TITLE PAGE

Protocol Title: An Observational, Longitudinal, Prospective, Long-Term Registry of Patients With Hypophosphatasia

Protocol Number: ALX-HPP-501

Amendment Number: 6.8 (EU, excluding Germany)

Compound Number: Not applicable

Study Phase: Postmarketing surveillance study

Short Title: Hypophosphatasia Registry

Sponsor Name: Alexion Pharmaceuticals, Inc.

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Regulatory Agency Identifier Number(s)

PASS: EUPAS13514, ClinicalTrials.gov Identifier: NCT02237625

Approval Date: 24 Nov 2020

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SPONSOR SIGNATORY

Protocol Title: An Observational, Longitudinal, Prospective, Long-Term Registry of Patients With Hypophosphatasia

Protocol Number: ALX-HPP-501

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25-Nov-2020 | 07:35:55 EST

Peter De Veene, MD, QPPV
Alexion Europe SAS

Date

PHYSICIAN'S AGREEMENT

I have read and understand all clinical and administrative sections of the protocol amendment 6.8. I agree to participate and conduct the study as outlined in the ALX-HPP-501 study protocol amendment 6.8 and in accordance with the guidelines and all applicable government regulations. I also agree to maintain the confidentiality of all information received or developed in connection with this protocol amendment.

_____

Printed Name of Physician

_____

Signature of Physician

_____

Date

PROTOCOL AMENDMENT SUMMARY OF CHANGES

Protocol/ Amendment Updates	Approval Date
Initial Protocol (Global)	20 Jun 2014
Amendment 1, version 1.1 (Global)	06 Oct 2014
Amendment 2 (Global)	14 Sept 2015
Amendment 3 (Global)	10 Nov 2015
Amendment 3.1 (USA)	19 Nov 2015
Amendment 4 (all participating countries, excluding USA and Japan)	11 Feb 2016
Amendment 4.1 (USA)	17 Feb 2016
Amendment 4.2 (EU, excluding Germany)	06 May 2016
Amendment 4.3 (Germany)	21 Jul 2016
Amendment 5.0 (USA and Rest of World, excluding the EU and Japan)	01 Jun 2016
Amendment 6.0 (USA and Rest of World, excluding the EU and Japan)	30 Jan 2020
Amendment 6.1 (natural history)	In preparation
Amendment 6.2 (EU, excluding Germany)	30 Jan 2020
Amendment 6.3 (Germany)	30 Jan 2020
Amendment 6.4 (EU, excluding Germany)	28 Aug 2020
Amendment 6.5 (Germany)	28 Aug 2020
Amendment 6.6 (EU, excluding Germany)	11 Sep 2020
Amendment 6.7 (Germany)	11 Sep 2020
Amendment 6.8 (EU, excluding Germany)	24 Nov 2020
Amendment 6.9 (Germany)	24 Nov 2020

Amendment 6.8 (24 Nov 2020)

Overall Rationale for the Amendment:

The protocol has been amended to include medication errors as a specific targeted event so as to align targeted events with those listed in the Risk Management Plan, to clarify the severity of injection site reactions collected in the Registry (severe and/or serious), and to add two new functional assessments for adults with HPP that are considered standard of care, details of which are available in Genest, 2020. Minor changes for clarification and consistency have also been made.

The main changes to the protocol in Amendment 6.8 are detailed in Table 1 and other administrative changes in Table 2.

Table 1: Main Changes to the Protocol

Section # and Name	Description of Change	Brief Rationale and/or Clarifications
Section 10.1.2 Targeted Events 1.2 Schedule of Data Collection, Table 4 3 Objectives and Outcomes 8.1.4 HPP Disease History 8.1.5 HPP Disease Status	Addition of medication errors (unintentional errors in the prescribing, dispensing, administration, or monitoring of a medicine) as targeted events	To align the targeted events with those listed in the Risk Management Plan.
Section 1.1 Synopsis, 1.2 Schedule of Data Collection, Table 4 3 Objectives and Outcomes 8.1.4 HPP Disease History 8.1.5 HPP Disease Status	Removal of hand-held dynamometry as an assessment and addition of two new functional assessments for adults with HPP: • TUG	Hand-held dynamometry has been removed as insufficient data have been collected to perform meaningful analyses, and it is not considered informative by advisors. The TUG and SPPB have been added because these two assessments are considered standard

Section # and Name	Description of Change	Brief Rationale and/or Clarifications
	• SPPB, which includes repeated chair rise test	of care, appropriate for this patient population based on recent data (Genest, 2020), and currently, there are only limited tools to measure physical function in adults with HPP
Section 10.1.2 Targeted Events Section 10.1.2.4 Definition of Injection-Site Reactions	The type of ISRs collected as targeted events clarified as severe and/or serious	To clarify the severity of ISRs collected in the Registry as targeted events (severe and/or serious), considering that the severe cases of ISRs can adversely impact patients' compliance with the treatment (EU Risk Management Plan).

Abbreviations: HPP = hypophosphatasia; ISR = injection site reaction; SPPB = Short Physical Performance Battery; TUG = Timed Up and Go test

Table 2: Other Administrative Changes to the Protocol

Section # and Name	Description of Change	Brief Rationale and/or Clarifications
Registry Contacts	Clinical Project Lead name change	To reflect that a new Clinical Project Lead is now responsible for the HPP Registry
All	Minor edits	For clarification and consistency within the protocol

REGISTRY CONTACTS

Table 3: Contact Information

Role in Program	Name	Contact Information
Clinical Project Lead	Daniel McVeigh	Alexion Pharma GmbH Giesshübelstrasse 30 8045 Zürich Telephone: +41 798747569 E-mail: Daniel.Mcveigh@alexion.com
Responsible Physician	Anna Petryk, MD	Alexion Pharma GmbH, Giesshübelstrasse 30, 8045 Zürich, Switzerland Telephone (office): +41 (0) 44 457 40 00 E-mail: Anna.Petryk@alexion.com
24-Hour Serious Adverse Event (and Pregnancy) Notifications	---	E-mail: ClinicalSAE@alexion.com Facsimile: + 1-203-439-9347 (local country numbers may be available)

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1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol title: An Observational, Longitudinal, Prospective, Long-Term Registry of Patients with Hypophosphatasia

Short Title: Hypophosphatasia Registry

Protocol amendment: Amendment 6.8 (EU, excluding Germany), 24 Nov 2020

Rationale:

Hypophosphatasia (HPP) is a rare, inherited, and potentially fatal disorder caused by deficiency of tissue-nonspecific alkaline phosphatase (TNSALP). Hypophosphatasia is characterized by defective bone mineralization and impaired phosphate and calcium regulation as a direct result of deficient TNSALP, which can lead to progressive damage to vital organs along with other severe clinical sequelae including deformity and destruction of bones, pain and profound muscle weakness, respiratory failure, seizures, impaired renal function, impaired mobility, and dental abnormalities.

HPP across patient ages is characterized by interdependent clinical manifestations, emanating from a failure to mineralize bone matrix due to elevated concentrations of the TNSALP substrate inorganic pyrophosphate (PPi). Elevations in extracellular PPi inhibit bone mineralization by blocking hydroxyapatite crystal formation, causing a pronounced accumulation of unmineralized bone matrix. Failure to mineralize bone matrix results in osteomalacia (softening of bones) in patients of all ages, and skeletal deformities of rickets (abnormal mineralized bone, dysmorphic long bones and ribs) and subsequent growth abnormalities in infants and children. In addition, severe functional deficits are often present in patients with HPP, including mobility defects (ambulation and gait impairments), muscle weakness, and inability to carry out activities of daily living, altogether affecting patient quality of life (QoL). TNSALP also dephosphorylates pyridoxal-5'-phosphate (PLP) into pyridoxal, allowing it to cross the plasma membrane into the central nervous system. Deficiency in TNSALP results in vitamin B_6 deficiency in the central nervous system, potentially leading to seizures as well as somnolence and symptoms of depression.

In infants with HPP, bone mineralization defects with resulting skeletal deformities and fractures and rachitic changes in the chest may lead to the inability of the rib cage to support normal respiratory function and increase the risk of ventilator dependence and premature death. In the most severely affected patients, mortality ranges from 50% through 100%. In patients surviving to adolescence and adulthood, long-term clinical sequelae include recurrent and nonhealing fractures, weakness, arthritis, the inability to remove internal fixation devices (due to the risk of recurrent fracture), pain, and the requirement for ambulatory assistive devices (wheelchairs, wheeled walkers and canes).

Historical classification of HPP includes pediatric-onset HPP forms (comprised of perinatal-, infantile-, and juvenile-onset HPP forms), where first symptoms of HPP present at < 18 years of age, and an adult-onset HPP form, where symptoms appear at ≥ 18 years of age. Other milder forms of the disease, including benign perinatal HPP and odontohypophosphatasia, have also been characterized.

Historically, clinical management of HPP has been mainly supportive and has addressed symptoms (eg, respiratory support, orthopedic intervention and pain relief medication) of the disease, but not the underlying pathophysiology. Thus, despite best efforts, the majority of patients have experienced significant morbidity (growth abnormalities, structural deficits, bone pain, physical dysfunction, and/or respiratory distress). More recently, Strensiq® (asfotase alfa), a bone-targeted enzyme replacement therapy, designed to address the underlying cause of HPP, has been approved for treatment of HPP in several countries including Japan, Canada, USA, countries of the European Union (EU), and Australia.

As noted above, HPP is a rare disease that has historically been largely treated symptomatically. Asfotase alfa is the only therapy designed and approved to treat the underlying cause of HPP. Due to the rare nature of this disease, and considering the lack of information regarding diagnosis patterns and health care management in a "real world" setting, this study will collect data on epidemiology, HPP history, clinical course, symptoms (including systemic aspects of the disease), and burden of disease from patients of all ages who have a diagnosis of HPP, including patients of any age and who are either untreated or receiving treatment with asfotase alfa for HPP. For patients treated with asfotase alfa, the Registry will collect data on asfotase alfa dosing, effectiveness of treatment, serious adverse events (SAEs), anti-drug antibodies (ADAs), pregnancy and neonatal outcome data. Targeted events will be collected for all patients. Accordingly, the Registry will permit better delineation between the natural disease course of HPP and the disease course in patients who are treated.

