Ionis presents new data from pivotal study of zilganersen in Alexander disease (AxD) at AAN 2026 Annual Meeting

April 21, 2026

– New data highlight potential treatment benefit across multiple AxD symptom domains, reinforcing zilganersen's positive impact on people living with this rare, often fatal neurological disease –

– PDUFA date set for September 22, 2026 –

CARLSBAD, Calif.--(BUSINESS WIRE)--Apr. 21, 2026-- Ionis Pharmaceuticals, Inc. (Nasdaq: IONS) today announced additional positive 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. These findings, which will be presented today at the 2026 American Academy of Neurology (AAN) annual meeting, build on previously reported positive topline data and provide a more comprehensive view of treatment effect across multiple clinically meaningful domains.

The study met its primary endpoint in individuals ≥5 years of age, with zilganersen 50 mg demonstrating statistically significant and clinically meaningful stabilization of gait speed as assessed by the 10-Meter Walk Test (10MWT), compared to control at Week 61. The 10MWT is a commonly used measure of gross motor function in neurologic disease. New data from the Gross Motor Function Measure-88 (GMFM-88), a well-established motor endpoint, supports the primary outcome of the study by demonstrating that treatment with zilganersen may improve gross motor function in younger children (2-4 years of age), compared to control. Key secondary endpoint results from patient/caregiver- and clinician-reported outcome assessments consistently favored zilganersen. Zilganersen demonstrated favorable safety and tolerability.

"As a clinician who cares for people living with Alexander disease, I see firsthand the profound and progressive impact this disease has on individuals and their families, particularly given the lack of disease modifying treatment options available today," said Amy Waldman, M.D., pediatric neurologist and lead investigator for the zilganersen study at Children's Hospital of Philadelphia. "These results mark a meaningful step forward for families who have waited so long for innovation in Alexander disease. Taken together, the consistent pattern across multiple clinically meaningful measures demonstrates that zilganersen has the potential to change the trajectory of this devastating disease."

AxD is a rare, genetic, progressive and often fatal neurological condition that is primarily associated with toxic over-production of glial fibrillary acidic protein (GFAP). It is estimated to occur in approximately 1 per 1 to 3 million people worldwide. Although symptoms vary depending on age of onset, individuals may experience progressive motor and cognitive dysfunction, a loss of independence and the inability to control muscles for swallowing, airway protection and purposeful movements. Zilganersen is an investigational RNA-targeted medicine designed to reduce overproduction of GFAP, the underlying cause of AxD.

Zilganersen Pivotal Study Results

The pivotal Phase 1-3 study of zilganersen included 53 people with AxD aged 2 to 53 years. Results presented today are from the 60-week double-blind, randomized controlled treatment period of the ongoing trial. Zilganersen met the primary endpoint in patients ≥5 years, resulting in statistically significant and clinically meaningful stabilization of gait speed on the 10MWT at Week 61 compared to control (least square mean difference 33.3%, p=0.041). Additionally, results from the GMFM-88 in children 2-4 years of age support that zilganersen may improve gross motor function at Week 61 compared to control (least square mean difference 22.9 points, nominal[1] p=0.034).

Key secondary endpoints favored zilganersen over control:

Key secondary endpoints evaluated the disease's heterogeneous presentation through assessments focused on the individual's most bothersome AxD symptom and their overall health. Across these measures, outcomes favored zilganersen-treated individuals, with more reporting improvement or no change and fewer reporting worsening compared to control.

- **Most Bothersome Symptom (MBS):**
  In the zilganersen group, 32% of patients rated their most bothersome symptom as "much better" compared to 0% on control. Only 5% of patients receiving zilganersen rated their most bothersome symptom as "much worse" compared to 31% on control.

- **Patient Global Impression of Severity (PGIS):**
  In the zilganersen group, 83% of patients reported improvement or no change in overall disease severity compared to 76%

on control. Only 17% of patients receiving zilganersen reported worsening compared to 24% on control.

