Targeting MicroRNAs With Antisense Drugs Produces Compelling Preclinical Data in Animal Studies

June 12, 2006

Antisense Inhibition of miR-122 Significantly Lowers Cholesterol and Triglycerides in Diabetic Mice

CARLSBAD, Calif., June 12 /PRNewswire-FirstCall/ -- Isis Pharmaceuticals, Inc. (Nasdaq: ISIS) today announced results from preclinical studies demonstrating that inhibition of miR-122, a liver-specific microRNA (miRNA), by a second-generation antisense drug significantly improves high cholesterol, fatty liver, and liver function without affecting blood glucose levels in diabetic mouse models. MiRNAs are a recently discovered class of natural antisense RNAs that are important in the regulation of cellular functions. These data demonstrate that antisense inhibition is a powerful technique to regulate the function of miRNAs and suggest that miR-122 may be an attractive therapeutic target for cardiovascular and metabolic diseases. Dr. Sanjay Bhanot, M.D., Ph.D., Vice President of Metabolic Disease Research and Development at Isis Pharmaceuticals presented these data today at the American Diabetes Association's (ADA) 66th Annual Scientific Sessions in Washington D.C.

"Inhibiting miRNAs using antisense drugs has the potential to lead to exciting new therapeutics. The specificity and efficiency of antisense technology allow us to make great progress in converting this opportunity into new therapeutics, just as they do with mechanisms such as RNAi and alternative splicing," Dr. Bhanot said. "Demonstrating pharmacological activity in vivo using well validated antisense chemistry to inhibit miRNAs is a testament to the utility of our antisense technology and our leadership role in the field. Our drugs are administered as simple solutions in saline and do not require any complex formulation or conjugation strategies."

Treatment of diabetic mice with an antisense drug targeted to miR-122 for four and a half weeks resulted in a 30% reduction in cholesterol and a 43% reduction in liver triglyceride levels. Reductions in fatty liver were also observed along with a 30% reduction in ALT levels and a 54% reduction in AST levels. ALT and AST are plasma markers of liver function. The treatment was well tolerated and did not affect body weight or food intake.

"We believe that miR-122 is an attractive therapeutic target for cardiovascular and metabolic diseases, since antisense inhibition improved cholesterol levels, liver function and fatty liver," Dr. Bhanot said. "Improvement in these risk factors is an important part of disease management in patients with cardiovascular and metabolic diseases."

These data presented at the ADA add to previously published data in the February 2006 issue of Cell Metabolism, demonstrating that inhibition of miR-122 in normal and high fat-fed mice resulted in a significant improvement in several metabolic and cardiovascular risk factors as evidenced by reduced plasma cholesterol levels, increased hepatic fatty-acid oxidation, decreased hepatic fatty-acid and cholesterol synthesis rates and reduced fat in the liver (steatosis).

ABOUT MicroRNA (miRNA) AND ANTISENSE

MiRNA molecules are a recently discovered class of small RNA molecules that occur naturally within all mammalian cells and are critical in cell function in humans, animals, and plants. There are at least 330 confirmed miRNA genes in the human genome and there are many other predicted miRNAs that remain yet to be confirmed. MiRNAs are believed to regulate at least one-third of genes in the human genome and are also likely to play significant roles in the manifestation of many disease states, including cancer and many metabolic and infectious diseases.

Antisense drugs bind to complementary RNA sequences, such as miRNAs, inhibiting the function of miRNAs. Research recently conducted by Isis has shown that antisense inhibition is a powerful technique to regulate the function of miRNAs.

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 15 drugs in development. Isis' drug development programs are aimed at treating cardiovascular, metabolic and inflammatory diseases. Isis' partners are focused in disease areas such as inflammatory, ocular, viral and neurodegenerative diseases, and cancer. In its Ibis division, Isis is developing and commercializing the IBIS 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 http://www.isispharm.com.

This press release includes forward-looking statements regarding the role of microRNA in metabolic disease and the therapeutic

and commercial potential of Isis' technologies and products in development. 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, 2005, and its quarterly report on Form 10-Q for the quarter ended March 31, 2006, which are on file with the SEC. Copies of these and other documents are available from the Company.

SOURCE Isis Pharmaceuticals, Inc.
06/12/2006

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