New England Journal of Medicine Publishes Results from Pivotal Study of TEGSEDI™ (inotersen) for the Treatment of Hereditary ATTR Amyloidosis

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-TEGSEDI treatment demonstrated substantial improvement in measures of neuropathy progression and quality of life-

-Akcea prepared for launch following approval-

CARLSBAD, Calif., and CAMBRIDGE, Mass., July 5, 2018 /PRNewswire/ -- Ionis Pharmaceuticals, Inc. (Nasdaq: IONS), the leader in antisense therapeutics, and its affiliate, Akcea Therapeutics (Nasdaq: AKCA), announced today that the final study results from NEURO-TTR, the pivotal study of TEGSEDI™ (inotersen) in patients with hereditary ATTR (hATTR) amyloidosis with polyneuropathy, were published in the July 5, 2018 issue of *The New England Journal of Medicine* in a manuscript titled "Inotersen Treatment for Patients with Hereditary Transthyretin Amyloidosis."

Results from the study demonstrated that patients treated with TEGSEDI experienced early, sustained and highly significant benefit in both co-primary endpoints: the modified Neuropathy Impairment Score +7 (mNIS+7), a measure of neuropathic disease progression, and the Norfolk Quality of Life Questionnaire-Diabetic Neuropathy (Norfolk QoL-DN), compared to placebo-treated patients. Furthermore, a substantial number of TEGSEDI-treated patients displayed improvements in disease symptoms as measured in both co-primary endpoints, compared to their baseline study entry values. The clinical benefits demonstrated by TEGSEDI were associated with substantial reductions in the transthyretin (TTR) protein, the underlying cause of hATTR amyloidosis. For the full text of this publication, please visit: https://www.nejm.org/doi/full/10.1056/NEJMoa1716793.

"hATTR amyloidosis is a progressive, systemic and fatal disease that relentlessly deprives people of their independence and dignity. People with hATTR amyloidosis experience misfolded TTR build up in various tissues and organs, resulting in progressively debilitating symptoms which lead to death within a few years of symptom onset," said Morie Gertz, M.D., Roland Seidler Jr. Professor of the Art of Medicine and chair of the department of Internal Medicine at the Mayo Clinic. "Unfortunately, currently available therapeutic options are inadequate to slow the progression of hATTR amyloidosis. I am encouraged with the benefit in neuropathy symptoms and quality of life observed in patients treated with TEGSEDI in this Phase 3 study. I believe TEGSEDI has promising potential to treat patients with this devastating disease."

"Based on these study results and the feedback we have received from physicians and patients, we believe TEGSEDI has the potential to provide people living with hATTR amyloidosis a greater degree of control over their disease and their lives together with the convenience of a once weekly, self-administered subcutaneous injection," said Sarah Boyce, president of Akcea Therapeutics. "The regulatory reviews in the U.S. and EU are progressing well and we anticipate approval soon, bringing us one step closer to achieving our mission to transform the lives of people with hATTR amyloidosis. We understand the urgent need for new treatments for this disease and are ready to launch TEGSEDI."

"We believe the NEURO-TTR Phase 3 results demonstrate a favorable benefit-risk profile for TEGSEDI to treat patients with this devastating disease. Patients treated with TEGSEDI experienced substantial improvements in measures of neuropathy and quality of life compared to placebo-treated patients, independent of TTR mutation type, disease stage or presence of cardiomyopathy. Remarkably, half of the TEGSEDI-treated patients in this study experienced improvement in their quality of life over the course of their treatment and nearly 40% improved in a measure of neurological disease progression," said Brett P. Monia, Ph.D., chief operating officer, senior vice president of antisense drug discovery and translational medicine at Ionis Pharmaceuticals.

ABOUT NEURO-TTR: TEGSEDI PHASE 3 CLINICAL STUDY

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 amyloidosis. The 15-month study measured the effects of treatment with TEGSEDI on neurological dysfunction and on quality-of-life by measuring the change from baseline both 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 TEGSEDI.

In the NEURO-TTR study, patients treated with TEGSEDI experienced 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, patients treated with TEGSEDI experienced significant benefit in both the Norfolk-QoL-DN and mNIS+7, independent of disease stage, types of mutation or presence of cardiomyopathy. Most TEGSEDI-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 79% at Week 65. These TTR reductions were associated with improvements from baseline in the Norfolk QoL-DN primary endpoint with 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, $p<0.001$). 50% of TEGSEDI-treated patients had improved Norfolk QoL scores compared to their baseline scores. Clinically meaningful benefit was also observed in TEGSEDI-treated patients compared to placebo-treated patients in the SF-36 physical component score, a measure of general health quality of life. In addition, TEGSEDI-treated patients benefited significantly in the co-primary endpoint assessing disease control, the mNIS+7, achieving a mean difference in magnitude of 19.73-points, compared to placebo-treated patients, at 15 months of treatment (mean change from baseline of 5.80 vs. 25.53, $p<0.001$). 36.5% of TEGSEDI-treated patients had improved mNIS+7 scores compared to their baseline scores. As previously reported, encouraging benefit was also observed in TEGSEDI-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.

