Ionis announces olezarsen FCS New Drug Application accepted for Priority Review and enrollment in Phase 3 sHTG program completed

June 25, 2024

– Olezarsen PDUFA date set for December 19, 2024 for treatment of familial chylomicronemia syndrome –

– Phase 3 enrollment completed in CORE, CORE2 and ESSENCE evaluating olezarsen for the treatment of severe hypertriglyceridemia, with results expected in 2H 2025 –

CARLSBAD, Calif., June 25, 2024 /PRNewswire/ -- Ionis Pharmaceuticals, Inc. (Nasdaq: IONS) today announced that the U.S. Food and Drug Administration (FDA) has accepted for Priority Review the New Drug Application (NDA) for olezarsen, an investigational RNA-targeted medicine for the treatment of adults with familial chylomicronemia syndrome (FCS). The FDA has set an action date of December 19, 2024 and indicated they are not currently planning an advisory committee meeting for olezarsen.

"FCS is a debilitating, rare, genetic disease that causes significant physical, emotional and financial burden with no approved treatment options in the U.S.," said Brett Monia, Ph.D., chief executive officer of Ionis. "The Priority Review underscores the urgent need people living with FCS have for a medicine that may help lower triglyceride levels and reduce incidence of life-threatening acute pancreatitis events. We look forward to partnering closely with the FDA during the review process as we work to bring this potentially breakthrough medicine to patients before the end of 2024. Separately, we are pleased with the progress of our now fully enrolled Phase 3 program investigating olezarsen in the much more common severe hypertriglyceridemia population."

Priority Review is a designation for medicines that have the potential to provide significant improvements in the treatment, prevention or diagnosis of a serious disease, with the expectation of the FDA taking action within six months, compared to 10 months under standard review. The application to the FDA was based on positive results from Balance, a global, multicenter, randomized, double-blind, placebo-controlled Phase 3 study. The study results were presented at the 2024 American College of Cardiology (ACC) Annual Meeting and published simultaneously in *The New England Journal of Medicine (NEJM)*.

The U.S. FDA granted olezarsen Fast Track designation for the treatment of FCS in January 2023, as well as Orphan Drug designation and Breakthrough Therapy designation in February 2024. Ionis is planning additional regulatory filings for the treatment of FCS in the European Union this year.

In addition to FCS, Ionis is evaluating olezarsen for the treatment of severe hypertriglyceridemia (sHTG) in three Phase 3 clinical trials – CORE, CORE2 and ESSENCE, all three of which completed enrollment in the first half of 2024. CORE and CORE2 enrolled more than 1,000 sHTG patients with fasting triglyceride levels ≥500 mg/dL; ESSENCE enrolled more than 1,400 high triglyceride patients with fasting triglyceride levels ≥150 mg/dL to <500 mg/dL who were diagnosed and/or at risk for atherosclerotic cardiovascular disease as well as patients with fasting triglycerides ≥500 mg/dL. sHTG is a common, life-threatening condition that can result in severe health complications, including potentially fatal acute pancreatitis (AP). Data are expected in the second half of 2025.

About Olezarsen

Olezarsen is an RNA-targeted investigational **LI**gand **C**onjugated **A**ntisense (LICA) medicine being evaluated for people at risk of disease due to elevated triglyceride levels, including those with familial chylomicronemia syndrome (FCS) and severe hypertriglyceridemia (sHTG). Olezarsen is designed to lower the body's production of apoC-III, a protein produced in the liver that regulates triglyceride metabolism in the blood.

Olezarsen is an investigational medicine that has not been reviewed or approved for the treatment of any disease by any regulatory authority.

About FCS

FCS is a rare, genetic disease characterized by extremely elevated triglyceride levels. It is caused by impaired function of the enzyme lipoprotein lipase (LPL). Because of limited LPL production or function, people with FCS cannot effectively break down chylomicrons, lipoprotein particles that are 90% triglycerides. FCS is estimated to impact one to 13 people per million in the U.S. People living with FCS are at high risk of acute pancreatitis (AP) in addition to other chronic health issues such as fatigue and severe, recurrent abdominal pain. People living with FCS are sometimes unable to work, adding to the burden of disease.

Currently, there are no U.S. FDA-approved therapies for the treatment of FCS and people with FCS are generally nonresponsive to standard triglyceride lowering therapies. People living with this condition currently rely solely on nutrition management through extremely restrictive and difficult to manage diets to navigate the health risks associated with FCS.

About sHTG

sHTG is a disease categorized by triglyceride levels of 500 mg/dL and above. It develops due to primary (genetic) and secondary causes including diet and lifestyle, other medical conditions and certain medications. More than three million people are currently estimated to live with sHTG in the

U.S. People living with sHTG are at high risk of pancreatitis and damage to the pancreas, as such, reducing the risk of pancreatitis is a critically important reason to treat sHTG. People with sHTG are also at risk of heart, brain and blood vessel damage.

There remains a need for additional therapeutic options for the treatment of sHTG. Endocrinology and cardiovascular treatment guidelines recommend treating triglyceride levels of ≥500 mg/dL to reduce the risk of pancreatitis. Multiple treatment guidelines recommend lifestyle interventions to reduce triglyceride levels in people with sHTG and the addition of a triglyceride lowering medicine such as a fibrate or omega-3 fatty acid if needed to reduce fasting triglycerides to appropriate levels. However, these interventions are not sufficient for all people with sHTG, for whom there remains a significant need for new treatments that may help further reduce triglyceride levels and the risk of pancreatitis.

About Ionis Pharmaceuticals, Inc.

For three decades, Ionis has invented medicines that bring better futures to people with serious diseases. Ionis currently has five marketed medicines and a leading pipeline in neurology, cardiology, and other areas of high patient need. As the pioneer in RNA-targeted medicines, Ionis continues to drive innovation in RNA therapies in addition to advancing new approaches in gene editing. A deep understanding of disease biology and industry-leading technology propels our work, coupled with a passion and urgency to deliver life-changing advances for patients. To learn more about Ionis, visit Ionis.com and follow us on X (Twitter) and LinkedIn.

Ionis Forward-looking Statements

This press release includes forward-looking statements regarding olezarsen, Ionis' business, and the therapeutic and commercial potential of Ionis' commercial medicines, additional medicines in development and technologies. Any statement describing Ionis' goals, expectations, financial or other projections, intentions, or beliefs is a forward-looking statement and should be considered an at-risk statement. Such statements are subject to certain risks and uncertainties, including but not limited to those related to our commercial products and the medicines in our pipeline, and particularly those inherent in the process of discovering, developing and commercializing medicines that are safe and effective for use as human therapeutics, and in the endeavor of building a business around such medicines. Ionis' forward-looking statements also involve assumptions that, if they never materialize or prove correct, could cause its results to differ materially from those expressed or implied by such forward-looking statements. Although Ionis' forward-looking statements reflect the good faith judgment of its management, these statements are based only on facts and factors currently known by Ionis. Except as required by law, we undertake no obligation to update any forward-looking statements for any reason. As a result, you are cautioned not to rely on these forward-looking statements. These and other risks concerning Ionis' programs are described in additional detail in Ionis' annual report on Form 10-K for the year ended Dec. 31, 2023, and most recent Form 10-Q, which are on file with the SEC. Copies of these and other documents are available at www.Ionis.com.

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