STRENSIQ®
(asfotase alfa)

1. NAME OF THE MEDICINAL PRODUCT

STRENSIQ solution for injection 40 mg/mL
STRENSIQ solution for injection 100 mg/mL

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

STRENSIQ is a formulation of asfotase alfa, which is a human recombinant tissue-non-specific alkaline phosphatase-Fc-deca-aspartate fusion protein and is an enzyme produced by recombinant DNA technology using mammalian Chinese Hamster Ovary (CHO) cell culture.

For the full list of excipients, please see Section 6.1.

3. PHARMACEUTICAL FORM

STRENSIQ is a sterile, preservative-free, non-pyrogenic, clear, slightly opalescent or opalescent, colorless to slightly yellow aqueous solution; few small translucent or white particles may be present.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

STRENSIQ is indicated for long-term enzyme replacement therapy in patients with pediatric-onset hypophosphatasia (HPP).

4.2 Posology and method of administration

Posology

Treatment should be initiated by a physician experienced in the management of patients with metabolic or bone disorders.

STRENSIQ is for subcutaneous injection only.

The dosing regimen consists of a total of 6 mg/kg/week of asfotase alfa administered by subcutaneous injection. The recommended dosage regimen of asfotase alfa is 2 mg/kg of body weight administered three times per week or 1 mg/kg of body weight administered six times per week.

Dosage for perinatal/infantile-onset HPP

The recommended dosage regimen of STRENSIQ for the treatment of perinatal/infantile-onset HPP is 6 mg/kg per week administered subcutaneously as either:

- 2 mg/kg three times per week, or

- 1 mg/kg six times per week. Injection site reactions may limit the tolerability of the six times per week regimen (see Section 4.8)

The dose of STRENSIQ may be increased for lack of efficacy (e.g., no improvement in respiratory status, growth, or radiographic findings) up to 9 mg/kg per week administered subcutaneously as 3 mg/kg three times per week.

Dosage for juvenile-onset HPP

The recommended dosage regimen of STRENSIQ for the treatment of juvenile-onset HPP is 6 mg/kg per week administered subcutaneously as either:

- 2 mg/kg three times per week, or
- 1 mg/kg six times per week. Injection site reactions may limit the tolerability of the six times per week regimen

Special populations

Pediatric population

The safety and effectiveness of STRENSIQ have been established in pediatric patients. Currently available data are described in Section 5.4.

Use in the elderly

The safety and efficacy of STRENSIQ in patients older than 65 years have not been established.

Renal and hepatic impairment

The safety and efficacy of STRENSIQ in patients with renal or hepatic impairment have not been evaluated and no specific dose regimen can be recommended for these patients.

Method of administration

STRENSIQ is for subcutaneous injection only. The maximum volume of medication per injection should not exceed 1 mL. If more than 1 mL is required, multiple injections may be administered on the same day, at different sites.

1. Administer STRENSIQ within 3 hours upon removal of the vial(s) from refrigeration. Take the unopened STRENSIQ vial(s) out of the refrigerator 15 to 30 minutes before injecting to allow the liquid to reach room temperature. Do not warm STRENSIQ in any other way (for example, do not warm it in a microwave or in hot water).
2. Rotate the injection from among the following sites to reduce the risk of lipodystrophy: abdominal area, thigh, deltoid, or buttocks (see Section 4.4 and Section 4.8).
3. Do NOT administer injections in areas that are reddened, inflamed, or swollen.
4. Inject STRENSIQ subcutaneously into the determined site and properly dispose of the syringe and the needle.
5. STRENSIQ vials are single use only. Discard any unused product.

Preparation for administration

Each vial of STRENSIQ is intended for single use only.

Use aseptic technique.

1. Determine the total weekly volume needed for the prescribed dosage based on the patient's weight and recommended dosage. Follow these steps to determine the patient dose:

   Total weekly dose (mg) = patient's weight (kg) x prescribed dose (mg/kg/week)

   Total injection volume (mL) per week = Total dose (mg/week) divided by the STRENSIQ concentration (40 mg/mL or 100 mg/mL)

   Round total injection volume to the nearest hundredth of a mL

   Total number of vials per week = Total injection volume divided by vial volume (mL)
2. Determine the number of injection days per week (three or six per week).
3. Determine dose per injection day. Patient weights should be rounded to the nearest kilogram when determining dose. Use the following tables for guidance, for patients administering 2 mg/kg three times per week (Table 1), 1 mg/kg six times per week (Table 2) and for dose escalations to 3 mg/kg three times per week, recommended only for patients with perinatal/infantile-onset HPP (Table 3) (see Section 4.2).
4. When preparing a volume for injection greater than 1 mL, split the volume equally between two or more syringes, and administer each injection using a separate site for each injection.

