Ionis and Akcea Present New Data from ATTR Amyloidosis Program at 16th International Symposium on Amyloidosis

March 26, 2018

Continued benefit with long-term inotersen treatment observed in both quality of life (Norfolk-QOL-DN) and neuropathy (mNIS+7) measures in hATTR amyloidosis patients;

Cardiac benefit with inotersen treatment observed in a Phase 2 study in patients with wild-type and hereditary ATTR cardiomyopathy

AKCEA-TTR-L Rx, a next-generation antisense drug designed to treat patients with all forms of ATTR amyloidosis, advancing into clinic

CARLSBAD, Calif., and CAMBRIDGE, Mass., March 26, 2018 /PRNewswire/ -- Ionis Pharmaceuticals, Inc. (Nasdaq: IONS), the leader in antisense therapeutics, and its affiliate, Akcea Therapeutics, Inc. (Nasdaq: AKCA), today announced Phase 3 data showing that inotersen-treated patients with hereditary ATTR (hATTR) amyloidosis who were treated for up to 27 months in the NEURO-TTR and open-label extension (OLE) studies continued to demonstrate sustained benefit in measures of quality of life and neuropathy.

New data from the OLE and an investigator-initiated Phase 2 study in patients with ATTR cardiomyopathy treated with inotersen will be presented at the 16th International Symposium on Amyloidosis (ISA) in Kumamoto, Japan, being held from March 26-29, 2018. In addition, six presentations related to the Ionis/Akcea ATTR amyloidosis program, including one on AKCEA-TTR-L$_{Rx}$, a Ligand Conjugated Antisense (LICA) drug in development for the treatment of people with all forms of ATTR amyloidosis, will be presented.

"I'm encouraged that inotersen-treated patients in the OLE continue to experience robust and sustained benefits in quality of life and measures of neuropathy impairment," said John L. Berk, M.D., associate professor of medicine at Boston University School of Medicine and a principal investigator in the NEURO-TTR study. "The rapid and sustained benefits observed with inotersen in the NEURO-TTR and OLE studies illustrate the substantial potential of inotersen to change the course of this devastating disease."

The NEURO-TTR study was a Phase 3 randomized (2:1), double-blind, placebo-controlled, international study in 172 patients with polyneuropathy due to hATTR. 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. The NEURO-TTR OLE is an ongoing study for patients who completed the NEURO-TTR study and is intended to evaluate the long-term efficacy and safety profile of inotersen.

Inotersen Clinical Result Highlights:

OLE Results

- The benefit observed with inotersen treatment in the NEURO-TTR study, as measured by Norfolk QOL-DN and mNIS+7, continued in the OLE, with up to 27 months of total treatment (15 months in NEURO-TTR and up to 12 months in OLE). In addition, the OLE results demonstrate that patients who initiated inotersen treatment 15 months earlier (at initiation of NEURO-TTR) experienced greater benefit in Norfolk QOL-DN and mNIS+7 than those who received placebo treatment in the NEURO-TTR study and progressed in their disease, and then initiated inotersen treatment in the OLE.
- Patients receiving placebo in the NEURO-TTR study experienced a rapid onset of effect following inotersen treatment that was sustained for up to 12 months in the OLE, including:
    - Improvements in quality of life and activities of daily living as measured by Norfolk QOL-DN
    - Decreased rate of disease progression as measured by mNIS+7 compared to their rate of progression in NEURO-TTR
- No new safety concerns were identified in the OLE. Total drug exposure, including NEURO-TTR and OLE, as of September 15, 2017 was 307 patient years. The median exposure was 692 days (n=161) and the longest exposure was 4.5 years.
    - Serious adverse events occurred in 22 patients (26%) and 11 patients (22%) in the inotersen-inotersen and placebo-inotersen groups, respectively, and were considered related to treatment in 2 patients (2%) and 1 patient (2%), respectively
    - 5 fatal adverse events occurred during the OLE; none were considered related to treatment

