EMA/617078/2020
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Strensiq

International non-proprietary name: asfotase alfa

Procedure No. EMEA/H/C/003794/II/0047

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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Status of this report and steps taken for the assessment				
Current step[1]	**Description**	**Planned date**	**Actual Date**	**Need for discussion[2]**
☐	Start of procedure	17 Aug 2020	17 Aug 2020	☐
☐	CHMP Rapporteur Assessment Report	21 Sep 2020	21 Sep 2020	☐
☐	CHMP members comments	05 Oct 2020	02 Oct 2020	☐
☐	Updated CHMP Rapporteur Assessment Report	08 Oct 2020	n/a	☐
☒	Opinion	15 Oct 2020	15 Oct 2020	☐

[1]Tick the box corresponding to the applicable step – do not delete any of the steps. If not applicable, add n/a instead of the date.

[2] Criteria for CHMP plenary discussion: substantial disagreement between the Rapporteur and other CHMP members and/or at the request of the Rapporteur or the Chair

Procedure resources	
Rapporteur	Armando Genazzani

Declarations

☒ The assessor confirms that reference to ongoing assessments or development plans for other products is not included in this assessment report, including in the Product Information, if any.

Whenever the above box is un-ticked please indicate section and page where confidential information is located here:

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1. Background information on the procedure

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Alexion Europe SAS submitted to the European Medicines Agency on 29 July 2020 an application for a variation.

The following changes were proposed:

Variation requested		**Type**	**Annexes affected**
C.I.4	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	Type II	I

Update of section 5.1 of the SmPC in order to remove the Paediatric Investigation Plan (PIP) compliance statement as per Article 28(3) of Regulation (EC) No 1901/2006, following submission of the results and reports of all the PIP measures, including results of the Extrapolation Study AXN100107PIP ("Extrapolation of Efficacy to Asfotase Alfa Treatment in Paediatric Patients Ages 6 months to <3 years with Juvenile-Onset Hypophosphatasia").

The requested variation proposed amendments to the Summary of Product Characteristics.

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0176/2019 on the agreement of a paediatric investigation plan (PIP).

PIP P/0176/2019 is completed. The PDCO issued an opinion on compliance for the PIP P/0176/2019.

2. Overall conclusion and impact on the benefit/risk balance

In support of this application the MAH submitted the results of the Extrapolation Study AXN100107PIP aimed to evaluate the impact on the benefit-risk profile of asfotase alfa (STRENSIQ) for patients aged 6 months to <3 years with Juvenile-Onset HPP.

Strensiq is indicated for long-term enzyme replacement therapy in patients with paediatric-onset hypophosphatasia to treat the bone manifestations of the disease. The recommended dose regimen of asfotase alfa is 2 mg/kg of body weight administered subcutaneously three times per week, or a dosage regimen of 1mg/kg of body weight administered subcutaneously six times per week. The maximum recommended dose is 6 mg/kg/week. The SmPC section 4.2 reports details on dose to be administered for patients from 3 kg to 100 kg body weight.

The extrapolation submitted in the contest of this variation concerns the population from 6 months to <3 years of age with Juvenile onset HPP (target population). The aim of this extrapolation was to compare the exposure, PLP and PPi response in the target population with those of the comparator groups (3 years of age < 18 years of age with Juvenile onset HPP and 6 months to < 18 years of age with perinatal/infantile onset HPP). The results of this extrapolation support the already known profile of asfotase alfa medicinal product and no additional information is needed in the SmPC. The statement in SmPC section 5.1 regarding the PIP compliance can be removed as the results and reports of all PIP measures have now been provided by the MAH and these results are reflected in the SmPC and, as appropriate, the Package Leaflet.

The benefit-risk balance of Strensiq, remains positive.

3. Recommendations

Based on the review of the submitted data, this application regarding the following change:

Variation requested		Type	Annexes affected
C.I.4	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	Type II	I

Update of section 5.1 of the SmPC in order to remove the Paediatric Investigation Plan (PIP) compliance statement as per Article 28(3) of Regulation (EC) No 1901/2006, following submission of the results and reports of all the PIP measures, including results of the Extrapolation Study AXN100107PIP ("Extrapolation of Efficacy to Asfotase Alfa Treatment in Paediatric Patients Ages 6 months to <3 years with Juvenile-Onset Hypophosphatasia").

