Ionis completes enrollment in pivotal trial evaluating zilganersen in people living with Alexander disease

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- *Zilganersen is the first investigational medicine in clinical development for people with Alexander disease, a rare, life-threatening neurological condition*

CARLSBAD, Calif., July 18, 2024 /PRNewswire/ -- Ionis Pharmaceuticals, Inc. (Nasdaq: IONS) announced today that it has completed enrollment in the pivotal trial of zilganersen (ION373), an investigational RNA-targeted medicine in development for the treatment of children and adults with a rare, progressive and ultimately fatal neurological disorder known as Alexander disease (AxD). The primary endpoint is percent change from baseline in gait speed as assessed by the 10-Meter Walk Test (10MWT). Topline data are anticipated in the second half of 2025.

AxD is estimated to occur in an estimated one in one million people in the U.S. and can present throughout life.[1-3] The disease is a result of genetic variants in the glial fibrillary acidic protein (*GFAP*) gene that disrupt the structure and function of astrocytes in the brain. AxD is generally characterized by cognitive dysfunction and progressive neurologic deterioration, including loss of independence and the ability to control muscles for large movements, swallowing and airway protection. Zilganersen is designed to stop the excess GFAP that accumulates because of disease-causing variants in the *GFAP* gene, with the goal of slowing or stabilizing disease progression in people living with AxD.

"Current approaches to disease management for Alexander disease can mitigate some symptoms of AxD but do not address the underlying cause or slow disease progression. Our zilganersen study is the first trial to evaluate an investigational medicine designed to address the underlying cause of Alexander disease," said Eugene Schneider, M.D., executive vice president and chief clinical development officer at Ionis. "We are grateful for the dedication and support from the patients, families and investigators in the Alexander disease community, whose partnership has made this milestone possible."

About the Zilganersen Study
The global, multicenter, randomized, double-blind, controlled, multiple-ascending dose (MAD) is a Phase 1-3 study (NCT04849741), which enrolled patients aged two to 65 with Alexander disease (AxD) across 13 sites in eight countries. Participants were randomized in a 2:1 ratio to receive zilganersen or control for a 60-week double-blind treatment period. At 60 weeks, all participants will receive zilganersen for a 180-week open-label treatment period, followed by 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) at the end of the double-blind treatment period. 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.

The study includes an open-label sub-study in eligible participants under the age of two years with AxD, which will continue to enroll into 2025.

About Zilganersen (ION373)
Zilganersen is an investigational antisense oligonucleotide medicine being developed as a potential treatment for people with genetically confirmed Alexander disease (AxD). Zilganersen is designed to stop the excess glial fibrillary acidic protein (GFAP) production 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 ultimately fatal neurological disease that 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 cognitive dysfunction and progressive neurologic deterioration, including loss of independence and the ability 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 disease modifying medicines approved for patients.

About Ionis Pharmaceuticals, Inc.
For three decades, Ionis has invented medicines that bring better futures to people with serious diseases. Ionis currently has five marketed medicines and a leading pipeline in neurology, cardiology, and other 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) and LinkedIn.

Ionis Forward-looking Statements
This press release includes forward-looking statements regarding Ionis' business, and the therapeutic and commercial potential of Ionis' commercial medicines, zilganersen, additional medicines in development and technologies. 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 but not limited to those related to our commercial products and the medicines in our pipeline, and particularly 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 Dec. 31, 2023, and most recent Form 10-Q, which are on file with the SEC. Copies of these and other documents are available at www.Ionis.com.

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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