



New Data from First Natural History Study in Juveniles with Hypophosphatasia (HPP) Showing Substantial Disease Burden, Including Musculoskeletal Abnormalities and Growth Deficiencies, Presented in Late-Breaking Oral Session at ENDO 2015

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Significant and persistent HPP-related impairments in walking, as well as activity-limiting pain and fatigue, described in gait assessment from juvenile natural history study

Significant improvements in physical function and muscle strength observed in children with HPP treated with asfotase alfa for three or more years in Phase 2 study

CHESHIRE, Conn.--(BUSINESS WIRE)-- Alexion Pharmaceuticals, Inc. (NASDAQ:ALXN) today announced that researchers presented new data from a retrospective, multinational natural history study of children (symptom onset ≥ 6 months to < 18 years) with hypophosphatasia (HPP). In this study, which included 32 patients with juvenile-onset HPP, children with HPP had a substantial disease burden, particularly with regard to musculoskeletal abnormalities and growth deficiencies.¹ The children from this cohort experienced HPP-related skeletal problems, other disease complications and morbidity that persisted despite standard efforts to control symptoms. These data were presented in a late-breaking oral session at the Endocrine Society's 97th Annual Meeting and Expo (ENDO) in San Diego.

Researchers also presented the following data:

- A gait assessment in a subset of children from the juvenile natural history study, presented as a late-breaking poster, showing clinically significant and persistent impairments in walking indicative of muscle weakness and reduced strength and balance²
- New data showing early and sustained improvements in physical function and muscle strength and decreases in pain in children who received asfotase alfa, an investigational enzyme replacement therapy for the treatment of HPP, for at least three years in the open-label extension phase of an ongoing Phase 2 clinical study^{3,4}
- Data from two patient-reported surveys indicating the high burden of disease in adults with HPP, including pain, multiple fractures and limited mobility⁵

HPP is a genetic, chronic and progressive ultra-rare metabolic disease characterized by defective bone mineralization that can lead to repeated fractures and deformity of bones, profound muscle weakness, seizures, respiratory failure and premature death.⁶⁻¹⁰

"Patients with HPP can experience debilitating muscle weakness, severe pain, skeletal deformities and frequent fractures, all of which can impede growth and impair a child's ability to engage in routine daily activities such as running, jumping and climbing the stairs," said Leonard Bell, M.D., Chairman and Chief Executive Officer of Alexion. "The findings from this natural history study confirm the high morbidity associated with juvenile-onset HPP and underscore the urgent need for an effective treatment option. In addition, new results from the ongoing asfotase alfa Phase 2 studies continue to provide long-term efficacy data in children with HPP, including early and sustained improvements in physical function and enhanced ability to perform daily activities."

A Retrospective, Multi-National, Non-Interventional, Natural History Study of the Childhood Form of Hypophosphatasia (Abstract LB-OR01-4)

In an oral session, Michael Whyte, M.D., Medical-Scientific Director of the Center for Metabolic Bone Disease and Molecular Research at Shriners Hospital for Children in St. Louis, presented new results from the first retrospective, multinational, non-interventional natural history study of children (ages ≥ 6 months to < 18 years at the onset of symptoms) with HPP. Dr. Whyte reported that children with HPP can have substantial morbidity, including HPP-related skeletal disease that persists throughout childhood in to early adolescence.¹

In this study, investigators reviewed the medical charts of 32 juvenile patients with HPP, all of whom had HPP-related skeletal abnormalities at baseline, to characterize the natural history of skeletal disease and patient growth over the study period. Primary outcome measures were change in bone health, as measured by the Radiographic Global Impression of Change (RGI-C) scale, and change in height Z-score, between 5 and 15 years of age.

Dr. Whyte reported that:

- Patients in the cohort manifested a wide range of HPP-related complications, including bowed long bones (59%), gait disturbance (or an abnormal way of walking, 59%), joint pain (53%), bone pain (50%), muscle weakness that limited daily activities (47%), muscle pain (38%) and fractures (34%).
- Eighty-eight percent of patients required surgical or medical intervention, 63% required medications for HPP symptoms and

13% required wheelchairs and/or walking aids.

