juvenile-onset HPP, aged 1 day to 58 years. The most serious safety concerns identified in the clinical development program included hypersensitivity reactions (a not unusual finding with therapeutic proteins), localized lipodystrophy, and ectopic calcifications (which may or may not be drug-related as they can occur with the disease as well). The most common adverse reaction was injection site reactions. In general, these were not severe and can be reduced by reducing the frequency of the injections. The incidence of anti-drug antibody (ADA) formation was high, as anticipated with this fusion protein. ADA+ subjects had reduced systemic asfotase alfa exposure, and appeared to have a higher incidence of injection site reactions and ectopic calcifications. The impact of ADA positivity on clinical efficacy could not be reliably determined. Drug product formulation issues impacted systemic asfotase alfa exposure, with the higher concentration formulation providing a 24% lower exposure. The impact of this lower exposure on clinical efficacy, especially in the more severe forms of perinatal/infantile-onset HPP, is unknown. (b) (4)

The major review issue was determining whether there was sufficient evidence to support an efficacy claim in the juvenile-onset HPP population. It is my opinion that the consistent demonstration of improvement across multiple clinically meaningful endpoints, coupled with the demonstration of an exposure-response relationship between asfotase alfa concentration and multiple pharmacodynamic measurements, provide compelling evidence to support approval in this population. One can also point to the robust demonstration of efficacy observed in the perinatal/infantile-onset patients, who had a more severe phenotype of the disease, as support for the efficacy in the juvenile-onset patients, who had a milder phenotype where demonstration of a substantial effect would be more difficult. I acknowledge the very small size of the population studied; this is not unusual in trials of rare diseases. I also believe that if FDA were to approve Strensiq solely for the perinatal/infantile-onset patients, the conduct of an additional clinical trial in the juvenile-onset patients, to assuage any lingering concerns regarding efficacy in this population, would be infeasible once the product is on the market. Therefore, I concur with the Division's recommendation to approve the product in both the perinatal/infantile-onset and juvenile-onset populations.

All safety concerns have been adequately addressed through labeling and post-marketing requirements and commitments.

Discussions regarding product labeling, and postmarketing study requirements and commitments have been satisfactorily completed. There are no inspectional issues that preclude approval. The benefit-risk analysis of Strensiq is favorable and supports approval. Strensiq will fill an unmet medical need for this serious and life-threatening condition.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
<u>Analysis of Condition</u>	<p>Hypophosphatasia (HPP) is a rare inherited disorder caused by inactivating mutations in the alkaline phosphatase liver-type (ALPL) gene, which encodes the tissue non-specific alkaline phosphatase (TNSALP) enzyme. Lack of TNSALP enzyme activity leads to accumulation of certain substrates including inorganic pyrophosphate (PPi), an inhibitor of skeletal mineralization, causing osteomalacia and rickets of long bones and ribs, and pyridoxal-5'-phosphate (PLP), a co-factor form of vitamin B6 which is involved in numerous enzymatic reactions. HPP can be transmitted in an autosomal dominant or recessive manner.</p> <p>HPP patients are classified by age of onset of signs and symptoms.</p> <ul style="list-style-type: none">“Perinatal onset” develops in utero and is evident at birth. It is characterized by severe skeletal hypomineralization, underdeveloped limbs, and severe rachitic chest deformities. It is associated with a high mortality rate due to respiratory insufficiency.“Infantile onset” follows a similar course; however, symptoms do not manifest until approximately 6 months of age. Patients typically present with difficulty feeding, failure to gain weight, rickets,	<p>HPP is a serious, debilitating and life-threatening condition. The more severe forms of the disease manifest during the neonatal or infant period at a frequency of approximately 1/100,000 births.</p> <p>Natural history studies were conducted to characterize the natural history of patients with perinatal-/infantile-onset and juvenile-onset HPP.</p>

	<p>increased intracranial pressure, papilledema, hypertelorism, and brachycephaly associated with premature cranial suture fusion.</p> <ul style="list-style-type: none"> “Juvenile onset” manifests at ≥6 months to ≤18 years of age, and has variable phenotypes. Patients may present with early loss of deciduous teeth, typical rickets-like changes including short stature, and delayed walking. “Adult onset” typically presents during middle age with a prior history of premature loss of deciduous and adult teeth, osteomalacia, metatarsal stress fractures, or radiologic pseudofractures. Adults may develop hyperparathyroidism and calcific periarthritis from periarticular calcium phosphate deposition. <p>The severe forms of HPP have an estimated frequency of 1/100,000 births.</p>	
<u>Current Treatment Options</u>	<p>There are no approved therapies for HPP.</p> <p>Supportive therapy is aimed at decreasing the morbidity associated with the disease, and have included orthopedic surgeries and neurosurgery (for craniosynostosis).</p> <p>In addition to surgical treatments, various symptomatic treatments have been attempted. Treatments with zinc and magnesium and pyridoxal 5'-phosphate have had limited success; non-steroidal anti-inflammatory agents have been shown to improve pain and the secondary metabolic inflammation resulting from the disease; and teriparatide has</p>	<p>There is no approved drug treatment for HPP. Treatment has generally been supportive. Symptomatic therapies have been attempted, some of which have been associated with improvement in various manifestations of the disease. Bone marrow transplantation has been attempted, and achieved some limited success. However, no treatments have been studied that address the underlying disease.</p>

