ADA Conference Presentations Highlight Isis' Metabolic Disease Program Research Activities

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CHICAGO and CARLSBAD, Calif., June 24, 2007 /PRNewswire-FirstCall via COMTEX News Network/ -- Isis Pharmaceuticals, Inc. (Nasdaq: ISIS) announced today the presentation of five research studies demonstrating potent and selective antisense inhibition of multiple gene targets involved in metabolic disorders such as diabetes, obesity and dyslipidemia. The presentations made during the American Diabetes Association's (ADA) 67th Scientific Sessions in Chicago included studies in a variety of animal models ranging from mice to monkeys in which the effects of antisense drugs against a diverse set of targets were evaluated, including PTP-1B, SGLT2 and PKC-delta for diabetes, and JNK1 and mDIC for obesity. The highlights of each study along with information about each target are provided below.

The use of advanced and proprietary antisense chemistries has allowed Isis to rapidly evaluate many potential targets for treatment of complex diseases such as diabetes and obesity in well established animal models. To date, Isis has analyzed the effects of inhibiting over 120 distinct gene targets in animals, and this efficiency in the drug discovery process has resulted in a rich supply of promising drugs with which to populate its future pipeline.

"As shown by the presentations, our program is making excellent progress expanding our metabolic disease franchise in diabetes, and we are also advancing well toward our recently-defined goal of identifying novel anti- obesity agents," said C. Frank Bennett, Ph.D., Senior Vice President of Research, Isis Pharmaceuticals. "In our pipeline we have ISIS 113715, a novel insulin sensitizer targeting PTP-1B which may also promote weight loss. In addition, we have ISIS 325568, targeting glucagon receptor, which inhibits glucagon action in the liver and has additional potentially disease-modifying effects in the pancreas. And we have ISIS 377131, targeting glucocorticoid receptor selectively in liver and fat, which has multiple metabolic effects in addition to lowering glucose such as anti-obesity and lipid-lowering effects. Finally, we are evaluating drugs targeted to SGLT2 that act in the kidney to increase glucose excretion in urine. Thus we have created a pipeline of drugs that work in unique and complementary ways to potentially treat diabetes."

Summary of the ADA presentations (including two late-breaking abstracts):

Increased Circulating Total and High Molecular Weight Adiponectin (HMW) Concentrations and Improved Insulin Sensitivity After Treatment with an Antisense Oligonucleotide Targeting Protein Tyrosine Phosphatase-1B (PTP-1B) in Obese Insulin-Resistant Rhesus Monkeys (late-breaking abstract)

Authors: P. J. Havel*, M. M. Swarbrick*, K. L. Stanhope*, S. F. Murray, B. P. Monia, S. Bhanot; Isis Pharmaceuticals, Inc.; *University of California, Davis, CA

ISIS 113715 is an antisense drug that inhibits the production of protein tyrosine phosphatase-1B (PTP-1B), an enzyme that reduces the activity of the insulin receptor in response to insulin stimulation. ISIS 113715 is currently in Phase 2 development for type 2 diabetes, and in human and animal studies to date, the drug has demonstrated reductions in blood glucose levels without causing hypoglycemia, metabolic acidosis, weight gain or nausea. The current study demonstrated that the glucose lowering effects of ISIS 113715 may be mediated in part by an increase in a key fat-derived hormone, adiponectin. Five obese, insulin-resistant monkeys that were treated with ISIS 113715 for 4 weeks demonstrated improved insulin sensitivity and reduced fasting insulin levels. The monkeys also had increased levels of adiponectin, particularly the most potent form (HMW adiponectin), which is known to improve insulin sensitivity. Results from these studies suggest that ISIS 113715 improves insulin sensitivity in part by increasing the levels of circulating adiponectin.

Sanjay Bhanot, M.D., Ph.D., Vice President of Metabolic Diseases Research & Development, Isis Pharmaceuticals, commented, "These data extend our previous findings and demonstrate that just 4 weeks of treatment with ISIS 113715 completely normalized insulin resistance in obese monkeys, which underscores the important role of PTP-1B in mediating insulin resistance in primates. Another novel finding from this study was that one major mechanism by which ISIS 113715 likely mediates its insulin enhancing effects is by increasing adiponectin levels, particularly the most potent form of this hormone. Increases in adiponectin could mediate both the insulin sensitizing and anti-obesity effects that have been observed with ISIS 113715 in preclinical studies. We look forward to exploring this potential mechanism as we further the drug in Phase 2 development."

