Ionis announces positive topline results from Phase 1/2a trial of ION582 for Angelman syndrome

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- *ION582 demonstrated consistent improvements across multiple functional domains in Angelman syndrome patients*
- *ION582 was safe and well tolerated at all dose levels*
- *Ionis plans to move ION582 into pivotal trial*
- *Detailed ION582 data to be presented at upcoming medical meeting*

CARLSBAD, Calif., May 16, 2024 /PRNewswire/ -- Ionis Pharmaceuticals, Inc. (Nasdaq: IONS) today announced positive topline data from the HALOS Phase 1/2a open-label study of ION582 in Angelman syndrome. ION582 was safe and well tolerated in the study and showed encouraging and consistent benefits in individuals living with Angelman syndrome, with the most robust improvements observed in key areas of functioning including cognition, communication and motor function.

Ionis also announced that it will independently advance ION582 as part of Ionis' leading portfolio of potentially transformational medicines for serious neurological diseases. Ionis plans to review the ION582 Phase 1/2a results with regulatory authorities to align on the design of the pivotal program. Biogen has elected not to exercise its option to license ION582.

"There are currently no approved treatments for Angelman syndrome, which causes developmental delays, cognitive impairment and severe communications challenges, with most individuals unable to speak or live independently," said Lynne Bird, M.D., professor of clinical pediatrics at UC San Diego and HALOS study investigator. "We are encouraged by the positive and consistent improvements seen in the HALOS study across multiple measures, as these functional improvements could have a transformative impact in the lives of people living with Angelman syndrome and their caregivers. We are also encouraged by the favorable safety and tolerability profile observed in the study, which is particularly important when treating children. We very much look forward to further evaluation of ION582 in a pivotal program."

Angelman syndrome is caused by a loss of function in the maternal UBE3A gene. ION582 is designed to unsilence the paternal UBE3A allele in order to increase production of the UBE3A protein in the brain. Angelman syndrome affects an estimated one in 12,000 to 20,000 people globally.[1] It presents as profound and severe developmental delays in motor, language and cognitive functioning, seizures and ataxia. It is a serious neurodevelopmental disorder that presents in early childhood, resulting in complete dependence on a caregiver.

"We are encouraged by the data from the HALOS study and pleased to add this promising medicine to our growing independent pipeline of neurology medicines," said Brett Monia, Ph.D., chief executive officer of Ionis. "We look forward to sharing detailed data at the upcoming Angelman Syndrome Foundation meeting and to advancing ION582 into a pivotal study. Individuals with Angelman syndrome face significant neuro-developmental challenges and have no approved therapies today. We are committed to working closely with the community, investigators and regulators to advance this promising investigational medicine."

Part 1 of the HALOS trial was a three-month, multiple-ascending dose (MAD) study in 51 patients aged 2-50, which evaluated three doses of ION582. All eligible patients transitioned into the Part 2 long-term extension (LTE) portion of the study, which is evaluating the two higher doses of ION582 for an additional 12 months. Part 3 of the study will evaluate eligible patients for an additional three years. Topline results were available for all patients at four months (one month after last MAD dose), and six months, and were consistent with preliminary findings reported at the Foundation for Angelman Syndrome Therapeutics (FAST) meeting in November 2023. Topline data included:

- Safety assessment was the primary objective of the trial and ION582 was safe and well tolerated at all dose levels. Adverse events in the trial were consistent with patient medical histories, Angelman syndrome diagnosis or related to intrathecal administration.
- ION582 showed consistent effects across multiple objective and subjective measures used to assess functioning in individuals living with Angelman syndrome. These include the Bayley-4, an objective physician assessment of clinical functioning, Angelman Syndrome Clinical Global Improvement Change (SAS-CGI-C) scale, which evaluates clinicians' impressions, and the Vineland-3 and Observer-Reported Communication Ability (ORCA) measures, which are parent-reported assessment tools. These positive results correlated with positive changes in EEG activity including a reduction in slow wave delta activity.
- At six months, approximately 65% of patients achieved an improvement in cognition on the Bayley-4. While no direct comparisons should be made, these improvements exceeded improvements seen in natural history studies over the same time period.
- At six months, approximately 70% of patients showed improvement on Bayley-4 measures of receptive and/or expressive communication. While no direct comparisons should be made, these changes exceeded improvements seen in natural history studies over the same time period.

- At six months, approximately 65% of patients showed improvements in Bayley-4 measures of fine and gross motor skills. While no direct comparisons should be made, these changes exceeded improvements seen in natural history studies over the same time period.

Ionis expects to report detailed results from the HALOS study at the Angelman Syndrome Foundation meeting in July. ION582 has received Orphan Drug designation in the U.S. The HALOS Phase 1/2a open-label trial is evaluating safety, tolerability, pharmacokinetics and pharmacodynamics in addition to certain clinical outcomes measures. ION582 is administered intrathecally into the cerebral spinal fluid with a lumbar puncture. For more information on the HALOS Study (NCT05127226), visit clinicaltrials.gov.

About Ionis' Neurology Franchise
Ionis' neurology franchise addresses all major brain regions and central nervous system cell types and currently has three Phase 3 studies ongoing with 11 therapies in clinical development, several of which Ionis plans to commercialize directly. Ionis is discovering and developing potential treatments for many neurological diseases for which there are few or no disease modifying treatments, including common diseases like Alzheimer's and Parkinson's as well as rare diseases such as amyotrophic lateral sclerosis (ALS) and Alexander disease. Ionis has discovered and developed three commercially available 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.

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 Ionispharma.com and follow us on X (Twitter) and LinkedIn.

Ionis Forward-looking Statements
This press release includes forward-looking statements regarding Ionis' business, financial guidance and the therapeutic and commercial potential of our commercial medicines, ION582, 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, 2023, 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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[1] Mertz LG, Christensen R, Vogel I, Hertz JM, Nielsen KB, Gronskov K, Ostergaard JR. Angelman syndrome in Denmark. birth incidence, genetic findings, and age at diagnosis. Am J Med Genet A. 2013;161A:2197–203.