Ionis receives U.S. FDA Breakthrough Therapy designation for ION582 in Angelman syndrome

September 9, 2025

- Pivotal Phase 3 REVEAL study enrollment on track to complete in 2026 -

CARLSBAD, Calif.--(BUSINESS WIRE)--Sep. 9, 2025-- Ionis Pharmaceuticals, Inc. (Nasdaq: IONS) today announced that the U.S. Food and Drug Administration (FDA) has granted Breakthrough Therapy designation to ION582 for the treatment of Angelman syndrome (AS), a rare neurological disease that often presents in infancy and is characterized by profound intellectual disability, impaired communication, motor impairment and debilitating seizures.

“With no approved disease-modifying treatments available for people living with Angelman syndrome, receiving this Breakthrough Therapy designation for ION582 underscores both the severity of this disease and the significant unmet need for treatment,” said Holly Kordasiewicz, Ph.D., senior vice president of neurology, Ionis. “This recognition also highlights the potential of ION582 to deliver meaningful benefits for individuals with Angelman syndrome. We are deeply grateful to the Angelman syndrome community and investigators who have made this progress possible, and we remain committed to advancing ION582 as quickly as possible to bring this potential treatment to those in need.”

This Breakthrough Therapy designation is based on results from the Phase 1/2 HALOS study of ION582 that showed consistent and encouraging clinical improvement on all AS functional domains including communication, cognition and motor function, as well as favorable safety and tolerability. 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.

Ionis initiated the global Phase 3 REVEAL study (NCT06914609) of ION582 earlier this year, which is anticipated to enroll children and adults with AS that have a maternal *UBE3A* gene deletion or mutation.

About ION582

ION582 is an investigational RNA-targeted antisense medicine designed to inhibit the expression of the UBE3A antisense transcript (UBE3A-ATS) and increase production of UBE3A protein, for the potential treatment of Angelman syndrome (AS). The U.S. Food and Drug Administration (FDA) and European Medicines Agency (EMA) granted Orphan Drug designation to ION582. Additionally, the FDA granted Fast Track and Rare Pediatric designations to ION582.

About Angelman Syndrome (AS)

AS is a rare, genetic neurological disease that affects an estimated 1 in 21,000 people worldwide and is caused by the loss of function of the maternal *UBE3A* gene. AS typically presents in infancy and is characterized by profound intellectual disability, balance issues, motor impairment and debilitating seizures. Most people with AS are unable to speak. Individuals with AS have a normal lifespan but require complete care from a caregiver. Some symptoms can be managed with existing medicines; however, there are no approved disease modifying therapies.

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 13 investigational medicines, of which eight 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 ION582, our commercial medicines, 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 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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