	<p>been successfully used to improve and resolve metatarsal stress fractures in adults with HPP. Some limited success has been seen with bone marrow cell transplantation and bone fragment and cultured osteoblast transplantation. Vitamin B6 has been used for neonatal seizures.</p> <p>Dietary phosphate restriction may provide some benefit.</p> <p>The goal of therapy is to reduce the accumulated substrates PPi and PLP and restore normal skeletal integrity.</p>	<p>The goal of therapy is to reduce the accumulated substrates PPi and PLP, caused by the defective enzyme and restore normal skeletal integrity.</p>
<u>Benefit</u>	<p>The subject of this BLA, Strensiq (asfotase alfa) is a human recombinant tissue-nonspecific alkaline phosphatase-Fc-deca-aspartate fusion protein that is administered by subcutaneous injection. The deca-aspartate peptide moiety is designed to bind specifically to hydroxyapatite, the most prevalent mineral component of bone. Administration of asfotase alfa to patients with HPP is expected to cleave PPi, releasing inorganic phosphate for combination with calcium, thereby promoting hydroxyapatite crystal formation, bone mineralization, and restoring normal skeletal integrity.</p> <p>Asfotase alfa binds with a high affinity (up to 97%) to hydroxyapatite. The efficacy of asfotase alfa was evaluated in a HPP knockout mouse model, Akp2^{-/-} mice. Following SQ administration to Akp2^{-/-} mice, asfotase alfa caused a reduction of plasma PPi levels, and caused a significant increase in bone mineralization of the feet, rib cages and pelvic limbs, and improved body weight gain and survival rate.</p>	<p>Relative to historical controls, Strensiq achieved robust and clinically meaningful improvement in overall survival and invasive ventilation-free survival in two open-label, single arm studies in subjects with severe perinatal-/infantile-onset HPP. Among those subjects who received the proposed dosing of 6 mg/kg/week, the survival rate was 98%. The efficacy of Strensiq was further supported by radiologic findings demonstrating clinically meaningful improvement in HPP-associated rickets, and improvements in height and weight z-scores.</p> <p>Population PK analyses demonstrated that there was an exposure-response</p>

Perinatal-/infantile-onset HPP:

Efficacy was assessed in an open-label, single-arm, 24-week study (Study 1) in 11 subjects aged 3 weeks to 39.5 months with severe perinatal-/infantile-onset HPP, and an ongoing open-label single-arm study (Study 2) in 59 patients aged 1 day to 78 months treated with Strensiq for up to 4 years. The comparator for both Studies 1 and 2 was an historical cohort of 48 untreated patients with severe perinatal-/infantile-onset HPP. Sixty-eight subjects from Studies 1 and 2 were considered in the efficacy analyses, based on clinical features that were similar to the natural history cohort, and consistent with a severe form of the disease. These clinical features included rachitic chest deformity, respiratory compromise, or seizures associated with severe disease.

In Study 1, subjects received a single 2 mg/kg intravenous infusion of Strensiq followed by subcutaneous (SQ) administration of 1 mg/kg/day of Strensiq 3 days per week (with escalation up to 3 mg/kg/day 3 days per week). In Study 2, patients received SQ administration of Strensiq at a dose of 6 mg/kg/week, either as 1 mg/kg/day 6 days per week or as 2 mg/kg/day 3 days per week.

The primary efficacy endpoint was overall survival, defined as time from birth to death. The key secondary endpoint was invasive ventilation-free survival, defined as time from birth to death or first day of ventilator support. Other endpoints that provided supportive evidence of efficacy included radiological assessment of HPP-related skeletal abnormalities

relationship with survival in the perinatal-/infantile-onset HPP population. Furthermore, in Study 1, improvement in one or more clinical parameters (respiratory status, RGI-C score, and/or growth parameters) occurred after dosing was increased from 3 mg/kg/week to doses of 6 mg/kg/week or higher.

While robust evidence of efficacy was provided for the perinatal/infantile-onset HPP subjects, it is acknowledged that all hypothesis testing must be considered exploratory given that the agreed upon endpoints, planned data integrations, and subsequent historical control comparisons were all determined well into the execution of the relevant perinatal/infantile-onset HPP studies. Therefore, no inferential statistics will be presented within the final product labeling

In the juvenile-onset HPP population, relative to historical controls Strensiq-treated subjects demonstrated improvement in gait as measured by the modified Performance Oriented Mobility Assessment-Gait (mPOMA-G);

and growth.

In Study 1, there were 11 subjects enrolled, of whom 64% were female, 91% were Caucasian, and the mean age was 59 weeks. In Study 2, there were 59 subjects enrolled, of whom 54% were female, 78% were Caucasian, and the mean age was 118 weeks. In the historical control group, there were 48 subjects enrolled, of whom 46% were female, 83% were Caucasian, and the median age at diagnosis of HPP was 8.6 weeks.

In Studies 1 and 2 combined, treatment with Strensiq improved overall survival relative to historical control patients. Sixty-two out of 68 subjects (91%) treated with Strensiq versus 13 out of 48 (27%) historical control patients survived during the 9.6-year time period evaluated (HR 0.09 [95% CI 0.04, 0.20]; $p<0.0001$). The survival rate for the subgroup of patients who received the proposed dosing regimen of 6 mg/kg/week without dose modifications was 98% (45/46 patients). At 48 weeks, the Kaplan-Meier estimate of overall survival was 97% for Strensiq-treated subjects versus 42% for historical controls. While survival rates observed in the historical control cohort improved over time (lowest in patients diagnosed prior to 1990 and highest in patients diagnosed in 2000 onward), likely due to improvement in supportive care over time, the survival rates were less than 50% by age 72 weeks even in the cohort of patients diagnosed after 2000, a cohort of patients approximately contemporary with treated patients. In Study 1, all 4 patients with a history of respiratory failure (3

however, reliance on the mPOMA-G was limited due to procedural and methodological issues. Therefore, the gait assessment analysis was deemed insufficient to serve as the sole evidence of efficacy in the juvenile-onset population.

Additional supportive evidence was drawn from:

- an assessment of mobility using the 6 Minute Walk Test. Improvement from baseline to Month 48 in percent predicted values within the normal range for age, sex, and height-matched peers was demonstrated in 6 of 7 (86%) Strensiq-treated subjects, and all 7 subjects were able to walk longer distances at Month 48.
- an assessment of growth, using height and weight z-scores. Relative to historical controls, Strensiq-treated juvenile-onset HPP subjects had improved height and weight growth over time.
- an assessment of change in rickets severity, as assessed

patients) or seizures (1 patient) were alive at the time of the data analysis cut-off date. For Study 2, 10/ 13 patients (77%) with a history of seizures were alive at the time of the data analysis cut-off date. In contrast, none of the historical control patients with a history of respiratory failure or vitamin B6-responsive seizures survived.

In Studies 1 and 2 combined, treatment with Strensiq improved invasive ventilation-free survival relative to historical control patients. Forty-five out of 68 subjects (66%) treated with Strensiq versus 12 out of 48 (25%) historical control patients had no ventilator use and survived during the 9.6-year time period evaluated (HR 0.28 [95% CI 0.16, 0.48]; p<0.0001). At 48 weeks, the Kaplan-Meier estimate of invasive ventilation-free survival was 96% for Strensiq-treated patients and 31% for historical control patients.

