Phase 2 Results on AKCEA-APO(a)-LRx Presented in Late-Breaking Clinical Trial Presentation at AHA Scientific Sessions

November 12, 2018

Approximately 98% of patients receiving highest dose achieved reductions in Lp(a) levels below the established threshold of risk for CVD events

Favorable safety and tolerability profile observed in largest study ever conducted in patients with cardiovascular disease and elevated Lp(a)

BOSTON and CARLSBAD, Calif., Nov. 12, 2018 (GLOBE NEWSWIRE) -- Akcea Therapeutics, Inc. (NASDAQ: AKCA), an affiliate of Ionis Pharmaceuticals, Inc., and Ionis Pharmaceuticals, Inc. (NASDAQ: IONS), today announced that data from the 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), were presented in a late-breaking clinical trial presentation at the American Heart Association Scientific Sessions in Chicago November 10, 2018.

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 treatable patients living with cardiovascular disease and elevated levels of Lp(a).

"Lp(a) is a hereditary cardiovascular disease risk factor that impacts millions of families and cannot be addressed by diet and exercise. A drug that reduces Lp(a) could be a paradigm shift for the cardiovascular community. Physicians are looking for a tool to treat their patients who today have no pharmacological option to sustainably reduce their Lp(a) levels below 50mg/dL, the threshold for a Lp(a)-driven cardiac event such as a heart attack or stroke," 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 and an international expert on Lp(a). "The data from this study represent an important step forward. These results demonstrate that AKCEA-APO(a)-L_{Rx} can greatly lower Lp(a) levels with a favorable safety and tolerability profile. These results warrant advancement of this program to Phase 3 and I look forward to participating in its future development."

Patients were treated with AKCEA-APO(a)-L_{Rx} or placebo for at least six months, with some patients treated up to one year. The study met all primary and secondary efficacy endpoints analyzed at 6 months. Results from the study show statistically significant and dose dependent reductions from baseline in Lp(a) levels:

Lp(a)	**Pooled placebo (n=47)**	**20 mg every 4 weeks (n=48)**	**40 mg every 4 weeks (n=48)**	**20 mg every 2 weeks (n=48)**	**60 mg every 4 weeks (n=47)**	**20 mg weekly (n=48)**
LSMean % change in Lp(a)	-6	-35 P=0.0032	-56 P<0.0001	-58 P<0.0001	-72 P<0.0001	-80 P<0.0001

*LSMean: Least squares mean

- Approximately 98% of patients in the 20mg weekly cohort and approximately 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.
- No patient in the study experienced a confirmed platelet count below 100,000/mm3. 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 discontinuation was comparable between the active (12.1%) and placebo (14.9%) groups.

"These data show that AKCEA-APO(a)-L_{Rx} significantly reduces Lp(a) in patients with pre-existing cardiovascular disease due to elevated Lp(a) levels. AKCEA-APO(a)-L_{Rx} is the first and only drug to show a clinically significant reduction of Lp(a) levels and a favorable safety and tolerability

profile in patients with this genetic condition," said Dr. Louis O'Dea, chief medical officer at Akcea Therapeutics. "This is a particularly important advancement as elevated Lp(a) can cause cardiac events for patients as early as in their 30s and 40s. We are actively working with Novartis to prepare for an end of Phase 2 meeting with FDA. We look forward to advancing this important development program into Phase 3."

AKCEA-APO(a)-L_{Rx} is an antisense drug developed using Ionis' proprietary LICA technology, which has potential to produce new drugs that 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.

"The AKCEA-APO(a)-L_{Rx} Phase 2 study is the largest and longest study to evaluate the Ionis LICA technology platform to date. We are encouraged by the robust reductions in Lp(a) levels and the favorable safety and tolerability profile," said Brett Monia, Ph.D., chief operating officer at Ionis. "Because Lp(a) cannot be easily targeted with small molecules or antibodies, inhibition of apolipoprotein(a) is a great example of how antisense technology can have an impact where no other therapeutic approaches have proven effective. We look forward to further assessing our LICA platform with the 13 programs now in development."

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 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 for AKCEA-APO(a)-L_{Rx} including a planned global Phase 3 cardiovascular outcomes study and, pending regulatory approval, global commercialization activities. As part of the collaboration, Akcea has the rights to co-commercialize AKCEA-APO(a)-L_{Rx} in selected markets, on mutually agreed terms and conditions.

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 dosing 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 approximately 100mg/dL [250 nmol/L]- more than three times the upper limit of normal). The trial had five cohorts: 20 mg (every 4 weeks), 40 mg (every 4 weeks), 60 (every 4 weeks), 20 mg (every 2 weeks), and 20 mg (every week). The primary efficacy endpoint was the percent change in Lp(a) from baseline at the primary analysis time point (6 months) compared to placebo. The secondary efficacy endpoints were mean percent change in LDL-C, apoB, OxPL-apoB, OxPL-apo(a), and the number of patients reaching pre-specific thresholds of <125 nmol/L (<50 mg/dL) or <75 nmol/L (<30 mg/dL). All patients were treated for at least six months, with some patients treated up to one year.

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 AkceaTherapeutics, 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.

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-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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