☒ is recommended for approval.

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to the Summary of Product Characteristics are recommended.

Paediatric data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/0176/2019 and the results of these studies are reflected in the SmPC and, as appropriate, the Package Leaflet.

Annex: Rapporteur's assessment comments on the type II variation

4. Introduction

The scope of this type II application is to remove the PIP compliance statement from section 5.1 of the SmPC as per Article 28(3) of Regulation (EC) No 1901/2006.

In support of this application the MAH submitted the results of the Extrapolation Study **AXN100107PIP** aimed to evaluate the impact on the benefit-risk profile of asfotase alfa (STRENSIQ) for patients aged 6 months to <3 years with Juvenile-Onset HPP.

5. Clinical Pharmacology aspects

In the initial PIP approved by the PDCO on 01 Mar 2013 (EMEA-000987-PIP01-10), the Marketing Authorisation Holder (MAH) committed to address the unstudied population of children from 6 months to <3 years of age with Juvenile-Onset HPP.

A final Paediatric Investigation Plan (PIP) compliance check was agreed by the Paediatric Committee (PDCO) on 18 Oct 2019 for asfotase alfa in the treatment of hypophosphatasia (HPP) (EMEA-000987-PIP01-10-M04), in accordance with Article 23 of Regulation (EC) No 1901/2006 ("paediatric regulation").

The results of all PIP measures have already been submitted to the Agency, apart from the results of the Extrapolation Study AXN100107PIP. This extrapolation is developed on the basis of the initial popPK/PD modelling and simulation analysis ("Population Pharmacokinetic and Pharmacodynamic Modeling and Simulation of Asfotase Alfa in Patients with Hypophosphatasia" included data from 60 patients) submitted withinthe initial MAA to establish a basis for asfotase alfa dose and regimen selection for treatment of patients with HPP.

The purpose of AXN100107PIP report was to present data supporting the assumption that the safety/efficacy of asfotase alfa treatment is likely to be similar in paediatric patients 6 months to <3 years of age with Juvenile-Onset HPP by any relevant characteristics compared to children aged 3 to <18 years with Juvenile-Onset and to children aged 6 months to 18 years with Infantile Onset HPP (also referred to as Perinatal/Infantile Onset HPP).

5.1. Methods – analysis of data submitted within AXN100107PIP report (Extrapolation of Efficacy to Asfotase Alfa Treatment in Paediatric Patients Ages 6 months to <3 years with Juvenile-Onset Hypophosphatasia)

The purpose of this analysis was to present data supporting the assumption that the safety/efficacy of asfotase alfa treatment is likely to be similar in paediatric patients 6 months to <3 years of age with Juvenile-Onset HPP by any relevant characteristics compared to children aged 3 to <18 years with Juvenile-Onset and to children aged 6 months to 18 years with Infantile Onset HPP (also referred to as Perinatal/Infantile Onset HPP).

The objectives of AXN100107PIP extrapolation report are:

• to summarize available pharmacokinetic (PK) and pharmacodynamic (PD) data in children ages 3 to <18 years with Juvenile-Onset hypophosphatasia (HPP) (comparator group 1, N=11) and children ages 6 months to <18 years with Perinatal/Infantile-Onset HPP (comparator group 2, N=32).

• to compare the previously-developed PK, PK-inorganic pyrophosphate (PPi), and PK-pyridoxal-5'-phosphate (PLP) model fits in the comparator groups to demonstrate that the models provide an adequate fit to the data in these specific patient sub-populations.
• to compare predicted exposure-response (ER) characteristics in the comparator patient sub-populations to support the assumption that the outcome of asfotase alfa treatment in the unstudied target population is expected to be similar to the comparator sub-populations by any relevant characteristics.
• to compare predicted exposure of patients ages 6 months to <3 years with Juvenile-Onset HPP to previously summarized exposure/safety relationships for ectopic calcification, injection/infusion associated reactions, and injection site reactions to bridge exposure/safety relationships to this unstudied patient population.

