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Improved Survival Observed in Pediatric Patients with Severe Hypophosphatasia (HPP) Who Were Treated with Investigational Asfotase Alfa for Up to Five Years

— In New Analysis Presented at ASBMR Meeting, Patients with HPP at High Risk of Death Treated with Asfotase Alfa in Two Phase 2 Studies Had Overall Survival of 89% Versus 27% for Untreated Matched Historical Controls —

— Patients Receiving Asfotase Alfa Also Had Significantly Improved Ventilator-Free Survival Compared to Historical Controls —

— Improvements in Physical Function Were Observed in New Data from Asfotase Alfa Infant and Juvenile Phase 2 Extension Studies Also Presented at ASBMR —

CHESHIRE, Conn.--(BUSINESS WIRE)-- Alexion Pharmaceuticals, Inc. (NASDAQ:ALXN) today announced that researchers presented new data from an integrated analysis of survival from two open-label, Phase 2 studies of asfotase alfa in pediatric patients (ages ≤5 years at enrollment) with hypophosphatasia (HPP) compared with data from a retrospective natural history study of untreated historical control patients matched for age and disease severity. In this analysis, survival in patients with HPP at high risk of death who were treated with asfotase alfa for up to five years was significantly improved (89% vs. 27%, $p < 0.0001$) compared with untreated historical control patients.[1] These late-breaking results were presented today at the American Society for Bone and Mineral Research (ASBMR) 2014 Annual Meeting in Houston, where researchers also presented new data from the ongoing open-label extension phases of two Phase 2 clinical studies in which sustained gains in physical function and reductions in disability and pain were observed in pediatric patients receiving asfotase alfa treatment for up to three years.[2,3]

HPP is a genetic, chronic and progressive ultra-rare metabolic disease that can lead to progressive damage to multiple vital organs, destruction and deformity of bones and premature death.[4-8] Asfotase alfa is an investigational enzyme replacement therapy for the treatment of HPP.

"Pediatric patients with severe HPP face a high risk of death as well as significant challenges related to respiratory function, growth, development and physical function," said Martin Mackay, Ph.D., Executive Vice President and Global Head of R&D at Alexion. "Survival was significantly improved among severely affected infants and children with HPP treated with asfotase alfa compared with a historical control of untreated patients, which is an important finding for the HPP community who currently has no approved treatment options."

Survival Data from Studies of Asfotase Alfa in Severely Affected Pediatric Patients Compared With Historical Controls (Abstract 1097)

In an oral session today, researchers reported that treatment with asfotase alfa significantly improved survival in pediatric patients (ages ≤5 years at enrollment) with severe HPP.[1] Over the five-year analysis period, 89% (33/37) of patients treated with asfotase alfa survived compared with 27% (13/48) of untreated historical control patients. Invasive ventilator-free survival was also significantly improved in treated patients ($p < 0.0001$); 83% (21/25) of treated patients required no invasive ventilation and survived, compared with 25% (12/48) of historical control patients.

These results were from an integrated analysis of survival from two multicenter, open-label, ongoing Phase 2 studies of patients with HPP who were treated with asfotase alfa, compared with data from a retrospective natural history study of untreated historical controls, matched for age and disease severity. Findings from the retrospective natural history study were previously reported at the Pediatric Academic Societies (PAS) meeting in May 2014.[9] Patients in the asfotase alfa trials were five years of age or younger at enrollment and had been diagnosed with HPP prior to six months of age. Included in the survival analysis were patients who had one or more of the following signs of severe HPP: rachitic chest, history of respiratory distress, or Vitamin B_6-responsive seizures. Median duration of treatment was two years, with patients treated for up to five years.

