# PROTOCOL ALX-HPP-501

# AN OBSERVATIONAL, LONGITUDINAL, PROSPECTIVE, LONG-TERM REGISTRY OF PATIENTS WITH HYPOPHOSPHATASIA

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|---|---|
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# PASS INFORMATION

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|---|---|
| **Title** | Protocol title: An Observational, Longitudinal, Prospective, Long-Term Registry of Patients With Hypophosphatasia<br>Protocol Amendment: 4.2, 06 May 2016<br>Primary author of protocol: [redacted]<br>Executive Medical Director, Global Medical Sciences<br>Alexion Pharmaceuticals, Inc. |
| **Protocol version identifier** | Amendment 4.2 |
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| **Active substance** | Asfotase alfa, ATC code: A16AB13 |
| **Medicinal product** | Strensiq™ (asfotase alfa) |
| **Product reference** | EU/1/15/1015/001-010 |
| **Procedure number** | EMEA/H/C/003794 |
| **Marketing authorisation holder(s)** | Alexion Europe SAS<br>1-15, avenue Edouard Belin<br>92500 Rueil-Malmaison, France |
| **Joint PASS** | No |
| **Research question and objectives** | Objectives of the HPP Registry are:<br>• To collect information on the natural history of hypophosphatasia (HPP) from patients of all ages, including infants, children, and adults with HPP, regardless of age at onset.<br>• 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.<br>• To evaluate the burden of disease for HPP and the multi-system aspects of HPP, including clinical outcomes and quality of life, in a "real-life" setting.<br>• 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:<br>– 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 permits):<br>o Growth and development parameters, including height/length, weight, head and chest circumference, and arm span<br>o Skeletal X-ray abnormalities (eg, rickets and osteomalacia)<br>o Clinical laboratories relevant to HPP (eg, pyridoxal-5'-phosphate [PLP])<br>o Functional outcomes relevant to HPP (eg, 6-Minute Walk Test [6MWT], Bayley Scales of Infant and Toddler Development®, Third Edition [Bayley-III], Peabody Developmental Motor Scale® Second Edition [PDMS-2], Pediatric Orthopedic Society of North |

| | |
|---|---|
| | America's [POSNA] Pediatric Outcomes Data Collection Instrument® [PODCI], and Hand Held Dynamometry)<br>– Collect and evaluate longitudinal safety data in asfotase alfa-treated patients in order to further characterize the safety profile of asfotase alfa and events of special interest, including, but not limited to, injection site reactions (ISRs), injection-associated reactions (IARs), immunogenicity, ectopic calcification, and craniosynostosis.<br>– 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). |
| **Country(-ies) of study** | As of 01 May 2016, the study is being conducted in the following countries: Australia, Austria, Belgium, Canada, Czech Republic, Denmark, Finland, France, Germany, Greece, Israel, Italy, Japan, Lithuania, Norway, Portugal, Russia, Saudi Arabia, Spain, Sweden, Switzerland, UK, and USA. |
| **Author** | E-mail: DeikerA@alxn.com |

# MARKETING AUTHORISATION HOLDER(S)

| | |
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| **Marketing authorisation holder(s)** | Alexion Europe SAS<br>1-15, Avenue Edouard Belin<br>92500 Rueil-Malmaison<br>France |
| **MAH contact person** | |

# 1. TABLE OF CONTENTS

## TABLE OF CONTENTS

PROTOCOL ALX-HPP-501 ..... 1
PASS INFORMATION ..... 2
MARKETING AUTHORISATION HOLDER(S) ..... 3
1. TABLE OF CONTENTS ..... 4
2. LIST OF ABBREVIATIONS ..... 8
3. RESPONSIBLE PARTIES ..... 10
4. ABSTRACT ..... 11
4.1. Title ..... 11
4.2. Rationale and Background ..... 11
4.3. Research Question and Objectives ..... 12
4.4. Study Design ..... 13
4.5. Population ..... 14
4.6. Variables ..... 14
4.7. Data Sources ..... 15
4.8. Study Size ..... 15
4.9. Data Analysis ..... 15
4.10. Milestones ..... 16
5. AMENDMENTS AND UPDATES ..... 17
6. MILESTONES ..... 18
7. RATIONALE AND BACKGROUND ..... 19
7.1. Overview of Hypophosphatasia ..... 19
7.2. Rationale for the Hypophosphatasia Registry ..... 20
8. RESEARCH QUESTION AND OBJECTIVES ..... 21
9. RESEARCH METHODS ..... 22
9.1. Study Design ..... 22
9.2. Setting ..... 22
9.2.1. Patient Inclusion Criteria ..... 23
9.2.2. Patient Exclusion Criteria ..... 23
9.3. Variables ..... 23

9.3.1. Demographic Data ....23
9.3.2. HPP Disease History....23
9.3.3. HPP Disease Status....26
9.3.4. Immunogenicity Testing....29
9.3.5. Patient-reported Outcomes Instruments ....29
9.3.6. Pregnancy ....30
9.3.7. Exposure to Asfotase Alfa During Pregnancy and Lactation....31
9.4. Data Sources ....31
9.4.1. Data Sources ....31
9.4.1.1. Clinical Data ....32
9.4.1.2. Patient-reported Outcomes Data....32
9.4.2. Schedule of Data Collection ....32
9.4.3. Scientific Advisory Board ....34
9.5. Study Size ....34
9.6. Data Management....34
9.7. Data Analysis....35
9.8. Quality Control ....37
9.8.1. Data Quality Assurance ....37
9.8.2. Inspection of Records ....37
9.8.3. Study Monitoring....37
9.8.4. Retention of Records ....38
9.9. Limitations of the Research Methods....38
9.10. Other Aspects....38
9.10.1. Selection and Withdrawal of Investigators....38
9.10.1.1. Investigator Participation and Responsibilities ....38
9.10.1.2. Investigator Withdrawal ....39
9.10.2. Selection and Withdrawal of Patients....39
9.10.2.1. Patient Participation....39
9.10.2.2. Patient Withdrawal ....39
10. PROTECTION OF HUMAN SUBJECTS ....40
10.1. Ethics Review ....40
10.2. Ethical Conduct of the Study....40
10.3. Written Informed Consent ....40

