# Biogen Announces Topline Results from the Tofersen Phase 3 Study and its Open-Label Extension in SOD1-ALS

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- 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
- Topline data being presented today at the American Neurological Association 2021 Annual Meeting
- Given the high unmet medical need, Biogen will expand its ongoing early access program (EAP) to the broader SOD1-ALS population

A Media Snippet accompanying this announcement is available by clicking on the image or link below:

CAMBRIDGE, Mass., Oct. 17, 2021 (GLOBE NEWSWIRE) -- Biogen Inc. (Nasdaq: BIIB) today announced topline results from its pivotal Phase 3 VALOR study of tofersen (BIIB067), an investigational antisense drug 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 biologic 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 of 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 is actively engaging with regulators, the medical community, patient advocacy groups and other key stakeholders around the world to determine potential next steps.

“The results from the VALOR study are encouraging as they show reduction of SOD1 protein, reduction of neurofilament, a potential biomarker for neurodegenerative disease, and positive signals across multiple key endpoints including measures of important aspects of the daily lives of SOD1-ALS patients,” said Timothy Miller, M.D., Ph.D., principal investigator of VALOR and ALS Center Director at Washington University School of Medicine, St. Louis. “The wait for new options has been long and difficult for the ALS community, and we welcome this important research advancement in this difficult to treat disease space.”

“Data from the tofersen Phase 3 study and its open-label extension showed signs of slowing disease progression in people with SOD1-ALS, a rare, devastating disease that leads to loss of everyday functions and ultimately death,” said Alfred Sandrock, Jr., M.D., Ph.D., Head of Research and Development at Biogen. “Following discussions with investigators, bioethicists, and having listened to the voice of patient advocacy groups, we will broaden early access to tofersen to all eligible SOD1-ALS patients through our already established expanded access program. We are grateful for the courageous efforts of patients, families, advocates, and the scientific community who have contributed to this important research.”

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.

*Click here for a fact sheet to learn more about genetic amyotrophic lateral sclerosis (ALS):*
http://ml.globenewswire.com/Resource/Download/ae9c9142-ae2a-4d95-8f6f-0b5cf6e80963

In light of the critical unmet need, Biogen 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 clear 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 Details**

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 on the website.

**Biogen's Commitment to ALS**
For over a decade, Biogen has been committed to advancing ALS research to provide a deeper understanding of the disease. The company has continued to invest in and pioneer research despite making the difficult decision to discontinue a late-stage ALS asset in 2013. Biogen has applied important learnings to its broad portfolio of assets for genetic and other forms of ALS, with the goal of increasing the probability of bringing a potential therapy to patients in need. These applied learnings include evaluating genetically validated targets in defined patient populations, pursuing the most appropriate modality for each target and employing sensitive clinical endpoints. Today, the company has a broad pipeline of investigational drugs being evaluated in ALS.

**About Tofersen**
Tofersen is an antisense drug 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. 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 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. Life expectancy for people with ALS is 3-5 years from time of symptom onset. Multiple genes have been implicated in ALS. Mutations in the SOD1 gene are responsible for approximately two percent of all ALS cases (SOD1-ALS). SOD1-ALS can occur in patients with or without a family history of ALS. Genetic testing may help determine if a person's ALS is associated with a genetic mutation, even in individuals without a family history of the disease.

**About Biogen**
At Biogen, our mission is clear: we are pioneers in neuroscience. Biogen discovers, develops and delivers worldwide innovative therapies for people living with serious neurological and neurodegenerative diseases as well as related therapeutic adjacencies. One of the world's first global biotechnology companies, Biogen was founded in 1978 by Charles Weissmann, Heinz Schaller, Kenneth Murray and Nobel Prize winners Walter Gilbert and Phillip Sharp. Today Biogen has the leading portfolio of medicines to treat multiple sclerosis, has introduced the first approved treatment for spinal muscular atrophy, commercializes biosimilars of advanced biologics and is focused on advancing research programs in multiple sclerosis and neuroimmunology, Alzheimer's disease and dementia, neuromuscular disorders, movement disorders, ophthalmology, neuropsychiatry, immunology, acute neurology and neuropathic pain.

We routinely post information that may be important to investors on our website at www.biogen.com. Follow us on social media Twitter, LinkedIn, Facebook, YouTube.

**Biogen Safe Harbor Statement**
This news release contains forward-looking statements, including statements made pursuant to the safe harbor provisions of the Private Securities Litigation Reform Act of 1995, including statements about results from the Phase 3 VALOR study of tofersen; the potential clinical effects of tofersen; the potential benefits, safety and efficacy of tofersen; the clinical development program for tofersen; the identification and treatment of ALS; our research and development program for the treatment of ALS; the potential of our commercial business and pipeline programs, including tofersen; and risks and uncertainties associated with drug development and commercialization. These forward-looking statements may be accompanied by words

such as “aim,” “anticipate,” “believe,” “could,” “estimate,” “expect,” “forecast,” “intend,” “may,” “plan,” “potential,” “possible,” “will,” “would” and other words and terms of similar meaning. Drug development and commercialization involve a high degree of risk and only a small number of research and development programs result in commercialization of a product. Results in early stage clinical trials may not be indicative of full results or results from later stage or larger scale clinical trials and do not ensure regulatory approval. You should not place undue reliance on these statements or the scientific data presented.

These statements involve risks and uncertainties that could cause actual results to differ materially from those reflected in such statements, including without limitation, uncertainty of success in the development and potential commercialization of tofersen; the risk that we may not fully enroll our clinical trials or enrollment will take longer than expected; unexpected concerns may arise from additional data, analysis or results obtained during our clinical trials; regulatory authorities may require additional information or further studies, or may fail or refuse to approve or may delay approval of our drug candidates, including tofersen; the occurrence of adverse safety events; the risks of unexpected hurdles, costs or delays; failure to protect and enforce our data, intellectual property and other proprietary rights and uncertainties relating to intellectual property claims and challenges; product liability claims; and the direct and indirect impacts of the ongoing COVID-19 pandemic on our business, results of operations and financial condition. The foregoing sets forth many, but not all, of the factors that could cause actual results to differ from our expectations in any forward-looking statement. Investors should consider this cautionary statement, as well as the risk factors identified in our most recent annual or quarterly report and in other reports we have filed with the U.S. Securities and Exchange Commission. These statements are based on our current beliefs and expectations and speak only as of the date of this news release.

We do not undertake any obligation to publicly update any forward-looking statements, whether as a result of new information, future developments or otherwise.

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