This Registry will also serve to fulfill postmarketing commitments and requirements, as applicable, and will be conducted, in part, as a Post Authorization Safety Study according to EU Directive 2001/83/EC (DIR) Art 1 (15) and DIR Art 107m-q and Commission Implementing Regulation No 520/2012 Art 36-38.

Note that throughout this document, asfotase alfa refers specifically to Strensiq.

Objectives and Outcomes:

Objectives of the HPP Registry are:

- To collect information on the natural history of HPP from patients of all ages, including pediatric patients and adults with HPP, regardless of age at onset.
- To characterize the epidemiology of the HPP population. Inclusion of all classifications of HPP is planned: pediatric-onset (perinatal-, infantile-, and juvenile-onset), adult-onset, benign perinatal, and odontohypophosphatasia.
- To evaluate the burden of disease for HPP and the systemic aspects of HPP, including clinical outcomes and QoL, in a "real-life" setting.
- To collect and evaluate long-term safety and effectiveness data in HPP patients who have/are receiving treatment with asfotase alfa. More specifically, this Registry will serve to:
  - Collect and evaluate longitudinal effectiveness data, including, but not limited to, the following in asfotase alfa-treated patients (for comparison to untreated patients and patients treated with other therapies, as data permit):

- Growth and development parameters, including height/length, weight, head and chest circumference, and arm span
- Information about skeletal assessments and treatments
- Clinical laboratory tests relevant to HPP (eg, PLP)
- Functional outcomes relevant to HPP (eg, 6-Minute Walk Test [6MWT], Bayley Scales of Infant and Toddler Development®, Third Edition [Bayley-III also called BSID-III], Bruininks-Oseretsky Test of Motor Proficiency Second Edition [BOT™-2], Peabody Developmental Motor Scale® Second Edition [PDMS-2], Pediatric Orthopedic Society of North America's [POSNA] Pediatric Outcomes Data Collection Instrument® [PODCI], Lower Extremity Functional Scale [LEFS], Timed Up and Go Test [TUG], and Short Physical Performance Battery [SPPB] including repeated chair rise test)

– Collect and evaluate longitudinal safety data in asfotase alfa-treated patients in order to further characterize the safety profile of asfotase alfa and targeted events, including, but not limited to, injection-site reactions (ISRs), injection-associated reactions (IARs), ADAs, ectopic calcifications, craniosynostosis, and medication errors. Information about ectopic calcifications and craniosynostosis should also be collected in untreated patients to monitor the natural history of these disease manifestations.

– Collect and evaluate information on asfotase alfa exposure in patient populations for which little or no information is currently available (eg, pregnant and lactating women, patients with hepatic or renal impairment, the elderly).

Overall Design:

This multinational, multicenter, observational, prospective, long-term registry is designed to collect data on epidemiology, HPP history, clinical course, symptoms (including systemic aspects of disease), and burden of disease from patients of all ages who have a diagnosis of HPP. In addition, the Registry will collect data on asfotase alfa dosing, effectiveness of treatment, SAEs, ADAs, pregnancy and neonatal outcome data (for patients treated with asfotase alfa only), and targeted events.

Data on patients participating in this Registry will be collected at the time of enrollment and subsequent data collection will be performed in the course of routine clinical care and through patient-reported outcome (PRO) methods, if collected as per standard of care practice, as indicated in the Schedule of Data Collection. Physicians will be asked to record data, collected from the patients' medical records, at least every 3 months for the first year of enrollment in the Registry, then at least every 6 months thereafter.

For all patients enrolled (including those receiving asfotase alfa treatment), data will be collected in the Registry for the lifecycle of the product, unless otherwise agreed to by governing regulatory agencies that all regulatory obligations for Registry conduct are met. Data will be collected through an electronic data capture (EDC) system.

Physicians will perform the study according to current clinical practice in their center with currently available treatment resources and information and in accordance with the regulations and guidelines governing medical practice and ethics.

At a minimum, patients will be enrolled from sites in North America, the EU and the JAPAC (Japan, Asia, Pacific) region. Registry participation will be offered, at a minimum, to all sites that enrolled patients in registration studies included in applications submitted for regulatory approval of asfotase alfa. For any former Alexion-sponsored clinical study patients considered for participation in the Registry who either declined participation or failed to qualify for participation, reasons the patient declined or failed to qualify for participation will be captured, as available.

Population

Patients of all ages with a diagnosis of HPP will be recruited for participation in the Registry, including those who have not received/are not receiving treatment with asfotase alfa, as well as those who have received/are receiving asfotase alfa treatment. The study population is male and female patients, of any age, with a confirmed diagnosis of HPP and documented alkaline phosphatase (ALP) activity below the lower limit of normal for age and sex, or a documented *ALPL* gene mutation. Patients cannot be currently participating in an Alexion-sponsored clinical study at the time of enrollment. Patients who have concluded participation in an Alexion-sponsored asfotase alfa clinical study are eligible to enroll in this Registry, and enrollment in the Registry will not exclude a patient from enrolling in a future clinical study.

Data Variables to be Collected

Data concerning patient treatment and clinical condition will be collected, when and if available, according to the site's usual practice. For patients treated with asfotase alfa, information on asfotase alfa dosing, effectiveness of asfotase alfa treatment, SAEs, targeted events of IARs and severe hypersensitivity reactions (including anaphylaxis), systemic immune complex-mediated reactions, ISRs, lack of efficacy, ADAs, and pregnancy and neonatal outcome data, medication errors (only for patients treated with asfotase alfa), ectopic calcification, craniosynostosis, hearing loss, and respiratory failure/respiratory insufficiency or compromise/pneumonia (for all patients whether treated or not with asfotase alfa), will also be collected according to the timeframes and procedures outlined in the protocol. This study will comply with relevant data protection and privacy regulations. Patients and their parent (or legal guardian), when appropriate, will be informed of the use and disclosure of their study data for the purposes of the study. Confidentiality of patient data will be maintained.

Patients with HPP are expected to display a very wide range of developmental stages, disease symptoms and severity, and frequency of clinical contact. Therefore, data for each patient will be collected using age- and developmentally-appropriate assessments.

If more than 1 sibling or other family member is enrolled in the Registry, each patient will be asked to have their data linked with that of their family members. Patients may choose not to have their data linked and still participate in the Registry.

Data Sources:

Clinical Data Collection

Data will be collected through an EDC system. At each data collection time point, data from the

previous interval will be obtained from the patient medical record.

Patient-Reported Outcomes

The patient or parent (or legal guardian) will be encouraged to complete age-appropriate PRO questionnaires, if available as per standard of care practice, throughout their participation in the Registry. These questionnaires should be available in the appropriate local language.

Number of Patients:

Due to the rarity of severe HPP and limited information on the prevalence of mild and moderate forms of this disease, the goal is to enroll at least 500 patients globally (including patients whether treated or not with asfotase alfa).

Statistical Analyses:

Prior to the conduct of data analysis each year, details of planned analyses and patient cohorts will be prespecified in an a priori Epidemiological and Statistical Analysis Plan (ESAP).

Categorical variables will be described using frequencies and percentages and modeled using logistic regression, while continuous variables will be described using means, standard deviations, medians, and inter-quartile ranges with modeling accomplished through generalized linear models, where appropriate.

Study results will be summarized and reviewed at appropriate intervals based on patient enrollment, scientific considerations, and regulatory requirements. At a minimum, study results will be summarized annually and reported. Following termination of the Registry, a final analysis and report will also be prepared.

1.2. Schedule of Data Collection

Table 4: Schedule of Data Collection

Assessment[a]	**Baseline Data at Registry Enrollment**	**Follow-up Data Year 1 (at Least Every 3 Months)[b]**	**Follow-up Data After Year 1 (at Least Every 6 Months)[b]**	**Patient Discontinuation/ Registry Termination**
Informed consent	X			
Demographics	X			
HPP disease history[c]	X			
HPP disease status[d]				
Clinical laboratory work[e]	X	X	X	X
Other medications taken for HPP and non-HPP-related indications	X	X	X	X
Orthopedic surgeries	X	X	X	X
Physiotherapies and occupational therapies	X	X	X	X
Respiratory assessment	X	X	X	X
Skeletal assessment[f]	X	X	X	X
Renal assessment[g]	X	X	X	X
Hearing assessment	X	X	X	X
Ophthalmologic assessment[h]	X	X	X	X
Gastrointestinal assessment	X	X	X	X

Assessment[a]	Baseline Data at Registry Enrollment	Follow-up Data Year 1 (at Least Every 3 Months)[b]	Follow-up Data After Year 1 (at Least Every 6 Months)[b]	Patient Discontinuation/ Registry Termination
Nutritional assessment	X	X	X	X
Growth and development	X	X	X	X
Details of Functional Outcomes Assessments Performed (eg, specific functional outcomes assessments performed [eg, 6MWT, Bayley-III, BOT-2, PDMS-2, POSNA PODCI, LEFS, TUG, and SPPB including repeated chair rise], training/qualifications of the administrator/assessor of the functional outcomes assessments, and results of the functional outcomes assessments)	X	X	X	X
Measures of health resource utilization	X	X	X	X
Asfotase alfa dosing[i]	X	X	X	X
SAE/Targeted Events reporting[j]	X	X	X	X
Patient-reported Outcomes[k]				
Pain	X	X	X	X
Quality of life	X	X	X	X
Functional status/ADL	X	X	X	X
Assistive devices/home modifications	X	X	X	X
Pregnancy[l]				
Pregnancy history/outcome	X	X	X	X
Conclusion of participation				X

[a] Assessments will be age-appropriate for each patient and visit. Available information will be recorded from the patient's medical records. There are no required clinical procedures for this Registry; the Physician will determine the assessments to be performed for each patient as part of routine clinical care.

[b] Physicians will be prompted to enter data at least every 3 months for the first year of enrollment in the Registry, then at least every 6 months after the first year (as long as this frequency is consistent with the standard of care). At each data collection time point, data covering the time interval since the last submission of data will be obtained from the patients' medical record.

