

Ionis' partner Biogen provides update on tofersen Phase 3 VALOR study in SOD1-ALS

October 17, 2021

- In the Phase 3 VALOR study, the primary endpoint as measured by the Revised Amyotrophic Lateral Sclerosis Functional Rating Scale (ALSFRS-R) did not reach statistical significance; however, signs of reduced disease progression across multiple secondary and exploratory endpoints were observed
- The totality of evidence from VALOR and its ongoing open-label extension showed that participants who started tofersen earlier experienced better outcomes, further suggesting a positive clinical effect
- Given the high unmet medical need, Biogen will expand its ongoing early access program (EAP) to the broader SOD1-ALS population
- Topline data being presented today at the American Neurological Association 2021 Annual Meeting

CARLSBAD, Calif., Oct. 17, 2021 /PRNewswire/ -- Ionis Pharmaceuticals, Inc. (NASDAQ: IONS) partner Biogen today announced topline results from its placebo-controlled pivotal Phase 3 VALOR study of tofersen (BIIB067), an investigational antisense medicine being evaluated for people with superoxide dismutase 1 (SOD1) amyotrophic lateral sclerosis (ALS). While tofersen did not meet the primary endpoint of change from baseline to week 28 in the Revised Amyotrophic Lateral Sclerosis Functional Rating Scale (ALSFRS-R), trends favoring tofersen were seen across multiple secondary and exploratory measures of disease activity and clinical function.

In addition, a pre-specified integration of data from VALOR and its ongoing open-label extension study (OLE) reinforced these findings and showed that early tofersen initiation led to less decline across multiple measures including motor function, respiratory function, muscle strength, and quality of life in people with SOD1-ALS. Most adverse events in both VALOR and OLE were mild to moderate in severity, including procedural pain, headache, pain in extremity, fall and back pain.

Biogen, which licensed tofersen from Ionis in 2018, also announced today that it is actively engaging with regulators, the medical community, patient advocacy groups and other key stakeholders around the world to determine next steps.

"The topline results of the Phase 3 VALOR study showed signs of reduced disease progression across key secondary and exploratory endpoints, including biomarker data, clinical outcomes and quality of life measures. These data represent an important step forward in our commitment to find new treatments for this devastating disease. We applaud the efforts of Biogen, whose advancement of tofersen reflects the promise of our broad partnership to develop medicines for the treatment of neurological diseases," said Brett P. Monia, Ph.D., chief executive officer of Ionis.

"Given Ionis' long-standing commitment to the ALS community, we are encouraged by the results of the Phase 3 VALOR study of tofersen and its open-label extension, which showed signs of slowing disease progression in people living with SOD1-ALS," said C. Frank Bennett, Ph.D., Ionis' executive vice president, chief scientific officer and franchise leader for neurological programs. "On behalf of all of us at Ionis, I would like to express our deep gratitude to the patients, families, scientific investigators, and others who participated in the VALOR study."

ALS is a progressive neurodegenerative disease that is uniformly fatal with an average survival of three to five years. The most common cause of death is respiratory failure. SOD1-ALS is a rare, genetic form of ALS that accounts for approximately two percent of the estimated 168,000 people who have the disease globally. Currently, there are no genetically targeted treatment options for ALS.

In light of the critical unmet need, Biogen announced that it will expand eligibility for its ongoing early access program (EAP) to all people with SOD1-ALS, in countries where such programs are permitted by local regulations and future access may be secured. EAP programs enable patients to gain access to a medicine free of charge before the treatment is licensed commercially. If a path forward for tofersen is not established, or if another controlled trial is required by regulators, Biogen may revise or discontinue the EAP.

The VALOR and Open-Label Extension Studies

VALOR was a 28-week Phase 3, randomized, double-blind, placebo-controlled study to evaluate the efficacy, safety and tolerability, pharmacodynamic, and biomarker effects of tofersen 100 mg in 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). Sixty of these participants met the study's protocol-defined enrichment criteria for rapid disease progression, comprising the primary analysis population ("faster progressing"). Forty-eight participants did not meet these prognostic enrichment criteria ("slower progressing").

The open-label extension study is an ongoing Phase 3 study for participants who completed VALOR. Of the 108 participants in VALOR, 95 enrolled in the OLE.

Topline Results

In VALOR the primary efficacy endpoint of change from baseline to week 28 in the Revised Amyotrophic Lateral Sclerosis Functional Rating Scale (ALSFRS-R) total score in the primary analysis (faster-progressing) population did not reach statistical significance as measured by a joint-rank analysis (difference of 1.2; p=0.97).