Supportive evidence was provided by pooled radiographic data from 64 subjects from Studies 1 and 2, and 4 subjects from Study 3 (discussed below). Change in rickets severity was assessed using the Radiographic Global Impression of Change (RGI-C) scale, a 7-point scale, ranging from a score of -3 (severe worsening of HPP-associated rickets) to 3 (complete or near complete healing of HPP-associated rickets). Patients achieving a minimum RGI-C scale of +2, indicating “substantial healing of rickets”, were defined as “responders”. Radiologic improvements were apparent by Month 24; at last assessment (mean time interval of 24 months), 50/68 (74%) Strensiq-treated subjects were rated as RGI-C responders. No comparative data were available.

using the Radiographic Global Impression of Change scale. All 8 Strensiq-treated subjects showed substantial healing of HPP-associated rickets over time, versus 6% of subjects in the historical control group.

- an analysis of matched bone biopsy pairs from all juvenile-onset subjects, which demonstrated that 7 of 8 subjects showed improvement in bone mineralization indices at 6 months.
- an analysis of exposure-response which demonstrated a relationship between asfotase alfa concentration at steady state and improvements in multiple pharmacodynamic measurements, including the 6MWT and the RGI-C, as well as PPi and PLP.

Supportive evidence was also provided by height and weight growth data in the perinatal-/infantile-onset HPP subjects. Height and weight measurements (as measured by z-scores) were available post-treatment for 72 perinatal/infantile-onset HPP patients, 68 from Studies 1 and 2, and 4 from Study 3. For patients enrolled in Studies 1 and 2, mean baseline height z-scores were -3.3 (range of -10.1 to 0.9). At the time of last assessment, the mean height z-score was -2.9 (range of -10.6 to 0.4). For patients enrolled in Studies 1 and 2, mean baseline weight z-scores were -3.2 (range of -23.8 to 0). At the time of last assessment, the mean weight z-score was -2.4 (range of -20.9 to 1). The mean time interval between baseline and last assessment was 21 months (range of 1 to 72 months). For patients enrolled in Study 3, mean baseline height z-scores were -2.6 (range of -6.6 to -0.7). At the time of last assessment, the mean height z-score was -1.5 (range of -5.8 to 0.4). For patients enrolled in Study 3, mean baseline weight z-scores were -2.5 (range of -8.2 to -1). At the time of last assessment, the mean weight z-score was -1.5 (range of -5.4 to 0.5). The mean time interval between baseline and last assessment was 56 months (range of 53 to 60 months).

It is also notable that the starting dose of Strensiq for all patients in Study 1 was 3 mg/kg/week, and all but one patient experienced improvement in one or more clinical parameters (respiratory status, RGI-C score, and/or growth) after dosing was increased to doses of 6 mg/kg/week or higher.

Juvenile-onset HPP:

Efficacy was assessed in one open-label single-arm, 24-week study (Study 3) in 8 subjects ages 5 to 12 years with a documented diagnosis of juvenile-onset HPP and open growth plates at the time of study entry (and 5 subjects with perinatal-/infantile-onset HPP) with an open-label extension phase of up to 60 months, compared to an historical cohort of 32 untreated juvenile-onset HPP patients aged 5 to 15 years.

In Study 3, subjects received subcutaneous (SQ) administration of either 2 mg/kg/day 3 days per week or 3 mg/kg/day 3 days per week. In the extension phase, subjects were treated with 3 mg/kg/week per the original protocol, which was subsequently amended to 6 mg/kg/week.

The primary efficacy endpoint in the historically-controlled analyses was change in gait as measured by the modified Performance Oriented Mobility Assessment-Gait (mPOMA-G) scale, a qualitative measure of gait. Secondary endpoints included growth and radiographic assessments.

In Study 3, there were 8 juvenile-onset HPP subjects enrolled, of whom 75% were male, 100% were Caucasian, and the mean age at symptom onset was 15.3 months. In the historical control group, there were 32 subjects enrolled, of whom 31% were female, 94% were Caucasian, and the mean age at diagnosis was 17.5 months.

In Study 3, including the extension phase, a gait analysis was conducted using videos from the 8 Strensiq-treated subjects compared to 6 historical control patients. The gait analysis demonstrated a difference in mean rate of change in mPOMA-G score for Strensiq-treated subjects (rate of change 2.25 per year), primarily due to improvement in step length. Seventy-five percent of subjects treated with Strensiq experienced at least a 1 point improvement in step length with either foot compared to 17% of historical control patients. However, reliance on the mPOMA-G instrument was limited due to the post-hoc nature of the analysis, the lack of validation of the instrument in the HPP population, differences in baseline disease severity, and test methodology. Because of these limitations, the gait assessment analysis was deemed insufficient to serve as the sole evidence to support an efficacy claim in the juvenile-onset population.

Mobility was also assessed using the 6 Minute Walk Test (6MWT) in 7 of the 8 Strensiq-treated subjects. The proportion of subjects who had 6MWT percent predicted values within the normal range for age, sex, and height-matched peers increased from 0/7 subjects at baseline to 6/7 subjects (86%) by Month 48, and all 7 subjects were able to walk longer distances at Month 48 compared to baseline.

Additional endpoint analyses were explored. Height and weight measurements (as measured by z-scores) were available post-treatment for 8 juvenile-onset HPP patients,

and 32 untreated HPP patients with similar clinical characteristics. Based on comparison with the historical control group, treated juvenile-onset patients had improved height and weight growth over time – an interval from first to last growth assessment ranging from 19-109 months for the historical control group and up to 60 months for Strensiq-treated subjects. For Strensiq-treated patients, mean baseline height z-scores were -1.5 (range of -3.8 to 0). At the time of last assessment, the mean height z-score was -0.9 (range of -2 to 0). For historical control patients, mean baseline height z-scores were -1.1 (range of -4.9 to 2.6). At the time of last assessment, the mean height z-score was -1.1 (range of -4.9 to 1.8). For Strensiq-treated patients, mean baseline weight z-scores were -1.1 (range of -3.5 to 2.3). At the time of last assessment, the mean weight z-score was 0 (range of -1.3 to 2.2). For historical control patients, mean baseline weight z-scores were -1.2 (range of -5 to 2.1). At the time of last assessment, the mean weight z-score was -1 (range of -5.7 to 2.1).

