April 4, 2016

# Data Presented at ENDO 2016 Show Sustained Improvements in Survival Rates, Bone Healing, Respiratory Support and Physical Function in Children with Hypophosphatasia (HPP) Receiving Long-Term Treatment with Strensiq® (asfotase alfa)

*- Researchers also report improvements in physical function for up to four years as measured by 6-Minute Walk Test and elimination or reduction of use of ambulatory assistance devices in adolescents and adult patients with HPP treated with Strensiq -*

NEW HAVEN, Conn.--(BUSINESS WIRE)-- Alexion Pharmaceuticals, Inc. (NASDAQ:ALXN) announced today that researchers presented new data showing children with perinatal- and infantile-onset hypophosphatasia (HPP) treated with Strensiq® (asfotase alfa) had statistically significant improvements in bone healing as assessed radiographically, which were sustained through 3.5 years of treatment.[1] The data were from an ongoing, open-label Phase 2 trial of Strensiq, which previously demonstrated a 90 percent overall observed survival rate and improvements in respiratory status that continue to be sustained. The data were presented at the Endocrine Society's 98th Annual Meeting and Expo (ENDO) in Boston.

Researchers also presented the following data:

- Clinically significant improvements in physical function were observed in children with HPP (ages 11-17 years at analysis) who were treated with Strensiq for up to 5 years (n=12).[2]
- New interim results indicating a reduction in two key tissue non-specific alkaline phosphatase (TNSALP) substrates that accumulate in HPP, as well as improvements in physical function in adolescent and adult patients with HPP (ages 13-66 years at study entry) treated with Strensiq, as measured by:[3]
  - 6 Minute Walk Test (6MWT) (n=19).
  - Reduction or elimination of ambulatory assistive devices during performance of the 6MWT by 2 years of treatment for all patients that required them at baseline (n=5).

"The study results presented at ENDO show clinically significant and sustained improvements across all key measures of pediatric-onset HPP, including bone healing, physical function and pain in patients who were treated with Strensiq," said Martin Mackay, Ph.D., Executive Vice President and Global Head of R&D at Alexion. "The data provide additional information on the long-term efficacy and safety of Strensiq, a highly innovative enzyme replacement therapy that treats the underlying cause of HPP by replacing the missing TNSALP enzyme."

Strensiq is approved in the United States as a treatment for patients with perinatal-, infantile- or juvenile-onset HPP.

### Improvements in Survival and Key Disease Parameters in Patients with Perinatal- or Infantile-Onset HPP Treated with Strensiq for Up to 3.5 Years[1]

In a poster preview session, Johannes Liese, M.D., Head of the Section of Pediatric Infectious Diseases and Immunology, University Children's Hospital, Würzburg Germany, presented new results from an ongoing multinational, open-label Phase 2 study in children with perinatal- or infantile-onset HPP (ages 5 years or younger at study entry; symptom onset < 6 months of age) who were treated with Strensiq for up to 3.5 years (n=59). Investigators previously reported up to 48-week findings in 28 patients from the study at the International Congress on Children's Bone Health in June, 2015.

Dr. Liese reported that patients treated with Strensiq had:

- Clinically significant improvements in skeletal manifestations of HPP at 6 months ($p < 0.0001$), the primary endpoint, that were sustained through 3.5 years, as measured by a median improvement of +2.3 in Radiographic Global Impression of Change (RGI-C) scores (7-point scale; -3=severe worsening; +3=near/complete healing; $p < 0.01$).
- A 67 percent reduction in the need for respiratory support among patients who required support during the study (including ventilation and supplemental oxygen).
- An overall survival rate of 90 percent at 3.8 years.

- Improvements in height Z-scores (a measure of patient growth) from baseline to 3.5 years of a median of +0.4 across patients.

"Pediatric patients with HPP face significant challenges related to growth and respiratory function, as well as a high risk of death," said Dr. Liese. "In this analysis, we saw meaningful improvements in bone mineralization in infants and children with infantile HPP who were treated with Strensiq. Further, these results were accompanied by improved patient outcomes of respiratory function, growth, physical activity and survival that were sustained through 3.5 years of treatment."

The most common adverse drug reactions (ADR) were mild-to-moderate injection-site reactions.

