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New Data Detailing the Devastating Nature of Hypophosphatasia (HPP) and Treatment Effect of Asfotase Alfa in Infants, Young Children and Juveniles with HPP Presented at the Pediatric Academic Societies Meeting

- First large natural history study shows high mortality in infants with severe perinatal and infantile HPP -

- Infants and children with life-threatening HPP who were treated with asfotase alfa for up to three years had rapid and sustained improvement in skeletal mineralization and respiratory status, with overall survival near 90% -

- Early and significant improvements in strength, agility, physical function, and stamina were observed in juveniles treated with asfotase alfa for up to three years -

CHESHIRE, Conn.--(BUSINESS WIRE)-- Alexion Pharmaceuticals, Inc. (Nasdaq:ALXN) today announced that researchers have presented new data from a large, retrospective, natural history study of patients with severe perinatal and infantile hypophosphatasia (HPP), an inherited, rare metabolic disorder that can lead to progressive damage to multiple vital organs, destruction and deformity of bones, and death. The natural history study details the devastating nature of the disease, with 73% mortality reported at five years. Additionally, early and sustained improvements were observed in infants, children and juveniles receiving asfotase alfa, an investigational therapy for the treatment of HPP, in the open-label extension phase of two on-going Phase 2 clinical studies. The data were presented in poster sessions at the joint meeting of the Pediatric Academic Societies (PAS) and the Asian Society for Pediatric Research in Vancouver, B.C., Canada.

"Patients with hypophosphatasia face a grim prognosis due to progressive deterioration of bones and muscle weakness, which can result in impaired respiratory function, disability and death," commented Martin Mackay, Ph.D., Executive Vice President and Global Head of Research and Development at Alexion. "The natural history study confirms the high mortality of patients with perinatal and infantile HPP receiving currently available supportive care and underscores the need for an effective treatment. The latest data from the asfotase alfa studies build upon previously reported findings, and provide additional long-term safety and efficacy data in infants, young children and juveniles with HPP who were treated for up to three years, where early and sustained improvements in all outcome measures were observed."

Retrospective Natural History Study in Patients with Perinatal- and Infantile-onset HPP

In a poster session today, researchers reported that the perinatal- and infantile-onset forms of HPP (i.e., onset at less than 6 months of age) are associated with high mortality, with an overall mortality rate of 73% at 5 years. Their findings were derived from a large, multicenter, multinational, retrospective, natural history study in which investigators reviewed medical charts of patients (living or deceased) with documented severe perinatal and infantile HPP who were ≤ 5 years of age at the time of diagnosis with onset of symptoms prior to 6 months of age.¹

Results showed that:

- Of the 48 patients enrolled in the study, 13 (27%) were alive on the date of data collection; 35 (73%) were deceased.
- All patients tested had documented low serum alkaline phosphatase (ALP) prior to enrollment, indicative of HPP.
- The majority of patients (58%) died within 1 year of birth. The median time to death was 8.9 months (95% confidence interval [CI]: 5.1, 14.1).
- Chest deformity (91%), failure to thrive (76%), craniosynostosis (early closure of some or all of the sutures in the skull of an infant, 61%) and nephrocalcinosis (kidney stones, 52%) were reported in the majority of patients for whom data were available.
- Respiratory compromise, particularly requiring mechanical ventilation via intubation or tracheostomy, was associated with poor outcomes, including death.
- Vitamin B6-responsive seizures and respiratory failure were associated with high mortality (100%).

"This retrospective natural history study of infants affected by HPP underscores the potentially lethal nature of this disorder when severe," said Michael P. Whyte, M.D., Medical-Scientific Director of the Center for Metabolic Bone Disease and Molecular Research at Shriners Hospital for Children in St. Louis, Mo. "Our findings confirm that if seizures and respiratory failure are present, they indicate high mortality. Patients who required respiratory support, particularly invasive ventilation via intubation or

tracheostomy, showed especially poor outcomes, including death. Our findings are consistent with clinical experience, showing that deformity of the rib cage that impairs respiratory function in these young patients often leads to pneumonia and death."