10.4. Confidentiality ....40
11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS ....42
11.1. Definitions ....42
11.1.1. Definition of an Adverse Event ....42
11.1.1.1. Definition of a Serious Adverse Event ....42
11.1.2. Events of Interest ....42
11.1.2.1. Definition of Injection-Associated Reaction and Severe Hypersensitivity Reactions ....43
11.1.2.2. Definition of Anaphylaxis ....43
11.1.2.3. Definition of Systemic Immune Complex-mediated Reactions (Type III Hypersensitivity) ....44
11.1.2.4. Definition of Injection Site Reaction ....45
11.1.2.5. Definition of Ectopic Calcification ....45
11.2. Severity Assessment ....45
11.3. Causality Assessment ....46
11.4. Reporting of Serious Adverse Events and Events of Interest ....46
11.4.1. Reporting of Serious Adverse Events ....46
11.4.2. Reporting of Events of Interest ....47
12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS ....48
13. REFERENCES ....49
APPENDIX 1. LIST OF STAND-ALONE DOCUMENTS ....50
APPENDIX 2. ENCEPP CHECKLIST FOR STUDY PROTOCOLS ....51
APPENDIX 3. ADDITIONAL INFORMATION ....52
PATIENT-REPORTED OUTCOMES ASSESSMENTS ....53
SPONSOR SIGNATURE PAGE ....54
SPONSOR QPPV SIGNATURE PAGE ....55
INVESTIGATOR'S AGREEMENT ....56

## LIST OF TABLES

Table 1: List of Abbreviations ....8
Table 2: Emergency Contact Information ....10
Table 3: Schedule of Data Collection ....33

Table 4: Clinical Criteria for Diagnosing Anaphylaxis .....43
Table 5: Clinical Characteristics and Management Considerations for Systemic Immune Complex-mediated Reactions.....44

# 2. LIST OF ABBREVIATIONS

## Table 1: List of Abbreviations

| Abbreviation or Specialist Term | Explanation |
|---|---|
| 6MWT | 6-Minute Walk Test |
| ADA | Anti-asfotase alfa antibodies |
| ADL | Activities of daily living |
| AE | Adverse event |
| ALP | Alkaline phosphatase |
| ALPL | Gene encoding the tissue-nonspecific alkaline phosphatase (TNSALP) isoenzyme |
| ALT | Alanine aminotransferase |
| AST | Aspartate aminotransferase |
| BP | Blood pressure |
| BPAP | Bilevel positive airway pressure |
| BPI-SF | Brief Pain Inventory (Short Form) |
| BUN | Blood urea nitrogen |
| Bayley-III | Bayley Scales of Infant and Toddler Development®, Third Edition |
| Ca | Calcium |
| CHAQ | Childhood Heath Assessment Questionnaire |
| CPAP | Continuous positive airway pressure |
| DEXA | Dual-energy X-ray absorptiometry |
| EC | Ethics Committee |
| eCRF | Electronic case report form |
| EDC | Electronic data capture |
| EDPA | European Data Protection Act |
| EOI | Events of interest |
| 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 |
| GCP | Good Clinical Practice |
| GI | Gastrointestinal |
| HAQ-DI | Heath Assessment Questionnaire – Disability Index |
| HIPAA | Health Insurance Portability and Accountability Act of 1996 |
| HPP | Hypophosphatasia |
| IAR | Injection-associated reaction |
| ICH | International Council for Harmonisation |
| IRB | Institutional Review Board |
| ISR | Injection site reaction |

## Table 1: List of Abbreviations (Continued)

| Abbreviation or Specialist Term | Explanation |
|---|---|
| MAA | Marketing Authorisation Application |
| MAR | Missing at random |
| MCAR | Missing completely at random |
| NAb | Neutralizing antibodies |
| NMAR | Not missing at random |
| NSAID | Non-steroidal anti-inflammatory drug |
| P | Phosphorus |
| 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 |
| pQCT | Peripheral quantitative computed tomography |
| PRO | Patient-reported outcome |
| PTH | Parathyroid hormone |
| QoL | Quality of life |
| SAE | Serious adverse event |
| SF-36 | Short Form Health Survey (36-item) |
| TNSALP | Tissue-nonspecific alkaline phosphatase |
| USA | United States |
| VAS | Visual analog scale |

# 3. RESPONSIBLE PARTIES

## Table 2: Emergency Contact Information

| Role in Program | Name | Contact Information |
|---|---|---|
| Clinical Project Lead | [redacted] | [redacted] |
| Responsible Physician | [redacted] | [redacted] |
| 24-Hour Serious Adverse Event (and Pregnancy) Notifications | --- | E-mail: ClinicalSAE@alxn.com<br>Facsimile: + 1-203-439-9347 |

# 4. ABSTRACT

## 4.1. Title

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

Protocol amendment: Amendment 4.2, 06 May 2016

Primary author of protocol: ,

Executive Medical Director, Global Medical Sciences

Alexion Pharmaceuticals, Inc.

## 4.2. Rationale and Background

Hypophosphatasia (HPP) is a rare, serious, and potentially fatal genetic disorder caused by loss-of-function mutations in the gene encoding 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.

Hypophosphatasia 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. 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).

Classifications of HPP include 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 Japan, Canada, the United States of America (USA), countries of the European Union (EU) and Australia, and it is also under regulatory review for approval in a number of other countries.

As noted above, HPP is a rare disease that has historically been largely treated symptomatically. Only one therapy designed to treat the underlying cause of the disease (Strensiq® [asfotase alfa]) has been recently 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 multi-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 for HPP. For patients treated with asfotase alfa, the Registry will collect data on asfotase alfa dosing, effectiveness of treatment, serious adverse events (SAEs), immunogenicity, pregnancy and neonatal outcome data, and targeted events of interest (EOI). 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 is also being conducted, in part, to fulfill postmarketing commitments and requirements agreed to by the Sponsor as a condition for asfotase alfa approval in the EU and the USA. In the EU, asfotase alfa was granted approval by the European Medicines Agency under exceptional circumstances in accordance with Article 14(8) of Regulation (EC) No 1901/2006, based on the fact HPP was considered a rare, seriously debilitating, and life-threatening metabolic disease with high unmet medical need for which no product had been previously approved, and comprehensive data on the efficacy and safety of asfotase alfa, under normal conditions of use, could not be provided at the time of initial regulatory review for approval. Considering this approval under exceptional circumstances, the Sponsor has a regulatory obligation to collect, among other things, long-term data on the clinical effectiveness and safety of asfotase alfa in the HPP Registry being conducted 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.