**Reduction in Pain and Improved Function and Activities of Daily Living in Children with HPP Treated with Strensiq for 5 years**[2]

In an oral session, Michael P. Whyte, M.D., Medical-Scientific Director of the Center for Metabolic Bone Disease and Molecular Research at Shriners Hospitals for Children in St. Louis, presented new results from the extension phase of a multinational, open-label Phase 2 study in children with HPP (ages 5-12 years at study entry and 11-17 at analysis) who were treated with Strensiq for up to 5 years (n=12). Three-year interim data from this study were previously presented by investigators at ENDO in March, 2015.

Dr. Whyte reported that patients treated with Strensiq had:

- Rapid and sustained improvements in strength and agility, as measured by median changes from baseline in the Bruininks-Oseretsky Test of Motor Proficiency, Second Edition (BOT-2) Strength subscale, and the BOT-2 Running Speed and Agility subscale. Median baseline scaled scores of 4 and 3 improved to median scaled scores of 15 and 13, respectively, at last assessment ($p < 0.0001$ for both). With these improvements, most patients reached the normal range for healthy peers by 6 months, which was sustained through 5 years.
- Significant and sustained decreases in disability through 5 years, as measured by median changes from baseline in the Pediatric Outcomes Data Collection Instrument (PODCI) Transfer and Basic Mobility subscale, the PODCI Sports/Physical Functioning subscale, and the Child Health Assessment Questionnaire (CHAQ) Disability Index. Median baseline scores of 37, 20 and 1 improved to median scores of 52, 49 and 0, respectively at last assessment ($p < 0.05$ for all scores).
- Significant decreases in pain, as measured by the PODCI Pain/Comfort subscale, a pain/comfort rating scale with higher scores representing better outcomes or health. The median baseline score of 39 increased to a median score of 56 at 5 years ($p < 0.05$), and was within normal range for health peers by 6 months and sustained for 5 years. Similar results were observed in the CHAQ scores.

The most common ADRs were injection-site reactions.

**Biological Activity of Strensiq and Improved Physical Function in Adolescents and Adults with HPP Treated with Strensiq for up to 4 Years**[3]

In an oral session, Priya S. Kishnani, M.D., Division Chief, Medical Genetics, Duke University Medical Center, Durham, North Carolina, presented new interim results from the ongoing extension phase of a randomized, open-label, dose-ranging Phase 2 study of adolescents and adults (ages 13-66 years at study entry) with HPP treated with Strensiq for up to 4 years.

In the initial phase of this study, patients were randomized to receive a control (n=6), 0.3 mg/kg/day of Strensiq (n=7), or 0.5 mg/kg/day of Strensiq (n=6) for 6 months. At 6 months, all 19 patients entered the extension phase of the study and were treated with 0.5 mg/kg/day of Strensiq, then changed to 1 mg/kg/day, 6 times a week, over the next 6 to 12 months. Data from both Strensiq dosage groups were pooled for the analysis.

Dr. Kishnani reported that in patients treated with Strensiq:

- Statistically significant reductions in plasma pyridoxal 5' phosphate (PLP) levels from baseline compared to controls were observed at 6 months ($p=0.0285$), supporting the biological activity of Strensiq. Patients also experienced a decrease in inorganic pyrophosphate (PPi) at 6 months ($p=0.0715$), compared to controls. Within group decreases in both substrates were statistically significant for the treated patients ($p < 0.0001$). PLP and PPi are tissue non-specific alkaline phosphatase (TNSALP) substrates that accumulate in HPP and are key indicators of disease activity.

Additional descriptive data collected during the 4 years of the extension phase of the trial demonstrated:

- Sustained decreases in PLP and PPi.
- Physical function, as measured by the Six Minute Walk Test (6MWT), improved from a median of 76 percent of that predicted for healthy peers at baseline (n=15; below normal range) to a median of 85 percent predicted (within the normal range) by 6 months in patients treated with Strensiq (n=16). Results were sustained through four years of treatment.
- All 5 patients who required ambulatory assistive devices in the performance of the 6MWT at study baseline reduced (n=2) or eliminated (n=3) their need by 2 years with ongoing Strensiq treatment.
- Speed and agility, as measured by median change from baseline in the BOT-2 Running Speed and Agility subscale, improved from a median total score of 6.5 at baseline to a median total score of 12 at 6 months (n=13). Improvement was sustained at four years (n=8).
- Strength, as measured by median change from baseline in the BOT-2 Strength subscale, increased by 2 points at 6 months (n=14) and by 1 after 4 years of treatment.