Investigators also reported the following results:

- Among patients with rachitic chest at baseline, 90% (27/30) of treated patients survived compared with 33% (13/40) of historical controls
- Among patients with history of respiratory compromise, 89% (24/27) of treated patients survived compared with 18% (7/40) of historical controls

- Among patients who experienced Vitamin B_6-responsive seizures, 85% (11/13) of treated patients survived compared with 0% (0/10) survival for historical controls

"In this first-ever analysis comparing survival of severely affected pediatric HPP patients, we observed a significant improvement in both overall survival and ventilator-free survival for patients treated with asfotase alfa compared to untreated historical control patients," said Michael P. Whyte, M.D., Medical-Scientific Director of the Center for Metabolic Bone Disease and Molecular Research at Shriners Hospitals for Children, St. Louis. "Improved survival in treated patients likely reflects better mineralization of the rib cage, which then had a positive effect on respiratory function. We were also pleased to report that the majority of treated patients who had Vitamin B_6-responsive seizures survived, whereas historically these seizures had always been a fatal complication."

Asfotase Alfa in Infants and Young Children with Life-Threatening HPP: New Extension Study Results (Abstract FR0435)

In an oral poster presented on September 12, Dr. Whyte and colleagues reported that severely affected infants and young children with HPP (age ≤3 years at study entry, N=11) treated with asfotase alfa for up to three years experienced sustained improvement in growth and physical function.[2] Findings were from the extension phase of a multinational, open-label Phase 2 study of asfotase alfa treatment in severely affected infants with HPP. Data from this study were previously presented by investigators at the PAS meeting in May 2014. Patients (N=11) had early (3 months, p=0.03) and sustained (3 years, p=0.008) bone healing as measured by the radiographic global impression of change (RGI-C) scale and the rickets severity scale (RSS). While 10 patients required respiratory support at or soon after entry into the study, only one patient continued to require respiratory support (supplemental oxygen) at the last assessment. Researchers reported a three-year survival rate of approximately 90%.[10]

New data presented at ASBMR included the following:

- For patients treated with asfotase alfa, improvement in growth as measured by height/length Z-score was observed. Median height/length Z-score was -3.7 at baseline, indicating marked delay relative to peers; over the course of treatment, median change from baseline in Z-score steadily increased from -0.3 at three months to +2.3 at three years.
- In asfotase alfa treated patients, improvement in functional development was observed as measured by the Bailey's Scales of Infant and Toddler Development 3rd Edition (BSID-3), with all evaluable patients (N=9) demonstrating increases in age-equivalent scores, indicating acquisition of new gross motor, fine motor and cognitive skills during treatment.

"We are very gratified to document that there have been three-year sustained improvements in growth and functional ability for infants and young children with life-threatening hypophosphatasia who had previously responded rapidly and significantly to treatment with asfotase alfa," said Dr. Whyte.

Asfotase alfa was well-tolerated in the extension study. The most common adverse events (AEs) were pyrexia (7/10), mild or moderate injection-site reactions (6/10) and upper respiratory tract infection (6/10). Three serious AEs were reported as possibly related to treatment: craniosynostosis, conductive deafness and mild chronic hepatitis. Both craniosynostosis and conductive deafness were reported in the same patient, and are findings previously described as associated with HPP. 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. Four patients tested positive for neutralizing antibodies, without apparent impact on treatment efficacy or safety.

Asfotase Alfa in Juveniles with HPP: New Extension Study Results (Abstract 1081)

In an oral plenary session today, Katherine L. Madson, M.D., Ph.D., from the Center for Metabolic Bone Disease and Molecular Research at Shriners Hospitals for Children, St. Louis, reported that children with HPP (N=13) who were treated with asfotase alfa experienced significant growth, rapid improvements in physical function, and decreases in disability and pain that were sustained over a period of three years.[3] The data were from the extension phase of a multinational, open-label Phase 2 study of asfotase alfa treatment in HPP patients aged 5-12 at study entry. Improvements in bone healing as measured by RGI-C and in two measures of physical function—distance walked in six minutes and strength and agility as measured by the Bruininks-Oseretsky Test of Motor Proficiency, Second Edition (BOT-2) composite score—were observed in data presented earlier this year at PAS.[11]

New data presented at ASBMR showed the following:

- In patients treated with asfotase alfa, a significant and clinically meaningful decrease in disability was observed, as measured by the Child Health Assessment Questionnaire (CHAQ), from a median of 1 at baseline to 0.25 at six months to 0 at 24 months and last assessment ($p \leq 0.007$).

