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FDA Grants Accelerated Approval for QALSODY™ (tofersen) for SOD1-ALS, a Major Scientific Advancement as the First Treatment to Target a Genetic Cause of ALS

- FDA granted accelerated approval of QALSODY based on a reduction of neurofilament, a marker of neurodegeneration
- Superoxide dismutase 1 (*SOD1*)-amyotrophic lateral sclerosis (ALS) is a devastating, uniformly fatal, and ultra-rare genetic form of ALS with approximately 330 people in the U.S. living with the disease

Biogen announced that the U.S. Food and Drug Administration (FDA) has approved QALSODY™ (tofersen) 100 mg/15mL injection for the treatment of amyotrophic lateral sclerosis (ALS) in adults who have a mutation in the superoxide dismutase 1 (*SOD1*) gene. This indication is approved under accelerated approval based on reduction in plasma neurofilament light chain (NfL) observed in patients treated with QALSODY. Continued approval for this indication may be contingent upon verification of clinical benefit in confirmatory trial(s). The ongoing Phase 3 ATLAS study of tofersen in people with presymptomatic *SOD1*-ALS will serve as the confirmatory trial.

Neurofilaments are proteins that are released from neurons when they are damaged, making them a marker of neurodegeneration.

“For more than a decade, Biogen has been steadfast in our commitment to pursuing treatments for ALS, and I want to thank the scientists as well as the entire ALS community who have all worked tirelessly to bring this first-of-its-kind treatment to people with *SOD1*-ALS,” said Christopher A. Viehbacher, President and Chief Executive Officer of Biogen. “Today also marks a pivotal moment in ALS research as we gained, for the first time, consensus that neurofilament can be used as a surrogate marker reasonably likely to predict clinical benefit in *SOD1*-ALS. We believe this important scientific advancement will further accelerate innovative drug development for ALS.”

QALSODY is the first approved treatment to target a genetic cause of ALS. Biogen collaborated with Ionis Pharmaceuticals on the early development of tofersen.

Warnings and precautions associated with QALSODY were serious neurologic events, including myelitis and/or radiculitis; papilledema and elevated intracranial pressure; and aseptic meningitis. If symptoms consistent with myelitis, radiculitis papilledema, elevated intracranial, or aseptic meningitis develop, diagnostic workup and treatment should be initiated according to the standard of care. Management may require interruption or discontinuation of QALSODY. The most common adverse reactions that occurred in ≥10% of

QALSODY treated participants and more than the placebo arm were pain, fatigue, arthralgia, cerebrospinal (CSF) white blood cell increased, and myalgia.

“Since *SOD1* mutations were first identified as a cause of ALS 30 years ago, the familial ALS community has been searching for genetically targeted treatments. QALSODY offers families who have lost generation after generation in the prime of their life to this devastating disease a therapy targeting the underlying cause of *SOD1*-ALS. Today marks an important moment in ALS research as QALSODY is the first ALS treatment approved based on a biomarker,” said Jean Swidler, chair of Genetic ALS & FTD: End the Legacy. “We are excited to see what future therapies are developed now that it is understood that lowering levels of neurofilament provides important evidence that a treatment is affecting the neurodegenerative process.”

The efficacy of QALSODY was assessed in a 28-week randomized, double-blind, placebo-controlled clinical study in patients 23 to 78 years of age with weakness attributable to ALS and a *SOD1* mutation confirmed by a central laboratory. One hundred eight (108) patients were randomized 2:1 to receive treatment with either QALSODY 100 mg (n=72) or placebo (n=36) for 24 weeks (3 loading doses followed by 5 maintenance doses). Concomitant riluzole and/or edaravone use was permitted for patients and at baseline 62% of patients were taking riluzone, and 8% of patients were taking edaravone.

