Ionis Pharmaceuticals Reports Positive Clinical Data from IONIS-ANGPTL3-L Rx

November 15, 2016

Significant reductions in ANGPTL3, triglycerides and LDL cholesterol observed
Interim data presented during the Late Breaker Session at the American Heart Association Meeting

CAMBRIDGE, Mass., Nov. 15, 2016 /PRNewswire/ -- Akcea Therapeutics, a wholly-owned subsidiary of Ionis Pharmaceuticals, Inc. (NASDAQ: IONS), today announced positive results from an interim analysis of a Phase 1/2a study of IONIS-ANGPTL3-L_{Rx}. In this study, subjects with elevated triglycerides achieved substantial and statistically significant mean reductions in angiopoietin-like 3 (ANGPTL3), triglycerides and LDL-cholesterol of up to 83 percent, 66 percent, and 35 percent, respectively. The study was presented today at the American Heart Association Scientific Sessions by Sotirios Tsimikas, M.D., professor of medicine and director of vascular medicine at the University of California, San Diego, and vice president of clinical development at Ionis Pharmaceuticals.

AKCEA™ THERAPEUTICS

A subsidiary of Ionis Pharmaceuticals, Inc.

"These data provide solid support for the therapeutic potential of ANGPTL3 to reduce multiple lipid risk factors in patients with cardiovascular disease and to affect liver fat accumulation in patients with NASH," said Dr. Tsimikas. "Pre-clinical studies in animal models of atherosclerosis and obesity demonstrate that lowering ANGPTL3 levels with antisense oligonucleotides significantly reduces progression of atherosclerosis and liver fat accumulation. The potential of ANGPTL3 reduction to improve cardiovascular risk is also supported by genetic studies in humans with both heterozygous and homozygous loss-of-function mutations in their ANGPTL3 gene showing that individuals with lower or absent plasma levels of ANGPTL3 protein exhibit low plasma levels of triglycerides and LDL cholesterol, which are both risk factors for cardiovascular disease."

Subjects who received multiple doses of 10 mg, 20 mg, 40 mg, or 60 mg of IONIS-ANGPTL3-L_{Rx} achieved dose-dependent, statistically significant mean reductions at Day 37 in ANGPTL3 of up to 83 percent ($p \leq 0.001$). These subjects also experienced statistically significant mean reductions in triglycerides of up to 66 percent ($p \leq 0.001$), in LDL-C of up to 35 percent ($p \leq 0.001$), and in total cholesterol of up to 36 percent ($p \leq 0.001$). In this study, IONIS-ANGPTL3-L_{Rx} displayed a favorable safety and tolerability profile. There were no discontinuations due to adverse events and no clinically meaningful platelet declines.

"These study results support the potential to develop IONIS-ANGPTL3-L_{Rx} to treat multiple diseases, such as severe dyslipidemias and NASH," said Paula Soteropoulos, president and chief executive officer of Akcea Therapeutics. "With its focus on cardio-metabolic disorders, Akcea is uniquely positioned to advance the therapeutic and commercial potential of IONIS-ANGPTL3-L_{Rx}."

IONIS-ANGPTL3-L_{Rx} is a Ligand Conjugated Antisense (LICA) drug designed to reduce the production of the ANGPTL3 protein, a key regulator of plasma lipids, such as triglycerides and LDL-cholesterol. Ionis' LICA technology is designed to enhance the potency of its drugs by increasing efficient drug uptake in target tissues, which provides the potential for improved therapeutic margin, improved tolerability and dosing schedule flexibility.

"In this study, IONIS-ANGPTL3-L_{Rx}, demonstrated, consistent with the data we have observed with our other LICA drugs, the ability to robustly lower its intended target at much lower doses than previously used to achieve similar target reduction with our non-LICA drugs," said Richard Geary, Ph.D., senior vice president of development at Ionis Pharmaceuticals. "These data further confirm that the profile conferred by our LICA technology demonstrate the potential of these advanced antisense drugs to address broader patient populations in cardiovascular and in non-cardiovascular indications because of the very low volume, infrequent and well-tolerated subcutaneous dosing these drugs can provide."

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, Lp(a) and LDL-cholesterol. 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 http://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 TTR amyloidosis; and SPINRAZA (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.

IONIS' FORWARD-LOOKING STATEMENT

This press release includes forward-looking statements regarding the development, activity, therapeutic and commercial potential and safety of IONIS-ANGPTL3-L_{Rx}. Any statement describing Ionis' 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. 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 Ionis' forward-looking statements reflect the good faith judgment of its management, these statements are based only on facts and factors currently known by Ionis. As a result, you are cautioned not to rely on these forward-looking statements. These and other risks concerning Ionis' programs are described in additional detail in Ionis' 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 from the Company.

In this press release, unless the context requires otherwise, "Ionis," "Company," "we," "our," and "us" refers to Ionis Pharmaceuticals and its subsidiaries.

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