Ionis Presents New Data from NEURO-TTR Study at European ATTR Amyloidosis Meeting

November 2, 2017

Significant benefit in quality of life and disease severity endpoints observed in inotersen-treated patients compared to placebo-treated patients

Consistent and significant differences observed between inotersen-treated and placebo-treated patients independent of disease stage, types of mutation, previous use of TTR stabilizers or presence of cardiomyopathy

Encouraging benefit observed across multiple cardiac measures in inotersen-treated patients with significant cardiac disease compared to placebo-treated patients

Conference call and webcast on Thursday, November 2, 7:00 a.m. ET at www.ionispharma.com

CARLSBAD, Calif., Nov. 2, 2017 /PRNewswire/ -- Ionis Pharmaceuticals, Inc. (NASDAQ: IONS), the leader in antisense therapeutics, today announced new data from the Phase 3 NEURO-TTR study, evaluating inotersen in patients with hereditary TTR amyloidosis (hATTR). Results from the study demonstrated early and significant benefit in both co-primary endpoints: Norfolk Quality of Life Questionnaire-Diabetic Neuropathy (Norfolk QoL-DN) and modified Neuropathy Impairment Score +7 (mNIS+7), a measure of neuropathic disease progression, in inotersen-treated patients compared to placebo-treated. A continued increase in benefit, relative to placebo, was observed in both endpoints through study completion. Statistically significant benefit was also observed in multiple other endpoints in the study, including the SF-36 Health Survey and cardiac measures. The data will be presented at the first annual meeting of the ATTR Amyloidosis Meeting in Paris, France.

"The data presented today show the potentially profound benefit that treatment with inotersen may provide to people suffering from hATTR - a devastating and progressive disease that robs people of their independence and dignity," said Dr. Morie A. Gertz, Roland Seidler Jr. Professor of the Art of Medicine and Chair of the Department of Internal Medicine Mayo Clinic in Rochester, Minnesota and study author. "Many patients treated with inotersen experienced improvement or stabilization in measures of their disease and the majority experienced improved quality of life, delivered with a convenient, once-weekly, subcutaneous injection that can be administered at home, providing greater control in managing the disease."

The NEURO-TTR study met both co-primary endpoints, the Norfolk QoL-DN, a validated instrument for physician-assessed quality of life, and mNIS+7, a validated instrument for evaluating hATTR disease severity. Consistent and significant benefit compared to placebo was observed in both co-primary endpoints at both eight months and 15 months. In addition, consistent and significant benefit was observed in both endpoints independent of disease stage, types of mutation, previous use of TTR stabilizers or presence of cardiomyopathy. Compared to placebo-treated patients, inotersen-treated patients experienced substantial and statistically significant benefits, including:

- A mean 11.68-point and a mean 6.14-point benefit compared to placebo in Norfolk QoL-DN at 15 months and eight months respectively (p=0.0006, p=0.032).
- A mean 3.59-point clinically meaningful benefit compared to placebo in the SF-36 Health Survey at 15 months (p=0.006). SF-36 is a commonly used and validated QoL instrument for assessing general health status across eight domains of health.
- A mean 19.73-point and a mean 8.69-point benefit compared to placebo in mNIS+7 at 15 months and eight months respectively (p=0.00000004, p=0.0005).
- Encouraging benefit compared to placebo in multiple cardiac measures in patients with significant cardiac disease at baseline (interventricular septum thickness, IVS ≥ 1.5 cm), including left ventricle mass (p=0.0288), IVS (p=0.0150), posterior wall thickness (p=0.0425), and trends in favor of inotersen treatment vs. placebo treatment in global longitudinal strain.
- Significant benefit compared to placebo in patients with cardiac disease at baseline in both primary endpoints (Norfolk QoL-DN, p=0.036 and mNIS+7, p<0.001) and in the SF-36 Health Survey endpoint (p=0.025) at 15 months.

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.

"The results from the NEURO-TTR study support a favorable benefit-risk profile for inotersen in patients with hATTR. We believe inotersen has the potential to give people living with this devastating, progressive, fatal disease new hope and the ability to regain freedom from the burden of their disease," said Brett P. Monia, senior vice president of drug discovery and franchise leader for oncology and rare diseases at Ionis Pharmaceuticals. "These data move us closer to our goal of changing the way hATTR is diagnosed and treated. We plan to file for marketing authorization in the EU tomorrow, where inotersen has been granted Accelerated Assessment, and in the U.S. in the next week. We are making substantial progress in advancing inotersen to the market. We are also in advanced discussions with potential co-commercialization partners. We believe the right partner can maximize the commercial success of inotersen."

WEBCAST INFORMATION
At 7:00 a.m. Eastern Time today, Ionis will host a live webcast and conference call to discuss these data, and to provide a comprehensive business update. 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 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. 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). 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).

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 progressing toward regulatory filings for marketing authorization. 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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