## 4.3. Research Question and Objectives

Objectives of the HPP Registry are:

- To collect information on the natural history of HPP from patients of all ages, including infants, children, 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 multi-system aspects of HPP, including clinical outcomes and quality of life, 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 permits):
    - Growth and development parameters, including height/length, weight, head and chest circumference, and arm span
    - Skeletal X-ray abnormalities (eg, rickets and osteomalacia)
    - 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], Peabody Developmental Motor Scale® Second Edition [PDMS-2], Pediatric Orthopedic Society of North America's [POSNA] Pediatric Outcomes Data Collection Instrument® [PODCI], and Hand Held Dynamometry)
  - Collect and evaluate longitudinal safety data in asfotase alfa-treated patients in order to further characterize the safety profile of asfotase alfa and events of special interest, including, but not limited to, injection site reactions (ISRs), injection-associated reactions (IARs), immunogenicity, ectopic calcification, and craniosynostosis.
  - 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).

## 4.4. Study Design

This multinational, multicenter, observational, prospective, long-term registry is designed to collect data on epidemiology, HPP history, clinical course, symptoms (including multi-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, immunogenicity, pregnancy and neonatal outcome data (for patients treated with asfotase alfa only), and targeted EOI.

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. Investigators 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.

Investigators 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.

**Study Procedures**

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. Specific efforts will be made to recruit patients who participated in registration studies included in the marketing authorisation application (MAA) for asfotase alfa. Efforts will be made to ensure enrollment in the Registry from all countries where patients with HPP are identified. At a minimum, patients will be enrolled from sites in North America, the EU, Latin America, Asia, and Australia. Registry participation will be offered, at a minimum, to all sites that enrolled patients in registration studies included in the MAA for 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.

At the time of enrollment, Baseline clinical and age-appropriate PRO data will be collected. During the study, clinical and age-appropriate PRO data will be recorded at clinic visits, which will be scheduled by the Investigators 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.

## 4.5. Population

The study population is male and female patients, of any age, with a confirmed diagnosis of HPP. 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.

## 4.6. Variables

Data concerning patient treatment and clinical condition will be collected, when and if available, according to the site's usual practice. For patients being treated with asfotase alfa, information on asfotase alfa dosing, effectiveness of asfotase alfa treatment, SAEs, targeted EOI of IARs and severe hypersensitivity reactions (including anaphylaxis), systemic immune complex-mediated reactions, ISRs, ectopic calcification, craniosynostosis, conductive deafness, respiratory depression/pneumonia, lack of efficacy, immunogenicity, and pregnancy and neonatal outcome data will also be collected according to the timeframes and procedures outlined in the protocol. Investigators 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 after

the first year. 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. Anonymity of patient data will be maintained.

Hypophosphatasia patients 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. Investigators 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.

If more than one 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.

## 4.7. 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 requested to complete age-appropriate PRO questionnaires throughout their participation in the Registry. These questionnaires will be available in the appropriate local language.

## 4.8. Study Size

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 (including patients treated with and without asfotase alfa). At a minimum, patients will be enrolled from sites in North America, the EU, Latin America, Asia, and Australia.

## 4.9. Data Analysis

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.

## 4.10. Milestones

Registry study milestones, either actual or planned, are indicated below. Data for enrolled patients will be collected in the Registry for the lifecycle of the product, until such time that it is agreed to by governing regulatory Agencies that all regulatory obligations for Registry conduct are met.

| Milestone | Planned date |
|---|---|
| Start of data collection | Jul 2016 |
| End of data collection | As applicable, based on agreed to regulatory requirements[a] |
| Study progress reports | Annually |
| Registration in the EU PAS register | Before study initiation |
| 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.

# 5. AMENDMENTS AND UPDATES

| **Protocol/ Amendment Updates** | **Approval Date** |
|---|---|
| Date of Initial Protocol | 20 Jun 2014 |
| Date of Amendment 1 | 06 Oct 2014 |
| Date of Amendment 2 | 14 Sep 2015 |
| Date of Amendment 3 | 10 Nov 2015 |
| Date of Amendment 3.1 (USA) | 19 Nov 2015 (USA) |
| Date of Amendment 4 | 11 Feb 2016 (all participating countries, excluding Japan) |
| Date of Amendment 4.1 (USA) | 17 Feb 2016 (USA) |
| Date of Amendment 4.2 (EU, excluding Germany) | 06 May 2016 (EU, excluding Germany) |

# 6. MILESTONES

Registry study milestones, either actual or planned, are indicated below. Data for enrolled patients will be collected in the Registry for the lifecycle of the product, until such time that it is agreed to by governing regulatory Agencies that all regulatory obligations for Registry conduct are met.

| **Milestone** | **Planned date** |
|---|---|
| Start of data collection | Jul 2016 |
| End of data collection | As applicable, based on agreed to regulatory requirements[a] |
| Study progress reports | Annually |
| Registration in the EU PAS register | Before study initiation |
| Final report of study results | As applicable, based on agreed to regulatory requirements[a] |

[a] Data will be collected in the Registry for the lifecycle 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.

# 7. RATIONALE AND BACKGROUND

## 7.1. Overview of Hypophosphatasia

Hypophosphatasia (HPP) is a rare, serious, and potentially fatal genetic disorder caused by loss-of-function mutations in the gene encoding 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.

Hypophosphatasia 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. 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).

Classifications of HPP include 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.

## 7.2. Rationale for the Hypophosphatasia Registry

As noted above, HPP is a rare disease that has historically been largely treated symptomatically. Only one therapy designed to treat the underlying cause of the disease (Strensiq® [asfotase alfa]) has been recently 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 multi-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. For patients treated with asfotase alfa, the Registry will collect data on asfotase alfa dosing, effectiveness of treatment, serious adverse events (SAEs), immunogenicity, pregnancy and neonatal outcome data, and targeted events of interest (EOI). 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 is also being conducted, in part, to fulfill postmarketing commitments and requirements agreed to by the Sponsor as a condition for asfotase alfa approval in the EU and the USA. In the EU, asfotase alfa was granted approval by the European Medicines Agency under exceptional circumstances in accordance with Article 14(8) of Regulation (EC) No 1901/2006, based on the fact HPP was considered a rare, seriously debilitating, and life-threatening metabolic disease with high unmet medical need for which no product had been previously approved, and comprehensive data on the efficacy and safety of asfotase alfa, under normal conditions of use, could not be provided at the time of initial regulatory review for approval. Considering this approval under exceptional circumstances, the Sponsor has a regulatory obligation to collect, among other things, long-term data on the clinical effectiveness and safety of asfotase alfa in the HPP Registry being conducted 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.

