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New England Journal of Medicine (NEJM) Publishes Pivotal Phase 3 Data on Kanuma™ (sebelipase alfa) in Children and Adults with Lysosomal Acid Lipase Deficiency (LAL-D)

CHESHIRE, Conn.--(BUSINESS WIRE)-- Alexion Pharmaceuticals, Inc. (NASDAQ:ALXN) announced today that data from the pivotal Phase 3 ARISE study evaluating the safety and efficacy of Kanuma™ (sebelipase alfa) in children and adults with lysosomal acid lipase deficiency (LAL-D) have been published in the September 10 issue of the *New England Journal of Medicine* (NEJM). In the study, Kanuma met the primary endpoint of alanine aminotransferase (ALT) normalization compared with placebo (31% vs. 7%, p=0.03) as well as six secondary endpoints.[1] Kanuma is an innovative enzyme replacement therapy that has been approved by the European Commission for the treatment of patients of all ages with LAL-D, a genetic, chronic, and progressive ultra-rare metabolic disease in which infants, children and adults suffer multi-organ damage and premature death.

"Patients with LAL-D often develop cirrhosis and severe dyslipidemia at an early age. Unfortunately, historical treatment approaches have not been effective in changing the devastating course of the disease," said lead study author Barbara K. Burton, M.D., Professor of Pediatrics at the Northwestern University Feinberg School of Medicine and Attending Physician at the Ann & Robert H. Lurie Children's Hospital of Chicago. "Importantly, in this study of children and adults with LAL-D, enzyme replacement therapy produced significant reductions in ALT as well as other disease-related lipid and liver abnormalities compared with placebo."

LAL-D is caused by genetic mutations that result in a marked decrease or loss in LAL enzyme activity in the lysosomes across multiple body tissues, leading to the chronic build-up of cholesteryl esters and triglycerides in the liver, blood vessel walls and other tissues. Patients with LAL-D often experience a rapid onset of life-threatening disease manifestations, and many patients may be asymptomatic until they experience a severe consequence of the disease.[2,3]

"LAL-D is a devastating and ultra-rare disorder in which half of children and adults will progress to fibrosis, cirrhosis, or liver transplant in three years," said David Hallal, Chief Executive Officer of Alexion. "Today, many patients with LAL-D are not accurately diagnosed, and those who are face severe consequences. As a global leader in rare diseases, Alexion recognizes the devastation that patients with LAL-D and their families face. The publication of these pivotal Phase 3 data in the *New England Journal of Medicine* will raise much-needed awareness of LAL-D in the medical community so patients can receive an accurate and rapid diagnosis."

In addition to the *NEJM* publication, the *Journal of Pediatric Gastroenterology & Nutrition* recently published the largest longitudinal review of children and adults with LAL-D. In this observational study, ALT was elevated in more than 90% of patients, LDL cholesterol was abnormal in nearly 65% of patients (mean value of 202.9 mg/dl), HDL cholesterol was abnormal in more than 40% of patients, and the overall frequency of liver transplantation was 13%. Reductions in LDL were typically small in patients taking lipid-lowering medication.[4] Findings from this study confirm the significant burden of LAL-D despite historical supportive care.

On September 1, 2015, Alexion announced that the European Commission approved Kanuma for the treatment of patients of all ages with LAL-D. In addition to data from the ARISE study, the summary of product characteristics (SmPC) for Kanuma in the European Union includes clinical data from a separate study showing a significant benefit in terms of survival (67%, or 6 out of 9) in patients with the infant form of LAL-D beyond 12 months, compared with 0 out of 21 patients in an untreated historical cohort.[5]

About the ARISE Study[1]

The multicenter, randomized, placebo-controlled ARISE (**A**cid Lipase **R**eplacement **I**nvestigating **S**afety and **E**fficacy) study of children and adults with LAL-D included a 20-week double-blind treatment period and an ongoing open-label period. Sixty-six patients (ages 4-58 years) were enrolled in the study (36 received Kanuma and 30 received placebo) and 65 patients entered the open-label period. Most patients (47/66) were under 18 years of age. All 66 patients had an elevated ALT at baseline (≥1.5 times the upper limit of normal). The primary efficacy endpoint was normalization of ALT levels. Additional efficacy endpoints included evaluations of other biochemical markers of liver function, serum lipid levels, hepatic fat content, organ volume, and liver histopathology in a subset of patients. Baseline assessments demonstrated significant disease burden in the patient population studied.