Over 28 weeks in VALOR, participants in the primary analysis population (n=60) treated with QALSODY experienced less decline from baseline as measured by the Revised Amyotrophic Lateral Sclerosis Functional Rating Scale (ALSFRS-R) compared to placebo, though the results were not statistically significant (QALSODY-placebo adjusted mean difference [95% CI]: 1.2 [-3.2, 5.5]). In the overall intent-to-treat population (n=108), QALSODY-treated participants experienced a 55% reduction in plasma NfL compared to a 12% increase in placebo-treated participants (difference in geometric mean ratios for QALSODY to placebo: 60%; nominal $p<0.0001$). Additionally, levels of CSF SOD1 protein, an indirect measure of target engagement, were reduced by 35% in the QALSODY-treated group compared to 2% in the corresponding placebo group (difference in geometric mean ratios for QALSODY to placebo: 34%; nominal $p<0.0001$).

At an interim analysis at 52 weeks of participants who had completed VALOR and enrolled in an open-label extension (OLE) study, reductions in NfL were seen in participants previously receiving placebo and who initiated QALSODY in the OLE, similar to the reductions seen in participants treated with QALSODY in VALOR. Earlier initiation of QALSODY compared to placebo/delayed-start of QALSODY was associated with trends for reduction in decline on measures of clinical function (ALSFRS-R), respiratory strength (slow vital capacity percent-predicted), and muscle strength (hand-held dynamometry megascore), though they were not statistically significant. QALSODY was also associated with a non-statistically significant trend towards reduction of the risk of death or permanent ventilation. These exploratory analyses should be interpreted with caution given the limitations of data collected outside of controlled study, which may be subject to confounding.

The approval of QALSODY was supported by 12-month integrated results from VALOR and its OLE comparing earlier initiation of tofersen (at the start of VALOR) to delayed initiation of tofersen (six months later, in the OLE), that were published in *The New England Journal of Medicine*.

“I have observed the positive impact QALSODY has on slowing the progression of ALS in people with *SOD1* mutations,” said Timothy M. Miller, MD, PhD, principal investigator of the

QALSODY clinical trials and co-director of the ALS Center at Washington University School of Medicine in St. Louis. “The FDA’s approval of QALSODY gives me hope that people living with this rare form of ALS could experience a reduction in decline in strength, clinical function, and respiratory function.”

QALSODY will be made available for shipment in the U.S. to healthcare providers in approximately one week. Biogen anticipates there may be variation in time to treatment as institutions and treatment centers learn about QALSODY.

What is QALSODY?
QALSODY™ (tofersen) is a prescription medicine used to treat amyotrophic lateral sclerosis (ALS) in adults who have a mutation in the superoxide dismutase 1 (*SOD1*) gene. This indication is approved under accelerated approval based on reduction in plasma neurofilament light chain (NfL) observed in patients treated with QALSODY. Continued approval for this indication may be contingent upon verification of clinical benefit in confirmatory trial(s).

About QALSODY™ (tofersen)
QALSODY is an antisense oligonucleotide (ASO) designed to bind to *SOD1* mRNA to reduce SOD1 protein production. QALSODY is indicated for the treatment of ALS in adults who have a mutation in the *SOD1* gene in the U.S. This indication is approved under accelerated approval based on reduction in plasma NfL observed in patients treated with QALSODY. Continued approval for this indication may be contingent upon verification of clinical benefit in confirmatory trial(s). QALSODY is administered intrathecally as three loading doses administered at 14-day intervals followed by maintenance doses administered once every 28 days thereafter.1 In people with *SOD1*-ALS, mutations in their *SOD1* gene cause their bodies to create a toxic misfolded form of SOD1 protein. This toxic protein causes motor neurons to degenerate, resulting in progressive muscle weakness, loss of function, and eventually, death.

Biogen licensed tofersen from Ionis Pharmaceuticals, Inc. under a collaborative development and license agreement. Tofersen was discovered by Ionis.

In addition to the ongoing OLE of VALOR, QALSODY is being studied in the Phase 3, randomized, placebo-controlled ATLAS study to evaluate whether QALSODY can delay clinical onset when initiated in presymptomatic individuals with a *SOD1* genetic mutation and biomarker evidence of disease activity (elevated plasma NfL). The primary efficacy endpoint is the proportion of participants with emergence of clinically manifest ALS. ATLAS is currently more than 50 percent enrolled with clinical trial sites in 14 countries worldwide with an estimated primary completion date in 2026. More details about ATLAS (NCT04856982) can be found at clintrials.gov

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