IONIS™ InBrief
10 July 2020

New England Journal of Medicine: Results of Phase 1/2 study of tofersen, an antisense oligonucleotide, demonstrate proof-of-concept and proof-of-biology of the Ionis-created therapy to treat SOD1 familial ALS

Patients treated with tofersen in the study demonstrated disease stabilization compared to patients on placebo after only three months

Researchers conducted a Phase 1/2 study evaluating tofersen in 50 adults with amyotrophic lateral sclerosis (ALS) due to superoxide dismutase 1 (SOD1) mutations. ALS is a heterogeneous disorder of progressive degeneration of upper and lower motor neurons that typically leads to death from ventilatory failure within five years of disease onset. It is believed that up to two percent of all ALS cases result from mutations in the SOD1 gene.

The primary objectives of the randomized, placebo-controlled, single- and multiple ascending (MAD) dose trial were evaluating the safety, tolerability and pharmacokinetics of tofersen in patients living with SOD1-ALS. The secondary outcome was the change in baseline in the cerebrospinal fluid (CSF) SOD1 protein concentration. Study participants were randomized to receive tofersen (20 mg, 40 mg, 60 mg or 100 mg) or placebo for three months. Of the 50 patients who were randomized, 48 received the planned treatment of doses or placebo.

The study published in the New England Journal of Medicine demonstrated that treatment with tofersen 100 mg over a three month period resulted in a 36 percent reduction in CSF SOD1 concentration compared to three percent in the placebo group. Reduction in neurofilament proteins in CSF and plasma were observed in the 100 mg dose group whereas they were unchanged in the placebo group. The rate of disease progression, as measured by the ALS Functional Rating Scale (ALSFRS-R) and slow vital capacity, a measure of pulmonary function, were reduced in patients treated with 100 mg of toferesen compared to placebo-treated patients after only three months of treatment. In those patients who have fast progressing SOD1 mutations, the effects of tofersen were even more evident; with a 0.84 point improvement in ALSFRS-R in subjects treated with 100 mg of tofersen compared to 16.73 point decline in placebo treated patients.

KEY TAKEAWAY

The findings published in NEJM support further clinical development of tofersen in the VALOR Phase 3 study, which is currently evaluating the efficacy and safety of tofersen versus placebo in adults with SOD1-ALS.

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All 50 study participants were included in the safety analysis. Adverse events were similar among patients treated with tofersen and placebo and there were no drug-related serious adverse events. Additional information can be found in NEJM.

Tofersen, the most advanced therapy in Ionis' robust pipeline, is the first investigational medicine to demonstrate clinical benefit in patients living with SOD1-ALS. The Phase 3 VALOR clinical trial, being conducted by Biogen, enlists an innovative study design with the potential to support registration. Data from the pivotal study is expected in 2021.

Created with Ionis' innovative antisense technology platform, tofersen is being developed with and will be commercialized by Biogen as part of a strategic collaboration between the two companies to develop antisense therapies for a broad range of neurological diseases.