Akcea Announces Publication of Positive Volanesorsen Clinical Data Showing Reduced Triglycerides and Improved Insulin Sensitivity in Patients with High Triglycerides and Type 2 Diabetes

June 27, 2016

CAMBRIDGE, Mass., June 27, 2016 /PRNewswire/ -- Akcea Therapeutics, a wholly owned subsidiary of Ionis Pharmaceuticals, Inc. (NASDAQ: IONS) today announced the publication in *Diabetes Care* of positive clinical data from a Phase 2 study of volanesorsen in patients with high plasma triglyceride (TG) levels and type 2 diabetes. Results from the study showed that, in addition to reductions in plasma TG and apolipoprotein C-III (ApoC-III), a key factor in TG regulation, volanesorsen improved insulin sensitivity and glucose control. Volanesorsen is currently being evaluated in two pivotal Phase 3 studies—the APPROACH FCS study in patients with familial chylomicronemia syndrome (FCS) and the BROADEN FPL study in patients with familial partial lipodystrophy (FPL). In addition, the COMPASS study—a Phase 3 study designed to support global regulatory filings—is also ongoing.

The paper titled "Antisense-Mediated Lowering of Plasma Apolipoprotein C-III by Volanesorsen Improves Dyslipidemia and Insulin Sensitivity in Type 2 Diabetes" (Digenio et al., *Diabetes Care* June 2016) reported data from a Phase 2 double-blind, placebo-controlled study in fifteen patients randomized to weekly subcutaneous treatment with 300 mg of volanesorsen or placebo (2:1) for 13 weeks. In patients treated with volanesorsen, ApoC-III and TG levels decreased on average 88% and 69%, respectively, compared to baseline, and HDL-cholesterol increased an average of 42%. In addition, insulin sensitivity increased an average of 50% and correlated well with reductions in both plasma ApoC-III ($r = -0.61$, $p=0.03$) and TG ($r = -0.68$, $p=0.01$).

In addition, improvements in markers of glycemic control were observed, including statistically significant decreases in glycated albumin and fructosamine after three months of dosing, and a decrease of 0.44 percentage points in HbA1C observed three months post-dosing. The majority of adverse events reported in both groups in the study were mild in severity with no discontinuations from the study due to adverse events. There were no clinically relevant changes in blood serum chemistries, hematology, urinalysis, inflammatory markers, electrocardiogram, or vital signs.

"One of the most interesting findings in this study was that, in volanesorsen-treated patients with high triglycerides, substantial reductions in ApoC-III and triglycerides led to improved insulin sensitivity and glucose control. This is different from what is observed with currently approved triglyceride-lowering medications, which are not typically associated with this effect," said Dr. Louis O'Dea, Akcea's chief medical officer.

ABOUT VOLANESORSEN, FCS AND FPL

Volanesorsen is an antisense drug in development intended to treat patients with severely high triglycerides either as a single agent or in combination with other triglyceride-lowering agents. Volanesorsen is designed to reduce the production of ApoC-III, a protein produced in the liver that plays a central role in the regulation of plasma triglycerides.

Volanesorsen is currently being evaluated in two Phase 3 registrational studies (APPROACH FCS and BROADEN FPL) and a third Phase 3 study (COMPASS) designed to support global regulatory filings. APPROACH FCS is in patients with familial chylomicronemia syndrome (FCS). FCS is a rare, genetic disorder and may also be called familial chylomicronemia or Fredrickson Type 1 hyperlipoproteinemia, or familial lipoprotein lipase deficiency. People with FCS are unable to effectively clear lipid particles called chylomicrons. As a result, they have extremely high levels of triglycerides and are at risk of significant morbidity and mortality, including potentially life-threatening pancreatitis. Additional information on FCS is available at

www.fcsfocus.com

A second Phase 3 study of volanesorsen (BROADEN) has begun in patients with familial partial lipodystrophy (FPL). FPL is a rare lipid disorder characterized by abnormal fat distribution across the body and a range of metabolic abnormalities, including severe insulin resistance, dyslipidemia and hypertriglyceridemia, hepatic steatosis and, in affected women, features of hyperandrogenism. People with FPL often present with polycystic ovarian syndrome or unusually insulin-resistant diabetes, and are at increased risk of acute pancreatitis in addition to long-term, progressive consequences including premature cardiovascular disease and liver disease, resulting in cirrhosis. They are unable to store fat or triglycerides in normal fat stores, so excess triglycerides are stored in the liver and muscle and accumulate at high levels in the bloodstream. Additional information on FPL is available through Lipodystrophy United at www.lipodystrophyunited.org.

For more information about this clinical trial program for volanesorsen, please visit www.apociii.com.

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 using advanced RNA-targeted antisense therapeutics. Akcea's drug pipeline includes novel antisense drugs designed 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 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.

Logo - http://photos.prnewswire.com/prnh/20160118/323100LOGO

To view the original version on PR Newswire, visit:http://www.prnewswire.com/news-releases/akcea-announces-publication-of-positive-volanesorsen-clinical-data-showing-reduced-triglycerides-and-improved-insulin-sensitivity-in-patients-with-high-triglycerides-and-type-2-diabetes-300290398.html

SOURCE Ionis Pharmaceuticals, Inc.

Investor and Media: D. Wade Walke, Ph.D., Vice President, Corporate Communications and Investor Relations, 760-603-2741