INTERNATIONAL ALLIANCE OF ALS/MND ASSOCIATIONS

Biogen – SOD1 Antisense Oligonucleotide (BIIB067 – Tofersen) – August 2022

Background

Biogen partnered with Ionis Pharmaceuticals to advance a type of therapy called antisense oligonucleotides (ASOs), which are biological substances that can block the production of a specific gene/protein target. The first ASO target for ALS is superoxide dismutase 1 (SOD1); the first gene discovered to cause ALS back in 1993. A small change in the composition of the SOD1 gene leads to an abnormal SOD1 protein. Over the years, it was determined that this abnormal protein causes ALS, not by losing its normal, protective function, but by becoming toxic to motor neurons. An ASO that blocks SOD1 production was suggested as a logical treatment target.

A phase 1-2 clinical trial of tofersen (the SOD1 ASO) with 50 participants was started in 2016 at 17 sites in the United States, Europe and Canada with the goal of assessing safety, tolerability and of understanding how it acts inside the human body. The study showed that these goals were met and a secondary measure of whether there was reduced SOD1 in the cerebrospinal fluid (a biomarker of effect) was also significantly achieved. Furthermore, there was a trend towards slowing of ALS progression in three measures including functional decline, respiratory function and muscle strength. This means that the treatment seemed to be very effective at slowing the loss of these three measures, but the number of participants was too low to form conclusions with statistical certainty. Results were published here in July 2020 and based on the promising results of these first two steps, tofersen was studied for safety and efficacy in a phase 3 clinical trial called VALOR, with readout planned for 2021.

In April 2021, Biogen announced the intent to offer a first stage of early access to a subset of individuals affected by SOD1-ALS beginning with individuals who have the most rapidly progressive disease. This program began in July 2021. The second stage, aimed at providing access to the broad SOD1-ALS population would be triggered by phase 3 study results that indicate safety and efficacy, yielding no need for additional studies.

On October 17, 2021, a presentation and press release described the results of the phase 3 VALOR study indicating that while tofersen did not demonstrate statistical significance in the primary measure of disease progression as measured by the ALSFRS-R, multiple secondary and exploratory measures of motor function, respiratory function, muscle strength and quality of life suggested the potential of a positive effect. Reduction in SOD1 levels resulting in a statistically significant reduction in CSF neurofilament light chain levels (NfL) also suggest potential perseveration of neuronal health. Further analysis of the trial data by the scientific and medical community will be necessary to better understand these complex results and how they correlate to a potential for a clinically meaningful effect in people living with ALS caused by mutations in the SOD1 gene.

On June 3, 2022, additional 12-month open label extension (OLE) data was presented, demonstrating a more robust effect for all participants originally randomized to tofersen in the first six months (termed “early-start”) as compared to those on placebo (termed “delayed-start”). Reduction of target SOD1 levels was sustained in months 6-12 of the OLE and plasma NfL levels in the delayed-start group were reduced to levels of the early start group. ALSFRS-R was significantly higher in the early-start group after twelve

months of OLE, as is respiratory function, muscle strength and two quality of life questionnaires. The data also indicates a trend towards stabilized or improved functions during months 6-12 in the delayed-start group, as well as effect on survival in the early-start group, but these should be interpreted with caution until longer term data is obtained.

On July 26, 2022, it was announced that the U.S. Food and Drug Administration (FDA) accepted Biogen's New Drug Application for tofersen and granted it Priority Review with an action date of January 25, 2023. The FDA has noted 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 biomarker, indicating that they intend it to predict clinical benefit. No information is available yet about applications to other jurisdictions for regulatory approval.

Early Access Program

Since 2021, Biogen has "expanded eligibility for its ongoing early access program to all people with SOD1-ALS, in countries where such programs are permitted by local regulations and future access may be secured." Individuals with an ALS diagnosis associated with a mutation in the SOD1 gene are eligible to receive tofersen free-of-charge provided their clinician is able to provide a prescription and demonstrated capability to deliver the treatment. Of note, Biogen is legally unable to provide financial support for the clinical delivery of tofersen so clinics would need to have the capacity to support treatment independently. It was also stated that they may revise or discontinue this program if no clear path forward is established for tofersen or if another trial is required.

