IONIS-HTT Rx (RG6042) Granted PRIME Designation by the European Medicines Agency for the Treatment of People with Huntington's Disease

August 2, 2018

IONIS-HTT Rx is the first and only drug to demonstrate reduction of mutant huntingtin protein, the underlying cause of Huntington's disease, in patients

Roche plans to initiate a pivotal study of IONIS-HTT Rx (RG6042)

CARLSBAD, Calif., Aug. 2, 2018 /PRNewswire/ -- Ionis Pharmaceuticals, Inc. (Nasdaq: IONS), the leader in antisense therapeutics, today announced that the European Medicines Agency (EMA) has granted Priority Medicines (PRIME) designation to IONIS-HTT_{Rx} (also known as RG6042) for the treatment of people with Huntington's disease (HD). IONIS-HTT_{Rx} is the first drug to demonstrate reduction of mutant huntingtin protein, the underlying cause of HD. EMA PRIME (PRIority MEdicines) status is granted to medicines that may offer a major therapeutic advantage over existing treatments, or benefit patients without treatment options. The purpose of the PRIME initiative is to enhance interaction and early dialogue with EU regulators to optimize clinical development and provide a pathway for accelerated assessment of promising medicines.

"PRIME designation for IONIS-HTT_{Rx} accelerates the review timelines and enhances interactions with the EMA, which can bring this potentially disease-modifying drug for people with Huntington's disease to regulatory approval faster. This designation will be useful as we work closely with Roche to quickly advance IONIS-HTT_{Rx} into a pivotal study," said Dr. C. Frank Bennett, senior vice president of research and franchise leader for the neurological programs at Ionis Pharmaceuticals. "This is our second antisense drug to demonstrate a strong safety profile and significant target engagement in the human central nervous system. This profile gives us further confidence in the potential of the many other drugs we have advancing in R&D for the treatment of neurological diseases."

ABOUT IONIS-HTT_{Rx} (RG6042)

IONIS-HTT_{Rx} (RG6042) is an antisense drug designed to reduce the production of all forms of the huntingtin protein (HTT), including its mutated variant, mHTT, which is the driver of HD. IONIS-HTT_{Rx} (RG6042) offers a unique approach to treat all patients with HD, irrespective of their individual HTT mutation. Roche and Ionis are collaborating to develop antisense drugs to treat HD. For more information on the collaboration see the press release here.

In a Phase 1/2 study, IONIS-HTT_{Rx} (RG6042) demonstrated a significant reduction in mHTT, which breaks down the nerve cells in the brain. The study demonstrated a mean 40% (up to 60%) reduction of the specific HD protein in the cerebrospinal fluid (CSF) of adult patients treated with IONIS-HTT_{Rx} (RG6042) for three months at the two highest doses. Furthermore, levels of mHTT measured in the CSF were still declining in the majority of treated patients (~70%) as of the last measurement in the study. IONIS-HTT_{Rx} (RG6042) was well tolerated in this study.

Roche plans to initiate a pivotal study to evaluate IONIS-HTT_{Rx} (RG6042) in a larger patient population to further characterize its safety and efficacy profile in adults with HD.

IONIS-HTT_{Rx} (RG6042) has been granted orphan drug designation by the U.S. Food and Drug Administration (FDA) and by the European Medicines Agency (EMA) for the treatment of patients with HD.

CHDI Foundation, Inc. provided financial and scientific support to Ionis' HD drug discovery program through a collaboration with Ionis.

ABOUT HUNTINGTON'S DISEASE

Huntington's Disease is a rare, genetic, progressive, neurodegenerative disease resulting in deterioration in mental abilities and physical control. In the U.S., there are approximately 30,000 individuals (one in 10,000) with symptomatic HD and more than 200,000 people at risk of inheriting HD. HD is referred to as a triplet repeat disorder and is one of a large family of genetic diseases in which certain gene sequences are mistakenly repeated. In HD, the trinucleotide sequence (cytosine-adenine-guanine, CAG) in the gene that encodes for the HTT protein is repeated more than 36 times. The resulting mHTT protein is toxic and gradually damages neurons in the brain. Symptoms of HD usually appear between the ages of 30 to 50 years and continually worsen over a 15- to 20-year period. Ultimately, the weakened individual succumbs to pneumonia, heart failure or other complications. Presently, there is no effective disease-modifying treatment for HD, and current products focus only on managing disease symptoms.

About Ionis Pharmaceuticals, Inc.

Ionis is the leading company in RNA-targeted drug discovery and development focused on developing drugs for patients who have the highest unmet medical needs, such as those patients with severe and rare diseases. Using its proprietary antisense technology, Ionis has created a large pipeline of

first-in-class or best-in-class drugs, with over 45 drugs in development. SPINRAZA® (nusinersen) has been approved in global markets for the treatment of spinal muscular atrophy (SMA). Biogen is responsible for commercializing SPINRAZA. TEGSEDI (inotersen) and WAYLIVRA (volanesorsen) are two antisense drugs that Ionis discovered and successfully advanced through Phase 3 studies. TEGSEDI is approved in the E.U. for the treatment of stage 1 or stage 2 polyneuropathy in adult patients with hereditary transthyretin amyloidosis, or hATTR, and is currently under regulatory review in the U.S. and Canada. WAYLIVRA is under regulatory review for marketing approval in the U.S., EU and Canada for the treatment of patients with familial chylomicronemia syndrome, or FCS. WAYLIVRA is also in a Phase 3 study in patients with familial partial lipodystrophy, or FPL. Akcea Therapeutics, an affiliate of Ionis focused on developing and commercializing drugs to treat patients with serious and rare diseases, will be responsible for commercializing TEGSEDI and WAYLIVRA. Ionis' patents provide strong and extensive protection for its drugs and technology. Additional information about Ionis is available at www.ionispharma.com**.**

Ionis' Forward-looking Statement

This press release includes forward-looking statements regarding Ionis' alliance with Roche and the development, activity, therapeutic potential, commercial potential and safety of IONIS-HTT_{Rx} (RG6042). 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, 2017, and its most recent Form 10-Q quarterly filing, which are 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.

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Ionis Pharmaceuticals Investor Contact: D. Wade Walke, Ph.D., Vice President, Investor Relations, 760-603-2741; Ionis Pharmaceuticals Media Contact: Roslyn Patterson, Vice President, Corporate Communications, 760-603-2681