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

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- FDA granted accelerated approval of QALSODY based on a reduction of neurofilament, a marker of neurodegeneration[1]
- Superoxide dismutase 1 (*SOD1*)-amyotrophic lateral sclerosis (ALS) is a devastating, uniformly fatal,[2] and ultra-rare genetic form of ALS[3-4] with approximately 330 people in the U.S. living with the disease[5]

CAMBRIDGE, Mass., April 25, 2023 (GLOBE NEWSWIRE) -- Biogen Inc. (Nasdaq: BIIB) announced today 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).[1] The ongoing Phase 3 ATLAS study of tofersen in people with presymptomatic *SOD1*-ALS will serve as the confirmatory trial.[1]

Neurofilaments are proteins that are released from neurons when they are damaged, making them a marker of neurodegeneration.[6]

“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.[1] 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.[1]

“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.[1]

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 $p<0.0001$).[1]

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.[1]

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*.[7]

“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).

IMPORTANT SAFETY INFORMATION

What is the most important information that I should know about QALSODY?

QALSODY can cause serious side effects, including:

Inflammation of the spinal cord (myelitis) and/ or irritation of the nerve roots (radiculitis), including serious cases, have been reported in patients treated with QALSODY. Contact your healthcare provider to learn more about symptoms associated with myelitis or radiculitis, and/ or if you believe you are experiencing either of these conditions. QALSODY may need to be interrupted or discontinued.

Swelling of the optic nerve (papilledema) and increased pressure inside the skull (elevated intracranial pressure), including serious cases, have been reported in patients treated with QALSODY. Contact your healthcare provider to learn more about symptoms associated with papilledema or elevated intracranial pressure, and/ or if you believe you are experiencing either of these conditions.

Inflammation of the brain linings (aseptic meningitis), including serious cases, have been reported in patients treated with QALSODY. Contact your healthcare provider to learn more about symptoms associated with aseptic meningitis, and/ or if you believe you are experiencing this condition.

What should I tell my HCP before I start using QALSODY?

Before taking QALSODY, tell your healthcare provider if you are pregnant, plan to become pregnant, or are breastfeeding or plan to breastfeed.

What are the possible side effects of QALSODY?

The most common adverse reactions reported in patients treated with QALSODY were pain (back pain, pain in arms or legs), feeling tired, muscle and joint pain and increased white blood cell count in the cerebrospinal fluid (CSF).

This information is not intended to replace discussions with your healthcare provider.

These are not all the possible side effects of QALSODY. Please talk to your healthcare provider if you experience any of these symptoms, or other new symptoms that concern you.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

Please see full Prescribing Information.

For more details on QALSODY, visit www.QALSODY.com.

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.8

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 clinicaltrials.gov.

Financial Assistance Programs and Access to QALSODY
Biogen provides comprehensive support services which includes insurance couseling and financial assistance for eligible individuals. Support Coordinators are available to help with understanding insurance coverage, navigating the access landscape, and exploring financial assistance options including the QALSODY (tofersen) Copay Program, which may lower the out-of-pocket costs for eligible commercially insured patients to as low as $0. They can be reached at 1-877-725-7639 between the hours of 8:30 AM – 8:00 PM ET, Monday to Friday.

ALS Identified™ Program
Up to 15 percent of people living with ALS are thought to have a genetic form of the disease, whether or not they have a known family history. As genetic testing is not broadly available, Biogen sponsors a genetic testing program, ALS Identified™, for people living with ALS and their families in the U.S.

Sponsored by Biogen and offered through Invitae, the ALS Identified™ program facilitates access to genetic counseling and testing for all individuals 18 years or older within the U.S. and Puerto Rico with a clinical diagnosis of ALS, or a family history of ALS at no charge. More information about ALS Identified is available at insideALS.com, a website designed in collaboration with outside medical experts and the ALS community that offers continuous updates on the emerging science that provides insights and information to the ALS community. Interested people with ALS should talk to their doctor about genetic testing options and can learn more at insideALS.com.

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.[2]

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 known family history of the disease. *SOD1*-ALS is diagnosed in approximately 2 percent of all ALS cases, with about 330 people in the United States living with the disease.[5] More than 15 percent of people with ALS are thought to have a genetic form of the disease;[8] however, they may not have a known family history of the disease.[5]

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. In addition to QALSODY, the company has a pipeline of investigational drugs being evaluated in ALS, including BIIB105.

About Biogen
Founded in 1978, Biogen is a leading global biotechnology company that has pioneered multiple breakthrough innovations including a broad portfolio of medicines to treat multiple sclerosis, the first approved treatment for spinal muscular atrophy, and two co-developed treatments to address a defining pathology of Alzheimer's disease. Biogen is advancing a pipeline of potential novel therapies across neurology, neuropsychiatry, specialized immunology and rare diseases and remains acutely focused on its purpose of serving humanity through science while advancing a healthier, more sustainable and equitable world.

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
This news release contains forward-looking statements, the potential clinical effects of QALSODY; the potential benefits, safety and efficacy of QALSODY; the clinical development program for QALSODY; 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 QALSODY; 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 our forward-looking statements.

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 speak only as of the date of this news release.

We do not undertake any obligation to publicly update any forward-looking statements.

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