Ionis announces positive topline results from Essence study of olezarsen in people with moderately elevated triglycerides

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– Olezarsen met the primary endpoint with a statistically significant mean reduction in triglycerides versus placebo at 80 mg and 50 mg doses –
– Olezarsen met all key secondary endpoints –
– Olezarsen demonstrated a favorable safety and tolerability profile –
– Nearly 1,500-person Phase 3 study supports the exposure database for olezarsen –
– Data from pivotal Phase 3 CORE and CORE2 studies of olezarsen in severe hypertriglyceridemia (sHTG) expected in Q3 2025 –

CARLSBAD, Calif.--(BUSINESS WIRE)--May 19, 2025-- Ionis Pharmaceuticals, Inc. (Nasdaq: IONS) today announced positive topline results from the Essence study of olezarsen in people with moderate hypertriglyceridemia (fasting triglycerides ≥150 mg/dL to <500 mg/dL) with or at risk for atherosclerotic cardiovascular disease (ASCVD). Nearly all the participants were on current standard of care lipid-lowering medicines. The trial met its primary endpoint with a statistically significant placebo-adjusted 61% and 58% reduction in triglyceride (TG) levels at 6 months with the 80 mg and 50 mg monthly doses, respectively ($p < 0.0001$). Olezarsen also met all key secondary endpoints in the study. The vast majority of participants reached <150mg/dL, reflecting a reduction to normal TG levels. Olezarsen demonstrated a favorable safety and tolerability profile in the study. Ionis plans to submit an abstract for presentation at an upcoming scientific conference. Data from the pivotal Phase 3 CORE and CORE2 studies evaluating olezarsen for the treatment of severe hypertriglyceridemia (sHTG) are expected in Q3 2025.

“The positive results of this study are an important step in bringing forward a potential new treatment for people with severely elevated triglycerides. Following the FDA approval and encouraging launch of TRYNGOLZA (olezarsen) for people living with familial chylomicronemia syndrome (FCS), a rare, genetic form of severely elevated TGs, these data support olezarsen’s potential to benefit the much broader population of people living with sHTG,” said Sam Tsimikas, M.D., senior vice president, global cardiovascular development at Ionis. “We look forward to seeing the results of our pivotal Phase 3 studies, CORE and CORE2, in Q3 2025, which will be the basis for our potential sNDA filing in sHTG by year-end.”

Olezarsen demonstrated a favorable safety and tolerability profile in the study. The most common treatment-emergent adverse event that occurred more frequently than placebo in the olezarsen groups was injection site reactions, with the majority being mild in severity.

About the Essence Study
The Phase 3 global, multicenter, randomized, double-blind, placebo-controlled study (Essence-TIMI 73b), conducted with Ionis’ research partner, The TIMI Study Group, supports the exposure database for olezarsen (NCT05610280). Essence enrolled 1,478 participants aged 18 and older with moderate hypertriglyceridemia (HTG), defined as fasting triglyceride levels ≥150 mg/dL to <500 mg/dL, who were diagnosed with or at risk for atherosclerotic cardiovascular disease (ASCVD). A small percentage of participants (9%) had fasting triglycerides ≥500 mg/dL at baseline. Participants in the study received stable and optimized standard of care lipid-lowering therapies for at least four weeks prior to screening. Participants were randomized to receive 50 mg (n=276) or 80 mg (n=832) of olezarsen or placebo (n=369) every 4 weeks via subcutaneous injection for 12 months.

The primary endpoint was the percent change from baseline in fasting TG levels at six months compared to placebo. Key secondary endpoints included percent changes in triglyceride levels at 12 months, proportion of patients who achieve fasting TG<150 mg/dL and percent changes in other lipid parameters, including apoC-III, remnant cholesterol, non-HDL-C and apoB, compared to placebo over the treatment period.

About Hypertriglyceridemia
Triglycerides (TG) are a type of fat the body uses as a source of energy. While optimal levels for adults are typically below 150 mg/dL, levels higher than 150 mg/dL are a sign of hypertriglyceridemia. Levels higher than 500 mg/dL are a sign of a common condition called severe hypertriglyceridemia (sHTG), which puts millions of people at risk of potentially life-threatening acute pancreatitis (AP) and atherosclerotic cardiovascular disease (ASCVD) despite current standard of care. People with sHTG whose triglyceride levels are more than 880 mg/dL, including those with familial chylomicronemia syndrome (FCS), face a greater risk of AP.

About Olezarsen
Olezarsen is an investigational RNA-targeted medicine being evaluated for the treatment of 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. The investigational medicine is currently being evaluated in two Phase 3 clinical trials – CORE and CORE2 – for the treatment of sHTG. Olezarsen has not been approved for the treatment of sHTG by regulatory authorities.

Olezarsen was recently approved in the U.S. as an adjunct to diet to reduce triglycerides in adults with FCS under the tradename TRYNGOLZA™ (olezarsen). For more information about TRYNGOLZA, visitTRYNGOLZA.com.

U.S. INDICATION for TRYNGOLZA™ (olezarsen)
TRYNGOLZA is an adjunct to diet to reduce triglycerides in adults with familial chylomicronemia syndrome (FCS).

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS
TRYNGOLZA is contraindicated in patients with a history of serious hypersensitivity to TRYNGOLZA or any of the excipients in TRYNGOLZA. Hypersensitivity reactions requiring medical treatment have occurred.

WARNINGS AND PRECAUTIONS

Hypersensitivity Reactions
Hypersensitivity reactions (including symptoms of bronchospasm, diffuse erythema, facial swelling, urticaria, chills and myalgias) have been reported in patients treated with TRYNGOLZA. Advise patients on the signs and symptoms of hypersensitivity reactions and instruct patients to promptly seek medical attention and discontinue use of TRYNGOLZA if hypersensitivity reactions occur.

ADVERSE REACTIONS
The most common adverse reactions (incidence >5% of TRYNGOLZA-treated patients and >3% higher frequency than placebo) were injection site reactions, decreased platelet count and arthralgia.

Please see full Prescribing Information for TRYNGOLZA.

About Ionis Pharmaceuticals, Inc.
For three decades, Ionis has invented medicines that bring better futures to people with serious diseases. Ionis currently has six marketed medicines and a leading pipeline in neurology, cardiology and select 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), LinkedIn and Instagram.

Ionis Forward-looking Statements
This press release includes forward-looking statements regarding Ionis' business and the therapeutic and commercial potential of our commercial medicines, olezarsen, 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 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 December 31, 2024, and most recent Form 10-Q, 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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