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New 12-Month Tofersen Data Show Clinically Meaningful Benefit in People With SOD1-ALS

- *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*

Biogen 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 at the European Network to Cure ALS (ENCALS) meeting in Edinburgh, Scotland.

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.”

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.

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