[c] Data will be recorded as available. For patients who initiated treatment with asfotase alfa prior to their enrollment, data on HPP disease history prior to treatment initiation will be collected. Information on historical use of asfotase alfa, and historical occurrence of targeted events of IARs and severe hypersensitivity reactions (including anaphylaxis), systemic immune complex-mediated reactions, ISRs, lack of efficacy, and medication errors will also be collected (see Section 8.1.4).

[d] Data will be recorded as available. Information on asfotase alfa dosing, effectiveness of asfotase alfa treatment, SAEs, targeted events of IARs and severe hypersensitivity reactions (including anaphylaxis), systemic immune complex-mediated reactions, ISRs, and lack of efficacy, ADAs, pregnancy and neonatal outcome data, and medication errors will be collected (see Section 8.1.5).

[e] Results of ADA testing will be collected for patients treated with asfotase alfa only. ADA testing will be performed at the discretion of the Physician as part of routine clinical care. For patients presenting with symptoms associated with systemic immune-complex mediated reactions, ADA testing is highly recommended.

[f] Results of standard radiographic reports if ordered by physicians as part of routine clinical practice to assess rickets will be recorded. This applies only to patients with open growth plates where rickets manifest radiographically.

[g] Alexion recommendation is that renal ultrasounds/computerized tomography be performed at Baseline and periodically throughout Registry conduct in accordance with local labeling.
[h] Alexion recommendation is that ophthalmologic examinations be performed at Baseline and periodically throughout Registry conduct in accordance with local labeling.
[i] For patients being treated with asfotase alfa only. For patients who initiated treatment with asfotase alfa prior to Registry enrollment, information on historical use of asfotase alfa will be collected at the time of enrollment. Information on access to, and receipt of, educational materials for asfotase alfa (ie, Injection Guide) will be collected at the time of enrollment and at each visit.
[j] For patients who initiated treatment with asfotase alfa prior to Registry enrollment, information on historical occurrence of targeted events will be collected at the time of enrollment. See Section 10.4 for definitions and reporting requirements.
[k] For pediatric patients, patient-reported outcomes instruments will be encouraged to be completed by the parent or legal guardian if collected as per standard of care practice.
[l] For patients ever treated with asfotase alfa, any pregnancy outcomes and neonatal characteristics collected during the Registry that meet the criteria for an SAE (eg, congenital anomaly) should be reported as outlined in Section 10.4.

Abbreviations: 6MWT = 6-Minute Walk Test; ADL = activities of daily living; Bayley-III = Bayley Scales of Infant and Toddler Development®, Third Edition; BOT-2 = Bruininks-Oseretsky Test of Motor Proficiency Second Edition; HPP = hypophosphatasia; IARs = injection-associated reactions; ISRs = injection-site reactions; LEFS = Lower Extremity Functional Scale; PDMS-2 = Peabody Developmental Motor Scale® Second Edition; PODCI = Pediatric Outcomes Data Collection Instrument®; POSNA = Pediatric Orthopedic Society of North America; SAE = serious adverse event; SPPB = Short Physical Performance Battery; TUG = Timed Up and Go Test

2. INTRODUCTION

2.1. Background

Hypophosphatasia (HPP) is a rare, inherited, and potentially fatal disorder caused by deficiency of tissue-nonspecific alkaline phosphatase (TNSALP) (Whyte, 2013). Hypophosphatasia is characterized by defective bone mineralization and impaired phosphate and calcium regulation as a direct result of deficient TNSALP, which can lead to progressive damage to vital organs along with other severe clinical sequelae including deformity and destruction of bones, pain and profound muscle weakness, respiratory failure, seizures, impaired renal function, impaired mobility, and dental abnormalities.

HPP across patient ages is characterized by interdependent clinical manifestations, emanating from a failure to mineralize bone matrix due to elevated concentrations of the TNSALP substrate inorganic pyrophosphate (PPi). Elevations in extracellular PPi inhibit bone mineralization by blocking hydroxyapatite crystal formation, causing a pronounced accumulation of unmineralized bone matrix. Failure to mineralize bone matrix results in osteomalacia (softening of bones) in patients of all ages, and skeletal deformities of rickets (abnormal mineralized bone, dysmorphic long bones and ribs) and subsequent growth abnormalities in infants and children. In addition, severe functional deficits are often present in patients with HPP, including mobility defects (ambulation and gait impairments), muscle weakness, and inability to carry out activities of daily living, altogether affecting patient quality of life (QoL). TNSALP also dephosphorylates pyridoxal-5'-phosphate (PLP) into pyridoxal, allowing it to cross the blood brain barrier into the central nervous system. Deficiency in TNSALP results in vitamin B_6 deficiency in the central nervous system, potentially leading to seizures as well as somnolence and symptoms of depression.

In infants with HPP, bone mineralization defects with resulting skeletal deformities and fractures and rachitic changes in the chest may lead to the inability of the rib cage to support normal respiratory function and increase the risk of ventilator dependence and premature death. In the most severely affected patients, mortality ranges from 50% through 100% (Caswell, 1991; Greenberg, 1993; Whyte, 2012). In patients surviving to adolescence and adulthood, long-term clinical sequelae include recurrent and nonhealing fractures, weakness, arthritis, the inability to remove internal fixation devices (due to the risk of recurrent fracture), pain, and the requirement for ambulatory assistive devices (wheelchairs, wheeled walkers and canes).

Historical classification of HPP includes pediatric-onset HPP forms (comprised of perinatal-, infantile-, and juvenile-onset HPP forms), where first symptoms of HPP present at < 18 years of age, and an adult-onset HPP form, where symptoms appear at ≥ 18 years of age (Whyte, 2013). Other milder forms of the disease, including benign perinatal HPP and odontohypophosphatasia, have also been characterized (Whyte, 2012).

Historically, clinical management of HPP has been mainly supportive and has addressed symptoms (eg, respiratory support, orthopedic intervention and pain relief medication) of the disease, but not the underlying pathophysiology. Thus, despite best efforts, the majority of patients have experienced significant morbidity (growth abnormalities, structural deficits, bone pain, physical dysfunction, and/or respiratory distress). More recently, Strensiq® (asfotase alfa), a bone-targeted enzyme replacement therapy, designed to address the underlying cause of HPP,

has been approved for treatment of HPP in Japan, Canada, the USA, countries of the EU, and Australia, and it is under regulatory review for approval in a number of other countries.

2.2. Registry Rationale

As noted above, HPP is a rare disease that has historically been largely treated symptomatically. Only 1 therapy designed to treat the underlying cause of the disease (Strensiq® [asfotase alfa]) has been approved for commercial use. Due to the rare nature of this disease, and considering the lack of information regarding diagnosis patterns and health care management in a "real world" setting, this study will collect data on epidemiology, HPP history, clinical course, symptoms (including systemic aspects of the disease), and burden of disease from patients who have a diagnosis of HPP, including patients of any age and who are either untreated or receiving treatment for HPP. The Registry will collect data on asfotase alfa dosing, effectiveness of treatment, serious adverse events (SAEs), anti-drug antibodies (ADAs), pregnancy and neonatal outcome data for patients treated with asfotase alfa only, and targeted events for all patients. Accordingly, the Registry will permit better delineation between the natural disease course of HPP and the disease course in patients who are treated.

This Registry will also serve to fulfill postmarketing commitments and requirements, as applicable, and will be conducted, in part, as a Post Authorization Safety Study according to EU Directive 2001/83/EC (DIR) Art 1 (15) and DIR Art 107m-q and Commission Implementing Regulation No 520/2012 Art 36-38.

2.3. Benefit/Risk Assessment

There is no direct benefit to patients who participate in the Alexion HPP Registry, as all patients will be receiving care according to the standard clinical practice as indicated by their treating Physician(s).

3. OBJECTIVES AND OUTCOMES

The objectives of the HPP Registry are:

- To collect information on the natural history of HPP from patients of all ages, including pediatric patients and adults with HPP, regardless of age at onset.
- To characterize the epidemiology of the HPP population. Inclusion of all classifications of HPP is planned: pediatric-onset (perinatal-, infantile-, and juvenile-onset), adult-onset, benign perinatal, and odontohypophosphatasia.
- To evaluate the burden of disease for HPP and the systemic aspects of HPP, including clinical outcomes and QoL, in a "real-life" setting.
- To collect and evaluate long-term safety and effectiveness data in HPP patients who have/are receiving treatment with asfotase alfa. More specifically, this Registry will serve to:
  - Collect and evaluate longitudinal effectiveness data, including, but not limited to, the following in asfotase alfa-treated patients (for comparison to untreated patients and patients treated with other therapies, as data permit):
    - Growth and development parameters, including height/length, weight, head and chest circumference, and arm span
    - Information about skeletal assessments and treatments
    - Clinical laboratories relevant to HPP (eg, PLP)
    - Functional outcomes relevant to HPP (eg, 6-Minute Walk Test [6MWT], Bayley-III [also known as the Bayley Scales of Infant and Toddler Development®, Third Edition, BSID-III], Bruininks-Oseretsky Test of Motor Proficiency Second Edition [BOT-2], Peabody Developmental Motor Scale® Second Edition [PDMS-2], Pediatric Orthopedic Society of North America [POSNA] Pediatric Outcomes Data Collection Instrument® [PODCI], Lower Extremity Functional Scale [LEFS], Timed Up and Go Test [TUG], and Short Physical Performance Battery [SPPB] including repeated chair rise test)
  - Collect and evaluate longitudinal safety data in asfotase alfa-treated patients in order to further characterize the safety profile of asfotase alfa and targeted events, including, but not limited to, injection-site reactions (ISRs), injection-associated reactions (IARs), ADAs, ectopic calcification, craniosynostosis, and medication errors.
  - Collect and evaluate information on asfotase alfa exposure in patient populations for which little or no information is currently available (eg, pregnant and lactating women, patients with hepatic or renal impairment, the elderly).

4. ALEXION HPP REGISTRY DESIGN

4.1. Overall Design

This multinational, multicenter, observational, prospective, long-term registry is designed to collect data on the epidemiology, HPP history, clinical course, symptoms (including systemic aspects of disease), and burden of disease from patients of all ages who have a diagnosis of HPP. In addition, the Registry will collect data on asfotase alfa dosing, effectiveness of treatment, SAEs, ADAs, pregnancy and neonatal outcome data (for patients treated with asfotase alfa only), and targeted events.

