Ionis announces positive topline results from pivotal study of zilganersen in Alexander disease

September 22, 2025

– First and only investigational medicine to demonstrate a clinically meaningful and disease-modifying impact on this rare, often fatal neurological condition –

– NDA submission planned in Q1 2026 –

CARLSBAD, Calif.--(BUSINESS WIRE)--Sep. 22, 2025-- Ionis Pharmaceuticals, Inc. (Nasdaq: IONS) today announced positive topline results from the pivotal study of zilganersen in children and adults living with Alexander disease (AxD), a rare, progressive and often fatal neurological condition with no approved disease-modifying treatments. Zilganersen 50 mg demonstrated statistically significant and clinically meaningful stabilization on the primary endpoint of gait speed as assessed by the 10-Meter Walk Test (10MWT) compared to control at week 61 (mean difference 33.3%, p=0.0412) with favorable safety and tolerability. Zilganersen also demonstrated consistent benefit in key secondary endpoints. These data mark the first time an investigational medicine has shown a positive disease-modifying impact in AxD.

“These unprecedented results highlight the potential of zilganersen to create new possibilities for people living with Alexander disease, a devastating, progressive and often fatal condition that most commonly begins in early childhood and can take away fundamental functions like walking, speaking and swallowing,” said Holly Kordasiewicz, Ph.D., senior vice president of neurology, Ionis. “These data demonstrate the promise of zilganersen to potentially transform the future treatment landscape for this condition and reinforce the power of our technology to address neurological diseases by directly targeting the underlying cause. We are deeply grateful to the patients, families and researchers whose participation has helped make this progress possible."

In addition to achieving the primary endpoint, zilganersen demonstrated consistent favorable trends across key secondary endpoints, indicating evidence of slowed disease progression, stabilization or improvement. Key secondary endpoints include change from baseline in patients' self-identified Most Bothersome Symptom (MBS) Score, Patient Global Impression of Severity (PGIS) Score, Patient Global Impression of Change (PGIC) Score and Clinician Global Impression of Change (CGIC) Score.

“Today’s news is a monumental step forward in advancing a potential treatment for Alexander disease, offering long-awaited hope for people living with this condition, their families and the community,” said Brett P. Monia, Ph.D., chief executive officer, Ionis. “These data show the power of Ionis' innovation to once again potentially establish a treatment standard for a devastating condition where none currently exists. Building on our legacy of delivering transformational treatments for spinal muscular atrophy and SOD1-amyotrophic lateral sclerosis, this outcome further underscores the strength of our proven platform to address severe neurological diseases. We look forward to working closely with the FDA to bring this wholly owned potential treatment forward for individuals and families in urgent need.”

Zilganersen demonstrated a favorable safety and tolerability profile, with most adverse events (AE) being mild or moderate in severity. Incidence of serious adverse events (SAEs) was numerically lower in the zilganersen arm as compared to the control arm.

Ionis plans to submit a new drug application (NDA) to the U.S. Food and Drug Administration in Q1 2026 and is evaluating the potential to initiate an Expanded Access Program (EAP) in the U.S. Detailed data will be presented at an upcoming medical conference.

About the Zilganersen Study

The global, multicenter, randomized, double-blind, controlled, multiple-ascending dose (MAD) Phase 1-3 study (NCT04849741) enrolled 54 participants with Alexander disease (AxD) between the ages of 1.5 and 53 years across 13 sites in eight countries. Most participants in the study were children, reflecting the early onset and severe progression of AxD in pediatric populations. Participants were randomized in a 2:1 ratio to receive zilganersen or control for a 60-week double-blind treatment period. The study included two dose cohorts, 25 mg and 50 mg, with the 50 mg dose cohort analyzed as the pivotal dose cohort, with dosing every 12 weeks. At 60 weeks, all eligible participants transitioned into an open-label treatment period, followed by a 120-week open-label, long-term extension treatment period, during which participants in the 25 mg dose cohort moved to the 50 mg dose cohort, and finally a 28-week post-treatment follow-up period. The primary endpoint is percent change from baseline in gait speed as assessed by the 10-Meter Walk Test (10MWT), an assessment of functional mobility, at the end of the double-blind treatment period. Key secondary endpoints include change from baseline in patients' self-identified Most Bothersome Symptom (MBS)

Score, Patient Global Impression of Severity (PGIS) Score, Patient Global Impression of Change (PGIC) Score and Clinician Global Impression of Change (CGIC) Score at the end of the double-blind treatment period.

About Zilganersen (ION373)

Zilganersen is an investigational antisense oligonucleotide medicine being evaluated as a treatment for people with genetically confirmed Alexander disease (AxD). Zilganersen is designed to stop production of excess glial fibrillary acidic protein (GFAP) that accumulates because of disease-causing variants in the *GFAP* gene. In 2020, the U.S. Food and Drug Administration (FDA) granted zilganersen Orphan Drug designation and Rare Pediatric designation. In addition, the European Medicines Agency (EMA) granted zilganersen Orphan Drug designation in 2019.

About Alexander Disease (AxD)

AxD is a rare, progressive and often fatal neurological disease that occurs in approximately 1 per 1 to 3 million people worldwide and affects a type of cell in the brain called astrocytes. Astrocytes have multiple roles in the brain to support neurons and oligodendrocytes, including maintenance of the myelin sheath that protects nerve fibers. AxD is caused by disease-causing variants in the glial fibrillary acidic protein (*GFAP*) gene and is generally characterized by progressive neurological deterioration resulting in loss of functional mobility, loss of independence and the inability to control muscles for large movements, swallowing and airway protection, though symptoms can vary depending on age of onset. AxD usually leads to death within 14-25 years after symptom onset. There are no approved disease-modifying medicines.

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 and the therapeutic and commercial potential of zilganersen, our commercial medicines, 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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