

VIA ELECTRONIC SUBMISSION

March 8, 2023

U.S. Food and Drug Administration
Peripheral and Central Nervous System Drugs Advisory Committee
Dockets Management Staff (HFA-305)
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

RE: Docket No. FDA-2022-N-0691 for “Peripheral and Central Nervous System Drugs Advisory Committee; Notice of Meeting; Establishment of a Public Docket; Request for Comments”

Dear Sir or Madam,

The ALS Association is pleased to provide comments in response to the meeting of the Peripheral and Central Nervous System Drugs Advisory Committee for new drug application (NDA) 215887, for tofersen (BIB067), submitted by Biogen, Inc., for the treatment of amyotrophic lateral sclerosis (ALS) associated with a mutation in the superoxide dismutase 1 (*SOD1*) gene. This meeting is a critical step in bringing new treatments and hope to people living with ALS.

Background

ALS is a progressive neurodegenerative disease that affects nerve cells in the brain and spinal cord. Ultimately, people with ALS become prisoners within their own bodies, unable to eat, breathe, or move on their own. Their minds, however, often remain sharp so they are aware of what’s happening to them. There is no cure for ALS, and most people with the disease die within 2-5 years of diagnosis. For unknown reasons, military veterans are twice as likely to develop ALS as the general population.

The ALS Association is dedicated to making ALS a livable disease until we can find a cure for everyone. We provide care services to more than 20,000 Americans living with ALS and certify a network of over 90 specialty multidisciplinary ALS clinics that deliver state-of-the-art care. We are also the world’s largest philanthropic funder of ALS research, supporting more than 140 ALS research projects around the globe at any given time.

Approximately 10% of ALS cases are characterized as familial (when a person has a family history of the disease), and 90% of cases are sporadic (meaning no family history of ALS). More than 40 genes have now been associated with ALS. The *SOD1* gene was the first one discovered, back in 1993. The *SOD1* gene contains the instructions needed to produce the SOD1 protein. SOD1 is an abundant enzyme within cells that serves to keep them safe from metabolic waste that can do damage if not rendered harmless. Mutations in the *SOD1* gene result in the formation of toxic SOD1 proteins. *SOD1* gene mutations account for approximately 15-20% of familial ALS, and the most common *SOD1* gene mutations in North America are associated with younger age of onset and shorter survival. In other words, *SOD1*-linked ALS is a particularly rare and aggressive form of this already rare and devastating disease.

Tofersen is an antisense oligonucleotide (ASO) drug that binds to SOD1 mRNA and targets it for degradation, thereby reducing production of the toxic SOD1 protein. The Food and Drug Administration (FDA) is reviewing tofersen’s NDA for accelerated approval. We would like to emphasize that the FDA instituted its Accelerated Approval Program “to allow for earlier approval of drugs that treat serious conditions, and fill an unmet medical



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OUR MISSION: To discover treatments and a cure for ALS, and to serve, advocate for, and empower people affected by ALS to live their lives to the fullest.

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need based on a surrogate endpoint.” Our understanding is that qualification for accelerated approval requires the drug to treat a serious condition, provide a meaningful advantage over existing therapies, and demonstrate an effect on a surrogate marker that is reasonably likely to predict clinical benefit. Given the data at this stage, tofersen meets all three of these conditions.

Treating a Serious Condition

SOD1-linked ALS is an ultra-rare and serious condition associated with an aggressive form of ALS. Currently, there are no specific therapies targeting this form of ALS. There are three FDA-approved drugs for all types of ALS that provide modest benefits on disease progression and survival.

Demonstrating an Effect on a Surrogate Marker

Tofersen is a first-in-class gene therapy developed specifically to target toxic *SOD1* mRNA and protein. The phase 3 VALOR trial and its open label extension (OLE) study showed that tofersen reduces total *SOD1* protein levels in cerebrospinal fluid (CSF) by 35% as early as 8 weeks after the start of treatment. However, the trial failed to reach its primary endpoint as measured by change in the Revised Amyotrophic Lateral Sclerosis Functional Rating Scale (ALSFRS-R) at 28 weeks. The totality of the evidence suggests that the 28 weeks allotted for the initial trial were not long enough to demonstrate clinical benefit but were long enough to demonstrate impact on an important biomarker, neurofilament light (NfL). By 12-16 weeks, tofersen reduced plasma NfL, a marker of axonal injury and neurodegeneration, by 50%.

NfL is uniquely expressed in brain cells and plays a role in the scaffolding of neurons. When neurons are degenerating, such as what happens in ALS, the scaffolding breaks down, and NfL eventually leaks into CSF and blood, where it can be measured as a marker of neuronal damage. Extensive evidence collected throughout the last decade shows that NfL levels are 5-10-fold higher in the CSF and blood of people with ALS. Even more importantly, these elevations in NfL precede the emergence of clinical symptoms of the disease, which correlates with the knowledge that over 50% of neurons have degenerated by time of diagnosis. In pre-symptomatic *SOD1* gene carriers (individuals with the mutated gene who have not yet developed symptoms of ALS), serum NfL levels were elevated 6-12 months prior to symptom onset, demonstrating a strong link between NfL levels and the risk of disease development. In addition to NfL being a potential risk biomarker, it may also serve as a prognostic marker. NfL levels across all forms of ALS (not only *SOD1*-linked ALS) have been correlated with rate of disease progression (as measured by ALSFRS-R) as well as survival.

