Multiple Second-Generation Antisense Drugs Show Potential as New Treatments for Diabetes and Metabolic Disease

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Isis Pharmaceuticals and Partners Present Preclinical Research From Broad Antisense Drug Discovery Programs Targeting Metabolic Disease at ADA

CARLSBAD, Calif., June 13, 2005 /PRNewswire-FirstCall via COMTEX/ -- Isis Pharmaceuticals, Inc. (Nasdaq: ISIS) announced today results from fourteen preclinical studies demonstrating potent, selective antisense inhibitors of gene targets, directly associated with therapeutic potential in a variety of preclinical models of metabolic diseases, including diabetes, non-alcoholic fatty liver disease (NASH) and metabolic syndrome. Findings from the studies were presented by Isis and several collaborators this week during the American Diabetes Association's (ADA) 65th Scientific Sessions in San Diego.

"Data presented this week demonstrate the strong potential of second-generation antisense drugs for metabolic disease. The data show the specificity, efficiency and versatility of second-generation antisense oligonucleotides to rapidly validate novel targets in vivo. This unique advantage of antisense allows us to select the best targets and drugs for drug development. Furthermore, since several of these molecular targets (such as phosphatases and transcription factors) are difficult to inhibit selectively with small molecules, we have a unique drug development opportunity to advance antisense drugs as innovative treatments for metabolic disorders," said C. Frank Bennett, Ph.D., Vice President, Antisense Research at Isis Pharmaceuticals.

This sentiment was echoed by two internationally recognized diabetes experts and Isis collaborators, Dr. Gerald Shulman from Yale University and Dr. Luciano Rossetti from the Albert Einstein College of Medicine, Bronx, New York. "Using Isis' potent antisense inhibitors, we were able to investigate the role of several molecular targets in animal models of diabetes and we identified a critical target that results in the inability of insulin to inhibit excessive glucose release by the liver in obese and insulin resistant rodents," said Dr. Luciano Rossetti, M.D., Professor of Medicine and Molecular Pharmacology and Director, Diabetes Research Center, Albert Einstein College of Medicine, Bronx, NY. "The Isis antisense inhibitors reduced the expression of this gene in the liver and completely restored normal hepatic insulin action."

"Over the past year, we have evaluated over a dozen of Isis' second-generation antisense oligonucleotides designed to target a variety of genes. Through these efforts we have identified several exciting targets, the inhibition of which prevents the development of fatty liver and fat induced insulin-resistance," said Dr. Gerald Shulman, M.D., Ph.D., Professor of Internal Medicine and Cellular and Molecular Physiology, Yale University School of Medicine. "Antisense inhibitors against these targets have great therapeutic potential for type 2 diabetes, obesity and fatty liver disease."

Key Presentations at the ADA:

Targeting Enzymes Involved in Intermediary Lipid Metabolism

In several presentations, optimized antisense inhibitors against key genes involved in intermediary lipid metabolism were evaluated in obese and diabetic animals that had a fatty liver and were insulin resistant. Inhibition of several genes, such as stearoyl-CoA desaturase 1 (SCD-1), acetyl-CoA carboxylases 1 (ACC1) and diacylglycerol acyltransferase 2 (DGAT2) resulted in decreased fat synthesis, increased fat oxidation (burning) and a clearing of fat in the liver. Since antisense oligonucleotides cause specific reduction of these enzymes in the liver and fat, side effects associated with antagonism of these enzymes in other key tissues such as the pancreas and brain were not observed. DGAT2, an enzyme involved in fat synthesis, emerged as one of the most promising targets for future antisense drug development.

Discovery of Novel Phosphatases as Drug Targets for Type 2 Diabetes

Using second-generation antisense oligonucleotides, Isis scientists evaluated more than twenty protein tyrosine phosphatases (PTPases) in animal models of diabetes and obesity. PTPases negatively regulate various cell signaling pathways, including pathways that mediate insulin action. However, traditional small molecule approaches to inhibit phosphatase targets are severely limited due to their lack of specificity. In contrast, specific targeting of phosphatases with antisense technology is a very effective approach to inhibit these targets very selectively. Data were presented demonstrating marked glucose lowering effects of specific antisense oligonucleotides that reduced hepatic expression of several novel phosphatases. Further, reduction of the expression of some of these phosphatases in the liver improved signaling via the insulin receptor and important post-receptor insulin-signaling enzymes. These phosphatases are distinct from protein tyrosine phosphatase-1 (PTP-1B), for which Isis has an antisense drug in Phase 2 clinical trials.

Additional presentations demonstrated glucose lowering effects and improvements in insulin sensitivity in animal models after reduction of hepatic expression of two transcription factors, Foxo1 (also known as Forkhead) and Carbohydrate Response Element Binding Protein (ChREBP), with antisense drugs. These exciting targets are also difficult to selectively inhibit with small molecules. The presentations further exemplify the versatility of the antisense approach for drug discovery and development.

Finally, Isis scientists presented data showing robust glucose lowering effects after reduction of the expression of renal sodium glucose transporter 2 (SGLT2) with an antisense drug optimized to target the kidney. The drug was extremely potent in inhibiting the target and caused greater than 80% reduction in SGLT2 expression at a dose less than 2 mg/kg/week, demonstrating about a 30-fold increase in potency compared to the standard phosphorothioate ASOs. This decrease in SGLT2 expression was accompanied by significant glucose lowering in several severely diabetic animal models including ob/ob and db/db mice.

ABOUT ISIS PHARMACEUTICALS, INC.

Isis Pharmaceuticals, Inc. 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 11 antisense drugs in development to treat metabolic, cardiovascular and inflammatory diseases, and cancer. In its Ibis division, Isis is developing and commercializing the TIGER biosensor system, a system that has the potential to revolutionize the identification of infectious organisms. As an innovator in RNA-based drug discovery and development, Isis is the owner or exclusive licensee of more than 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 development, therapeutic potential and safety of Isis’ antisense drugs and in the treatment of metabolic diseases. Any statement describing our 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. Our forward-looking statements also involve assumptions that, if they never materialize or prove correct, could cause our results to differ materially from those expressed or implied by such forward-looking statements. Although our forward-looking statements reflect the good faith judgment of our management, these statements are based only on facts and factors currently known by us. 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 on Form 10-K for the year ended December 31, 2004, and quarterly report on Form 10-Q for the quarter ended March 31, 2005, which are on file with the SEC. Copies of these and other documents are available from the Company.

SOURCE Isis Pharmaceuticals, Inc.

Claudine Prowsse, PhD of Isis Pharmaceuticals, Inc., +1-760-603-2331

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