Isis Reports Phase 2 Data on ISIS-APOCIII Rx Showing Significant Reductions of ApoC-III and Triglycerides in Patients With High Triglycerides Taking Fibrates

July 22, 2013

Reductions of up to 64 percent in Triglycerides Achieved
Majority of Patients Reached Triglyceride Levels Below 150 mg/dL
Conference call webcast and slide presentation Monday, July 22, 8:30 a.m. ET at www.isispharm.com

CARLSBAD, Calif. , July 22, 2013 /PRNewswire/ -- Isis Pharmaceuticals, Inc. (NASDAQ: ISIS) announced data from a Phase 2 study of ISIS-APOCIII$_{Rx}$ in patients with high to severely high triglycerides on stable doses of fibrates. In this study, patients treated with ISIS-APOCIII$_{Rx}$ experienced reductions of up to 70 percent in apolipoprotein C-III (apoC-III) and up to 64 percent in triglycerides. In addition, patients treated with ISIS-APOCIII$_{Rx}$ experienced an up to 52 percent increase in high-density lipoprotein cholesterol (HDL-C), the 'good' cholesterol, and an up to 77 percent reduction in apoC-III-associated very low-density lipoprotein (VLDL) particles. Isis is also evaluating ISIS-APOCIII$_{Rx}$ in this Phase 2 study as a monotherapy in patients with severely high triglycerides and plans to report these data at the European Society of Cardiology on August 31 in Amsterdam .

The Phase 2 study of ISIS-APOCIII$_{Rx}$ was a double-blind, randomized, placebo-controlled 13-week study designed to assess the safety and activity of ISIS-APOCIII$_{Rx}$. The portion of the study reported today was conducted in patients with high to severely elevated triglyceride levels (between 225 and 2,000 mg/dL) on stable doses of fibrates.

Table 1: ISIS-APOCIII$_{Rx}$ Produced Statistically Significant Reductions of Triglycerides, ApoC-III and ApoC-III Associated VLDL in a Phase 2 Study in Patients With High Triglyceride Levels Treated With Stable Doses of Fibrates. Mean % Changes From Baseline at Primary Endpoint.

	Placebo + Fibrate (n=8)	ISIS-APOCIII$_{Rx}$ 200 mg + Fibrate (n=8)	ISIS-APOCIII$_{Rx}$ 300 mg + Fibrate (n=10)
ApoC-III	-2.2%	-59.4% (p<0.0001)	-70% (p<0.0001)
Triglycerides *[# patients achieving triglyceride level <150 mg/dL]*	-7.7% [0/8]	-49.7% (p=0.03) [5/8]	-63.9% (p=0.003) [7/10]
ApoC-III VLDL	+8.4%	-65.9% (p=0.0006)	-77.4% (p=0.0003)
HDL-C	+5.9%	+47.4% (p=0.02)	+51.8% (p=0.008)

P value = vs. placebo + fibrate.

After 13 weeks of dosing, robust and prolonged, statistically significant mean percent reductions from baseline in apoC-III, triglycerides and VLDL-associated apoC-III particles were observed in both dose cohorts. Furthermore, patients treated with ISIS-APOCIII$_{Rx}$ demonstrated a rapid, prolonged and statistically significant mean percent increase from baseline in HDL-C in both dose cohorts with no statistically significant increase in low-density lipoprotein cholesterol (LDL-C) or non-HDL-C. The effects of ISIS-APOCIII$_{Rx}$ observed on these lipid parameters were in addition to those achieved with each patient's existing therapeutic regimen of fibrates.

"Patients with very high levels of triglycerides are at significant risk for cardiovascular disease, diabetes, pancreatitis and other complications. For these patients, there are very limited treatment options. Fibrates have been shown to reduce triglycerides; however fibrate therapy is not always effective nor widely used by these patients," said Daniel Gaudet, M.D., Ph.D., from the department of medicine, University of Montreal and scientific director, Genome Quebec Biobank Technology Center. "The data presented today on ISIS-APOCIII$_{Rx}$ are very encouraging because they show that ISIS-APOCIII$_{Rx}$ is additive to fibrates and are consistent with Isis' previous Phase 2 data in patients with moderately elevated triglycerides and type 2 diabetes. In both studies, rapid, robust reductions in apoC-III and triglycerides were observed. The positive effect of ISIS-APOCIII$_{Rx}$ on other key lipid parameters demonstrates the potential for ISIS-APOCIII$_{Rx}$ to provide therapeutic benefit to patients with very high triglycerides."

In this study, 26 patients received either 200 mg or 300 mg dose of ISIS-APOCIII$_{Rx}$, or placebo via weekly subcutaneous injections. All patients were on stable doses of fibrates with average baseline levels of fasting triglycerides between 282 mg/dL and 457 mg/dL. The three groups of patients were reasonably well balanced in baseline characteristic.

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 and consisted of mild erythema that typically resolved within one to two days. There were no flu-like symptoms, no 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. There was one patient who, four days after treatment, experienced a transient episode of a rash, low-grade fever, chills and headache, which resolved completely. This event was reported by the investigator as related to treatment, and classified as a serum sickness-like reaction (a serious AE). Subsequent detailed investigations demonstrated that it was not serum sickness.

"We are very encouraged by the two sets of positive data we have reported this summer demonstrating that treatment with ISIS-APOCIII$_{Rx}$ produced highly statistically significant and clinically meaningful reductions in apoC-III and triglycerides, and increases in HDL-C in patients with high triglycerides. 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 broad therapeutic profile in addition to triglyceride lowering for patients with severely high triglycerides. We are also pleased with the data reported today. They demonstrate that ISIS-APOCIII$_{Rx}$ is additive to fibrates with robust reductions of apoC-III and triglycerides," said Richard Geary, Ph.D., senior vice president of development at Isis. "We look forward to sharing

the results from our ongoing Phase 2 study evaluating ISIS-APOCIII$_{Rx}$ as a monotherapy in patients with severely high triglycerides. In this study, we hope to show that treatment with ISIS-APOCIII$_{Rx}$ in patients with severely high triglycerides also produces significant effects on apoC-III, triglycerides and HDL-C. Following completion of the Phase 2 program, we plan to discuss our Phase 3 plans with regulators and move rapidly into a Phase 3 program next year in patients with severely high triglycerides (greater than 880 mg/dL)."

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 8:30 a.m. Eastern Time today, July 22, 2013 , Isis will conduct a live webcast and slide presentation conference call to discuss the positive Phase 2 data. 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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