The most common ADRs were mild to moderate injection-site reactions.

In a separate presentation at ENDO today, researchers will report preclinical findings on the effect of Strensiq on muscle strength in *Akp2*$^{-/-}$mice, a model of HPP which mimics the muscle weakness observed in patients.[4]

**About Hypophosphatasia (HPP)**

HPP is a genetic, chronic, progressive, and life-threatening ultra-rare metabolic disease characterized by low alkaline phosphatase (ALP) activity and defective bone mineralization that can lead to destruction and deformity of bones and other skeletal abnormalities, as well as systemic complications such as profound muscle weakness, seizures, pain, and respiratory failure leading to premature death in infants.[5-9] Ultra-rare diseases are defined as diseases that affect fewer than 20 patients per 1 million of the general population.[10]

HPP is caused by mutations in the gene encoding an enzyme known as tissue non-specific alkaline phosphatase (TNSALP).[5,6] The genetic deficiency in HPP can affect people of all ages.[5] HPP is traditionally classified by the age of the patient at the onset of symptoms of the disease, with perinatal-, infantile- and juvenile-onset HPP defined by the onset of the first symptom prior to 18 years of age.

HPP can have devastating consequences for patients at any stage of life.[5] 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 percent at 5 years.[11] In these patients, mortality is primarily due to respiratory failure.[5,9,12] In patients surviving and those with juvenile-onset HPP, long-term clinical sequelae include recurrent and non-healing fractures, profound muscle weakness, debilitating pain and the requirement for ambulatory assistive devices such as wheelchairs, wheeled walkers and canes.[5,8]

**About Strensiq® (asfotase alfa)**

Strensiq® (asfotase alfa) is a highly innovative bone-targeted enzyme replacement therapy that treats the underlying cause of HPP by replacing the missing TNSALP enzyme. In clinical studies of patients with HPP who had their first symptom prior to the age of 18, treatment with Strensiq improved overall survival in infants, enhanced bone mineralization and improved height, weight and mobility.

Strensiq is approved in the United States, European Union, Japan and Canada.

**IMPORTANT SAFETY INFORMATION**

Hypersensitivity reactions have been reported in STRENSIQ-treated patients. In clinical trials, 1 out of 99 treated patients (1%) experienced signs and symptoms consistent with anaphylaxis.

Localized lipodystrophy, including lipoatrophy and lipohypertrophy, has been reported at injection sites after several months in patients treated with STRENSIQ.

Patients with HPP are at increased risk for developing ectopic calcifications. In clinical trials, 14 cases (14%) of ectopic calcification of the eye including the cornea and conjunctiva, and the kidneys (nephrocalcinosis) were reported. There was insufficient information to determine whether or not the reported events were consistent with the disease or due to STRENSIQ. No visual changes or changes in renal function were reported.

**ADVERSE REACTIONS**

The most common adverse reactions reported were injection site reactions, lipodystrophy, ectopic calcifications, and hypersensitivity reactions.

Please click here for the full Prescribing Information.

**About Alexion**

Alexion is a global biopharmaceutical company focused on developing and delivering life-transforming therapies for patients with devastating and rare disorders. Alexion developed and commercializes Soliris® (eculizumab), the first and only approved complement inhibitor to treat patients with paroxysmal nocturnal hemoglobinuria (PNH) and atypical hemolytic uremic syndrome (aHUS), two life-threatening ultra-rare disorders. As the global leader in complement inhibition, Alexion is strengthening and broadening its portfolio of complement inhibitors, including evaluating potential indications for eculizumab in additional severe and ultra-rare disorders. Alexion's metabolic franchise includes two highly innovative enzyme replacement therapies for patients with life-threatening and ultra-rare disorders, Strensiq® (asfotase alfa) to treat patients with hypophosphatasia (HPP) and Kanuma™ (sebelipase alfa) to treat patients with lysosomal acid lipase deficiency (LAL-D). In addition, Alexion is advancing the most robust rare disease pipeline in the biotech industry with highly innovative product candidates in multiple therapeutic areas. This press release and further information about Alexion can be found at: www.alexion.com.

