Ionis Pharmaceuticals Licenses IONIS-HTT Rx to Partner Following Successful Phase 1/2a Study in Patients with Huntington's Disease

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Dose-dependent Reductions of Mutant Huntingtin Protein Observed
Ionis Earns $45 Million License Fee

CARLSBAD, Calif., Dec. 11, 2017 /PRNewswire/ -- Ionis Pharmaceuticals, Inc. (NASDAQ: IONS) announced today that Roche has exercised its option to license IONIS-HTT$_{Rx}$ following the completion of a Phase 1/2a randomized, placebo-controlled, dose escalation study of IONIS-HTT$_{Rx}$ in people with Huntington's disease (HD). Roche will now be responsible for all development and commercial activities. IONIS-HTT$_{Rx}$ is the first therapy in clinical development designed to target the underlying cause of HD by reducing the production of the toxic mutant huntingtin protein (mHTT). In conjunction with the decision to license IONIS-HTT$_{Rx}$, Ionis earned a $45 million license fee from Roche.

Ionis Pharmaceuticals (PRNewsfoto/Ionis Pharmaceuticals, Inc.)

In the Phase 1/2a study, dose-dependent reductions of mHTT were observed in participants treated with IONIS-HTT$_{Rx}$. In addition, the safety and tolerability profile of IONIS-HTT$_{Rx}$ observed in the Phase 1/2a study supports continued development. Ionis and Roche plan to present results from this study at medical conferences in the first half of 2018 and plan to submit the study results for publication in a peer-reviewed medical journal. Ionis and Roche have also recently initiated an open-label extension (OLE) study for patients who completed the Phase 1/2a study.

"We are encouraged by the performance of IONIS-HTT$_{Rx}$ in the Phase 1/2a clinical study. The dose-dependent reductions of mHTT we observed in the study substantially exceeded our expectations and we were equally encouraged by the safety profile of the drug," said Dr. C. Frank Bennett, senior vice president of research at Ionis Pharmaceuticals. "We are grateful to the patients and investigators participating in this study. We could not have reached this important milestone without their commitment and that of the broader HD community."

"We are extremely pleased that to have reached this important milestone in our collaboration with Roche to discover and develop a therapy for people with Huntington's disease," said B. Lynne Parshall, chief operating officer at Ionis Pharmaceuticals. "This is our second antisense drug targeting a neurodegenerative disease to demonstrate a positive impact on a disease target in the CNS."

"The results of this trial are of ground-breaking importance for Huntington's disease patients and families. For the first time, a drug has lowered the level of the toxic disease-causing protein in the nervous system, and the drug was safe and well tolerated. The key now is to move quickly to a larger trial to test whether IONIS-HTT$_{Rx}$ slows disease progression," said Dr. Sarah Tabrizi, professor of clinical neurology, director of the University College London's Huntington Centre and the global lead investigator on the Phase 1/2a study.

Roche is now responsible for all IONIS-HTT$_{Rx}$ development, regulatory and commercialization activities and costs. The two companies will work together to transition the ongoing OLE to Roche which will be responsible for managing this study and all future studies.

This transaction is subject to clearances under the Hart-Scott-Rodino Antitrust Improvements Act.

ABOUT IONIS-HTT$_{Rx}$ and HUNTINGTON'S DISEASE (HD)
IONIS-HTT$_{Rx}$ is an antisense drug in development for the treatment of HD. IONIS-HTT$_{Rx}$ is designed to reduce the production of all forms of the huntingtin (HTT) protein, which in its mutated variant (mHTT) is responsible for HD. As such, IONIS-HTT$_{Rx}$ offers a unique approach to treat all patients with HD, irrespective of their individual HTT mutation. IONIS-HTT$_{Rx}$ 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.

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 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 10- to 25-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/ROCHE COLLABORATION
Roche and Ionis are collaborating to develop antisense drugs to treat HD. The alliance combines Ionis' antisense expertise with Roche's knowledge in clinical development of anti-neurodegenerative therapeutics. To date, Ionis has earned $55 million in upfront and milestone payments from its relationship with Roche and is eligible to earn additional milestone payments as the drug progresses in development, as well as royalties on sales of IONIS-HTT$_{Rx}$ if it is commercialized.

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 three dozen 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. Drugs that have successfully completed Phase 3 studies include inotersen, an antisense drug Ionis is developing to treat patients with hereditary TTR amyloidosis (hATTR), and volanesorsen, an antisense drug discovered by Ionis and co-developed by Ionis and Akcea Therapeutics to treat patients with either familial chylomicronemia syndrome or familial partial lipodystrophy. Akcea, an affiliate of Ionis, is a biopharmaceutical company focused on developing and commercializing drugs to treat patients with serious cardiometabolic diseases caused by lipid disorders. If approved, volanesorsen will be commercialized through Ionis' affiliate, Akcea. Inotersen filings for marketing approval have been submitted in the U.S. and EU. Volanesorsen filings for marketing approval have been submitted in the U.S., EU, and Canada. 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$_{Rx}$. 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, 2016, and its most recent quarterly report on Form 10-Q, 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.

SOURCE Ionis Pharmaceuticals, Inc.

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