# 8. RESEARCH QUESTION AND OBJECTIVES

Objectives of the HPP Registry are:

- To collect information on the natural history of HPP from patients of all ages, including infants, children, 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 multi-system aspects of HPP, including clinical outcomes and quality of life, 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 permits):
    - Growth and development parameters, including height/length, weight, head and chest circumference, and arm span
    - Skeletal X-ray abnormalities (eg, rickets and osteomalacia)
    - Clinical laboratories relevant to HPP (eg, PLP)
    - Functional outcomes relevant to HPP (eg, 6MWT, Bayley-III, PDMS-2, POSNA PODCI, and Hand Held Dynamometry)
  - Collect and evaluate longitudinal safety data in asfotase alfa-treated patients in order to further characterize the safety profile of asfotase alfa and events of special interest, including, but not limited to, injection site reactions (ISRs), injection-associated reactions (IARs), immunogenicity, ectopic calcification, and craniosynostosis.
  - 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).

# 9. RESEARCH METHODS

## 9.1. Study Design

This multinational, multicenter, observational, prospective, long-term registry is designed to collect data on the epidemiology, HPP history, clinical course, symptoms (including multi-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, immunogenicity, pregnancy and neonatal outcome data (for patients treated with asfotase alfa only), and targeted EOI.

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. Investigators 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.

Investigators 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.

## 9.2. 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. Specific efforts will be made to recruit patients who participated in registration studies included in the MAA for asfotase alfa. Efforts will be made to ensure enrollment in the Registry from all countries where patients with HPP are identified. At a minimum, patients will be enrolled from sites in North America, the EU, Latin America, Asia, and Australia. Registry participation will be offered, at a minimum, to all sites that enrolled patients in registration studies included in the MAA for 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.

At the time of enrollment, baseline clinical and age- and developmentally-appropriate PRO data will be collected (see Appendix 3). During the study, clinic visits will be scheduled by the Investigators 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.

Investigators will be prompted to enter follow-up data, collected from the patients' medical records, as described in Section 9.4. In addition, patients will be asked to self-report selected disease burden information at intervals via age-appropriate PRO. For infants and juveniles, 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.

### 9.2.1. Patient 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 or parent (or legal guardian) is able to read and/or understand the informed consent and study questionnaires in the local language.
3. 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.

### 9.2.2. Patient 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.

## 9.3. Variables

### 9.3.1. 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 first menarche and age at menopause (if applicable)

### 9.3.2. 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 on historical use of asfotase alfa, historical results of immunogenicity testing, and historical occurrence of targeted EOI of IARs and severe hypersensitivity reactions (including anaphylaxis), systemic immune complex-mediated reactions, ISRs, and lack of efficacy will also be collected.

**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 alkaline phosphatase [ALP], calcium [Ca], phosphorus [P], 25(OH) vitamin D, parathyroid hormone [PTH], alanine aminotransferase [ALT], aspartate aminotransferase [AST], total bilirubin, direct bilirubin, indirect bilirubin, blood urea nitrogen [BUN], creatinine, urine calcium:creatinine ratio, 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, urine calcium:creatinine ratio, 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, acetaminophen, non-steroidal anti-inflammatory drugs [NSAIDs], opioids)
- Other medications taken for HPP and non-HPP-related indications

**History of Orthopedic Therapies:**

- Past surgical procedures/hardware installed, other interventions
- Past orthopedic physiotherapies

**Respiratory History:**

- Respiratory support used (eg, supplemental nasal oxygen, continuous positive airway pressure [CPAP]/bilevel positive airway pressure [BPAP], endotracheal tube [ETT], or tracheostomy)
- 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 (DEXA)/peripheral quantitative computed tomography (pQCT)
- Skeletal X-ray abnormalities/clinical diagnosis (rickets, osteomalacia)

**Renal History:**

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

**Hepatic Impairment History**

**Hearing History**

**Ophthalmologic Assessment (for signs of papilledema and ectopic calcification):**

- Visual acuity
- Adnexa
- Slit-lamp biomicroscopy with examination of anterior chamber, lens, conjunctiva, cornea, and fundus
- Dilated 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, PDMS-2, POSNA PODCI, and Hand Held Dynamometry)
- Training/qualifications of the administrator of the functional outcomes assessments
- Results of the functional outcomes assessments

**Severity of Disease/HPP Event Incidence:**

- Respiratory crises, seizures
- Fractures, pseudofractures (including location)
- Premature tooth loss, dental problems (eg, excessive cavities), delayed tooth eruption, anodontia
- Rheumatologic complications (pseudogout, chondrocalcinosis)

**Historical Occurrence of Targeted EOI:**

- IARs and severe hypersensitivity reactions, including anaphylaxis (for patients who received asfotase alfa prior to Registry enrollment)
- Systemic immune complex-mediated reactions
- ISRs (for patients who received asfotase alfa prior to Registry enrollment)
- Lack of efficacy/drug effect (for patients who received asfotase alfa prior to Registry enrollment)
- Ectopic calcifications
- Respiratory depression/pneumonia
- Conductive deafness
- Craniosynostosis

**Historical Results of Immunogenicity Testing (for patients who received asfotase alfa prior to Registry enrollment)**

**History of Assistive Devices/Home Modifications:**

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

**History of health resource utilization (eg, emergency room [ER] visits, hospitalization)**

### 9.3.3. 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 EOI of IARs and severe hypersensitivity reactions (including anaphylaxis), systemic immune complex-mediated reactions, ISRs, and lack of efficacy, immunogenicity, and pregnancy and neonatal outcome data will be collected for patients treated with asfotase alfa only. There are no required clinical procedures for this Registry study; the Investigator 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, urine calcium:creatinine ratio, albumin, potassium, and immunogenicity (testing performed at Investigator discretion for patients treated with asfotase alfa only; see Section 9.3.4 and Section 11.1.2.3 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 (see Section 9.3.7) and safety information for any reported SAE or adverse event (AE) of special interest (see Section 11.1.2). 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 Investigator and identify the missing lot number.
- Information on access to, and receipt of, educational materials for asfotase alfa (ie, Injection Guide) (collected annually at a minimum)

**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)

**Respiratory Status:**

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

**Skeletal Assessment:**

- DEXA/pQCT
- Skeletal X-ray abnormalities (rickets, osteomalacia)

