Akcea and Ionis Announce Publication of Long-Term Clinical Data of TEGSEDI® in Patients with Polyneuropathy Driven by Hereditary Transthyretin Amyloidosis Demonstrating Sustained Improvements and Even Greater Stabilization in Patients Starting Earlier Treatment

May 28, 2020

Results from the ongoing, open-label extension (OLE) study of the pivotal NEURO-TTR trial published in the European Journal of Neurology show that patients treated with TEGSEDI® (inotersen) experienced sustained improvements in measures of neuropathic progression at 39 months of therapy, and clinically relevant improvements in measures of quality of life compared to the natural history of the disease

No new safety signals were identified

TEGSEDI is an at-home subcutaneous injection

BOSTON and CARLSBAD, Calif., May 28, 2020 (GLOBE NEWSWIRE) -- Akcea Therapeutics, Inc. (NASDAQ: AKCA), a majority-owned affiliate of Ionis Pharmaceuticals, Inc., and Ionis Pharmaceuticals, Inc. (NASDAQ: IONS), today announced publication of long-term data from the open-label extension (OLE) of the pivotal NEURO-TTR study of TEGSEDI® (inotersen) in patients with hereditary transthyretin (hATTR) amyloidosis with polyneuropathy. The primary objective of the OLE study was to evaluate the safety and tolerability of long-term dosing with TEGSEDI. Secondary objectives of the study included understanding progression based on measures such as the modified Neuropathy Impairment Score +7 (mNIS+7) and the Norfolk Quality of Life Questionnaire-Diabetic Neuropathy (Norfolk QoL-DN). Understanding changes over time in generic health-related quality of life based on the Short Form 36 Health Survey (SF-36) was an exploratory objective. This interim analysis, published in the *European Journal of Neurology*, show that treatment with TEGSEDI was not associated with additional safety concerns or signs of increased toxicity in study participants treated for up to five years. Treatment with TEGSEDI resulted in continued efficacy in patients after two years. Results also showed that patients who started treatment with TEGSEDI earlier (received TEGSEDI treatment in the NEURO-TTR study) achieved greater long-term disease stabilization compared to those who switched from placebo to TEGSEDI in the OLE study. For the full text of this publication, please visit: https://onlinelibrary.wiley.com/doi/abs/10.1111/ene.14285

"These data further validate the favorable benefit-risk profile seen in hATTR patients treated with TEGSEDI for their polyneuropathy," said Louis O'Dea, MB, BCh, BAO. FRCP(C), chief medical officer of Akcea Therapeutics. "Patients living with hATTR amyloidosis are faced with progressive and debilitating symptoms. These results demonstrate that the benefits we observed in the original 15-month Phase 3 study, such as improved outcomes relative to placebo for neuropathy progression and quality of life, are extended with long term treatment."

"The burden of hATTR amyloidosis is significant as patients suffer from progressive neuropathic, gastrointestinal and psychosocial symptoms that can affect every aspect of their lives including the ability to work, take care of their families or participate in everyday activities. Without therapeutic intervention, patient quality of life rapidly deteriorates," said Thomas Brannagan, M.D., director of the Peripheral Neuropathy Center at Columbia University Medical Center and a principal author of the study. "As someone who sees firsthand the devastating effects of this disease on patients and their families, the availability of an evidence-based therapy in treating the polyneuropathy symptoms of hATTR amyloidosis over the long term, as shown with these OLE study data, is critical."

hATTR amyloidosis is an under-recognized, debilitating and progressive disease that is caused by the buildup of TTR proteins that misfold due to inherited mutations. It is characterized by the deposition of amyloid fibrils throughout the body including in nervous tissue and can have a devastating impact on patients' quality of life. TEGSEDI is a once-weekly, at-home subcutaneous injection that targets the polyneuropathy of hATTR amyloidosis at its source by reducing production of the TTR protein.

Results from the pivotal, randomized, double-blind, placebo-controlled NEURO-TTR study demonstrated that hATTR amyloidosis patients treated with TEGSEDI experienced significant benefit compared to patients treated with placebo across both co-primary endpoints: mNIS+7, a measure of neuropathic disease progression and the Norfolk QoL-DN. At the end of the study, participants were given the opportunity to enroll in the OLE study and continue treatment with TEGSEDI or switch from placebo. Of the 139 patients who completed the NEURO-TTR study, 135 participants (97%) continued in the OLE study. Among those who participated in the ongoing OLE study, 85 continued to receive TEGSEDI and 50 switched from placebo to TEGSEDI.