- No significant change in RGI-C score was observed between the first and last assessment, as measured over a median of 4.25 years (+0.33; p=0.08).
- No significant change in height Z-score was observed from first to last assessment (p=0.63). Median height Z-score was -0.9 at both baseline and last assessment, indicating less than average relative to peers. There also was no significant change in weight Z-score.

"This retrospective natural history study underscores the persistent nature of HPP in children and adolescents. These findings enhance our understanding of the clinical course of HPP with currently available supportive care and further illustrate the important impact this disease can have on patients," said Dr. Whyte.

Gait Assessment in Children with Childhood Hypophosphatasia: Impairments in Muscle Strength and Physical Function (Abstract LBS-039)

Dawn Phillips, Ph.D., Physical Therapist and Functional Outcomes Specialist, UNC Division of Physical Therapy, Chapel Hill, N.C., presented results from a clinical gait assessment in a subset of children (n=6) enrolled in the juvenile natural history study. The analysis was based on video recordings over a median of 4.1 years. Researchers assessed gait performance, or walking ability, using the 12-point Performance-Oriented Mobility Assessment (POMA-G), modified to provide improved sensitivity for HPP-related impairments (MPOMA-G) (12=no impairments; lower scores indicate greater impairment). A physical therapy descriptor checklist and chart provided further information on physical function.

At first assessment, median MPOMA-G score was 6.0, representing substantial gait defects, and all patients displayed trunk sway (movements of the trunk or arms to maintain balance). At last assessment, all patients had persistent gait impairments, with a median MPOMA-G score of 7.5. No consistent pattern of change in any MPOMA-G component was observed. In addition, 66% (4/6) of patients were unable to achieve a "period of flight" at last assessment, indicating inability to run; all patients (6/6) required self-support with a hand to transition from the floor to standing; and all patients (6/6) reported limitation of activity due to pain/fatigue.²

"The significant and persistent impairments in walking and balance observed in this study help illustrate the significant burden of disease some children with HPP face. Muscle weakness, reduced core strength, and poor balance can make it challenging for these children to perform daily activities and to actively participate in their communities," said Dr. Phillips.

Significantly Improved Muscle Strength, Running Speed, and Agility in Children with Hypophosphatasia Treated with Asfotase Alfa (Abstract OR29-4)

In an oral session, researchers reported results from the extension phase of a multinational, open-label Phase 2 study in children with HPP (N=12, ages 5-12 at study entry) who were treated with asfotase alfa for at least three years. Select findings from this study were presented at the American Society for Bone and Mineral Research (ASBMR) meeting in September 2014, including improvements in certain measures of physical function and agility, as measured by the Bruininks-Oseretsky Test of Motor Proficiency, Second Edition (BOT-2); disability, as measured by the Child Health Assessment Questionnaire (CHAQ); and pain, as measured by the Pediatric Outcomes Data Collection Instrument (PODCI).¹¹

New data presented at ENDO showed that:

- Hip and knee strength, as measured by Hand Held Dynamometry (HDD) (including hip extension and flexion, and knee extension and flexion), improved over time and was sustained at last assessment (P<0.05).³
- Physical function, as measured by the BOT-2 Strength subtest (including standing long jump, push-ups, sit-ups, wall sit and V-ups), improved rapidly from a median scaled score of 4 at baseline to a median score of 15 at last assessment (P<0.0001), and was within the normal range for healthy peers by treatment Month 6.³
- Running speed and agility, as measured by the BOT-2 Running Speed and Agility subtest (including 50 ft. shuttle run, sideways steps over balance beam, and 1- and 2-legged hops), improved rapidly from a median scaled score of 4 at baseline to a score of 12 at last assessment (P<0.0001).³

"At the start of this study, children with HPP had substantial muscle weakness and impaired function compared with healthy peers," said Dr. Phillips. "During the treatment period with asfotase alfa, patients experienced rapid and sustained improvements in muscle strength and physical function, allowing them to engage in physical activity more typical of healthy children their age."