Change in rickets severity was assessed using the Radiographic Global Impression of Change (RGI-C) scale, a 7-point scale, ranging from a score of -3 (severe worsening of HPP-associated rickets) to 3 (complete or near complete healing of HPP-associated rickets). Based on a responder criterion for substantial healing of rickets, defined as achieving RGI-C score of 2 or higher, all 8 Strensiq-treated subjects were considered responders at the time of last assessment, versus 6% in the historical control patients.

	<p>Matched bone biopsy pairs from all juvenile-onset subjects were analyzed. Seven of 8 subjects showed improvement in bone mineralization indices at 6 months.</p> <p>An exposure-response relationship was observed between estimated average asfotase alfa concentration at steady state ($C_{avg,ss}$) and multiple pharmacodynamic measurements, including the 6MWT and the RGI-C, as well as PPi and PLP, thus providing further supportive evidence of efficacy.</p>	
<u>Risk</u>	<p>The safety of Strensiq was assessed in 99 patients with perinatal/infantile- or juvenile-onset HPP, aged 1 day to 58 years, at doses of 0.9 mg/kg/week to 28 mg/kg/week. Fifty-one patients received at least 96 weeks of treatment and 39 patients received 168 weeks or more of treatment.</p> <p>The most common adverse reaction reported with Strensiq treatment was injection site reaction (63%). Injection site reaction was reported more frequently in patients with juvenile-onset HPP and in patients who received injections 6 times per week than in those who received injections 3 times per week. One patient withdrew from the trial due to a severe injection site reaction, and two patients required dose reductions due to injection site reactions.</p> <p>Other common adverse reactions included hypersensitivity reactions (12%; including one case of anaphylaxis), localized lipodystrophy (28%; including lipoatrophy), and ectopic calcifications (14%; including the cornea and kidneys).</p>	<p>Serious safety concerns identified in the Strensiq clinical development program included hypersensitivity reactions (including one case of anaphylaxis), lipodystrophy (including lipoatrophy and lipohypertrophy), and ectopic calcifications. Patients with HPP are at increased risk for developing ectopic calcification, including nephrocalcinosis, conjunctival calcifications and band keratopathy; however, in the clinical studies, ectopic calcifications were observed involving deeper layers of the cornea or other ophthalmic structures.</p> <p>Mechanistically, treatment with Strensiq raises a concern for the potential formation of ectopic calcifications in other tissues as inorganic phosphate released through</p>

Ectopic calcification was an adverse event of special interest that was assessed throughout the clinical development program with renal ultrasounds and ophthalmology examinations. Ectopic calcifications occurred more commonly in patients with juvenile-onset HPP. There were no ectopic calcification-associated visual changes or changes in renal function reported in the clinical trials. Ectopic calcifications, including nephrocalcinosis, conjunctival calcifications and band keratopathy are known complications of HPP. Treatment with asfotase alfa raises a concern for the potential formation of ectopic calcifications in other tissues as inorganic phosphate released through enzymatic activity binds with calcium to form hydroxyapatite crystals. Based on the clinical reviewer's assessment of the available safety data, there was insufficient information to determine whether some of the reported events represented known disease complications (i.e., band keratopathy) or new safety signals (i.e., calcifications involving deeper layers of the cornea or other ophthalmic structures).

Ten deaths were reported in clinical trial and compassionate use programs; all deaths were attributed to HPP-related disease complications.

A total of 274 non-fatal serious adverse events (SAEs) were reported in 48 patients, the majority of whom (42 patients) were perinatal/infantile onset patients. Eight patients experienced SAEs that the investigator assessed as treatment-related, including injection site reactions, hypersensitivity reactions, craniosynostosis (2 patients each),

enzymatic activity binds with calcium to form hydroxyapatite crystals. There was insufficient information to determine whether some of the reported calcification events represented known disease complications or new safety signals related to Strensiq.

Similarly, the relatedness of serious adverse events of craniosynostosis and conductive deafness to Strensiq versus the disease itself could not be reliably determined.

The most common adverse reactions were injection site reactions, which are known adverse effects with drugs administered subcutaneously and with therapeutic proteins.

Peripheral neuropathy secondary to vitamin B6 toxicity is a potential concern with treatment with Strensiq due to increased levels of pyridoxal formed with the metabolism of PLP. This is primarily a concern with intravenous administration of Strensiq. There are no non-clinical data on the concomitant use of vitamin B6 and

	<p>conductive deafness, chronic hepatitis, and a drug dosing error (1 patient each). Relatedness of craniosynostosis and conductive deafness to Strensiq versus the disease itself cannot be reliably determined. Strensiq may have played a role in the case of chronic hepatitis. Although the case was confounded, the liver is a target organ for asfotase alfa and therefore, it is mechanistically plausible that treatment with Strensiq may have contributed to this event.</p> <p>The applicant noted that peripheral neuropathy secondary to vitamin B6 toxicity was a potential concern with Strensiq treatment (primarily intravenous administration) due to increased levels of pyridoxal (the primary form of vitamin B6 found in the central nervous system) formed with the metabolism of PLP. The applicant noted that no evidence of peripheral neurotoxicity was observed in a non-clinical trial even at very high doses of asfotase alfa. However, there are no non-clinical data on the concomitant use of vitamin B6 and asfotase alfa. One patient being treated with pyridoxine for HPP-related seizures did not receive an initial intravenous dose of Strensiq out of concern that the patient would be exposed acutely to a critical level of pyridoxal. No events of peripheral neuropathy were reported in clinical trials, despite some subjects receiving concomitant vitamin B6.</p> <p>Asfotase alfa is a fusion protein, therefore, the incidence of anti-drug antibodies (ADA) is expected to be high. Among 71 subjects with post baseline immunogenicity data, 57 (80%) subjects were ADA+. Among the 57 ADA+ subjects, 25 (44%) were positive for neutralizing antibodies (NAb+) and 32 (56%)</p>	<p>asfotase alfa; however, no evidence of peripheral toxicity was observed in a non-clinical trial even at very high doses of asfotase alfa. Some subjects in the clinical program were receiving Strensiq and vitamin B6 concomitantly, and no events of peripheral neuropathy were reported.</p> <p>The incidence of ADA in the clinical studies was high, and ADA positivity was associated with lower asfotase alfa exposure. The impact of this on clinical efficacy could not be reliably assessed. ADA positivity was also associated with increased rates of injection site reactions and ectopic calcifications.</p> <p>An assessment of CRIM status has not been performed. Such an assessment could potentially help identify patients who are most at risk for developing ADA.</p> <p>The mechanism of action of asfotase alfa does not target ligands or cell surface antigens; however, asfotase alfa does contain a CH2 domain that can potentially bind to C1q. While asfotase alfa is not expected to bind</p>
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were NAb-. Immunogenicity had a negative impact on the PK of asfotase alfa. Asfotase alfa exposure in ADA- subjects was approximately 1.5- to 2-fold greater than the exposure in ADA+ subjects. The impact of immunogenicity on clinical efficacy could not be evaluated adequately for either the perinatal/infantile-onset HPP patients or the juvenile-onset HPP patients.

