

## Positive Clinical Data From Lp(a) Lowering Drug ISIS-APO(a) Rx Published in The Lancet

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### Publication highlights importance of Lp(a) as a risk factor for cardiovascular disease and the therapeutic potential of antisense drugs

CARLSBAD, Calif. and CAMBRIDGE, Mass., July 22, 2015 /PRNewswire/ -- Isis Pharmaceuticals, Inc. (NASDAQ: ISIS), the leader in RNA-targeted therapeutics, and Akcea Therapeutics announced today that *The Lancet* has published clinical data evaluating ISIS-APO(a)<sub>Rx</sub> in healthy volunteers with elevated lipoprotein(a) or Lp(a). An accompanying editorial was also published. ISIS-APO(a)<sub>Rx</sub> is a Generation 2.0+ antisense drug that is part of Isis' lipid franchise, which is being developed and commercialized by Akcea Therapeutics, Isis' wholly owned subsidiary.



*A subsidiary of Isis Pharmaceuticals, Inc.*

"Although not as widely recognized as LDL-cholesterol, a growing body of scientific and medical evidence has identified Lp(a) as an important and independent, genetically caused risk factor for cardiovascular disease," said Joseph Witztum, M.D., distinguished professor of medicine and director of the atherosclerosis research group at the University of California, San Diego and co-author on the paper. "There is no drug available today to specifically and effectively lower elevated Lp(a) levels in patients with high Lp(a) levels. The publication of these study results today in *The Lancet* shows the therapeutic potential of antisense drugs, such as ISIS-APO(a)<sub>Rx</sub>, to specifically affect important, newly identified therapeutic targets like Lp(a)."

"The introduction of a selective Lp(a)-lowering therapy is very exciting," said Erik Stroes, M.D., Ph.D., professor of internal medicine, department of vascular medicine, University of Amsterdam. "It is estimated that up to 20% of the population have elevated Lp(a) levels that put them at higher risk for cardiovascular disease but because there has been no therapeutic option for lowering elevated Lp(a) levels, most healthcare providers have not been monitoring this important risk factor. However, the availability of a therapeutic agent capable of lowering Lp(a) should lead to the widespread testing of Lp(a) levels."

"Several seminal publications over the past five years, including human genetic studies, have established Lp(a) as an important risk factor for cardiovascular disease. It is a testament to the efficiency of antisense technology that we were able to create ISIS-APO(a)<sub>Rx</sub> and advance it into human clinical trials so rapidly. We are looking forward to the results from our Phase 2 clinical trials in patients with very high Lp(a) later this year," said Rosanne M. Crooke, vice president of cardiovascular research at Isis Pharmaceuticals. "ISIS-APO(a)<sub>Rx</sub> is a Generation 2.0+ antisense drug that specifically and potently reduces Lp(a) without affecting other lipoproteins."

"ISIS-APO(a)<sub>Rx</sub>, as well as its next generation LICA version, ISIS-APO(a)-L<sub>Rx</sub>, are the first drugs in development to directly target Lp(a), and among the various drugs in the Akcea pipeline to treat patients with serious cardiometabolic lipid disorders," said Paula Soteropoulos, president and chief executive officer of Akcea Therapeutics. "Akcea is uniquely positioned to drive development and rapidly advance these drugs to market for these patients who are underserved with today's therapies."

The paper titled "Antisense therapy targeting apolipoprotein(a): a randomized, double-blind, placebo-controlled phase 1 study" (Tsimikas et al, *The Lancet* 2015: published online today), reported data from the Phase 1 study evaluating single and multiple ascending doses of ISIS-APO(a)<sub>Rx</sub> in healthy volunteers with elevated Lp(a) concentrations of 25 nmol/L (100 mg/L) or more. Results of this study demonstrated potent, dose-dependent, selective reductions of plasma Lp(a) up to 89% (mean reduction up to 78%) in patients treated with ISIS-APO(a)<sub>Rx</sub>. In addition, up to 90 percent reduction (mean reduction up to 84%) was observed in Lp(a) associated oxidized phospholipids, which play an important role in proinflammatory and proatherogenic processes. The Lp(a) knockdown, together with safety and tolerability support continued clinical development of ISIS-APO(a)<sub>Rx</sub> as a potential therapeutic drug to reduce the risk of cardiovascular disease and calcific aortic valve stenosis in patients with elevated Lp(a) concentration. Isis and Akcea are currently evaluating ISIS-APO(a)<sub>Rx</sub> in a Phase 2 study in patients with elevated Lp(a) levels and plan to report data from this study around the year end. Isis and Akcea are also developing ISIS-APO(a)-L<sub>Rx</sub>.

#### **ABOUT Lp(a)**

Lp(a) is considered an independent risk factor for cardiovascular disease due to its association with an increased risk of coronary heart disease, atherosclerotic plaque formation and calcific aortic valve stenosis. Lp(a) is a lipoprotein particle that is assembled in the liver and consists of the apolipoprotein(a) protein covalently linked to LDL-cholesterol. Lp(a) levels in blood can vary greatly between individuals due primarily to genetic variations in the gene that encodes for apolipoprotein(a). As a result, Lp(a) levels are genetically determined and remain constant throughout the life of the individual. Diet and lifestyle changes have little impact on Lp(a) levels and current therapies are not able to adequately reduce elevated levels of Lp(a) to acceptable levels in patients who have severely elevated Lp(a). As a general guideline for ideal Lp(a) levels, the European Atherosclerosis Society recommends that Lp(a) levels be less than or equal to 50 mg/dL.

#### **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<sup>®</sup>, 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<sub>Rx</sub>, a drug Isis is developing with GSK to treat patients with the polyneuropathy and cardiomyopathy forms of TTR amyloidosis; and ISIS-SMN<sub>Rx</sub>, 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](http://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](http://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 ISIS-APO(a)<sub>Rx</sub>, 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.



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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