



Isis Pharmaceuticals Reports Positive Phase 1 Data Demonstrating ISIS-APO(a) Rx Produces Significant Reductions in Lp(a) Levels

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CARLSBAD, Calif., Nov. 16, 2013 /PRNewswire/ -- Isis Pharmaceuticals, Inc. (NASDAQ: ISIS) announced today positive results from a Phase 1 study with ISIS-APO(a)_{Rx}. These data were presented by Dr. Sotirios Tsimikas at the Vascular Biology Working Group global chapter meeting occurring concurrently with the American Heart Association (AHA) in Dallas, Texas. These data will also be presented at the AHA on Sunday, November 17 at 3:00 p.m. Central Time in the poster session titled 'Mechanisms and Regulation of Hepatic Lipid Metabolism.' In this study, healthy volunteers treated with ISIS-APO(a)_{Rx} achieved dose-dependent reductions of up to 95 percent in lipoprotein(a), or Lp(a), an independent risk factor for coronary heart disease.

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"Patients with elevated levels of Lp(a) have an increased risk of cardiovascular disease and there is evidence that elevated Lp(a) levels may contribute directly to heart attacks. Because elevated Lp(a) is principally a genetically determined condition that is not responsive to lifestyle changes, patients are unable to adequately control their Lp(a) levels through diet or increased physical activity. Although Lp(a) can be measured during a routine lipid blood panel, the lack of drugs that effectively lower Lp(a) have made treating patients with high Lp(a) levels difficult," said Sotirios Tsimikas, M.D., professor of medicine and director of vascular medicine at the University of California San Diego. "By inhibiting the production of apolipoprotein(a), ISIS-APO(a)_{Rx} is designed to reduce the levels of Lp(a), thereby offering a unique and specific approach to treating patients who have high cardiovascular risk due to high Lp(a) levels."

The Phase 1 study of ISIS-APO(a)_{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-APO(a)_{Rx}. ISIS-APO(a)_{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, 200 mg and 300 mg for the multiple dose. After only 3 weeks of dosing, subjects in the 100, 200 and 300 mg multiple-dose cohorts displayed a mean reduction of Lp(a) of 36, 62 and 82 percent, respectively, from baseline. The incoming range of Lp(a) in the study ranged from 10 mg/dL to 98 mg/dL. ISIS-APO(a)_{Rx} reduction of Lp(a) was independent of the baseline Lp(a) measurement. In addition to Lp(a) activity, subjects treated with 300 mg of ISIS-APO(a)_{Rx} also experienced an up to 59 percent reduction in oxidized phospholipids, lipids that play an important role in proinflammatory and proatherogenic processes believed to be associated with Lp(a). In this study, ISIS-APO(a)_{Rx} demonstrated a good safety profile and was generally well tolerated.

"We are very encouraged with these early data demonstrating that ISIS-APO(a)_{Rx} can significantly lower Lp(a) in a dose-dependent manner in these subjects. We are also encouraged by the associated reduction in oxidized phospholipids, which suggest that ISIS-APO(a)_{Rx} has the potential to provide benefit beyond Lp(a) lowering," said Walter Singleton, M.D., vice president of development and chief medical officer at Isis. "The safety and tolerability observed in our Phase 1 study also support our plan to begin a Phase 2 program on ISIS-APO(a)_{Rx} next year that will evaluate ISIS-APO(a)_{Rx} in patients with existing cardiovascular disease and high Lp(a) levels. Individuals with high Lp(a) levels are at increased risk for cardiovascular events and need to substantially reduce their Lp(a). We look forward to getting this program underway."

"Patients with high Lp(a) levels are at significant cardiovascular risk. Unfortunately for these patients, current lipid-lowering drugs, such as statins, are unable to lower Lp(a) to recommended safe levels. As such, new treatment approaches are needed. As a patient with high Lp(a) and the president and founder of the Lipoprotein(a) Foundation, I am gratified with the increased emphasis in the cardiovascular community on Lp(a) and for the work that is being done on developing focused, targeted approaches to lowering Lp(a)," said Sandra Revill Tremulis, president and founder of the Lipoprotein(a) Foundation. "I am encouraged by the Phase 1 data presented today on ISIS-APO(a)_{Rx} and hopeful that this approach to lowering Lp(a) could, for the first time, offer patients an effective, direct option to reducing their Lp(a)."

ISIS-APO(a)_{Rx} is a wholly owned antisense drug targeting apolipoprotein(a) for the treatment of atherosclerosis. Apolipoprotein(a) contributes to the formation of plaque in arteries through its attachment to an LDL-C particle in a complex called Lp(a). High levels of Lp(a) are associated with an increased risk of atherosclerosis, coronary heart disease, heart attack and stroke. While statins and other lipid-lowering drugs have a modest effect on lowering Lp(a), patients with elevated Lp(a) are unable to reach recommended safe Lp(a) levels. ISIS-APO(a)_{Rx} is designed to reduce Lp(a) by inhibiting the production of apolipoprotein(a). Isis plans to develop ISIS-APO(a)_{Rx} to treat patients with high Lp(a) levels who are at high risk of experiencing cardiovascular events. ISIS-APO(a)_{Rx} is part of Isis' strategy to create a cardiovascular disease franchise comprised of drugs that target all the key

components of cardiovascular disease, including various atherogenic lipids, inflammation and thrombosis.

ABOUT Lp(a)

Lp(a) is considered an independent risk factor for cardiovascular disease due to its association with an increased risk of coronary heart disease and atherosclerotic plaque formation. Lp(a) is a lipoprotein particle that is assembled in the liver that consists of an LDL-C-like particle and apolipoprotein(a). Lp(a) levels in blood can vary greatly between individuals due primarily to genetic variations in the gene that encodes for apolipoprotein(a). As a result, Lp(a) levels are genetically determined and remain constant throughout the life of the individual. Diet and lifestyle changes have little impact on Lp(a) levels and current therapies are not able to adequately reduce elevated levels of Lp(a) to acceptable levels in patients who have severely elevated Lp(a). As a general guideline for ideal Lp(a) levels, the European Atherosclerosis Society recommends that Lp(a) levels be less than or equal to 50 mg/dL.

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 31 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 for the treatment of patients with HoFH. 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, activity, therapeutic potential and safety of ISIS-APO(a)_{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, 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.

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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