Ionis announces positive olezarsen topline results from Phase 3 study in people with familial chylomicronemia syndrome

September 26, 2023

- *Olezarsen met the primary endpoint with a statistically significant reduction in triglyceride levels versus placebo*
- *First study to show an absolute reduction in acute pancreatitis in FCS patients, with olezarsen 80 mg monthly dose reducing events by 100 percent*
- *Olezarsen demonstrated a favorable safety and tolerability profile*
- *Ionis plans to file a New Drug Application with U.S. FDA in preparation for first potential independent launch*
- *Phase 3 studies continue evaluating olezarsen in broader patient population with severe hypertriglyceridemia (SHTG)*
- *Ionis to host webcast today at 11 a.m. ET*

CARLSBAD, Calif., Sept. 26, 2023 /PRNewswire/ -- Ionis Pharmaceuticals, Inc. (Nasdaq: IONS) today announced positive topline results for the Phase 3 Balance study of olezarsen in people with familial chylomicronemia syndrome (FCS). The trial met its primary efficacy endpoint with a statistically significant reduction in triglyceride (TG) levels with the olezarsen 80 mg monthly dose at six months compared to placebo (p=0.0009); triglyceride lowering continued to improve at 12 months. In addition, olezarsen 80 mg showed a 100 percent reduction in acute pancreatitis events compared to placebo (0 events for olezarsen versus 11 events for placebo), a key secondary endpoint.

Treatment with olezarsen 80 mg resulted in a >75% reduction in apoC-III, a protein produced in the liver that regulates TG metabolism in the blood. In addition to the 80 mg monthly dose, the study also evaluated a lower 50 mg monthly dose. Olezarsen demonstrated a dose-dependent effect, with both study doses showing a substantial reduction in pancreatitis. The lower 50 mg dose did not reach statistical significance at six months on the primary endpoint of triglyceride lowering (p=0.0775).

Ionis plans to file a New Drug Application in early 2024 with the U.S. Food and Drug Administration (FDA) in addition to EU regulatory filings. If approved, olezarsen would be the first available treatment in the U.S. for FCS, a rare, debilitating genetic disease that can lead to acute, potentially fatal pancreatitis attacks. The FDA granted olezarsen Fast Track designation for the treatment of FCS in 2023, which is designed to expedite the FDA's review of innovative, new drugs that demonstrate the potential to address unmet medical need. Ionis will present the Phase 3 olezarsen FCS data at a future medical congress.

"These positive olezarsen topline results represent an important advance for people with FCS who live in constant fear of unpredictable and potentially fatal attacks of acute pancreatitis. With no currently FDA-approved treatments, people with FCS live with debilitating abdominal pain and must maintain an extremely restrictive diet consisting of less than 20 grams of fat per day," said Sam Tsimikas, M.D., senior vice president, global cardiovascular development at Ionis. "In this study, people with FCS treated with olezarsen along with background therapy and a low-fat diet had a substantially reduced risk of recurrent attacks of acute pancreatitis. These results strengthen our confidence in olezarsen's potential to deliver benefits to FCS patients and in the larger population with SHTG following completion of ongoing Phase 3 studies."

Olezarsen demonstrated a favorable safety and tolerability profile in the study. There were more adverse events in the placebo group compared to the olezarsen groups, primarily due to pancreatitis events. The majority of adverse events in the olezarsen groups were mild in severity. There was a low incidence of injection site reactions. No hepatic or renal toxicity events occurred and there were no clinically meaningful platelet reductions. One death was reported in the study, which was deemed as not related to study drug.

"Today is a proud moment in our company's evolution, as olezarsen is poised to be a long-awaited advance for FCS patients and Ionis' first potential independent commercial launch," said Brett P. Monia, Ph.D., chief executive officer of Ionis. "We believe olezarsen has the potential to become the new standard of care for patients with FCS and we are excited about its potential in the broader population of patients with SHTG where we have ongoing pivotal trials. We want to express our gratitude to the patients, caregivers, investigators and study teams who participated in the Balance study. We look forward to submitting these data to the FDA and anticipate that olezarsen will be the first of many medicines from our wholly owned pipeline that we bring to people with debilitating diseases."

Webcast

Ionis will conduct a webcast today at 11:00 a.m. Eastern time to discuss this announcement. Interested parties may access the webcast here. A webcast replay will be available for a limited time at the same address. Visit www.ionispharma.com for more information and to register.

About the Balance Study

The global, multicenter, randomized, double-blind, placebo-controlled Phase 3 Balance study (NCT04568434) enrolled 66 patients aged 18 and older with confirmed FCS. Patients in the study received background therapies including statins, fibrates and omega-3 fatty acids. Patients were randomized in a 1:1:1 ratio to receive olezarsen 80 mg or 50 mg or placebo via subcutaneous injection once every four weeks for 53 weeks. The primary endpoint was the percent change from baseline in fasting triglyceride levels at six months compared to placebo. Secondary endpoints included triglyceride levels at 12 months and adjudicated acute pancreatitis event rate.

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 break down chylomicrons, lipoprotein particles that are 90% triglycerides. FCS is estimated to impact 1-2 people per million worldwide. People living with FCS are at high risk for acute pancreatitis in addition to other chronic health issues such as fatigue and severe, recurrent abdominal pain. They are sometimes unable to work, adding to their disease burden.

Currently, there are no FDA-approved therapies for the treatment of FCS. People living with this condition currently rely solely on nutrition

management through extremely restrictive diets to navigate the health risks associated with FCS.

About Olezarsen

Olezarsen is an investigational **LI**gand **C**onjugated **A**ntisense (LICA) medicine being evaluated for people at risk of disease due to elevated triglyceride (TG) levels including those with familial chylomicronemia syndrome, or FCS. Olezarsen is designed to inhibit the body's production of apoC-III, a protein produced in the liver that regulates TG metabolism in the blood. The FDA granted olezarsen Fast Track designation for the treatment of FCS in Q1 2023. In addition to FCS, Ionis is evaluating olezarsen for the treatment of severe hypertriglyceridemia (SHTG) in Phase 3 clinical trials.

About Ionis Pharmaceuticals, Inc.

For more than 30 years, Ionis has been a leader in RNA-targeted therapy, pioneering new markets and changing standards of care. Ionis currently has four marketed medicines and a promising late-stage pipeline highlighted by cardiovascular and neurological franchises. Our scientific innovation began and continues with the knowledge that sick people depend on us, which fuels our vision to become the leader in genetic medicine, utilizing a multi-platform approach to discover, develop and deliver life-transforming therapies.

To learn more about Ionis visit www.ionispharma.com and follow us on Twitter @ionispharma.

Ionis' Forward-looking Statements

This press release includes forward-looking statements regarding Ionis' business and the therapeutic and commercial potential of olezarsen, Ionis' technologies and other products in development. 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 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. 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, 2022, and the most recent Form 10-Q quarterly filing, which are on file with the Securities and Exchange Commission. Copies of these and other documents are available from the Company.

In this press release, unless the context requires otherwise, "Ionis," "Company," "we," "our," and "us" all refer to Ionis Pharmaceuticals and its subsidiaries.

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