New Data Presented at Peripheral Nerve Society Meeting Further Support Potential Benefit of Inotersen

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Significant benefit observed for both clinical measurements of neurological disease progression and quality of life at 8 and 15 months in patients with FAP

CARLSBAD, Calif., July 10, 2017 /PRNewswire/ -- Ionis Pharmaceuticals, Inc. (NASDAQ: IONS) presented new top-line data from the Phase 3 NEURO-TTR study of inotersen in patients with familial amyloid polyneuropathy (FAP) at the 2017 Peripheral Nerve Society Meeting. Results from the study demonstrated benefit across both primary endpoints of the study: modified Neuropathy Impairment Score +7 (mNIS+7) and Norfolk Quality of Life Questionnaire-Diabetic Neuropathy (Norfolk QoL-DN) at 15 months of treatment. Inotersen-treated patients benefited significantly in quality of life compared to placebo, with a difference in magnitude of 11.68 points in the Norfolk QoL-DN score at 15 months of treatment (mean change from baseline of 0.99 vs. 12.67, p=0.0006). Statistically significant benefit was also observed for both mNIS+7 and Norfolk QoL-DN at eight months of treatment with inotersen. The results continue to support the favorable benefit-risk profile for inotersen in patients with FAP. A detailed review of efficacy and safety from the study is ongoing.

"The magnitude of benefit on quality of life achieved with inotersen treatment has never been observed before in patients with FAP," said Teresa Coelho, MD, neurologist and neurophysiologist at Santo António Hospital, Porto, Portugal. "As their disease progresses, FAP patients lose the ability to do even simple activities like feeding themselves, which can limit their independence. They also suffer from debilitating symptoms, like severe extremity pain and diarrhea. The quality of life score assesses almost every aspect of this devastating disease on a patient's life. The nearly 12-point difference observed with inotersen treatment from placebo represents a clinically meaningful benefit and provides hope that inotersen could allow FAP patients to maintain greater independence by alleviating debilitating symptoms and preserving their ability to perform daily activities."

"The clinically meaningful benefit in quality of life bring a new energizing level of hope to the amyloidosis community around the world, a community whose critical needs have not been sufficiently addressed," said Isabelle Lousada, president and chief executive officer of the Amyloidosis Research Consortium (ARC). "Going from Phase 1 to Phase 3, inotersen's development program hallmarks the importance of rapidly advancing valuable, life-changing therapies that can have transformational benefits on patients' lives. We hope for a rapid approval process for inotersen to create access and availability of this important medicine, which has the potential to help patients maintain their independence and provide a brighter future for patients who suffer from this desperate and devastating disease."

The Phase 3 NEURO-TTR study met both its primary endpoints, Norfolk QoL-DN and mNIS+7, with high statistical significance. Statistical significance was observed regardless of TTR mutation (V30M vs. Non-V30M) or disease severity (Stage 1 vs. Stage 2). The Norfolk QoL-DN measures patients' perception of symptoms associated with specific nerve fiber damage. The questionnaire includes questions assessing physical function, disease symptoms, activities of daily living, physical sensation and autonomic neuropathy. The mNIS+7 is a composite score that includes measures of muscle strength, quantitative sensation testing and nerve conduction.

- Treatment with inotersen resulted in a statistically significant benefit in Norfolk QoL-DN score compared to placebo of 6.14 points at 8 months of treatment (mean change from baseline of 0.81 vs. 6.95, p=0.032) and 11.68 points at 15 months of treatment (mean change from baseline of 0.99 vs. 12.67, p=0.0006).
- Treatment with inotersen resulted in a statistically significant benefit in mNIS+7 compared to placebo at eight months of treatment (p=0.0005) and at 15 months of treatment (p=0.00000004).
- As previously identified, the key safety findings in the NEURO-TTR study were thrombocytopenia and renal dysfunction. Enhanced platelet and renal monitoring have effectively managed these safety events since implementation in the

NEURO-TTR study.

"The new top-line data presented today reaffirm inotersen's effect in patients with FAP. Importantly, we observed statistically significant disease benefit with inotersen treatment at only eight months of treatment, and this benefit was further amplified at the end of study analysis. We are very encouraged by the significant benefit demonstrated in quality of life, and, these results further support a strong relationship between patients' perception of benefit in quality of life and clinical measurements of neurological disease progression," said Brett Monia, senior vice president of drug discovery and franchise leader for oncology and rare diseases at Ionis Pharmaceuticals. "We are continuing to review the full data package from the NEURO-TTR study and prepare the regulatory marketing applications for submission this year. We look forward to sharing detailed results in future publications and medical meetings."

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.

GSK has the option to license inotersen prior to the submission of regulatory applications.

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. and Europe for the treatment of spinal muscular atrophy (SMA) in pediatric and adult patients. Biogen is responsible for commercializing 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 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 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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SOURCE Ionis Pharmaceuticals, Inc.

Ionis Pharmaceuticals Investor and Media Contacts: D. Wade Walke, Ph.D., Vice President, Corporate Communications and Investor Relations, 760-603-2741, Alissa Santa Maria, Assistant Director, Corporate Development, 760-603-2643, Jennifer Capuzelo, Assistant Director, Corporate Communications and Investor Relations, 760-603-2606