Isis Reports Interim Phase 2 Data on ISIS-APOCIII Rx as a Single Agent in Patients With Very High to Severely High Triglycerides

August 31, 2013

Statistically Significant Reductions of up to 75 percent in Triglycerides and up to 79 percent in ApoC-III
Conference call webcast and slide presentation Tuesday, Sept. 3, 11:30 a.m. ET at www.isispharm.com

CARLSBAD, Calif., Aug. 31, 2013 /PRNewswire/ -- Isis Pharmaceuticals, Inc. (NASDAQ: ISIS) announced interim data from an ongoing Phase 2 study of ISIS-APOCIII$_{Rx}$ as a monotherapy in patients with very high to severely high triglycerides. These data were presented today by Dr. Daniel Gaudet at a PACE session occurring concurrently with the European Society of Cardiology in Amsterdam. In this study, patients treated with ISIS-APOCIII$_{Rx}$ achieved statistically significant mean reductions of up to 79 percent in apolipoprotein C-III (apoC-III) and up to 75 percent in triglycerides. In addition, patients treated with ISIS-APOCIII$_{Rx}$ achieved statistically significant mean increases of up to 57 percent in high-density lipoprotein cholesterol (HDL-C), the 'good' cholesterol. Patients also achieved up to 89 percent mean reduction in apoC-III-associated very low-density lipoprotein (VLDL) particles.

(Logo: http://photos.prnewswire.com/prnh/20130807/LA60006LOGO)

"Patients with very high levels of triglycerides experience a significant number of health problems, including type 2 diabetes, obesity, cardiovascular disease and, for patients with severely elevated triglycerides, pancreatitis. For these patients, there are very limited treatment options and what is needed is a much more effective drug that can be used as a single agent or in combination with other triglyceride-lowering agents," said Daniel Gaudet, M.D., Ph.D., from the department of medicine, University of Montreal and scientific director, Genome Quebec Biobank Technology Center. "The comprehensive Phase 2 data reported this summer demonstrate that ISIS-APOCIII$_{Rx}$ has the potential to fill this need."

The monotherapy portion of the ongoing Phase 2 study of ISIS-APOCIII$_{Rx}$ is a double-blind, randomized, placebo-controlled 13-week study designed to assess the safety and activity of ISIS-APOCIII$_{Rx}$ in patients with very high to severely high triglyceride levels (between 440 and 2,000 mg/dL). The data reported today is an interim analysis of 28 patients who completed 13 weeks of treatment with ISIS-APOCIII$_{Rx}$ or placebo. In this study, patients treated with ISIS-APOCIII$_{Rx}$ experienced dose-dependent, robust and prolonged, mean percent reductions from baseline in apoC-III, triglycerides and apoC-III-associated VLDL particles. Furthermore, these patients demonstrated a rapid, prolonged and statistically significant mean percent increase from baseline in HDL-C.

Table 1: ISIS-APOCIII$_{Rx}$ Produced Statistically Significant Reductions of Triglycerides, ApoC-III and ApoC-III-associated VLDL as a Single Agent in a Phase 2 Study in Patients with Very High to Severely High Triglyceride Levels. Mean % Changes From Baseline at Primary Endpoint.*

	Placebo (n=9)	ISIS-APOCIII$_{Rx}$ 100 mg (n=9)	ISIS-APOCIII$_{Rx}$ 200 mg (n=5)	ISIS-APOCIII$_{Rx}$ 300 mg (n=5)
ApoC-III	+5%	-43% (p=0.04)	-72% (p=0.004)	-79% (p=0.003)
Triglycerides	+26%	-31% (p=0.08)	-65% (p=0.02)	-75% (p=0.004)
ApoC-III VLDL	+19%	-27% (p=0.17)	-73% (p=0.003)	-89% (p=0.004)
HDL-C	+3%	+30% (p=0.08)	+51% (p=0.002)	+57% (p=0.001)
non-HDL	+17%	-8% (p=0.16)	-5% (p=0.36)	-39% (p=0.007)
P value = vs. placebo *Interim analysis				