Immunogenicity appeared to have an impact on the rate of injection site reactions and ectopic calcifications; ADA+ subjects had slightly higher rates of the two adverse events.

An assessment of Cross Reactive Immunological Material (CRIM) status to help identify patients without endogenous TNSALP who are most at risk for producing antibodies that may result in loss of efficacy of Strensiq was not performed.

Asfotase alfa contains a CH2 domain that can potentially bind to C1q. However, the mechanism of action of asfotase alfa involves the catalysis of soluble substrates such as PPi and PLP and is not targeted toward ligands or cell surface antigens. Therefore, asfotase alfa is not expected to bind and form multivalent antigen-antibody complexes on cell surfaces and as a result the drug is not expected to trigger activation of the complement system.

The formulation concentration had a significant impact on the systemic exposure of asfotase alfa in patients with HPP. The asfotase alfa exposure for the higher concentration formulation (80 mg/mL) was approximately 24% lower

and form antigen-antibody complexes on cell surfaces and is not expected to trigger activation of the complement system, this risk remains unknown.

The higher concentration formulation (80 mg/mL) resulted in lower asfotase alfa exposures relative to the lower concentration formulations at the same dose of asfotase alfa. This may have an effect on the efficacy of the product. The 80 mg/mL concentration formulation was not tested in perinatal/infantile-onset HPP patients.

(b) (4)

asfotase alfa. The current specifications are adequate to support approval; however, specifications will need to be further [redacted] (b) (4) post-approval.

A deficiency in the [redacted] (b) (4) controls for endotoxin was identified. Sterility assurance and microbiology product quality processes and controls are adequate for approval of the application, but will require further remediation post-marketing.

	<p>compared to the lower concentration formulations at the same dose of asfotase alfa.</p> <p>(b) (4)</p>	
	<p>A deficiency in the (b) (4) controls for endotoxin was identified in the microbiology review. ONDP deemed the sterility assurance and microbiology product quality processes and controls to be adequate for approval of the application with remediation of the (b) (4) endotoxin controls to be addressed post-marketing.</p>	
<u>Risk Management</u>	<ol style="list-style-type: none"> 1. Strensiq is associated with hypersensitivity reactions (including anaphylaxis), lipodystrophy (including lipohypertrophy and lipoatrophy), and ectopic calcifications. 2. Strensiq was associated with injection site reactions in 63% of subjects. 3. Serious adverse events of craniosynostosis and conductive deafness were observed in subjects receiving Strensiq. Relatedness of these adverse events to Strensiq versus the disease itself could not be reliably determined. 	<ol style="list-style-type: none"> 1. Product labeling will carry Warnings regarding: <ul style="list-style-type: none"> • the potential for hypersensitivity reactions, including anaphylaxis. Labeling will recommend discontinuation of Strensiq treatment if a severe hypersensitivity reaction occurs. • the potential occurrence of localized lipodystrophy. Labeling will recommend proper injection technique and rotation of injection sites to mitigate this

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| | <p>4. ADA positivity resulted in lower asfotase alfa exposure, which may have an effect on the efficacy of Strensiq.</p> <p>5. ADA positivity appeared to increase the incidence of injection site reactions (ISR) and ectopic calcifications.</p> <p>6. An assessment of CRIM status has not been performed. Such an assessment could potentially help identify patients without endogenous TNSALP who are most at risk for producing antibodies that may result in loss of efficacy of Strensiq.</p> <p>7. The ability of asfotase alfa to form antigen-antibody complexes and to trigger activation of the complement system has not been assessed.</p> <p>8. The formulation concentration had a significant impact on the systemic exposure of asfotase alfa in patients with HPP. The asfotase alfa exposure for the higher concentration formulation (80 mg/mL) was approximately 24% lower compared to the lower concentration formulations at the same dose of asfotase alfa. Furthermore, the 80 mg/mL formulation was not tested in perinatal/infantile-onset HPP patients.</p> <p>9.</p> | <p>risk.</p> <ul style="list-style-type: none"> the potential for formation of ectopic calcifications in the eyes and kidneys. Labeling will recommend ophthalmology examinations and renal ultrasounds at baseline and periodically during treatment with Strensiq, as well as monitoring for changes in vision or renal function. <p>Additionally, the applicant will be required to conduct a prospective observational study to assess the long-term safety of treatment with Strensiq with respect to incidence rates of severe hypersensitivity reactions (including anaphylaxis) and ectopic calcification events.</p> <p>2. Product labeling will acknowledge the common occurrence of injection site reactions and will recommend that such reactions can be reduced by using a less frequent, i.e., 3 times per week, dosing regimen.</p> |
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10. A deficiency in the [REDACTED]^{(b) (4)} controls for endotoxin was identified.

- [REDACTED]^{(b) (4)}
- 4. The impact of immunogenicity on clinical efficacy will be further assessed in the required post-marketing observational study.
 - 5. To provide further insight into the impact of immunogenicity on safety, long term immunogenicity and safety assessments will be required in the post-marketing observational study.
 - 6. The applicant has committed to develop post-marketing a validated CRIM assay for patients with HPP and test patient samples in a cohort of untreated patients, and to correlate the results with antibody response, genetic mutations, enzyme activity level and clinical outcome in patients who are receiving Strensiq treatment.
 - 7. To address the Agency's concerns regarding the capacity of asfotase alfa to activate complement in comparison to human IgG1, the applicant will be required post-marketing to develop an assay to directly compare the complement activating capacity of asfotase alfa to that of human IgG1.