Table 1 Weight-Based Dosing for Administration of 2 mg/kg Three Times per Week

Body Weight (kg)*	Dose to Inject	Volume to Inject	Vial Configuration
3	6 mg	0.15 mL	18 mg/0.45 mL
4	8 mg	0.20 mL	18 mg/0.45 mL
5	10 mg	0.25 mL	18 mg/0.45 mL
6	12 mg	0.30 mL	18 mg/0.45 mL
7	14 mg	0.35 mL	18 mg/0.45 mL
8	16 mg	0.40 mL	18 mg/0.45 mL
9	18 mg	0.45 mL	18 mg/0.45 mL
10	20 mg	0.50 mL	28 mg/0.7 mL
15	30 mg	0.75 mL	40 mg/1.0 mL
20	40 mg	1.00 mL	40 mg/1.0 mL
25	50 mg	1.25 mL	Two 28 mg/0.7 mL vials
30	60 mg	1.50 mL	Two 40 mg/1.0 mL vials
35	70 mg	1.75 mL	Two 40 mg/1.0 mL vials
40	80 mg	0.80 mL	80 mg/0.8 mL
50	100 mg	1.00 mL	Two 80 mg/0.8 mL vials
60	120 mg	1.20 mL**	Two 80 mg/0.8 mL vials
70	140 mg	1.40 mL**	Two 80 mg/0.8 mL vials

Body Weight (kg)*	Dose to Inject	Volume to Inject	Vial Configuration
80	160 mg	1.60 mL**	Two 80 mg/0.8 mL vials

* Do not use the 80 mg/0.8 mL vial of STRENSIQ in pediatric patients weighing less than 40 kg (see Section 5).

** When preparing a volume for injection greater than 1 mL, split the volume equally between two syringes, and administer two injections. When administering the two injections, use two separate injection sites.

Table 2 Weight-Based Dosing for Administration of 1 mg/kg Six Times per Week

Body Weight (kg)*	Dose to Inject	Volume to Inject	Vial Configuration
3	3 mg	0.08 mL	18 mg/0.45 mL
4	4 mg	0.10 mL	18 mg/0.45 mL
5	5 mg	0.13 mL	18 mg/0.45 mL
6	6 mg	0.15 mL	18 mg/0.45 mL
7	7 mg	0.18 mL	18 mg/0.45 mL
8	8 mg	0.20 mL	18 mg/0.45 mL
9	9 mg	0.23 mL	18 mg/0.45 mL
10	10 mg	0.25 mL	18 mg/0.45 mL
15	15 mg	0.38 mL	18 mg/0.45 mL
20	20 mg	0.50 mL	28 mg/0.7 mL
25	25 mg	0.63 mL	28 mg/0.7 mL
30	30 mg	0.75 mL	40 mg/1 mL
35	35 mg	0.88 mL	40 mg/1 mL
40	40 mg	1.00 mL	40 mg/1 mL
50	50 mg	0.50 mL	80 mg/0.8 mL
60	60 mg	0.60 mL	80 mg/0.8 mL
70	70 mg	0.70 mL	80 mg/0.8 mL
80	80 mg	0.80 mL	80 mg/0.8 mL
90	90 mg	0.90 mL	Two 80 mg/0.8 mL vials
100	100 mg	1.00 mL	Two 80 mg/0.8 mL vials

* Do not use the 80 mg/0.8 mL vial of STRENSIQ in pediatric patients weighing less than 40 kg (see Section 5).

Table 3 Weight-Based Dosing for Administration of 3 mg/kg Three Times per Week – Only for Perinatal/Infantile-Onset HPP*

Body Weight (kg)**	Dose to Inject	Volume to Inject	Vial Configuration
3	9 mg	0.23 mL	18 mg/0.45 mL
4	12 mg	0.30 mL	18 mg/0.45 mL

Body Weight (kg)**	Dose to Inject	Volume to Inject	Vial Configuration
5	15 mg	0.38 mL	18 mg/0.45 mL
6	18 mg	0.45 mL	18 mg/0.45 mL
7	21 mg	0.53 mL	28 mg/0.7 mL
8	24 mg	0.60 mL	28 mg/0.7 mL
9	27 mg	0.68 mL	28 mg/0.7 mL
10	30 mg	0.75 mL	40 mg/1 mL
15	45 mg	1.13 mL***	Two 28 mg/0.7 mL vials
20	60 mg	1.50 mL***	Two 40 mg/mL vials
25	75 mg	1.88 mL***	Two 40 mg/mL vials

* A regimen of 3 mg/kg three times per week is recommended only for patients with perinatal/infantile-onset HPP (see Section 4.2).

** Do not use the 80 mg/0.8 mL vial of STRENSIQ in pediatric patients weighing less than 40 kg (see Section 5).

***When preparing a volume for injection greater than 1 mL, split the volume equally between two or more syringes, and administer each injection using a separate site for each injection.

5. Inspect the solution in the vial(s) for particulate matter and discoloration. STRENSIQ is supplied as a clear, slightly opalescent or opalescent, colorless to slightly yellow aqueous solution; a few small translucent or white particles may be present. Discard any vials(s) not consistent with this appearance.
6. Assemble injection supplies. Administer STRENSIQ using sterile disposable 1 mL syringes and ½ inch injection needles, between 25 to 29 gauge are recommended. The use of two different gauge needles is recommended, a larger bore needle (e.g. 25 gauge) for withdrawal of the medication, and a smaller bore needle (e.g. 29 gauge) for the injection. For doses greater than 1 mL, the injection volume should be split equally between two 1 mL syringes. Always use a new syringe and needle for each injection.
7. Remove vial cap, aseptically prepare the vial and insert the syringe into the vial to withdraw the prescribed dose for administration.
8. Remove any air bubbles in the syringe and verify the correct dose.

4.3 Contraindications

Severe or life-threatening hypersensitivity to the active substance or to any of the excipients if hypersensitivity is not controllable (see Section 4.4).

4.4 Special warnings and special precautions for use

Hypersensitivity

Hypersensitivity reactions have been reported in STRENSIQ-treated patients including signs and symptoms consistent with anaphylaxis. These symptoms included difficulty breathing, choking sensation, periorbital edema, and dizziness. The reactions have occurred within minutes after subcutaneous administration of STRENSIQ.