In the ongoing study, patients received 100 mg, 200 mg or 300 mg dose of ISIS-APOCIII$_{Rx,}$ or placebo via weekly subcutaneous injections. In this interim analysis, patients had an average fasting triglyceride level of 602 mg/dL with incoming triglyceride levels up to 1,822 mg/dL. In this study ISIS-APOCIII$_{Rx}$ was found to be generally safe and well tolerated. The most common adverse event (AE) was injection site reactions, which were infrequent, predominantly mild and typically resolved rapidly. There were no flu-like symptoms, no treatment-related elevations of liver enzymes greater than three times upper limit of normal, no abnormalities in renal function and no clinically meaningful changes in other laboratory values.

"We are pleased with the performance of ISIS-APOCIII$_{Rx}$ to date. We have now demonstrated that ISIS-APOCIII$_{Rx}$ is equally effective in patients with high to severely high triglycerides as well as in patients with high triglycerides and type 2 diabetes. We have demonstrated that ISIS-APOCIII$_{Rx}$ can work equally well as a single agent and in combination with fibrates to produce significant reductions in apoC-III and triglycerides, and increases in HDL-C. In addition, the positive effect of ISIS-APOCIII$_{Rx}$ treatment on lipid parameters, improvements in glucose control and trends toward improvements in insulin sensitivity, suggest that ISIS-APOCIII$_{Rx}$ could have a very attractive therapeutic profile for patients with severely high triglycerides, who often also have diabetes or metabolic syndrome," said Richard Geary, Ph.D., senior vice president of development at Isis. "We look forward to discussing our Phase 3 plans with regulators and moving rapidly into a Phase 3 program next year in patients with severely high triglycerides."

ISIS-APOCIII$_{Rx}$ is an antisense drug intended to treat patients with severely high triglycerides either as a single agent or in combination with other triglyceride-lowering agents. ISIS-APOCIII$_{Rx}$ targets apoC-III, a gene produced in the liver that plays a central role in the regulation of serum triglycerides. Humans who do not produce apoC-III have lower levels of triglycerides and lower instances of cardiovascular disease. In clinical studies, patients with lower levels of apoC-III and triglycerides exhibit lower cardiovascular event rates. Humans with elevated levels of apoC-III have increased dyslipidemia associated with multiple metabolic abnormalities, such as insulin resistance and/or metabolic syndrome. In addition, the

prevalence of type 2 diabetes is increased in patients with elevated triglycerides.

Conference Call
At 11:30 a.m. Eastern Time Tuesday, Sept. 3, 2013, Isis will conduct a live webcast and slide presentation conference call to discuss the positive Phase 2 data presented today. Interested parties may listen to the call by dialing 866-652-5200, or access the webcast with or without audio at www.isispharm.com. A webcast replay will be available for a limited time at the same address.

ABOUT ISIS PHARMACEUTICALS, INC.
Isis is exploiting its leadership position in antisense technology to discover and develop novel drugs for its product pipeline and for its partners. Isis' broad pipeline consists of 29 drugs to treat a wide variety of diseases with an emphasis on cardiovascular, metabolic, severe and rare diseases, and cancer. Isis' partner, Genzyme, is commercializing Isis' lead product, KYNAMRO™, in the United States for the treatment of patients with HoFH. Genzyme is also pursuing marketing approval of KYNAMRO in other markets. 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 discovery, development, and potential of drugs for cardiovascular diseases, and the development, activity, therapeutic potential and safety of ISIS-APOCIII$_{Rx}$. Any statement describing Isis' goals, expectations, financial or other projections, intentions or beliefs, including the commercial potential of KYNAMRO, 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, 2012 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.

SOURCE Isis Pharmaceuticals, Inc.

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