Ionis announces that FDA accepts New Drug Application and grants Priority Review of tofersen for a rare, genetic form of ALS

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- *SOD1-ALS is a rare genetic form of ALS that affects approximately 330 people in the U.S., it is progressive, leads to the loss of everyday functions and is uniformly fatal*
- *If approved, tofersen would be the first treatment to target a genetic cause of ALS*
- *12-month data included in the filing show that earlier initiation of tofersen slowed decline across measures of clinical and respiratory function, strength, and quality of life; tofersen also led to robust and sustained reductions in neurofilament, a marker of neurodegeneration*

CARLSBAD, Calif., July 26, 2022 /PRNewswire/ -- Ionis Pharmaceuticals (Nasdaq: IONS) today announced that the U.S. Food and Drug Administration (FDA) has accepted a New Drug Application (NDA) for tofersen, an investigational antisense medicine for the treatment of superoxide dismutase 1 amyotrophic lateral sclerosis (SOD1-ALS). The NDA was submitted by Biogen, which licensed tofersen from Ionis in 2018. The application has been granted priority review and given a Prescription Drug User Fee Act action date of Jan. 25, 2023. The FDA has noted that it is currently planning to hold an Advisory Committee meeting for this application. The average life expectancy for people with ALS is three to five years from time of symptom onset; patients with some SOD1 mutations have an even shorter life expectancy. There is currently no treatment targeted for SOD1-ALS.

"Acceptance of the new drug application for tofersen is a monumental milestone, not just for Ionis but for all people with SOD1-ALS, their families and healthcare professionals battling this devastating disease. To them we extend our deepest gratitude. Their courage has been instrumental to the achievement of this goal," said C. Frank Bennett, Ph.D., executive vice president, chief scientific officer and franchise leader for neurological programs at Ionis. "We also want to thank Biogen for their commitment to advancing tofersen, which, if approved, will be the first treatment that targets a genetic cause of ALS." Dr. Bennett added, "Acceptance of the NDA for tofersen further strengthens Ionis' platform strategy to target all forms of ALS and central nervous system disorders more broadly."

Biogen is seeking approval of tofersen under the FDA's accelerated approval pathway, based on the use of neurofilament as a surrogate biomarker that is reasonably likely to predict clinical benefit. Neurofilaments are normal proteins found in healthy neurons, that are increased in blood and cerebrospinal fluid when damage has been done to neurons or their axons and are a marker of neurodegeneration. In ALS, higher levels of neurofilaments have been found to predict more rapid decline in clinical function and shortened survival. Tofersen study results suggest reductions in neurofilament preceded and predicted slowing of decline in measures of clinical and respiratory function, strength and quality of life. Biogen has stated its commitment to ongoing data generation and finalizing the confirmatory package with the FDA.

The tofersen NDA included results from a Phase 1 study in healthy volunteers, a Phase 1/2 study evaluating ascending dose levels, the Phase 3 VALOR study, and the open label extension (OLE) study. Also included are the most current 12-month integrated results from VALOR and the OLE study, recently presented at the European Network to Cure ALS (ENCALS) annual meeting.

As reported in October 2021, VALOR, a six-month Phase 3 randomized study, did not meet the primary endpoint of change from baseline to week 28 in the Revised Amyotrophic Lateral Sclerosis Functional Rating Scale. However, trends of reduced disease progression across multiple secondary and exploratory endpoints were observed. The 12-month VALOR and OLE integrated data showed that earlier initiation of tofersen led to sustained reductions in neurofilament, a marker of neurodegeneration, and slowed decline across multiple efficacy endpoints.

In the 12-month data, the most common adverse events (AEs) in participants receiving tofersen in VALOR and the OLE study were headache, procedural pain, fall, back pain and pain in extremities. Most AEs in both VALOR and the OLE were mild to moderate in severity. Serious AEs were reported in 36.5 percent of participants who received tofersen in VALOR and/or the OLE and 17.3 percent of participants discontinued treatment due to an AE.

During the FDA review period Biogen will maintain its early access program for tofersen, now with participants in over a dozen countries. The open-label extension and Phase 3 ATLAS study in presymptomatic individuals with a SOD1 genetic mutation remain ongoing. Biogen is actively engaging with other regulators around the world and will provide updates when appropriate.

About Tofersen

Tofersen is an antisense medicine being evaluated for the potential treatment of SOD1-ALS. Tofersen binds to SOD1 mRNA, allowing for its degradation by RNase-H in an effort to reduce synthesis of SOD1 protein production. In addition to the ongoing open label extension of VALOR, 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. Average life expectancy for people with ALS is three to five years from time of symptom onset. Patients with some SOD1 mutations have an even shorter life expectancy.

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. Mutations in the SOD1 gene are responsible for approximately 2 percent of the estimated 168,000 people who have ALS globally (SOD1-ALS).

About Ionis Pharmaceuticals, Inc.

For more than 30 years, Ionis has been the leader in RNA-targeted therapy, pioneering new markets and changing standards of care with its novel antisense technology. Ionis currently has three marketed medicines and a premier late-stage pipeline highlighted by industry-leading cardiovascular and neurological franchises. Our scientific innovation began and continues with the knowledge that sick people depend on us, which fuels our vision of becoming a leading, fully integrated biotechnology company.

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 those related to the impact COVID-19 could have on our business, and 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, 2021, and the most recent Form 10-Q quarterly filing, 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" refers to Ionis Pharmaceuticals and its subsidiaries.

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