NEURO-TTR Results

- Significant benefit was observed in inotersen-treated 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 way they felt and functioned in the SF-36 Health Survey endpoint (p=0.025) at 15 months, compared to placebo.
- Most inotersen treated patients experienced substantial reductions in TTR. Nearly 90% of patients achieved >50% TTR reduction and nearly 50% achieved over 75% TTR reduction at 15 months. Median TTR reduction was 75-79% between weeks 13-65. These TTR reductions were associated with an improvement from baseline in 50% of patients, as measured by Norfolk QOL-DN, and an improvement from baseline in 37% of patients, as measured by mNIS+7. Whether or not a patient improved in either measure could not be predicted by TTR reduction alone. Most patients achieved benefit regardless of whether they were in the 50-75% reduction range or in the 75-95% reduction range.
- Encouraging benefit was observed in inotersen-treated patients with significant cardiac disease at baseline (interventricular septum thickness, IVS ≥ 1.5 cm) in multiple cardiac measures, including mean decreases in left ventricle mass (p=0.0288), IVS (p=0.0150) and posterior wall thickness (p=0.0425), which increased, on average, in placebo-treated patients.

Investigator-sponsored Phase 2 Results (as of January 2018)

Results from an ongoing investigator-sponsored Phase 2 study in cardiomyopathy patients with hATTR amyloidosis and wild-type ATTR (wtATTR) amyloidosis treated with inotersen further support cardiac benefit observed in NEURO-TTR study:

- Reduction of 8.5% in left ventricular mass (LVM) at 24 months in both hATTR and wtATTR amyloidosis patients (n=10) treated with inotersen, compared to an increase of 8% at 12 months in hATTR amyloidosis patients (n=9) with similar disease characteristics in a prior natural history study[1]
- Mean improvement from baseline in 6-minute walk test (6-MWT) of 29 meters and 41 meters at 12 and 24 months, respectively, in hATTR amyloidosis patients (n=8) treated with inotersen, compared to a decrease of 117.5 meters over 18 months in hATTR amyloidosis patients (n=3) in a prior natural history study[1]
- No drug-related serious adverse events occurred. There were no severe thrombocytopenia or renal adverse events.

"The clinical benefits observed with inotersen treatment, coupled with the flexibility offered by a once-weekly, self-administered subcutaneous injection, can restore greater independence that many hATTR amyloidosis patients have lost to their disease," said Sarah Boyce, chief business officer at Ionis. "We believe that inotersen has the potential to transform the lives of patients with hATTR amyloidosis, and we are committed to rapidly bringing this important new treatment to patients following marketing approval."

"Our commitment to patients with ATTR amyloidosis goes beyond those with the hereditary form of the disease. We are developing AKCEA-TTR-L_{Rx}, our next generation antisense drug, to treat patients with all forms of the disease. This highly potent LICA drug offers the potential for monthly or less frequent subcutaneous administration with very low doses. We and Akcea plan to advance AKCEA-TTR-L_{Rx} into clinical studies later this year," said Brett P. Monia, chief operating officer, senior vice president of antisense drug discovery and translational medicine at Ionis Pharmaceuticals.

"The results with inotersen and AKCEA-TTR-L_{Rx} highlighted at ISA are important examples of our innovative antisense platform and how we can use it to pursue our mission to bring innovative medicines to patients with severe diseases," Monia said.

ISA Presentations:

Oral Presentation: Monday, March 26, 2018 from 5:10 to 5:30 pm JST

- '*Inotersen treatment for ATTR amyloidosis'* oral presentation by Merrill D. Benson, M.D., Indiana University School of Medicine