The extrapolation analysis relied on a previously pooled dataset from 7 Phase I/II studies conducted in paediatric and adult patients with HPP and the final PK/PD models developed for PK-PPi and PK-PLP response endpoints used in the Pop-PK/PD report, that was submitted during the initial MAA.
The final population PK model analysed the IV and SC data simultaneously from the entire patient population and included first-order absorption following SC administration and a two-compartment disposition with elimination from the central compartment.
The final population PK model accounted for factors responsible for altering drug disposition (body weight, sialic acid content for lot of asfotase alfa administered, asfotase alfa batch size, and immunogenicity effects). Linking PK with PD data provided model-based characterization of asfotase alfa to response data from plasma biomarkers (inorganic pyrophosphate (PPi) and pyridoxal-5'-phosphate (PLP)), functional endpoints (Bruininks-Iserestsky Test of Motor Proficiency, Second Edition (BOT-2) and Six-Minute Walk Test(6MWT), and radiographic-based measures Rickets Severity Scale (RSS) for wrist and knee and Radiographic Global Impression of Change (RGI-C)).Once developed, the models were used to perform simulations exploring ER relationships for each response endpoint. Additionally, relationships between quartiles of average concentration since first dose and the incidence rate of adverse events were examined for ectopic calcification, injection/infusion associated reactions, and injection site reactions. These safety summaries revealed no dependence on exposure. These relationships were used together to inform the dose selection for asfotase alfa in HPP patients.
The results of the prior analyses were used in this current analysis to predict the ER relationship in a currently unstudied paediatric subset of HPP patients 6 months up to 3 years of age with Juvenile-Onset HPP. The dataset used in this analysis contains a greater number of patients in this age range (N=12), than was previously available in the EMA submission (N=6), though all of these patients are of the Infantile-Onset HPP phenotype and not the Juvenile-Onset phenotype of interest.
The current analysis includes a total of 11 patients with both PK and PPi data and 10 patients with PLP data for the Juvenile comparator group 1. For the Infantile comparator group 2, the dataset included 32 patients with PK data, 31 patients with PPi data and 27 patients with PLP data.

Table 1: Patient and Observation Counts in NONMEM PK and PKPD Datasets by Group

Data	0 to 6mo	6 months to <3 years	3 to <18 years	3 to <18 years	Comparator 1*	Comparator 2*
	Infantile	Infantile	Infantile	Juvenile	Juvenile	Infantile
PK	15 (189)	12 (202)	20 (362)	11 (202)	11 (202)	32 (564)
PLP	4 (34)	8 (75)	19 (177)	10 (116)	10 (116)	27 (252)
PPI	14 (119)	11 (87)	20 (178)	11 (125)	11 (125)	31 (265)

Shown are number of patients in the group and, in parenthesis, number of observations in the analysis dataset in that group
*Comparator 1 = Juvenile patients ages 3 years to <18 years, Comparator 2 = Infantile patients ages 6 months to <18 years.
Source code: /script/DataSummary_AXN100107PIP.R
Source tex: /deliv/table/PIPDataSummary.tex

The purpose of this analysis is to compare the ER relationships across two comparator groups that share relevant characteristics of the target population. Specifically, and where applicable, asfotase alfa treatment outcome measures was compared between paediatric patients aged 3 to <18 years with

Juvenile-Onset HPP (N=11) and paediatric patients aged 6 months to <18 years with Perinatal/Infantile-Onset HPP (N=32). This comparison bridges the gaps in ages and phenotypes of the un-studied target population. Predicted exposure in the un-studied target population was also compared to the safety quartile summaries from the prior analysis to bridge the safety/exposure relationships for ectopic calcification, injection/infusion associated reactions, and injection site reactions.
The extrapolation includes a graphical and tabular summary of observed (Comparator groups only) and simulated data of the Target and Comparator populations.
Previously developed population PK and PD model results were evaluated specifically in the comparator groups to assess how well the models described the subset data. Diagnostic plots for the PK , PLP, and PPi models suggest a good fit to the comparator group data. Additionally, previously simulated visual predictive check (VPC) results were also subset on the comparator group data and showed a reasonable fit with all three endpoints (PK,PLP and PPi).

