Olezarsen significantly reduces triglycerides and acute pancreatitis events in landmark pivotal studies for people with severe hypertriglyceridemia (sHTG)

September 2, 2025

– Up to 72% (p<0.0001) placebo-adjusted mean reduction in fasting triglycerides –

– 85% (p=0.0002) reduction in acute pancreatitis events, the first and only time achieved for the treatment of sHTG –

– Favorable safety and tolerability profile –

– sNDA submission planned by end of year –

– Ionis to host webcast today at 8:30 a.m. ET –

CARLSBAD, Calif.--(BUSINESS WIRE)--Sep. 2, 2025-- Ionis Pharmaceuticals, Inc. (Nasdaq: IONS) today announced positive topline results from the pivotal Phase 3 CORE and CORE2 studies of olezarsen in people with severe hypertriglyceridemia (sHTG). In the studies, olezarsen demonstrated a highly statistically significant placebo-adjusted mean reduction in fasting triglycerides of up to 72% and a highly statistically significant reduction in acute pancreatitis events of 85% with favorable safety and tolerability. CORE and CORE2 make up the largest pivotal program for sHTG, with nearly 1,100 patients who were required to be on standard of care lipid-lowering therapy throughout the treatment period.

“These data are groundbreaking, demonstrating that olezarsen is the first therapy for sHTG to significantly reduce acute pancreatitis events,” said Sam Tsimikas, M.D., senior vice president, global cardiovascular development, Ionis. “Despite current standard of care and lifestyle changes, people with sHTG – who could have triglyceride levels reaching into the thousands – remain vulnerable to unpredictable and life-threatening acute pancreatitis attacks. These results reinforce our confidence that olezarsen has the potential to change the sHTG treatment paradigm.”

The CORE and CORE2 studies met the primary endpoint, with both 80 mg and 50 mg monthly doses of olezarsen demonstrating a highly statistically significant placebo-adjusted mean reduction in fasting triglyceride levels at six months:

	Olezarsen 80 mg	Olezarsen 50 mg	Placebo
CORE			
Percent reduction from baseline[1]	73%	63%	0.5%
Percent placebo-adjusted reduction[2]	**72%**	**63%**	
P-value[3]	p<0.0001	p<0.0001	
CORE2			
Percent reduction from baseline[1]	68%	63%	14%
Percent placebo-adjusted reduction[2]	**55%**	**49%**	
P-value[3]	p<0.0001	p<0.0001	

1. Least-squares mean. 2. Least-squares mean difference of percent reduction in fasting triglycerides. 3. P-values are based on comparison between each olezarsen group and placebo group in percent reduction in fasting triglycerides.

Additionally, the studies met the secondary endpoint of reduction in acute pancreatitis events. Olezarsen demonstrated a highly statistically significant 85% reduction in events (p=0.0002) compared to placebo. This was a prespecified analysis of pooled olezarsen groups compared to pooled placebo groups across both studies at 12 months.

“Building on our success in familial chylomicronemia syndrome, the exceptional CORE and CORE2 results position Ionis to set a new treatment standard for the many people with sHTG who are at risk of debilitating acute pancreatitis attacks,” said Brett P. Monia, Ph.D., chief executive officer, Ionis. “If approved, olezarsen for sHTG will mark our third independent launch in under two years and our first launch in a prevalent population, marking a major step forward in delivering transformative care to those who need it most.”

Olezarsen demonstrated a favorable safety and tolerability profile. Adverse events were generally balanced across treatment groups, and serious adverse events occurred less frequently in the olezarsen groups compared to placebo. Injection site reactions,

which were mostly mild, were the most common adverse event and occurred more frequently in the olezarsen groups compared to placebo. More than 90% of patients who completed CORE and CORE2 chose to continue into the open-label extension study.

Ionis plans to submit a supplemental new drug application (sNDA) to the U.S. Food and Drug Administration by end of year. Detailed data will be presented at an upcoming medical conference.

Essence study data published in NEJM and presented at ESC Congress

Detailed data from the Phase 3 Essence study evaluating olezarsen in people with moderate hypertriglyceridemia (fasting triglycerides ≥150 mg/dL) and elevated cardiovascular risk were recently published in *The New England Journal of Medicine* (NEJM) and presented during a Hot Line session at the European Society of Cardiology (ESC) Congress. Olezarsen met the primary endpoint, demonstrating a statistically significant reduction in fasting triglyceride levels at six months, and all key secondary endpoints. Olezarsen demonstrated a favorable safety and tolerability profile, and the approximately 1,500-person study supports the olezarsen safety database.

Webcast

Ionis will host a webcast to discuss the topline results from the CORE and CORE2 studies on Tuesday, September 2 at 8:30 a.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 throughout the treatment period. 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.

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. as TRYNGOLZA® as an adjunct to diet to reduce triglycerides in adults with familial chylomicronemia (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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