The most common AEs were injection site reactions (none serious or severe). There were no deaths, other serious AEs or withdrawals due to AEs.

Improved Activities of Daily Living and Physical Function, with Decreased Pain, in Children with Hypophosphatasia Treated for Three Years with Asfotase Alfa: Results from the Childhood Health Assessment Questionnaire and the Pediatric Outcomes Data Collection Instrument (Abstract FRI-224)

In a poster session at ENDO, researchers presented new data from the extension phase of the same multinational, open-label Phase 2 study in children with HPP. These data showed that:

- Patients had a median pain score of 20.0 at baseline, as measured by the CHAQ discomfort index, which rapidly decreased to 0.0 at 6 months (P=0.082). Median scores were sustained at 0 through last assessment (p<0.05) at three years, indicating that most patients remained pain-free.⁴
- Functional status, as measured by the parent-reported PODCI, improved across several key categories:⁴

- o Median Global Functioning scores improved from 27 at baseline to 49 at 6 months (P=0.003) and continued to improve to 52.5 (P<0.001), within healthy range, by last assessment
- o Median Sports/Physical Functioning scores improved from 20 at baseline to 43.5 at 6 months (P=0.0002), within healthy range, and continued to improve to 47.5 at last assessment (P=0.0002)
- o Median Transfer and Basic Mobility scores improved from 37 at baseline to 52 at 6 months (P=0.033), within healthy range, and sustained at 52 through last assessment (P=0.008)

The most common AEs were injection site reactions (none serious or severe). There were no deaths, serious adverse events (AEs) or withdrawals due to AEs.

Burden of Disease in Adult Patients with Hypophosphatasia: Results from Patient-Reported Outcome Surveys (Abstract FRI-240)

In a poster session, researchers reported findings from the Hypophosphatasia Impact Patient Survey (HIPS) and the Hypophosphatasia Outcomes Study Telephone interview (HOST), which were completed by 125 adult patients (≥18 years old) with a mean age of 45 years.⁵ Patients were classified into two subgroups based on age at onset: <18 years (pediatric-onset, n=84) and ≥18 years (adult-onset, n=34; onset information was unknown in 7 patients). This was the first study to describe patient-reported burden of disease and morbidity in patients with HPP.

Key findings from the study are as follows:⁵

- Pain was prevalent and reported in almost all patients (119/125, or 95%); 90% (113/125) reported that pain was recent
- Seventy-six percent (68/89, HIPS only) reported bone pain severe enough to limit activity
- The majority of patients (108/125, or 86%) reported experiencing at least one fracture; the average number of fractures sustained was 12.9 (13.7 for patients with pediatric-onset disease and 10.3 for patients with adult-onset disease)
- Commonly reported clinical manifestations included muscle weakness (62% overall, 64% for pediatric-onset, and 65% for adult-onset) and unusual gait (52% overall, 61% for pediatric-onset, and 36% for adult-onset)
- More than half of patients had used an assistive device for mobility at some time (60% overall and 62% each for pediatric-onset and adult-onset); at the time of the survey, 34% of patients overall reported using an assistive device to walk and 22% overall required a wheelchair

Researchers concluded that, in this cohort of self-reported information, HPP results in a high burden of disease in adulthood regardless of age of onset.

About Hypophosphatasia (HPP)

HPP is a genetic, chronic and progressive ultra-rare metabolic disease characterized by defective bone mineralization that can lead to destruction and deformity of bones, muscle weakness, pain, seizures, respiratory failure and premature death.⁶⁻¹⁰

HPP is caused by mutations in the gene encoding an enzyme known as tissue non-specific alkaline phosphatase (TNSALP).^{6,7} The genetic deficiency in HPP can affect people of all ages.⁶ HPP is classified by the age of the patient at the onset of symptoms of the disease, with infantile- and juvenile-onset HPP defined as manifestation of the first symptom prior to 18 years of age.

