Isis Reports Phase 2 Data on ISIS-APOCIII Rx Showing Significant Reductions in Triglycerides and APOC-III in Patients With High Triglycerides and Type 2 Diabetes

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Improvements in glucose control and insulin sensitivity also observed
Conference call webcast and slide presentation Monday, June 24, 8:30 a.m. ET at www.isispharm.com

CARLSBAD, Calif., June 23, 2013 /PRNewswire/ -- Isis Pharmaceuticals, Inc. (NASDAQ: ISIS) announced that data from the Phase 2 study of ISIS-APOCIII$_{Rx}$ in patients with high triglycerides and type 2 diabetes were presented today at the American Diabetes Association Scientific Sessions in Chicago. In this study, patients treated with ISIS-APOCIII$_{Rx}$ experienced an 88 percent reduction in apolipoprotein C-III (apoC-III), a 72 percent reduction in triglyceride levels, a 40 percent increase in high-density lipoprotein cholesterol (HDL-C), the 'good' cholesterol, and improvements in other atherogenic lipid parameters. In addition, patients dosed with ISIS-APOCIII$_{Rx}$ showed consistent trends toward enhanced insulin sensitivity with improvements in multiple measures of glucose control. Isis is also evaluating ISIS-APOCIII$_{Rx}$ in a separate Phase 2 study in patients with moderate to severe high triglycerides and plans to report data from this study this summer.

"Patients with high levels of triglycerides are at a significant risk for cardiovascular disease and stroke. Because high triglyceride levels are also associated with obesity and insulin insensitivity, reducing apoC-III and triglycerides in high-risk patients, like type 2 diabetic patients, may lead to improved insulin sensitivity and improvement of metabolic syndrome," said Joseph L. Witztum, M.D., professor of medicine, University of California, San Diego. "The data presented today on ISIS-APOCIII$_{Rx}$ are very encouraging and unique in that there is a significant and substantial reduction in both apoC-III and triglyceride levels with a significant increase in HDL and improvements across the board in the overall lipid parameters, including non-HDL-C. In addition, unlike many available triglyceride-lowering therapies, including diet, ISIS-APOCIII$_{Rx}$ did not raise LDL-C in these patients. There is no other drug in development that demonstrates the potential for such a broad therapeutic profile. The dramatic effect of ISIS-APOCIII$_{Rx}$ on all of these parameters could translate into significant benefit to many patients, including patients with high triglycerides and type 2 diabetes."

The Phase 2 study of ISIS-APOCIII$_{Rx}$ was a blinded, randomized, placebo-controlled 13-week study designed to assess the safety and activity of ISIS-APOCIII$_{Rx}$ in patients with high triglycerides levels (between 200 and 500 mg/dL) and type 2 diabetes. After only 13 weeks of dosing, robust and prolonged, statistically significant mean reductions of 88 percent from baseline in apoC-III levels ($p<0.03$) and 72 percent from baseline in fasting plasma triglyceride levels ($p<0.03$) were observed. All treated patients achieved triglyceride levels of less than 100 mg/dL by four weeks of dosing, and the average triglyceride level was 71 mg/dL at the end of treatment. Furthermore, patients treated with ISIS-APOCIII$_{Rx}$ demonstrated a rapid, prolonged and statistically significant mean increase in HDL-C of 40 percent from baseline ($p<0.03$) with improvements in overall lipid parameters, including non-HDL-C and VLDL-C, and no increase in LDL-C.

In addition, consistent improvements in HbA1c and other measures of glucose control, including serum fructosamine and glycated albumin, were observed in patients dosed with ISIS-APOCIII$_{Rx}$. The effects of ISIS-APOCIII$_{Rx}$ observed on measures of glucose control were in addition to those achieved with each patient's existing therapeutic regimen of metformin. Improvements in indicators of insulin sensitivity were also observed in patients suggesting that inhibition of apoC-III could improve insulin sensitivity in patients with high triglycerides and type 2 diabetes. ISIS-APOCIII$_{Rx}$ demonstrated a good safety profile in the study and was well tolerated in all subjects with no discontinuations, no clinically meaningful elevations in liver enzymes, no flu-like symptoms, no significant adverse events, and a low incidence of mild injection site reactions which were infrequent and typically resolved within a day or two.

"Our focus is to bring ISIS-APOCIII$_{Rx}$ to the market for patients with severe hypertriglyceridemia. These are patients who cannot reduce their triglycerides to safe levels with currently available medicines. We plan to report data from our ongoing Phase 2 program in very high triglyceride patients later this summer evaluating ISIS-APOCIII$_{Rx}$ in combination with fibrates and as a monotherapy," said Richard Geary, Ph.D., senior vice president of clinical development at Isis. "In the study we are reporting today, we observed rapid and prolonged reductions of apoC-III, triglycerides and other lipid parameters, as well as improvements in glucose control and insulin sensitivity. These data suggest that ISIS-APOCIII$_{Rx}$ could provide therapeutic benefit to patients with high triglycerides who are insulin insensitive, including patients who are obese or have type 2 diabetes. In addition, the positive effect of ISIS-APOCIII$_{Rx}$ on all atherogenic lipid parameters measured and the observed increase in HDL, significantly enhances the potential profile of the drug."

In this study, 11 patients were randomized 2:1 to receive a 300 mg dose of ISIS-APOCIII$_{Rx}$ or placebo via weekly subcutaneous injections for 13 weeks. Patients entering the study had a mean apoC-III level of 14.3 mg/dL, a mean triglyceride level of 259 mg/dL and a mean HDL level of 43.4 mg/dL.

ISIS-APOCIII$_{Rx}$ is an antisense drug that 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 8:30 a.m. Eastern Time tomorrow, June 24, 2013, Isis will conduct a live webcast and slide presentation conference call to discuss the positive Phase 2 data presented today at the American Diabetes Association. 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 28 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™, inthe 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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