No new safety concerns were identified in patients treated with TEGSEDI in the OLE study. There was also no evidence of increased risk for grade 4 thrombocytopenia or acute glomerulonephritis with increased duration of exposure to TEGSEDI. Regular, required platelet and renal monitoring proved to be effective in managing patients' risk. The most common (>10%) adverse events (AEs) include nausea, urinary tract infection, vomiting, diarrhea, fatigue, peripheral edema, injection site pain and thrombocytopenia. Overall, 19 (14.1%) patients discontinued TEGSEDI due to treatment-emergent adverse events (TEAEs). Nine (6.7%) patients died during the OLE study but none of the deaths were considered related to TEGSEDI.

Patients administered TEGSEDI throughout the NEURO-TTR and OLE studies experienced substantial reductions in TTR protein levels (77% reduction on average) compared to their baseline from the NEURO-TTR study. In addition, those treated with TEGSEDI for 39 cumulative months in the NEURO-TTR and OLE studies showed sustained benefit compared to the predicted worsening with placebo. Likewise, those patients who switched from placebo to TEGSEDI demonstrated sustained improvement of neurologic disease progression and quality of life as measured by the mNIS+7, the Norfolk QoL-DN, and the SF-36 Physical Component Summary score (PCS) compared with a continued predicted worsening with placebo. Finally, patients treated earlier with TEGSEDI achieved greater benefit in mNIS+7 (17.06 points) and Norfolk QoL-DN (11.89 points) compared to patients who switched from placebo to TEGSEDI in the OLE study, highlighting the importance of early commencement of TEGSEDI in appropriate patients.

"We are very proud of our role in addressing an area of significant unmet medical need for patients and will continue our efforts to bring TEGSEDI to more patients with the polyneuropathy of hATTR around the world," said Brett P. Monia, Ph.D., chief executive officer at Ionis Pharmaceuticals. "We look forward to reviewing future data from this ongoing OLE study and to the prospect of patients with this debilitating disease having access to a treatment that can deliver long-term clinical benefits."

ABOUT *TEGSEDI® (INOTERSEN)*

TEGSEDI was approved by the U.S. Food and Drug Administration (FDA) for the treatment of the polyneuropathy of hereditary transthyretin-mediated

(hATTR) amyloidosis in adults. TEGSEDI, discovered and developed by Ionis Pharmaceuticals, is the world's first and only subcutaneous RNA-targeting drug designed to reduce the production of human transthyretin (TTR) protein. TEGSEDI also received marketing authorization in the European Union and Canada for the treatment of stage 1 or stage 2 polyneuropathy in adult patients with hereditary transthyretin amyloidosis.

The approval is based on data from the NEURO-TTR study that was a Phase 2/3 randomized (2:1), double-blind, placebo-controlled, 15-month, international study in 172 patients with hATTR amyloidosis with symptoms of polyneuropathy. In NEURO-TTR, TEGSEDI demonstrated significant improvement compared to placebo in measures of neuropathy and quality of life as measured by the modified Neuropathy Impairment Score +7 (mNIS+7) and in the Norfolk Quality of Life Questionnaire-Diabetic Neuropathy (Norfolk QOL-DN) total score. Patients treated with TEGSEDI experienced similar benefit regardless of subgroups such as age, sex, race, region, Neuropathy Impairment Score (NIS), Val30Met mutation status, and disease stage.

The approval is also based on early data from the NEURO-TTR OLE that is an ongoing study for patients who completed the NEURO-TTR study. The OLE study is designed to evaluate the long-term safety and efficacy of TEGSEDI.

For TEGSEDI's full prescribing information, please visit www.TEGSEDI.com.