Data on patients participating in this Registry will be collected at the time of enrollment (ie, Baseline), and subsequent data collection will be performed in the course of routine clinical care and through patient-reported outcome (PRO) methods, as indicated in the Schedule of Data Collection (Table 4).

Physicians will be asked to record data, collected from the patients' medical records, at least every 3 months for the first year of enrollment in the Registry, then at least every 6 months thereafter. For all patients enrolled, data will be collected in the Registry for the lifecycle of the product, unless otherwise agreed to by governing regulatory Agencies that all regulatory obligations for Registry conduct are met. Data will be collected through an electronic data capture (EDC) system.

Physicians will perform the study in accordance with the regulations and guidelines governing medical practice and ethics in the country of the study and in accordance with currently available treatment resources and information.

4.2. Milestones

Registry study milestones, either actual or planned, are indicated below.

Milestone	Planned (or actual) date
First patient enrolled	Jan 2015
End of data collection	As applicable, based on agreed to regulatory requirements[a]
Study progress reports	Annually or as per regulatory requirements
Registration in the EU PAS register	20 May 2016
Final report of study results	As applicable, based on agreed to regulatory requirements[a]

[a] Data will be collected in the Registry for the life cycle of the product (a final Registry report will not be prepared), unless otherwise agreed to by governing regulatory Agencies that all regulatory obligations for Registry conduct are met.

4.3. Setting

Patients of all ages with a diagnosis of HPP will be recruited to participate in the Registry, including those who have not received/are not receiving treatment with asfotase alfa, as well as those who have received/are receiving asfotase alfa treatment. Registry participation will be offered, at a minimum, to all sites that enrolled patients in registration studies included in applications submitted for regulatory approval of asfotase alfa. For any patients considered for participation in the Registry who either declined participation or failed to qualify for participation, reasons the patient declined or failed to qualify for participation will be captured, as available.

During the study, clinic visits will be scheduled by the Physicians in accordance with their usual clinical practice. Frequency of visits may vary depending upon several factors, including the age of the patient and severity of disease.

At the time of enrollment, Baseline clinical and age- and developmentally-appropriate PRO data will be collected if available as per standard of care practice (see Appendix 1). Physicians will also be prompted to enter follow-up data, collected from the patients' medical records, as described in Section 8.1.1. In addition, patients will be encouraged to self-report selected disease burden information at intervals via age-appropriate PRO if consider as part of standard of care practice. For pediatric patients, PRO data will be reported by the parent or legal guardian.

For all patients enrolled (including those receiving asfotase alfa treatment), data will be collected in the Registry for the lifecycle of the product, unless otherwise agreed to by governing regulatory agencies that all regulatory obligations for Registry conduct are met. After this time, Alexion reserves the right to discontinue the Registry at any time for clinical or administrative reasons. Discontinuation of data collection will not impact continuing treatment care plans that are in effect for these patients.

5. SELECTION AND WITHDRAWAL OF PHYSICIANS

5.1. Responsibilities

To be eligible for HPP Registry participation, Physicians should meet the following qualifications:

- Agree to comply with HPP Registry processes.
- Agree to complete electronic case report forms (eCRFs) with patient's data at enrollment (ie, Baseline) and during each follow-up.
- Agree to comply with the Health Insurance Portability and Accountability Act of 1996 (HIPAA) regulations or General Data Protection Regulation, as applicable, and/or institution/country-specific patient privacy requirements, as applicable.

5.2. Physician Withdrawal

Should a Physician leave his/her medical practice, Alexion should be informed in advance, and another Physician should be identified to whom patients will be referred. The replacing Physician will be trained on HPP Registry-specific procedures, and then will assume Registry responsibilities for patients enrolled in the HPP Registry.

Patient data entered in the HPP Registry by the leaving Physician will remain in the database.

6. REGISTRY POPULATION

6.1. Inclusion Criteria

The following criteria should be used to identify patients for the HPP Registry:

1. Male and female patients, of any age, with a confirmed diagnosis of HPP.
2. Patient must have documented alkaline phosphatase (ALP) activity below the lower limit of normal for age and sex, or a documented *ALPL* gene mutation.
3. Patient or parent (or legal guardian) is able to read and/or understand the informed consent and study questionnaires in the local language.
4. Signed informed consent and medical records release by the patient or parent (or legal guardian). Patient or patient's parent (or legal guardian) must be willing and able to give written informed consent, and the patient must be willing to give written informed assent, if appropriate and required by local regulations.

6.2. Exclusion Criteria

1. Currently participating in an Alexion-sponsored clinical study. Patients who have concluded participation in an Alexion-sponsored asfotase alfa clinical study are eligible to enroll in this Registry, and enrollment in the Registry will not exclude a patient from enrolling in a future clinical study.

7. PATIENT SELECTION AND DISCONTINUATION/WITHDRAWAL

7.1. Patient Participation

Patients with HPP and their parent or legal guardian (as appropriate) will receive information regarding participation from the Physician. Patient data will only be collected and entered in the eCRF after informed consent has been obtained from the patient or parent/legal representative and eligibility criteria for Registry participation have been assessed (Section 6.1 and Section 6.2) and the patient determined eligible. Where appropriate and required by local regulations, patient assent should also be obtained.

For any patients considered for participation in the Registry who either declined participation or failed to qualify for participation, reasons the patient declined or failed to qualify for participation will be captured, as available.

7.2. Patient Discontinuation/Withdrawal From the Registry

Participation in the HPP Registry is voluntary. Patients may decide to discontinue participation in the HPP Registry (by notifying the Physician verbally or in writing) at any time without penalty and without affecting future medical care. Details on any patient discontinuations from the Registry (including specific reasons for discontinuation) will be recorded in the eCRF and summarized in Registry reports. In the event of a discontinuation, previously collected data will continue to be used for analyses.

For patients who discontinue treatment with asfotase alfa after enrollment, Registry participation may be continued.

Information should continue to be submitted to the Registry for all ongoing SAEs (until resolution). Any new SAEs identified after discontinuation of asfotase alfa assessed by the Physician as treatment-related should be reported during the 30-day follow-up period and followed up until resolution.

Following the fulfillment of any regulatory or other legal obligation, the Registry may be stopped by Alexion for any reason. A patient may be withdrawn from the Registry by Alexion or the participating Physician if:

1. The Registry is stopped by Alexion
2. It is discovered that the patient did not meet the requirements for participation in the Registry
3. The Institution and/or Registry Physician is no longer participating in the Registry
4. Relevant Regulatory Authorities and/or Institutional Review Board (IRB)/Independent Ethics Committee (IEC) decide to stop the Registry.

8. REGISTRY PROCEDURES AND DATA COLLECTION

8.1. Data Sources

8.1.1. Data Sources

Data from patients participating in the Registry will be collected through an EDC system. This study will comply with relevant data protection and privacy regulations. Patients and their parent (or legal guardian) will be informed of the use and disclosure of their study data for the purposes of the study. Anonymity of patient data will be maintained.

If more than 1 sibling or other family member is enrolled in the Registry, each patient will be asked to have their data linked with that of their family members. Patients may choose not to have their data linked and still participate in the Registry.

8.1.1.1. Clinical Data

At each data collection time point, data covering the time interval since the last submission of data will be obtained from the patients' medical records.

8.1.1.2. Patient-reported Outcomes Data

The patient or parent (or legal guardian) will be encouraged to complete age-appropriate PRO questionnaires throughout their participation in the Registry; these questionnaires should be available in the appropriate local language. For pediatric patients, PRO data will be reported by the parent or legal guardian per standard of care. PROs are summarized by domain and age group in Section 13**.**

8.1.2. Schedule of Data Collection

Registry data will be collected according to the recommended schedule in Table 4. Data will be collected from the patients' medical records at least every 3 months for the first year of enrollment in the Registry, then at least every 6 months after the first year. At each data collection time point, data covering the time interval since the last submission of data will be obtained from the patients' medical records.

8.1.3. Demographic Data

- Date of birth, sex, geographical location, ethnicity/race (where permitted by local regulations)
- Tanner stage (up to stage 5 or 18 years of age, whichever comes first)
- For females, age at menopause (if applicable)

8.1.4. HPP Disease History

The following information related to HPP disease history, if available, will be collected from the patients' medical records at the time of enrollment in the HPP Registry. For patients who initiated treatment with asfotase alfa prior to their enrollment in the HPP Registry, data on HPP disease history prior to treatment initiation will be collected.

Information will be collected on historical use of asfotase alfa and historical occurrence of targeted events of IARs and severe hypersensitivity reactions, including, for patients treated with asfotase alfa, anaphylaxis, systemic immune complex-mediated reactions, ISRs, lack of efficacy/drug effect, and medication errors. For all patients whether treated or not with asfotase alfa, the following will be collected: ectopic calcifications, respiratory failure/respiratory insufficiency or compromise/pneumonia, hearing loss, and craniosynostosis.

