Isis Pharmaceuticals and Akcea Therapeutics Announce Start of Phase 3 Study of Volanesorsen in Patients with Familial Partial Lipodystrophy

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Trial marks second study for volanesorsen in a rare, genetic lipid disorder

CARLSBAD, Calif., and CAMBRIDGE, Mass., Nov. 5, 2015 /PRNewswire/ -- Isis Pharmaceuticals, Inc. (NASDAQ: ISIS) and its wholly owned subsidiary, Akcea Therapeutics, today announced the start of a Phase 3 study to evaluate the efficacy and safety of volanesorsen in patients with familial partial lipodystrophy (FPL). Akcea is currently conducting an international, multi-center Phase 3 study of volanesorsen in patients with Familial Chylomicronemia Syndrome (FCS). Akcea is developing and plans to commercialize volanesorsen for two ultra-rare diseases, FCS and FPL.

AKCEA™ THERAPEUTICS

A subsidiary of Isis Pharmaceuticals, Inc.

Familial partial lipodystrophy is a rare, genetic disorder characterized by metabolic abnormalities, including hypertriglyceridemia and extreme insulin resistance, and abnormalities in the distribution of body fat. Patients with FPL have a high risk at an early age of diabetes, liver disease, and cardiovascular disease. In addition, extreme hypertriglyceridemia puts them at risk for potentially life-threatening pancreatitis. Since it is most often an inherited, autosomal dominant disorder, FPL can be passed down from one generation to the next in affected families.

"Every day, people with FPL struggle to manage the burden this disease brings across virtually every major organ system in their body," describes Dr. Elif Oral of the University of Michigan. "FPL takes an enormous toll on those affected – both physically and psychologically. There is still no pharmacologic therapy developed specifically for this patient population. For these patients in particular, the potential benefit of inhibiting the synthesis of apoC-III is very promising."

According to Paula Soteropoulos, CEO of Akcea Therapeutics: "The late-stage development of volanesorsen for people with FPL perfectly reflects Akcea's vision, which is to bring transformative therapies to patients and address the root causes of serious, underserved cardiometabolic disorders. Akcea's initiation of this second Phase 3 program reflects our focus and expertise at developing and commercializing medicines for complex disorders that are not addressable through other therapeutic modalities."

Volanesorsen is a Gen. 2.0+ antisense drug designed to reduce the production of apoC-III, a protein that acts as a key regulator of triglyceride levels in the blood. Patients with elevated triglyceride levels are at significant risk for coronary artery disease and diabetes. Extremely high triglyceride levels put patients at risk of pancreatitis, a serious and potentially life-threating illness. In addition, elevated levels of apoC-III are recognized as an independent contributor to cardiovascular disease.

The Phase 3 study announced today is a randomized, double-blind, placebo-controlled, multi-center, international study in approximately 50 patients with FPL. The study's primary objective is to evaluate the efficacy and safety of a 300 mg once weekly dose of volanesorsen given over 12 months. The primary endpoint of the study is percent change in fasting triglycerides from baseline after three months of dosing.

ABOUT VOLANESORSEN, FCS and FPL

Volanesorsen (formerly ISIS-APOCIII$_{Rx}$) 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 a Phase 3 study in patients with FCS. Patients with FCS are unable to effectively clear lipid particles called chylomicrons, and as a result, have extremely high levels of triglycerides, putting them at risk of potentially life-threatening pancreatitis. FCS is a rare, genetic disorder and may also be called familial chylomicronemia or Fredrickson Type 1 hyperlipoproteinemia, or familial lipoprotein lipase deficiency.

A second Phase 3 study of volanesorsen has begun in patients with FPL, 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. Patients with FPL are at increased risk of pancreatitis, hepatic steatosis and NASH, enlarged livers, polycystic ovarian syndrome and premature cardiovascular disease. Patients with FPL 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 is available through Lipodystrophy United at http://www.lipodystrophyunited.org/ .

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

ABOUT ISIS PHARMACEUTICALS, INC.

Isis 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, Isis 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 Isis is developing and plans to commercialize through its wholly owned subsidiary, Akcea Therapeutics, to treat patients with familial chylomicronemia syndrome and familial partial lipodystrophy; ISIS-TTR_{Rx}, a drug Isis is developing with GSK to treat patients with all forms of TTR amyloidosis; and ISIS-SMN_{Rx}, a drug Isis is developing with Biogen to treat infants and children with spinal muscular atrophy. Isis' patents provide strong and extensive protection for its drugs and technology. Additional information about Isis is available at www.isispharm.com.

ABOUT AKCEA THERAPEUTICS

Akcea Therapeutics is a development and commercialization company focused on transforming the lives of patients with serious cardiometabolic lipid disorders. Established as a wholly-owned subsidiary of Isis 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 LDL-Cholesterol, apoC-III, triglycerides and Lp(a). Akcea's most advanced program, volanesorsen, is in Phase 3 development to treat patients with ultra-orphan lipid disorders that are characterized by extremely high triglycerides and apoC-III, including familial chylomicronemia syndrome (FCS) and familial partial lipodystrophy (FPL). Akcea is located in Cambridge, Massachusetts. Additional information about Akcea is available at www.akceatx.com.

ISIS PHARMACEUTICALS' FORWARD-LOOKING STATEMENT

This press release includes forward-looking statements regarding Isis' business, the business of Akcea Therapeutics, the development, activity, therapeutic and commercial potential and safety of volanesorsen for the treatment of patients with FCS and FPL. Any statement describing Isis' 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. Isis' 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 Isis' forward-looking statements reflect the good faith judgment of its management, these statements are based only on facts and factors currently known by Isis. As a result, you are cautioned not to rely on these forward-looking statements. These and other risks concerning Isis' programs are described in additional detail in Isis' annual report on Form 10-K for the year ended December 31, 2014, 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.

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SOURCE Isis Pharmaceuticals, Inc.

Isis Pharmaceuticals and Akcea Therapeutics Contacts: D. Wade Walke, Ph.D., Vice President, Corporate Communications and Investor Relations, 760-603-2741, Amy Williford, Ph.D., Associate Director, Corporate Communications, 760-603-2772