Ionis Announces Submission of Marketing Authorization Application for Inotersen to the European Medicines Agency

November 3, 2017

Inotersen MAA to be reviewed under EMA Accelerated Assessment program

CARLSBAD, Calif., Nov. 3, 2017 /PRNewswire/ -- Ionis Pharmaceuticals, Inc. (NASDAQ: IONS) announced today that the company submitted a marketing authorization application (MAA) to the European Medicines Agency (EMA) for inotersen, based on the phase 3 NEURO-TTR study in patients with hereditary TTR amyloidosis (hATTR). The MAA for inotersen will be reviewed under the EMA's Accelerated Assessment program, which is intended to expedite access to drugs that the EMA considers to be of major therapeutic interest.

"The submission of the inotersen MAA to the EMA represents a critical milestone for Ionis and for European patients suffering from ATTR. We are pleased that we met the last deadline for Accelerated Assessment in the EU for 2017. Next week, we also plan to submit the NDA to the FDA. Today's submission to the EMA puts us one step closer to our goal of fundamentally changing the treatment landscape for patients and families globally who are facing this devastating, progressive, fatal disease, and for the healthcare professionals who treat them," said Sarah Boyce, chief business officer of Ionis Pharmaceuticals. "In the Phase 3 NEURO-TTR study, half of inotersen-treated patients saw improvement in their quality of life. Combined with significant efficacy and superior convenience offered with inotersen, we believe inotersen will be the treatment of choice for this patient population. We are making substantial progress in advancing inotersen to market, and we are in advanced discussions with potential co-commercialization partners. We believe the right partner can maximize the commercial success of inotersen."

"Patients with ATTR experience TTR build up in various tissues and major organs, including peripheral nerves, heart, intestinal tract, kidney and bladder, which causes debilitating symptoms, such as severe extremity pain and gastrointestinal manifestations, and eventually results in death. As their disease progresses, these patients lose the ability to perform even simple activities, such as feeding and dressing themselves, significantly limiting their independence," said Teresa Coelho, MD, neurologist and neurophysiologist at Santo António Hospital, Porto, Portugal. "Therapeutic options for the treatment of hATTR are very limited and include liver transplant for early-stage patients. I am encouraged by the results from the Phase 3 NEURO-TTR study with inotersen, which demonstrated substantial benefit in both quality of life and neurological function for inotersen-treated patients compared to placebo-treated patients."

"TTR amyloidosis is devastating, not only for patients but also for caregivers and family members. We are grateful that today we are closer than ever to having an effective treatment to fight this disease. Ionis has demonstrated great commitment to hATTR and these patients, and we look forward to collaborating further with the Ionis team as we work towards potential regulatory and subsequent market access and payer approval for this important therapy," said Eric Low, head of global strategy, Amyloidosis Research Consortium UK.

ABOUT INOTERSEN

Inotersen is an antisense drug designed to reduce the production of transthyretin, or TTR, to treat patients with TTR amyloidosis (ATTR), a severe, rare and fatal disease. In patients with ATTR, both the mutant and wild type (wt), TTR builds up as fibrils in tissues, such as the peripheral nerves, heart, gastrointestinal system, eyes, kidneys, central nervous system, thyroid and bone marrow. The presence of TTR fibrils interferes with the normal functions of these tissues. As the TTR protein fibrils enlarge, more tissue damage occurs and the disease worsens, resulting in poor quality of life and eventually death.

The U.S. Food and Drug Administration has granted Orphan Drug Designation and Fast Track Status to inotersen for the treatment of patients with polyneuropathy due to hATTR. Inotersen is under regulatory review for marketing authorization in the EU. The European Medicines Agency has granted Accelerated Assessment and Orphan Drug Designation to inotersen for the treatment of patients with ATTR.

ABOUT INOTERSEN PHASE 3 CLINICAL STUDY
Inotersen completed a Phase 3 study, NEURO-TTR, in patients with polyneuropathy due to hereditary TTR amyloidosis (hATTR) in May 2017. Results from the study demonstrated benefit compared to placebo across both primary endpoints of the study: the Norfolk Quality of Life Questionnaire-Diabetic Neuropathy (Norfolk QoL-DN) and the modified Neuropathy Impairment Score +7 (mNIS+7) at both eight and 15 months of treatment. In addition, consistent and significant benefit was observed in both the Norfolk-QoL-DN and mNIS+7, independent of disease stage, types of mutation, previous treatment with TTR protein stabilizers or presence of cardiomyopathy. Inotersen-treated patients benefited significantly in the quality of life primary endpoint 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). Half of inotersen-treated patients saw improvement from baseline in the Norfolk QoL-DN score at 15 months of treatment. In addition, clinically meaningful benefit compared to placebo was observed in the SF-36 physical component score, a measure of general health quality of life. Inotersen-treated patients also benefited significantly in the co-primary endpoint of disease control, mNIS+7, with a mean 19.73-point benefit observed after 15 months of treatment, compared to placebo-treated patients (p = 0.00000004).

Two key safety issues were identified during the study: thrombocytopenia and safety signals related to renal function. Enhanced monitoring was implemented during the study to support early detection and management of these issues. Serious platelet and renal events were infrequent and easily managed with routine monitoring, which has proven effective since implementation. Other serious adverse events were observed in 24.1% of inotersen-treated patients and 21.7% of placebo-treated patients. No cumulative toxicities have been identified with long-term exposure.

Adverse events occurring in ≥10% of patients and twice as frequently in inotersen-treated patients compared with placebo-treated patients, included thrombocytopenia/platelet count decreases, nausea, pyrexia, chills, vomiting and anemia. Injection site reactions accounted for less than 1% of all injections and were mild or moderate in severity. There were no discontinuations due to injection site reactions.

The overall mortality rate in the NEURO-TTR study was 2.9% and was lower than mortality rates reported in other studies in hATTR patients. There was a total of five deaths in the study, five (4.7%) in the inotersen arm and zero in the placebo arm. Four deaths in the inotersen arm were associated with disease progression and considered unrelated to treatment. As previously reported, there was one fatal intracranial hemorrhage in conjunction with serious thrombocytopenia. No serious thrombocytopenia was observed following implementation of more frequent monitoring.

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. Volanesorsen filings for marketing approval have been submitted in the U.S., EU and Canada. Inotersen is under review for marketing authorization in the EU and is progressing toward regulatory filing in the U.S. 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 the therapeutic and commercial potential of inotersen and other products in development. 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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