Isis Pharmaceuticals Reports Positive Phase 1 Data on Isis-ANGPTL3Rx

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CARLSBAD, Calif., March 23, 2015 /PRNewswire/ -- Isis Pharmaceuticals, Inc. (NASDAQ: ISIS) announced today positive results from a Phase 1 study with ISIS-ANGPTL3$_{Rx}$. In this study, healthy volunteers treated with ISIS-ANGPTL3$_{Rx}$ achieved dose-dependent, statistically significant reductions in angiopoietin-like 3 (ANGPTL3) of up to 93 percent with a mean reduction of up to 84 percent from baseline ($p<0.001$). In addition, statistically significant reductions from baseline in lipid parameters were observed, including up to 63% with a mean reduction of up to 49% ($p<0.01$) in triglycerides and up to 46% with a mean reduction of up to 28% ($p<0.001$) in total cholesterol. ANGPTL3 is a protein that acts as a key regulator of these blood lipids. These data were presented at the 83rd European Atherosclerosis Society in Glasgow, United Kingdom.

"We are encouraged with the performance of ISIS-ANGPTL3$_{Rx}$ in healthy volunteers. Based on data from preclinical models of hyperlipidemia, we expect to see even greater lipid reductions in patients with hyperlipidemia than in healthy volunteers," said Richard Geary, senior vice president at Isis Pharmaceuticals. "In fact, in this study we observed that healthy volunteers with higher baseline lipid levels experienced larger lipid reductions than those with lower baseline lipid levels."

"ANGPTL3 is a very interesting target for the management of both plasma triglycerides and cholesterol at the same time. We know from genetic studies of patients who are heterozygous for loss-of-function mutations in their ANGPTL3 gene that they have half-normal levels of plasma ANGPTL3, and correspondingly, lower levels of plasma triglycerides and cholesterol. Patients who are homozygous for such loss-of-function mutations have exceedingly low plasma levels of triglycerides and cholesterol, which are both risk factors for cardiovascular disease. In contrast, humans with different mutations in ANGPTL3 that raise plasma ANGPTL3 levels have increased lipid levels. In addition, pre-clinical studies in animal models demonstrate that raising plasma ANGPTL3 levels increase, and lowering plasma ANGPTL3 levels decrease triglyceride and cholesterol levels," said Joseph L. Witztum, M.D., professor of medicine at the University of California, San Diego. "All of these data strongly support the idea that lowering plasma ANGPTL3 in humans is a potentially important strategy to reduce multiple cardiovascular risk factors."

"ISIS-ANGPTL3$_{Rx}$ is one of the drugs in our lipid franchise that our wholly owned subsidiary, Akcea Therapeutics, is developing and plans to commercialize. The team at Akcea has already begun to outline the development and commercialization plans for ISIS-ANGPTL3$_{Rx}$, together with the other drugs in our lipid franchise, to provide the best opportunity for each drug to succeed and bring the highest possible value to those patients who need these therapies the most," said Lynne Parshall, chief operating officer at Isis.

The Phase 1 study of ISIS-ANGPTL3$_{Rx}$ was a blinded, placebo-controlled, dose-escalation study in healthy volunteers. The study was designed to assess the safety, tolerability and pharmacokinetics of ISIS-ANGPTL3$_{Rx}$. ISIS-ANGPTL3$_{Rx}$ was evaluated in single and multiple doses ranging from 50 mg per week up to 400 mg per week for the single dose and 100 mg per week up to 400 mg per week for the multiple dose. In this study, ISIS-ANGPTL3$_{Rx}$ was generally well tolerated.

ISIS-ANGPTL3$_{Rx}$ is an antisense drug designed to reduce ANGPTL3. ANGPTL3 is produced in the liver and regulates lipid, glucose and energy metabolism. In preclinical studies, antisense inhibition of ANGPTL3 resulted in robust reductions of multiple lipid parameters, including total-cholesterol, and triglycerides. ISIS-ANGPTL3$_{Rx}$ is part of Isis' lipid franchise and, as such, Akcea Therapeutics, Isis' wholly owned subsidiary, is responsible for developing ISIS-ANGPTL3$_{Rx}$.

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 ISIS-APOCIII$_{Rx}$, a drug Isis is developing and plans to commercialize through its wholly owned subsidiary, Akcea Therapeutics, to treat patients with familial chylomicronemia syndrome and 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 Idec 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.

ISIS PHARMACEUTICALS' FORWARD-LOOKING STATEMENT
This press release includes forward-looking statements regarding the development, activity, therapeutic potential and safety of ISIS-ANGPTL3$_{Rx}$ and the discovery, development and therapeutic potential of an antisense drug for the treatment of patients with elevated LDL-cholesterol. 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, which is on file with the SEC. Copies of this and other documents are available from the Company.

In this press release, unless the context requires otherwise, "Isis," "Company," "we," "our," and "us" refers to Isis Pharmaceuticals and its subsidiaries.

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