Short (12-nucleotide) 2nd Generation Antisense Oligonucleotides Selectively Inhibit SGLT2 Expression Across Multiple Species and are Bioavailable Following Intrajejunal Administration

Authors: E. V. Wancewicz, A. Siwkowski, B. Meibohm*, C. R. Yates*, M. Pearce, J. Matson, N. Y. K. Chew, C. E. Lillie, L. Tillman, G. Hung, R. S. Geary, S. Bhanot, B. P. Monia; Isis Pharmaceuticals, Inc.; *University of Tennessee Health Science Center, Memphis, TN

The sodium dependent glucose transporter type 2 (SGLT2) contributes to glucose re-absorption in the kidney. Decreasing SGLT2 function promotes glucose excretion to help reduce blood sugar levels, making it an attractive target for the treatment of diabetes. In the study presented at the ADA conference, the authors demonstrated in several animal species that antisense inhibitors of SGLT2 effectively reduced target mRNA levels, increased urinary glucose excretion and consequently lowered blood glucose levels without causing dangerously low levels of blood sugar known as hypoglycemia. The data reported included studies conducted in dogs and rats with treatment periods ranging from 6-20 weeks. In the ZDF diabetic rats, weekly treatment with a low dose (1.6 mg/kg/week) of the antisense inhibitor of SGLT2 produced a sustained and significant (>40%) decrease in fed plasma glucose levels and a HbA1c decrease of >4 percentage points compared to untreated or control treated groups. Collectively, the studies not only confirm SGLT2 as a good therapeutic target for diabetes, but also demonstrate that Isis' antisense SGLT2 inhibitors are highly potent and have significant potential for oral delivery. These compounds effectively and specifically inhibit the production of SGLT2 in the kidney tissue, without having any effect on related gene products such as SGLT1 and SGLT3.

"We think a drug that improves glucose excretion will be an exciting addition to our pipeline of diabetes drugs which act through distinct mechanisms," said Brett P. Monia, Ph.D., Vice President of Antisense Drug Discovery, Isis Pharmaceuticals. "This is the first kidney target that we have approached with our second-generation drugs, and we are certainly encouraged by what we have seen in the animal models. The high potency of our optimized antisense drugs targeted to SGLT2, coupled with the drugs' selectivity in inhibiting production of SGLT2 without affecting SGLT1 or SGLT3, makes a compelling case for the development of such molecules for the treatment of diabetes."

Acute Inhibition of Liver PKC-Delta Prevents Hepatic Insulin Resistance Caused by Short-Term Lipid Infusion (late-breaking abstract)

Authors: E. Park*, X. Guan*, B. Tse*, A. I. Oprescu*, I. G. Fantus*, S. Bhanot, R. McKay, A. Giacca; Isis Pharmaceuticals, Inc.; *University of Toronto, Toronto, Ontario, Canada

Protein kinase C-delta (PKC-delta) activity has been associated with certain types of liver insulin resistance, but whether it is a mediator of this problem has been difficult to determine because of the lack of selective inhibitors. These experiments were designed to determine whether PKC-delta plays a key role in free fatty acid (FFA)-induced insulin resistance that may contribute to diabetes. In this study the authors demonstrated that potent and specific antisense inhibition of PKC-delta in the liver led to reduced FFA-induced hepatic insulin resistance in rats without affecting insulin sensitivity. The results provide evidence for a contribution of PKC-delta in causing hepatic insulin resistance and point to the therapeutic potential of PKC-delta as a target to treat type 2 diabetes.

Reduction in JNK1 Expression Lowers Adiposity and Improves Insulin Sensitivity in Diet-Induced Obese Mice

Authors: S. F. Murray, L. M. Watts, S. Booten, J. Tokorcheck, B. P. Monia, S. Bhanot, X. X. Yu; Isis Pharmaceuticals, Inc.

A number of studies indicate that c-Jun N-terminal kinase 1 (JNK1) contributes to diet-induced obesity and insulin resistance. The authors have previously presented their observations that treatment of genetically obese mice with antisense inhibitors of JNK1 reduced body fat content and improved metabolic syndrome (insulin resistance and dyslipidemia). This study extends those observations to mice with diet-induced obesity. The mice were fed a high-fat diet and subsequently treated twice weekly for 6.5 weeks with an antisense inhibitor of JNK1 or a control compound. The JNK1 antisense drug did not affect food intake but reduced JNK1 mRNA in the appropriate tissues (liver and fat), and reduced body weight, reduced body fat content, and increased metabolic rate. Mechanistically, these effects were consistent with various secondary changes in gene expression triggered by reduced JNK1 levels. The results suggest that therapeutic inhibition of JNK1 in the tissues where antisense drugs naturally distribute could provide clinical benefit for obesity and metabolic syndrome.

Antisense Reduction of mDIC Expression Lowers Body Weight and Improves Insulin Sensitivity in ob/ob Mice

Authors: X. X. Yu, L. Watts, S. L. Booten, S. F. Murray, J. Tokorcheck, P. E. Scherer*, B. P. Monia, S. Bhanot; Isis Pharmaceuticals, Inc.; *University of Texas Southwestern Medical Center, Dallas, TX

Mitochondrial dicarboxylate carrier (mDIC) is an enzyme that is thought to be involved in obesity. In this study the authors demonstrated that genetically obese mice treated with an antisense inhibitor of mDIC experienced significantly reduced weight gain and body fat content without a significant impact on food consumption. Antisense treatment also improved hyperglycemia, glucose and insulin tolerance. The mice also showed reductions in liver fat accumulation, which correlated with increases in whole body metabolic rate and decreases in total triglyceride levels. These positive effects indicate that mDIC plays an important role in the body's metabolism and energy management and suggest a potential clinical benefit for mDIC-targeted antisense drugs in the treatment of obesity and metabolic syndrome.

