

Akcea Announces Publication in The New England Journal of Medicine of Data with AKCEA-ANGPTL3-L_{Rx} Showing Favorable Cardiometabolic Effects

Cambridge, Mass., May 25, 2017 /PRNewswire/ -- Akcea Therapeutics, a wholly owned subsidiary of Ionis Pharmaceuticals, Inc. (NASDAQ: IONS), today announced the publication in *The New England Journal of Medicine* of key preclinical findings with angiopoietin-like 3 (ANGPTL3)-targeting drugs and Phase 1/2 clinical study results with AKCEA-ANGPTL3-L_{Rx} (formerly IONIS-ANGPTL3-L_{Rx}). In the Phase 1/2 clinical study, treatment with AKCEA-ANGPTL3-L_{Rx} resulted in substantial, dose-dependent reductions in multiple lipids and lipoproteins, including triglycerides, LDL cholesterol, apolipoprotein B, non-HDL cholesterol and apolipoprotein C-III. AKCEA-ANGPTL3-L_{Rx} was well tolerated with no serious adverse events. Ionis and Akcea are developing AKCEA-ANGPTL3-L_{Rx} to treat rare hyperlipidemias, non-alcoholic fatty liver disease (NAFLD) and combined dyslipidemias to potentially prevent and treat cardiovascular disease.

"ANGPTL3 is a key modulator of plasma lipoprotein levels, making it an attractive cardiometabolic therapeutic target. In the first clinical study evaluating AKCEA-ANGPTL3-L_{Rx}, patients achieved reductions in multiple atherogenic lipoproteins resulting in improvements across their overall lipid profile. Furthermore, in preclinical studies, we have shown that targeting ANGPTL3 translated to enhanced insulin sensitivity, reduced hepatic steatosis and reduced atherosclerosis progression in several experimental models," said Sotirios Tsimikas, M.D., senior author of the paper, 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. "Taken together, these results support targeting ANGPTL3 with AKCEA-ANGPTL3-L_{Rx} as an attractive therapeutic approach to treat patients with uncontrolled triglycerides, remnant cholesterol and LDL cholesterol, NAFLD and cardiovascular disease."

The paper titled "Cardiovascular and Metabolic Effects of ANGPTL3 Antisense Oligonucleotides" (Graham et al., *NEJM*, Advanced Online Publication, May 2017) documents the results of preclinical studies and a Phase 1/2 randomized, placebo-controlled study evaluating the safety, tolerability and efficacy of antisense drugs designed to lower ANGPTL3 levels. The clinical findings were published in partnership with the Sulpizio Cardiovascular Center at the University of California San Diego School of Medicine.

In a Phase 1/2 clinical study in volunteers with elevated triglycerides, treatment with multiple doses of AKCEA-ANGPTL3-L_{Rx} resulted in dose-dependent reductions in ANGPTL3 protein of up to 85% after six weeks of treatment. Treatment with AKCEA-ANGPTL3-L_{Rx} also resulted in substantial and dose-dependent reductions in triglycerides, LDL cholesterol, VLDL cholesterol, non-HDL cholesterol, apolipoprotein B and apolipoprotein C-III protein. AKCEA-ANGPTL3-L_{Rx} was well tolerated in the study. No serious adverse events, including no significant changes in platelet count, and no injection site reactions were reported. Further, there were no discontinuations during the treatment period.

In preclinical studies, murine-specific ANGPTL3-targeting antisense drugs produced dose-dependent reductions in ANGPTL3 protein, triglycerides, LDL cholesterol, VLDL cholesterol and non-HDL cholesterol, which were associated with decreased liver triglyceride content, improvement in insulin sensitivity and a reduction in atherosclerosis progression.

"At Akcea, we are focused on developing novel cardiometabolic drugs addressing the next wave of lipid risk factors. We believe targeting ANGPTL3 represents a unique opportunity given its pleiotropic effect on multiple lipid parameters and its potential to address the unmet need in both rare and more prevalent cardiometabolic diseases," said Dr. Louis O'Dea, chief medical officer at Akcea Therapeutics. "The results highlighted in today's publication provide support for the therapeutic potential of AKCEA-ANGPTL3-L_{Rx} across multiple lipid disorders and NAFLD with metabolic complications and we look forward to further advancing this drug in development."

ABOUT AKCEA-ANGPTL3-L_{Rx}

AKCEA-ANGPTL3-L_{Rx} is a Generation 2+ ligand conjugated antisense (LICA) drug designed to reduce angiopoietin-like 3 protein, or ANGPTL3. People with lower levels of ANGPTL3 have lower LDL-C and triglyceride levels and lower risk of heart attacks. Ionis and Akcea are developing AKCEA-ANGPTL3-L_{Rx} to treat multiple lipid disorders including rare hyperlipidemias and NAFLD with metabolic complications.

ABOUT AKCEA THERAPEUTICS

Akcea Therapeutics is a late-stage pharmaceutical company focused on developing and commercializing drugs to treat patients with serious cardiometabolic diseases caused by lipid disorders. Akcea is advancing a mature pipeline of four novel drugs with the potential to treat multiple diseases, including volanesorsen, AKCEA-APO(a)-L_{Rx}, AKCEA-ANGPTL3-L_{Rx} and AKCEA-APOCIII-L_{Rx}, which are all based on antisense technology developed by Ionis Pharmaceuticals, Inc. The most advanced drug in its pipeline, volanesorsen, has successfully completed a Phase 3 clinical program for the treatment of familial chylomicronemia syndrome, or FCS, and is currently in Phase 3 clinical development for the treatment of familial partial lipodystrophy, or FPL. Akcea is assembling the infrastructure to commercialize its drugs globally with a focus on lipid specialists as the primary call point. Akcea is a wholly owned subsidiary of Ionis Pharmaceuticals, Inc. and is located in Cambridge, Massachusetts. Additional information about Akcea is available at www.akceatx.com.

FORWARD-LOOKING STATEMENT

This press release includes forward-looking statements regarding the business of Akcea Therapeutics, Inc., a subsidiary of Ionis Pharmaceuticals, and the therapeutic and commercial potential of AKCEA-ANGPTL3-L_{Rx}. 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 Ionis Pharmaceuticals, Inc.'s annual report

on Form 10-K for the year ended December 31, 2016, 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", "Akcea," "Company," "Companies" "we," "our," and "us" refers to Ionis Pharmaceuticals and/or Akcea Therapeutics.

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