Ionis announces positive detailed results from the HALOS Study of ION582 in people with Angelman syndrome

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- *ION582 showed robust and consistent benefit in communication, cognition and motor function in a broad patient population evaluated with a comprehensive set of assessment tools that collect input from parents and clinicians*
- *97% of patients in the medium and high dose groups saw improvement in overall Angelman syndrome symptoms as measured by the SAS-CGI-C*
- *Improvements on the Bayley-4 in cognition, communication and motor function exceeded those observed in natural history studies*
- *Ionis plans to initiate Phase 3 development in H1 2025*
- *Ionis to host webcast on Monday, July 22 at 8:00am ET*

CARLSBAD, Calif., July 22, 2024 /PRNewswire/ -- Ionis Pharmaceuticals, Inc. (Nasdaq: IONS) today announced positive results from the completed multiple ascending dose (MAD) portion of the Phase 1/2 open-label study of ION582 in people with Angelman syndrome (AS) demonstrating consistent and encouraging clinical improvement on measures assessing all functional domains including communication, cognition and motor function. Overall, 97% of people in the medium and high dose groups saw an improvement in overall AS symptoms as measured by the Symptoms of Angelman Syndrome–Clinician Global Impression-Change (SAS-CGI-C). ION582 showed favorable safety and tolerability at all dose levels in the study. Detailed results will be presented in a company webcast today and at the 2024 Angelman Syndrome Foundation (ASF) Family Conference in Sandusky, Ohio on July 24, 2024.

"Ionis looks forward to collaborating with investigators, regulators and members of the Angelman syndrome community to initiate Phase 3 development for ION582 in the first half of 2025," said Brett Monia, Ph.D., chief executive officer of Ionis. "Ionis has pioneered the discovery and development of groundbreaking medicines for serious neurological conditions including spinal muscular atrophy and amyotrophic lateral sclerosis. These encouraging results from the HALOS study position ION582 to be the cornerstone of Ionis' next wave of transformational, wholly owned medicines for neurological conditions, which currently includes five clinical-stage programs."

AS is a serious, rare neurodevelopmental disorder that is caused by a loss of function in the maternal UBE3A gene. It affects an estimated 1 in 21,000 people worldwide and presents in early childhood as profound and severe developmental delays in motor, language and cognitive functioning, seizures and ataxia. ION582 is an investigational antisense medicine designed to unsilence the normal paternal UBE3A gene to increase production of the UBE3A protein in the brain.

"Angelman syndrome is a serious neurodevelopmental disorder with life-long impairments and dependence on caregivers, for which we currently have only supportive care," said Lynne Bird, M.D., professor of clinical pediatrics at UC San Diego and HALOS study investigator. "We are very encouraged by these promising data with ION582, showing consistent improvements over what we observe in the natural course of the disease."

HALOS Study Results
HALOS included 51 people with AS, and allowed participants aged two-50 to enroll. Results presented today are from the final timepoint of the completed MAD portion of the study at six months. These results include:

- ION582 showed favorable safety and tolerability at all dose levels.
- Evidence of consistent benefit observed across all ages and genotypes as well as clinical improvement observed across key functional areas:
    - Improvements in communication, cognition and motor function exceeding the Angelman Syndrome Natural History Study (NHS) were observed on the Bayley-4, an objective and direct clinician-administered assessment of clinical functioning. See details in Table 1 below.
    - Clinical improvements were observed across key functional areas in the Vineland-3 and Observer-Reported Communication Ability (ORCA), which are both parent-reported assessment tools.
    - 97% of participants showed clinically meaningful overall improvement on the SAS-CGI-C, which evaluates clinicians' impressions of AS symptoms in study participants.

Table 1: Majority of Participants Demonstrated Benefit in Nearly all Domains Assessed in the HALOS Study[1]

The percent of participants who improved across the four AS tools evaluated in HALOS is noted below. These results exceed the improvements seen in the NHS, where available, in which people with AS show profound developmental delay from birth through adulthood with function remaining stable with essentially no improvement after ~4 years of age.

	Bayley-4[2,3]	Vineland-3[2,4]	ORCA[2,5-8]	SAS-CGI-C[9-12]
Cognition	**67 %**	—	—	**85 %**
Receptive Communication	**67 %**	**89 %**	**60 %**	—
Expressive Communication	**69 %**	**84 %**		**69 %**
Gross Motor	**46 %**	**53 %**	—	**74 %**
Fine Motor	**72 %**	**63 %**	—	**64 %**
Daily Living Skills	*	**74-82%** [13]	—	**62 %**
Socialization	*	**63-87%** [14]	—	—
Sleep	—	—	—	**61 %**
Behavior	*	*	—	**56 %**

* Analyzed with alternate assessment tool(s)
— Not in assessment

1. Medium and high dose groups at 6 months. 2. Improvement exceeds Natural History. 3. Bayley N. Aylward GP. *Bayley Scales of Infant and Toddler Development-Fourth Edition*. NCS Pearson. (2019). 4. Sparrow S, et. Al. *Vineland Adaptive Behavior Scales-Third Edition (Vineland-3).* NCS Pearson. (2016). 5. Improvement on ORCA exceeding proposed minimal clinically meaningful difference of ≥2. 6. Zigler CK, et al. *Am J Intellect Dev Disabil*. (2023). 7. Duke University. *Observer-Reported Communication Ability (ORCA) measure scoring manual*. Pattern Health. (2023). 8. ORCA T-score range: 25.8–83.8, (standardized, mean=50, SD=10). 9. Improvement on SAS-CGI-C exceeding proposed minimal clinically meaningful difference of ≥1 point. 10. Connor-Ahmad, S. et al. *Orphanet J. Rare Dis.* (2023). 11. Adapted from Standard CGI-C. 12. SAS-CGI-C response range: Very Much Worse-Very Much Improved. 13. Range across 3 subdomains (personal, community and domestic). 14. Range across 3 subdomains (Coping skills, interpersonal relationships and play and leisure)

Ionis plans to meet with regulators to review and confirm their Phase 3 study design later this year, which puts the company on track for a pivotal study initiation in H1 2025.

Webcast
Ionis will hold a webcast today at 8:00am ET to discuss this update. Interested parties may access the webcast here. A webcast replay will be available for a limited time.

About the HALOS Study
The global, open-label, multiple-ascending dose (MAD) Phase 1-2a study (NCT05127226) includes 51 patients with Angelman syndrome (AS) aged two – 50 across 11 sites in six countries. Part 1 of the HALOS trial was a three-month, MAD study which evaluated three doses of ION582, with final assessments at six months. 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 up to an additional four years. The primary endpoint is safety and tolerability of multiple doses of ION582 administered by intrathecal administration. Key exploratory measures include change in measures of clinical function: communication, cognition, motor function, sleep, seizures and daily living skills.

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 amyotrophic lateral sclerosis (ALS) 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) 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, 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 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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