- **Patient Global Impression of Change (PGIC):**
  In the zilganersen group, 21% of patients reported feeling “much better” overall compared to 0% on control. Only 4% of patients receiving zilganersen reported feeling “much worse” compared to 18% on control.

- **Clinical Global Impression of Change (CGIC):**
  Clinicians rated 75% of patients receiving zilganersen as improved (“a little better”) or “no change” compared to 47% on control. Clinicians rated 25% of patients receiving zilganersen as “a little worse” and 0% as “much worse” compared to 41% as “a little worse” and 12% as “much worse” on control.

Results from additional secondary and exploratory endpoints assessing communication, swallowing, gastrointestinal and autonomic symptoms, consistently support that zilganersen may have a positive impact across AxD symptoms.

In an exploratory analysis, zilganersen reduced plasma GFAP levels by 33.6% at Week 61 compared to control (nominal[1] p=0.003)[2], consistent with its mechanism of targeting *GFAP* RNA in the central nervous system.

“These data further build on the promise of zilganersen and reinforce its potential to help transform the treatment landscape for people living with Alexander disease,” said Holly Kordasiewicz, Ph.D., executive vice president, chief development officer, Ionis. “The zilganersen results underscore the strength of our technology in targeting the underlying cause of disease, even in complex and heterogenous neurological conditions such as Alexander disease. We are deeply grateful to the patients, families, investigators and broader community who made this research possible. As we look ahead to the FDA action date in September, we remain focused on bringing this potential new treatment to a community that has long been underserved.”

Zilganersen demonstrated a favorable safety and tolerability profile, with most adverse events (AE) mild or moderate in severity. Serious treatment-emergent adverse events (TEAEs) occurred less frequently in the zilganersen group compared to control (37.5% zilganersen 25 mg or 50 mg; 47.1% pooled control).

Zilganersen is currently under Priority Review by the U.S. Food and Drug Administration (FDA) with a Prescription Drug User Fee Act (PDUFA) action date of September 22, 2026.

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[1] Nominal p-value; statistical analysis was not controlled for multiplicity

[2] Ratio (zilganersen vs. pooled control) of least-squares geometric mean ratio to baseline 0.664

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 patients' self-identified Most Bothersome Symptom (MBS) Score, change from baseline in Patient Global Impression of Severity (PGIS) Score and 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

Zilganersen is an investigational RNA-targeted medicine being evaluated as a treatment for people with Alexander disease (AxD). Zilganersen is designed to inhibit production of excess glial fibrillary acidic protein (GFAP) that accumulates because of disease-causing variants in the *GFAP* gene. The U.S. Food and Drug Administration (FDA) granted zilganersen Breakthrough Therapy, Orphan Drug and Rare Pediatric Disease designations. In addition, the European Medicines Agency (EMA) granted zilganersen Orphan Drug designation.

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 Neurology

Ionis has been at the forefront of discovering and developing leading neurological disease medicines, including SPINRAZA® (nusinersen), the first approved treatment for spinal muscular atrophy, WAINUA® (eplontersen), a medicine to treat hereditary transthyretin-mediated amyloid polyneuropathy (ATTRv-PN), and QALSODY® (tofersen) for SOD1-ALS. The clinical-stage portfolio includes 12 investigational medicines, of which six are wholly owned by Ionis. Ionis' investigational portfolio includes medicines for which there are few or no disease modifying treatments, such as rare diseases including Angelman syndrome, prion disease, multiple system atrophy, Huntington's disease and Alexander disease, as well as more common conditions such as Alzheimer's disease.

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, 2025, which is 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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Ionis Investor Contact:
D. Wade Walke, Ph.D.
IR@ionis.com
760-603-2331

Ionis Media Contact:
Hayley Soffer
media@ionis.com
760-603-4679

Source: Ionis Pharmaceuticals, Inc.