8. Due to the lower exposure with the 80 mg/mL formulation strength and the lack of clinical experience with the 80 mg/mL strength product in pediatric infantile-onset HPP patients to inform its efficacy with respect to overall survival, product labeling will caution against the use of the 80 mg/mL formulation in pediatric patients weighing less than 40 kg.
9. The applicant has committed to evaluate the asfotase alfa manufacturing process and develop a control strategy around sialic acid levels to reduce variability in the sialic acid content and to produce asfotase alfa with total sialic acid content that ensures consistent patient exposure.
10. The applicant has committed to re-evaluate the (b) (4) endotoxin limits and (b) (4) the (b) (4) limits to reflect manufacturing process capability.

Other Background

Regulatory History

In June 2007, a pre-IND meeting was held. The Agency and the applicant discussed the applicant's intended uses of asfotase alfa in the various HPP populations. FDA expressed concern regarding the potential for off-label use and recommended that all populations be studied in a timely manner.

In June 2008, IND 100,619 was opened for the study of asfotase alfa in adults. A compassionate use program for patients with infantile onset HPP was also proposed; however, the Agency issued a Partial Clinical Hold due to insufficient non-clinical data to support dosing for the infantile HPP protocol.

In September 2008, a Type C meeting was held with the applicant to discuss non-clinical studies needed to support chronic dosing in clinical trials.

In November 2008, the Agency removed the Partial Clinical Hold.

In May 2009, asfotase alfa was granted Fast Track Designation.

In December 2009, an End-of-Phase 1 meeting was held at which the Agency recommended that the applicant establish natural history comparator groups for the intended study populations.

In May 2011, an End-of-Phase 2 meeting was held.

In April 2013, subsequent to a change in sponsorship of the IND that occurred in June 2012, a Type C meeting was held with the applicant to discuss the clinical development program.

In May 2013, asfotase alfa was granted Breakthrough Therapy Designation (BTD) for perinatal-, infantile- and juvenile-onset HPP. BTD was not granted for adult-onset HPP due to insufficient clinical evidence (b) (4)

In September 2013, a post-BTD meeting was held. The Agency agreed that a historical control group may be acceptable for clinical trials to support an indication in the infantile-onset and juvenile-onset populations; however, the applicant may need to conduct other studies to support labeling for the juvenile-onset population.

In November 2013, the Agency held a pre-BLA meeting to discuss CMC aspects of the BLA.

In January 2014, the Agency held post-BTD meetings to discuss the overall immunology, clinical pharmacology, and clinical plans for asfotase alfa.

In March 2014, the Agency granted the sponsor's request for a rolling submission and review of the BLA, and the applicant submitted the first wave of the rolling submission.

In July 2014, the Agency held a pre-BLA meeting, at which the applicant clarified that the primary efficacy endpoint for the juvenile-onset HPP population would be gait assessment.

The final wave of the BLA was submitted on December 23, 2014. The BLA was granted priority review; however, a major amendment received on March 20, 2015 resulted in an extended user fee goal date of November 23, 2015.

Dosing

Strensiq is administered as a subcutaneous injection as either 2 mg/kg three times per week, or 1 mg/kg six times per week. The dose may be increased up to 9 mg/kg three times per week for lack of efficacy, defined as no improvement in respiratory status, growth, or radiographic findings. The available exposure-response relationships for effectiveness of asfotase alfa support this proposed dosing regimen.

Strensiq is available in multiple presentations of the 40 mg/mL concentration (18 mg/0.45 mL, 28 mg/0.7 mL, 40 mg/mL) and one presentation of the 100 mg/mL concentration (80 mg/0.8 mL). Maximum administered volume per injection cannot exceed 1 mL. Dosage strengths tested in the clinical trials were 40 mg/mL (in younger children with lower body weight) and 80 mg/mL (in older children with higher body weight). Based on population PK analyses, the 80 mg/mL strength achieved a lower exposure with a relative bioavailability of 76.5% compared to the 40 mg/mL strength.

Product Quality

There are no product quality issues that preclude approval.

Drug Substance: Assay validation for the drug substance is considered acceptable.

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(b) (4) In addition, the sponsor has agreed to a postmarketing commitment (PMC) to evaluate the asfotase alfa manufacturing process and develop a control strategy (b) (4)

ONDp concluded that the drug substance (DS) container closure is acceptable. The data provided support the DS (b) (4)

Drug Product (DP): All excipients are standard pharmacopeial excipients; there are no human or novel excipients in the DP. Sterility, particulate, and extractable volume testing conform to USP

and Ph. Eur. standards and are acceptable. The photostability studies showed that the DP is sensitive to light

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. The container closure system is appropriate for (b) (4) storage of the DP. The data provided support the DP 24-month shelf-life at 2 to 8°C.

The Office of Process and Facilities' final reports of manufacturing facility inspections were completed on September 23, 2015, and were found acceptable.

ONDП granted the applicant's claim for Categorical Exclusion for the Environmental Assessment.

Immunogenicity

The immunogenicity assays for anti-drug antibodies to asfotase alfa were determined to be appropriately validated with adequate sensitivity.

Non-clinical Pharmacology/Toxicology

There are no pharmacology/toxicology issues that preclude approval.

The Pharmacology/Toxicology review concluded that the applicant had submitted adequate nonclinical studies (pharmacology, pharmacokinetic, toxicology and reproductive and developmental toxicology) of asfotase alfa. The NOAEL doses in the six-month IV toxicity study in rats and SC toxicity study in juvenile monkeys were 13 and 10 mg/kg/day (the highest doses tested), respectively which are approximately 6 and 5 times, respectively, the human AUC at the 2 mg/kg/day dose administered three times weekly.

Asfotase alfa was not fetotoxic, embryo lethal or teratogenic in rats and rabbits at doses 21 and 24 times, respectively, the exposure at the recommended human dose, and had no effect on fertility or pre- and post-natal development in rats at IV doses up to 21 times exposure at the recommended human dose.

Product related impurities were determined to be within acceptable limits and are qualified. The levels of all potential leachables from the container closure system are within the recommended safety limit and appear acceptable.

Consistent with FDA policy for enzyme replacement therapies, long-term studies in animals to evaluate carcinogenic potential or studies to evaluate mutagenic potential were not performed with asfotase alfa.

Clinical Pharmacology

There are no clinical pharmacology issues that preclude approval.

