A Longitudinal, Prospective, Long-Term Registry of Patients With Hypophosphatasia

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INTRODUCTION

- Hypophosphatasia (HPP) is a rare, inherited metabolic disease caused by inactivating mutations in the gene encoding tissue-nonspecific alkaline phosphatase (TNSALP)[1]
  - Low TNSALP activity leads to extracellular accumulation of inorganic pyrophosphate (PPi), pyridoxal 5'-phosphate (PLP [active form of vitamin B_6]), and phosphoethanolamine (PEA), resulting in bone mineralization defects, rickets, osteomalacia, and multiple systemic complications
- The clinical expression of signs and symptoms of HPP may differ depending on when it presents to the clinician and may include[1,2]:
  - Infant – severe hypomineralization of the skeleton, failure to thrive, respiratory failure and/or respiratory compromise requiring ventilator support, vitamin B_6 responsive seizures, hypercalcemia, nephrocalcinosis, fractures, high risk of mortality
  - Juvenile – premature loss of deciduous teeth, skeletal and skull deformities resulting from rickets and craniosynostosis, respectively, and fractures, muscle weakness, poor growth, pain, compromised physical function including diminished ambulation
  - Adult – osteomalacia, recurrent, poorly healing and/or nontraumatic fractures, pain, muscle weakness, ectopic calcification in the joints, compromised mobility, and nephrocalcinosis
  - Odontohypophosphatasia – dental symptoms only, such as premature tooth loss, discoloration of teeth, and poor dentition (although dental symptoms may be the presenting features of systemic HPP)
- Additional research is required to fully understand the presentation, current management, and clinical course of the disease

OBJECTIVE

- To establish a prospective patient registry study that will document demographics, biochemical, laboratory and radiologic phenotypes, clinical course, and functional impact of HPP in patients of all ages

METHODS

Design

- Multinational, multicenter, observational, prospective, registry study
- Planned duration of ≥5 years
- Planned enrollment of ≥500 patients across all ages
- Compliance with all local regulations and guidelines governing medical practice and ethics
- Compliance with all relevant data protection and privacy regulations, including patient anonymity
- Study registered with ClinicalTrials.gov: NCT02306720
- Sponsored by Alexion Pharmaceuticals, Cheshire, CT, USA
- The registry will be conducted in 2 phases
  - The registry will open with a 6-site pilot phase to ensure appropriate endpoints are collected
  - In the second phase, any changes from the pilot phase will be incorporated, and the registry will be broadened to include additional global sites

Patients

- Inclusion criteria
  - Male and female patients of any age with a confirmed diagnosis of HPP
  - The confirmed diagnosis of HPP is based on the judgement of the physician
  - Signed informed consent and medical records release by the patient or patient's parent or legal guardian
- Exclusion criteria
  - Current participation in an Alexion-sponsored clinical trial or received asfotase alfa, an investigational drug in development for HPP
    - Enrollment in the registry will not exclude a patient from participation in a future clinical trial

Data Collection

- Data concerning patients' treatment and clinical condition will be collected as available from medical records at registry entry (baseline) and at a minimum of every 6 months thereafter
- Patients may choose to link their records with those of family members also participating in the HPP Registry Study
- Data will be collected in the course of routine clinical care
  - Performance of specific clinical procedures is not mandated
  - Follow-up visits will occur at least every 6 months and at registry study termination
- Data will include
  - Demographics
  - HPP disease history and diagnosis
    - Date of first symptoms/diagnosis and identifying signs and symptoms
    - Family history of HPP
    - Genotype (if available)
    - Tests and procedures used to confirm HPP diagnosis
    - Pregnancy history and outcomes
    - Medical specialty responsible for diagnosis
  - HPP clinical history at baseline and disease status at follow-up visits
    - Clinical chemistry (e.g., bone-specific ALP, plasma PLP/vitamin B_6, urine PEA, urine or serum PPi, PTH, Ca, P, 25(OH)vitamin D)
    - HPP-related pain medication
    - Orthopedic treatment
    - Respiratory assessments (e.g., respiratory support, pulmonary function tests)
    - Skeletal assessments including dual-emission X-ray absorptiometry and peripheral quantitative computed tomography results
    - Renal function
    - Hearing
    - Gastrointestinal abnormalities
    - Growth and development history, including skeletal and dental abnormalities
    - HPP-related events (e.g., mortality, respiratory crises, seizures, fractures, pseudofractures, premature tooth loss, dental problems, rheumatologic complications)
    - Use of assistive devices (e.g., oxygen, wheelchair, walker, cane, braces, ramps, baths)
    - Pregnancies
  - Patient-reported outcomes at baseline and follow-up visits (**Table 1**)
    - Age-appropriate instruments
    - Caregivers will report for infants and juveniles