**Renal Assessment:**

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

- Kidney function results
- Dialysis

**Hearing Assessment**

**Ophthalmologic Assessment (for signs of papilledema and ectopic calcification):**

- Visual acuity
- Adnexa
- Slit-lamp biomicroscopy with examination of anterior chamber, lens, conjunctiva, cornea, and fundus
- Dilated 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, PDMS-2, POSNA PODCI, and Hand Held Dynamometry)
- Training/qualifications of the administrator of the functional outcomes assessments
- Results of the functional outcomes assessments

**Severity of Disease/HPP-related events:**

- Respiratory crises, seizures
- Fractures, pseudofractures (including location)
- Premature tooth loss, dental problems (eg, excessive cavities), delayed tooth eruption, anodontia
- Rheumatologic complications (eg, pseudogout and chondrocalcinosis)

**Serious Adverse Events (for patients receiving treatment with asfotase alfa; see Section 11.4.1 for details on reporting SAEs)**

**Targeted EOI (see Section 11.4.2 for details on reporting EOI):**

- IARs and severe hypersensitivity reactions, including anaphylaxis (for patients treated with asfotase alfa only)
- Systemic immune complex-mediated reactions (for patients treated with asfotase alfa only)
- ISRs (for patients treated with asfotase alfa only)
- Lack of efficacy/drug effect (for patients treated with asfotase alfa only)

- Ectopic calcifications
- Respiratory depression/pneumonia
- Conductive deafness
- Craniosynostosis

**Measures of health resource utilization (eg, ER visits and hospitalization)**

### 9.3.4. Immunogenicity Testing

Considering that asfotase alfa is an exogenous protein, monitoring for the development of anti-asfotase alfa antibodies (ADAs) and neutralizing antibodies (NAbs) has been routinely performed in clinical studies of asfotase alfa. Over 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.

Investigators enrolling patients treated with asfotase alfa in the Registry may collect blood samples for immunogenicity (ie, ADA and NAb) testing if considered part of standard clinical care. Immunogenicity testing will be performed at the discretion of the Investigator as part of routine clinical care. For patients presenting with symptoms associated with systemic immune-complex mediated reaction, immunogenicity testing to assess for the presence of ADAs is recommended (see Section 11.1.2.3).

At Registry sites collecting blood samples for immunogenicity testing, shipment, processing, and testing of blood samples will be supported by Alexion without any charge to the Investigator 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 Investigator for clinical management of the patient and recorded in the electronic case report form (eCRF) for the Registry.

### 9.3.5. Patient-reported Outcomes Instruments

Age-appropriate PRO data will be collected using the instruments described below; for infants and juveniles, these instruments will be completed by the parent or legal guardian (Appendix 3).

**Burden of Disease:**

- Pain:
  - Brief Pain Inventory, Short Form (BPI-SF) (patients ≥ 18 years of age)
  - Childhood Health Assessment Questionnaire (CHAQ), Pain Index, visual analog scale (VAS) (patients > 2 years of age to < 18 years of age)
- Motor Capacity:

- Motor assessments (included in Quality of Life [QoL] instruments below)

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

- Health Assessment Questionnaire – Disability Index (HAQ-DI) (patients ≥ 18 years of age)
- CHAQ, Disability Index (patients > 2 years of age to < 18 years of age)

**QoL:**

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

**Assistive Devices/Home Modifications:**

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

### 9.3.6. 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, along with the following information regarding the outcome of pregnancy and neonatal condition, if available:

- 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 11.4.1. In addition, any AEs an infant may experience following possible exposure to asfotase alfa via breastfeeding must also be reported to the Alexion Pharmacovigilance group or designee (see Section 9.3.6 for further details on exposure to asfotase alfa during pregnancy and lactation).

### 9.3.7. 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, the Investigator must submit a pregnancy form to Alexion's Pharmacovigilance group or designee via the same method as SAE reporting (see Section 11.4.1). A copy of this form, the Pregnancy Reporting and Outcome/Breast Feeding form, will be supplied to the Investigator by Alexion's Pharmacovigilance group or designee.

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 Investigator and identify the missing lot numbers. If additional follow-up is required, the Investigator will be requested to provide the information. Data regarding the pregnancy will also be recorded in the patient's eCRF as outlined in Section 9.6.

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 11.4.1). 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's Pharmacovigilance group or designee on the Pregnancy Reporting and Outcome/Breast Feeding form. Any AEs an infant may experience following possible exposure to asfotase alfa via breastfeeding must also be reported to the Alexion Pharmacovigilance group or designee.

## 9.4. Data Sources

### 9.4.1. Data Sources

Data concerning patient treatment and clinical condition 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. Data 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 one 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.

#### 9.4.1.1. 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.

#### 9.4.1.2. Patient-reported Outcomes Data

The patient or parent (or legal guardian) will be requested to complete age-appropriate PRO questionnaires throughout their participation in the Registry; these questionnaires will be available in the appropriate local language. For infants and juveniles, PRO data will be reported by the parent or legal guardian. PROs are summarized by domain and age group in Appendix 3.

### 9.4.2. Schedule of Data Collection

Registry data will be collected according to the recommended schedule in Table 3. 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.

## Table 3: 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 therapies | X | X | X | X |
| Respiratory assessment | X | X | X | X |
| Skeletal assessment | X | X | X | X |
| Renal assessment[f] | X | X | X | X |
| Hearing assessment | X | X | X | X |
| Ophthalmologic assessment[g] | X | X | X | X |
| Gastrointestinal assessment | X | X | X | X |
| 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, PDMS-2, POSNA PODCI, and Hand Held Dynamometry], training/qualifications of the administrator of the functional outcomes assessments, and results of the functional outcomes assessments) | X | X | X | X |
| HPP-related events | | X | X | X |
| Measures of health resource utilization | X | X | X | X |
| Asfotase alfa dosing[h] | X | X | X | X |
| SAE/EOI reporting[i] | X | X | X | X |
| Patient-reported Outcomes[j] | | | | |
| Burden of Disease | | | | |
| Pain | X | X | X | X |
| Motor capacity | 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[k] | | | | |
| Pregnancy history/outcome | X | X | X | X |
| Neonatal characteristics | | 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 Investigator will determine the assessments to be performed for each patient as part of routine clinical care.

[b] Investigators 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. 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, historical results of immunogenicity testing, and historical occurrence of targeted EOI of IARs and severe hypersensitivity reactions (including anaphylaxis), systemic immune complex-mediated reactions, ISRs, and lack of efficacy will also be collected (see Section 9.3.2).

