Ionis receives U.S. FDA Breakthrough Therapy designation for zilganersen for Alexander disease (AxD)

December 2, 2025

– First and only investigational medicine for this rare, often fatal neurological condition –

– On track to submit new drug application (NDA) in Q1 2026 –

CARLSBAD, Calif.--(BUSINESS WIRE)--Dec. 2, 2025-- Ionis Pharmaceuticals, Inc. (Nasdaq: IONS) today announced that the U.S. Food and Drug Administration (FDA) has granted Breakthrough Therapy designation to zilganersen for the treatment of Alexander disease (AxD), a rare, progressive and often fatal neurological condition. Over time, it can lead to loss of mobility and independence, along with difficulties walking, speaking, swallowing and breathing. There are currently no approved disease-modifying treatments for AxD. Breakthrough Therapy designation is intended to expedite the review of medicines that treat a serious or life-threatening condition and have shown preliminary clinical evidence indicating the potential for substantial improvement over available therapies.

“People living with Alexander disease have gone far too long without a treatment capable of changing the course of their disease, which makes this Breakthrough Therapy designation particularly meaningful,” said Holly Kordasiewicz, Ph.D., senior vice president of neurology, Ionis. “Our pivotal zilganersen study provides the first evidence that an investigational treatment can modify the underlying disease and improve outcomes, representing an important step forward for the Alexander disease community. We are deeply grateful to the individuals, families, caregivers and investigators who made this progress possible, and we are committed to working closely with the FDA to bring this potential treatment to those in urgent need.”

The FDA’s designation is supported by the topline results from the pivotal study of zilganersen in children and adults living with AxD. In the study, 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.

“Receiving back-to-back Breakthrough Therapy designations for olezarsen in severe hypertriglyceridemia and zilganersen in Alexander disease demonstrates how Ionis’ innovation can make a transformative difference for people living with serious diseases,” said Brett P. Monia, Ph.D., chief executive officer, Ionis. “We look forward to independently bringing both these medicines to patients in 2026. Our marketed medicines and exceptional late-stage pipeline of wholly owned and partnered medicines position Ionis for accelerating revenue growth and substantial value creation.”

Ionis plans to submit an NDA to the U.S. FDA in Q1 2026 and is working to initiate an Expanded Access Program (EAP) in the U.S.

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

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. The U.S. Food and Drug Administration (FDA) granted zilganersen Breakthrough Therapy, Orphan Drug and Rare Pediatric 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 11 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, 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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Source: Ionis Pharmaceuticals, Inc.