Groundbreaking pivotal study results of olezarsen for severe hypertriglyceridemia (sHTG) presented as a late breaker at AHA Scientific Sessions

November 8, 2025

– Up to 72% placebo-adjusted mean reduction in fasting triglyceride levels at six months, with reductions sustained through 12 months –

– 86% of olezarsen-treated patients achieved triglyceride levels less than 500 mg/dL, below the risk threshold for acute pancreatitis –

– First and only investigational treatment for sHTG to significantly reduce acute pancreatitis events –

– Data simultaneously published in *The New England Journal of Medicine* –

– Ionis to host webcast today at 3:00 p.m. ET–

CARLSBAD, Calif.--(BUSINESS WIRE)--Nov. 8, 2025-- Ionis Pharmaceuticals, Inc. (Nasdaq: IONS) today announced positive results from the pivotal Phase 3 CORE and CORE2 studies of olezarsen in people with severe hypertriglyceridemia (sHTG). The studies met the primary endpoint, with olezarsen achieving a highly statistically significant placebo-adjusted mean reduction in fasting triglyceride (TG) levels of up to 72% at six months. The reductions were sustained through 12 months. Olezarsen showed a highly statistically significant 85% reduction in acute pancreatitis events, the first and only time achieved in sHTG. Additionally, 86% of olezarsen-treated patients achieved triglyceride levels less than 500 mg/dL, below the risk threshold for acute pancreatitis. Olezarsen demonstrated favorable safety and tolerability.

These data were presented today during a late-breaking session at the American Heart Association (AHA) Scientific Sessions, taking place November 7-10 in New Orleans, and simultaneously published in *The New England Journal of Medicine*.

“CORE and CORE2 are the first studies to show a significant reduction in acute pancreatitis events in sHTG, with most patients on olezarsen achieving triglyceride levels below the risk threshold for these potentially life-threatening episodes,” said Nicholas Marston, M.D., M.P.H, presenting author, cardiologist, Brigham and Women's Hospital, Harvard Medical School. “As a lipid specialist who takes care of sHTG patients, I have seen the major consequences of acute pancreatitis, including cases with recurrent events requiring frequent hospitalizations. Given the modest effects of conventional therapies, these impactful data are a welcome advance and underscore the potential of olezarsen to transform the way we treat sHTG.”

Nearly 1,100 patients were enrolled in the CORE and CORE2 studies, which is the largest pivotal program ever conducted in sHTG, and patients were required to be on standard of care lipid-lowering therapy. The CORE and CORE2 studies met the primary endpoint across doses, with olezarsen demonstrating an up to 72% ($p<0.001$) placebo-adjusted mean reduction in fasting triglyceride levels at six months. The reductions were sustained through 12 months. Additionally, among patients with baseline levels above these thresholds at 12 months:

- **TGs <880 mg/dL:** 89% and 88% of patients on olezarsen 50 mg and 80 mg, respectively, achieved triglyceride levels less than 880 mg/dL, the level associated with the highest risk of acute pancreatitis.
- **TGs <500 mg/dL:** 86% of patients on olezarsen 50 mg and 80 mg achieved triglyceride levels less than 500 mg/dL, below the risk threshold for sHTG and acute pancreatitis.
- **TGs <150 mg/dL:** 34% and 54% of patients on olezarsen 50 mg and 80 mg, respectively, achieved normal triglyceride levels less than 150 mg/dL.

Olezarsen demonstrated a highly statistically significant 85% reduction in adjudicated acute pancreatitis events at 12 months ($p<0.001$). These results were based on a total of 22 events in 17 patients in the placebo group, compared to seven events in five patients in the olezarsen group.

- In an overall pooled analysis of the number of patients needed to treat (NNT), treating 20 patients with olezarsen is estimated to prevent one acute pancreatitis event over one year.
- In the highest risk group, patients with triglyceride levels greater than or equal to 880 mg/dL and a history of acute pancreatitis, treating four patients is estimated to prevent one event over one year.

Olezarsen also showed an overall favorable lipid profile, with significant reductions in the secondary endpoints of apoC-III, remnant cholesterol and non-HDL-C.