[d] Data will be recorded as available. Information on asfotase alfa dosing, effectiveness of asfotase alfa treatment, SAEs, targeted EOI of IARs and severe hypersensitivity reactions (including anaphylaxis), systemic immune complex-mediated reactions, ISRs, and lack of efficacy, immunogenicity, and pregnancy and neonatal outcome data will be collected for patients treated with asfotase alfa only (see Section 9.3.3).

[e] Results of immunogenicity testing will be collected for patients treated with asfotase alfa only. For patients who initiated treatment with asfotase alfa prior to Registry enrollment, information on historical results of immunogenicity testing will be collected at the time of enrollment. Immunogenicity testing will be performed at the discretion of the Investigator as part of routine clinical care. For patients presenting with symptoms associated with systemic immune-complex mediated reactions, immunogenicity testing is highly recommended.

[f] Sponsor recommendation is that renal ultrasounds/computerized tomography be performed at Baseline and periodically throughout Registry conduct in accordance with local labeling.

[g] Sponsor recommendation is that ophthalmologic examinations be performed at Baseline and periodically throughout Registry conduct in accordance with local labeling.

[h] 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 annually, at a minimum, thereafter.

[i] For patients who initiated treatment with asfotase alfa prior to Registry enrollment, information on historical occurrence of EOI will be collected at the time of enrollment. See Section 11.4 for definitions and reporting requirements.

[j] For infants and juveniles, patient-reported outcomes instruments will be completed by the parent or legal guardian.

[k] For patients 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 11.4.1.

Abbreviations: 6MWT = 6-minute walk test; ADL = activities of daily living; Bayley-III = Bayley Scales of Infant and Toddler Development®, Third Edition; EOI = events of interest; HPP = hypophosphatasia; IARs = injection-associated reactions; ISRs = injection site reactions; 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

### 9.4.3. Scientific Advisory Board

A Scientific Advisory Board, comprising key experts and opinion leaders, will provide guidance to the HPP Registry. The Scientific Advisory Board will be responsible for providing direction related to scientific decisions regarding the HPP Registry.

## 9.5. Study Size

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 (including patients treated with and without asfotase alfa). At a minimum, patients will be enrolled from sites in North America, the EU, Latin America, Asia, and Australia.

## 9.6. Data Management

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

The Sponsor or its designee will provide the Investigator with an eCRF, which will be used to collect and store patient data that can then be accessed by the Sponsor. 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 Investigators. Should an Investigator'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 AEs and concomitant diseases collected in the Registry will be coded by the Sponsor or its designee using Medical Dictionary for Regulatory Activities version 18.1 or higher.

Verification of source data and/or study records for EOI 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 9.8).

## 9.7. Data Analysis

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, EOI, immunogenicity, 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 pre-specified 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 are 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 or as a covariate in models (to prevent sample attrition, if necessary). In the analysis of the current study, propensity scores will 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, two 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 three-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.

## 9.8. Quality Control

### 9.8.1. Data Quality Assurance

To ensure accurate, complete, and reliable data, the Sponsor or its designee will do the following:

- Provide instructional material to participating Registry sites, as appropriate.
- Provide start-up training to Investigators and other Registry personnel. This training will give instruction on the protocol, the completion of the eCRFs, and other Registry procedures.
- Make periodic visits to Registry sites, as appropriate.
- Be available for consultation and stay in contact with Registry site personnel by email, telephone, and/or fax.
- Review and evaluate eCRF data and use standard computer edits to detect errors in data collection for correction, when appropriate.
- Conduct periodic quality reviews of the Registry database.

To ensure accurate, complete, and reliable data, participating Investigators will also be instructed to keep records of all clinical notes and medical records in the patient files as original source documents for the Registry. If requested, the Investigator will provide the Sponsor or its designee, applicable regulatory Agencies, and applicable Institutional Review Boards (IRB)/Ethics Committees (EC) with direct access to original source documents for Registry-related inspections (see Section 9.8.2) and monitoring (Section 9.8.3) purposes.

### 9.8.2. Inspection of Records

Investigators and institutions involved in the Registry will permit study-related monitoring, audits, IRB/EC review, and regulatory inspections by providing direct access to source data/documents and/or study records. In the event of an audit/inspection, the Investigator agrees to allow the Sponsor, its designee, or regulatory authorities access to all study records.

The Investigator should promptly notify the Sponsor or its designee of any inspections scheduled by any regulatory authorities and promptly forward copies of any audit reports received to the Sponsor or its designee.

### 9.8.3. Study Monitoring

The process for study monitoring will be detailed in the HPP Registry Monitoring Plan. The purpose of this monitoring plan will include verification that EOI 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 EOI and other Registry data will be conducted on a routine basis by the site monitor.

#### 9.8.4. Retention of Records

Essential documents should be retained for at least 5 years after completion of the Registry. These documents should be retained for a longer period, however, if required by the applicable regulatory requirements or by an agreement with the Sponsor. It is the responsibility of the Investigator to make provisions for study record retention. It is the responsibility of the Sponsor to inform the Investigator or sub-Investigator/institution as to when these documents no longer need to be retained.

## 9.9. 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.

## 9.10. Other Aspects

#### 9.10.1. Selection and Withdrawal of Investigators

##### 9.10.1.1. Investigator Participation and Responsibilities

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

- Agree to comply with HPP Registry processes.
- Agree to complete a questionnaire with patient’s data at enrollment (ie, Baseline) and during follow-up, and enter the data into the HPP Registry eCRF.
- Agree to comply with the Health Insurance Portability and Accountability Act of 1996 (HIPAA) regulations or European Data Protection Act (EDPA), as applicable, and/or institution/country-specific patient privacy requirements, as applicable.

#### 9.10.1.2. Investigator Withdrawal

Should an Investigator leave his/her medical practice, Alexion should be informed in advance, and another Investigator should be identified to whom patients will be referred. The replacing Investigator 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 Investigator will remain in the database.

### 9.10.2. Selection and Withdrawal of Patients

#### 9.10.2.1. Patient Participation

Patients with HPP and their parent or legal guardian (as appropriate) will receive information regarding participation from the Investigator. 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 9.2.1 and Section 9.2.2) 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.

#### 9.10.2.2. Patient Withdrawal

Patients may decide to discontinue participation in the HPP Registry (by notifying the Investigator 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.

