Dear ALS Community,

We are writing to share an exciting update on our progress towards developing a treatment for patients with amyotrophic lateral sclerosis (ALS) with mutations in the fused in sarcoma FUS gene. Ionis has initiated a global, multi-center, placebo-controlled Phase 3 trial of ION363, an investigational medicine that targets the production of the FUS protein. ION363 targets and destroys the FUS messenger RNA, copies of the FUS gene, reducing the production of the FUS protein. By targeting the root cause of FUS-ALS, we believe that ION363 has the potential to reduce or prevent disease progression in FUS-ALS patients.

The initiation of this clinical trial is an important step forward for the ALS community. While it is exciting to have a drug in development that may be disease-modifying for patients living with ALS with FUS mutations, we recognize that this may only help a very small percentage of ALS patients. The rare ALS patients with a mutation in the *FUS* gene can develop ALS in adolescence or early adulthood, when the disease can progress very rapidly, as well as later in life. Indeed, FUS-ALS is the most common genetic cause of juvenile-onset ALS (e.g., ALS with onset < 25 years). Therefore, genetic counseling and testing in newly diagnosed ALS patients who are under the age of 30 years is critical to the diagnosis of FUS-ALS.

The multi-centered Phase 3 trial of ION363 will recruit up to 64 patients who have a FUS mutation. There are two parts of the study, the first part of the trial will consist of patients randomized to receive ION363 or placebo for 29 weeks. The second part of the study will be an open-label period of the study in which all participating patients will receive ION363 for 73 weeks. For more details on who may be able to participate in the study, please visit: www.clinicaltrials.gov (NCT04768972)

The study will be led by Neil Shneider, M.D., Ph.D., director of Columbia University's Eleanor and Lou Gehrig ALS Center. As many of you know, Ionis began collaborating with Dr. Shneider when the company learned of his efforts to develop a treatment for Jaci Hermstad, an Iowa woman living with FUS-ALS. Ionis shared its research and expertise with Dr. Shneider, resulting in an experimental treatment developed for Jaci, subsequently named "jacifusen" . While Jaci has since passed, her spirit and courage have inspired us all. Since Jaci, several FUS-ALS patients have received treatment with ION363 under Dr. Shneider's investigator-initiated program through the U.S. Food and Drug Administration's expanded access pathway, sometimes called "compassionate use." However, because the demand for Dr Shneider's compassionate use program has been overwhelming, Ionis made the decision to work with the FDA to design an adequately controlled clinical study to define the safety and efficacy of ION363 and make this a therapeutic option for all patients who may benefit from it.

We are very grateful to all individuals and families who volunteer to take part in research and drug development efforts. Only with your support can we advance potential therapies towards clinical trials. We look forward to continuing our partnership with the community as we advance towards a treatment for FUS-ALS, and we will continue to update the community regularly on our progress.

Sincerely,
The Ionis FUS-ALS Team

For additional questions, please contact: patients@ionisph.com