Hypersensitivity reactions have been observed as late as more than 1 year after treatment initiation. Other hypersensitivity reactions included vomiting, nausea, fever, headache, flushing, irritability, chills, erythema, rash, pruritus, and oral hypoesthesia (see Section 4.8).

If a severe hypersensitivity reaction occurs, discontinue STRENSIQ treatment and initiate appropriate medical treatment. Consider the risks and benefits of re-administering STRENSIQ to individual patients following a severe reaction, taking other factors into account that may contribute to the risk of a hypersensitivity reaction, such as concurrent infection and/ or use of antibiotics. If the decision is made to re-administer the product, the re-challenge should be made under medical supervision and consideration may be given to use of appropriate pre-medication. Patients should be monitored for reoccurrence of signs and symptoms of a severe hypersensitivity reaction. Severe or potentially life-threatening hypersensitivity is a contraindication to re-challenge, if hypersensitivity is not controllable (see Section 4.3).

Lipodystrophy

Localized lipodystrophy, including lipoatrophy and lipohypertrophy, has been reported at injection sites after several months in patients treated with STRENSIQ in clinical trials (see Section 4.8). Advise patients to follow proper injection technique and to rotate injection sites (see Section 4.2).

Injection site reactions

Administration of asfotase alfa may result in local injection site reactions (including, but not limited to, erythema, rash, discoloration, pruritus, pain, papule, nodule, atrophy) defined as any related adverse event occurring during the injection or until the end of the injection day (see Section 4.8). These have been generally assessed as non-serious, mild to moderate in severity and self-limiting.

Rotation of injection sites may help to minimize these reactions.

STRENSIQ administration should be interrupted in any patient experiencing severe injection reactions and appropriate medical therapy administered.

Immunogenicity

As with all therapeutic proteins, there is potential for immunogenicity. During clinical trials, anti-drug antibodies have been detected in patients receiving treatment with STRENSIQ using an electrochemiluminescent (ECL) immunoassay. Antibody positive samples were tested to determine the presence of neutralizing antibodies based on in vitro inhibition of the catalytic activity of STRENSIQ. Among 109 patients with hypophosphatasia (HPP) enrolled in the clinical studies and who had post-baseline antibody data available, 97/109 (89.0%) tested positive for anti-drug antibodies at some time point after starting STRENSIQ treatment. Among those 97 patients, 55 (56.7%) also showed the presence of neutralizing antibodies at some time point post-baseline. No correlation was observed between the anti-drug antibody titer and neutralizing antibody (% inhibition) values. Formation of anti-drug antibody resulted in a reduced systemic exposure of asfotase alfa (see Section 5).

The detection of antibody formation is dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing

of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of the antibodies to STRENSIQ with the incidence of antibodies to other products may be misleading (see Section 4.8).

Ectopic calcification

Patients with HPP are at increased risk for developing ectopic calcifications due to their disease. Ophthalmology examinations and renal ultrasounds are recommended at baseline and periodically during treatment with STRENSIQ to monitor for signs and symptoms of ophthalmic and renal ectopic calcifications and for changes in vision or renal function.

Events of ectopic calcification, including ophthalmic (conjunctival and corneal) calcification and nephrocalcinosis, have been reported in the clinical trial experience with STRENSIQ. There was insufficient information to determine whether or not the reported events were consistent with the disease or due to STRENSIQ. No visual changes or changes in renal function were reported resulting from the occurrence of ectopic calcifications.

Craniosynostosis

Craniosynostosis as a manifestation of hypophosphatasia is documented in published literature and occurred in 61.3% of patients between birth and 5 years of age in a natural history study of untreated infantile onset hypophosphatasia patients. Craniosynostosis can lead to increased intracranial pressure. Periodic monitoring (including fundoscopy for signs of papilloedema) and prompt intervention for increased intracranial pressure is recommended in hypophosphatasia patients below 5 years of age.

In asfotase alfa clinical studies, adverse events of craniosynostosis (associated with increased intracranial pressure), including worsening of pre-existing craniosynostosis have been reported in hypophosphatasia patients below 5 years of age. There are insufficient data to establish a causal relationship between exposure to STRENSIQ and progression of craniosynostosis.

Serum parathyroid hormone and calcium

Serum parathyroid hormone concentration may increase in hypophosphatasia patients receiving asfotase alfa, most notably during the first 12 weeks of treatment. It is recommended that serum parathyroid hormone and calcium be monitored in patients treated with asfotase alfa. Supplements of calcium and oral vitamin D may be required (see Section 5.1).

Excipients

This medicinal product contains less than 1 mmol sodium (23 mg) per vial, i.e. essentially ‘sodium-free’ (see Section 6.1).

4.5 Interaction with other medicinal products and forms of interaction

No interaction studies have been performed with asfotase alfa. Based on its structure and pharmacokinetics, asfotase alfa is an unlikely candidate for Cytochrome P450 mediated interactions.

Serum alkaline phosphatase

High serum ALP measurements detected through clinical laboratory testing are expected in patients receiving STRENSIQ and reflect circulating concentrations of asfotase alfa.

Do not rely on serum ALP measurements for clinical decision making in patients treated with STRENSIQ.

