New Data from IONIS-HTT Rx Phase 1/2 Study Demonstrates Correlation Between Reduction of Disease-causing Protein and Improvement in Clinical Measures of Huntington's Disease

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First drug to demonstrate lowering of mutant huntingtin, the disease-causing protein, in people with Huntington's disease

CARLSBAD, Calif., April 24, 2018/PRNewswire/ -- Ionis Pharmaceuticals, Inc. (NASDAQ: IONS), the leader in antisense therapeutics, today presented top-line data from the Phase 1/2 study of IONIS-HTT$_{Rx}$ (RG6042) in people with early stage Huntington's disease (HD) at the 70thAmerican Academy of Neurology (AAN) meeting in Los Angeles, California. Results from exploratory analyses of data from the study demonstrated correlations between reductions in mutant huntingtin (mHTT), the disease-causing protein, and improvements in clinical measures of Huntington's disease.

Ionis Pharmaceuticals (PRNewsfoto/Ionis Pharmaceuticals, Inc.)

HD is a rare, progressive, neurodegenerative disease caused by genetic mutation in the huntingtin gene, resulting in the production of mHTT protein, which gradually destroys neurons in the brain and results in deterioration in mental ability and physical control. Ionis designed IONIS-HTT$_{Rx}$ (RG6042), a Generation 2+ antisense drug, to specifically reduce the production of the huntingtin protein, including mHTT.

"Since the discovery of the gene that causes Huntington's disease 25 years ago, we've been working to discover a drug that targets the cause of the disease—the mutant huntingtin protein. With the results from the Phase 1/2 study with IONIS-HTT$_{Rx}$, we have cleared the first major hurdle in developing such a drug. The substantial lowering of the mutant huntingtin protein, combined with additional data from exploratory clinical measures presented today and the good safety profile we observed in the study, give us hope that this new drug may have the potential to slow, or perhaps halt, the progression of this devastating disease," said Dr. Sarah Tabrizi, professor of clinical neurology, director of the University College London's Huntington's Disease Centre and the global lead investigator on the study. "The next step is to advance the drug into a larger study designed to demonstrate the potential clinical benefit of reducing the toxic mutant huntingtin protein in people with Huntington's disease."

Phase 1/2 Study Results:

- Significant, dose-dependent reductions in mHTT were observed in CSF of treated participants with mHTT reductions of up to approximately 60% and mean reductions of approximately 40% in CSF observed at the two highest doses, 90 mg ($p<0.01$) and 120 mg ($p<0.01$).
    - A 40% to 60% reduction in CSF corresponds to an estimated 55% to 85% reduction in mHTT in the cortex and 20% to 50% in the caudate regions of the brain in humans, based on a predictive model developed from data collected in rodents and non-human primates.
- mHTT levels were continuing to decline at the last measurement time in the study with further decreases in mHTT anticipated; based on modelling and clinical results, maximum reduction predicted at approximately six months after first dose.
- No serious adverse events were reported in treated participants and most adverse events (AEs) were mild and considered unrelated to study drug. No participants discontinued from the study.

Exploratory Clinical Outcome Results:

- In an exploratory post-hoc analysis, the degree of mHTT lowering was correlated with improved scores at three months in several clinical measures commonly used in Huntington's disease clinical studies.
    - Total Motor Score (TMS): rho=0.39 (p=0.007)
    - Symbol Digit Modalities Test (SDMT): rho=-0.30 (p=0.044)
    - Stroop Word Reading Test (SWRT): rho=0.08 (p=0.60)
    - Total Functional Capacity (TFC) score: rho=-0.27 (p=0.066)
- In addition, a significant correlation was observed with the degree of mHTT lowering and the Composite Unified Huntington's Disease Rating Scale (cUHDRS) score at Day 85 (rho=-0.41, p=0.004).

"These important clinical results further demonstrate that targeting the reduction of the toxic mutant huntingtin protein with IONIS-HTT$_{Rx}$ has the potential to be disease-modifying," added Dr. C. Frank Bennett, senior vice president of research and franchise leader for the neurological programs at Ionis Pharmaceuticals. "Following SPINRAZA for the treatment of patients with spinal muscular atrophy, this is our second antisense drug to show good target engagement in the CNS. These drugs, along with the two others we have in clinical studies and the five we have in preclinical development further validate the broad potential of our antisense technology to treat patients with neurological diseases."

About the Phase 1/2 Study

The study was a randomized, placebo-controlled dose escalation study in 46 people with early stage Huntington's disease. Study participants were treated for 13 weeks with four intrathecal injections of 10 mg, 30 mg, 60 mg, 90 mg or 120 mg of IONIS-HTT$_{Rx}$ (RG6042) or placebo (3:1 active to placebo), administered monthly. The study's primary objective was to evaluate the safety and tolerability of IONIS-HTT$_{Rx}$ (RG6042). The study was also designed to measure the effect of IONIS-HTT$_{Rx}$ (RG6042) on levels of the mutant huntingtin protein in the cerebral spinal fluid (CSF). Exploratory analyses included several clinical measures commonly used in Huntington's disease studies.

An open-label extension (OLE) study for patients who participated in the Phase 1/2 study is ongoing.

Ionis' partner, Roche, exercised its option to license IONIS-HTT$_{Rx}$ following the completion of a Phase 1/2 study and is responsible for all development and commercial activities. Planning is already underway for Roche to advance IONIS-HTT$_{Rx}$ (RG6042) to a pivotal study to demonstrate the clinical efficacy and safety of IONIS-HTT$_{Rx}$.

About Huntington's Disease (HD)

Huntington's Disease (HD) 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 having inherited 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 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-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. 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.

About Ionis/Roche Collaboration

Roche and Ionis are collaborating to develop antisense drugs to treat HD. The alliance combines Ionis' antisense expertise with Roche's knowledge and experience in clinical development of anti-neurodegenerative therapeutics. In December 2017, Roche licensed IONIS-HTT$_{Rx}$ from Ionis for $45 million and has renamed the investigational molecule RG6042. In total, Ionis has generated $100 million in up-front, milestone and license payments and is eligible to receive an additional $335 million in milestone payments as IONIS-HTT$_{Rx}$ (RG6042) progresses in development and regulatory approval. If commercialized, Ionis is eligible to receive tiered double-digit royalties up to the mid-teens on sales of IONIS-HTT$_{Rx}$ (RG6042). Roche is responsible for all IONIS-HTT$_{Rx}$ (RG6042) development, regulatory and commercialization activities and costs.

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 40 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. Inotersen and volanesorsen are two antisense drugs that Ionis discovered and successfully advanced through Phase 3 studies. Inotersen is under regulatory review for marketing approval in the U.S. and EU for the treatment of patients with hereditary ATTR amyloidosis. Volanesorsen 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. Volanesorsen is also in a Phase 3 study in patients with familial partial lipodystrophy, or FPL. Akcea, an affiliate of Ionis focused on developing and commercializing drugs to treat patients with serious and rare diseases, will commercialize inotersen and volanesorsen, if approved. 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, 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.

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