5.2. Results

Patient body weight is an important predictor of the PK of asfotase alfa. Due to the strong correlation between age and weight in the HPP paediatric patients, weight acts as a surrogate for age in the population PK model. Though not included in the model, comparison groups for this analysis were subset by age for ease of reference.

Exposure/response
Final PK/PD models for PPi and PLP response endpoints were used to simulate the expected (median) exposure-response relationships across several asfotase alfa dosing regimens.
Simulations of both biomarker endpoints resulted in responses which improved with rising exposures in all groups and neared or established a plateau in the exposure-response relationships (Figures 18, 20, and 22). The median exposure-responses were higher in the Infantile phenotype for both biomarkers. Hence, at similar average concentration during the dosing interval at steady-state (Cavg,ss) concentration, the median responses would be expected to be greater in Infantile patients as compared with Juvenile patients. For PLP, relatively large standard errors of the PD response parameter estimates resulted in wide, overlapping confidence interval (CI)s in the expected exposure-response relationships for the comparator groups (Fig.18). For PPi, the median and 90% CIs of the exposure-response relationships at Weeks 7 and 24 showed some separation between the Juvenile and Infantile comparison groups (Fig. 20 and 22).

Figure 18: PLP: Simulated Week 24 Response

Plots represent the median (solid line) and 90% confidence intervals (shaded) for typical exposure-response in the comparator and target groups. Also shown are the median simulated C_{avg} values for each regimen and the range of subject-specific estimates of $C_{\text{avg,study}}$ values based on modeling of observed data. Asterisks (*) indicate dose regimens studied in the clinical development program. Comparator Group 1 = Juvenile patients ages 3 years to <18 years, Comparator Group 2 = Infantile patients ages 6 months to <18 years. Target = Juvenile patients ages 6 months to < 3 years

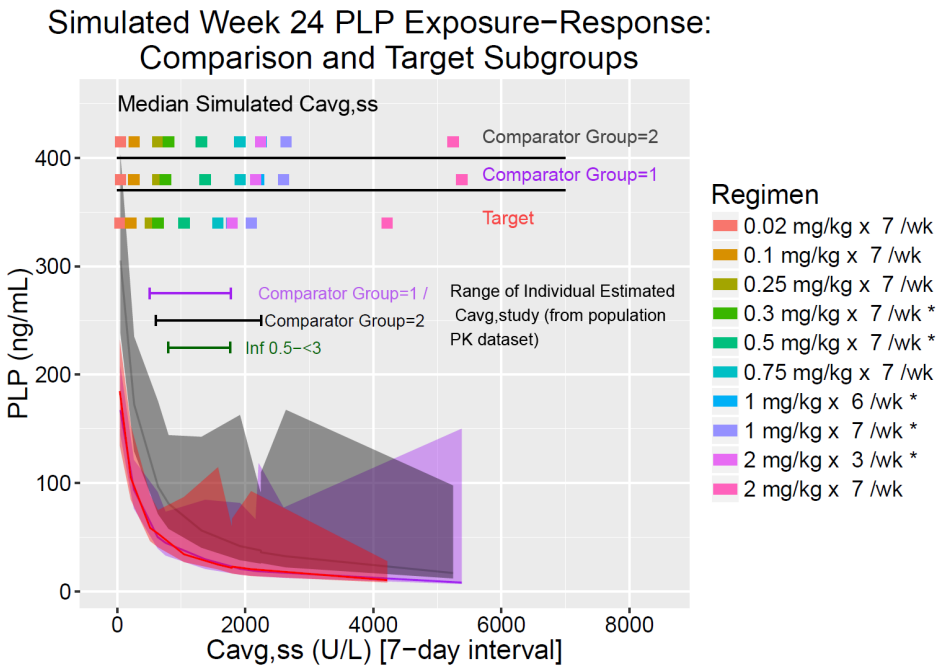
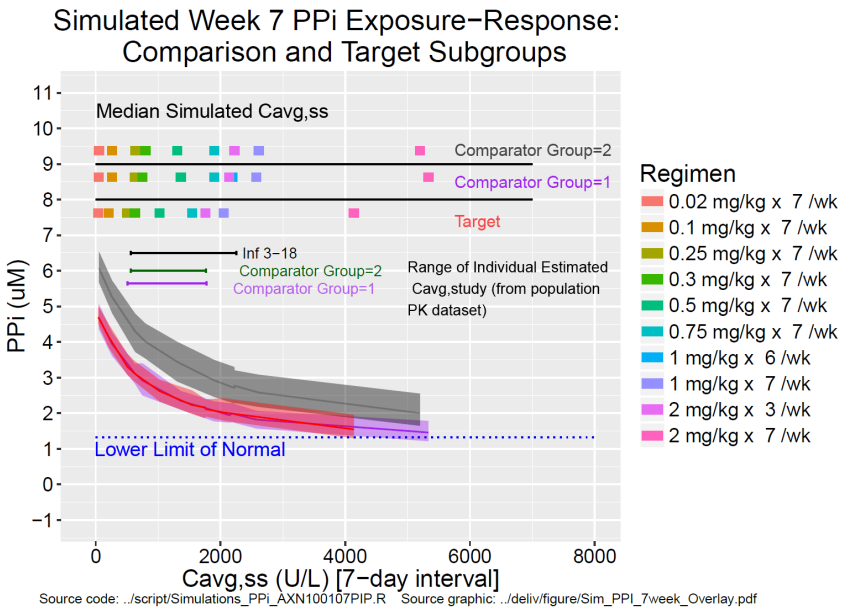