For the primary efficacy endpoint, Kanuma was associated with a significantly greater proportion of patients achieving ALT

normalization compared with placebo (31% vs. 7%, p=0.03). In addition, patients treated with Kanuma showed significant improvement versus placebo in six secondary endpoints, including change in LDL cholesterol (-28.4% vs. -6.2%, p < 0.001), change in non-HDL cholesterol (-28.0% vs. -6.9%, p < 0.001), AST normalization (42% vs. 3%, p < 0.001), change in triglycerides (-25.5% vs. -11.1%, p=0.04), change in HDL cholesterol (19.6% vs. -0.3%, p < 0.001), and change in hepatic fat content assessed by MRI (-32.0% vs. -4.2%, p < 0.001). Decreases in LDL cholesterol were seen irrespective of baseline lipid-lowering medication status. In addition, the decrease from baseline in mean ALT was significantly greater for Kanuma than for placebo (-58 U/L vs. -7 U/L, p < 0.001). All patients treated with Kanuma showed a reduction in ALT levels.

A reduction in steatosis occurred more frequently in the Kanuma group than in the placebo group but the difference did not reach significance. While patients in the Kanuma group had greater reductions in liver volume compared with placebo, the pre-specified hypothesis testing nullified the significance of this secondary endpoint.

Three serious adverse events were reported during the 20-week double-blind period; two were in the Kanuma group with one considered treatment-related (an infusion-related reaction that was assessed as serious). Infusion-associated reactions were uncommon. The most common treatment-emergent adverse events that were more frequent in patients receiving Kanuma than placebo were headache (28%), fever (25%), oropharyngeal pain (17%), nasopharyngitis (11%), asthenia (8%), constipation (8%), and nausea (8%).

In addition, preliminary results from the open-label study period were included in today's publication and demonstrated further improvements in LDL cholesterol and non-HDL cholesterol. ALT and LDL cholesterol levels that were persistently elevated in patients receiving placebo during the double-blind period markedly decreased when those patients entered the open-label period and began treatment with Kanuma. The safety profile of Kanuma during the open-label period was consistent with that observed in the double-blind period.

About Lysosomal Acid Lipase Deficiency (LAL-D)

LAL-D is a genetic, chronic and progressive ultra-rare metabolic disease associated with significant morbidity and premature mortality. In patients with LAL-D, genetic mutations result in decreased activity of the LAL enzyme. This leads to marked accumulation of cholesteryl esters and triglycerides in vital organs, blood vessels, and other tissues, resulting in progressive and multi-organ damage including fibrosis, cirrhosis, liver failure, accelerated atherosclerosis, cardiovascular disease, and other devastating consequences.[2,3]

LAL-D affects patients of all ages with clinical manifestations from infancy through adulthood and may have sudden and unpredictable clinical complications. Infants experience profound growth failure, liver fibrosis, and cirrhosis with a median age of death at 3.7 months.[6] In an observational study, approximately 50% of children and adults with LAL-D progressed to fibrosis, cirrhosis, or liver transplant in 3 years.[7] The median age of onset of LAL-D is 5.8 years and the disease can be diagnosed with a simple blood test.[4,8]

About Kanuma™ (sebelipase alfa)

Kanuma™ (sebelipase alfa) is an innovative enzyme replacement therapy designed to address the underlying cause of lysosomal acid lipase deficiency (LAL-D) by aiming to reduce substrate accumulation in the lysosomes of cells throughout the body, including the liver, to prevent vital organ damage and premature death.

Kanuma is approved in the European Union for the treatment of patients of all ages with LAL-D. The FDA granted Breakthrough Therapy designation for Kanuma for LAL Deficiency presenting in infants and accepted the Kanuma BLA for Priority Review. In addition, a New Drug Application for Kanuma has been submitted to Japan's Ministry of Health, Labour and Welfare.

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. Alexion is also establishing a premier global metabolic rare disease franchise, which includes Kanuma™ (sebelipase alfa) for patients with lysosomal acid lipase deficiency (LAL-D), and Strensiq™ (asfotase alfa) for patients with hypophosphatasia (HPP). In addition, Alexion is advancing the most robust rare disease pipeline in the biotech industry, with highly innovative product candidates in multiple therapeutic areas. As the global leader in complement inhibition, the Company is strengthening and broadening its portfolio of complement inhibitors across diverse platforms, including evaluating potential indications for Soliris in additional severe and ultra-rare disorders. This press release and further information about Alexion can be found at: www.alexion.com.

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Forward-Looking Statements

This news release contains forward-looking statements, including statements related to potential medical benefits of Kanuma™ (sebelipase alfa) for lysosomal acid lipase deficiency (LAL-D), expectations regarding the FDA regulatory process, the outcome of the FDA's review, and guidance regarding anticipated financial results for 2015. 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 Kanuma for LAL-D, delays in arranging satisfactory manufacturing capabilities and establishing commercial infrastructure for Kanuma for LAL-D, the possibility that results of clinical trials are not predictive of safety and efficacy results of Kanuma in broader or different patient populations, the risk that third party payors (including governmental agencies) will not reimburse for the use of Kanuma at acceptable rates or at all, the risk that estimates regarding the number of patients with Kanuma and observations regarding the natural history of patients with Kanuma 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, 2015. 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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