



Isis Highlights New Data on Antisense Drugs to Treat Type 2 Diabetes and Obesity at ADA Scientific Sessions

June 9, 2009

NEW ORLEANS and CARLSBAD, Calif., June 9 /PRNewswire-FirstCall/ -- Isis Pharmaceuticals, Inc. (Nasdaq: ISIS) announced today that Isis' antisense drugs were highlighted with eight presentations (including three oral talks and two late-breaking posters) during the American Diabetes Association's (ADA) 69th Scientific Sessions in New Orleans by Isis and its collaborators. Isis' scientists presented new preclinical data on ISIS-SGLT2Rx showing a robust and sustained reduction in sodium dependent glucose co-transporter type 2 (SGLT2) levels that resulted in a significant reduction in blood glucose levels in multiple animal species. Isis and its collaborators also presented data on a number of other promising new targets demonstrating that reducing levels of these targets with antisense drugs can significantly lower blood glucose levels and increase the body's sensitivity to insulin. Additionally, data was presented from Isis' anti-obesity drug discovery program showing antisense drugs reduced fat mass and body weight in animals by reducing levels of targets in peripheral tissues such as liver and fat without affecting the central nervous system, further validating Isis' anti-obesity therapeutic strategy.

In the oral presentation titled "ISIS 388626, an SGLT2 Antisense Drug, Causes Robust and Sustained Glucosuria in Multiple Species and is Safe and Well-Tolerated," Dr. Sanjay Bhanot highlighted data that demonstrated that antisense reduction of SGLT2, a key transporter involved in glucose re-absorption in the kidney, produced the following results in preclinical models:

- Dose-dependent reduction in kidney levels of SGLT2 with >75% reduction at the highest dose accompanied by a significant increase (>100-fold) in glucose excretion in the urine in multiple species including monkeys
- Secondary improvements in glucose tolerance and insulin sensitivity
- Significant reduction in plasma glucose levels in extremely hyperglycemic animals
- No harmful effects such as low blood glucose levels (hypoglycemia) or detrimental changes in kidney function with 3-6 month exposure in normal or diabetic animals.

"Our preclinical research during the past year on ISIS-SGLT2Rx extends previous findings and demonstrates potent and sustained reduction of blood glucose levels with good safety and tolerability in multiple animal models including non-human primates. Collectively, the data suggest that ISIS-SGLT2Rx could result in sustained and significant reductions in blood glucose levels in diabetic patients and could be used as an infrequent injectable drug to help control blood sugar. This year, we have initiated our first clinical trial on ISIS-SGLT2Rx that will not only assess the safety of the drug in healthy volunteers, but may also provide us with information on the activity of the drug by measuring the effect of ISIS-SGLT2Rx on glucose excretion in urine. We are excited to continue to move this drug forward through development," said Sanjay Bhanot, M.D., Ph.D., Vice President of Metabolic Disorders and Head of Translational Medicine at Isis Pharmaceuticals.

Isis scientists presented new data demonstrating that antisense reduction of retinal binding protein 4 (RBP4) caused significant improvements in insulin sensitivity with associated improvement in cardiac glucose metabolism. These data suggest that RBP4 could be an important new therapeutic target for type 2 diabetes and associated cardiac disease.

In addition to new data demonstrating the ability of antisense drugs to significantly improve insulin sensitivity in diabetic animals, Isis also presented data from its obesity drug discovery program. In an oral presentation, Isis reported that antisense reduction of fibroblast growth factor receptor 4 (FGFR4) lowered adiposity and improved insulin sensitivity in mice, indicating that FGFR4 plays a role in the regulation of energy expenditure and adiposity. Selective inhibition of FGFR4 with antisense drugs in peripheral tissues could be a unique therapeutic approach for the treatment of obesity and related metabolic disorders.

"We are looking forward to expanding our metabolic disease pipeline by adding antisense drugs to treat obesity, an area with great unmet need where our peripherally acting drugs could have significant therapeutic utility without the potential for central nervous system toxicities that plague many centrally acting anti-obesity drugs," continued Dr. Bhanot. "Obesity is just one example of the many therapeutic areas that are amenable to our antisense drug discovery efforts. We continue to expand our discovery efforts and broaden our drug pipeline to address new diseases within our core therapeutic programs in cardiovascular, metabolic and severe neurodegenerative diseases and cancer."