NfL is reduced by clinically effective therapeutics in other neurodegenerative diseases, such as multiple sclerosis and spinal muscular atrophy. Tofersen has consistently reduced NfL levels in preclinical studies and in two subsequent clinical trials, and these reductions were significant, robust, and sustained over time. More importantly, these reductions preceded slowing of clinical decline. Given NfL’s role as a risk, prognostic, and treatment marker and in predicting ALS with high specificity and sensitivity, it is very likely that reduction of NfL by tofersen can serve as a surrogate endpoint reasonably likely to predict future clinical benefit in *SOD1*-linked ALS.

Providing a Meaningful Advantage over Existing Therapies

As previously noted, by the time someone is diagnosed with ALS, they have lost over half their motor neurons. That deterioration continues for the remainder of their life, so being able to dramatically reduce the rate of neurodegeneration after 4 months of treatment is important. However, it can take even longer for that impact to translate into clinical benefit. By 52 weeks, that benefit becomes clear. Earlier initiation of tofersen significantly slowed decline of clinical function as measured by ALSFRS-R by an average of 3.5 points when compared to a comparison group who received tofersen 6 months later. Complementary to effects on ALSFRS-R, tofersen also significantly reduced decline in respiratory function, muscle strength, and patient-reported outcome measures of

quality of life (such as ASLAQ-5 and EQ-5D-5L). To our knowledge, this is the first drug to have effects on ALSFRS-R, respiratory function, muscle strength, and quality of life measures, thus providing a meaningful advantage over existing therapies. When combined with tofersen's substantial effect on lowering NfL in people with a particularly aggressive form of an already devastating disease, this evidence supports all three conditions necessary for accelerated approval.

Additional Considerations

We recognize that the FDA has a tough decision to make. The original randomized, double-blind VALOR trial did not meet its primary endpoint even though there were trends suggesting slowing of clinical decline in faster-progressing people with ALS. There are always concerns around the methodology of data collected during the OLE (and unblinded) phase after a blinded clinical trial. It is important to note that for drugs granted accelerated approval, post-marketing trials have been required to confirm the anticipated clinical benefit. Given the fact that *SOD1*-linked ALS impacts about 2% of people diagnosed with the disease and the heterogeneity within this population, it would not be ethically or operationally possible to run a new larger and longer randomized trial. However, Biogen's ongoing ATLAS prevention trial of tofersen in pre-symptomatic *SOD1* mutation carriers is a randomized, double-blind, placebo-controlled trial that could serve as a confirmatory trial. This trial is projected to be completed in 2027. Four years is a very long time for people with ALS, where survival is typically only 2-5 years after diagnosis, but it is well within the commonly accepted timeframe for generation of confirmatory evidence following accelerated approval.

Larry Falivena is a person living with *SOD1*-linked ALS who serves on The ALS Association's Board of Trustees. Larry participated in the VALOR trial and the OLE and has continued to access tofersen through an expanded access program. Larry says about tofersen that "while there's no history of my particular genetic mutation in my family, I do know several people who've had to deal with the tragedy of familial ALS and have lost numerous members of their family across generations. It's like having this giant boulder hanging over your head. You never know when or if it's just going to drop down and crush you. I can't imagine trying to deal with that anxiety on a daily basis. But that's the life of someone with familial ALS. And that's why finding these treatments, hopefully finding prevention for genetic ALS, can make a huge difference to families who've already experienced so much loss."

ALS Association Investment and Review Process

The ALS Association was the first to fund research of ASOs in ALS back in 2004 when it was a nascent technology. We have subsequently funded five additional studies, including preclinical efficacy and safety, pharmacodynamic measurements, and tofersen's first-in-human phase 1 trial assessing safety and target engagement. The ALS Association has committed more than \$1.3 million to ASO technology and the development of tofersen over the last two decades. We are pleased that our funding has resulted in advancement of the first-ever gene therapy for ALS.

ALS Association grants typically include pay-back provisions, but it is unclear at this time whether the relevant grants contain such provisions and whether The ALS Association would receive any financial return resulting from its financial support if the drug is approved. If this were to occur, any return will be applied solely to ongoing research efforts to help improve the lives of people with ALS. Biogen and Ionis have been sponsors of The ALS Association for many years.

The Association only makes recommendations on drug approvals after seeking independent peer review, as described at <https://www.als.org/research/emerging-drugs/our-position-supporting-approval-experimental-therapies/>. Specifically, we ask sponsors to share data that will be submitted to the FDA and engage the recommendations of external experts who are not conflicted in any way with the program or the sponsor. Consistent with that policy, The ALS Association has consulted with independent experts to conclude that the

safety and efficacy evidence in the context of NfL are sufficient for approval of tofersen through an accelerated approval pathway. People with *SOD1*-linked ALS and their health care providers should have full access to this drug as soon as possible.

Conclusion

We urge the Advisory Committee to take into consideration that *SOD1*-linked ALS is an ultra-rare and aggressive form of ALS, that the ongoing ATLAS trial will serve as a confirmatory trial to fulfill the requirements of accelerated approval and to make a favorable recommendation. The FDA, in turn, should move swiftly to approve tofersen for *SOD1*-linked ALS. Our community cannot wait.

Sincerely,

A handwritten signature in black ink, appearing to read 'Calaneet Balas', written in a cursive style.

Calaneet Balas

President & CEO