Enrollment in Phase 1/2a Study of IONIS-HTT$_{Rx}$ in Patients with Huntington's Disease Completed and Open-Label Extension Study to Open in 2H 2017

Carlsbad, Calif., June 22, 2017 – Ionis Pharmaceuticals, Inc. (NASDAQ: IONS) today announced the completion of enrollment in the Phase 1/2a randomized, placebo-controlled, dose escalation study of IONIS-HTT$_{Rx}$ in patients with Huntington's disease (HD). Dosing in the final patient cohort continues, and Ionis plans to report top-line results from this study around year-end 2017. The safety and tolerability profile of IONIS-HTT$_{Rx}$ in the completed cohorts of the Phase 1/2a study supports its continued development. Patients who complete the Phase 1/2a study will be eligible to participate in an open-label extension (OLE) study that Ionis plans to initiate in the next several months. Roche, Ionis' partner for this drug, continues to advance and support the program. IONIS-HTT$_{Rx}$ is the first therapy in clinical development targeting the cause of HD by reducing the production of the toxic mutant huntingtin protein (mHTT) from the mutated huntingtin gene.

"We are encouraged by the safety profile of IONIS-HTT$_{Rx}$ we have observed to date in the completed dosing cohorts in the Phase 1/2a study. Upon completion and full analysis of this study, the next step for this program will be to conduct a study to investigate whether decreasing mutant huntingtin protein with IONIS-HTT$_{Rx}$ can slow the progression of this terrible disease," said C. Frank Bennett, Ph.D., senior vice president of research at Ionis Pharmaceuticals. "We believe that IONIS-HTT$_{Rx}$, which is designed to reduce the production of all forms of the huntingtin (HTT) protein – the known cause of HD, represents the most promising opportunity to address this significant unmet medical need. Together with our partners at Roche, we are committed to developing IONIS-HTT$_{Rx}$, which has the potential to transform the treatment of HD."

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 symptomatic patients 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 gene that encodes for the HTT protein contains a trinucleotide sequence that is repeated in the gene 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 available, and current approaches only focus on managing some of the 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. Roche has the option to license IONIS-HTT_{Rx} from Ionis through the completion of the Phase 1/2a study. Prior to option exercise, Ionis is responsible for the discovery and development of IONIS-HTT_{Rx}. If Roche exercises its option, it will assume responsibility for global clinical development, regulatory and commercialization activities for the drug.

CHDI Foundation, Inc. provided financial and scientific support to Ionis' HD drug discovery program through a development collaboration with Ionis. Over time, CHDI will be reimbursed for its support of Ionis' program out of milestone payments received by Ionis.

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) is a drug that has been approved in the U.S. and Europe for the treatment of spinal muscular atrophy (SMA) in pediatric and adult patients. Biogen is responsible for commercialization of SPINRAZA. Drugs that have successfully completed Phase 3 studies include volanesorsen, a drug Ionis is developing and plans to commercialize through its subsidiary, Akcea Therapeutics, to treat patients with either familial chylomicronemia syndrome or familial partial lipodystrophy; and inotersen (IONIS-TTR_{Rx}), a drug Ionis is developing with GSK to treat patients with TTR amyloidosis. Both drugs are progressing toward regulatory filings in the second half of 2017. 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.

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