New England Journal of Medicine Publishes Results from Phase 2 Study of AKCEA-APO(a)-LRx in Patients with Lp(a)-driven Cardiovascular Disease

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Patients treated with AKCEA-APO(a)-L_{Rx} received pre-specified endpoints for Lp(a) levels with favorable safety and tolerability profile

Global Lp(a)HORIZON Phase 3 cardiovascular outcomes study underway

BOSTON and CARLSBAD, Calif., Jan. 02, 2020 (GLOBE NEWSWIRE) -- Akcea Therapeutics, Inc. (NASDAQ: AKCA), a majority-owned affiliate of Ionis Pharmaceuticals, Inc., and Ionis Pharmaceuticals, Inc. (NASDAQ: IONS), announced that results from a Phase 2 study evaluating AKCEA-APO(a)-L_{Rx}, also known as TQJ230, in patients with established cardiovascular disease (CVD) and elevated levels of lipoprotein(a), or Lp(a), were published today in *The New England Journal of Medicine* (*NEJM*). The article is titled "*Lipoprotein(a) Reduction in Persons with Cardiovascular Disease."* For the full text of this publication, please visit: www.NEJM.org.

Elevated Lp(a) is an independent, genetic risk factor for CVD that cannot be well controlled with lifestyle modifications such as diet or exercise or with treatment using existing lipid-lowering therapies. It is estimated that there are more than eight million patients living with CVD and elevated levels of Lp(a) worldwide. AKCEA-APO(a)-L_{Rx} was discovered by Ionis and co-developed through Phase 2 by Akcea and Ionis. It is an antisense medicine developed using Ionis' advanced LICA technology designed to inhibit the production of apolipoprotein(a) and thus reduce Lp(a) levels.

"The Phase 2 study data show that we can get 98% of patients below 125 nmol/L (<50 mg/dL), the established threshold for a Lp(a)-driven CVD in people already on statin medications. The millions of people living with CVD and elevated Lp(a) are at risk of recurrent events such as myocardial infarction, stroke and peripheral arterial disease and currently have no effective pharmacological options that specifically target Lp(a)," said Dr. Sotirios Tsimikas, vice president of global cardiovascular development at Ionis Pharmaceuticals, professor of medicine and director of vascular medicine at the University of California San Diego and a principal author of the NEJM paper. "We, along with the community of patients and physicians managing Lp(a), look forward to the Phase 3 clinical program that is now underway."

Following treatment, patients experienced significant dose-dependent reductions in Lp(a) at all dose levels studied with up to an 80% reduction in Lp(a) at the highest cumulative dose regimen (equivalent to 80 mg monthly). Approximately 98% of patients at the 80 mg monthly dose regimen achieved Lp(a) levels below 125 nmol/L (~50 mg/dL). Significant dose-dependent reductions in LDL-C, apoB, OxPL-apoB and OxPL-apo(a) from baseline were also observed. The majority of adverse events were mild or moderate, with the most frequent adverse events being injection site reactions (ISRs). ISRs occurred in 27% and 6% of patients on treatment and those on placebo, respectively, and were mostly mild. One patient discontinued treatment due to an ISR. There were no differences in platelet counts, liver and renal parameters, or flu-like symptoms in patients administered AKCEA-APO(a)-L_{Rx}.

The randomized, double-blind, placebo-controlled, dose-ranging study of 286 patients across five countries with established CVD and elevated Lp(a) is the largest ever conducted specifically for people with elevated Lp(a). It is also the largest and longest study to date evaluating the Ionis LICA technology platform, with patients treated for up to 1 year and all patients treated for a minimum of six months. The goal was to assess the safety and tolerability of AKCEA-APO(a)-L_{Rx} and inform the dose and dose frequency for the planned Phase 3 cardiovascular outcomes study, being led by Novartis. Patients were administered AKCEA-APO(a)-L_{Rx} (20, 40 or 60 mg every 4 weeks, 20 mg every 2 weeks, or 20 mg every week) or placebo subcutaneously for six to 12 months.