Figure 20: PPi: Simulated Week 7 Response

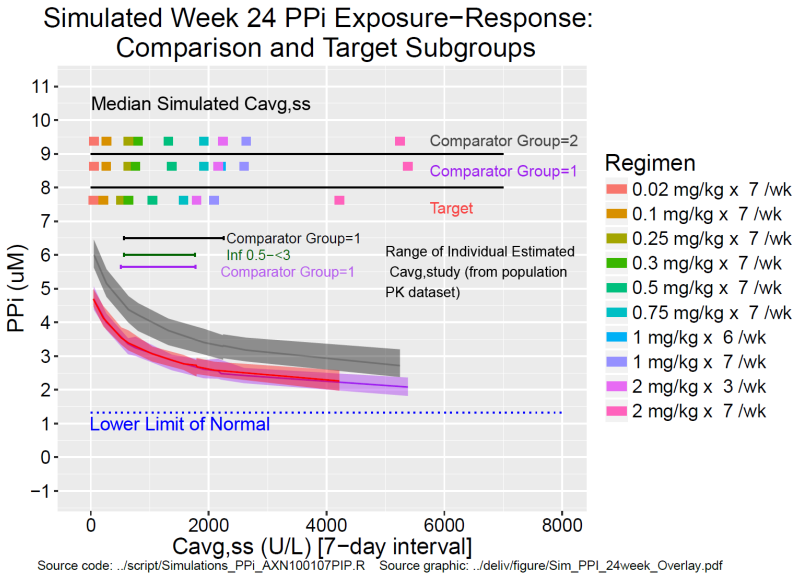
Plots represent the median (solid line) and 90% confidence intervals (shaded) for typical exposure-response in the comparator and target groups at Week 7. Also shown are the median simulated $C_{avg,ss}$ values for each regimen and the range of subject-specific estimates of $C_{\text{avg,study}}$ values based on modeling of observed data. Comparator Group 1 = Juvenile patients ages 3 years to <18 years, Comparator Group 2 = Infantile patients ages 6 months to <18 years. Target = Juvenile patients ages 6 months to < 3 years



Source code: ../script/Simulations_PPi_AXN100107PIP.R Source graphic: ../deliv/figure/Sim_PPI_7week_Overlay.pdf

