INTERNATIONAL ALLIANCE OF ALS/MND ASSOCIATIONS

Biogen – SOD1 Antisense Oligonucleotide (BIIB067 – Tofersen) – October 2021

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 clinical trial of tofersen (the SOD1 ASO) with 50 participants was run at 17 sites in the United States, Europe and Canada with the goal of assessing safety, tolerability and 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.

In April 2021, Biogen announced the intent to offer a first stage of compassionate use 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.

Biogen also announced their intent to continue with "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." It was 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.

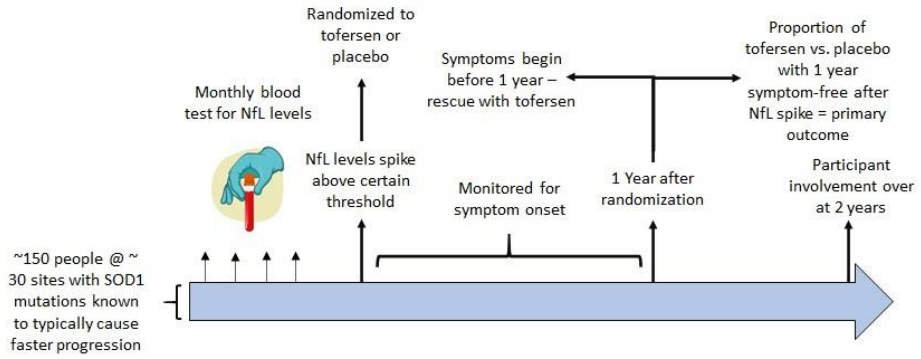
In recent years, a significant amount of work has yielded the protein called neurofilament light chain (NfL) as a potential blood biomarker to indicate that nervous system damage has occurred. While this is not specific for ALS, when combined with known, disease-causing genetic mutations, it may provide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

Biogen and Ionis are currently collaborating on two other antisense oligonucleotide clinical trials. One is targeting the most common genetic mutation in ALS, called C9ORF72, and is already recruiting in phase 1 at several multinational sites. C9ORF72 mutations are the most commonly found genetic alteration in hereditary/familial ALS, but they are also found in about 5-10% of sporadic cases. The other will target a gene encoding a protein called ataxin-2 and will aim to treat certain people with sporadic ALS. It is anticipated that this strategy will be used to target other genes in the years to come.

Recommendation

Further discussion around the data from the VALOR trial in the days ahead will help to establish a better understanding of what can be concluded, and this briefing note will be updated as that becomes clearer. Biogen should explore any 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. Pursuing 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.