Asfotase alfa

[REDACTED] is a soluble fusion glycoprotein comprised of two [REDACTED]^{(b) (4)} polypeptide chains. Each polypeptide chain contains the catalytic domain of human TNSALP, the human IgG1 Fc domain [REDACTED]^{(b) (4)} and a D10 domain used for bone-targeting. The two polypeptide chains are connected by two [REDACTED]^{(b) (4)} disulfide bonds [REDACTED]^{(b) (4)}. Asfotase alfa is expressed in the engineered Chinese hamster ovary (CHO) cell line [REDACTED]^{(b) (4)}

The elimination half-life following a single intravenous administration was approximately 5 days. Following SQ administration of multiple doses of Strensiq 2 mg/kg three times per week for 6 weeks, peak plasma concentrations were achieved in 15 to 20 hours. Following multiple SQ doses of Strensiq, accumulation of asfotase alfa was approximately 2.5- to 4-fold. Steady state exposure is achieved as early as three weeks following initial dose administration. No studies on the metabolism of asfotase alfa have been performed in humans or in animals. Asfotase alfa is a therapeutic protein which is expected to be degraded via peptide hydrolysis to amino acids. Given its molecular weight, the excretion of unchanged asfotase alfa in urine is not expected.

Asfotase alfa is initially distributed in the intra-vascular space and then distributes to the extra-vascular space. Body weight is a significant covariate for the central and peripheral volume of distribution and clearance of asfotase alfa; asfotase alfa exposure increases with body weight. Immunogenicity is a covariate for clearance; formation of anti-drug antibody is associated with a higher clearance of asfotase alfa, 11% higher in the presence of ADA without neutralizing capability and 21% higher in the presence of ADA with neutralizing capability.

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

Given the large number of distinct ALPL genotypes reported, the impact of ALPL genotype on the exposure and/or response to asfotase alfa could not be reliably assessed.

QT prolongation potential. No formal QT/QTc studies were performed for asfotase alfa. As the drug is a therapeutic protein [REDACTED]^{(b) (4)} the risk for prolongation of QT/QTc interval is considered minimal. There was no cardiovascular safety signal in a 6-month study in monkeys, and there was no clinically significant QT prolongation observed in the clinical development program.

Effect of age. No patients with perinatal/infantile- or juvenile-onset HPP aged 65 years or older were enrolled in clinical trials of Strensiq. There is no information to determine whether patients aged 65 years and over respond differently from younger patients.

No dose adjustments are needed because age is correlated with body weight and the dosing is weight-based.

Renal impairment. Based on population PK analyses, renal function by eGFR was not found to influence asfotase alfa clearance. Dose adjustment is not needed.

Hepatic impairment. Based on population PK analyses, hepatic function by liver transaminase levels was not found to influence asfotase alfa clearance. Dose adjustment is not needed.

Clinical/Statistical – Efficacy

Results of the analyses of the primary and key secondary endpoints from Studies 1 and 2, as well as analyses of growth in perinatal/infantile-onset patients from Studies 1, 2, and 3, and juvenile-onset patients from Study 3 are provided in the tables and figures below:

Table 1: Survival and Invasive Ventilation-Free Survival in STRENSIQ-Treated versus Historical Control Patients with Perinatal/ Infantile-Onset HPP[†]

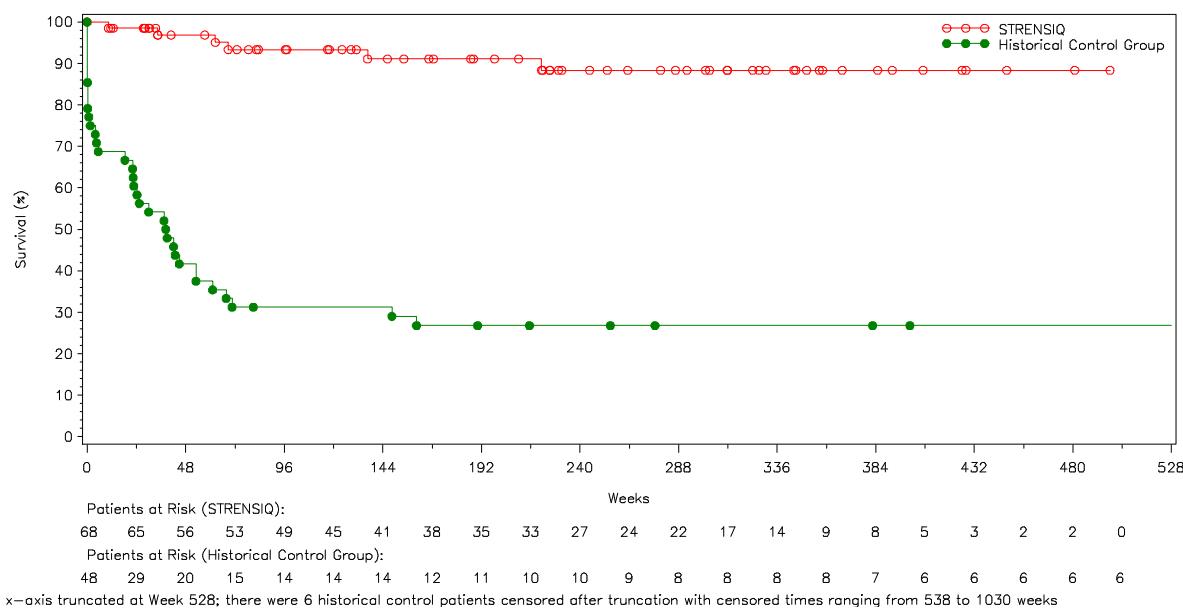
	STRENSIQ-Treated	Historical Controls
Survival (N)	68	48
Alive at Point of Last Contact, n (%)	62 (91)	13 (27)
Hazard Ratio (STRENSIQ/Historical Control), 95% Confidence Interval*	0.14 (0.05, 0.39)	
Kaplan-Meier Estimate of Alive at Age 1 Year (Week 48) (%)	97	42
Invasive Ventilation-Free Survival (N)**	54	48
Alive and Not on Ventilation at Point of Last Contact, n (%)	46 (85)	12 (25)
Hazard Ratio (STRENSIQ/Historical Control), 95% Confidence Interval*	0.21 (0.09, 0.51)	
Kaplan-Meier Estimate of Alive and Not on Ventilation at Age 1 Year (Week 48) (%)	96	31

[†] From applicant submission dated October 21, 2015.

*Adjusted for year of diagnosis.

** Alive and not initiating invasive ventilation after start of STRENSIQ treatment. STRENSIQ-treated patients on invasive ventilation at baseline were excluded from this analysis.