Laboratory tests utilizing alkaline phosphatase as a detection reagent

Alkaline Phosphatase (ALP) is used as the detection reagent in many routine laboratory assays. Studies have shown that there may be analytical interference between asfotase alfa and laboratory tests that utilize an alkaline phosphatase (ALP)-conjugated test system, rendering potentially erroneous test results in patients treated with STRENSIQ. ALP-conjugated test systems are utilized to measure substances such as hormones, bacterial antigens and antibodies. Therefore, it is recommended that laboratory assays which do not have ALP-conjugate technology be used when testing samples from patients who are receiving STRENSIQ.

To avoid erroneous test results for patients treated with STRENSIQ, inform laboratory personnel that the patient is being treated with STRENSIQ and discuss the use of a testing platform which does not utilize an ALP-conjugated test system.

4.6 Pregnancy and lactation

Pregnancy

There are insufficient data from the use of asfotase alfa in pregnant women to determine if asfotase alfa exposure during pregnancy poses any risk to the mother or foetus.

Following repeated subcutaneous administration to pregnant mice in the therapeutic dose range (>0.5 mg/kg), asfotase alfa levels were quantifiable in fetuses at all doses tested, suggesting cross-placental transport of asfotase alfa. Animal studies are insufficient with respect to reproductive toxicity (see Section 5.3). Asfotase alfa is not recommended during pregnancy and in women of childbearing potential not using contraception.

Breastfeeding

There is insufficient information on the excretion of asfotase alfa in human milk. A risk to the newborns/infants cannot be excluded. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from asfotase alfa therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Fertility

Preclinical fertility studies were conducted and showed no evidence of effect on fertility and embryo-fetal development.

4.7 Effects on ability to drive and use machines

STRENSIQ has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

The data described below reflect exposure to STRENSIQ in 112 patients with perinatal/infantile-onset (n = 89), juvenile-onset (n = 22), and adult onset (n = 1) HPP (age at enrollment from 1 day to 66.5 years) treated with STRENSIQ, most for more than 2 years (range from 1 day to 391.9

weeks [7.5 years]): a majority of patients (69) received at least 120 weeks (2.3 years) of treatment of which 44 patients received 240 weeks (4.6 years) or more of treatment.

Injection site reactions occurred in 74% of patients receiving STRENSIQ. The majority of injection site reactions resolved within a week. One patient withdrew from the trial due to an injection site hypersensitivity.

Table 4 gives the adverse reactions observed from clinical trials.

Adverse reactions with STRENSIQ are listed by system organ class and preferred term using MedDRA frequency convention very common (≥ 1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000) and not known (cannot be estimated from the available data). Due to the small patient population (n = 112), the frequency categorization may not reflect the occurrence of an adverse reaction in a larger patient population. Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 4 Adverse Reactions Reported in Clinical Trials in HPP Patients (1 Day to 66.5 Years of Age, treatment duration range from 1 day to 391 weeks [7.5 years])

MedDRA System Organ Class	**Very Common (≥ 1/10)**	**Common (≥1/100 to <1/10)**	**Uncommon (≥1/1,000 to <1/100)**	**Rare (≥1/10,000 to <1/1,000)**	**Very Rare (<1/10,000)**
General disorders and administration site conditions	Injection site reactions (ISRs)[a] Injection associated reaction (IARs)[b]				
Immune system disorders		Hypersensitivity[c]			
Skin and subcutaneous tissue disorders		Skin discolouration	Skin hyperpigmentation		
Renal and urinary disorders		Nephrolithiasis			
Metabolism and nutrition		Hypocalcaemia			

[a] Preferred terms considered as ISRs are presented in section below

[b] Preferred terms considered as IARs reactions are presented in section below

[c] Signs and symptoms consistent with anaphylaxis have been observed (see Section 4.4)

Injection site reactions (ISRs)

ISRs (including injection site atrophy, abscess, erythema, discoloration, pain, pruritus, macule, swelling, contusion, bruising, lipodystrophy (lipoatrophy or lipohypertrophy), induration, reaction, nodule, rash, papule, haematoma, inflammation, urticaria, calcification, warmth, haemorrhage, cellulitis, scar, mass, extravasation, exfoliation and vesicles) are the most common adverse reactions, observed in approximately 74% of the patients in the clinical studies.

Injection associated reactions (IARs)

IARs (including hypersensitivity, irritability, pyrexia, rash, pruritis, chills, erythema, nausea, vomiting, flushing, oral hypoesthesia, headache, tachycardia and cough) are very common adverse reactions, observed in approximately 22/112 (19.6%) of the patients in the clinical studies. A few case reports of anaphylactoid/hypersensitivity reaction have also been received and were associated with signs and symptoms of difficulty breathing, choking sensation, periorbital edema and dizziness.

Immunogenicity

No trends in adverse events (AEs) based on antibody status were observed in completed clinical trials. Furthermore, patients confirmed positive for antibodies have not shown signs of tachyphylaxis following subcutaneous STRENSIQ administration.

Cases from the post-approval setting suggest that development of inhibitory antibodies may be associated with a decreased clinical response.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via their national reporting system.

4.9 Overdose

The maximum dose of asfotase alfa used in clinical studies is 28 mg/kg/week. No dose-related toxicity or change in the safety profile has been observed in clinical studies to date; therefore, no overdose level has been determined.

5. PHARMACOLOGICAL PROPERTIES

Pharmacotherapeutic group: Other alimentary tract and metabolism products, enzymes, ATC code: A16AB13.

