Second-Generation Antisense Inhibitors Provide New Insights Into Metabolic Disease and Potential Treatments

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Isis and Collaborators Present Data From 4 Preclinical Studies at American Diabetes Association Annual Meeting

CARLSBAD, Calif., June 9 /PRNewswire-FirstCall/ -- Isis Pharmaceuticals, Inc. (Nasdaq: ISIS) announced today results from preclinical studies demonstrating the utility of four second-generation antisense inhibitors in identifying new diabetes and related metabolic disease targets for drug discovery and as potential innovative treatments for these conditions. Findings from the studies were presented by Isis and several collaborators this week during the American Diabetes Association's (ADA) 64th Scientific Sessions in Orlando.

"Cumulative data presented this week show that second-generation antisense inhibitors have a distinct, unique role in identifying new treatments for metabolic diseases. With our inhibitors we can rapidly validate and invalidate drug targets in order to focus our and partners' development programs on the most worthwhile and valuable targets. Further, the same inhibitor used to validate a target can become a promising new drug," said C. Frank Bennett, Ph.D., Isis Vice President, Antisense Research. "In diabetes and obesity, antisense technology is breaking new ground by rapidly and efficiently discovering new targets and potential antisense drugs that address large commercial markets and major areas of unmet medical need, such as blood glucose regulation."

Key Presentations at the ADA Meeting:

* Oral Presentations:

  * Using its proprietary second-generation antisense inhibitors, Isis and a large pharmaceutical collaborator successfully inhibited glucose-6-phosphatase transport protein T1 (G6Pase T1) in ob/ob and db/db mouse models of diabetes. G6Pase T1 is an enzyme involved in increased glucose production by the liver. In the study, inhibition of this target resulted in a marked reduction in blood glucose levels and an approximately 80-85 percent reduction in G6Pase T1 mRNA expression in the liver. Notably, the marked decrease in blood glucose levels was achieved without producing many of the side effects often seen with global inhibition of the enzyme including hypoglycemia, kidney enlargement, neutropenia, hyperlipidemia or increased hepatic glycogen content.

  * In a second session, Isis scientists described the company's strategic approach of broadly exploiting various antisense mechanisms to develop therapeutics for metabolic disease. The most advanced product candidates are antisense inhibitors that work through the RNase H mechanism of action, including ISIS 113715, which is the industry's most advanced inhibitor of protein tyrosine phosphatase (PTP-1B) and currently in Phase 2 studies in patients with type 2 diabetes.

    PTP-1B is an enzyme that appears to reduce insulin's ability to regulate blood sugar levels. The inhibition of PTP-1B may allow the insulin receptors to stay active longer, allowing for more glucose uptake into cells and lowers levels in the blood stream. The successful inhibition of PTP-1B may allow for the administration of lower doses of insulin to diabetic patients while still maintaining satisfactory blood sugar levels.

    In the meeting, Isis researchers presented Phase 1 (please see company press release September 16, 2003) and preclinical data on ISIS 113715. Company scientists also presented progress in the

company's research program to develop inhibitors that work through the RNA interference (siRNA) mechanism of action.

* Poster Presentations:

  * In collaboration with the laboratory of Luciano Rossetti, M.D., Professor and Director, Albert Einstein College of Medicine, Diabetes Research and Training Center, the following two studies focused on using Isis' second-generation antisense inhibitors to identify or elucidate the role of two proteins in metabolic disease:

    * The first study evaluated the role of resistin in diet-induced liver insulin resistance using Isis' second-generation antisense inhibitors. Resistin is a hormone that is secreted by fat tissue and is thought to link excessive amounts of fat in tissues to insulin resistance. In the experiment, high-fat fed mice were treated with an optimized resistin antisense inhibitor for one week. After treatment with the antisense inhibitor the mice demonstrated normalized plasma resistin levels and a reversal in liver insulin resistance. These findings support the physiological role of resistin in the development of liver insulin resistance.

    * A second study used a second-generation antisense inhibitor as a tool to investigate the function of the insulin receptor protein in hepatic insulin action. The insulin receptor plays a key role in modulating and regulating glucose production, is decreased in metabolic diseases such as obesity and may contribute to higher-than-normal levels of insulin in the blood and to insulin resistance.

      To test this hypothesis, investigators treated mice with a high dose of an antisense inhibitor to the insulin receptor. Results from the study demonstrated that a 90 percent decrease in the insulin receptor in the liver for one week did not result in insulin resistance. From this study Dr. Rossetti's lab concluded that a more prolonged inhibition of the insulin receptor expression or complete inhibition of the target may be required for the stimulation of hepatic insulin resistance.

About Isis Pharmaceuticals' Metabolic Disease Program

Isis Pharmaceuticals' metabolic disease program has screened inhibitors for more than 70 gene targets that may be involved in diabetes or obesity in animal models of disease. Its most advanced product, ISIS 113715, is currently in Phase 2 clinical trials. ISIS 113715 targets the gene encoding for PTP-1B. The compound's antisense mechanism of action may offer new treatment options to patients who do not adequately respond to currently available therapies such as glitazones, sulfonylureas, and biguanides.

About Type 2 Diabetes

According to the American Diabetes Association, diabetes affects nearly 17 million people and type 2 diabetes constitutes 90 percent of those cases.

Isis Pharmaceuticals, Inc. is exploiting its expertise in RNA to discover and develop novel human therapeutic drugs for its pipeline and for its partners. The company has successfully commercialized the world's first antisense drug and has 11 antisense products in development to treat metabolic, cardiovascular, inflammatory and viral diseases and cancer. Through its Ibis Therapeutics® program, Isis is developing a biosensor to identify

infectious organisms, and discovering small molecule drugs that bind to RNA. As an innovator in RNA-based drug discovery and development, Isis is the owner or exclusive licensee of more than 1,300 issued patents worldwide. Additional information about Isis is available at www.isispharm.com.

This press release contains forward-looking statements about the potential of the Isis' metabolic disease program, the investigational compound ISIS 113715 for type 2 diabetes and the potential of Isis and its collaborators' drug discovery and development programs. 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' clinical goals. Such statements are subject to certain risks and uncertainties, particularly those inherent in the process of developing technology and systems used to identify infectious agents, in discovering and commercializing drugs that are safe and effective for use as human therapeutics and in the endeavor of building a business around such products and services. Actual results could differ materially from those discussed in this press release. As a result, you are cautioned not to rely on these forward-looking statements. These and other risks concerning Isis' research and development programs are described in additional detail in Isis' Annual Report on Form 10-K for the year ended December 31, 2003, and quarterly report on Form 10-Q for the quarter ended March 31, 2004, which are on file with the U.S. Securities and Exchange Commission. Copies of these and other documents are available from the company.

SOURCE Isis Pharmaceuticals, Inc.