Asfotase Alfa in Infants and Young Children: Extension Study Results

In a poster presented on May 4, Dr. Whyte and colleagues reported that treatment with asfotase alfa for up to three years resulted in rapid and sustained improvement in skeletal mineralization and respiratory status in infants and young children with life-threatening HPP.² The results were from the extension phase of a previously reported multinational, open-label Phase 2 study in which asfotase alfa, administered for up to 48 weeks, was reported to improve skeletal mineralization, respiratory status, physical function, and cognitive development, with up to 90% of patients showing substantial skeletal healing at 48 weeks.³ Results from the current extension phase demonstrate sustained efficacy across all of these parameters to 3 years. Eleven patients entered the initial phase of the study. One patient withdrew after the initial intravenous dose due to an injection associated reaction. Of the 10 patients who continued treatment, 9 patients survived (the one patient death was due to sepsis and was considered by the investigator to be unrelated to study treatment) through the last assessment in the extension trial, reflecting a 3-year survival rate of approximately 90%.² The survival results are in contrast to prior studies in similar patient populations, which reported mortality rates greater than 50%.^{1,4}

The primary efficacy endpoint was change in the skeletal manifestations of HPP, as assessed by radiography. Response to treatment was defined as a mean improvement of two or more points, in a composite score from the chest, wrists, and knees, as rated by a panel of three independent radiologists blinded to treatment time point, on a seven-point scale known as the radiographic global impression of change (RGI-C) scale, with scores ranging from -3 (severe worsening of rickets) to +3 (complete or near complete healing of rickets). Using the RGI-C, a responder was defined as a patient who had a mean score of +2 or greater at a given time point. Skeletal changes were also assessed using the 10-point rickets severity scale (RSS), which measured skeletal abnormalities at the wrists and knees, with scores ranging from 10 (severe rickets) to 0 (absence of rickets). Investigators reported the following results:²

- Significant improvement in rickets was noted as early as 3 months ($p=0.03$). Improvements continued and were sustained through 3 years ($p=0.008$).
- At 6 months, the primary endpoint analysis, the median RGI-C score was significantly increased (+2, $p=0.004$).
- For the eight patients with evaluable data at three years, treatment with asfotase alfa was associated with sustained improvement over baseline in both median RGI-C (+2.50; $p = 0.008$) and median change in RSS (-6.25; $p = 0.016$), two markers of bone health.
- Eight of the ten patients that entered the extension phase of the study had required respiratory support at some time in the study. Three patients remained on respiratory support on entry into the extension phase of the study. A single patient continued to require respiratory support (supplemental oxygen) at the last assessment in the extension trial (3.5 years).

"Our results from the extension phase of this study support our published findings and show that infants and young children with life-threatening HPP treated with asfotase alfa had early improvement in skeletal mineralization, which was sustained over three years," Dr. Whyte noted. "Now, all but one patient do not need respiratory support, and survival has been 90%. In contrast, our retrospective natural history study of a similar patient population showed mortality rates of greater than 50%."

Asfotase alfa was well-tolerated in the extension study. The most common adverse events (AEs) were mild or moderate injection-site reactions in six patients and upper respiratory tract infection in six patients. Three serious AEs were reported as possibly related to treatment: craniosynostosis, conductive deafness, and mild chronic hepatitis. The report of hepatitis was in a patient taking a medication for asthma, which was discontinued; liver function tests were within normal limits at last assessment. Both craniosynostosis and conductive deafness were reported in the same patient, and are findings previously described as associated with HPP.²

Asfotase Alfa in Juveniles: Extension Study Results

In another poster presented today, researchers reported that juveniles who were compromised by rickets and impaired physical function from HPP experienced significant early and sustained improvement in bone health, gross motor function, strength, agility, and stamina with ongoing asfotase alfa treatment. The data were from the extension phase of a 6-month randomized, multinational, open-label study of asfotase alfa in patients aged 5-12 years. Twelve of 13 patients (one withdrew due to elective surgery) entered the extension study and received at least 3 years of treatment overall. Sixteen aged-matched, untreated patients with HPP served as historical controls (HCs), of whom 15 had scored radiographs over a two-year period.⁵

Compared to historical control patients, trial patients treated with asfotase alfa had significant improvement in rickets severity (RGI-C) at 6 months (primary endpoint, $p=0.0007$) that was maintained at 2 years ($p=0.0011$). Specifically, the median RGI-C score in historical control patients was 0 at both 6 months and 2 years, indicating no change in bone health, whereas the RGI-C

score in patients treated with asfotase alfa was +2 at both time points, indicating substantial bone healing. Compared to baseline, patients treated with asfotase alfa had significant and early (6 weeks, $p < 0.0001$) improvement in bone health that was maintained over 3 years of treatment ($p=0.0078$).⁵

Improved bone health was accompanied by significant improvement in physical function:⁵

