

Biogen – SOD1 Antisense Oligonucleotide (BIIB067 – Tofersen) – Summer 2019

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 genetic sequence 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.

As a result of these findings, Biogen has extended the current Phase 1 trial into an immediate Phase 3 trial that will add participants and aim to determine if the effect on disease course is significant enough to warrant an application for approval and availability to people living with ALS as quickly as possible.

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 people with sporadic ALS.

Recommendation

Despite these clinical trial results being amongst the most impressive ever seen in ALS, we still only know that tofersen is safe and tolerable, and do not know if it actually works to slow progression. As a result, it should be explained that the results of the Phase 1 were promising and the current Phase 3 trial is aiming to have an answer by the middle of 2020.

Further information

Inevitably, if tofersen proves to be effective for people with SOD1 mutations, there will be some individuals asking about its ability in ALS cases without the mutation, including the largely sporadic population, but also those with other mutations. There is a lot of literature suggesting that SOD1 might be a common factor in spreading the disease from cell-to-cell for everyone, but it is controversial and far from proven. However, the public may latch on to that work and the messaging will need to be that there is no consensus that SOD1 plays a prominent role in these other forms of ALS and until Biogen tests the ASO in a trial with wider eligibility, there is no indication or suggestion that it would work.

The SAC will continue to monitor Biogen and Toferson, and provide updates to the Alliance as they are needed or requested.