5.1 Pharmacodynamic properties

Mechanism of action

Asfotase alfa is a human recombinant tissue-nonspecific alkaline phosphatase (ALP)-Fc-deca-aspartate fusion protein that is expressed in an engineered Chinese hamster ovary (CHO) cell line. Asfotase alfa is a soluble glycoprotein composed of two identical polypeptide chains, each with a

length of 726 amino acids made from (i) the catalytic domain of human tissue-nonspecific ALP, (ii) the human immunoglobulin G1 Fc domain and (iii) a deca-aspartate peptide domain.

HPP is caused by a deficiency in TNSALP enzyme activity, which leads to elevations in several TNSALP substrates, including inorganic pyrophosphate (PPi). Elevated extracellular levels of PPi block hydroxyapatite crystal growth which inhibits bone mineralization and causes an accumulation of unmineralized bone matrix which manifests as rickets and bone deformation in infants and children and as osteomalacia (softening of bones) once growth plates close, along with muscle weakness. Replacement of the TNSALP enzyme upon STRENSIQ treatment reduces the enzyme substrate levels.

Pharmacodynamic effect

Perinatal/infantile-and juvenile-onset HPP patients treated with STRENSIQ had reductions in plasma TNSALP substrates, PPi and pyridoxal 5'-phosphate (PLP) within 6 to 12 weeks of treatment. Reductions in plasma PPi and PLP levels did not correlate with clinical outcomes. In adult patients with pediatric-onset HPP, the pharmacodynamics of asfotase alfa was consistent with those observed in pediatric patients with perinatal/infantile-onset or juvenile-onset HPP.

Bone biopsy data from perinatal/infantile-onset and juvenile-onset HPP patients treated with STRENSIQ demonstrated decreases in osteoid volume and thickness indicating improved bone mineralization.

5.2 Pharmacokinetic properties

Based on data in 38 HPP patients, the pharmacokinetics of asfotase alfa exhibit dose proportionality across the dose range of 0.3 mg/kg to 3 mg/kg once every other day for three times a week, and appear to be time-independent. Steady state exposure was achieved as early as three weeks after the administration of the first dose. The elimination half-life following subcutaneous administration was approximately 5 days. In adult patients with pediatric-onset HPP, the pharmacokinetics of asfotase alfa at doses of 0.5, 2 and 3 mg/kg administered three times per week were consistent with those observed in pediatric patients with pediatric-onset HPP, and thus supported the approved dose of 6 mg/kg per week in treating adult patients with pediatric-onset HPP.

Table 5 summarizes the pharmacokinetic parameters following multiple doses in 20 HPP patients after subcutaneous administration of STRENSIQ at 2 mg/kg three times per week in Study 2 (age of less than or equal to 5 years) and Study 3 (age of greater than 5 to 12 years), indicating the pharmacokinetics were similar between patients in the two age groups.

Table 5 Summary of Pharmacokinetic Parameters Following Multiple Subcutaneous Administration of STRENSIQ 2 mg/kg Three Times per Week

	Study 2	**Study 3**
N	14	6
Age (year)	3.4 ± 2.1	8.6 ± 2.2
	(0.2, 6.2)	(6.1, 12.6)
Weight at baseline (kg)	11.2 ± 5.0	21.2 ± 7.9

	Study 2	Study 3
	(2.9, 17.1)	(11.4, 35.4)
t_{last} (h)	48.1 ± 0.1 (47.9, 48.3)	48.0 ± 0.1 (48.0, 48.1)
t_{max} (h)	14.9 ± 10.4 (0, 32.2)	20.8 ± 10.0 (11.9, 32.2)
C_{max} (ng/mL)	1794 ± 690 (856, 3510)	2108 ± 788 (905, 3390)
AUC_t (h*ng/mL)	66042 ± 25758	89877 ± 33248
	(27770, 119122)	(37364, 142265)
Accumulation Ratio[a]	1.5	3.9

[a] Ratio values reflect the fold increase of AUCt from Week 1 based on mean AUCt, values.
Data are presented as mean ± standard deviation (range). Study 3 includes patients with perinatal/infantile-or juvenile-onset of disease. tlast, time of last concentration; tmax, time of maximal concentration; Cmax, maximal concentration; AUCt, area under the concentration-time curves over a dosing interval of 48 hours.

Population PK analysis of asfotase alfa concentrations supports weight-based dosing because body weight is a major covariate of asfotase alfa clearance. The formulation concentration had an impact on the systemic exposure of asfotase alfa in HPP patients. The higher concentration formulation (80 mg/0.8 mL vial) achieved an approximately 25% lower systemic asfotase alfa exposure (i.e., concentrations and AUC) compared to the lower concentration formulations (18 mg/0.45 mL, 28 mg/0.7 mL or 40 mg/mL vials) at the same dose of STRENSIQ (see Section 4.2).

Formation of anti-drug antibodies resulted in reduced systemic exposure of asfotase alfa.

5.3 Preclinical safety data

In nonclinical safety testing in rats, no body system-specific adverse effects were noted at any dose or route of administration.

Dose- and time-dependent acute injection reactions that were transient and self-limiting were noted in rats at intravenous use doses of 1 to 180 mg/kg.

Ectopic calcifications and injection site reactions were observed in monkeys when asfotase alfa was administered subcutaneously at daily doses up to 10 mg/kg through 26 weeks. These effects were restricted to injection sites and were partially or completely reversible.

There was no evidence of ectopic calcification observed in any other tissues examined.

Preclinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity or toxicity to reproduction and development. However, in pregnant rabbits administered intravenous doses of up to 50 mg/kg/day asfotase alfa, anti-drug antibodies were detected in up to 75% of animals, which could affect the detection of reproductive toxicity.

