New 12-Month Tofersen Data Presented at ENCALS Meeting Show Clinically Meaningful Benefit in People With SOD1-ALS

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- *12-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 the loss of everyday functions and affecting approximately 2% of people with ALS*

CAMBRIDGE, Mass., June 03, 2022 (GLOBE NEWSWIRE) -- Biogen Inc. (NASDAQ: BIIB) today announced new 12-month data for tofersen, an investigational antisense drug for people with superoxide dismutase 1 (SOD1) amyotrophic lateral sclerosis (ALS). The data show that earlier initiation of tofersen compared to delayed initiation (six months later in the open-label extension [OLE] study) 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 pivotal Phase 3 VALOR study and its OLE study.

The data were presented today at the European Network to Cure ALS (ENCALS) meeting in Edinburgh, Scotland between 9-10:25 a.m. BST. An archived version of the presentation will be available on the Investors section of Biogen's website at investors.biogen.com.

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 initial six-month and now 12-month results show that tofersen had an impact on important measures critical to people with SOD1-ALS," said Timothy Miller, M.D., Ph.D., principal investigator of VALOR and ALS Center co-Director at Washington University School of Medicine, St. Louis. "These new 12-month data showed tofersen consistently slowed disease progression across endpoints and, if approved, may meaningfully change the lives of people living with SOD1-ALS."

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 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.

"In ALS, people with more rapidly progressing disease have higher neurofilament levels, most likely because their neurons and axons are degenerating more quickly," said Merit Cudkowicz, M.D., co-principal investigator of the VALOR trial and co-founder of the Northeast ALS Consortium, Director of the Healey & AMG Center for ALS and Chair of Neurology at Massachusetts General Hospital and the Julieanne Dorn Professor of Neurology at Harvard Medical School. "Tofersen lowered neurofilament levels by approximately 40-50 percent. The combination of these biomarker results and the clinical outcomes data provide additional evidence of tofersen's potential to effectively slow the relentless progression of SOD1-ALS."

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.

"For more than a decade Biogen has pursued new medicines for ALS. These additional data further reinforce our belief in tofersen and we will continue to follow the science to change the course of this cruel and deadly disease," said Toby Ferguson, M.D., Ph.D., Vice President and Head of the Neuromuscular Development Unit at Biogen. "Biogen is engaging with FDA and regulators around the world, the medical community and patient advocacy groups and will provide updates on next steps when appropriate."

ENCALS Annual Meeting Details
Friday, June 3, 2022, 9-10:25 a.m. BST - *Evaluating the Efficacy and Safety of Tofersen in Adults with ALS and a SOD1 Mutation: Results from the Phase 3 VALOR Trial and Open-Label Extension,* presented by Timothy Miller, M.D., Ph.D., principal investigator of VALOR and ALS Center co-Director at Washington University School of Medicine, St. Louis. ENCALS is an annual scientific meeting to review advancements 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. 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 Pharmaceuticals, Inc. 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.[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 2 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]

Biogen's Continuous Commitment to ALS
For over a decade, Biogen has been committed to advancing ALS research to provide a deeper understanding of all forms 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 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 pipeline of investigational drugs being evaluated in ALS, including tofersen and BIIB105.

About Biogen
As pioneers in neuroscience, Biogen discovers, develops, and delivers worldwide innovative therapies for people living with serious neurological 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, Sir Kenneth Murray, and Nobel Prize winners Walter Gilbert and Phillip Sharp. Today, Biogen has a leading portfolio of medicines to treat multiple sclerosis, has introduced the first approved treatment for spinal muscular atrophy, and developed the first and only approved treatment to address a defining pathology of Alzheimer's disease. Biogen is also commercializing biosimilars and focusing on advancing one of the industry's most diversified pipeline in neuroscience that will transform the standard of care for patients in several areas of high unmet need.

In 2020, Biogen launched a bold 20-year, $250 million initiative to address the deeply interrelated issues of climate, health, and equity. Healthy Climate, Healthy Lives™ aims to eliminate fossil fuels across the company's operations, build collaborations with renowned institutions to advance the science to improve human health outcomes, and support underserved communities.

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 or its OLE; 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.

References:

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2. 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. PMID: 34247168.
3. Bali T, et al. Defining SOD1 ALS natural history to guide therapeutic clinical trial design. J Neurol Neurosurg Psychiatry. 2017 Feb;88(2):99-105. doi: 10.1136/jnnp-2016-313521. Epub 2016 Jun 3. PMID: 27261500; PMCID: PMC5136332.

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