Disease History and Diagnosis

- Date of first symptoms/diagnosis, and identifying symptoms
- Family history of HPP
- Genotype: gene encoding the TNSALP isoenzyme (*ALPL*) gene mutation analysis (if available)
- Tests and procedures used to confirm the diagnosis (eg, urine phosphoethanolamine [PEA], PLP, urine or serum PPi, total ALP, calcium, phosphorus, 25(OH) vitamin D, parathyroid hormone [PTH], alanine aminotransferase [ALT], aspartate aminotransferase [AST], total bilirubin, direct bilirubin, indirect bilirubin, blood urea nitrogen [BUN], creatinine, albumin, potassium; radiographic evidence of HPP)
- Health care provider responsible for the diagnosis (eg, rheumatologist, pediatrician, pediatric endocrinologist, pediatric nephrologist, endocrinologist, geneticist)
- Concomitant diseases

History of HPP-related and Other Relevant Clinical Laboratory Abnormalities

- Total ALP, plasma PLP, urine PEA, urine or serum PPi, PTH, Ca, P, 25(OH) vitamin D, ALT, AST, total bilirubin, direct bilirubin, indirect bilirubin, BUN, creatinine, albumin, potassium

Historical Use of Asfotase Alfa (for Patients who Received Asfotase Alfa Prior to Registry Enrollment)

- Start date and stop date (and reasons for discontinuation), if applicable
- Dosing regimen (eg, dose [mg/kg], frequency, missed doses, treatment interruptions)
- Changes in dosing regimen (eg, dose [mg/kg], frequency, missed doses, treatment interruptions)
- Lot numbers of asfotase alfa administered
- Information on access to, and receipt of, educational materials for asfotase alfa (ie, Injection Guide)

Other Medication History

- Other HPP therapies attempted (eg, PTH, bisphosphonates)
- Previous HPP-related pain medications (eg, non-steroidal anti-inflammatory drugs [NSAIDs], opioids)
- Other medications taken for HPP and non-HPP-related indications

History of Orthopedic Surgeries/Physiotherapies

- Surgery performed, hardware installed, other interventions
- Physiotherapy (number/time interval, eg, week or month)
- Occupational therapy

Respiratory History

- Respiratory support used (eg, supplemental nasal oxygen, continuous positive airway pressure [CPAP]/bilevel positive airway pressure [BPAP], invasive ventilation)
- Pulmonary function testing (eg, forced vital capacity [FVC] and forced expiratory volume in 1 second [FEV_1], if available)

Skeletal History

- Dual-energy X-ray absorptiometry (DXA)
- Information about skeletal assessments and treatments
- Results of standard radiographic reports if ordered by physicians as part of routine clinical practice to assess rickets will be recorded. This applies only to patients with open growth plates where rickets manifest radiographically.

Renal History

- Renal ultrasound results (eg, nephrocalcinosis, nephrolithiasis)
- Kidney function results
- History of renal impairment
- History of dialysis

Hepatic Impairment History

Hearing History

- Hearing loss and type
- Use of hearing aid

Ophthalmologic Assessment (for Signs of Papilledema and Ectopic Calcification)

- Visual acuity
- Slit-lamp and retina examination

Gastrointestinal History

Nutritional History

Growth and Development History

- Skeletal and dental abnormalities, developmental delays
- Baseline height/length, weight, head and chest circumference, arm span

Details of Functional Outcomes Assessments Performed

- Specific functional outcomes assessments performed (eg, 6MWT, Bayley-III [also known as BSID-III], BOT-2, PDMS-2, POSNA PODCI, LEFS, TUG, and SPPB including repeated chair rise)
- Training/qualifications of the administrator/assessor of the functional outcomes assessments

Historical Occurrence of Targeted Events

- IARs and severe hypersensitivity reactions, including anaphylaxis
- Systemic immune complex-mediated reactions
- ISRs
- Lack of efficacy/drug effect
- Ectopic calcifications
- Respiratory failure/respiratory insufficiency or compromise/pneumonia
- Hearing loss
- Craniosynostosis
- Medication errors

History of Assistive Devices/Home Modifications

- Wheelchair/walker/cane/braces
- Ramps/bath
- Other

History of Health Resource Utilization

- For example, emergency room (ER) visits, hospitalization

8.1.5. HPP Disease Status

The following information related to HPP disease status, if available, will be collected from the patients' medical records during ongoing patient follow-up in the Registry. Information on asfotase alfa dosing, effectiveness of asfotase alfa treatment, SAEs, targeted events of IARs and severe hypersensitivity reactions (including anaphylaxis), systemic immune complex-mediated reactions, ISRs, and lack of efficacy, immunogenicity (as assessed by ADAs), pregnancy and neonatal outcome data, and medication errors will be collected for patients treated with asfotase alfa only. There are no required clinical procedures for this Registry study; the Physician will determine the assessments, laboratory tests, imaging procedures, and other evaluations to be performed for each patient as part of routine clinical care.

Clinical Laboratory Assessments

- Total ALP, plasma PLP, urine PEA, urine and/or serum PPi, PTH, Ca, P, 25(OH) vitamin D, ALT, AST, total bilirubin, direct bilirubin, indirect bilirubin, BUN,

creatinine, albumin, potassium, and immunogenicity (testing performed at Physician discretion for patients treated with asfotase alfa only; see Section 8.1.6 and Section 10.1.2.3 for further details on testing considerations)

Asfotase Alfa Dosing (for Patients Treated With Asfotase Alfa)

- Start date and stop date (and reasons for discontinuation), if applicable
- Dosing regimen (eg, dose [mg/kg], frequency, missed doses, treatment interruptions)
- Changes in dosing regimen (eg, dose [mg/kg], frequency, missed doses, treatment interruptions)
- Lot numbers of asfotase alfa administered
  - Lot numbers of asfotase alfa will be collected along with information on any pregnancy (Section 8.1.8) and safety information for any reported SAE or targeted events (see Section 10.1.2). In the event that the lot number is not indicated in the initial report, Alexion or its designee will use due diligence to follow-up with the Physician and identify the missing lot number.
- Information on access to, and receipt of, educational materials for asfotase alfa (ie, Injection Guide) (collected at every visit)

Other Medications

- Other HPP therapies (eg, PTH and bisphosphonates)
- Other medications taken for HPP and non-HPP-related indications

Orthopedic Therapies

- Surgery performed, hardware installed, other interventions
- Physiotherapy (number/time interval, eg, week or month)
- Occupational therapy

Respiratory Status

- Respiratory support used since previous visit (eg, supplemental nasal oxygen, CPAP/BPAP, endotracheal tube [ETT], or tracheostomy)
- Pulmonary function testing (eg, FVC and FEV_1)

Skeletal Assessment

- DXA
- Information about skeletal assessments and treatments
- Results of standard radiographic reports if ordered by physicians as part of routine clinical practice to assess rickets will be recorded. This applies only to patients with open growth plates where rickets manifest radiographically.

Renal Assessment

- Renal ultrasound/computerized tomography [CT] scan results (eg, nephrocalcinosis, nephrolithiasis)
- Kidney function results
- Dialysis

Hearing Assessment

Ophthalmologic Assessment

- Visual acuity
- Slit-lamp and retina examination

Gastrointestinal Assessment

Nutritional Assessment

Growth and Development Parameters

- Height/length, weight, head and chest circumference, arm span

Details of Functional Outcomes Assessments Performed

- Specific functional outcomes assessments performed (eg, 6MWT, Bayley-III [also known as BSID-III], BOT-2, PDMS-2, POSNA PODCI, LEFS, TUG, and SPPB including repeated chair rise)
- Training/qualifications of the administrator/assessor of the functional outcomes assessments
- Results of the functional outcomes assessments

Serious Adverse Events

- See Section 10.4 for details on reporting SAEs

Targeted Events

See Section 10.4 for details on reporting Targeted Events

- IARs and severe hypersensitivity reactions, including anaphylaxis
- Systemic immune complex-mediated reactions
- ISRs – severe and/or serious
- Lack of efficacy/drug effect
- Ectopic calcifications
- Respiratory failure/respiratory insufficiency or compromise/pneumonia
- Hearing loss
- Craniosynostosis
- Medication errors

Measures of health resource utilization

- For example, ER visits and hospitalization

8.1.6. Anti-drug Antibody testing

Considering that asfotase alfa is an exogenous protein, monitoring for the development of ADAs and neutralizing antibodies (NAbs) against asfotase alfa has been routinely performed in clinical studies of asfotase alfa. More than 75% of patients in clinical studies of asfotase alfa tested positive for ADAs at one or more time points after initiation of treatment; of patients testing positive for ADAs, approximately 45% tested positive for NAbs at one or more time points. Overall, the magnitude of the immunogenicity response was considered small and time-variant in patients and results of analyses performed did not suggest there was an appreciable impact of ADAs or NAbs on efficacy or the safety profile of asfotase alfa. Cases from the post-approval setting suggest that development of inhibitory antibodies may be associated with a decreased clinical response.

Physicians enrolling patients treated with asfotase alfa in the Registry may consider ADA testing when lack of asfotase alfa efficacy is suspected due to re-emergence of HPP signs and symptoms, indicating worsening clinical presentation (eg, reoccurrence of rickets). Although the association of lack of efficacy with ADA titers or NAb % inhibition has not been established in the asfotase alfa clinical trial program, in some post-marketing cases, apparent lack of efficacy with asfotase alfa treatment has been hypothesized as immune-mediated. In case of potential lack of efficacy, ADA testing may be requested as part of standard of care. Patients who are not currently enrolled in the Registry may be referred to the nearest Registry site to be enrolled in the Registry to be eligible for ADA testing (see Section 10.1.2.3).

At Registry sites collecting blood samples for ADA testing, shipment, and testing of blood samples will be supported by Alexion without any charge to the Physician or patient.

Testing of blood samples for ADAs and NAbs, if applicable, will be performed centrally and results (including whether sample tested positive for ADAs and, if sample tested positive for ADAs, ADA titer and whether sample tested positive for NAbs) provided to the Physician for clinical management of the patient.

8.1.7. Patient-reported Outcomes Instruments

Age-appropriate PRO data will be collected using the instruments described below if considered part of the standard of care; for pediatric patients, these instruments will be completed by the parent or legal guardian) per standard of care.

Burden of Disease

- Pain:
  - Brief Pain Inventory, Short Form (BPI-SF) (patients ≥ 18 years of age)
- Motor Capacity:
  - Motor assessments (included in QoL instruments below)

Functional Status/Disability, including Activities of Daily Living (ADL)

- Health Assessment Questionnaire – Disability Index (HAQ-DI) (patients ≥ 18 years of age)

Quality of Life

- Pediatric Quality of Life Inventory (PedsQL) (patients > 2 years of age to < 18 years of age)
- Short Form Health Survey, 36-item version 2 (SF-36 v2) (patients ≥ 18 years of age)

Assistive Devices/Home Modifications

- Wheelchair/walker/cane/braces
- Ramps/bath
- Other

8.1.8. Pregnancy

Female patients of childbearing potential treated with asfotase alfa are requested to provide information about any past pregnancies, and report any pregnancy occurring during the study.