No animal studies have been conducted to evaluate the genotoxic and carcinogenic potential of asfotase alfa.

5.4 Clinical efficacy and safety

Perinatal/infantile-onset HPP

Study ENB-002-08/ENB-003-08 was a 24-week prospective single-arm trial in 11 patients aged 3 weeks to 39.5 months with severe perinatal/infantile-onset HPP; 7/11 (64%) were female and 10/11 (91%) were white. Severe perinatal/infantile-onset HPP was defined as biochemical, medical history and radiographic evidence of HPP as well as the presence of any of the following: rachitic chest deformity, vitamin B6-dependent seizures, or failure to thrive. Ten of 11 patients completed the 24-week trial and continued treatment in the extension phase. Nine patients have been treated for at least 5 years (60 months) and 4 patients have been treated for more than 7 years (84 months). Patients received STRENSIQ at 3 mg/kg per week for the first month; subsequently, dose increases up to 9 mg/kg per week were allowed for changes in weight and/or for lack of efficacy. All 10 patients required dose increases to 6 mg/kg per week or higher; 9 patients increased between 4 and 24 weeks after starting treatment and 1 patient increased after 70 weeks due to suboptimal clinical response. One patient's dose was decreased from 9 mg/kg per week to 6 mg/kg per week based on PK data. In the extended treatment period, the dose in one patient increased from 9 mg/kg per week to 12 mg/kg per week.

Study ENB-010-10 was a prospective open-label study in 69 patients, aged 1 day to 72 months with perinatal/ infantile-onset HPP; 54/69 (78%) were white. Patients received STRENSIQ at 6 mg/kg per week for the first 4 weeks. All patients began the study on a dose of asfotase alfa 6 mg/kg per week. The dose of asfotase alfa was increased for 11 patients during the study. Of these 11 patients, 9 patients had their doses increased specifically to improve clinical response. The recommended dosage regimen of STRENSIQ for the treatment of perinatal-/ infantile-onset HPP is 6 mg/kg per week, up to 9 mg/kg per week administered subcutaneously as 2 mg/kg or 3 mg/kg three times per week (see Section 4.2).

Thirty-eight patients were treated for at least 2 years (24 months) and 6 patients have been treated for at least 5 years (60 months).

Survival and ventilation-free survival

Survival and invasive ventilation-free survival were compared in STRENSIQ-treated patients (Studies ENB-002-08/ENB-003-08 and ENB-010-10) with a historical cohort of untreated patients with similar clinical characteristics (Table 6 and Figure 1).

Table 6 Survival and Invasive Ventilation-Free Survival in STRENSIQ-Treated versus Historical Control Patients with Perinatal/ Infantile-Onset HPP

	STRENSIQ-	**Historical Controls**
Survival	n = 78	n = 48
Alive at Point of Last Contact (%)	69 (88%)	13 (27%)
Hazard Ratio (STRENSIQ/Historical Control), 95% Confidence Interval*	0.174 (0.072, 0.421)	

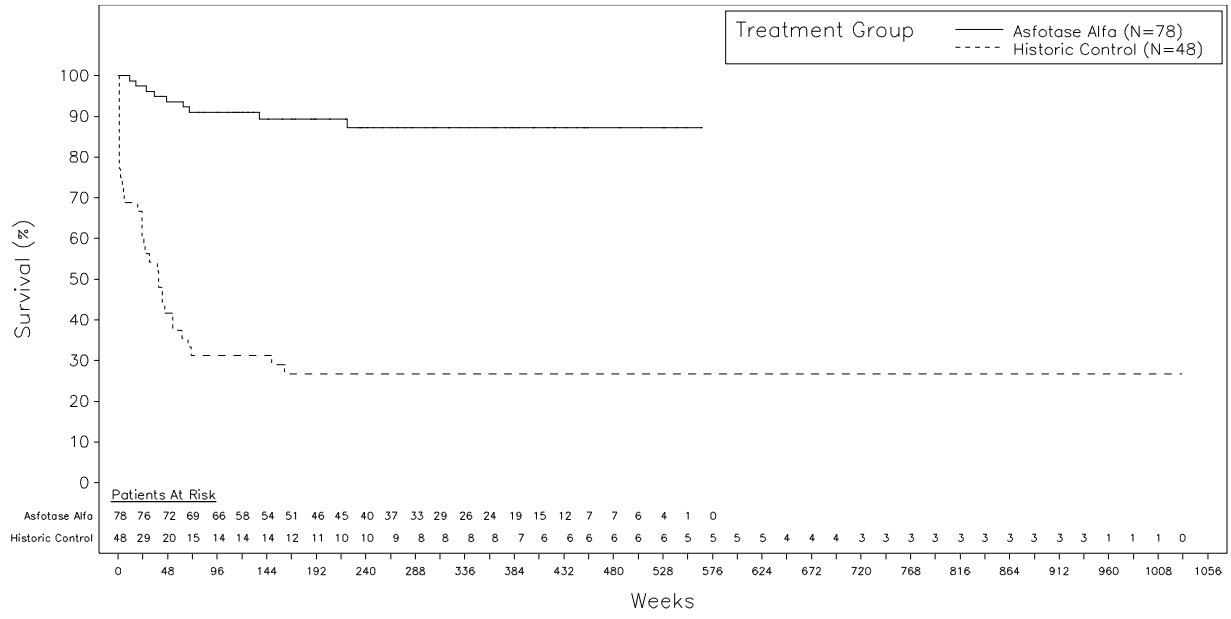
	STRENSIQ-	Historical Controls
Kaplan-Meier Estimate and Alive at Age 1 Year (Week 48) (%)	94	42
Invasive Ventilation-Free Survival**	n = 62	n =48
Alive and Not on Ventilation at Point of Last Contact (%)	51 (82%)	12 (25%)
Hazard Ratio (STRENSIQ/Historical Control), 95% Confidence Interval*	0.236 (0.103, 0.540)	
Kaplan-Meier Estimate of Alive and Not on Ventilation at Age 1 Year (Week 48) (%)	92	31

* 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.

