

Isis Pharmaceuticals' Oral Formulation of ISIS 301012 Reduces Cholesterol in Humans

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Positive Results Broaden Therapeutic Potential of Second-generation Antisense Drugs

CARLSBAD, Calif., Feb. 7 /PRNewswire-FirstCall/ -- Isis Pharmaceuticals, Inc. (Nasdaq: ISIS) announced today that it has completed a Phase I study of an oral formulation of ISIS 301012 and has demonstrated oral bioavailability and pharmacological activity of the drug in this study. ISIS 301012, a second-generation antisense drug, targets apoB-100, a protein critical to the synthesis and transport of the "bad" cholesterol involved in heart disease -- low density lipoprotein cholesterol (LDL-C) and very low density lipoprotein (VLDL). One month of dosing in healthy volunteers with an oral capsule formulation of ISIS 301012 resulted in an average of 6% bioavailability and a statistically significant average reduction of approximately 13% in apoB-100, and commensurate reductions in LDL-C as compared to placebo. Lowering cholesterol levels is a key component in the prevention and management of cardiovascular disease.

In the trial, healthy volunteers received either oral ISIS 301012 or placebo over a one month period. The formulation in the oral capsules used in the study contained a penetration enhancer that was previously shown to increase the oral bioavailability of second-generation antisense drugs. Treatment with ISIS 301012 resulted in a statistically significant average reduction in apoB-100 of approximately 13% as compared to placebo ($p=0.005$). Reductions in LDL-C were also statistically significant ($p=0.001$). Pharmacological effects were correlated with maximum plasma concentration, with healthy volunteers who absorbed more drug demonstrating greater pharmacological effects. The oral form of ISIS 301012 was generally well tolerated. Only mild intermittent gastrointestinal symptoms were observed. No healthy volunteers withdrew from the study because of side-effects.

"We are continuing to make progress in the oral delivery of second-generation antisense drugs," said Mark Wedel, MD, JD, Senior Vice President of Development and Chief Medical Officer at Isis Pharmaceuticals. "Achieving oral bioavailability and statistically significant pharmacological activity in humans with oral ISIS 301012 is a significant step for the technology. We intend to report these data at an appropriate scientific meeting later this year."

"Importantly, the formulation used for oral ISIS 301012 can be used with all of our second-generation antisense drugs. With the encouragement of these data, we will continue to work toward developing a commercially attractive oral form of our second-generation antisense drugs," Dr. Wedel added. "With drugs in development for metabolic, cardiovascular and inflammatory diseases, and cancer, oral antisense drugs would offer patients and physicians increased convenience, which may enhance the commercial profile of our drugs. Clearly, the conclusion of this study represents an important step toward achieving that long-term goal."

ABOUT CHOLESTEROL AND CARDIOVASCULAR DISEASE

According to the American Heart Association, an estimated 106.9 million American adults have total blood cholesterol values of 200 mg/dL and higher, and of these about 37.7 million American adults have levels of 240 or above. In adults, total cholesterol levels of 240 mg/dL or higher are considered "high risk". Levels from 200 to 239 mg/dL are considered "borderline-high risk". Low-density lipoprotein, or LDL, known as the "bad" cholesterol, can clog arteries, increasing the risk of heart attack and stroke.

According to the World Health Organization (WHO), heart disease and stroke kill 17 million people a year, which is almost one-third of all deaths globally. By 2020, the WHO projects that heart disease and stroke will become the leading cause of both death and disability worldwide, with the number of fatalities projected to increase to over 20 million a year and by 2030 to over 24 million a year.

ABOUT ISIS PHARMACEUTICALS, INC.

Isis is exploiting its expertise in RNA to discover and develop novel drugs for its product pipeline and for its partners. The Company has successfully commercialized the world's first antisense drug and has 12 antisense drugs in development to treat metabolic, cardiovascular, ocular and inflammatory diseases, and cancer. In its Ibis division, Isis is developing and commercializing the TIGER biosensor system, a revolutionary system to identify infectious organisms. As an innovator in RNA-based drug discovery and development, Isis is the owner or exclusive licensee of approximately 1,500 issued patents worldwide. Additional information about Isis is available at www.isispharm.com.

This press release includes forward-looking statements regarding the development and therapeutic potential of oral ISIS 301012 to lower high cholesterol. Any statement describing Isis' goals, expectations, intentions or beliefs is a forward-looking statement and should be considered an at-risk statement, including those statements that are described as Isis' goals. 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 products. 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, 2004, and its quarterly report on Form 10-Q for the quarter ended September 30, 2005, 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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CONTACT: Navjot Rai, Investor Relations & Corporate Communications of Isis Pharmaceuticals, Inc., +1-760-603-2331

Web site: <http://www.isispharm.com>

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