Ionis Pharmaceuticals Announces Phase 3 NEURO-TTR Study of Inotersen (IONIS-TTR$_{Rx}$) Meets Both Primary Endpoints

Webcast to Discuss Results May 15, 2017 at 8:30 am ET

Carlsbad, Calif., May 15, 2017 – Ionis Pharmaceuticals, Inc. (NASDAQ: IONS) announced today that the Phase 3 NEURO-TTR study of inotersen (IONIS-TTR$_{Rx}$) in patients with familial amyloid polyneuropathy (FAP) met both primary endpoints. Over the 15-month period of the study, inotersen-treated patients achieved statistically significant benefit compared to placebo in the modified Neuropathy Impairment Score +7 (mNIS+7) and the Norfolk Quality of Life Questionnaire-Diabetic Neuropathy (Norfolk QoL-DN) ($p<0.0001$ and $p=0.0006$, respectively). Statistically significant differences were also observed for both endpoints at eight months.

"Familial amyloid polyneuropathy is a devastating genetic disease that is painful and rapidly progressive leading to early death. The positive results from the NEURO-TTR study today are very encouraging for this underserved patient population," said Morie Gertz, MD, M.A.C.P., Division of Hematology, Roland Seidler Jr. Professor Department of Medicine, College of Medicine, Mayo Distinguished Clinician. "I have been treating patients with this disabling disease for many years, and I am excited about the promise that inotersen holds to restore their lives. I believe inotersen has the potential to transform the current standard of care for patients with TTR amyloidosis."

Treatment-emergent adverse events considered related to treatment were seen more commonly with inotersen than placebo. Two key safety findings were observed during the study that required changes to the monitoring schedule. Three serious adverse events of thrombocytopenia were observed in inotersen-treated patients; two patients recovered and one patient died due to intracranial hemorrhage. One additional inotersen-treated patient discontinued treatment due to non-serious thrombocytopenia. Four inotersen-treated patients discontinued treatment due to a renal observation; two patients met a predefined renal stopping rule and two experienced serious renal adverse events, one of whom experienced chronic renal insufficiency. One placebo-treated patient also met a predefined renal stopping rule. Enhanced monitoring was implemented during the study to support early detection and management of the thrombocytopenia and renal issues. All five serious adverse events occurred before enhanced monitoring was fully implemented. A detailed review of safety data from the study is ongoing.

"Data showing symptomatic patients experience a quality of life benefit is truly exciting and provides hope for the amyloidosis community. We are excited by this very important milestone and welcome the opportunity of inotersen to potentially address the unmet and critical needs of amyloidosis patients and transform lives," said Isabelle Lousada, president and chief executive officer of the Amyloidosis Research Consortium (ARC). "The ARC is committed to building collaborative relationships to advance the best research and speed new therapies to market for this disease that has truly devastated generations of affected families. With no FDA-approved drugs, treatment options are extremely limited and desperately needed."

"We are grateful to the patients who participated in the NEURO-TTR study, along with their families, the investigators and the broader TTR amyloidosis community, for their dedication, commitment and support. We share the collective sense of urgency to bring a new treatment to patients and their families facing this devastating disease," said Brett P. Monia, senior vice president of drug discovery and franchise leader for oncology and rare diseases at Ionis Pharmaceuticals. "We are excited about the positive topline results from the Phase 3 NEURO-TTR study. We observed a benefit in disease progression in patients treated with inotersen, regardless of disease stage (Stage 1 and Stage 2) or TTR mutation (V30M and non-V30M). We believe these preliminary results suggest a favorable benefit-risk profile for inotersen in patients with FAP."

Long-term safety and efficacy data with inotersen are currently being collected in an open-label extension of the Phase 3 NEURO-TTR study. More than 80% of patients completed the NEURO-TTR study, of these more than 95% participated in the open-label extension study.

Review of the full data package from the NEURO-TTR study by Ionis and GSK is ongoing and detailed results from the study will be presented at an upcoming medical meeting and submitted for publication in a peer-reviewed medical journal.

The preparation of regulatory marketing applications for inotersen is underway. GSK has the option to license inotersen following review of additional data and prior to the submission of regulatory applications.

WEBCAST INFORMATION

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 INOTERSEN

Inotersen (IONIS-TTR$_{Rx}$) is a generation 2.0+ antisense drug Ionis is developing for the treatment of TTR amyloidosis. Inotersen is administered once weekly as a single 300 mg subcutaneous injection. The drug is designed to inhibit the production of all forms of TTR protein, including both the hereditary and wild-type forms, offering a unique approach to treat all types of TTR amyloidosis. Inotersen has demonstrated sustained and robust TTR reductions in clinical studies in different populations of patients with TTR-related amyloidosis.

The U.S. Food and Drug Administration has granted Orphan Drug Designation and Fast Track Status to inotersen for the treatment of patients with FAP. The European Medicines Agency has granted Orphan Drug Designation to inotersen for the treatment of patients with TTR amyloidosis.

ABOUT TTR AMYLOIDOSIS – FAP

FAP, now referred to as hereditary transthyretin amyloidosis with polyneuropathy (hATTR-PN), is a progressive, debilitating and fatal genetic disease in which patients experience TTR build up in major organs, including peripheral nerves, heart, intestinal tract, kidney and bladder.

Patients with hATTR-PN primarily experience nerve damage throughout their body resulting in the progressive loss of motor functions, such as walking. As TTR accumulates in major organs, it progressively impacts organ function and eventually leads to death. Therapeutic options for the treatment of hATTR-PN are very limited and there are currently

no drugs approved for the treatment of hATTR-PN in the United States. There are an estimated 10,000 hATTR-PN patients worldwide.

ABOUT THE NEURO-TTR PHASE 3 STUDY

Inotersen was evaluated in a Phase 3 randomized (2:1), double-blind, placebo-controlled, international study in 172 patients with hATTR-PN. The study was designed to support an application for marketing approval of inotersen in patients with hATTR-PN. The 15-month study measured the effects of inotersen on neurological dysfunction and on quality-of-life by measuring the change from baseline in the modified Neuropathy Impairment Score +7 (mNIS+7) and in the Norfolk Quality of Life Questionnaire-Diabetic Neuropathy (Norfolk QOL-DN) total score. For further study information, please visit www.clinicaltrials.gov and search for the identifier number NCT01737398.

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. for the treatment of spinal muscular atrophy (SMA) in pediatric and adult patients. Biogen is responsible for commercialization of SPINRAZA. Drugs currently in Phase 3 development 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, a drug Ionis is developing with GSK to treat patients with TTR amyloidosis. 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 GSK and the therapeutic and commercial potential of inotersen. 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 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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