Akcea and Ionis Report Positive Data from Phase 2 Study of AKCEA-APO(a)-LRx

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Study demonstrates significant Lp(a) reduction, favorable safety and tolerability profile

Largest and longest study of Ionis' LICA technology

Data to be presented as a late-breaking clinical trial presentation at AHA on November 10 in Chicago

CAMBRIDGE, Mass. and CARLSBAD, Calif., Sept. 24, 2018 (GLOBE NEWSWIRE) -- Akcea Therapeutics, Inc. (NASDAQ: AKCA), an affiliate of Ionis Pharmaceuticals, Inc., and Ionis Pharmaceuticals, Inc. (NASDAQ: IONS), today announced positive topline results from a Phase 2 clinical study of AKCEA-APO(a)-L_{Rx} in patients with established cardiovascular disease (CVD) and elevated levels of lipoprotein(a), or Lp(a). Additional data from the Phase 2 study will be presented as a late-breaking clinical trial presentation at the American Heart Association Scientific Sessions in Chicago November 10-12, 2018.

The goal of the Phase 2 study was to characterize the safety and tolerability of AKCEA-APO(a)-L_{Rx} and to inform dose and dose frequency selection for the planned Phase 3 cardiovascular outcomes study. The randomized, double-blind, placebo-controlled, dose-ranging study included 286 patients with established CVD and high Lp(a) (baseline mean of approximately 100 mg/dL [250 nmol/L] – more than three times the upper limit of normal). All patients were treated for at least six months, with some patients treated up to one year. Results from the study show:

- 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}.
- Most patients in the active group achieved Lp(a) reductions below the established threshold of risk for CVD events.
- Treatment emergent adverse events were balanced between the active and placebo groups.
- Most common adverse event was injection site reactions (ISRs). ISRs were mostly mild and occurred in a minority of patients.
- No patient in the study experienced a confirmed platelet level below 100,000/mm^3. The incidence of platelet levels below normal (140,000/mm^3) was comparable between the active (10.5%) and placebo (14.9%) groups.
- Approximately 90% of patients completed treatment and the rate of treatment discontinuation was comparable between the active and placebo groups.

"These data represent an important step forward for patients who have significant risk of premature death from cardiovascular disease due to their high levels of Lp(a). In this large Phase 2 study AKCEA-APO(a)-L_{Rx}, robustly lowered Lp(a) with a favorable safety and tolerability profile. In addition, the data from this study support the potential to treat patients with convenient, low volume monthly doses," said Paula Soteropoulos, chief executive officer of Akcea Therapeutics. "These results are also encouraging as we continue to develop our LICA pipeline."

Elevated Lp(a) is an independent, hereditary risk factor for CVD that cannot be well-controlled with lifestyle modifications, such as diet or exercise, or with treatment using existing cholesterol-lowering therapies. It is estimated that there are 8 to 10 million people living with established cardiovascular disease driven by elevated levels of Lp(a). The Phase 2 clinical study of AKCEA-APO(a)-L_{Rx} is the largest study conducted specifically for patients with elevated Lp(a).

"After my personal experience at age 39 with severe Lp(a)-induced heart disease and nearly having a heart attack myself, I have met many others living with this silent killer that is under-recognized in the wider population," said Sandra Revill Tremulis, founder of the Lipoprotein(a) Foundation. "Even after diagnosis, with no treatment the increased risk of heart disease and heart attack remains a serious burden. This is an important advancement in the identification of a potential novel medicine for patients with Lp(a)-driven cardiovascular disease."

"Those of us who are on the front lines treating patients with elevated Lp(a) who have aggressive, premature heart disease recognize the significant need for a treatment like AKCEA-APO(a)-L_{Rx}. Recent data have shown that patients are particularly at risk when their Lp(a) levels go over 50 mg/dL. The data from this study are very encouraging as they show that AKCEA-APO(a)-L_{Rx} consistently reduced Lp(a) levels below this risk threshold," said Dr. Sotirios Tsimikas, vice president of global cardiovascular development at Ionis Pharmaceuticals and professor of medicine and director of vascular medicine at the University of California, San Diego. "There are currently no treatment options available to patients that specifically target Lp(a). The introduction of a safe and effective therapeutic would represent a major advance in patient care."

Ionis discovered AKCEA-APO(a)-L_{Rx} using its proprietary ligand-conjugated antisense (LICA) technology and has co-developed the drug with Akcea. AKCEA-APO(a)-L_{Rx} is part of an exclusive, worldwide option and collaboration agreement between Akcea and Novartis. Ionis' LICA technology has the potential to produce new drugs that are highly potent and can be used at lower doses and with less frequent administration than non-LICA antisense drugs. Results from separate Phase 1 studies of eight LICA drugs in development, including three at Akcea, have shown that doses up to 30-fold lower than non-LICA drugs can result in consistent target reductions with a favorable safety and tolerability profile.

“With 13 LICA programs now in development, this study represents the largest and longest study to date to evaluate the Ionis LICA platform. The favorable safety and tolerability profile, coupled with the potent reductions in Lp(a) levels demonstrated in this study, bolster our confidence in the LICA platform and further validate the significant potential that LICA represents for both rare and common diseases with great unmet medical needs,” said Brett Monia, Ph.D., chief operating officer at Ionis.

Development of AKCEA-APO(a)-L_{Rx} is part of a strategic collaboration between Akcea and Novartis. If Novartis exercises its option to license AKCEA-APO(a)-L_{Rx} after the successful completion of an end of Phase 2 meeting with the FDA, Akcea will receive a $150 million milestone payment of which 50% will be paid to Ionis. After exercise of its option, Novartis will be responsible for all future development activities including a currently planned global Phase 3 cardiovascular outcome study and, if approved, global commercialization activities. Akcea retains the right to co-commercialize any successful drug through its specialty sales force focused on lipid specialists on terms, conditions and in selected markets to be agreed upon with Novartis.

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 randomized, double-blind, placebo-controlled, dose-ranging study evaluated the safety and efficacy of different doses of AKCEA-APO(a)-L_{Rx} in 286 patients with elevated levels of Lp(a) and established cardiovascular disease. The study had a five to one randomization testing different doses and dose frequencies of AKCEA-APO(a)-L_{Rx}. Weekly, every other week and monthly doses were tested ranging from 20mg to 60mg. Patients were dosed for at least six months with some patients dosed up to one year. The primary efficacy endpoint was the percent change in Lp(a) from baseline at the primary analysis time point (6 months) compared to placebo.

ABOUTLp(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., 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 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. WAYLIVRA is under regulatory review 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 Boston, 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 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 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 AND IONIS FORWARD-LOOKINGSTATEMENT

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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