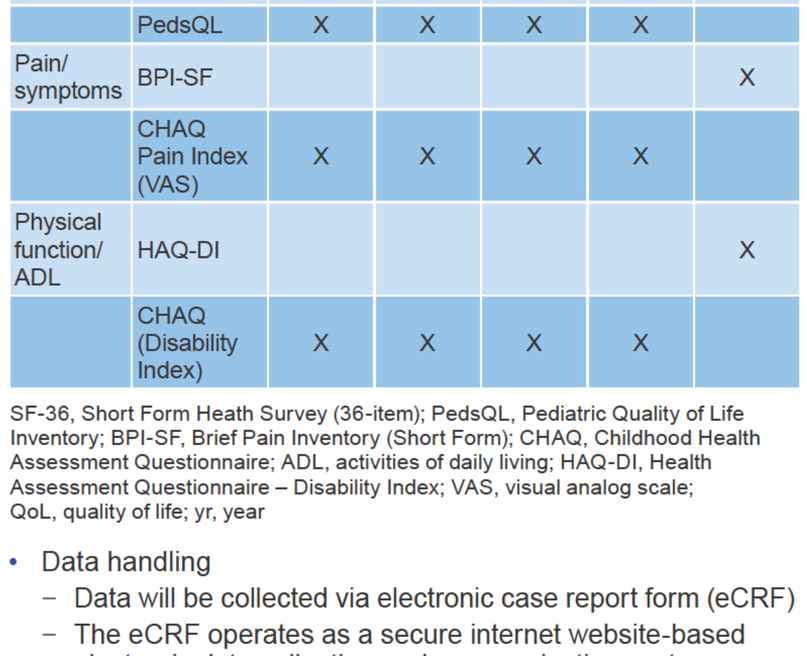
Table 1. Patient-reported outcome assessments

Domain	Instrument	Patient Age Group				
		Toddler (2–4 yr)	Young Child (5–7 yr)	Child (8–12 yr)	Juvenile (13–18 yr)	Adult (>18 yr)
QoL	SF-36					X
	PedsQL	X	X	X	X	
Pain/ symptoms	BPI-SF					X
	CHAQ Pain Index (VAS)	X	X	X	X	
Physical function/ ADL	HAQ-DI					X
	CHAQ (Disability Index)	X	X	X	X	

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

- Data handling
  - Data will be collected via electronic case report form (eCRF)
  - The eCRF operates as a secure internet website-based electronic data collection and communication system (**Figure 1**)
  - Patient confidentiality will be maintained

Figure 1. Schematic representation of data collection, analysis, and results dissemination



Scientific Advisory Board

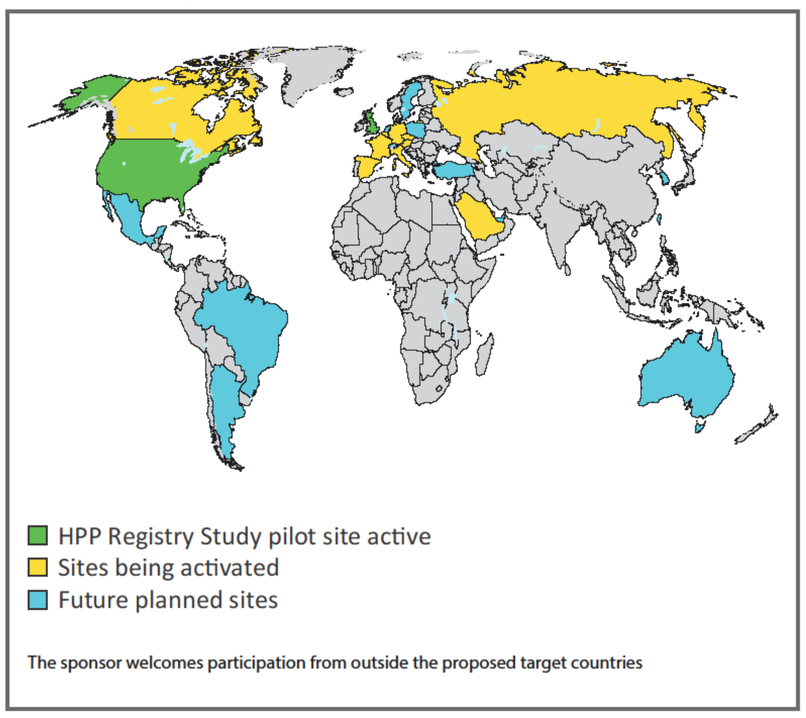
- Comprised of the authors of this poster[a]
- Provides scientific direction to the HPP Registry Study
- Approves and prioritizes all requests for data analysis and publication
  - Data analysis will be conducted by study sponsor

[a]Alexander Cole, the registry epidemiologist at the time of abstract acceptance, is not a member of the Scientific Advisory Board.

STUDY STATUS

- The HPP Registry Study is currently in the pilot phase
- 19 patients have enrolled as of September 09, 2015
  - 4 sites are active in 2 countries (3 US, 1 UK) (**Figure 2**)
  - Sites in 10 additional countries are in the process of being activated in anticipation of starting the broader phase of the study (Austria, Belgium, Canada, Czech Republic, France, Germany, Italy, Russia, Spain, Saudi Arabia)
  - Identification of additional sites for the broader phase of the study is ongoing

Figure 2. HPP Registry Study: Current and anticipated natural history site locations



CONCLUSIONS

- The HPP Registry Study will provide a comprehensive, real-life, longitudinal profile of patients with HPP, including:
  - Demographics
  - Diagnosis patterns
  - Genotype-phenotype correlations
  - HPP-associated complications or disease characteristics
  - Country-specific findings
  - Impact of HPP on activities of daily living and quality of life
- Analysis of information gathered by the HPP Registry Study will lead to a better understanding of HPP which, in turn, will increase awareness, aid diagnosis, and improve patient care
- The HPP Registry Study is open for additional sites to participate. For more information about participation in the HPP Registry Study, contact:

HPPRegistryStudy@quintiles.com

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DISCLOSURES

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Bone

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