

Isis Publishes Data Demonstrating Antisense Targeting of ApoC-III Significantly Reduces ApoC-III and Triglycerides

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Research Shows Antisense Inhibition of ApoC-III and Triglycerides in Multiple Species Including Humans

CARLSBAD, Calif., April 1, 2013 /PRNewswire/ -- Isis Pharmaceuticals, Inc. (NASDAQ: ISIS) announced today the publication of new data in the journal *Circulation Research* [[doi:10.1161/CIRCRESAHA.111.300367](https://doi.org/10.1161/CIRCRESAHA.111.300367)] demonstrating that antisense targeting of apolipoprotein C-III (apoC-III) resulted in significant reductions in apoC-III and triglycerides, each an independent risk factor for cardiovascular disease. Hypertriglyceridemia is a serious medical condition associated with premature coronary artery disease and an increased risk for pancreatitis. Isis is developing its antisense apoC-III inhibitor, ISIS-APOCIII_{Rx}, for the treatment of patients with severe hypertriglyceridemia and plans to report top-line data in the middle of this year.

"Patients with high triglycerides and high apoC-III levels are at significant risk of developing cardiovascular disease, metabolic syndrome, diabetes and pancreatitis. Despite currently available triglyceride-lowering agents, many patients cannot reduce their triglycerides to acceptable levels. Because apoC-III is a key regulator of triglyceride clearance from the blood and itself is an independent risk factor for cardiovascular disease, lowering both apoC-III and triglycerides could provide significant therapeutic benefit," said Richard Geary, Ph.D., senior vice president of development at Isis. "In this paper, we report consistent activity of antisense inhibition of apoC-III to lower both apoC-III and triglycerides in multiple rodent models of dyslipidemia, in non-human primates and in man. These data support the potential therapeutic benefit a selective apoC-III inhibitor could offer patients with hypertriglyceridemia and elevated apoC-III. Following the completion of the Phase 2 study, we plan to move rapidly into a Phase 3 study in the most severe patients with triglyceride levels greater than 880 mg/dL who are unable to reach acceptable triglyceride levels with currently available treatments."

In the published data, treatment with an antisense compound targeting apoC-III produced a variety of potential cardio-protective effects including significant dose-dependent reductions of apoC-III and triglycerides in all models and species, including man. In addition, treatment with an antisense compound targeting apoC-III resulted in enhanced triglyceride clearance from blood following a high-fat meal, reduction of VLDL particles and a slight increase in HDL-C levels. In all models and in the Phase 1 study, antisense inhibition of apoC-III was well tolerated. These data were consistent across multiple preclinical models and species and in a Phase 1 study in healthy volunteers demonstrating that Isis' antisense technology was able to produce predictable and consistent responses among different animal models that translate into corresponding activity in man. In the Phase 1 study, treatment with ISIS-APOCIII_{Rx} was well tolerated and produced rapid, dose-dependent median reductions of up to 44 percent in plasma triglycerides and up to 78 percent in apoC-III protein, with two out of the three subjects in the highest dose group achieving undetectable levels of apoC-III.

ABOUT ISIS-APOCIII_{Rx}

ISIS-APOCIII_{Rx} inhibits the production of apoC-III, a traditionally 'undruggable' target that inhibits the clearance of triglycerides from the blood. People who do not produce apoC-III have lower levels of triglycerides and lower instances of cardiovascular disease. ApoC-III is elevated in patients with dyslipidemia, or an abnormal concentration of lipids in the blood, and is frequently associated with multiple metabolic abnormalities, such as insulin resistance and/or metabolic syndrome. In human population studies, lower levels of apoC-III and triglycerides correlated with a lower rate of cardiovascular events.

ABOUT HYPERTRIGLYCERIDEMIA

Hypertriglyceridemia can be caused by genetic defects, diet, obesity and uncontrolled diabetes and can lead to serious health problems, including cardiovascular disease and pancreatitis. Triglycerides are an important measure of heart health and are routinely measured along with LDL-cholesterol and HDL-cholesterol. Triglyceride levels of less than 150 mg/dL are considered within a normal range, and the American Heart Association recommends that a triglyceride level of less than 100 mg/dL is optimal. Triglyceride levels of greater than 500 mg/dL are considered very high and levels greater than 1,000 mg/dL are considered to be severely high. In these patients, diet and exercise have limited therapeutic benefit. Patients with severely high triglycerides are at a higher risk of developing pancreatitis, a painful and sometimes fatal disease that requires hospitalization and close monitoring. Based on prevalence data, Isis estimates there are greater than 200,000 patients with severely high triglycerides in the United States and Europe despite currently available therapies.

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™, 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 for drugs for cardiovascular diseases, and the development activities, therapeutic and commercial 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, 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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