First patient dosed in pivotal Phase 3 REVEAL clinical study of ION582 in Angelman syndrome

June 11, 2025

- Completion of enrollment anticipated in 2026 -

CARLSBAD, Calif.--(BUSINESS WIRE)--Jun. 11, 2025-- Ionis Pharmaceuticals, Inc. (Nasdaq: IONS) today announced that the first participant has been dosed in the global Phase 3 REVEAL study, which is designed to evaluate the efficacy and safety of ION582, an investigational medicine for the treatment of people living with Angelman syndrome (AS), a serious and rare neurodevelopmental disorder that leads to significant physical and cognitive impairments.

"Dosing the first person with Angelman syndrome in our pivotal REVEAL study marks an important milestone for this underserved community, who currently have no approved disease modifying treatments," said Holly Kordasiewicz, Ph.D., senior vice president of neurology, Ionis. "This placebo-controlled study will evaluate ION582 in both children and adults with either UBE3A deletion or mutation and builds on earlier encouraging findings from our Phase 1/2 HALOS study. This milestone reflects our commitment to those impacted by Angelman syndrome and builds on our legacy of innovation in neurology including the development of SPINRAZA and QALSODY. With ION582, we continue to advance our leading wholly owned neurology pipeline, which includes eight medicines in clinical development across a range of rare and more prevalent diseases."

REVEAL (NCT06914609) is a global, randomized, double-blind, placebo-controlled Phase 3 study that will enroll approximately 200 children and adults with AS that have a maternal *UBE3A* gene deletion or mutation. During the 52-week treatment period, participants will be randomized 2:1 to receive either ION582 or placebo. Participants in the active treatment groups will receive quarterly 40 mg or 80 mg doses of ION582. Following the treatment period, eligible participants will transition into the long-term extension portion of the study where all participants will receive ION582 for up to 2 years. The primary endpoint is improvement in expressive communication as assessed by the Bayley Scales for Infant and Toddler Development-4 (Bayley-4), an objective and direct clinician-administered assessment of clinical functioning. Deficits in expressive communication are reported to be the symptoms most challenging to caregivers of people with AS. Secondary endpoints include overall disease severity, cognition, communication, sleep, motor functioning and daily living skills, in addition to other exploratory endpoints.

In the completed multiple ascending dose (MAD) portion of the Phase 1/2 open-label HALOS study, ION582 provided consistent and encouraging clinical improvement on all functional domains including communication, cognition and motor function and showed favorable safety and tolerability at all dose levels in the study.

For more information on the REVEAL clinical study, please visit www.ionisrevealstudy.com and www.clinicaltrials.gov.

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 maternally inherited *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 therapies, 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 Prion disease and Alexander disease and more common conditions such as Alzheimer's and Parkinson'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 six marketed medicines and a leading pipeline in neurology, cardiology, 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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Source: Ionis Pharmaceuticals, Inc.