Past pregnancies

- Pregnancy history (date confirmed, delivery date, if available)
- Pregnancy outcome (including, but not limited to, normal birth, full-term, preterm, low birth weight, fetal loss/stillbirth, spontaneous miscarriage, induced abortion, elective termination, and/or congenital abnormality, if available)

The following information regarding the outcome of pregnancy and neonatal condition, if available, should be reported via the Pregnancy/Breastfeeding Reporting and Outcome Form for pregnancies occurring during the study:

- Pregnancy history (date confirmed, delivery date, if available)
- Pregnancy outcome (including, but not limited to, normal birth, full-term, preterm, low birth weight, fetal loss/stillbirth, spontaneous miscarriage, induced abortion, elective termination, and/or congenital abnormality, if available)
- Neonatal characteristics (if available):
  - Apgar scores
  - Respiratory distress or other complications
  - Admission to neonatal intensive care unit/length of stay
  - Congenital anomalies

For patients being treated with asfotase alfa, any pregnancy outcomes and neonatal characteristics collected during the Registry that meet the criteria for an SAE (eg, congenital anomaly) should be reported as outlined in Section 10.4.

8.1.8.1. Exposure to Asfotase Alfa During Pregnancy and Lactation

If a patient within this Registry or the partner of a patient within this Registry becomes pregnant while treated or exposed to asfotase alfa or within 6 months of the last dose, the Physician must submit a pregnancy form to Alexion Global Drug Safety (GDS) or designee via the same method as SAE reporting (see Section 10.4). A copy of this form, the Pregnancy/Breastfeeding Reporting and Outcome Form, will be supplied to the Physician by Alexion's GDS group or designee.

Exposure during pregnancy (both maternal and fetal events), lactation, and follow-up of neonates for 3 months after delivery (all patients, regardless of treatment approach, and female partners of male patients) will be reported. The patient should be followed until the details of the outcome of the pregnancy (including, but not limited to, normal birth, full-term, preterm, low birth weight, fetal loss/stillbirth, spontaneous miscarriage, induced abortion, elective termination, and/or congenital abnormality) are known, even if the patient discontinues treatment with asfotase alfa or discontinues from the Registry. When the outcome of the pregnancy becomes known, the form should be completed and returned to Alexion's Pharmacovigilance group or designee. In the event that the lot numbers the patient received are not indicated in the initial report, Alexion or its designee will use due diligence to follow-up with the Physician and identify the missing lot numbers. If additional follow-up is required, the Physician will be requested to provide the information. Data regarding the pregnancy will also be recorded in the patient's eCRF as outlined in Section 9.1.

Pregnancy in itself is not regarded as an AE unless there is a suspicion that asfotase alfa may have interfered with the effectiveness of a contraceptive medication. However, complications of pregnancy and abnormal outcomes of pregnancy are AEs, and many may meet criteria for an SAE. Complications of pregnancy and abnormal outcomes of pregnancy such as ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly would meet criteria of a SAE and thus, should be reported as such (see Section 10.4). Elective abortions without complications should not be handled as AEs.

In addition to pregnancy, possible exposure of an infant to asfotase alfa during breastfeeding should be reported to Alexion GDS or designee on the Pregnancy/ Breastfeeding Reporting and Outcome Form. Any AEs an infant may experience following possible exposure to asfotase alfa via breastfeeding must also be reported to Alexion GDS or designee via the Pregnancy/Breastfeeding Reporting and Outcome Form.

9. STATISTICAL CONSIDERATIONS

9.1. Data Management

As part of the responsibilities assumed by participating in the Registry, the Physician agrees to maintain adequate case histories for the patients treated as part of the research under this protocol.

Alexion or its designee will provide the Physician with an eCRF, which will be used to collect and store patient data that can then be accessed by Alexion. The eCRF will operate as a secure internet website-based electronic data collection and communication system. All requested information should be entered into the eCRF for each observation. Detailed instructions and training for completing the eCRF will be provided. A vendor specializing in the development of internet website-based EDC systems will design and maintain the website and provide training and ongoing technical support for the Physicians. Should a Physician's internet access become either temporarily or permanently disconnected, the country-specific number provided should be contacted so that alternative data management processes can be arranged.

All SAEs, targeted events, and concomitant diseases collected in the Registry will be coded by Alexion or its designee using Medical Dictionary for Regulatory Activities version (MedDRA) 18.1 or higher.

Verification of source data and/or study records for targeted events and other data collected for the Registry will be conducted on a routine basis by site monitor. The process for study monitoring will be detailed in the HPP Registry Monitoring Plan (Section 11.2.2).

9.2. Number of Patients

Due to the rarity of severe HPP and limited information on the prevalence of mild and moderate forms of this disease, the goal is to enroll at least 500 patients globally (including patients whether treated or not with asfotase alfa). At a minimum, patients will be enrolled from sites in North America, the EU, and the JAPAC (Japan, Asia, Pacific) region.

9.3. Statistical Analyses

The HPP Registry has been established for the conduct of an observational prospective cohort study. Data analyses will be periodically conducted upon the request of regulatory agencies and for support of scientific manuscripts and/or conference abstracts. At a minimum, data analyses will be conducted annually. Prior to implementation of data analysis each year, details of planned analyses and patient cohorts will be prespecified in an a priori Epidemiological and Statistical Analysis Plan (ESAP).

As part of annual analyses, patient disposition (including the number of patients considered for Registry participation who declined participation (and reasons the patient declined), the number of patients considered for Registry participation who failed to qualify for participation (and reasons the patient did not qualify), the number of enrolled patients, and the number of discontinued patients (and reasons the patient discontinued) will be summarized.

Primary analyses will assess safety and effectiveness outcomes, including occurrence and time to first event for safety, targeted events, ADAs, death, and pregnancy. These outcomes will be

evaluated longitudinally during annual analyses and compared in patients receiving asfotase alfa to the same in patients receiving other treatments, as appropriate. All safety outcomes will be described using relevant statistical summaries and their clinical interpretations will be provided. Initial primary interim analyses will be descriptive in nature and are considered to be hypothesis generating. However, as enough data accrue, analyses will include the assessment of potential risk factors, along with regression models and statistical hypothesis testing.

Data permitting, individual ESAPs will be developed to guide secondary analyses including descriptive statistics of the patient population (eg, patient demographics, genotypes, clinical characteristics, and comorbid conditions), HPP-specific treatments and prespecified concomitant medications used in this patient population and changes to these treatments, progression of disease (eg, pulmonary function), and clinical outcomes (eg, laboratory parameters and fractures). Patient characteristics, clinical outcomes, and progression of disease may be compared in patients receiving asfotase alfa to patients receiving other forms of disease management modalities. In addition to assessing differences among HPP treatment cohorts, subpopulations of interest may be identified for analysis (eg, patients with invasive ventilation versus those without). Analyses may be stratified based on these criteria and will be detailed in a prespecified ESAP.

Patients may switch from non-asfotase alfa treatment to asfotase alfa treatment and/or may discontinue asfotase alfa treatment but remain in the Registry using other treatments. In general, the time during which patients are receiving treatment with asfotase alfa will be included in person-years denominator when estimating rates of safety outcomes for asfotase alfa, while the time they are not receiving asfotase alfa will contribute to person-years of non-asfotase alfa treatment (regardless of treatment type).

Categorical variables will be described using frequencies and percentages and modeled using logistic regression, while continuous variables will be described using means, standard deviations, medians, and inter-quartile ranges with modeling accomplished through generalized linear models, where appropriate. Repeated measures techniques will be used for outcomes collected at more than one time point for the same patients. Repeated measures analysis takes into account the correlation of the recurring outcome within patients and handles missing values and truncation in an optimal way, by taking into account the time patterns of the available data.

In the analysis of observational data, propensity scores may be used to control for differences between nonrandomized groups (Rubin, 1997). The propensity score is typically developed using a logistic regression model and is the conditional probability that a patient will be assigned to a particular treatment given a vector of observed covariates. The propensity score may be used as a stratifying variable, a matching variable, a weighting variable, or as a covariate in models (to prevent sample attrition, if necessary). In the analysis of the current study, propensity scores may be used to account for differences between patients who receive asfotase alfa and those who do not.

Survival analysis techniques (life table analysis, Kaplan-Meier curves, and Cox proportional hazards modeling) will be used for time-to-event outcomes such as time to first fracture, time to first assistive device, and mortality (all-cause and HPP-specific mortality). In mortality analyses, the time from diagnosis to death will be estimated. However, the data are likely to be left truncated (ie, patients do not come under observation until after they are already at risk and have

survived for some time). To account for left truncation, data permitting, 2 statistical models will be used: Cox proportional hazards and stratified Cox proportional hazards models.

Because the aim of this Registry is to obtain data under conditions of routine clinical care (ie, naturalistic settings), some patients may have missing values for some variables. To address missing data, a 3-step approach will be followed:

- Identification of reasons for missing data, such as: due to loss to follow-up (eg, patient drop out or death), skip question patterns in the eCRF, or random data collection issues
- Understanding distribution and type of missing data: certain patient groups may be more likely to have missing values, certain responses may be more likely to be missing, and type of missing data (ie, missing completely at random [MCAR], missing at random [MAR] or not missing at random [NMAR])
- Selection of appropriate methods of analysis, such as maximum likelihood and multiple imputation

The ESAPs will describe in detail the methods and variables used in analyses, including those pertaining to truncated and missing data. Furthermore, the extent of missing or truncated data within the analysis datasets will be described in Registry reports.

Data for ever treated patients with unconfirmed HPP will continue to be collected and will be analyzed separately, with a focus on targeted events of interest and SAEs.

9.4. Limitations of the Research Methods

A number of limitations are inherent to registry-based research. While every effort will be made to reduce their impact on study results, it is important to note some of them herein.

- Since HPP is a rare disease, the registry will enroll as many patients as possible in target countries. As such, it will be very challenging to use sampling methods to ensure coverage or representativeness of the wider HPP patient population. This may limit the external validity of study results.
- Residual confounding is a common limitation in registry studies. It describes the amount of variation not explained by variables included in analyses. However, the inclusion of additional confounders, such as comorbidities or socioeconomic factors, can reduce the amount of residual confounding and improve the predictive accuracy of statistical models used.
- Due to the global nature of the registry, access to and completeness of patient medical records are likely to vary across countries. This is due to country/regional differences, such as differences in medical chart documentation practices, data confidentiality policies, data linkages within one or more healthcare systems.

10. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

10.1. Definitions

10.1.1. Definition of an Adverse Event

An adverse event (or adverse experience) is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable or unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

NOTE: Only AEs that are considered SAEs or targeted events will be collected for this Registry.

