July 26, 2022

Dear ALS Community,

We are writing to let you know that Biogen announced that the U.S. Food and Drug Administration (FDA) has accepted Biogen's New Drug Application for tofersen, an investigational drug for superoxide dismutase 1 (SOD1) amyotrophic lateral sclerosis (ALS). The FDA granted priority review and has given a Prescription Drug User Fee Act action date of January 25, 2023. The FDA has stated that it is currently planning to hold an Advisory Committee meeting for this application, on a yet-to-be-determined date.

Biogen is seeking approval of tofersen under the FDA's accelerated approval pathway, based on the use of neurofilament as a surrogate marker that is reasonably likely to predict clinical benefit. The reductions in neurofilament are supported by signs of slower clinical decline in participants that received tofersen.

What is the Accelerated Approval Pathway? [1, 2]

The FDA instituted its Accelerated Approval Program to allow for earlier approval of drugs that treat serious conditions, and that fill an unmet medical need based on a surrogate endpoint. A surrogate endpoint is a marker, such as a laboratory measurement, radiographic image, physical sign, or other measure that is thought to predict clinical benefit, but is not itself a measure of clinical benefit. The use of a surrogate endpoint can considerably shorten the time required prior to receiving FDA approval.

The FDA has approved at least 278 drugs under the accelerated approval pathway. All sponsors whose medicines receive accelerated approval must complete and submit results from a confirmatory clinical trial to the FDA within a pre-specified timeframe to obtain traditional approval. If the confirmatory trial does not show that the drug provides clinical benefit, FDA has regulatory procedures in place that could lead to removing the drug from the market.

What are neurofilaments?[3]

Neurofilaments are normal proteins that are found in healthy motor neurons. However, when damage has been done to neurons or their axons, the amount of neurofilament found in the cerebrospinal fluid or blood rises. In ALS, higher levels of neurofilaments have been found to predict more rapid decline in clinical function and shortened survival.

What data were included in the submission to the FDA?

The NDA for tofersen contains results from several different clinical trials: 1) a Phase 1 study in healthy volunteers, 2) a Phase 1/2 study evaluating ascending dose levels[4], 3) the Phase 3 VALOR study, and 4) the open-label extension (OLE) study. Also included are the latest 12-month integrated results from VALOR and the OLE study, recently presented at the European Network to Cure ALS (ENCALS) annual meeting.

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) as announced in October 2021. However, integrated 12-month data from the VALOR study and its OLE (reported at the ENCALS meeting in June 2022) show that earlier start of tofersen slowed decline across efficacy endpoints (ALSFRS-R, slow vital capacity (SVC), handheld dynamometry megascore (HHD), and amyotrophic lateral sclerosis assessment questionnaire

(ALSAQ-5)). Tofersen study results also suggest that reductions in neurofilament preceded and predicted these outcomes.

The most common adverse events (AEs) in participants receiving tofersen in VALOR and OLE were headache, procedural pain, fall, back pain, and pain in extremity. Serious neurologic events were observed in 6.7% of participants receiving tofersen in VALOR and the 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.

The NDA for tofersen contains data produced by more than 150 people who volunteered to be part of these clinical research studies. We are deeply humbled by the bravery and commitment each person has brought to the tofersen clinical research program since it began in 2016.

Will there be any changes to the OLE, EAP, or ATLAS?

During the FDA review period, Biogen will maintain its early access program for tofersen, now open with participants in over a dozen countries. The open-label extension and Phase 3 ATLAS study in presymptomatic individuals with a SOD1 genetic mutation remain ongoing.

While the FDA is the regulatory body that approves the marketing of medicines in the US, Biogen is also engaging with regulators in other countries, as well.

Thank you again for requesting information about the status of the tofersen program. We will provide additional updates as available.

Sincerely,
Biogen

References:

1. Accelerated Approval Program, FDA Website https://www.fda.gov/drugs/information-health-care-professionals-drugs/accelerated-approval-program Accessed July 25, 2022
2. About the Accelerated Approval Pathway, Every Life Foundation Webpage https://everylifefoundation.org/accelerated-approval/ Accessed July 25, 2022
3. Thompson AG et al. Multicentre appraisal of amyotrophic lateral sclerosis biofluid biomarkers shows primacy of blood neurofilament light chain. Brain Commun. 2022;4(1):fcac029. Published 2022 Feb 9. doi:10.1093/braincomms/fcac029
4. Miller T et al. Phase 1–2 Trial of Antisense Oligonucleotide Tofersen for SOD1 ALS. N Engl J Med. 2020;283(2). Published 2020 July 9. doi: 10.1056/NEJMoa2003715