Ionis announced FDA advisory committee voted unanimously for a potential accelerated approval of tofersen for SOD1-ALS

March 23, 2023

- *If approved, tofersen will be the first treatment targeting a genetic cause of ALS and the next marketed Ionis-discovered antisense medicine*
- *FDA decision expected by April 25, 2023*

CARLSBAD, Calif., March 22, 2023 /PRNewswire/ -- Ionis (Nasdaq: IONS) today announced the outcome of the U.S. Food and Drug Administration's (FDA) Peripheral and Central Nervous System Drugs Advisory Committee meeting on tofersen, an investigational antisense medicine for the treatment of people with superoxide dismutase 1 (SOD1) amyotrophic lateral sclerosis (ALS). SOD1-ALS is a rare genetic form of ALS that leads to the loss of everyday functions and ultimately death.

On the question, "Is the available evidence sufficient to conclude that a reduction in plasma neurofilament light chain (NfL) concentration in tofersen-treated patients is reasonably likely to predict clinical benefit of tofersen for treatment of patients with SOD1-ALS?", the committee voted unanimously yes (9 yes to 0 no) for consideration of a potential accelerated approval. On the second question, "Does the clinical data from the placebo-controlled study and available long-term extension study results, with additional supporting results from the effects on relevant biomarkers (i.e., changes in plasma NfL concentration and/or reductions in SOD1), provide substantial evidence of the effectiveness of tofersen in the treatment of patients with SOD1-ALS?", the committee voted 3 (yes), 5 (no) and 1 (abstain) for consideration of a potential traditional approval.

Additionally, the committee discussed both of these topics and reached consensus that the benefit-risk profile was favorable based on the review of the totality of data for tofersen in people with SOD1-ALS.

"We are encouraged by the outcome of today's advisory committee meeting. If approved, tofersen would be the first medicine targeting a known cause of familial ALS, a devastating neurodegenerative disease that diminishes motor function and leads to death within two to five years of diagnosis," said C. Frank Bennett, Ph.D., executive vice president and chief scientific officer at Ionis. "Tofersen is the lead investigational medicine from our innovative pipeline of neurological therapies designed to target the root cause of intractable diseases. We are diligently advancing these programs to potentially benefit patients in need."

Advisory Committees provide non-binding recommendations for consideration by the FDA. The New Drug Application for tofersen for the treatment of SOD1-ALS was submitted to the FDA for consideration under accelerated approval. The FDA is continuing its review of tofersen with a Prescription Drug User Fee Act (PDUFA) action date of April 25, 2023.

About Tofersen

Tofersen is an investigational antisense medicine being evaluated as a treatment for SOD1-ALS. In people with this form of the disease, mutations in their SOD1 gene cause their bodies to create a toxic form of SOD1 protein. This toxic protein causes motor neurons to degenerate, resulting in progressive muscle weakness. Tofersen is designed to bind to SOD1 mRNA and reduce SOD1 protein production.

In addition to the ongoing open label extension of the Phase 3 VALOR study, tofersen is being studied in the Phase 3 ATLAS study designed to evaluate whether tofersen can delay clinical onset when initiated in presymptomatic individuals with a SOD1 genetic mutation and biomarker evidence of disease activity. Biogen licensed tofersen from Ionis under a collaborative development and license agreement.

About Amyotrophic Lateral Sclerosis and SOD1-ALS

Amyotrophic lateral sclerosis (ALS) is a rare, progressive and fatal neurodegenerative disease that results in the loss of motor neurons in the brain and the spinal cord that are responsible for controlling voluntary muscle movement. People with ALS experience muscle weakness and atrophy, causing them to lose independence as they steadily lose the ability to move, speak, eat, and eventually breathe. Mean life expectancy for people with ALS is between three to five years from time of symptom onset.

Multiple genes have been implicated in ALS. Genetic testing helps determine if a person's ALS is associated with a genetic mutation, even in individuals without a family history of the disease. Currently, there are no genetically targeted treatment options for ALS. SOD1-ALS is diagnosed in approximately 2% of all ALS cases, impacting about 330 people in the U.S.[1] While there are medications approved for broad ALS, no available treatments target a genetic mutation associated with ALS. Approximately 5%-10% of people with ALS are thought to have a genetic form of the disease;[2] however, they may not have a known family history of the disease.

About Ionis Pharmaceuticals, Inc.

For more than 30 years, Ionis has been a leader in RNA-targeted therapy, pioneering new markets and changing standards of care. Ionis currently has three marketed medicines and a promising late-stage pipeline highlighted by cardiovascular and neurological franchises. Our scientific innovation began and continues with the knowledge that sick people depend on us, which fuels our vision to become the leader in genetic medicine, utilizing a multi-platform approach to discover, develop and deliver life-transforming therapies.

To learn more about Ionis visit www.ionispharma.com and follow us on Twitter @ionispharma.

Ionis' Forward-looking Statements

This press release includes forward-looking statements regarding Ionis' business and the therapeutic and commercial potential of Ionis' technologies, tofersen and other products in development. 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. 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, 2022, which is on file with the Securities and Exchange Commission. Copies of this and other documents are available from the Company.

In this press release, unless the context requires otherwise, "Ionis," "Company," "we," "our," and "us" refers to Ionis Pharmaceuticals and its subsidiaries.

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[1]Brown CA, Lally C, Kupelian V, Flanders WD. Estimated Prevalence and Incidence of Amyotrophic Lateral Sclerosis and SOD1 and C9orf72 Genetic Variants. Neuroepidemiology. 2021;55(5):342-353. doi: 10.1159/000516752. Epub 2021 Jul 9.

[2]National Institute of Neurological Disorders and Stroke. Amyotrophic Lateral Sclerosis (ALS) Fact Sheet. Available at: https://www.ninds.nih.gov/amyotrophic-lateral-sclerosis-als-fact-sheet. Accessed: January 2023.

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