IMPORTANT SAFETY INFORMATION

BOXED WARNING: THROMBOCYTOPENIA AND GLOMERULONEPHRITIS

Thrombocytopenia

- **TEGSEDI causes reductions in platelet count that may result in sudden and unpredictable thrombocytopenia, which can be life-threatening. One clinical trial patient died from intracranial hemorrhage**
- **TEGSEDI is contraindicated in patients with a platelet count below 100 x 109 /L**
- **Prior to starting TEGSEDI, obtain a platelet count. During treatment, monitor platelet counts weekly if values are 75 x 10^9 /L or greater, and more frequently if values are less than 75 x 10^9 /L**
- **If a patient develops signs or symptoms of thrombocytopenia, obtain a platelet count as soon as possible. The patient should not receive additional TEGSEDI unless a platelet count is determined to be interpretable and acceptable by a medical professional**
- **Following discontinuation of treatment for any reason, continue to monitor platelet count for 8 weeks, or longer if platelet counts are less than normal, to verify that platelet counts remain above 75 x 10^9 /L**

Glomerulonephritis

- **TEGSEDI can cause glomerulonephritis that may require immunosuppressive treatment and may result in dialysis-dependent renal failure. One clinical trial patient who developed glomerulonephritis and did not receive immunosuppressive treatment remained dialysis dependent. In clinical trials, cases of glomerulonephritis were accompanied by nephrotic syndrome, which can have manifestations of edema, hypercoagulability with venous or arterial thrombosis, and increased susceptibility to infection**
- **TEGSEDI should generally not be initiated in patients with urinary protein to creatinine ratio (UPCR) of 1000 mg/g or higher**
- **Prior to starting TEGSEDI, measure the serum creatinine, estimated glomerular filtration rate (eGFR), urine protein to creatinine ratio (UPCR), and perform a urinalysis. During treatment, monitor serum creatinine, eGFR urinalysis, and UPCR every 2 weeks. TEGSEDI should not be given to patients who develop a UPCR of 1000 mg/g or higher or eGFR below 45 mL/minute/1.73 m^2, pending further evaluation of the cause**
- **If a dose is held, once eGFR increases to ≥45 mL/minute/1.73 m^2, UPCR decreases to below 1000 mg/g, or the underlying cause of the decline in renal function is corrected, weekly dosing may be reinitiated. In patients with UPCR of 2000 mg/g or higher, perform further evaluation for acute glomerulonephritis, as clinically indicated. If acute glomerulonephritis is confirmed, TEGSEDI should be permanently discontinued**

TEGSEDI REMS Program

- **Because of the risks of serious bleeding caused by severe thrombocytopenia and because of glomerulonephritis, both of which require frequent monitoring, TEGSEDI is available only through a restricted distribution program under a Risk Evaluation and Mitigation Strategy (REMS) called the TEGSEDI REMS Program**

CONTRAINDICATIONS

TEGSEDI is contraindicated in patients with

- Platelet count below 100 x 10^9 /L
- History of acute glomerulonephritis caused by TEGSEDI
- History of a hypersensitivity reaction to TEGSEDI

WARNINGS AND PRECAUTIONS

Thrombocytopenia

TEGSEDI causes reductions in platelet count that may result in sudden and unpredictable thrombocytopenia that can be life-threatening. In Study 1, platelet counts below 100 x 10^9 /L occurred in 25% of TEGSEDI-treated patients compared with 2% of patients on placebo. Platelet counts below 75 x 10^9 /L occurred in 14% of TEGSEDI-treated patients compared with no patients on placebo. One patient in a clinical trial experienced a fatal intracranial hemorrhage. Do not initiate TEGSEDI in patients with a platelet count below 100 x 10^9 /L. Follow recommended monitoring and treatment recommendations for platelet count.

Symptoms of thrombocytopenia can include unusual or prolonged bleeding (eg, petechiae, easy bruising, hematoma, subconjunctival bleeding, gingival bleeding, epistaxis, hemoptysis, irregular or heavier than normal menstrual bleeding, hematemesis, hematuria, hematochezia, melena), neck stiffness, or atypical severe headache. Patients and caregivers should be instructed to be vigilant for symptoms of thrombocytopenia and seek immediate medical help if they have concerns.

Glomerulonephritis and Renal Toxicity

TEGSEDI can cause glomerulonephritis that may result in dialysis-dependent renal failure. In Study 1, glomerulonephritis occurred in 3 (3%) TEGSEDI-treated patients compared with no patients on placebo. One patient did not receive immunosuppressive treatment and remained dialysis-dependent. If glomerulonephritis is suspected, pursue prompt diagnosis and initiate immunosuppressive treatment as soon as possible. Follow recommended monitoring and treatment recommendations for renal parameters. TEGSEDI should generally not be initiated in patients with a UPCR of 1000 mg/g or greater. If acute glomerulonephritis is confirmed, TEGSEDI should be permanently discontinued.