Figure 22: PPi: Simulated Week 24 Response

Plots represent the median (solid line) and 90% confidence intervals (shaded) for typical exposure-response in the comparator and target groups at Week 24. Also shown are the median simulated $C_{avg,ss}$ values for each regimen and the range of subject-specific estimates of $C_{avg,study}$ values based on modeling of observed data. Comparator Group 1 = Juvenile patients ages 3 years to <18 years, Comparator Group 2 = Infantile patients ages 6 months to <18 years. Target = Juvenile patients ages 6 months to < 3 years



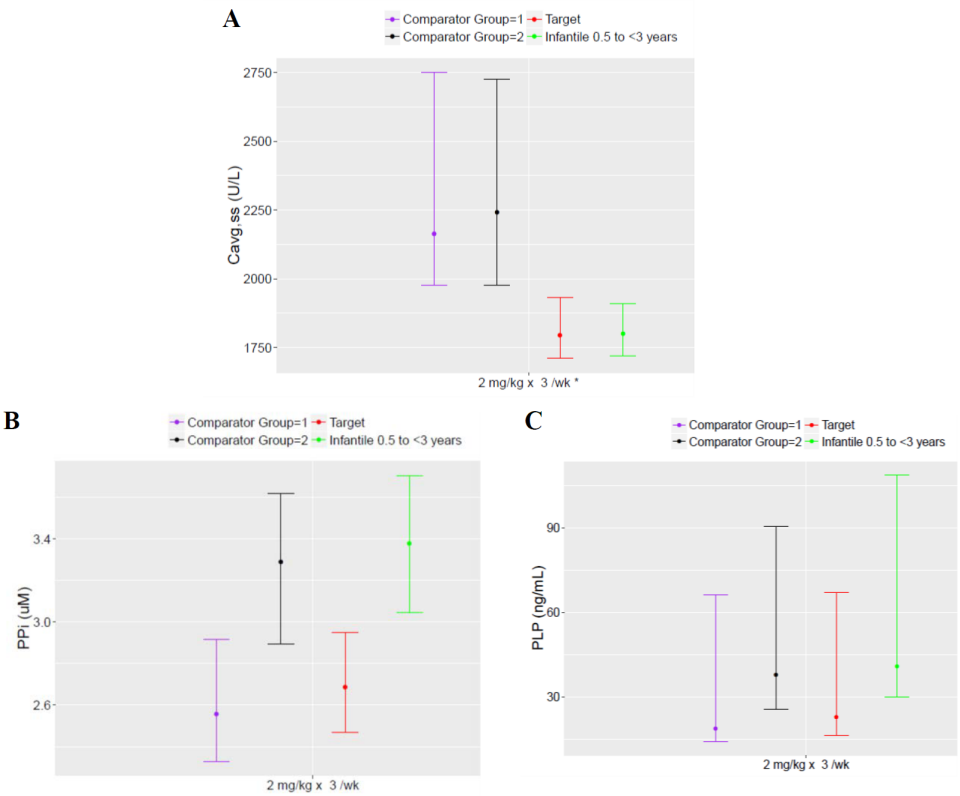
Source code: ../script/Simulations_PPi_AXN100107PIP.R Source graphic: ../deliv/figure/Sim_PPI_24week_Overlay.pdf

For both PLP and PPi, the exposure-response relationship for the target population (red) most closely resembled that of the Juvenile 3 to <18 years population (comparator group 1, Figures 18, 20, and 22). Since the age and, therefore, weight ranges between comparison groups 1 and 2 differ, the expected Cavg,ss values at this dose also differ, as do the ERs. When comparing groups of similar ages (6 months to <3 years) but with differing phenotypes for the approved 2 mg/kg x 3/week asfotase alfa dose only, the similar expected exposures resulted in lower median PLP and PPi responses in patients with the Juvenile-Onset phenotype as compared to patients with the Infantile-Onset phenotype.

In summary, exposure is expected to be similar between patients in the same age range independent of the disease onset, while the biomarker ER relationships of the unstudied population of children aged 6 months to <3 years with Juvenile-Onset HPP is expected to be similar to that of other Juvenile patients (Figure 1 below).

