Akcea Announces Publication in The Lancet of Clinical Results with Lp(a)-Lowering Drugs Designed to Treat Cardiovascular Disease

September 22, 2016

CAMBRIDGE, Mass., Sept. 22, 2016 /PRNewswire/ -- Akcea Therapeutics, a wholly-owned subsidiary of Ionis Pharmaceuticals, Inc. (NASDAQ: IONS), today announced the publication in *The Lancet* of key clinical results of two randomized, controlled studies of IONIS-APO(a)$_{Rx}$ and IONIS-APO(a)-L$_{Rx}$, the company's Lp(a)-lowering drugs designed to treat cardiovascular disease and aortic valve stenosis. Lipoprotein(a), or Lp(a), is an independent, causal, genetic risk factor for cardiovascular disease and aortic valve narrowing (stenosis). In these studies, substantial Lp(a) reductions of up to 99% were noted, regardless of starting Lp(a) levels. In addition, reductions in low-density lipoprotein-cholesterol - (LDL-C) and pro-inflammatory oxidized phospholipids were observed, as well as a decrease in the inflammatory effects of white blood cells, which can initiate and accelerate cardiovascular disease.

"Patients with Lp(a)-driven cardiovascular disease have no viable therapeutic options today for significantly lowering their Lp(a) to a level where risk can be minimal. And, since a patient's Lp(a) level is genetically determined, changes in lifestyle, such as diet and exercise, have minimal, if any, impact," said Sotirios Tsimikas, M.D., senior author of the paper, vice president of clinical development at Ionis Pharmaceuticals and professor of medicine and director of vascular medicine at the University of California, San Diego. "The results from these studies show, for the first time, a new therapy that can substantially reduce Lp(a), regardless of a patient's starting Lp(a) level."

The paper titled "Antisense oligonucleotides targeting apolipoprotein(a) in people with raised lipoprotein(a): two randomised, double-blind, placebo-controlled, dose-ranging trials" (Viney et al., *The Lancet*) documents the results of two clinical studies testing the safety, tolerability and efficacy of antisense drugs designed to lower elevated Lp(a) levels. The published clinical findings are a result of a partnership with the Sulpizio Cardiovascular Center at the University of California San Diego School of Medicine.

The IONIS-APO(a)$_{Rx}$ study is the first randomized clinical study to evaluate a specific Lp(a)-lowering therapy in patients with or at high risk for cardiovascular disease with elevated Lp(a) levels. Treatment with IONIS-APO(a)$_{Rx}$ in patients with high (50-175 mg/dL or 125-437 nmol/L) or very high (>175 mg/dL or >437 nmol/L) Lp(a) levels resulted in a mean reduction in Lp(a) of 67-72%, with up to a 94% reduction. In addition, a significant reduction was noted in pro-inflammatory oxidized phospholipids and the inflammatory effects of monocytes, as well LDL-C.

The IONIS-APO(a)-L$_{Rx}$ trial studied an optimized and more potent LICA drug that contains a GalNAc moiety that enhances delivery of drug to hepatocytes where Lp(a) is made and assembled. In this first-in-man study, multiple doses of IONIS-APO(a)-L$_{Rx}$ resulted in mean reductions in Lp(a) of 66% in the 10 mg group, 80% in the 20 mg group, and 92% in the 40 mg group, and up to a 99% reduction. In these short-term studies, the drug was well tolerated. No side effects were noted in any laboratory tests and there were no injection site reactions.

"IONIS-APO(a)-L$_{Rx}$ has shown more than 30-fold greater potency compared to IONIS-APO(a)$_{Rx}$. This means that with much lower doses of IONIS-APO(a)-L$_{Rx}$ we can achieve similar or better efficacy than IONIS-APO(a)$_{Rx}$ and monthly or even less frequent dosing may be feasible," said Richard Geary, Ph.D., senior vice president of development at Ionis Pharmaceuticals. "IONIS-APO(a)-L$_{Rx}$ has the potential to eliminate nearly all Lp(a)-mediated risk by normalizing Lp(a) levels in almost all patients and reducing oxidized phospholipid levels and monocyte inflammation. It has also demonstrated that it can reduce LDL-cholesterol on top of current therapies. Furthermore, Ionis' LICA technology shows unprecedented potency and tolerability

and represents the transformative potential for antisense drugs, both in cardiovascular and in non-cardiovascular arenas."

