

Ionis partner Biogen announces that results from Phase 3 VALOR study and open-label extension of tofersen showed clinical benefit in SOD1-ALS patients

June 3, 2022

- *Twelve-month data 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*
- *SOD1-ALS is a rare, progressive and fatal genetic form of the disease leading to loss of everyday functions and affecting approximately 2% of people with ALS*

CARLSBAD, Calif., June 3, 2022 /PRNewswire/ - Ionis Pharmaceuticals, Inc. (Nasdaq: IONS) partner Biogen today announced results from the Phase 3 VALOR study and its open-label extension (OLE) of tofersen, an investigational antisense medicine being evaluated for people with superoxide dismutase 1 (SOD1) amyotrophic lateral sclerosis (ALS). The data show that earlier initiation of tofersen, compared to delayed initiation, slowed declines in clinical function, respiratory function, muscle strength and quality of life. At the time of the analysis, because the majority of participants survived without permanent ventilation (PV), the median time to death or PV could not be estimated. However, early survival data suggest a lower risk of death or PV with earlier initiation of tofersen. These results are based on new integrated data from the VALOR pivotal study and its OLE study.

The results were presented at the European Network to Cure ALS (ENCALS) meeting in Edinburgh, Scotland. An archived version of the presentation will be available on the Investors section of Biogen's website at investors.biogen.com.

"We are very pleased with these new 12-month data, which show that tofersen slowed disease progression and lowered neurofilament levels. Together, these results offer compelling evidence of tofersen's potential to provide meaningful clinical benefit to people living with SOD1-ALS," said C. Frank Bennett, Ph.D., executive vice president, chief scientific officer and franchise leader for neurological programs at Ionis.

Clinical Results

As previously 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 (ALSFRS-R). However, trends of reduced disease progression across multiple secondary and exploratory endpoints were observed. The new 12-month data further build on the results previously observed in the initial readout.

The 12-month data compare early initiation of tofersen (at the start of VALOR) to delayed initiation of tofersen (six months later, in the OLE). Over 12 months in the overall study population, results favored earlier start tofersen on measures of:

- Clinical function as measured by ALSFRS-R (difference of 3.5 points; 95% confidence interval [CI]: 0.4, 6.7)
- Respiratory function as measured by slow vital capacity (difference of 9.2 percent-predicted; 95% CI: 1.7, 16.6)
- Muscle strength as measured by the handheld dynamometry megascore (difference of 0.28; 95% CI: 0.05, 0.52)
- Quality of life as measured by the 5-item amyotrophic lateral sclerosis assessment questionnaire (ALSAQ-5) (difference of 10.3 points; 95% CI: -17.3, -3.2)

At the time of the analysis, because the majority of participants survived without permanent ventilation (PV), the median time to death or PV and median time to death, could not be estimated. However, early survival data suggest a lower risk of death or PV (Hazard ratio [HR] 0.36; 95% CI: 0.137, 0.941) and death (HR 0.27; 95% CI: 0.084, 0.890) with earlier initiation of tofersen.

Biomarker Results

The latest 12-month results show that reductions in total SOD1 protein (a marker of target engagement) and neurofilament (a marker of axonal injury and neurodegeneration) were sustained over time.

Tofersen reduced total CSF SOD1 protein and plasma neurofilament levels in both early- and delayed-start groups as follows:

- 33 percent and 21 percent reduction in SOD1 protein, the intended target for tofersen, respectively
- 51 percent and 41 percent reduction in plasma neurofilament, a marker of neuron injury, respectively

Safety Results

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 extremity. 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. Serious neurologic events including myelitis, radiculitis, aseptic meningitis, and papilledema, were reported in 6.7 percent of participants receiving tofersen in VALOR and its OLE. There were 14 deaths reported in tofersen-treated participants in VALOR and the OLE, all of which were determined not to be related to tofersen.

About VALOR and the OLE

VALOR was a 28-week Phase 3, randomized, double-blind, placebo-controlled study to evaluate the effects of tofersen 100 mg in 108 adults with ALS

associated with a SOD1 mutation. In total, 108 participants were randomized in VALOR (n=72 to tofersen 100 mg and n=36 to placebo). Of these participants, 95 enrolled in the ongoing OLE. At the time of the analysis all participants had an opportunity for at least 12 months of follow-up, with a median exposure to tofersen of approximately 20 months (range: 1 – 34 months).

To account for disease heterogeneity, the planned clinical analyses adjusted for neurofilament levels as a marker of the disease progression rate at baseline. Neurofilaments are proteins that increase in blood and cerebrospinal fluid when neurons or their axons are damaged. Neurofilaments have been shown to be a prognostic marker of disease progression and survival in ALS.

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-H1 to reduce synthesis of SOD1 protein production. Tofersen is also being studied in the Phase 3 ATLAS study, which is designed to evaluate the ability of tofersen to 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 3-5 years from time of symptom onset.¹

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 two percent of the estimated 168,000 people who have ALS globally (SOD1-ALS).² Life expectancy in SOD1-ALS varies widely, from less than one year to more than 20 years.³

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 Statement

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 December 31, 2021, and the most recent Form 10-Q quarterly filing, which are on file with the SEC. 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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¹ Brown. N Engl J Med 2017;377:162-72.

² Brown C, et al. Neuroepidemiology. 2021;55(5):342-353.

³ Bali T, et al. J Neurol Neurosurg Psychiatry 2017;88:99–105.

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