

## Akcea and Ionis Announce Approval of TEGSEDI™ (inotersen) in the European Union

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CAMBRIDGE, Mass. and CARLSBAD, Calif., July 11, 2018 (GLOBE NEWSWIRE) -- Akcea Therapeutics, Inc. (NASDAQ:AKCA), an affiliate of Ionis Pharmaceuticals, Inc., and Ionis Pharmaceuticals, Inc. (NASDAQ:IONS), announced today that TEGSEDI™ (inotersen) has received marketing authorization approval from the European Commission (EC) for the treatment of stage 1 or stage 2 polyneuropathy in adult patients with hereditary transthyretin amyloidosis (hATTR). This follows the positive opinion recommending approval provided by the Committee for Medicinal Products for Human Use (CHMP) of European Medicines Agency (EMA). [Click here](#) to view the EC's decision.



"With the EC's decision, TEGSEDI is now the world's first and only RNA-targeted therapeutic approved for patients with hATTR amyloidosis. With subcutaneous delivery, TEGSEDI puts treatment in the patients' hands while bringing the significant benefits shown in the NEURO-TTR study in both measures of neuropathy and quality of life for people living with this serious and fatal disease. This is an important day for the hATTR amyloidosis community as we believe TEGSEDI enables people and their families impacted by this disease to move forward with their lives," said Paula Soteropoulos, chief executive officer at Akcea Therapeutics. "Today is a milestone for Akcea with our first drug approval. It is an achievement we share with the courageous hATTR patient community in Europe and around the globe. We are ready to launch TEGSEDI along with our patient and physician support services across Europe."

The abnormal formation and aggregation of transthyretin (TTR) protein results in TTR amyloid deposits throughout the body and is the underlying cause of hATTR amyloidosis. TEGSEDI is designed to block production of the TTR protein. In the NEURO-TTR study, treatment with TEGSEDI produced substantial reductions in the levels of the TTR protein regardless of mutation type or stage of disease.

"hATTR amyloidosis is an inherited, progressive and fatal disease for which treatment options are limited. The approval of TEGSEDI brings us into a new era of treatment with an efficacious and disease modifying medicine that potentially allows patients to achieve a greater degree of independence," said Teresa Coelho, M.D., neurologist and neurophysiologist at Santo António Hospital, Porto, Portugal. "TEGSEDI has demonstrated rapid and sustained benefits in improving the course of this disease and preserving quality of life."

The European Commission's approval of TEGSEDI was based on results from the Phase 3 NEURO-TTR study in patients with hATTR amyloidosis with symptoms of polyneuropathy. Results from that study demonstrated that patients treated with TEGSEDI experienced significant benefit compared to patients treated with placebo across both co-primary endpoints: the Norfolk Quality of Life Questionnaire-Diabetic Neuropathy (Norfolk QoL-DN) and modified Neuropathy Impairment Score +7 (mNIS+7), a measure of neuropathic disease progression.

TEGSEDI is associated with risk of thrombocytopenia and glomerulonephritis. Enhanced monitoring is required to support early detection and management of these identified risks.

"Today, we are thrilled to see our successful research and development efforts result in the approval of an important new medicine for patients with hATTR amyloidosis. Using our antisense technology platform, we set out to design a therapy to block the production of the underlying cause of this disease, the TTR protein," said Brett P. Monia, Ph.D., chief operating officer at Ionis Pharmaceuticals. "Approval of TEGSEDI further establishes Ionis as a multi-product company. We are confident that the experienced team at Akcea will deliver on the promise of TEGSEDI. We are grateful to all of the physicians and patients who participated in the TEGSEDI clinical program and who made this landmark approval possible."

For important safety information for TEGSEDI, including method of administration, special warnings, drug interactions and adverse drug reactions, please see the European Summary of Product Characteristics (SmPC), available from the EMA website at [www.ema.europa.eu](http://www.ema.europa.eu).

TEGSEDI is also under regulatory review in the United States and Canada. TEGSEDI's U.S. Prescription Drug User Fee Act, or PDUFA, date is October 6, 2018.

In April, Akcea licensed the worldwide rights to commercialize TEGSEDI from Ionis. Based on the EC authorization of TEGSEDI, Ionis will receive a \$40 million milestone payment from Akcea payable in shares of Akcea common stock. Commercial profits and losses from TEGSEDI will be split 60% to Ionis and 40% to Akcea.

### ABOUT TEGSEDI™ (INOTERSEN)

TEGSEDI™ (inotersen) is an antisense oligonucleotide (ASO) inhibitor of human transthyretin (TTR) production. TEGSEDI is approved in the E.U. for the treatment of stage 1 or stage 2 polyneuropathy in adult patients with hereditary transthyretin amyloidosis (hATTR) and is currently under regulatory review in the U.S. and Canada.

The approval is based on data from the NEURO-TTR study which was a Phase 3 randomized (2:1), double-blind, placebo-controlled, international study in 172 patients with hATTR amyloidosis with symptoms of polyneuropathy. The 15-month study measured the effects of TEGSEDI on neurological function 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. TEGSEDI provided significant benefit on both of these co-primary endpoints in the NEURO-TTR study, including improvement in disease relative to baseline measurements in both co-primary endpoints for a substantial portion of patients.

TEGSEDI is associated with risk of thrombocytopenia and glomerulonephritis. Enhanced monitoring is required to support early detection and management of these identified risks. The most frequently observed adverse reactions during treatment with TEGSEDI were events associated with injection site reactions. The other most commonly reported adverse reactions (over 10%) seen with TEGSEDI were nausea, anaemia, headache, pyrexia, peripheral oedema, chills, vomiting, thrombocytopenia and platelet count decreased.

The approval is also based on data from the NEURO-TTR Open Label Extension (OLE) which is an ongoing study for patients who completed the NEURO-TTR study, designed to evaluate the long-term efficacy and safety of TEGSEDI.

The TEGSEDI expanded access program (EAP) ([NCT03400098](https://clinicaltrials.gov/ct2/show/study/NCT03400098)) has been initiated in the U.S. and is currently enrolling eligible patients. [Click here](#) for more information on the TEGSEDI EAP. For more information on TEGSEDI, please visit [www.TEGSEDI.eu](http://www.TEGSEDI.eu).

#### **ABOUT HEREDITARY TRANSTHYRETIN (hATTR) AMYLOIDOSIS**

hATTR amyloidosis is a progressive, systemic and fatal inherited 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, 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. Patients with hATTR amyloidosis often present with a mixed phenotype and experience overlapping symptoms of polyneuropathy and cardiomyopathy.

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](http://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)-LR<sub>x</sub>, AKCEA-ANGPTL3-LR<sub>x</sub>, AKCEA-APOCIII-LR<sub>x</sub>, and AKCEA-TTR-LR<sub>x</sub>, 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 approved in the E.U. for the treatment of stage 1 or stage 2 polyneuropathy in adult patients with hereditary transthyretin amyloidosis (hATTR) and is currently under regulatory review in the US and Canada. WAYLIVRA is under regulatory review in the U.S., E.U. 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](http://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 approved in the E.U. for the treatment of stage 1 or stage 2 polyneuropathy in adult patients with hereditary transthyretin amyloidosis, or hATTR, and is currently under regulatory review in the U.S. and Canada. WAYLIVRA is under regulatory review for marketing approval in the U.S., E.U., 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](http://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 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.

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.

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