Ionis' third novel antisense medicine for ALS, its first designed to treat a broad ALS population, begins clinical trial

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- Trial will evaluate ION541 (BIIB105) for treatment of most forms of ALS regardless of family history

- Tofersen and IONIS-C9Rx also currently in clinical trials targeting genetic forms of the disease

CARLSBAD, Calif., Oct. 22, 2020 /PRNewswire/ -- Ionis Pharmaceuticals, Inc. (NASDAQ: IONS), the leader in antisense therapeutics, today announced that the first patients have been dosed with ION541 (also known as BIIB105), an investigational antisense medicine being developed as a potential therapy to treat most forms of amyotrophic lateral sclerosis (ALS) regardless of family history. This is another milestone in the continuing progress of Ionis' ambitious program to develop novel treatments for ALS. Almost all cases of ALS share the pathological hallmark of TDP-43 protein aggregation in motor neurons. ION541 targets ataxin-2 RNA (ATXN2), which has been shown to prevent or reverse TDP-43 toxicity in preclinical models of ALS.

ALS is a rare, progressive and fatal neurodegenerative disorder that affects approximately 55,000 people globally.[i] About 90 percent of ALS cases occur in people who have no apparent family history of the disease. People with ALS experience muscle weakness, loss of movement, and difficulty breathing and swallowing, resulting in a severely declining quality of life and potentially death.

"As our third medicine designed to treat different forms of ALS to enter clinical trials, ION541 represents yet another example of the power of Ionis' antisense technology to potentially target root causes of devastating neurodegenerative diseases," said Frank Bennett, Ph.D., Ionis' chief scientific officer and franchise leader for neurological programs. "Initiation of this clinical trial for ION541 marks an important milestone in Ionis' ALS program and reaffirms our commitment to the ALS community."

Ionis received a payment of $10 million from Biogen for initiation of this Phase 1/2 clinical trial of ION541. Biogen is developing ION541 as part of a broad strategic collaboration with Ionis to advance novel antisense therapies for the treatment of neurological disorders.

Learn more about the Phase 1/2 trial of ION541 at: https://clinicaltrials.gov/ct2/show/NCT04494256?term=biib105&draw=2&rank=1

Ionis' other leading investigational medicines to treat ALS are tofersen (BIIB067) and IONIS-$C9_{Rx}$ (BIIB078), both partnered with Biogen. Tofersen is designed to reduce the production of superoxide dismutase 1 (SOD1), the cause of a genetic form of ALS, referred to as SOD1-ALS, that results from mutations in the *SOD1* gene. SOD1-ALS is the second most common genetic form of ALS, accounting for up to 20 percent of genetic ALS. Tofersen is currently in a Phase 3 clinical trial in SOD1-ALS patients with data expected in 2021. IONIS-$C9_{Rx}$ is designed to selectively reduce the mutant C9ORF72 RNA and associated neurotoxicity. Mutations in the *C9orf72* gene account for greater than 30 percent of genetic ALS cases and five to 10 percent of all patients with ALS. It is the most common genetic form of ALS worldwide. IONIS-$C9_{Rx}$ is the first drug to enter clinical development that specifically targets the mutant C9ORF72 RNA and is a potentially first-in-class therapy for patients with C9orf72-ALS, referred to as C9-ALS. IONIS-$C9_{Rx}$, which earlier this year received Fast Track designation from the U.S. Food and Drug Administration, is currently in a Phase 1/2 trial in C9-ALS patients.

Ionis' Forward-looking Statement

This press release includes forward-looking statements regarding Ionis' business and the therapeutic potential of ION541, tofersen and IONIS-$C9_{Rx}$. 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, particularly those inherent in the process of discovering, developing and commercializing drugs that are safe and effective for use as human therapeutics, and in the endeavor of building a business around such drugs. 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, 2019, and the most recent Form 10-Q quarterly filing, which are on file with the SEC. Copies of these 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.

About Ionis Pharmaceuticals

As the leader in RNA-targeted drug discovery and development, Ionis has created an efficient, broadly applicable, drug discovery platform called antisense technology that can treat diseases where no other therapeutic approaches have proven effective. Our drug discovery platform has served as a springboard for actionable promise and realized hope for patients with unmet needs. We created the first and only approved treatment for all patients, children and adults with spinal muscular atrophy as well as the world's first RNA-targeted therapeutic approved for the treatment of polyneuropathy in adults with hereditary transthyretin amyloidosis. Our sights are set on all the patients we have yet to reach with a pipeline of more than 40 novel medicines designed to potentially treat a broad range of disease, including neurological, cardio-renal, metabolic, infectious, and pulmonary diseases.

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

[i] G7 countries: Canada, France, Germany, Italy, Japan, the United Kingdom, and the United States.

View original content to download multimedia:http://www.prnewswire.com/news-releases/ionis-third-novel-antisense-medicine-for-als-its-first-designed-to-treat-a-broad-als-population-begins-clinical-trial-301157526.html

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