10.1.1.1. Definition of a Serious Adverse Event

An AE will be considered an SAE if it meets one or more of the following criteria:

- Results in death
- Is immediately life-threatening
  NOTE: The term “life-threatening” means that the patient was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death if it were more severe.
- Requires inpatient hospitalization or prolongation of existing hospitalization. In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the Physician’s office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether “hospitalization” occurred or was necessary, the AE should be considered serious.
  - Note: Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.
- Results in persistent or significant disability/incapacity. The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- Results in a congenital anomaly/birth defect
- Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition.
- Other situations:

- Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
- Examples of such events include invasive or malignant cancers, intensive treatment in an ER or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse

10.1.2. Targeted Events

Data will be collected for the following targeted events:

- IARs and severe hypersensitivity reactions, including anaphylaxis (for patients ever-treated with asfotase alfa, with continued collection, even if asfotase alfa is discontinued; see definition of IAR and severe hypersensitivity reactions in Section 10.1.2.1 and definition of anaphylaxis in Section 10.1.2.2)
- Systemic immune complex-mediated reactions (for patients ever-treated with asfotase alfa, with continued collection, even if asfotase alfa is discontinued; see definition of systemic immune complex-mediated reactions in Section 10.1.2.3)
- Severe and/or serious ISRs (for patients ever-treated with asfotase alfa, with continued collection, even if asfotase alfa is discontinued; see definition of ISR in Section 10.1.2.4)
- Lack of efficacy/drug effect (for patients ever-treated with asfotase alfa, with continued collection, even if asfotase alfa is discontinued)
- Ectopic calcifications (for all patients whether treated or not with asfotase alfa, with continued collection, even if asfotase alfa is discontinued; see definition of ectopic calcifications in Section 10.1.2.5)
- Respiratory failure/respiratory insufficiency or compromise/pneumonia for all patients whether treated or not with asfotase alfa
- Hearing loss for all patients whether treated or not with asfotase alfa
- Craniosynostosis for all patients whether treated or not with asfotase alfa
- Medication errors (unintentional errors in the prescribing, dispensing, administration, or monitoring of a medicine)

10.1.2.1. Definition of Injection-Associated Reaction and Severe Hypersensitivity Reactions

IARs are defined as systemic signs/symptoms/findings (eg, generalized urticaria or itching, hypotension, or respiratory distress) that occur within 3 hours after administration of asfotase alfa that are assessed by the Physician as possibly, probably, or definitely related to asfotase alfa.

Events that are characterized as IARs may reflect a systemic hypersensitivity reaction (eg, combination of 2 or more of the following types of signs/symptoms: generalized urticaria or itching, hypotension, difficulty breathing, swelling of the eyelids or lips or generalized edema) and anaphylaxis (see Section 10.1.2.2). IARs that are assessed by the Physician as severe in intensity (Section 10.2) are defined as severe hypersensitivity reactions.

10.1.2.2. Definition of Anaphylaxis

Clinical criteria for diagnosis of anaphylaxis can be found in Table 5 (Sampson, 2006).

Table 5: Clinical Criteria for Diagnosing Anaphylaxis

Anaphylaxis is highly likely when any 1 of the following 3 criteria is fulfilled:
Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (eg, generalized hives, pruritus or flushing, swollen lips-tongue-uvula) AND at least 1 of the following: • Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, hypoxemia) • Reduced BP[a] or associated symptoms of end-organ dysfunction (eg, hypotonia, collapse, syncope, incontinence)
Two or more of the following that occur rapidly (minutes to several hours) after exposure to a likely allergen for that patient: • Involvement of the skin-mucosal tissue (eg, generalized hives, itch-flush, swollen lips-tongue-uvula) • Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, hypoxemia) • Reduced BP[a] or associated symptoms (eg, hypotonia, collapse, syncope, incontinence) • Persistent GI symptoms (eg, crampy abdominal pain, vomiting)
Reduced BP (minutes to several hours) after exposure to a known allergen for that patient: • Pediatric patients: Low systolic BP[a] (age specific) or > 30% decrease from that person's Baseline • Systolic BP of < 90 mm Hg or > 30% decrease from that person's Baseline

[a] Low systolic blood pressure for children defined as < 70 mmHg from age 1 month to 1 year; < (70 mmHg + [2 x age]) from age 1 to 10 years; and < 90 mmHg from age 11 to 17 years.
Abbreviations: BP = blood pressure; GI= gastrointestinal

10.1.2.3. Definition of Systemic Immune Complex-mediated Reactions (Type III Hypersensitivity)

Systemic immune complex-mediated reactions (Type III hypersensitivity reactions) occur when antigens and immunoglobulin G or M (IgG or IgM) antibodies are present in equal amounts and cross-link to form immune complexes that deposit in tissues and induce inflammation (Riedl, 2003; Wooten, 2010).

These reactions can occur from hours to weeks after antigen exposure, and cause diseases such as systemic lupus erythematosus, serum sickness, vasculitis, and glomerulonephritis. Symptoms of systemic immune complex-mediated reactions may include fever, lymphadenopathy, cutaneous reactions, and arthralgia (Riedl, 2003; Kuljanac, 2008; Khan, 2010).

Hydralazine-induced systemic lupus erythematosus is an example of a disease caused by a drug-induced systemic immune complex-mediated reaction (Wooten, 2010).

Systemic immune complex-mediated reactions may be associated with IgG antibody development.

For patients presenting with symptoms associated with systemic immune complex-mediated reactions, ADA testing is highly recommended (see Section 8.1.6).

A summary of systemic immune complex-mediated (Type III hypersensitivity) reactions, including clinical manifestations and testing and management considerations (Riedl, 2003), can be found in Table 6.

Table 6: Clinical Characteristics and Management Considerations for Systemic Immune Complex-mediated Reactions

Clinical Manifestations	Laboratory Testing for Consideration	Management Considerations
The following may occur, generally within 1 to 3 weeks of drug exposure: • Serum sickness • Fever • Rash • Urticaria • Arthralgias • Lymphadenopathy • Glomerulonephritis • Vasculitis	• ADA testing for asfotase alfa (see Section 8.1.6) • Erythrocyte sedimentation rate • C-reactive protein • Circulating immune complexes • Complement studies (eg, CH50, C3, C4) • Antinuclear antibody testing • Antihistone antibody testing • Tissue biopsy for immunofluorescence studies	• Discontinue drug • Consider treatment with nonsteroidal anti-inflammatory drugs, antihistamines or systemic corticosteroids; or plasmapheresis (if severe)

10.1.2.4. Definition of Injection-Site Reaction

For the purpose of this study, injection-site reactions are defined as events localized to the site of asfotase alfa administration that occur at any time during Registry participation and are assessed by the Physician as possibly, probably, or definitely related to asfotase alfa that are severe (eg, ulceration or necrosis; severe tissue damage; operative intervention indicated) or are considered SAEs (results in death; life-threatening; requires inpatient hospitalization or prolongation of existing hospitalization; results in persistent or significant disability/incapacity; results in a congenital anomaly/birth defect). Injection-site reactions may occur at any time point after asfotase alfa administration.

10.1.2.5. Definition of Ectopic Calcification

Ophthalmic calcifications are known to be influenced by disturbances in calcium homeostasis associated with HPP and have been previously reported in the literature in association with the disease (Roxburgh, 1983). Similarly, nephrocalcinosis is a known complication of HPP (Whyte, 2012). Nephrocalcinosis occurred in 51.6% of patients between birth and 5 years of age

in a natural history study of untreated infantile-onset HPP patients. In a natural history study of juvenile-onset HPP patients, nephrocalcinosis was documented in the HPP disease history of 6.3% of patients.

In asfotase alfa clinical studies, ophthalmic (conjunctival and corneal) calcification and nephrocalcinosis (identified on renal ultrasound) have been reported in patients with HPP. There are insufficient data to establish a causal relationship between exposure to asfotase alfa and ectopic calcifications observed.

Periodic renal ultrasounds (or CT scans, if necessary) and ophthalmology examinations are recommended for monitoring for ectopic calcification in HPP patients and are included as part of recommended Registry assessments. Recommendation is renal ultrasounds/CT scans and ophthalmology examinations be performed at Baseline and periodically throughout Registry conduct in accordance with local labeling.

10.2. Severity Assessment

All SAEs and targeted events (including historical occurrence of targeted events) will be assessed for severity by the Physician. Severity will be assessed as mild, moderate, or severe using the following criteria:

- Mild: Event requires minimal or no treatment and does not interfere with the patient's daily activities.
- Moderate: Event results in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
- Severe: Event interrupts a patient's usual daily activities and may require systemic drug therapy or other treatment. Severe events are usually incapacitating.

Changes in the severity of an event must be documented to allow an assessment of the duration of the event at each level of intensity. Events characterized as intermittent require documentation of onset and duration of each episode if the severity of the intermittent event changes.

Severity and seriousness must be differentiated. Severity describes the intensity of an AE, while the term seriousness refers to an event that has met the criteria for an SAE.

10.3. Causality Assessment

A causality assessment (Not related, Unlikely related, Possibly related, Probably related, or Definitely related) must be provided for SAEs and targeted events. This assessment must be made by the Physician and recorded on the eCRF (see Section 10.4), as appropriate. The definitions for the causality assessments are provided below.

- Not related: This relationship suggests that there is no causal association between asfotase alfa and the reported event.
- Unlikely related: This relationship suggests that the clinical picture is highly consistent with a cause other than asfotase alfa, but attribution cannot be made with absolute certainty. However, given reasonable possibility, the event is considered not causally related to asfotase alfa.

- Possibly related: This relationship suggests that treatment with asfotase alfa may have caused or contributed to the event, ie, the event follows a reasonable temporal sequence from the time of asfotase alfa administration and/or follows a known response pattern to asfotase alfa but could also have been attributed to other factors.
- Probably related: This relationship suggests that a reasonable temporal sequence of the event with asfotase alfa administration exists and there is likely a causal association of the event with asfotase alfa. This assessment should be based on the known pharmacological action of asfotase alfa, known or previously reported adverse reactions to asfotase alfa, or the Physician's clinical experience with asfotase alfa.
- Definitely related: Temporal relationship to asfotase alfa and/or other conditions (concurrent illness, concurrent medication reaction, or progression/expression of disease state) do not appear to explain the event, the event corresponds with the known pharmaceutical profile, improvement of the event is observed on discontinuation, and the event re-appears on re-challenge.