TEGSEDI is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the TEGSEDI REMS Program because of risks of serious bleeding caused by severe thrombocytopenia and because of glomerulonephritis.

Stroke and Cervicocephalic Arterial Dissection

TEGSEDI may cause stroke and cervicocephalic arterial dissection. In clinical studies, 1 of 161 (0.6%) TEGSEDI-treated patients experienced carotid artery dissection and stroke. Educate patients on the symptoms of stroke and central nervous system arterial dissection. Instruct patients to seek help as soon as possible if symptoms of stroke or arterial dissection occur.

Inflammatory and Immune Effects

Inflammatory and immune changes are an effect of some antisense oligonucleotide drugs, including TEGSEDI. In clinical studies, serious inflammatory and immune adverse reactions occurred in TEGSEDI treated patients, including immune thrombocytopenia and glomerulonephritis, as well as a single case of antineutrophil cytoplasmic autoantibody (ANCA)–positive systemic vasculitis.

Liver Injury

In clinical studies, 8% of TEGSEDI-treated patients had an increased alanine aminotransferase (ALT) at least 3 times the upper limit of normal (ULN) compared with 3% of patients on placebo; 3% of TEGSEDI treated patients had an ALT at least 8 times the ULN compared with no patients on placebo. Monitor ALT, aspartate aminotransferase, and total bilirubin at baseline and every 4 months during treatment with TEGSEDI. If a patient develops clinical signs or symptoms suggestive of hepatic dysfunction, promptly measure serum transaminases and total bilirubin and interrupt or discontinue treatment with TEGSEDI, as appropriate.

Liver Transplant Rejection

In a clinical study, cases of liver transplant rejection were reported 2-4 months after starting TEGSEDI in patients whose liver allografts had previously been clinically stable (for over 10 years) prior to starting TEGSEDI. In these cases, the patients clinically improved and transaminase levels normalized after glucocorticoid administration and cessation of TEGSEDI.

In patients with a history of liver transplant, monitor ALT, AST, and total bilirubin monthly. Discontinue TEGSEDI in patients who develop signs of liver transplant rejection.

Hypersensitivity Reactions/Antibody Formation

TEGSEDI can cause hypersensitivity reactions. In clinical studies, 6 of 161 (4%) TEGSEDI-treated patients stopped treatment because of a hypersensitivity reaction. These reactions generally occurred within 2 hours of administration of TEGSEDI. Antibodies to TEGSEDI were present when the reactions occurred. If a hypersensitivity reaction occurs, discontinue administration of TEGSEDI and initiate appropriate therapy. Do not use in patients who have a history of hypersensitivity reactions to TEGSEDI.

Uninterpretable Platelet Counts: Reaction Between Antiplatelet Antibodies and Ethylenediaminetetraacetic acid (EDTA)

In Study 1, 23% of TEGSEDI-treated patients had at least 1 uninterpretable platelet count caused by platelet clumping compared with 13% of patients on placebo. If there is suspicion of EDTA-mediated platelet clumping, perform a repeat platelet count using a different anticoagulant (eg, sodium citrate, heparin) in the blood collection tube. Recheck the platelet count as soon as possible if a platelet measurement is uninterpretable. Hold TEGSEDI dosing until an acceptable platelet count is confirmed with an interpretable blood sample.

Reduced Serum Vitamin A Levels and Recommended Supplementation

TEGSEDI treatment leads to a decrease in serum vitamin A levels. Supplementation at the recommended daily allowance of vitamin A is advised for patients taking TEGSEDI. Patients should be referred to an ophthalmologist if they develop ocular symptoms suggestive of vitamin A deficiency (eg, night blindness).

ADVERSE REACTIONS

The most common adverse reactions that occurred in at least 20% of TEGSEDI-treated patients and more frequently than in those on placebo were injection site reactions, nausea, headache, fatigue, thrombocytopenia, and fever. Serious adverse reactions were more frequent in TEGSEDI-treated patients (32%) than in patients on placebo (21%).

DRUG INTERACTIONS

Because of the risk of thrombocytopenia, caution should be used when using antiplatelet drugs (including nonprescription products that affect platelets) or anticoagulants concomitantly with TEGSEDI. Because of the risk of glomerulonephritis and renal toxicity, caution should be used when using nephrotoxic drugs and other drugs that may impair renal function concomitantly with TEGSEDI.