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 manageable with routine monitoring, which has proven effective since implementation.

Adverse events occurring in >=10% of patients and twice as frequently in TEGSEDI-treated patients compared with placebo-treated patients included thrombocytopenia/platelet count decreases, nausea, pyrexia, chills, vomiting, and anemia. Injection site reactions were observed in about 1% of all injections and were mild or moderate in severity. There were no discontinuations due to injection site reactions. There were five deaths in the study, five (4.5%) in the TEGSEDI arm and zero in the placebo arm. The mortality rate in the drug-treatment arm is comparable to the death rate expected in this patient population as evidenced in other clinical trials. Four deaths 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 in the NEURO-TTR study.

ABOUT TEGSEDI (inotersen)
TEGSEDI™ (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. TEGSEDI is currently under regulatory review for marketing approval in the U.S., EU and Canada. The U.S. Food and Drug Administration has granted TEGSEDI Orphan Drug Designation and Fast Track Status, and the European Medicines Agency has granted TEGSEDI Orphan Drug Designation. In the U.S., TEGSEDI has a PDUFA date of October 6, 2018. The Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA) adopted a positive opinion recommending approval of TEGSEDI for the treatment of Stage 1 or Stage 2 polyneuropathy in adult patients with hereditary transthyretin amyloidosis (hATTR). The TEGSEDI expanded access program (EAP) has been initiated for eligible patients in the U.S. Click here for more information on the TEGSEDI EAP.

ABOUT HEREDITARY ATTR (hATTR) AMYLOIDOSIS
hATTR amyloidosis is a progressive, systemic and fatal hereditary 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. 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. People with hATTR amyloidosis often present with a mixed phenotype and experience overlapping symptoms of polyneuropathy and cardiomyopathy. People with hATTR with symptoms of polyneuropathy are classified into 3 stages: Stage 1 patients do not require assistance with ambulation, Stage 2 patients do require assistance with ambulation and Stage 3 patients are confined to a wheelchair or are bedridden.

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 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 and rare diseases. Akcea is advancing a mature pipeline of six novel drugs, including TEGSEDI™ (inotersen), WAYLIVRA™ (volanesorsen), AKCEA-APO(a)-L_{Rx}, AKCEA-ANGPTL3-L_{Rx}, AKCEA-APOCIII-L_{Rx}, and AKCEA-TTR-L_{Rx}, all with the potential to treat multiple diseases. All six drugs were discovered by and are being co-developed with Ionis, a leader in antisense therapeutics, and are based on Ionis' proprietary antisense technology. TEGSEDI is under regulatory review in the U.S., EU and Canada for the treatment of people with hereditary transthyretin amyloidosis, or hATTR. WAYLIVRA is under regulatory review in the U.S., EU and Canada for the treatment of familial chylomicronemia syndrome, or FCS, and is currently in Phase 3 clinical development for the treatment of people with familial partial lipodystrophy, or FPL. Akcea is building the infrastructure to commercialize its drugs globally. Akcea is a global company headquartered in Cambridge, Massachusetts. Additional information about Akcea is available at www.akceatx.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 40 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. TEGSEDI™ (inotersen) and WAYLIVRA (volanesorsen) are two antisense drugs that Ionis discovered and successfully advanced through Phase 3 studies. TEGSEDI is under regulatory review for marketing approval in the U.S., EU and Canada for the treatment of patients with hereditary ATTR amyloidosis, or hATTR. WAYLIVRA is under regulatory review for marketing approval in the U.S., EU, and Canada for the treatment of patients with familial chylomicronemia syndrome, or FCS. WAYLIVRA is also in a Phase 3 study in patients with familial partial lipodystrophy, or FPL. Akcea Therapeutics, an affiliate of Ionis focused on developing and commercializing drugs to treat patients with serious and rare diseases, will commercialize TEGSEDI and WAYLIVRA, if approved. Ionis' patents provide strong and extensive protection for its drugs and technology. Additional information about Ionis is available at www.ionispharma.com.

AKCEA'S AND IONIS' FORWARD-LOOKING STATEMENT
This press release includes forward-looking statements regarding the business of Akcea Therapeutics, Inc. and Ionis Pharmaceuticals, Inc. and the therapeutic and commercial potential of TEGSEDI™. Any statement describing Akcea's or Ionis' goals, expectations, financial or other projections, intentions or beliefs, including the commercial potential of TEGSEDI, WAYLIVRA or other of Akcea's or Ionis' 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. Akcea's and 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 Akcea's and Ionis' forward-looking statements reflect the good faith judgment of its management, these statements are based only on facts and factors currently known by Akcea and Ionis. 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 quarterly reports on Form 10-Q and annual reports on Form 10-K, which are on file with the SEC. Copies of these and other documents are available from each company.

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