Poster Presentations: Monday, March 26, 2018 at 1:30 pm JST

- '*A ligand conjugated antisense oligonucleotide for the treatment of Transthyretin amyloidosis (ATTR)'* poster presentation by Brett P. Monia, Ph.D., Ionis Pharmaceuticals
- '*Burden of hereditary transthyretin amyloidosis (hATTR) with polyneuropathy (hATTR-PN) in patients enrolled in the phase 3 study NEURO-TTR'* poster presentation by John L. Berk, M.D., Boston University
- '*Inotersen improves Norfolk quality of life–diabetic neuropathy (Norfolk QOL-DN) measures in patients with hereditary transthyretin amyloidosis (hATTR) polyneuropathy (PN) in the phase 3 study NEURO-TTR'* poster presentation by Michael J. Polydefkis, M.D., Johns Hopkins University
- '*Open label extension of the phase 3 NEURO-TTR study to assess the long-term efficacy and safety of inotersen in patients with hereditary transthyretin amyloidosis (hATTR)*' poster presentation by Thomas Brannagan, M.D., Columbia University Medical Center
- '*Inotersen improves quality of life (QOL) in patients with hereditary transthyretin amyloidosis (hATTR) with polyneuropathy (PN) and cardiomyopathy (CM): results of the phase 3 study NEURO-TTR'* poster presentation by Mathew S. Maurer, M.D., Columbia University Medical Center
- *'Safety and efficacy of inotersen in patients with hereditary transthyretin amyloidosis (hATTR) with polyneuropathy (hATTR-PN) in the NEURO-TTR study'* poster presentation by Morie A. Gertz, M.D., Mayo Clinic, Rochester, MN

For the 2018 program and a full list of presentations please visit the ISA website at www.isa2018.com.

ABOUT INOTERSEN
Inotersen is an antisense drug designed to reduce the production of transthyretin, or TTR protein, to treat ATTR amyloidosis, a systemic, progressive and fatal disease. Inotersen is currently under Priority Review for marketing authorization in the U.S. and Accelerated Assessment in the EU. The U.S. Food and Drug Administration has granted inotersen Orphan Drug Designation and Fast Track Status, and the European Medicines Agency has granted inotersen Orphan Drug Designation.

The NEURO-TTR study was a Phase 3 randomized (2:1), double-blind, placebo-controlled, international study in 172 patients with polyneuropathy due to hATTR. 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. The NEURO-TTR OLE is an ongoing study for patients who completed the NEURO-TTR study and is intended to evaluate the long-term efficacy and safety profile of inotersen.

Results from the Phase 3 NEURO-TTR study demonstrated that most inotersen-treated patients experienced substantial reductions in TTR. Nearly 90% of patients achieved >50% reduction and nearly 50% achieved over 75% TTR reduction at 15 months. Median TTR reductions was 75-79% between weeks 13-65. These TTR reductions were associated with benefit compared to placebo in 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 or presence of cardiomyopathy at the beginning of the study. Inotersen-treated patients benefited significantly in the quality of life primary endpoint with 50% of patients experiencing improved scores compared to baseline and a mean difference in magnitude of 11.68 points, compared to placebo-treated patients, at 15 months of treatment (mean change from baseline of 0.99 vs. 12.67, $p<0.001$). 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 37% of patients experiencing improved scores compared to baseline and a mean difference in magnitude of 19.73 -points, compared to placebo-treated patients, at 15 months of treatment, ($p < 0.001$). Whether or not a patient improved in either Norfolk QOL-DN or mNIS+7 could not be predicted by TTR reduction alone. Most patients achieved benefit regardless of whether they were in the 50-75% reduction range or in the 75-95% reduction range.

Significant benefit was observed in inotersen-treated patients with cardiac disease at baseline (interventricular septum thickness, IVS ≥ 1.5 cm) 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, compared to placebo. Encouraging benefit was also observed in multiple cardiac measures, including mean decreases in left ventricle mass ($p=0.0288$), IVS ($p=0.0150$) and posterior wall thickness ($p=0.0425$), which increased, on average, in placebo-treated patients.

Thrombocytopenia and safety signals related to renal function were identified during the study. 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 overall 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 inotersen expanded access program (EAP) has been initiated for eligible patients in the U.S.

Ionis recently licensed worldwide rights to commercialize inotersen to Akcea for an upfront licensing fee of $150 million, payable to Ionis in shares of common stock. The combined Ionis inotersen and Akcea teams are preparing to launch inotersen in the U.S. and EU following planned approvals in mid-2018 to treat people with hATTR amyloidosis. Regulatory approval of inotersen in the U.S. and EU will trigger a milestone payment to Ionis of $50 million and $40 million, respectively, with additional milestone payments due upon approval of both programs in various other geographies. Commercial profits and losses from inotersen will be split 60% to Ionis and 40% to Akcea. This transaction is subject to shareholder approval and customary closing conditions.