Please see full Prescribing Information, including boxed WARNING, at TEGSEDIhcp.com.

ABOUT HEREDITARY TRANSTHYRETIN (hATTR) AMYLOIDOSIS

Hereditary ATTR amyloidosis is a severe, progressive, and life-threatening disease caused by the abnormal formation of the TTR protein and aggregation of TTR amyloid deposits in various tissues and organs throughout the body, including in peripheral nerves, the heart and intestinal tract. The progressive accumulation of TTR amyloid deposits in these organs often leads to intractable peripheral sensorimotor neuropathy, autonomic neuropathy, and/or cardiomyopathy, as well as other disease manifestations. Hereditary ATTR amyloidosis causes significant morbidity and progressive decline in quality of life, severely impacting activities of daily living. The disease often progresses rapidly and can lead to premature death. The median survival is 4.7 years following diagnosis. Additional information on Hereditary ATTR amyloidosis, including a full list of organizations supporting the hATTR amyloidosis community worldwide, is available at www.hattrchangethecourse.com or by visiting www.hATTRGuide.com.

ABOUT IONIS PHARMACEUTICALS, INC.

As the leader in RNA-targeted drug discovery and development, Ionis has created an efficient, broadly applicable, drug discovery platform called antisense technology that can treat diseases where no other therapeutic approaches have proven effective. Our drug discovery platform has served as a springboard for actionable promise and realized hope for patients with unmet needs. We created the first and only approved treatment for children and adults with spinal muscular atrophy as well as the world's first RNA-targeted therapeutic approved for the treatment of polyneuropathy in adults with hereditary transthyretin amyloidosis. Our sights are set on all the patients we have yet to reach with a pipeline of more than 40 novel medicines designed to potentially treat a broad range of disease, including neurological, cardiovascular, infectious, and pulmonary diseases. To learn more about Ionis visit www.ionispharma.com and follow us on Twitter @ionispharma.

ABOUT AKCEA THERAPEUTICS, INC.

Akcea Therapeutics, Inc., a majority-owned affiliate of Ionis Pharmaceuticals, Inc. (NASDAQ: IONS), is a biopharmaceutical company focused on developing and commercializing drugs to treat patients with serious and rare diseases. Akcea is commercializing TEGSEDI® (inotersen) and WAYLIVRA® (volanesorsen), as well as advancing a mature pipeline of novel drugs, including AKCEA-APO(a)-L_{Rx}, vupanorsen (AKCEA-ANGPTL3-L_{Rx}), AKCEA-APOCIII-L_{Rx}, and AKCEA-TTR-L_{Rx}, with the potential to treat multiple diseases. All six drugs were discovered by Ionis, a leader in antisense therapeutics, and are based on Ionis' proprietary antisense technology. TEGSEDI is approved in the U.S., E.U., Canada and Brazil. WAYLIVRA is approved in the E.U. and is currently in Phase 3 clinical development for the treatment of people with familial partial lipodystrophy, or FPL. Akcea is headquartered in Boston, Massachusetts and is building the infrastructure to commercialize its drugs globally. Additional information about Akcea is available at www.akceatx.com and you can follow the Company on Twitter at @akceatx.

AKCEA 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® (inotersen). Any statement describing Akcea's or Ionis' goals, expectations, financial or other projections, intentions or beliefs, including the commercial potential of TEGSEDI 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. In particular, we caution you that our forward-looking statements are subject to the ongoing and developing circumstances related to the COVID-19 pandemic, which may have a material adverse effect on our business, operations and future financial results. As a result, you are cautioned not to rely on these forward-looking statements. These and other risks concerning Akcea's and Ionis' programs are described in additional detail in Akcea's and Ionis' 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.

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.

Akcea Investor Contact:
Matthew Roache
Director, Investor Relations
(617)-841-9535
mroache@akceatx.com

Akcea Media Contacts:
Angelyn Lowe
Executive Director, Corporate Communications & Investor Relations
(617)-207-8509
alowe@akceatx.com

Bill Berry
Berry & Company
T: 212 253-8881
bberry@berrypr.com

Ionis Investor Contact:
D. Wade Walke, Ph.D.
Vice President, Investor Relations
760-603-2741
wwalke@ionisph.com

Ionis Media Contact:
Roslyn Patterson
Vice President, Corporate Communications
760-603-2681
rpatterson@ionisph.com

Source: Akcea Therapeutics, Inc.