"The publication of AKCEA-APO(a)-L_{Rx} data in *The New England Journal of Medicine* highlights the significance of this investigational compound and its potential to address a major area of unmet need in global health," said Dr. Louis O'Dea , chief medical officer of Akcea Therapeutics. "We are very proud of our role in the development of AKCEA-APO(a)-L_{Rx} to date and will continue to support Novartis in our goal of making this treatment option available to patients around the world in the years ahead."

For information on the Lp(a)HORIZON Phase 3 cardiovascular outcomes study being run by Novartis, please visit www.clinicaltrials.gov.

ABOUT AKCEA-APO(a)-L_{Rx} AND THE PHASE 2 STUDY

AKCEA-APO(a)-L_{Rx} is an antisense drug that uses Ionis' advanced **LI**gand **C**onjugated **A**ntisense, or LICA, technology. AKCEA-APO(a)-L_{Rx} inhibits the production of apolipoprotein(a), or apo(a), protein, thereby reducing Lp(a).

The Phase 2 study was designed to evaluate the safety and tolerability of AKCEA-APO(a)-L_{Rx} and to determine the appropriate dose and dose regimen for the currently ongoing Phase 3 cardiovascular outcomes study being led by Novartis. The randomized, double-blind, placebo-controlled, dose-ranging Phase 2 study included 286 patients with established cardiovascular disease (CVD) and high Lp(a) levels (baseline mean of 90 mg/dL [225 nmol/L]- more than three times the upper limit of normal).

Results from the study showed statistically significant dose-dependent reductions of Lp(a) compared to placebo at all dose levels, including low monthly doses of AKCEA-APO(a)-L_{Rx}. In the Phase 2 study, 98% of patients in the 20 mg weekly cohort and 81% of patients in the 60 mg every 4 weeks cohort achieved clinically significant reductions in Lp(a) levels bringing them below the recommended threshold of risk for CVD events (<50 mg/dL). Treatment with AKCEA-APO(a)-L_{Rx} was associated with decreases in LDL-C, apoB, OxPL-apoB, OxPL-apo(a). Most adverse events were mild. The most frequent adverse events were injection site reactions (ISRs). ISRs occurred in 27% of patients and were mostly mild with one patient discontinuing due to an ISR. There were no safety concerns related to platelet counts, liver function or renal function. Approximately 90% of patients completed treatment and the rate of discontinuation was comparable between the active and placebo groups. All patients were treated for at least six months, with some patients treated up to one year.

ABOUT Lp(a)

Lipoprotein(a), or Lp(a), is made up of apo(a) protein bound to LDL cholesterol and contains oxidized phospholipids, resulting in an atherogenic, pro-inflammatory and thrombogenic lipoprotein. Elevated Lp(a) is recognized as an independent, genetic cause of cardiovascular disease present in approximately 20-30% of the population. Lp(a) levels are determined at birth and, therefore, lifestyle modifications, including diet and exercise, do not impact Lp(a) levels.

For additional information about Lp(a), please see the Lipoprotein(a) Foundation at http://www.lipoproteinafoundation.org/.

ABOUT AKCEA THERAPEUTICS, INC.

Akcea Therapeutics, Inc., a majority-owned 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 commercializing TEGSEDI® (inotersen) and WAYLIVRA® (volanesorsen), as well as advancing a mature pipeline of novel drugs, including AKCEA-APO(a)-L_{Rx}, 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. and Canada. 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 building the infrastructure to commercialize its drugs globally. Akcea is a global company headquartered in Boston, Massachusetts. Additional information about Akcea is available at www.akceatx.com and you can follow us on Twitter at @akceatx.

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 treat a broad range of diseases including cardiovascular diseases, neurological diseases, infectious diseases, pulmonary diseases and cancer.

To learn more about Ionis follow us on twitter @ionispharma or visit 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 AKCEA-APO(a)-L_{Rx}. Any statement describing Akcea's or Ionis' goals, expectations, financial or other projections, intentions or beliefs, including the commercial potential of AKCEA-APO(a)-L_{Rx} 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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