Biogen has also initiated the ATLAS study in 2021 to determine if pre-symptomatic treatment of SOD1 mutation carriers may represent more optimal timing of intervention. Given that individuals with SOD1 mutations can be recognized as at-risk of developing ALS through genetic testing prior to onset of symptoms, tofersen represents a tremendous opportunity to determine if treatment in pre-symptomatic individuals could provide a more robust effect on disease progression.

Early intervention has long been considered as likely optimal in ALS/MND, though it has never been clinically tested. The ability to initiate experimental and proven treatments upstream of clinical symptom onset is a milestone that requires a biological indicator (biomarker) of underlying disease processes being triggered.

In recent years, a significant amount of work has yielded the protein called neurofilament light chain (NfL) as a potential blood biomarker to indicate that nervous system damage has occurred. While this is not specific for ALS, when combined with known, disease-causing genetic mutations, it may provide an opportunity to visualize the pre-clinical triggering of ALS/MND processes.

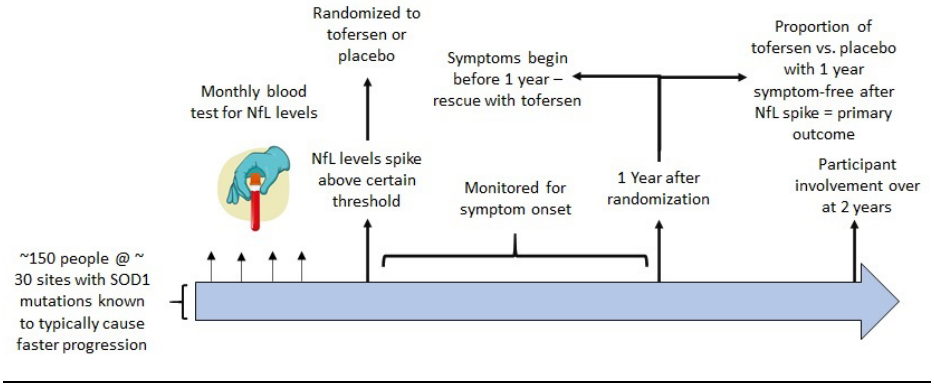
The ATLAS clinical trial will study approximately 150 individuals with SOD1 mutations that are typically associated with rapid disease progression. Participants will be screened monthly for NfL levels and when there is a rise in levels above a particular threshold, they will be enrolled into the portion of the study where they will be randomized to either tofersen or placebo. Any participant, upon developing clinical

symptoms of ALS/MND, will be moved to an open-label portion where they will receive tofersen. This ensures that no one in the study who has been diagnosed by an ALS clinician will be treated with placebo.

The novel primary measure of evaluation will be the proportion of participants who develop clinical symptoms of ALS within one year of randomization. Given that the participants will have SOD1 mutations associated with rapid progression, if a significant number do not have clinical symptoms after one year, it would suggest that tofersen is able to delay the disease process. Participants will be treated for up to two years as part of the study.

Future Pre-symptomatic Clinical Trials

It is hoped that the ATLAS trial will pave the way for more pre-symptomatic trials in the future. Should therapies become proven as effective for other known genetic mutations, these pre-symptomatic studies may indicate the next logical step and will have learned from ATLAS in the effectiveness of using NfL as a trial initiation biomarker in practice. For cases where there is no identifiable mutation in a known ALS gene, researchers will need to identify additional biomarker(s) that can differentiate between nervous system damage indicating ALS versus that of many other conditions. As of 2021, there is nothing fitting this criterion that is close to clinical use, but a strong effort is underway in labs around the world.



ATLAS trial design overview

Summary

Based on the available evidence, it is the opinion of the SAC that tofersen is likely to have a significant benefit for people living with ALS caused by a mutation in the SOD1 gene, particularly in those starting treatment earlier. Despite currently being under review by the FDA for approval, further data should continue to be collected and monitored to determine if this benefit is confirmed and sustained. The pre-symptomatic ATLAS trial is an important next step in the evaluation of tofersen for SOD1-ALS and represents a landmark for all future ALS trials. Biogen should continue to explore options that could provide access to people living with SOD1-ALS who stand to benefit from tofersen as indicated by detailed analysis of the data presented to date. The SAC encourages any member organization to reach out to the company directly to enquire whether any plans exist for their country or region.