ABOUT Lp(a)
Lipoprotein (a), or Lp(a), is an independent, causal, genetic risk factor for cardiovascular disease, including myocardial infarction, stroke, peripheral arterial disease and calcific aortic valve stenosis. Lp(a) is a lipoprotein particle that is synthesized and assembled in the liver and consists of one apolipoprotein(a) protein covalently linked to one LDL particle. Elevated Lp(a) levels in blood are primarily due to genetic variations in the LPA gene that encodes for apolipoprotein(a) and cannot be lowered by diet, exercise or other lipid-lowering therapies, such as statins. In fact, statins may raise Lp(a) levels. Normal Lp(a) levels in the United States are considered to be <30 mg/dL (<~75 nmol/L). The European Atherosclerosis Society suggests an optimal Lp(a) level is <50 mg/dL (<125 nmol/L) levels. Elevated Lp(a) is highly prevalent, with ~20% of the population having levels >50 mg/dL and ~30% of the population having levels >30 mg/dL. Lp(a) levels are not included in routine lipid profile tests and frequently the risk of elevated Lp(a) goes undetected until a cardiovascular event occurs. Additional information is available through Lipoprotein(a) Foundation at www.lipoproteinafoundation.org.

ABOUT IONIS-APO(a)-L_{Rx}
IONIS-APO(a)-L_{Rx} is a LIgand Conjugated Antisense (LICA) drug designed to reduce apolipoprotein(a) in the liver to offer a direct approach for reducing plasma levels of lipoprotein(a), or Lp(a). IONIS-APO(a)-L_{Rx} is in development to treat patients with high Lp(a) levels. Akcea has the first and only clinical program to selectively and robustly reduce Lp(a) in patients by inhibiting apo(a) and plans to develop IONIS-APO(a)-L_{Rx} with a robust program that addresses near, mid and long-term commercial opportunities by focusing initially on patients who have the greatest need and, in the long-term, on patients with more generalized Lp(a)-driven cardiovascular risk.

ABOUT AKCEA THERAPEUTICS
Akcea Therapeutics is focused on developing and commercializing drugs for patients with serious cardiometabolic diseases caused by lipid disorders. Established as a wholly owned subsidiary of Ionis Pharmaceuticals, Inc., Akcea has a robust portfolio of development-stage drugs covering multiple targets and disease states. The drugs in Akcea's pipeline are designed using Ionis' advanced RNA-targeted antisense technology to address a number of lipid risk factors, including ApoC-III, triglycerides and Lp(a). Akcea's most advanced program, volanesorsen, is in Phase 3 development to treat patients with either familial chylomicronemia syndrome (FCS) or familial partial lipodystrophy (FPL), two orphan lipid disorders that are characterized by extremely high triglycerides and ApoC-III. Akcea is located in Cambridge, 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 a dozen drugs in mid- to late-stage development. Drugs currently in Phase 3 development include volanesorsen, a drug Ionis is developing and plans to commercialize through its wholly owned subsidiary, Akcea Therapeutics, to treat patients with either familial chylomicronemia syndrome or familial partial lipodystrophy; IONIS-TTR_{Rx}, a drug Ionis is developing with GSK to treat patients with all forms of TTR amyloidosis; and nusinersen, a drug Ionis is developing with Biogen to treat infants and children with spinal muscular atrophy. Ionis' patents provide strong and extensive protection for its drugs and technology. Additional information about Ionis is available at www.ionispharma.com.

FORWARD-LOOKING STATEMENT
This press release includes forward-looking statements regarding the business of Akcea Therapeutics, Inc., a wholly owned subsidiary of Ionis Pharmaceuticals and the therapeutic and commercial potential of Akcea's technologies and products in development, including volanesorsen, and other products in development. Any statement describing Akcea's goals, expectations, financial or other projections, intentions or beliefs 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 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 forward-looking statements reflect the good faith judgment of its management, these statements are based only on facts and factors currently known by Akcea. As a result, you are cautioned not to rely on these forward-looking statements. These and other risks concerning Akcea's programs are described in additional detail in Akcea's parent company, Ionis Pharmaceuticals, Inc.'s annual report on Form 10-K for the year ended December 31, 2015, and its most recent quarterly report on Form 10-Q, which are on file with the SEC. Copies of these and other documents are available at www.ionispharma.com.

In this press release, unless the context requires otherwise, "Akcea," "Company," "we," "our," and "us" refers to Akcea Therapeutics.

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To view the original version on PR Newswire, visit:http://www.prnewswire.com/news-releases/akcea-announces-publication-in-the-lancet-of-clinical-results-with-lpa-lowering-drugs-designed-to-treat-cardiovascular-disease-300332387.html

SOURCE Ionis Pharmaceuticals, Inc.

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