“Building on olezarsen’s success in treating familial chylomicronemia syndrome, a rare form of sHTG, these groundbreaking results position us to reach a significantly larger patient population who remain at risk of dangerous acute pancreatitis attacks,” said Brett P. Monia, Ph.D., chief executive officer, Ionis. “Olezarsen will be one of two independent launches for Ionis in 2026, our first in a broad population if approved, and is a powerful example of how we are turning groundbreaking science into meaningful medicines that have the potential to change lives.”

Olezarsen demonstrated a favorable safety and tolerability profile in the CORE and CORE2 studies. Adverse events were balanced across treatment arms (75% olezarsen 50 mg; 76% olezarsen 80 mg; 75% placebo). Serious adverse events occurred less frequently in the olezarsen group compared to placebo (9% olezarsen 50 mg; 11% olezarsen 80 mg; 14% placebo). The most common treatment-emergent events were injection site reactions, which were mostly mild and occurred more frequently with olezarsen (10% olezarsen 50 mg; 17% olezarsen 80 mg; 1% placebo).

Several additional parameters were generally consistent with previous study results. At the 80 mg dose, asymptomatic increases in liver enzymes ≥3 times the upper limit of normal occurred in 7% of patients compared to 2% in the placebo group. These were not associated with clinical complications and generally resolved with continued dosing. No cases met the criteria for Hy’s law. Consistent with previously reported results with apoC-III-targeting therapies, small absolute mean elevations in liver fat (2.28% olezarsen 50 mg; 4.18% olezarsen 80 mg; 0.14% placebo) and hemoglobin A1c (HbA1c) (0.25% olezarsen 50 mg; 0.24% olezarsen 80 mg; placebo-adjusted) were observed. Increases in liver fat were not correlated with transaminase elevations and were not associated with clinical sequelae. There were no imbalances in HbA1c in non-diabetic patients.

Ionis is on track to submit a supplemental new drug application for both the 50 mg and 80 mg doses to the FDA by the end of the year. An open-label extension (OLE) study of olezarsen for sHTG is ongoing. More than 90% of patients who completed CORE and CORE2 chose to continue into the OLE.

Webcast

Ionis will host a webcast to discuss the results from the CORE and CORE2 studies on Saturday, November 8 at 3:00 p.m. ET. Interested parties may access the webcast here. A webcast replay will be available for a limited time.

About the CORE and CORE2 Studies

CORE (NCT05079919; n=617) and CORE2 (NCT05552326; n=446), conducted with The TIMI Study Group, are Phase 3 global, multicenter, randomized, double-blind, placebo-controlled trials investigating the safety and efficacy of olezarsen for severe hypertriglyceridemia (sHTG). Participants aged 18 and older with triglyceride levels ≥500 mg/dL were enrolled. Participants were required to be on standard of care therapies for elevated triglycerides. At baseline, 47% and 37% of participants had baseline fasting triglycerides ≥880 mg/dL in CORE and CORE2, respectively. Participants were randomized to receive 50 mg or 80 mg of olezarsen or placebo every 4 weeks via subcutaneous injection for 12 months. The primary endpoint is the percent change from baseline in fasting triglycerides at six months compared to placebo.

About Severe Hypertriglyceridemia

Severe hypertriglyceridemia (sHTG) is defined by severely high triglycerides (≥500 mg/dL) and characterized by an increased risk of acute pancreatitis and other morbidities. Considered a medical emergency, acute pancreatitis causes debilitating abdominal pain that often requires prolonged hospitalization, can lead to permanent organ damage and can become life-threatening. Preventing the first attack is key. In people with a history of acute pancreatitis episodes, the risk of future attacks is even greater. Current standard of care therapies for sHTG and lifestyle modifications (such as diet and exercise) do not sufficiently or consistently lower triglyceride levels or reduce the risks of sHTG in all patients. Approximately 3 million people are living with sHTG in the U.S., including more than 1 million who are considered high risk. High-risk sHTG includes those with triglycerides ≥880 mg/dL or triglycerides ≥500 mg/dL and a history of acute pancreatitis or other comorbidities.

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. Olezarsen is approved in the U.S. and the European Union as TRYNGOLZA® for adults with familial chylomicronemia syndrome (FCS).

About Ionis Pharmaceuticals, Inc.

For three decades, Ionis has invented medicines that bring better futures to people with serious diseases. Ionis currently has marketed medicines and a leading pipeline in neurology, cardiometabolic disease 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, the therapeutic and commercial potential of our commercial medicines, olezarsen, additional medicines in development and technologies, and our expectations regarding development and regulatory milestones. 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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