



Positive Clinical Data From Volanesorsen Published in the New England Journal of Medicine

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Publication highlights the therapeutic potential of volanesorsen to address unmet needs in patients with high apoC-III and triglyceride levels

CARLSBAD, Calif. and CAMBRIDGE, Mass., July 29, 2015 /PRNewswire/ -- Isis Pharmaceuticals, Inc. (NASDAQ: ISIS), the leader in RNA-targeted therapeutics, and Akcea Therapeutics, its wholly owned subsidiary, announced today that *The New England Journal of Medicine* (NEJM) has published positive clinical results from a Phase 2 clinical study evaluating volanesorsen (formerly ISIS-APOCIII_{RX}) in patients with very high to severely high triglycerides. This publication follows the December 2014 publication in the NEJM of the positive Phase 2 results from a clinical study of volanesorsen in patients with familial chylomicronemia syndrome (FCS).¹ Volanesorsen is part of Isis' lipid franchise, which is being developed and commercialized by Akcea Therapeutics.



A subsidiary of Isis Pharmaceuticals, Inc.

"These publications emphasize the significant interest from the medical community in the therapeutic potential of antisense drugs, such as volanesorsen, to substantially affect novel cardiometabolic targets, like apoC-III," said Sekar Kathiresan, director of preventive cardiology at Massachusetts General Hospital and researcher in medical and population genetics at the Broad Institute of Massachusetts Institute of Technology and Harvard University. "These and other findings from the medical and scientific communities are confirming the importance of apoC-III and triglycerides as risk factors for cardiovascular and metabolic disease. The recent results with volanesorsen indicate that an RNA-targeted antisense approach is proving to be an ideal way to target these risk factors."

"We have consistently demonstrated significant reductions in apoC-III and triglycerides in patients treated with volanesorsen. We have also reported significant improvements in glucose parameters in patients with high triglycerides and type 2 diabetes treated with volanesorsen. These data highlight the potential therapeutic value that volanesorsen can bring to patients with serious cardiometabolic lipid disorders. Akcea is building a world class team focused on the development and commercialization of drugs to treat rare lipid disorders. Preparations for global commercialization of volanesorsen are underway," said Paula Soteropoulos, president and chief executive officer of Akcea Therapeutics. "Volanesorsen is the most advanced drug in Akcea's portfolio of lipid drugs. Together with ISIS-APOCIII-L_{RX}, our more potent LICA follow on drug for patients with severely high triglycerides, and the other drugs in our pipeline, we have the opportunity to provide complementary therapeutic solutions to physicians treating patients with lipid disorders."

"We continue to see growing interest in the therapeutic potential of our antisense drugs to specifically affect important, genetically validated targets, like apoC-III and Lp(a), that are often not approachable with other therapeutic modalities," said Richard Geary, Ph.D., senior vice president of development at Isis Pharmaceuticals. "The publication of four manuscripts in the last few months in either *The New England Journal of Medicine* (3 papers) or *The Lancet* (one paper), represents substantial recognition from the medical community of our technology and its broad applicability to address newly identified targets."

The paper, titled "Antisense Inhibition of APOC3 in Patients with Hypertriglyceridemia" (Gaudet et al, *N Engl J Med* 2015: published online July 29), reported data from the Phase 2 study of volanesorsen, a double-blind, randomized, placebo-controlled 13-week study designed to assess the safety and activity of volanesorsen in patients as a monotherapy and as an add-on to fibrates. Patients treated with volanesorsen achieved mean reductions of up to 80 percent in apoC-III and up to 71 percent in triglycerides and average increases of up to 46 percent in HDL-C. The efficacy, safety and tolerability of volanesorsen in patients

with very high to severely high triglycerides to date support continued development.

ABOUT VOLANESORSEN, FCS and FPL

Volanesorsen (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 target apoC-III, a protein produced in the liver that plays a central role in the regulation of plasma triglycerides.² Humans who do not produce apoC-III have lower levels of plasma triglycerides and a lower prevalence of cardiovascular disease.³ Humans with elevated levels of apoC-III have high triglycerides associated with multiple metabolic abnormalities, including insulin resistance and/or metabolic syndrome.⁴ Humans with severely elevated levels of triglycerides are at risk of many serious health conditions, including pancreatitis,⁴ which can be life-threatening and require hospitalization.

Volanesorsen is currently being evaluated in a Phase 3 study in patients with FCS. FCS is a rare genetic disorder characterized by extremely high levels of triglycerides and a history or risk of pancreatitis. Patients with FCS are unable to effectively clear chylomicrons, and as such, have high levels of triglycerides, which increase their risk of pancreatitis, which can be life-threatening, type 2 diabetes and other serious illnesses.

A second Phase 3 study of volanesorsen is planned to begin later this year in patients with familial partial lipodystrophy (FPL). FPL is a rare lipid disorder characterized by both selective loss of fat from various areas of the body and a range of metabolic abnormalities, including elevated apoC-III and triglycerides, as well as diabetes. 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. Patients with FPL are at increased risk of pancreatitis, hepatic steatosis and NASH, enlarged livers, elevated liver enzymes and premature cardiovascular disease.

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

ABOUT ISIS PHARMACEUTICALS, INC.

Isis is exploiting its leadership position in RNA-targeted technology to discover and develop novel drugs for its product pipeline and for its partners. Isis' broad pipeline consists of 38 drugs to treat a wide variety of diseases with an emphasis on cardiovascular, metabolic, severe and rare diseases, including neurological disorders, and cancer. Isis' partner, Genzyme, is commercializing Isis' lead product, KYNAMRO[®], in the United States and other countries for the treatment of patients with homozygous FH. Isis has numerous drugs in Phase 3 development in severe/rare diseases and cardiovascular diseases. These 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 the polyneuropathy and cardiomyopathy forms of TTR amyloidosis; and ISIS-SMN_{Rx}, a drug Isis is developing with Biogen to treat infants and children with spinal muscular atrophy, a severe and rare neuromuscular disease. 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-C, 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 Pharmaceuticals and Isis' business and the commercial potential of Isis' technology and lipid franchise drugs, including the development, activity, therapeutic potential and safety of volanesorsen, and the business of Akcea Therapeutics and the commercial potential of drugs and technologies Akcea develops. 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.

References:

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2. Zheng, C. (2014). Updates on apolipoprotein CIII: fulfilling promise as a therapeutic target for hypertriglyceridemia and cardiovascular disease. *Curr Opin Lipidol*, 25(1), 35-39.
3. Jørgensen, A.B., Frikke-Schmidt, R., Nordestgaard, B.G. & Tybjærg-Hansen, A. (2014) Loss-of-function mutations in APOC3 and risk of ischemic vascular disease. *N Engl J Med*, 371(1), 32-41
4. Christian, J.B., Arondekar, B., Buysman, E.K., Jacobson, T.A., Snipes, R.G., Horwitz, R. (2014). Determining triglyceride reductions needed for clinical impact in severe hypertriglyceridemia. *Am J Med*, 127(1), 36-44.



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