- Median distance walked in six minutes increased by 242 meters, from 350 meters at baseline to 592 meters at 3 years of asfotase alfa treatment. Overall, median distance walked in 6 minutes improved from 61% predicted for sex, age, and height-matched healthy children at baseline, to 85% predicted at 6 months and 86% predicted at 3 years ($P \leq 0.0001$ at all time points) of treatment, indicating early and sustained normalization of ambulation for these patients, all of whom had abnormal gait or way of walking/running at baseline.⁶
- Strength and agility, measured as a composite of Running Speed/Agility and Strength sub-tests of the Bruininks-Oseretsky Test of Motor Proficiency, Second Edition (BOT-2), improved from well below normal at baseline to significant improvement at 3 months ($p=0.004$), and to achieving normal range at 3 years of asfotase alfa treatment ($p < 0.0001$).

"Children with rickets, difficulty walking, and muscle weakness due to HPP experienced early and sustained improvements in bone mineralization with significant gains in physical function over 3 years of treatment with asfotase alfa," commented lead investigator Katherine L. Madson, M.D., Ph.D., a pediatric endocrinologist at the Center for Metabolic Bone Disease and Molecular Research at Shriners Hospital in St. Louis. "Although these children entered the study with severe gross motor impairment, by three years they increased their walking distance over six minutes by nearly 250 meters, which is approximately 2 and one-half football fields. These improvements in gross motor function and stamina were significant, allowing these children with HPP to progress from well below normal in physical function, to within normal range in many cases."

Asfotase alfa was well-tolerated in the study. The most common AEs were mild or moderate injection-site reactions, which occurred in all patients. There were no deaths, serious AEs, or AEs leading to withdrawal over the 3 years of treatment in this juvenile study.⁵

About Hypophosphatasia (HPP)

Hypophosphatasia (HPP) is a chronic, potentially life-threatening, genetic, and rare metabolic disease characterized by defective bone mineralization that can lead to destruction and deformity of bones, profound muscle weakness, seizures, and respiratory failure.⁸⁻¹¹

HPP is caused by inactivating mutations in *ALPL*, the gene encoding an enzyme known as tissue non-specific alkaline phosphatase (TNSALP).¹²

The genetic deficiency in HPP can affect people of all ages.⁸ HPP is traditionally classified by the age of the patient at the onset of symptoms of the disease. Patients with perinatal-onset HPP manifest their first signs of disease in utero or at birth. This form of the disease often leads to death at or soon after birth. Those patients who survive birth often have severe rickets and severely compromised respiratory function.¹³

Patients with infantile-onset HPP develop their first signs or symptoms of HPP before 6 months of age. Individuals with this form of disease develop rickets, skeletal abnormalities, fractures, failure to thrive and respiratory failure. The prognosis of these patients may be poor with high mortality.⁸

Patients with juvenile-onset HPP exhibit their first signs or symptoms of HPP after 6 months of age and before 18 years of age. Individuals with this form of the disease are at risk for rickets, skeletal complications including fractures, and can have delayed acquisition of age-appropriate motor skills due to skeletal hypomineralization and muscle weakness leading to the need for walking assistance; some may never walk.⁸

About Asfotase Alfa

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

In April 2014, Alexion announced that the Company has initiated the rolling submission of a Biologics License Application (BLA) for asfotase alfa for the treatment of patients with HPP. In 2013, the U.S. Food and Drug Administration (FDA) granted Breakthrough Therapy designation for asfotase alfa in pediatric-onset HPP, defined as patients whose first signs or symptoms of HPP occurred prior to 18 years of age, including perinatal-, infantile-, and juvenile-onset forms of the disease. According to

the FDA, a Breakthrough Therapy designation is designed to expedite the development of a drug to treat a serious or life-threatening disease when preliminary clinical evidence indicates that the drug may demonstrate substantial improvement over existing therapies on one or more clinically significant endpoints. The Breakthrough Therapy designation is part of the FDA Safety and Innovation Act (FDASIA) of 2012.¹⁴

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 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.alexionpharma.com.

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 Quarterly Report on Form 10-Q for the period ended March 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.

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Alexion Pharmaceuticals, Inc.

Irving Adler, 203-271-8210

Executive Director, Corporate Communications

or

Kim Diamond, 203-439-9600

Senior Director, Corporate Communications

or

Investors:

Elena Ridloff, 203-699-7722

Executive Director, Investor Relations

Source: Alexion Pharmaceuticals, Inc.

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