ABOUT HEREDITARY TRANSTHYRETIN (hATTR) AMYLOIDOSIS
hATTR amyloidosis is a progressive, systemic, and fatal genetic disease caused by the inappropriate formation and aggregation of TTR amyloid deposits in various tissues and organs throughout the body, including in peripheral nerves, heart, intestinal tract, eyes, kidneys, central nervous system, thyroid and bone marrow. Patients with hATTR amyloidosis often present with a mixed phenotype and experience overlapping symptoms of polyneuropathy and cardiomyopathy. The progressive accumulation of TTR amyloid deposits in these tissues and organs leads to sensory, motor and autonomic dysfunction often having debilitating effects on multiple aspects of a patient's life.

Unfortunately, hATTR amyloidosis is often overlooked in the differential diagnosis and accurate identification is unnecessarily delayed for years. Ultimately, hATTR amyloidosis results in death within three to fifteen years of symptom onset. Therapeutic options for the treatment of patients with hATTR amyloidosis are limited and there are currently no disease-modifying drugs approved for the disease. There are an estimated 50,000 patients with hATTR amyloidosis worldwide. Additional information on hATTR amyloidosis, including a full list of organizations supporting the hATTR amyloidosis community worldwide, is available at www.hattrchangethecourse.com.

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 ATTR (hATTR) amyloidosis, 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. Inotersen is under regulatory review in the U.S. and EU. Volanesorsen is under regulatory review in the U.S., EU, and

Canada. Ionis' patents provide strong and extensive protection for its drugs and technology. Additional information about Ionis is available at www.ionispharma.com.

ABOUT AKCEA THERAPEUTICS

Akcea Therapeutics, Inc., an affiliate of Ionis Pharmaceuticals, Inc., is a biopharmaceutical company focused on developing and commercializing drugs to treat patients with serious rare diseases. Akcea is advancing a mature pipeline of four novel drugs, including volanesorsen, AKCEA-APO(a)-L_{Rx}, AKCEA-ANGPTL3-L_{Rx} and AKCEA-APOCIII-L_{Rx}. All four drugs were discovered by and are being co-developed with Ionis, a leader in antisense therapeutics, and are based on Ionis' proprietary antisense technology. Volanesorsen is under regulatory review in the U.S., EU and Canada for the treatment of familial chylomicronemia syndrome, or FCS. Akcea is building the infrastructure to commercialize its drugs globally. Akcea is located in Cambridge, Massachusetts. Additional information about Akcea is available at www.akceatx.com.

IONIS' AND AKCEA'S FORWARD-LOOKING STATEMENT

This press release includes forward-looking statements regarding the therapeutic and commercial potential of inotersen and AKCEA-TTR-L_{Rx}. Any statement describing Ionis' or Akcea's goals, expectations, financial or other projections, intentions or beliefs, including the commercial potential of inotersen, volanesorsen or other of Ionis' or Akcea's drugs in development 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' and Akcea's 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' and Akcea's forward-looking statements reflect the good faith judgment of its management, these statements are based only on facts and factors currently known by Ionis and Akcea. As a result, you are cautioned not to rely on these forward-looking statements. These and other risks concerning Ionis' and Akcea's programs are described in additional detail in Ionis' and Akcea's annual reports on Form 10-K for the year ended December 31, 2017 and Akcea's preliminary proxy statement with respect to the transaction which are on file with the SEC. Copies of these and other documents are available from each company.

In this press release, unless the context requires otherwise, "Ionis", "Akcea," "Company," "Companies" "we," "our," and "us" refers to Ionis Pharmaceuticals and/or Akcea Therapeutics.

References:
1. Ruberg FL, Maurer MS, Judge DP, et al. Prospective evaluation of the morbidity and mortality of wild-type and V122I mutant transthyretin amyloid cardiomyopathy: the Transthyretin Amyloidosis Cardiac Study (TRACS). Am Heart J. 2012;164(2):222-228.e1.

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SOURCE Ionis Pharmaceuticals, Inc.; Akcea Therapeutics, Inc.

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