# 10. PROTECTION OF HUMAN SUBJECTS

## 10.1. Ethics Review

Federal, provincial, and local regulations and International Council for Harmonisation (ICH) guidelines, if relevant, require that approval be obtained from an IRB/EC prior to participation of human patients in research studies. Where required and prior to the Registry onset, the IRB/EC must approve the protocol, informed consent, advertisements to be used for patient recruitment, and any other written information regarding this study to be provided to the patient or the patient's parents/legal guardian. The site will maintain and make available for review by Alexion or its designee documentation of all IRB/EC approvals and of the IRB/EC compliance with ICH Guidance E6: Good Clinical Practice, if relevant.

All IRB/EC approvals should be signed by the IRB/EC Chairman or designee and must identify the IRB/EC name and address, the study protocol by title and/or protocol number and the date of approval and/or favorable opinion was granted.

## 10.2. Ethical Conduct of the Study

The Investigator will conduct all aspects of this Registry in accordance with all national, provincial, and local laws of the pertinent regulatory authorities.

## 10.3. Written Informed Consent

Written informed consent (and assent, where appropriate and required) shall be obtained from each patient or their parent/legal guardian prior to collection of any data for the Registry. Alexion or its designee may provide an informed consent template to the sites. If the site makes any institution-specific modifications, the Sponsor or its designee may review the consent prior to IRB/EC submission. The Investigator or the Sponsor will submit the approved, revised consent to the appropriate IRB/EC for review and approval prior to the start of the Registry. If the consent form is revised during the course of the Registry, all active participating patients or their parent/legal representative to whom the revision may have an impact must sign the revised form.

Before recruitment and enrollment, patients and their parent or legal representative will receive a full explanation of the Registry and be allowed to read the approved Informed Consent Form. Patient data will only be collected and entered after informed consent has been obtained from the patient or parent/legal guardian. Where appropriate and required by local regulations, patient assent should also be obtained.

The Investigator shall provide a copy of the signed Informed Consent/Assent to the patient and/or the patient's parent/legal guardian. The original forms shall be maintained in the Registry files at the site.

## 10.4. Confidentiality

All evaluation forms, reports, and other records for the Registry will be identified in a manner designed to maintain patient confidentiality. All records will be kept in a secure storage area with

limited access. Clinical information will not be released without the written permission of the patient or the patient's parent/legal guardian, except as necessary for monitoring by Alexion, its designee, the Food and Drug Administration/regulatory authorities, or the IRB/EC.

The Investigator and all employees and coworkers involved with this Registry shall not disclose or use for any purpose, other than performance of the study, any data, records or other unpublished, confidential information disclosed to those individuals for the purpose of the Registry. Prior written agreement from the Sponsor or its designee must be obtained for the disclosure of any said confidential information to other parties.

# 11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

## 11.1. Definitions

### 11.1.1. Definition of an Adverse Event

An AE is any unfavorable and unintended sign (including an abnormal laboratory finding or diagnostic or therapeutic procedure, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. Only AEs that are considered SAEs or EOI will be collected for this Registry.

#### 11.1.1.1. 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
- Results in persistent or significant disability/incapacity
- 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.

### 11.1.2. Events of Interest

Data will be collected for the following EOI:

- IARs and severe hypersensitivity reactions, including anaphylaxis (for patients treated with asfotase alfa only; see definition of IAR and severe hypersensitivity reactions in Section 11.1.2.1 and definition of anaphylaxis in Section 11.1.2.2)
- Systemic immune complex-mediated reactions (see definition of systemic immune complex-mediated reactions in Section 11.1.2.3)
- ISRs (for patients treated with asfotase alfa only; see definition of ISR in Section 11.1.2.4)
- Lack of efficacy/drug effect (for patients treated with asfotase alfa only)
- Ectopic calcifications (see definition of ectopic calcifications in Section 11.1.2.5)
- Respiratory depression/pneumonia

- Conductive deafness
- Craniosynostosis

#### 11.1.2.1. 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 Investigator 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 11.1.2.2). IARs that are assessed by the Investigator as severe in intensity (Section 11.2) are defined as severe hypersensitivity reactions.

#### 11.1.2.2. Definition of Anaphylaxis

Clinical criteria for diagnosis of anaphylaxis can be found in Table 4 (Sampson, 2006).

**Table 4: 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:<br>• Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, hypoxemia)<br>• 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:<br>• Involvement of the skin-mucosal tissue (eg, generalized hives, itch-flush, swollen lips-tongue-uvula)<br>• Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, hypoxemia)<br>• Reduced BP[a] or associated symptoms (eg, hypotonia, collapse, syncope, incontinence)<br>• Persistent GI symptoms (eg, crampy abdominal pain, vomiting) |
| Reduced BP (minutes to several hours) after exposure to a known allergen for that patient:<br>• Infants and children: Low systolic BP (age specific)[a] or > 30% decrease from that person's Baseline<br>• 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

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

Systemic immune complex-mediated reactions (Type III hypersensitivity reactions) occur when antigens and 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, immunogenicity testing is highly recommended (see Section 9.3.4).

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 5.

**Table 5: 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:<br>• Serum sickness<br>• Fever<br>• Rash<br>• Urticaria<br>• Arthralgias<br>• Lymphadenopathy<br>• Glomerulonephritis<br>• Vasculitis | • Immunogenicity testing for asfotase alfa (see Section 9.3.4)<br>• Erythrocyte sedimentation rate<br>• C-reactive protein<br>• Circulating immune complexes<br>• Complement studies (eg, CH50, C3, C4)<br>• Antinuclear antibody testing<br>• Antihistone antibody testing<br>• Tissue biopsy for immunofluorescence studies | • Discontinue drug<br>• Consider treatment with nonsteroidal anti-inflammatory drugs, antihistamines or systemic corticosteroids; or plasmapheresis (if severe) |

#### 11.1.2.4. Definition of Injection Site Reaction

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 Investigator as possibly, probably, or definitely related to asfotase alfa. Injection site reactions may occur at any time point after asfotase alfa administration.

#### 11.1.2.5. 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.

## 11.2. Severity Assessment

All SAEs and EOI in patients receiving treatment with asfotase alfa will be assessed for severity by the Investigator. 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.

## 11.3. Causality Assessment

A causality assessment (Not related, Unlikely related, Possibly related, Probably related, or Definitely related) must be provided for SAEs and EOI in patients treated with asfotase alfa. This assessment must be made by the Investigator and recorded on the eCRF (see Section 11.4.1), 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 Investigator'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 Investigator to be possibly, probably, or definitely related to asfotase alfa shall be considered related to asfotase alfa.