Including presentations highlighting SGLT2 and FGFR4, Isis and its collaborators presented a total of eight presentations (including three oral talks and two late-breaking posters) at this year's ADA conference. The additional presentations highlighted antisense inhibitors to a number of metabolic targets in a variety of animal species that reduced mRNA target levels in specific tissues and provided therapeutic benefit such as improved insulin sensitivity, reduced fat mass and body weight in various models of disease. Complete abstracts for the presentations can be found on the ADA Web site at www.diabetes.org.

ISIS 388626, an SGLT2 Antisense Drug, Causes Robust and Sustained Glucosuria in Multiple Species and Is Safe and Well-Tolerated (Oral Presentation) □

Authors: S. Bhanot, S.F. Murray, S.L. Booten, K. Chakravarty, T. Zanardi, S. Henry, L.M. Watts, E.V. Wancewicz, A. Siwkowski, B.P. Monia.

Antisense Reduction of FGFR4 Gene Expression Lowers Body Weight and Adiposity and Improves Insulin Sensitivity in Rodents (Oral Presentation)

Authors: X.X. Yu, L.M. Watts, P. Manchem, S.L. Booten, B.P. Monia, S. Bhanot. □

Antisense Inhibition of cAMP Response Element Binding Protein (CREB) Expression Lowers Plasma Glucose and Lipids in Diabetic Rodents (Oral Presentation) □

Authors: S.F. Murray, S.L. Booten, L.M. Watts, B.P. Monia, S. Bhanot.

A Newly Identified Role of Nuclear Receptor Corepressor, SMRT (Silencing □ Mediator of Retinoid and Thyroid) in Improving Hyperglycemia and Insulin Sensitivity in Obese and Diabetic Mice (Late-Breaking Poster)

Authors: S.K. Pandey, S.F. Murray, S. Guo, L.M. Watts, S.L. Booten, A. Siwkowski, D. Witchell, P. Manchem, S. Bhanot, B.P. Monia.

Inhibition of Transthyretin Expression by Antisense Oligonucleotides Lowers RBP4 Levels, Improves Insulin Sensitivity and Increases Heart Glucose Uptake in Diet-Induced Obese Mice (Late-Breaking Poster)

Authors: P. Manchem, S.F. Murray, S.L. Booten, X.X. Yu, L.M. Watts, B.P. Monia, S. Bhanot.

Antisense Reduction of RBP4 Expression Causes a Marked Improvement in Hepatic and Peripheral Insulin Sensitivity and Improves Cardiac Glucose Uptake in Diet-Induced Obese Mice

Authors: P. Manchem, X.X. Yu, S.L. Booten, L.M. Watts, S.F. Murray, B.P. Monia, S. Bhanot.

Knockdown of Carbohydrate Response Element Binding Protein (ChREBP) in Liver Protects Against Fructose Induced Hyperlipidemia and Insulin Resistance □

Authors: D.M. Erion, J.J. Hsiao, S. Yonemitsu, R. Stark, J. Dong, Y. Nagai, T. May, M. Kahn, X.X. Yu, S.F. Murray, S. Bhanot, B.P. Monia, G.W. Cline, V.T. Samuel, G.I. Shulman. □

Matrix Metalloproteinase-9: Association With Insulin Resistance and Obesity and PKC-alpha Mediated Regulation by Pioglitazone

Authors: R. Unal, A. Yao-Borengasser, V. Varma, N. Rasouli, B. Phanavanh, C. Labbate, B.P. Monia, P.A. Kern, G. Ranganathan.

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 19 drugs in development. Isis' drug development programs are focused on treating cardiovascular, metabolic and severe neurodegenerative diseases and cancer. Isis' partners are developing antisense drugs invented by Isis to treat a wide variety of diseases. Isis and Alnylam Pharmaceuticals are joint owners of Regulus Therapeutics Inc., a company focused on the discovery, development and commercialization of microRNA therapeutics. Isis also has made significant innovations beyond human therapeutics resulting in products that other companies, including Abbott, are commercializing. As an innovator in RNA-based drug discovery and development, Isis is the owner or exclusive licensee of over 1,600 issued patents worldwide. Additional information about Isis is available at www.isispharm.com.

This press release includes forward-looking statements regarding Isis' business, its drug discovery and development pipeline, and the therapeutic potential of antisense drugs for the treatment of cardiovascular and 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. 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, 2008, and its most recent quarterly report on Form 10-Q, which are on file with the SEC. Copies of these and other documents are available from the Company.

In this press release, unless the context requires otherwise, "Isis," "Company," "we," "our," and "us" refers to Isis Pharmaceuticals and its subsidiaries, including Regulus Therapeutics Inc.

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06/09/2009

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2613 06/09/2009 07:00 EDT <http://www.prnewswire.com>