Figure 1: Simulated Week 24 Response Following 2 mg/kg x 3/week Dose of Asfotase Alfa

A: Asfotase alfa activity ($C_{avg,ss}$), B: PPi response, C: PLP response.



Notes: Plots represent the median (solid circles) and 90% confidence intervals for typical exposure-response for each comparator and target group assuming a 2 mg/kg x 3/week asfotase alfa dose. Comparator group 1 = Juvenile patients ages 3 years to <18 years and comparator group 2 = Infantile patients ages 6 months to <18 years. Target = Juvenile patients ages 6 months to <3 years.

Abbreviations: PLP = pyridoxal-5'- phosphate; PPi = inorganic pyrophosphate.

The following tables show the simulated Cavg,ss for the currently approved dose regimens and the PLP and PPi responses.

Simulated Cavg,ss (U/L) and PLP (ng/mL) Response in Comparator and Target HPP Patients

Group	Regimen	Cavg,ss (U/L)	PLP (ng/mL)
Comparator Group=1	1 mg/kg x 6 /wk	2210 (1970, 2630)	18.5 (13.9, 118)
Comparator Group=1	2 mg/kg x 3 /wk	2160 (1980, 2750)	18.8 (14.2, 66.3)
Comparator Group=2	1 mg/kg x 6 /wk	2250 (1980, 2740)	36.0 (26.2, 110)
Comparator Group=2	2 mg/kg x 3 /wk	2240 (1980, 2730)	37.8 (25.7, 90.4)
Infantile 0.5 to <3 years	1 mg/kg x 6 /wk	1800 (1710, 1910)	39.1 (29.8, 99.8)
Infantile 0.5 to <3 years	2 mg/kg x 3 /wk	1800 (1720, 1910)	41.0 (30.0, 109)
Target	1 mg/kg x 6 /wk	1790 (1720, 1930)	21.7 (16.6, 59.1)
Target	2 mg/kg x 3 /wk	1800 (1710, 1930)	22.8 (16.4, 67.0)

Median and 90% CI of simulated asfotase alfa Cavg,ss for each dosing regimen is reported. Median and 90% CI of PLP response at median Cavg,ss is reported. Asfotase alfa product characteristics in the typical value simulations were a sialic acid level of 2.2 (mol/mol), a 20,000 L batch size, and a drug activity of 990 U/mg.
Source code: /script/Simulations_PLP_AXN100107PIP.R

Simulated Cavg,ss (U/L) and PPi (uM) Response in Comparator and Target HPP Patients: Week 24

Group	Regimen	Cavg,ss (U/L)	PPi (uM)
Comparator Group=1	1 mg/kg x 6 /wk	2210 (1970, 2630)	2.48 (2.30, 2.88)
Comparator Group=1	2 mg/kg x 3 /wk	2160 (1980, 2750)	2.56 (2.33, 2.92)
Comparator Group=2	1 mg/kg x 6 /wk	2250 (1980, 2740)	3.31 (2.94, 3.64)
Comparator Group=2	2 mg/kg x 3 /wk	2240 (1980, 2730)	3.29 (2.89, 3.62)
Infantile 0.5 to <3 years	1 mg/kg x 6 /wk	1800 (1710, 1910)	3.41 (3.04, 3.67)
Infantile 0.5 to <3 years	2 mg/kg x 3 /wk	1800 (1720, 1910)	3.38 (3.04, 3.71)
Target	1 mg/kg x 6 /wk	1790 (1720, 1930)	2.73 (2.40, 2.87)
Target	2 mg/kg x 3 /wk	1800 (1710, 1930)	2.69 (2.47, 2.95)

Median and 90% CI of simulated asfotase alfa Cavg,ss for each dosing regimen is reported. Median and 90% CI of PPi response at median Cavg,ss is reported. Asfotase alfa product characteristics in the typical value simulations were a sialic acid level of 2.2 (mol/mol), a 20,000 L batch size, and a drug activity of 990 U/mg. Source code: /script/Simulations_PPi_AXN100107PIP.R

Exposure/safety

An exploratory evaluation of population exposure-response relationships for specific adverse event(ectopic calcification, injection/infusion associated reactions, and injection site reaction events during the entire treatment duration for all relevant patients in the comparator groups in the dataset) was implemented. When viewed as a function of exposure quartiles, AE summaries revealed no dependence on exposure.