Overall survival was improved in the cohort of treated patients with severe perinatal- or infantile-onset HPP, compared to historical control group, with 69/78 (88%) treated patients vs. 13/ 48 (27%) historical controls alive at last contact. In patients who required any form of respiratory support, 23 of 29 (79%) of the treated patients survived through their last assessment (median age at last assessment was 3.9 years of age), versus 1 of 20 (5%) of historical controls.

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



Skeletal manifestations

Radiographs from 81 STRENSIQ-treated perinatal/infantile-onset HPP patients, including 77 patients in Studies ENB-002-08/ENB-003-08 and ENB-010-10, and 4 patients in Study ENB-006-09/ENB-008-10, were examined to assess HPP-related rickets using the 7-point Radiographic

Global Impression of Change (RGI-C) scale. Patients with a minimum RGI-C score of +2 were defined as "responders". Radiologic improvements could be seen by Month 24; at last assessment, 63/81 [78%] treated patients were rated as RGI-C responders. No comparative data were available from historical controls. The mean time interval between the baseline and last RGI-C assessment was 35.7 months (range was 2.5 months to 89.4 months).

Radiographs were evaluated for severity of rickets using the 10-score Rickets Severity Scale (RSS), which assess the severity of rickets in the wrists and knees based on the degree of metaphyseal fraying and cupping and the proportion of growth plate affected. A score of 10 represents severe rickets, while a score of 0 represents an absence of rickets. Change in RSS scores were also statistically significant, with progressive improvements (at 24 weeks, median change in RSS score was -1.5, and at last overall assessment, the median change was -3.0).

Twenty-three perinatal/infantile-onset HPP patients experienced fractures during the course of treatment. The incidence of fractures was slightly lower in HPP patients following the initiation of STRENSIQ treatment than prior to treatment. There were insufficient data to determine the effect of STRENSIQ on fractures healing in those patients with fractures.

Growth

Height and weight measurements (as measured by Z-scores) were available post-treatment for 82 perinatal/infantile-onset HPP patients, including 78 patients enrolled in Studies 1 and 2, and 4 patients enrolled in Study 3 (Table 7).

Table 7 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[a] (N = 78)	-3.3	-10.1, 0.9	-2.9	-12.3, 0.7	-3.2	-23.8, 0	-2.3	-19.9, 1.4
Study 3 (N = 4)[b]	-2.6	-6.6, -0.7	-1.4	-5.4, 0.4	-2.5	-8.2, -1.0	-1.6	-5.4, 0.6

[a] The mean time interval between baseline and last assessment was 33.8 months (range was 0.7 month to 89.4 months).

[b] The mean time between baseline and last assessment was 77.6 months (range was 76.6 months to 79.0 months).

Juvenile-onset HPP

Study ENB-006-09/ENB-008-10 was a prospective open-label 24-week trial that included 8 juvenile-onset HPP patients and 5 perinatal/ infantile-onset HPP patients; 11/13 (85%) were male and 12/13 (92%) were white; on entry, patients were 6 to 12 years of age. Twelve of the 13 juvenile-onset patients entered the extension study and were treated for at least 6 years (72 months). At study entry, patients were randomized to receive STRENSIQ at 6 mg/kg per week or 9 mg/kg per week. Three patients received dose reductions during the primary treatment period, including one patient who experienced a decrease in vitamin B6 levels and 2 patients who

experienced recurrent injection site reactions. During the extension phase, the dosing regimen for all patients was initially changed to 3 mg/kg per week. Dosing was subsequently increased to 6 mg/kg per week, with no patients requiring doses higher than 6 mg/kg per week. The recommended dosage regimen of STRENSIQ for the treatment of juvenile-onset HPP is 6 mg/kg per week (see Section 4.2).

Growth

Height and weight measurements (as measured by Z-scores) in 8 STRENSIQ-treated patients were compared with a historical cohort of 32 untreated patients with similar clinical characteristics (Table 8). Height and weight data for historical patients were collected from medical records.

Table 8 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)[a]	-1.5	-3.8, 0	-0.77	-1.9, 0.3	-1.1	-3.5, 2.3	0.4	-1.1, 2.7
Control (N = 32)[b]	-1.1	-4.9, 2.6	-1.1	-4.9, 1.8	-1.2	-5, 2.1	-1	-5.7, 2.1

[a] The mean time interval between baseline and last assessment was 77 months (range was 75.9 months to 78.6 months).

[b] The mean time interval between baseline and last assessment was 61 months (range was 19 months to 109 months).

Skeletal manifestations

Radiographs from 8 STRENSIQ-treated patients and 32 historical controls were compared to assess HPP-related rickets using the 7-point RGI-C (Radiographic Global Impression of Change) scale. Patients who achieved a RGI-C score of 2 or higher (corresponding to substantial healing of rickets) were classified as being responders to treatment. All 8 treated patients were rated as responders by Month 54 of treatment. The mean duration between the baseline and last RGI-C assessments for control patients was 56 months (range was 8 to 95 months). At last assessment, 2/32 (6%) of control patients were rated as responders.

