Isis Reports Final Phase 2 Data on ISIS-APOCIII Rx in Patients With Familial Chylomicronemia

May 2, 2014

Significant reductions of more than 1,500 mg/dL in triglycerides observed
Significant reductions in chylomicrons observed

CARLSBAD, Calif., May 2, 2014 /PRNewswire/ -- Isis Pharmaceuticals, Inc. (NASDAQ: ISIS) announced the final data from its Phase 2 study of ISIS-APOCIII$_{Rx}$ as a monotherapy in patients with familial chylomicronemia syndrome, or FCS. In this open-label study, three patients with FCS treated with ISIS-APOCIII$_{Rx}$ achieved substantial reductions in triglycerides with all three patients achieving a triglyceride level below 500 mg/dL, which substantially reduces the risk of an acute pancreatitis event. In addition, significant reductions in chylomicrons were observed that correlated with reductions in triglyceride levels. These data were presented today by Dr. Daniel Gaudet at the National Lipid Association clinical lipid update meeting in Orlando, Florida.

"Familial chylomicronemia syndrome is a rare and very serious genetic disorder that is estimated to affect 3,000 to 5,000 patients worldwide. FCS patients are characterized by their extremely high levels of triglycerides, often higher than 2,000 mg/dL. These patients accumulate chylomicrons, which are derived from dietary intake and are the largest of the triglyceride-rich particles. FCS patients are difficult to treat because, due to their genetic defect, they are unable to clear triglyceride particles which build up in their blood. As such, a drug is needed that can help effectively clear chylomicrons from the blood, thereby reducing triglyceride levels in 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. "Although these data are in a small number of patients, the correlation between chylomicron-triglyceride and total triglyceride reduction suggests that ISIS-APOCIII$_{Rx}$ is able to significantly reduce these large triglyceride-rich particles from the blood. I am extremely encouraged about the therapeutic potential for ISIS-APOCIII$_{Rx}$ in patients with extremely high triglycerides, especially for FCS patients who have very limited therapeutic options."

The Phase 2 open-label cohort was designed to assess the safety and activity of ISIS-APOCIII$_{Rx}$ in patients with extremely high triglyceride levels and a genetic confirmation of FCS. The data reported today are the final data from three FCS patients who all had baseline triglyceride levels greater than 1,400 mg/dL and completed 13 weeks of treatment with 300 mg of ISIS-APOCIII$_{Rx}$. Isis reported an interim analysis of these data in September 2013. In this study, all three patients treated with ISIS-APOCIII$_{Rx}$ achieved substantial reductions in total triglyceride levels with a mean reduction of 69 percent that correlated with a comparable reduction of 69 percent in chylomicron-triglycerides. In addition, these patients experienced positive effects on other lipid parameters, including a mean reduction of 81 percent in apoC-III, a mean reduction of 81 percent in apoC-III-associated VLDL-C, and a mean increase of 78 percent in HDL-C. Because FCS is an extremely rare genetic disorder affecting one to two people per million, clinical trials in this disease are generally quite small.

ISIS-APOCIII$_{Rx}$ was well tolerated in the study. The most common adverse event was injection site reactions, which were 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, no clinically meaningful changes in other laboratory values and no treatment-related serious adverse events.

"Our initial focus is to bring ISIS-APOCIII$_{Rx}$ to the market for patients with FCS. These are patients who cannot reduce their triglycerides to safe levels with currently available medicines. We are extremely pleased with the performance of ISIS-APOCIII$_{Rx}$ to date. We believe that the significant unmet medical need for an effective triglyceride-lowering drug for patients with FCS and the robust, consistent effects we observe with ISIS-APOCIII$_{Rx}$ should enable us to rapidly move forward," said Richard Geary, Ph.D., senior vice president of development at Isis. "We look forward to initiating a Phase 3 program for ISIS-APOCIII$_{Rx}$ this year."

FCS is a rare genetic disorder that affects approximately one to two out of a million people. The most common genetic cause of FCS is a defect in the lipoprotein lipase (LPL) gene, which results in extremely low levels of LPL activity and a significant reduction in the breakdown of triglycerides from the blood. In the study reported today, all three patients were homozygotes for null LPL gene mutations resulting in undetectable LPL activity.

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 protein 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. Humans with elevated levels of apoC-III have high triglycerides 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. Humans with elevated levels of triglycerides are at risk of many serious health conditions, including pancreatitis, which can be life-threatening and require hospitalization.

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 32 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' 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 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, 2013, 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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