## 11.4. Reporting of Serious Adverse Events and Events of Interest

### 11.4.1. Reporting of Serious Adverse Events

All SAEs must be reported to Alexion Pharmacovigilance within 24 hours of first awareness of the event by the Investigator or designee. The reporting timelines must be followed for all initial SAE cases and follow-up reports to the initial case.

The Investigator must record the SAE data in the patient's eCRF and verify the accuracy of the information recorded pages with the corresponding source documents. The SAE information will be sent via the Safety Gateway, a tool within the EDC system, to Alexion Global Pharmacovigilance.

**Please note** - The fax number and email are provided below as a back-up/contingency for the site to report the SAE in case the site is unable to send the report via Safety Gateway.

**Email: ClinicalSAE@alxn.com**

**Fax: +1-203-439-9347**

If applicable or requested, additional information such as relevant medical records and/or diagnostic information should be reported to Alexion Global Pharmacovigilance via the email or fax address as noted above.

Any new follow-up information regarding the SAE should be entered in the patient's eCRF and sent electronically via the Safety Gateway to Alexion Global Pharmacovigilance within the same timeframe as the initial report stated above.

For all SAEs reported via email/fax, the Investigator must provide the following:

- Patient's Registry ID number
- Causality of the SAEs to asfotase alfa
- Outcome of the SAEs (ie, resolved, resolving, resolved with sequelae, not resolved, or death)
- Relevant medical records and laboratory/diagnostic information (eg, a copy of death certificate and/or autopsy results, if applicable, for SAE reports involving a death)
- Appropriate and requested follow-up information in the time frame detailed above.
- Lot number

Alexion is responsible for notifying the relevant regulatory authorities of certain events. Depending on local regulations, the Sponsor, the Sponsors designee, or the Investigator will be responsible for notifying the IRB/EC of all SAEs that occur at a site per local IRB/EC-established guidelines for submission. Investigators 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/EC per local regulations.

### 11.4.2. Reporting of Events of Interest

Information on targeted EOI and the lot number of the asfotase alfa product will be collected as part of the eCRF for all patients enrolled in the Registry, and will be reported in accordance with regulatory commitments. These targeted adverse EOI will be recorded in the eCRF prior to the patient's next visit and throughout the patient's participation in the Registry. EOIs that meet the criteria of an SAE should also be reported in accordance with the procedures in Section 11.4.1.

# 12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

Each participating site/physician will enter into a Registry Agreement with Alexion governing the terms and obligations of the parties in the Registry. Individual patients' Registry data may be longitudinally represented within the Registry and accessed by participating physicians at their sites. The Registry will be overseen by a Scientific Advisory Board, comprised of international experts involved in the research or care of patients with hypophosphatasia. The Scientific Advisory Board's activities will include, but not be limited to, facilitating analysis and dissemination of Registry data via medical conferences and peer-reviewed publications. Furthermore, the Scientific Advisory Board and the Sponsor will have the opportunity to review and comment on publications of Registry data, including but not limited to manuscripts, abstracts, and conference posters/presentations prepared by participating physicians. Participating physicians will retain control of the patient data that they collect and may use those data accordingly. Aggregate analyses will be the property of the Sponsor and will be disseminated according to this governance structure. The Sponsor retains the right to use Registry data for any regulatory or reimbursement requirements without obtaining prior approval from the Scientific Advisory Board.

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# APPENDIX 1. LIST OF STAND-ALONE DOCUMENTS

Available upon request

# APPENDIX 2. ENCEPP CHECKLIST FOR STUDY PROTOCOLS

# APPENDIX 3. ADDITIONAL INFORMATION

# PATIENT-REPORTED OUTCOMES ASSESSMENTS

| **Domain** | **Population** | | |
|---|---|---|---|
| Questionnaire | Infant (≤24 months) | Toddler through Juvenile[a] (>2 to <18 years) | Adult (≥18 years) |
| **QoL** | | | |
| SF-36 | | | X |
| PedsQL | | X | |
| **Pain/Symptoms** | | | |
| BPI-SF | | | X |
| CHAQ Pain Index (VAS) | | X | |
| **Functioning/ADL** | | | |
| HAQ-DI | | | X |
| CHAQ (Disability Index) | | X | |

[a] Toddler is >2 to ≤5 years; young child is >5 to ≤8 years; child is >8 to ≤13 years; and juvenile is >13 to <18 years. For toddlers through juveniles, patient-reported outcomes instruments will be completed by the parent or legal guardian.

Abbreviations: ADL = activities of daily living; BPI-SF = Brief Pain Inventory (Short Form); CHAQ = Childhood Health Assessment Questionnaire; HAQ-DI = Health Assessment Questionnaire – Disability Index; PedsQL = Pediatric Quality of Life Inventory; QoL = Quality of Life; SF-36 = Short Form Health Survey (36-item); VAS = visual analog scale

# SPONSOR SIGNATURE PAGE

**PROTOCOL TITLE: An Observational, Longitudinal, Prospective, Long-Term Registry of Patients with Hypophosphatasia**

**PROTOCOL NUMBER: ALX-HPP-501 (Amendment 4.2)**

_____

Andrew Denker, MD, PhD
Executive Medical Director, Global Medical Sciences
Alexion Pharmaceuticals, Inc.

_____

Date

# SPONSOR QPPV SIGNATURE PAGE

**PROTOCOL TITLE: An Observational, Longitudinal, Prospective, Long-Term Registry of Patients with Hypophosphatasia**

**PROTOCOL NUMBER: ALX-HPP-501 (Amendment 4.2)**

_____

Qualified Person Responsible for Pharmacovigilance in the EEA
Alexion Europe SAS
1-15, avenue Edouard Belin
92500 Rueil-Malmaison, France

_____

Date

# INVESTIGATOR'S AGREEMENT

I have received and read the current Investigator's Brochure for asfotase alfa. I have read the ALX-HPP-501 study protocol and agree to conduct the study in accordance with this protocol, all applicable government regulations, the principles of the ICH E6 Guidelines for Good Clinical Practice (GCP), and the principles of the World Medical Association Declaration of Helsinki. I also agree to maintain the confidentiality of all information received or developed in connection with this protocol.

_____

Printed Name of Investigator

_____

Signature of Investigator

_____

Date