AKCEA-APO(a)-LRx advances as leading pharmaceutical company exercises option to license

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Phase 3 planning and initiation activities underway

Akcea earns $150M license fee

BOSTON and CARLSBAD, Calif., Feb. 25, 2019 (GLOBE NEWSWIRE) -- Akcea Therapeutics, Inc. (NASDAQ: AKCA), an affiliate of Ionis Pharmaceuticals, Inc., and Ionis Pharmaceuticals, Inc. (NASDAQ: IONS), today announced that Novartis has exercised its option to license AKCEA-APO(a)-L_{Rx}, a drug to treat patients with elevated levels of lipoprotein(a), or Lp(a), and established cardiovascular disease (CVD). AKCEA-APO(a)-L_{Rx}, referred to by Novartis as TQJ230, was discovered by Ionis and co-developed by Akcea and Ionis.

Elevated Lp(a) is an independent genetic risk factor for CVD that cannot be managed by lifestyle modifications, including diet or exercise, or with treatment using existing cholesterol-lowering therapies[1,2]. It is estimated that there are more than eight million patients living with CVD and elevated levels of Lp(a).

“We are very pleased that Novartis, an established global leader in drug development and commercialization, will now shepherd this landmark therapy through late-stage clinical development and toward the market,” said Paula Soteropoulos, chief executive officer at Akcea. “The Phase 2 study results presented last year at AHA showed that AKCEA-APO(a)-L_{Rx} significantly reduced Lp(a) levels below the recognized threshold for cardiovascular risk in patients living with cardiovascular disease and elevated Lp(a) levels with a favorable safety and tolerability profile. AKCEA-APO(a)-L_{Rx} is the first and only medicine to do this. We believe that this therapy has the potential to be a significant advance for millions of people affected by cardiovascular disease around the world.”

Novartis will assume responsibility for all future development activities for AKCEA-APO(a)-L_{Rx}, including a planned global Phase 3 cardiovascular outcomes study and, pending regulatory approval, global commercialization activities.

AKCEA-APO(a)-L_{Rx} is an antisense drug developed based on Ionis’ proprietary **LI**gand **C**onjugated **A**ntisense, or LICA, technology platform. Ionis’ proprietary LICA technology platform has the potential to produce new drugs that can be used at lower doses and with less frequent administration compared to non-LICA antisense drugs. AKCEA-APO(a)-L_{Rx} is designed to inhibit production of apolipoprotein(a), or Apo(a) protein, thereby reducing systemic levels of Lp(a).

“The Ionis LICA platform is a game-changing breakthrough for our antisense technology. AKCEA-APO(a)-L_{Rx}, our most advanced LICA medicine, is a particularly exciting and important new medicine because of its potential to treat millions of patients with cardiovascular disease. This treatment represents one of many important new medicines within our LICA pipeline and illustrates our continued commitment to innovation and in bringing transformative medicines to patients in great need,” said Brett Monia, chief operating officer at Ionis.

Based on the strategic collaboration agreement between Akcea and Novartis, Akcea will receive a $150 million license fee that will be split equally with Ionis. Akcea will settle its $75 million obligation to Ionis in Akcea common stock.

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 a planned Phase 3 cardiovascular outcomes study. The randomized, double-blind, placebo-controlled, dose-ranging Phase 2 study included 286 patients with established CVD and high Lp(a) levels (baseline mean of 100mg/dL [250 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 20mg weekly cohort and 81% of patients in the 60mg every 4 week 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 26% of patients and were mostly mild and one patient discontinued 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., 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 U.S., E.U. 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 and you can follow us on twitter at @akceatx.

About Ionis Pharmaceuticals
As the leader in RNA-targeted drug discovery and development, Ionis has created an efficient, broadly applicable, proprietary antisense technology platform with the potential to 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 – such as children and adults with spinal muscular atrophy (SMA). We created SPINRAZA® (nusinersen)* and are proud to have brought new hope to the SMA community by developing the first and only approved treatment for this disease.
Our sights are set on all the patients we have yet to reach with a pipeline of more than 40 drugs with the potential to treat patients with cardiovascular disease, rare diseases, neurological diseases, infectious diseases and cancer. We created TEGSEDI™ (inotersen), the world's first RNA-targeted therapeutic approved for the treatment of polyneuropathy in adult patients with hereditary transthyretin (TTR) amyloidosis (ATTR) that our affiliate Akcea Therapeutics is commercializing. Together with Akcea, we are also bringing new medicines to patients with cardiometabolic lipid disorders.

To learn more about Ionis follow us on twitter @ionispharma or visit http://ir.ionispharma.com/.
*Spinraza is marketed by Biogen.

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 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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2. Kronenberg , Utermann G; J Intern Med. 2013 Jan;273(1):6-30. doi: 10.1111/j.1365-2796.2012.02592.x. Epub 2012 Nov 12.

Source: Akcea Therapeutics, Inc.

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