Events that are deemed by the Physician to be possibly, probably, or definitely related to asfotase alfa shall be considered related to asfotase alfa.

10.4. Reporting of Serious Adverse Events and Targeted Events

All SAEs occurring in patients receiving asfotase alfa must be reported to Alexion GDS within 24 hours of first awareness of the event by the Physician or designee. The reporting timelines must be followed for all initial SAE cases and follow-up reports to the initial case.

Targeted events must be reported for all patients. The Physician/site must submit the SAE/targeted event into the EDC system using the Adverse Event electronic CRF.

Any new SAEs identified after discontinuation of asfotase alfa assessed by the Physician as treatment-related should be reported during the 30-day follow-up period and followed up until resolution.

In the event that the EDC system is unavailable at the site(s) and an SAE needs to be reported, please refer to the SAE Contingency Form for reporting the SAE on a paper case report form (CRF).

If additional supporting information is available (ie, hospital discharge summary, relevant laboratory reports and/or diagnostic data, medical records, death certificate), the Physician should complete, sign, and date the SAE cover page, verify the accuracy of the information recorded on the SAE cover page, and send the SAE cover page along with the associated (redacted) source documents to Alexion GDS via:

Email: ClinicalSAE@alexion.com

*Fax: + 1-203-439-9347

*Please note - Email is the preferred route of transmission. However, the Fax# is provided as a back-up/contingency plan for the Investigational site to report the SAE in the event that the site is unable to email the report. Alexion is responsible for notifying the relevant regulatory authorities of certain events. Depending on local regulations, Alexion, Alexion's designee, or the Physician will be responsible for notifying the IRB/EC/REB of all SAEs that occur at a site per

local IRB/EC/REB-established guidelines for submission. Physicians will also be notified of all unexpected, serious, drug-related events that have been expedited to regulatory authorities during the Registry. These additional SAEs will also be reported to sites IRB/Ethics Committee (EC)/Research Ethics Board (REB) per local regulations.

11. REGULATORY, ETHICAL, AND REGISTRY OVERSIGHT CONSIDERATIONS

11.1. Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
- Applicable laws and regulations

The protocol, protocol amendments, informed consent form (ICF), and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the Physician and reviewed and approved by the IRB/IEC before the study is initiated.

Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study patients.

The Physician will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
- Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
- Providing oversight of the conduct of the study at the site.

11.1.1. Financial Disclosure

Physicians will provide Alexion with sufficient, accurate financial information as requested to allow Alexion to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Physicians are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

11.2. Informed Consent Process

The physician or his/her representative will explain the nature of the study to the patient or his/her legally authorized representative and answer all questions regarding the study.

Patients must be informed that their participation is voluntary. Patients or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, HIPAA requirements, where applicable, and the IRB/IEC or study center.

The medical record must include a statement that written informed consent was obtained before the patient was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.

Patients must be re-consented to the most current version of the ICF(s) during their participation in the study.

A copy of the ICF(s) must be provided to the participant or the patient's legally authorized representative.

11.2.1. Data Protection

- Patients will be assigned a unique identifier by Alexion. Any patient records or datasets that are transferred to Alexion will contain the identifier only; patient names or any information which would make the patient identifiable will not be transferred.
- The patient must be informed that his/her personal study-related data will be used by Alexion in accordance with local data protection law. The level of disclosure must also be explained to the patient.
- The patient must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by Alexion, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

11.2.2. Data Quality Assurance

- All patient data relating to the study will be recorded on printed or electronic CRF unless transmitted to Alexion or designee electronically (eg, laboratory data). The Physician is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- The Physician must maintain accurate documentation (source data) that supports the information entered in the CRF.
- The Physician must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- The Physician should promptly notify Alexion, or its designee of any inspections scheduled by any regulatory authorities and promptly forward copies of any audit reports received to Alexion or its designee.
- Alexion or designee is responsible for the data management of this study including quality checking of the data.
- Study monitors will perform ongoing remote data review and confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of patients are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, and all applicable local regulations.
- The process for study monitoring will be detailed in the HPP Registry Clinical Operating Plan. The purpose of this monitoring plan will include verification that SAEs/targeted events and other Registry data are accurate, complete, and verifiable against source documents and/or study records. Verification of source data and/or

study records for SAEs/targeted events and other Registry data will be conducted on a routine basis by the site monitor.

- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Physician for 5 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of Alexion. No records may be transferred to another location or party without written notification to Alexion.

11.2.3. Scientific Advisory Board

A Scientific Advisory Board (SAB), comprised of key experts and opinion leaders, will provide guidance to the HPP Registry. The SAB will be responsible for providing advice related to scientific decisions regarding the HPP Registry.

11.3. REGISTRY TRAINING AND SUPPORT

11.3.1. Site Training

Each site will participate in a training session conducted by Alexion or designee. Sites may contact Alexion or designee, with any questions by telephone or email.

11.3.2. Ongoing Site Support

Sites will have access to continuous technical support throughout the HPP Registry, including HPP Registry protocol questions, assistance with EDC website operations, and the HPP Registry program. Sites will be provided a contact list containing a country specific phone number, country specific fax number, and email address

Alexion staff or its designee may contact Registry sites to clarify entered data or to request additional data. All involved parties are expected to provide the clarifying information in a timely manner, so that the HPP Registry data are kept up-to-date and accurate.

12. PUBLICATIONS

The Registry will be overseen by the SAB, comprised of international experts involved in the research or care of patients with HPP. The SAB's activities will include, but not be limited to, facilitating analysis and dissemination of Registry data via medical conferences of relevant international and national professional societies and through peer-reviewed publications. Publication of Registry data will be subject to initial review and approval from the SAB. The SAB, in conjunction with Alexion, will define a plan for regular publications based on analysis of global Registry data, including the contents of such publications. For each publication, the SAB and Alexion will collaborate in guiding data analyses, interpretation of data analyses, and publication writing. The SAB will be responsible for reviewing publication proposals, analysis requests, and identifying journals, venues, and audiences of interest.

Any participating Registry Physician may publish data analysis based on his/her own patient and any Physician, may submit for review an analysis request to support a publication. The SAB will evaluate the scientific merit of the analysis request and the alignment with the Registry publication strategy. Prioritization of publication will be based on academic/scientific importance of the questions and the source of the request (eg, participating Registry Physician, non-participating Physician).

Participating Physicians and patients will retain control of the patient data that they submit to the Registry and may use those data accordingly. Aggregate analyses will be the property of Alexion and will be disseminated according to this governance structure. Alexion retains the right to use Registry data for any regulatory or reimbursement requirements without obtaining prior approval from the SAB.

Responsibilities of the SAB are outlined in the SAB Charter.

13. APPENDICES

APPENDIX 1. ENCEPP CHECKLIST FOR STUDY PROTOCOLS

APPENDIX 2. PATIENT REPORTED OUTCOMES ASSESSMENTS

Domain Questionnaire	Population		
	≤ 24 months[a]	**> 2 to < 18 years**[a]	**≥ 18 years**
QoL			
SF-36v2			X
PedsQL		X	
Pain/Symptoms			
BPI-SF			X
Functioning/ADL			
HAQ-DI			X

[a] For pediatric patients, patient-reported outcomes instruments will be completed by the parent or legal guardian if collected as part of the standard of care practice.

Abbreviations: ADL = activities of daily living; BPI-SF = Brief Pain Inventory (Short Form); HAQ-DI = Health Assessment Questionnaire – Disability Index; PedsQL = Pediatric Quality of Life Inventory; QoL = Quality of Life; SF-36v2 = Short Form Health Survey (36-item) version 2.

APPENDIX 3. ABBREVIATIONS

Abbreviation or Specialist Term	Explanation
6MWT	6-Minute Walk Test
ADA	anti-drug antibodies
ADL	activities of daily living
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
Bayley-III or BSID-III	Bayley Scales of Infant and Toddler Development®, Third Edition
BOT-2	Bruininks-Oseretsky Test of Motor Proficiency Second Edition
BPAP	bilevel positive airway pressure
BPI-SF	Brief Pain Inventory (Short Form)
BUN	blood urea nitrogen
CPAP	continuous positive airway pressure
CRF	case report form
CT	computed tomography
DEXA	fual-energy X-ray absorptiometry
EC	Ethics Committee
eCRF	electronic case report form
EDC	electronic data capture
ER	emergency room
ESAP	Epidemiological and Statistical Analysis Plan
ETT	endotracheal tube
EU	European Union
FEV_1	forced expiratory volume in 1 second
FVC	Forced vital capacity
GDS	Global Drug Safety
HAQ-DI	Heath Assessment Questionnaire – Disability Index
HIPAA	Health Insurance Portability and Accountability Act of 1996
HPP	hypophosphatasia
IAR	injection-associated reaction
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IgG/IgM	immunoglobulin G/M
IRB	Institutional Review Board
ISR	injection-site reaction
JAPAC	Japan, Asia, Pacific (region)
LEFS	Lower Extremity Functional Scale
MAR	missing at random
MCAR	missing completely at random

Abbreviation or Specialist Term	Explanation
MedDRA	Medical Dictionary for Regulatory Activities
NAb	neutralizing antibody
NMAR	not missing at random
NSAID	non-steroidal anti-inflammatory drug
PDMS-2	Peabody Developmental Motor Scale® Second Edition
PEA	phosphoethanolamine
PedsQL	Pediatric Quality of Life Inventory
PLP	pyridoxal-5'-phosphate
PPi	inorganic pyrophosphate
PODCI	Pediatric Outcomes Data Collection Instrument®
POSNA	Pediatric Orthopedic Society of North America's
PRO	patient-reported outcome
PTH	parathyroid hormone
QoL	quality of life
REB	Research Ethics Board
SAB	Scientific Advisory Board
SAE	serious adverse event
SF-36v2	Short Form Health Survey (36-item) version 2
SPPB	Short Physical Performance Battery
TNSALP	tissue-nonspecific alkaline phosphatase
TUG	Timed Up and Go Test
USA	United States of America

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