Figure 1: Overall Survival in Strengiq-Treated versus Historical Control Patients with Perinatal/Infantile-Onset HPP*



*From applicant submission dated October 21, 2015.

Table 2: Perinatal/Infantile-Onset Height and Weight Measurements as Measured by Z-Score⁺

	Height Z-score				Weight Z-score			
	Baseline		Last Assessment		Baseline		Last Assessment	
	Mean	Min, Max	Mean	Min, Max	Mean	Min, Max	Mean	Min, Max
Studies 1 and 2* (N=68)	-3.3	-10.1, 0.9	-2.9	-10.6, 0.4	-3.2	-23.8, 0	-2.4	-20.9, 1.1
Study 3 (N=4)**	-2.6	-6.6, -0.7	-1.5	-5.8, 0.4	-2.5	-8.2, -1.0	-1.5	-5.4, 0.5

⁺ From applicant submission dated October 21, 2015.

Table 3: Juvenile-Onset Height and Weight Measurements as Measured by Z-Score

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

The Office of Scientific Investigations (OSI) conducted inspections of two clinical investigator sites and the sponsor. OSI determined that the data generated by the sponsor could be used in support of the respective indication.

Advisory Committee

No Advisory Committee input was sought on this application. Although Strensiq is a New Molecular Entity, there were no controversial issues that would benefit from advisory committee discussion.

Pregnancy Considerations

Consistent with the Pregnancy and Lactation Labeling Rule guidelines, The **Use in Specific Populations** section, **Pregnancy** subsection, of the product label will state that there are no available data on Strensiq use in pregnant women to inform any drug-associated risks, and will provide the results of the animal reproduction studies.

It is not known whether Strensiq is present in human milk. Product labeling will caution that the developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Strensiq and any potential adverse effects on the breastfed infant from Strensiq or from the underlying maternal condition.

(b) (4)

Pediatrics

Pediatric Use. The **Use in Specific Populations** section, **Pediatric Use** subsection, of the product label will state that the safety and effectiveness of Strensiq have been established in pediatric patients, based on data submitted from the four prospective, open-label clinical trials conducted in 99 adult and pediatric patients with perinatal/infantile-onset or juvenile-onset HPP.

Pediatric Rare Disease Voucher. Section 908 of the Food and Drug Administration Safety and Innovation Act (FDASIA) modified the Rare Pediatric Disease Priority Review Voucher Incentive Program to allow the issuance of a “priority review voucher” to the sponsor of a rare pediatric disease product application. The holder of such voucher is entitled to priority review of a single human drug application submitted under section 505(b)(1) after the date of approval of the rare pediatric disease product application. Under the statute, ‘rare pediatric disease’ is defined as:

1. The disease primarily affects individuals aged from birth to 18 years, including age groups often called neonates, infants, children, and adolescents.
2. The disease is a rare disease or condition, within the meaning of section 526.

The term ‘rare pediatric disease product application’ means a human drug application that

1. is for a drug or biological product—
 - a. that is for the prevention or treatment of a rare pediatric disease; and
 - b. that contains no active ingredient (including any ester or salt of the active ingredient) that has been previously approved in any other application under section 505(b)(1), 505(b)(2), or 505(j) of this Act or section 351(a) or 351(k) of the Public Health Service Act;
2. is submitted under section 505(b)(1) of this Act or section 351(a) of the Public Health Service Act;
3. the Secretary deems eligible for priority review;
4. that relies on clinical data derived from studies examining a pediatric population and dosages of the drug intended for that population;
5. that does not seek approval for an adult indication in the original rare pediatric disease product application; and
6. is approved after the date of the enactment of the Prescription Drug User Fee Amendments of 2012.

In the final wave of the rolling NDA submission, the applicant requested that a Rare Pediatric Disease Priority Review Voucher be awarded at the time of product approval. In a memo dated August 11, 2015, OOPD provided a checklist that supported that HPP meets the FDASIA definition of a rare pediatric disease, and that the Strensiq NDA submission represents a rare pediatric disease product application as defined above. Therefore, a Priority Review Voucher will be granted at the time of approval.

Other Relevant Regulatory Issues

Tradename Review

The Division of Medication Error Prevention and Analysis concluded that the applicant's proposed proprietary name "Strensiq" is acceptable from both a promotional and safety perspective. The applicant was informed of this determination on April 13, 2015.

Consults

Division of Bone Reproductive and Urologic Products (DBRUP)

DBRUP was asked to comment on the significance of the applicant's efficacy data analyses of HPP-related bone disease (bone biopsy and radiographic data).

Division of Neurology Products (DNP)

DNP was consulted to provide an assessment of the appropriateness of the modified Performance Oriented Mobility Assessment-Gait (mPOMA-G) endpoint and its relationship to the Six Minute Walk Test (6MWT) and strength assessments for studies in juvenile-onset HPP.

Office of Prescription Drug Promotion (OPDP)

OPDP provided a consultative review of the proposed prescribing information and carton and container labeling, and suggested revisions to ensure that the labeling was free of promotional language.

Division of Medical Policy Programs (DMPP)

DMPP reviewed the patient package insert (PPI) and Instructions for Use (IFU) and provided a collaborative review with the Office of Prescription Drug Promotion.

Division of Medication Error, Prevention, and Analysis (DMEPA)

DMEPA was consulted to review the proposed prescribing information and carton labels for possible sources of medication errors. DMEPA recommended changes to improve clarity and understanding for safe use of the product.

Division of Pediatric and Maternal Health (DPMH)

DPMH was consulted to provide input for appropriate labeling of the pregnancy and lactation subsections of the Strensiq label. A review of the published literature revealed no data with asfotase alfa use in pregnant or lactating women. DPMH recommended edits to the Strensiq label to ensure compliance with the Pregnancy and Lactation Labeling Rule guidelines.

DPMH provided input on several sections of labeling to ensure the safe and effective use of the product in the pediatric population.

Division of Risk Management (DRISK)

DRISK was consulted to determine the need for risk mitigation strategies beyond professional labeling. DRISK concluded that the benefit-risk profile for Strensiq was acceptable and a Risk Evaluation and Mitigation Strategy was not warranted.

Postmarketing Requirements and Commitments

Post Marketing Requirements

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

Post Marketing Commitments

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

(b) (4)

Provide detailed summaries of all data utilized to support the revised control strategy

(b) (4)

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

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/s/

AMY G EGAN
10/23/2015