One of 8 (12.5%) patients with juvenile-onset HPP experienced new fractures during the course of treatment. There were insufficient data to assess the effect of STRENSIQ on fractures.

Gait/mobility

Gait was assessed using a modified Performance Oriented Mobility Assessment-Gait (MPOMA-G) scale) in 8 STRENSIQ-treated patients at 6-month intervals out to 36 months. Mobility was also assessed using the 6 Minute Walk Test (6MWT) in 7 of the 8 patients. Step length improved by at least 1 point in either foot in 6/8 patients compared to 1/6 (17%) control patients. At last assessment, all 7 patients had an improvement in distance walked of at least the minimal clinically important difference. The mean increase from baseline for distance walked is 222.4 meters (range from 81 to 297 meters). Mean walking distance reached the normal range after 6 months of treatment and improvements were sustained over 6 years.

Bone biopsy

Tetracycline for bone-labelling was administered in two 3-day courses (separated by a 14-day interval) prior to acquisition of the bone biopsy. Trans-iliac crest bone biopsies were obtained by standard procedure. Histological analysis of biopsies used Osteomeasure software (Osteometrics, US). Nomenclature, symbols and units followed recommendations of the American Society for Bone and Mineral Research.

In the per-protocol set (excludes those patients who received oral vitamin D between baseline and week 24), 7 juvenile-onset HPP patients underwent biopsy of the trans-iliac bone crest before and after receiving asfotase alfa. The median (min, max) change from baseline to 24 weeks in osteoid thickness is -5.7 (-9.2, 7.1) µm, in osteoid volume / bone volume is -3.5 (-15.5, 14.2)%, and in mineralization lag-time is -11 (-167, 663) days.

In adolescent and adult patients with HPP

Study ENB-009-10 was an open-label, randomized study. Patients were randomly assigned to treatment groups or to the control group for the 24-week primary treatment period. All patients received asfotase alfa treatment in the extended treatment period. Nineteen patients were enrolled, 14 completed, and 5 discontinued. At study completion, the median treatment period was 60 months (range, 24 to 68 months). Four patients had perinatal/infantile-onset HPP, 14 patients had juvenile-onset HPP, and 1 patient had adult-onset HPP. Age was 13 to 66 years at inclusion and was between 17 and 72 years at study completion.

Treatment with asfotase alfa resulted in reductions from baseline to Week 24 in the plasma concentrations of PPi (p=0.0715) and PLP (p=0.0285), and reductions were maintained with treatment for up to 288 weeks of exposure.

There was no improvement in height in the overall study population in Study 4, however, this was expected given that 3/19 of the patients were adolescents at the time of enrolment.

Patients underwent biopsy of the trans-iliac bone crest either as part of a control group or before and after exposure to asfotase alfa:

- Control group, standard of care (5 evaluable patients): mean (SD) mineralization lag-time was 226 (248) days at baseline and 304 (211) days at Week 24
- 0.3 mg/kg/day asfotase alfa group (4 evaluable patients): mean (SD) mineralization lag-time was 1236 (1468) days at baseline and 328 (200) days at Week 48
- 0.5 mg/kg/day asfotase alfa group (5 evaluable patients): mean (SD) mineralization lag-time was 257 (146) days at baseline and 130 (142) days at Week 48

After approximately 48 weeks, all patients were adjusted to the recommended dose 6.0 mg/kg/week.

At Week 24, change from baseline in distance walked in 6 minutes (6MWT) was 35.0 (2, 182) m for the combined treatment group and 6.5 (46, 113) m for the control group. The difference between treated and untreated patients did not achieve statistical significance due to the small

sample size of the study. During the extended treatment period, most patients had sustained or increased improvements.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride
Dibasic sodium phosphate, heptahydrate
Monobasic sodium phosphate, monohydrate
Water for injection

6.2 Shelf life

Refer to the outer carton and/or inner product label for expiration date.

Chemical and physical in-use stability has been demonstrated for up to 3 hours at a temperature between 23°C to 27°C.

6.3 Special precautions for storage

Store in refrigerator between 2°C and 8°C.
Do not freeze or shake.
Store in the original package in order to protect from light.

6.4 Nature and contents of container

STRENSIQ is supplied in single-use 2 mL or 3 mL (Type I glass) vials, with a stopper (butyl rubber) and a seal (aluminum) with a flip-off cap (polypropylene). The following strengths are available:

STRENSIQ 40 mg/ml solution for subcutaneous injection

18 mg/0.45 mL, 28 mg/0.7 mL, 40 mg/mL

STRENSIQ 100 mg/ml solution for subcutaneous injection

80 mg/0.8 mL

Pack sizes: cartons of 1 or 12 vials. Not all pack sizes may be marketed.

6.5 Special precautions for disposal and other handling

Each vial of STRENSIQ is intended for single use only. Any unused solution in the vial should be discarded. Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

STRENSIQ should be administered using sterile disposable syringes and injection needles. The syringes should be of small enough volume that the prescribed dose can be withdrawn from the vial with reasonable accuracy. An aseptic technique should be used (see Section 4.2).

Product Owner

Alexion Pharmaceuticals International Operations Limited

College Business & Technology Park
Blanchardstown Road North
Dublin 15
Ireland

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