Ionis Announces Pivotal Phase 3 Trial Design for ION582 in Angelman Syndrome

November 6, 2024

- Positive End of Phase 2 discussion with FDA, including alignment on Phase 3 design
- Bayley-4 expressive communication selected as Phase 3 study primary endpoint
- Initiation of ION582 Phase 3 study planned for H1 2025
- Ionis to share ION582 program update at the FAST Global Science Summit in November

CARLSBAD, Calif., Nov. 6, 2024 /PRNewswire/ -- Ionis Pharmaceuticals, Inc. (Nasdaq: IONS) today announced the pivotal Phase 3 study design following successful alignment with the U.S. Food and Drug Administration (FDA) on ION582, an investigational medicine for the treatment of people living with Angelman syndrome (AS). AS typically presents in infancy and is characterized by profound intellectual disability, impaired verbal abilities and severe motor impairment.

"Following positive results for ION582 in the Phase 2 HALOS trial, we are pleased to have alignment with the FDA on the design of our Phase 3 REVEAL trial, which will address clinical endpoints that reflect the most pressing and meaningful outcomes for people living with AS and their caregivers," said Brett Monia, Ph.D., chief executive officer of Ionis. "We will enroll a broad group of individuals living with AS in the global pivotal Phase 3 trial, planned to begin in the first half of 2025. We look forward to working with the community to advance a potential new treatment targeting the underlying cause of disease in this debilitating neurological condition that has no approved medicines."

The planned global, randomized, placebo-controlled Phase 3 study will enroll approximately 200 children and adults with AS that have a maternal *UBE3A* gene deletion or mutation. The primary analysis will occur after approximately one year of treatment, followed by all patients transitioning into an open-label long-term extension (LTE) phase of the study. Patients will be randomized 2:1 to active therapy or placebo, and ION582 will be evaluated at two dose levels which will be dosed quarterly without a loading regimen. The primary endpoint will be 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. The study will evaluate several secondary endpoints including overall disease severity, cognition, communication, sleep, motor functioning and daily living skills, in addition to other exploratory endpoints.

The End of Phase 2 meeting was supported by data from the Phase 2 open-label HALOS study. In the recently completed multiple ascending dose (MAD) portion of the study, ION582 treatment provided strong evidence of clinically meaningful improvement on all functional domains including communication, cognition and motor function. Overall, 97% of people in the medium and high dose groups assessed in the study saw an improvement in overall AS symptoms as measured by the Angelman Syndrome Clinical Global Improvement Change (SAS-CGI-C) scale, which evaluates clinicians' impressions. ION582 showed favorable safety and tolerability at all dose levels in the study.

At the FAST Global Science Summit this weekend (November 8-9), Ionis will provide an update to the community on the Phase 3 program and review data from the MAD portion of the HALOS trial.

About ION582

ION582 is an investigational 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). In 2022, the U.S. Food and Drug Administration (FDA) granted ION582 Orphan Drug designation and Rare Pediatric designation.

About Angelman Syndrome (AS)

AS is a rare, genetic neurological disease 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 patients 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 Franchise

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 therapies, of which five 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 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), LinkedIn and Instagram.

Ionis Forward-looking Statements

This press release includes forward-looking statements regarding Ionis' business, and the therapeutic and commercial potential of Ionis' commercial medicines, ION582 and Ionis' 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.

Ionis Pharmaceuticals® is a registered trademark of Ionis Pharmaceuticals, Inc.

ION582 is an investigational medicine that has not been approved for the treatment of any disease by regulatory authorities.

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