IONIS-HTT$_{Rx}$ (RG6042) Top-Line Data Demonstrate Significant Reductions of Disease-Causing Mutant Huntingtin Protein in People with Huntington's Disease

Phase 1/2 study first to demonstrate disease-modifying potential

Up to ~60% reduction (mean ~40%) in the mutant huntingtin protein (mHTT) observed in the cerebral spinal fluid (CSF) of patients treated for three months with IONIS-HTT$_{Rx}$ (RG6042) at the two highest doses tested with mHTT levels continuing to decline at the last measurement

mHTT reductions of 40-60% in CSF correspond to an estimated 55%-85% reduction in the cortex of the brain, where mHTT is highly expressed, based on preclinical data

mHTT reductions observed in the Phase 1/2 study exceeded reductions that produced disease benefit in animal models of HD

Roche is working to quickly advance IONIS-HTT$_{Rx}$ (RG6042) to a pivotal study

Conference call and webcast tomorrow, March 2nd, 11:00 a.m. ET

CARLSBAD, Calif., March 1, 2018 – Ionis Pharmaceuticals, Inc. (NASDAQ: IONS), a leader in antisense therapeutics, today announced the presentation of positive top-line data from a completed Phase 1/2 study of IONIS-HTT$_{Rx}$ (RG6042) in people with early stage Huntington's disease (HD) at the 13th Annual CHDI HD conference. The data demonstrate that IONIS-HTT$_{Rx}$ (RG6042) is the first drug in development to lower the disease-causing protein in people with HD.

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

"For nearly twenty years, I have seen many families devastated from losses to this progressive neurodegenerative disease. With IONIS-HTT$_{Rx}$ (RG6042), the HD community has new hope for a therapy that can reduce the cause of HD, and therefore, may slow the progression and potentially prevent the disease in future generations, which is truly groundbreaking," 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. "I look forward to a longer-term, larger study that can establish the benefit of reducing the toxic mutant huntingtin protein in people with HD."

Phase 1/2 Study Results:

- 46 people with early stage Huntington's disease 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, administered monthly.

- 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 ($p<0.01$).
- Based on a predictive model developed from data collected in rodents and non-human primates, 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.
- mHTT levels were continuing to decline at the last measurement with further decreases in mHTT anticipated; maximum reduction expected by approximately six months after first dose.
- No serious adverse events were reported in treated participants and most adverse events (AEs) were mild and considered to be unrelated to study drug. No participants discontinued from the study.

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

Roche has been working closely with Ionis on this program since 2013 and is now leading the development of IONIS-HTT_{Rx} (RG6042) and collaborating with the HD community. Roche is currently planning a pivotal trial to determine the clinical efficacy and safety of IONIS-HTT_{Rx} (RG6042).

"We designed IONIS-HTT_{Rx} to treat all patients with HD. These important clinical results demonstrate that our approach of targeting the toxic mutant huntingtin protein can significantly reduce the underlying cause of this terrible disease. In this study, we were able to achieve mutant huntingtin protein reductions in study participants that were higher than those that produced disease benefit in preclinical models of HD," added Dr. C. Frank Bennett, senior vice president of research and franchise leader for the neurological programs at Ionis Pharmaceuticals. "We were pleased that this antisense approach, which targets all forms of the huntingtin protein, proved to be safe and well tolerated in this study. We look forward to working with Roche to quickly advance IONIS-HTT_{Rx} (RG6042) into a pivotal study, which we hope will lead to marketing approval for this new drug for people with HD."

"IONIS-HTT_{Rx} is the latest example of the innovation and productivity of our antisense technology," said Brett P. Monia, chief operating officer, senior vice president of antisense drug discovery and translational medicine at Ionis Pharmaceuticals. "Our efforts to develop antisense drugs for neurological diseases has already produced one commercial drug, SPINRAZA, another under review for marketing approval, inotersen, four drugs approaching definitive clinical studies, six preclinical-stage drugs, and more than 20 discovery-stage programs."

CONFERENCE CALL AND WEBCAST

At 11:00 a.m. Eastern Time tomorrow, March 2nd, 2018, Ionis will host a live webcast and conference call to discuss these results**.** The Ionis management team will be joined on the call by Dr. Sarah Tabrizi, global lead investigator on the Phase 1/2 study, and Dr. Scott Schobel, associate group medical director and clinical science leader of product development neuroscience at Hoffman-La Roche Pharmaceuticals. Interested parties may listen to the call by dialing 877-443-5662 or access the webcast at www.ionispharma.com. A webcast replay will be available for a limited time at the same address.

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 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. 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 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$_{Rx}$ (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 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.

Ionis Pharmaceuticals™ is a trademark of Ionis Pharmaceuticals, Inc. Akcea Therapeutics™ is a trademark of Ionis Pharmaceuticals, Inc. SPINRAZA® is a registered trademark of Biogen.

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