Ionis initiates Phase 3 trial of novel antisense medicine to treat leading cause of juvenile-onset ALS

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- ION363, the first medicine to specifically target FUS-ALS, is among Ionis' wholly owned assets the company plans to commercialize

- ALS portfolio now includes four clinical-stage investigational antisense medicines designed to treat the root causes of genetic and non-genetic forms of the disease

- Journey to pivotal clinical study began with Ionis' commitment to Jaci Hermstad, the first patient treated with ION363 under a 'compassionate use' protocol led by Dr. Neil Shneider of Columbia University

CARLSBAD, Calif., April 5, 2021 /PRNewswire/ -- Ionis Pharmaceuticals, Inc. (NASDAQ: IONS) today announced the initiation of a Phase 3 clinical trial of ION363 in patients with amyotrophic lateral sclerosis (ALS) with mutations in the *fused in sarcoma* gene (*FUS*). Patients with a mutation in the *FUS* gene develop a rare form of ALS, referred to as FUS-ALS, which is the most common cause of juvenile-onset ALS. There is substantial evidence that mutations in the *FUS* gene are responsible for a toxic gain of function that can lead to rapid, progressive loss of motor neurons in patients with FUS-ALS. ION363 is an investigational antisense medicine targeting the FUS RNA to reduce the production of the FUS protein. Antisense-mediated reduction of mutant FUS protein in a FUS-ALS mouse model prevents motor neuron loss. By targeting the root cause of FUS-ALS, ION363 has the potential to reduce or prevent disease progression in FUS-ALS patients.

ALS is a rare, rapidly progressing and fatal neurodegenerative disorder that affects approximately 55,000 people globally.[i] FUS-ALS is the third most common genetic cause of ALS. People with ALS experience muscle weakness, loss of movement, and difficulty breathing and swallowing, resulting in a severely declining quality of life and eventually death.

"There is an urgent need for novel treatments for all forms of ALS, a devastating disease that affects far too many patients and their families. Advancement of ION363 to a pivotal trial is the latest example of the power of Ionis' antisense technology to potentially target the root causes of neurological diseases," said C. Frank Bennett, Ph.D., Ionis' chief scientific officer and franchise leader for neurological programs. "Driven by our experience in developing medicines for motor neuron diseases such as ALS and spinal muscular atrophy and our intimate connection to the ALS patient community, Ionis made the decision to advance ION363 to the clinic and, ultimately, to the market because we believe we are uniquely positioned to make it available to patients living with FUS-ALS."

The trial will be led by Neil Shneider, M.D., Ph.D., director of Columbia University's Eleanor and Lou Gehrig ALS Center. 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 designed specifically for Jaci. Inspired by Jaci's spirit and courage, Ionis made the decision to invest in clinical studies so that many more patients can gain access to ION363, also known as "jacifusen." Since Jaci, several FUS-ALS patients have received treatment with ION363 under Dr. Shneider's investigator-initiated study through the U.S. Food and Drug Administration's expanded access pathway, sometimes called "compassionate use."

"FUS-ALS is an atypically aggressive form of the disease, involving the youngest of ALS patients. Building on our expanded access program, a controlled clinical trial is the best way to demonstrate the efficacy of ION363 and to make this therapeutic available to all patients who could potentially benefit from it," said Dr. Shneider.

The Phase 3 trial of ION363 is a global, multi-center study in up to 64 patients. Part one of the trial will consist of patients randomized to receive a multi-dose regimen of ION363 or placebo for 29 weeks, followed by part two, which will be an open-label period in which all patients in the trial will receive ION363 for 73 weeks.

Learn more about the Phase 3 trial of ION363 at: https://clinicaltrials.gov/ct2/show/NCT04768972?term=ion363&draw=2&rank=1

Ionis' other leading investigational medicines to treat ALS are tofersen (BIIB067), IONIS-C9$_{Rx}$ (BIIB078) and ION541 (BIIB105).

About Ionis' Neurology Franchise

The Ionis neurology franchise addresses all major brain regions and central nervous system types and currently has three Phase 3 studies ongoing with eight medicines in clinical development, five of which are wholly owned. Ionis is leading the way in treating the root causes of many neurological diseases and developing antisense medicines for common diseases like Alzheimer's and Parkinson's as well as rare diseases like amyotrophic lateral sclerosis (ALS) and Alexander disease. Ionis' marketed neurological disease medicines include SPINRAZA®, the global foundation of care for spinal muscular atrophy (SMA), commercialized by Biogen, and TEGSEDI®, the first and only self-administered, subcutaneous treatment for the polyneuropathy of hereditary ATTR amyloidosis in adults.

About Ionis Pharmaceuticals

For more than 30 years, Ionis has been the leader in RNA-targeted therapy, pioneering new markets and changing standards of care with its novel antisense technology. Ionis currently has three marketed medicines and a premier late-stage pipeline highlighted by industry-leading neurological and cardiometabolic franchises. Our scientific innovation began and continues with the knowledge that sick people depend on us, which fuels our vision of becoming one of the most successful biotechnology companies.

To learn more about Ionis visit www.ionispharma.com and follow us on twitter @ionispharma.

Ionis' Forward-looking Statement

This press release includes forward-looking statements regarding Ionis' business, Ionis' technologies, tofersen, IONIS-C9$_{Rx}$, ION541, ION363 and other products in development. Any statement describing Ionis' goals, expectations, financial or other projections, intentions or beliefs is a forward-looking statement and should be considered an at-risk statement. Such statements are subject to certain risks and uncertainties, including those related to the impact COVID-19 could have on our business, and including but not limited to those related to our commercial products and the medicines in our pipeline, and particularly those inherent in the process of discovering, developing and commercializing medicines that are safe and effective for use as human therapeutics, and in the endeavor of building a business around such medicines. Ionis' forward-looking statements also involve assumptions that, if they never materialize or prove correct, could cause its results to differ materially from those expressed or implied by such forward-looking statements. Although Ionis' forward-looking statements reflect the good faith judgment of its management, these statements are based only on facts and factors currently known by Ionis. As a result, you are cautioned not to rely on these forward-looking statements. These and other risks concerning Ionis' programs are described in additional detail in Ionis' annual report on Form 10-K for the year ended December 31, 2020, which is on file with the SEC. Copies of this and other documents are available from the Company.

In this press release, unless the context requires otherwise, "Ionis," "Company," "we," "our," and "us" refers to Ionis Pharmaceuticals and its subsidiaries.

Ionis Pharmaceuticals® is a trademark of Ionis Pharmaceuticals, Inc.

Tofersen, IONIS-C9$_{Rx}$ and ION541 are partnered with Biogen.

[i] France, Germany, Italy, Japan, Spain, the United Kingdom and the United States.

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