Trends favoring tofersen were seen across multiple secondary and exploratory measures of biologic activity and clinical function, including motor function, respiratory function and quality of life. On the first key secondary endpoint of change from baseline in total CSF SOD1 protein, a marker of target engagement, differences were observed between the tofersen and placebo groups of 38% and 26% in the faster- and slower-progressing populations, respectively. On the second key secondary endpoint of change from baseline in plasma neurofilament light chain (NfL), a potential marker of neuronal degeneration, differences were observed between the tofersen and placebo groups of 67% and 48% in the faster- and slower-progressing populations, respectively.

In the faster-progressing population, trends favored tofersen on measures of respiratory function (Slow Vital Capacity (SVC); difference of 7.9 percent-predicted) and muscle strength (Hand-held dynamometer (HHD); difference of 0.02). Similar trends were observed across multiple exploratory patient-

reported outcome measures of disease severity, quality of life, and fatigue. Median time to event could not be estimated for survival analyses due to the low number of events over the 28-week period.

In addition, with longer-term follow up in the OLE, earlier tofersen initiation consistently led to a reduction in decline in measures of clinical function across the population.

The most common adverse events (AEs) in participants receiving tofersen in the VALOR study were procedural pain, headache, pain in extremity, fall and back pain. Most AEs in both VALOR and the OLE were mild to moderate in severity. In VALOR, serious AEs were reported in 18.1% of participants receiving tofersen and 13.9% of those receiving placebo. In the tofersen group, 5.6% of participants discontinued treatment due to an AE. There were no discontinuations due to AEs in the placebo group. Serious neurologic events were reported in 4.8% of patients receiving tofersen in VALOR and its OLE, including 2 cases of myelitis (2.0%). There was one death reported in the tofersen-treated group in VALOR, which was determined not to be related to tofersen.

American Neurological Association (ANA) Annual Meeting Presentation:

Results from VALOR and the OLE are being presented at the ANA Annual Meeting.

Sunday, October 17, 2021, 4:20 p.m. ET – Results from the Phase 3 VALOR study and its open-label extension: evaluating the clinical efficacy and safety of tofersen in adults with ALS and confirmed SOD1 mutation, presented by Timothy Miller, M.D., Ph.D., principal investigator of VALOR and ALS Center Director at Washington University School of Medicine, St. Louis.

To access the presentation, please go to the Investors section of Biogen's website at investors.biogen.com. Following the event, an archived version will be available at <https://investors.biogen.com/>

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 Pharmaceuticals, Inc. under a collaborative development and license agreement.

About the Phase 3 VALOR Study (NCT02623699)

VALOR was a Phase 3, randomized, double-blind, placebo-controlled study to evaluate the efficacy, safety, tolerability and pharmacodynamic effects of tofersen 100 mg in adults with ALS and a confirmed SOD1 mutation. Subjects were randomized to receive tofersen or placebo. In total, 108 participants were randomized in VALOR (n=72 to tofersen 100 mg and n=36 to placebo). Sixty of these participants met the study's prognostic enrichment criteria for rapid disease progression based on SOD1 mutation type and pre-randomization ALSFRS-R slope decline and comprised the primary analysis population ("faster-progressing population"). Forty-eight participants did not meet these prognostic enrichment criteria ("slower-progressing population"). For more information about the Phase 3 VALOR study, visit www.clinicaltrials.gov.

About Ionis' Neurology Franchise

The Ionis neurology franchise addresses all major brain regions and central nervous system cell types and currently has four Phase 3 studies ongoing with 11 medicines in clinical development, three of which are wholly owned. Ionis is leading the way in treating root causes of many neurological diseases and developing antisense medicines for common diseases like Alzheimer's and Parkinson's as well as rare diseases like amyotrophic lateral sclerosis (ALS) and Alexander disease. Ionis' marketed neurological disease medicines include SPINRAZA[®], a global foundation of care for spinal muscular atrophy (SMA), licensed to and commercialized by Biogen.

About Ionis Pharmaceuticals

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 neurological and cardiometabolic franchises. Our scientific innovation began and continues with the knowledge that sick people depend on us, which fuels our vision of becoming one of the most successful biotechnology companies.

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, 2020, 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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 View original content to download multimedia: <https://www.prnewswire.com/news-releases/ionis-partner-biogen-provides-update-on-tofersen-phase-3-valor-study-in-sod1-als-301401807.html>

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