- A significant reduction in pain was observed in treated patients, as measured by the Pediatric Outcomes Data Collection Instrument (PODCI), from a median baseline score of 78 to a median score of 100 at last assessment (p=0.0389). The PODCI is a comfort/pain rating scale, with 100 representing best possible outcome or best health.
- Improvements in strength and agility were observed for treated patients as measured by the shuttle run, one-legged hop test and standing long jump, three components of the BOT-2. Median time to complete a 50 foot shuttle run improved from 22 seconds at baseline to 9 seconds at last assessment ($p < 0.0001$). The median number of one-legged stationary hops completed in 15 seconds improved from 0 at baseline to 21 hops at last assessment (p=0.0001). The median distance jumped via a standing long jump improved from 11 inches at baseline to 46 inches at 36 months ($p < 0.0001$).
- Improvement in growth, as measured by height Z-score, was observed in treated patients, from a median of -1.26 at baseline to a median of -0.72 at last assessment (p=0.0027).

"In the data presented at ASBMR, we observed rapid and sustained healing of bones, increased physical function, reduced disability, reduced pain and improvements in growth in children with HPP who were treated with asfotase alfa for up to three years," said Dr. Madson. "These new physical function data, which include an improved ability to run, jump and hop, reflect better strength and agility for these children who were previously faced with significant skeletal and muscular challenges."

Asfotase alfa was well-tolerated in the study. The most common AEs were mild or moderate injection site reactions. There were no deaths, serious AEs or withdrawals due to AEs over the three years of treatment in this study. Twelve patients tested positive for anti-asfotase antibodies, two of whom had neutralizing antibodies with no apparent effect on efficacy or safety.

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, profound muscle weakness, seizures, respiratory failure and premature death.[4-8]

HPP is caused by mutations in the gene encoding an enzyme known as tissue non-specific alkaline phosphatase (TNSALP).[4,5] The genetic deficiency in HPP can affect people of all ages.[4] HPP is classified by the age of the patient at the onset of symptoms of the disease, and pediatric-onset HPP is 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.[4] Pediatric patients with HPP have a high mortality rate, with 73% mortality reported in a natural history study at 5 years.[7] In these patients, mortality is primarily due to respiratory failure.[1,4,8] In patients surviving to adolescence and adulthood, long-term clinical sequelae include recurrent and non-healing fractures, debilitating weakness, severe pain and the requirement for ambulatory assistive devices such as wheelchairs, wheeled walkers and canes.[4,7]

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 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.

In 2013, the U.S. Food and Drug Administration (FDA) granted Breakthrough Therapy designation for asfotase alfa. 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.

In April 2014, Alexion initiated the rolling submission of a Biologics License Application (BLA) for asfotase alfa as a treatment for patients with HPP with the FDA. In July 2014, the Marketing Authorization Application (MAA) for asfotase alfa was validated and granted accelerated assessment by the European Medicines Agency (EMA).

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.alexionpharma.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 Quarterly Report on Form 10-Q for the period ended June 30, 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. Whyte MP, Simmons JH, Lutz RE. Enzyme-replacement therapy in life-threatening hypophosphatasia: The 3-year experience with asfotase alfa. Poster presented at the American Society for Bone and Mineral Research (ASBMR) 2014 Annual Meeting, Houston, September 12, 2014. Abstract FR0435.

3. Madson KL, Rockman-Greenberg C, Whyte MP. Asfotase alfa: Sustained improvements in hypophosphatasia-related rickets, physical function, and pain during 3 years of treatment for severely affected children. Poster presented at the American Society for Bone and Mineral Research (ASBMR) 2014 Annual Meeting, Houston, September 14, 2014. Abstract 1081.

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10. Whyte MP, Simmons JH, Bishop N, et al. Asfotase alfa: sustained efficacy and tolerability in infants and young children with life-threatening hypophosphatasia. Poster presented at the 2014 Pediatric Academic Societies and Asian Society for Pediatric Research Joint Meeting, Vancouver, B.C., Canada, May 4, 2014. Abstract 752396.

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