[ALXN-G]

***Forward-Looking Statements***

*This news release contains forward-looking statements, including statements related to potential medical benefits of Strensiq® (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, risks and uncertainties of drug development, decisions of regulatory authorities regarding marketing approval or material limitations on the marketing of Strensiq for HPP, delays in arranging satisfactory manufacturing capabilities and establishing commercial infrastructure for Strensiq for HPP, the possibility that results of clinical trials are not predictive of safety and efficacy results of Strensiq in broader or different patient populations, the risk that estimates regarding the number of patients with Strensiq and observations regarding the natural history of patients with Strensiq 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, 2015 and in Alexion's other filings with the SEC. 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**

1. Liese J, Hofmann C, Harmatz P, et al. Efficacy and Safety of Asfotase Alfa in Patients with Infantile Hypophosphatasia Treated for up to 3.5 Years: Results from a Phase II, Open-Label, Uncontrolled Study. Poster preview presented at the Endocrine Society Annual Meeting and Expo, Boston, April 3, 2016.

2. Phillips D, Madson KL, Rockman-Greenberg C, et al. Reduction in Pain and Improved Function and Activities of Daily Living in Children with Hypophosphatasia Treated with Asfotase Alfa for 5 years. Oral presented at the Endocrine Society Annual Meeting and Expo, Boston, April 3, 2016.

3. Kishnani P, Madson K, Whyte M, et. al. Biochemical and Physical Function Outcomes in Adolescents and Adults with Hypophosphatasia Treated with Asfotase Alfa for up to 4 Years: Interim Results from a Phase II Study. Oral presented at the Endocrine Society Annual Meeting and Expo, Boston, April 3, 2016.

4. Marozsan A. Muscular Function in *Akp2*$^{-/-}$ Mice and Evaluation of the Effect of Asfotase Alfa on the *Akp2*$^{-/-}$ Phenotype. Oral presented at the Endocrine Society Annual Meeting and Expo, Boston, April 4, 2016.

5. Rockman-Greenberg C. Hypophosphatasia. *Pediatr Endocrinol Rev*. 2013; 10(suppl 2):380-388.

6. Whyte MP. Hypophosphatasia: nature's window on alkaline phosphatase function in humans. In: Bilezikian JP, Raisz LG, Martin TJ, eds. Principles of Bone Biology. Vol 1. 3rd ed. San Diego, CA: Academic Press; 2008:1573-1598.

7. Whyte MP, Greenberg CR, Salman N, et al. Enzyme-replacement therapy in life-threatening hypophosphatasia. *N Engl J Med.* 2012; 366(10):904-913.

8. Seshia SS, Derbyshire G, Haworth JC, Hoogstraten J. Myopathy with hypophosphatasia. *Arch Dis Child*. 1990; 65(1):130-131.

9. Baumgartner-Sigl S, Haberlandt E, Mumm S, et al. Pyridoxine-responsive seizures as the first symptom of infantile hypophosphatasia caused by two novel missense mutations (c.677T > C, p.M226T; c.1112C > T, p.T371I) of the tissue-nonspecific alkaline phosphatase gene. *Bone*. 2007; 40(6):1655-1661.

10. REGULATION (EU) No 536/2014 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC. http://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32014R0536&qid=1421232837997&from=EN.

11. Whyte MP, Leung E, Wilcox W, et al. Hypophosphatasia: a retrospective natural history study of the severe perinatal and infantile forms. Poster presented at the 2014 Pediatric Academic Societies and Asian Society for Pediatric Research Joint Meeting, Vancouver, B.C., Canada, May 5, 2014. Abstract 752416.

12. Whyte MP, Rockman-Greenberg C, Hofmann C, et al. Improved survival with asfotase alfa treatment in pediatric patients with hypophosphatasia at high risk of death. Poster presented at the American Society for Bone and Mineral Research (ASBMR) 2014 Annual Meeting, Houston, September 14, 2014. Abstract 1097.

View source version on businesswire.com: http://www.businesswire.com/news/home/20160404005355/en/

Alexion Pharmaceuticals, Inc.
Media
Stephanie Fagan, 203-271-8223
Senior Vice President, Corporate Communications
or
Emily Vlasak, 203-699-4760
Associate Director, Corporate Communications
or
Investors
Elena Ridloff, CFA, 203-699-7722
Vice President, Investor Relations

Source: Alexion Pharmaceuticals, Inc.

News Provided by Acquire Media