"The data from JNK1 and mDIC antisense studies indicate that targeting peripheral tissues with our drugs can lead to significant effects not only on body fat content, but also on several other metabolic defects that often co-exist in obese patients," said C. Frank Bennett, Ph.D., Senior Vice President of Research, Isis Pharmaceuticals. "Importantly, these studies provide initial validation for our discovery approach of developing our compounds as anti-obesity drugs that have a peripheral mechanism of action but do not cross the blood-brain barrier, thereby minimizing the potential of central nervous system side-effects that are observed with several weight loss drugs on the market or in development. As we advance multiple drugs for the treatment of diabetes, we look forward to expanding our discovery effort in the area of obesity, which is a disease with high unmet medical need."

About Isis' Metabolic Disease Drugs in Development

ISIS 113715, targeting protein tyrosine phosphatase-1B (PTP-1B)

PTP-1B is responsible for turning off the activated insulin receptor, so by reducing levels of PTP-1B, ISIS 113715 enhances the activity of insulin. Because ISIS 113715 is an insulin sensitizer that acts by increasing the activity of the insulin receptor in response to insulin, Isis plans to develop this drug initially as an adjunct to insulin therapy in the diabetes treatment paradigm. PTP-1B has long been recognized as an attractive target for treatment of diabetes, but due to structural similarities among closely related proteins, it has been difficult to identify small molecule drugs with sufficient specificity to be safe. ISIS 113715 selectively inhibits the production only of PTP-1B, making it possible to reduce PTP-1B activity without having effects on closely related proteins that would likely lead to unwanted side effects. Isis has previously presented positive Phase 2 results in patients with newly-diagnosed type 2 diabetes treated with ISIS 113715 as a single agent, and it is currently conducting a combination study of ISIS 113715 in patients uncontrolled on other oral anti-diabetic drugs. Because the initial registration plan calls for using ISIS 113715 as an adjunct to insulin therapy, this study is evaluating it in combination with sulfonylureas. Sulfonylureas, which are commonly prescribed oral anti-diabetic drugs, increase insulin secretion in the body and therefore they offer the best approximation of a combination with insulin therapy in the milder disease setting appropriate for this first combination experience with ISIS 113715.

ISIS 325568, targeting glucagon receptor (GCGR)

Glucagon is a hormone that opposes the action of insulin and stimulates the liver to produce glucose. In type 2 diabetes, unopposed action of glucagon can lead to increased blood glucose levels. Reducing the expression of liver GCGR using antisense inhibitors is expected to reduce excessive liver glucose production and thereby lower blood glucose levels, resulting in improved glycemic control. In preclinical studies, antisense inhibitors of GCGR led to substantial improvements in glucose control and a concomitant reduction in the levels of blood triglycerides without producing hypoglycemia. In addition, treatment with ISIS 325568 led to an increase in circulating glucagon-like peptide, or GLP-1, which is a hormone that helps to preserve pancreatic function, thereby enhancing insulin secretion. These results suggest that ISIS 325568 has a dual mechanism that affects both the liver and pancreas and could demonstrate disease modifying effects. Isis plans to initiate Phase 1 clinical trials for ISIS 325568 in 2007.

ISIS 377131, targeting glucocorticoid receptor (GCCR)

Glucocorticoid hormones have a variety of effects throughout the body, including promotion of liver glucose production and fat storage. Although inhibition of GCCR has long been recognized as an attractive strategy for development of therapeutics for type 2 diabetes, the side effects associated with systemic GCCR inhibition have challenged development of traditional drugs. Antisense inhibitors of GCCR take advantage of the unique tissue distribution of oligonucleotides that allows the antisense drugs to antagonize glucocorticoid action primarily in liver and fat tissues. Notably, antisense

drugs do not reduce GCCR expression in the central nervous system or adrenal glands - inhibition of GCCR expression in these two organs can lead to systemic side effects. Preclinically, Isis has shown that ISIS 377131 has a broad therapeutic profile that includes reduction of blood glucose levels, a dramatic and favorable effect on lipid levels including cholesterol and triglycerides, and a reduction in body fat. Therefore, this drug may prove to have an attractive therapeutic profile that includes attenuation of diabetic dyslipidemia and obesity which often goes hand-in-hand with type 2 diabetes. Isis plans to begin IND-enabling preclinical studies for ISIS 377131 in 2007.

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 17 drugs in development. Isis' drug development programs are focused on treating cardiovascular and metabolic diseases. Isis' partners are developing drugs for cancer and inflammatory and other diseases. As an innovator in RNA-based drug discovery and development, Isis is the owner or exclusive licensee of over 1,500 issued patents worldwide. Additional information about Isis is available at www.isispharm.com.

This press release includes forward-looking statements regarding the therapeutic and commercial potential of Isis' technologies and products in development for the treatment of metabolic diseases. Any statement describing Isis' goals, expectations, financial or other projections, 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, 2006, and its quarterly report on Form 10-Q for the quarter ended March 31, 2007, which are 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" means Isis Pharmaceuticals and its subsidiaries.

SOURCE Isis Pharmaceuticals, Inc.

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