HPP can have devastating consequences for patients at any stage of life.⁶ In a natural history study, infants who had their first symptom of HPP within the first 6 months of life had high mortality, with an overall mortality rate of 73% at 5 years.¹² In these patients, mortality is primarily due to respiratory failure.^{6,10,13} In patients surviving to adolescence and adulthood, long-term clinical sequelae can include recurrent and non-healing fractures, muscle weakness, pain and the requirement for ambulatory assistive devices such as wheelchairs, wheeled walkers and canes.^{6,9}

About Asfotase Alfa

Asfotase alfa is an investigational, highly innovative, first-in-class enzyme replacement therapy. Asfotase alfa is designed to address the underlying cause of HPP by aiming to restore the genetically defective metabolic process, thereby preventing or reversing the severe and potentially life-threatening complications of life-long dysregulated mineral metabolism.

About Alexion

Alexion is a biopharmaceutical company focused on serving patients with severe and rare disorders through the innovation, development and commercialization of life-transforming therapeutic products. Alexion is the global leader in complement inhibition and has developed and markets Soliris® (eculizumab) as a treatment for patients with paroxysmal nocturnal hemoglobinuria (PNH) and atypical hemolytic uremic syndrome (aHUS), two debilitating, ultra-rare and life-threatening disorders caused by chronic uncontrolled complement activation. Soliris is currently approved in nearly 50 countries for the treatment of PNH and in nearly 40 countries for the treatment of aHUS. Alexion is evaluating other potential indications for Soliris in additional severe and ultra-rare disorders beyond PNH and aHUS, and is developing other highly innovative biotechnology product candidates, including asfotase alfa, across multiple therapeutic areas. This press release and further information about Alexion can be found at: www.alexion.com.

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Safe Harbor Statement

This news release contains forward-looking statements, including statements related to potential medical benefits of asfotase alfa for hypophosphatasia (HPP). Forward-looking statements are subject to factors that may cause Alexion's results and plans to differ from those expected, including, for example, decisions of regulatory authorities regarding marketing approval or material limitations on the marketing of asfotase alfa for HPP, delays in arranging satisfactory manufacturing capabilities and establishing commercial infrastructure for asfotase alfa for HPP, the possibility that results of clinical trials are not predictive of safety and efficacy results of asfotase alfa in broader or different patient populations, the risk that third party payors (including governmental agencies) will not reimburse for the use of asfotase alfa (if approved) at acceptable rates or at all, the risk that estimates regarding the number of patients with asfotase alfa and observations regarding the natural history of patients with asfotase alfa are inaccurate, and a variety of other risks set forth from time to time in Alexion's filings with the Securities and Exchange Commission, including but not limited to the risks discussed in Alexion's Annual Report on Form 10-K for the period ended December 31, 2014. Alexion does not intend to update any of these forward-looking statements to reflect events or circumstances after the date hereof, except when a duty arises under law.

References

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2. Phillips D, Griffin D, Przybylski T, et al. Gait Assessment in Children with Childhood Hypophosphatasia: Impairments in Muscle Strength and Physical Function. Poster presented at the Endocrine Society's Annual Meeting and Expo (ENDO), San Diego, March 7. Abstract LB-039.
3. Phillips D, Hamilton K, Moseley S, et al. Significantly Improved Muscle Strength, Running Speed, and Agility in Children with Hypophosphatasia Treated with Asfotase Alfa. Poster presented at the Endocrine Society's Annual Meeting and Expo (ENDO), San Diego, March 7. Abstract OR29-4.
4. Phillips D, Hamilton K, Moseley S, et al. Improved Activities of Daily Living and Physical Function, with Decreased Pain, in Children with Hypophosphatasia Treated for Three Years with Asfotase Alfa: Results from the Childhood Health Assessment Questionnaire and the Pediatric Outcomes Data Collection Instrument. Poster presented at the Endocrine Society's Annual Meeting and Expo (ENDO), San Diego, March 6. Abstract FRI-224.
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