The median (90% CI) of the expected Cavg,ss for a 2mg/kg x 3/week asfotase alfa dose in Juvenile HPP patients 6 months to <3 years of age was 1800 (1710, 1930) U/L after 24 weeks. This range falls within the range of the Infantile comparator group and is at the upper end of the range of the Juvenile comparator group Cavg,study values from this exposure/safety analysis. The simulated Cavg,ss of the target population, therefore, is not expected to be predictive of ectopic calcification, injection/infusion associated reactions, or injection site reaction events when viewed as a function of exposure quartiles.

MAH's conclusion

Based on the data included in this submission, and in line with the above discussion, no changes are proposed to the Pharmacological properties section of the asfotase alfa SmPC in light of results of the Extrapolation Study AXN100107PIP.

Considering that the other completed PIP measures have already been assessed as part of the procedure EMEA/H/C/003794/II/0035/G, the MAH proposes removal of the following paragraph from Section 5.1 of the SmPC:

~~*Paediatric population*~~

~~*The European Medicines Agency has deferred the obligation to submit the results of studies with Strensiq in one or more subsets of the paediatric population in hypophosphatasia (see section 4.2 for information on paediatric use).*~~

5.3. Discussion

A Paediatric Investigation Plan (PIP) was agreed with the PDCO on 01 March 2013 (EMEA-000987-PIP01-10) for asfotase alfa in the treatment of HPP and a final compliance check was approved in October 2019 (EMEA-C-000987-PIP01-10-M04) including all agreed measures. Among other measures already submitted, the MAH was committed to address the unstudied population of children from 6 months to < 3 years of age with Juvenile-onset HPP. To address the PDCO request, an extrapolation study ANX100107PIP was submitted aiming to compare the safety/efficacy of asfotase alfa

treatment in paediatric patients 6 months to <3 years of age with Juvenile-onset HPP (target population) with children aged 3 to <18 years with Juvenile-onset HPP (comparator group 1) and children aged 6 months to 18 years with Infantile-onset HPP (comparator group 2). The extrapolation was performed on the basis of a final PK/PD model developed at the time of the initial submission. The dataset was enriched with data from additional 6 patients in the age range considered (6 months < 3 years of age), but all these patients belong to the Infantile-onset phenotype. In the current analysis, the Juvenile comparator group 1 included 11 patients with PK and PPi data and10 patients with PLP data. For the Infantile comparator group 2, the dataset included 32 patients with PK data, 31 patients with PPi data and 27 patients with PLP data. It can also be noted that the dataset contained 12 patients with PK data, 11 patients with PPi data and 8 patients with PLP data from the Infantile group with ages 6 months to <3 years. The final PKPD models for PPL and PPi endpoints was used to simulate the Cavg,ss and responses for several asfotase alfa dose regimes in the comparator and target groups and both models also estimate the effect of phenotypes on response. Data provided showed that the exposure in the target population is similar to that in infantile patients in the same age range and this is due to the fact that patient body weight, and consequently age, is a predictor of asfotase alfa exposure. In terms of efficacy, data showed that the estimated PLP and PPi responses in the target population are more similar to that expected in the comparator group 1 (3 to < 18 years of age with Juvenile-onset HPP).

Regarding safety, no relationship is identified between exposure and safety endpoints, therefore the exposure reached in the target population is no expected to have impact on ectopic calcification, injection/infusion associated reactions, or injection site reaction events.

Taken together, the results of this extrapolation support the already known knowledge about asfotase alfa medicinal product and no additional information is needed to be added in the SmPC. The statement in section 5.1 regarding the PIP can be removed.

6. Changes to the Product Information

As a result of this variation, section 5.1 of the SmPC is being updated in order to remove the Paediatric Investigation Plan (PIP) compliance statement as requested by the MAH.