Isis Highlights New Data on Antisense Drugs to Treat Type 2 Diabetes and Obesity From Its Broad Metabolic Disease Franchise at ADA Scientific Sessions

June 29, 2010

ORLANDO, Fla. and CARLSBAD, Calif., June 29 /PRNewswire-FirstCall/ -- Isis Pharmaceuticals, Inc. (Nasdaq:ISIS - News) announced today that data from seven programs in Isis' broad metabolic disease franchise were presented at the American Diabetes Association's (ADA) 70th Scientific Sessions in Orlando. These presentations included two oral talks highlighting data from Isis' Phase 2 study of ISIS 113715 in patients with type 2 diabetes and Isis' Phase 1 study of ISIS-GCGRRx. Isis and collaborators also presented new data from five other programs demonstrating that antisense drugs can approach novel targets to treat metabolic diseases and may provide new therapeutic options for patients.

In the oral presentation titled "ISIS 113715, a Novel PTP-1B Antisense Inhibitor, Improves Glycemic Control and Dyslipidemia and Increases Adiponectin Levels in T2DM Subjects Uncontrolled on Stable Sulfonylurea Therapy," Dr. Sanjay Bhanot presented the results of a Phase 2 study evaluating ISIS 113715 in patients with type 2 diabetes whose glucose levels were uncontrolled despite being treated with maximum doses of sulfonylureas. The study produced the following results:

- Statistically significant reductions in multiple short and intermediate measures of glucose control at the 200 mg/week dose
- Statistically significant decrease of approximately 11 mg/dL in LDL Cholesterol
- Reduction in body weight that was preceded by a statistically significant increase in circulating adiponectin, supporting the role of PTP-1B in the regulation of body weight
- No clinically significant adverse events or observations of hypoglycemia. The most common adverse event was mild injection site reactions.

"We have demonstrated that our PTP-1B inhibitor has a very attractive profile in two Phase 2 studies in patients with type 2 diabetes. A novel insulin sensitizer that reduces high blood glucose without resulting in hypoglycemia, reduces LDL-cholesterol and decreases weight would be a significant advance in the treatment of type 2 diabetes," said Sanjay Bhanot, M.D., Ph.D., Vice President of Metabolics and Translational Medicine at Isis. "In this study, we observed reductions in multiple measures of glucose control that were consistent with our expectations for a 13-week study. We believe that with longer-term treatment we should also see reductions in longer-term measures of glucose control. We are excited to continue to move this program forward and to evaluate PTP-1B inhibition in longer studies in combination with other commonly prescribed type 2 diabetes drugs."

In the oral presentation titled "First Proof of Pharmacology of a Novel Glucagon Receptor Antisense Drug in Humans," Dr. Bhanot presented the results of a Phase 1 study on ISIS-GCGRRx. The study, which included a glucagon challenge that doubled both plasma glucagon and glucose levels, produced the following results:

- Statistically significant improvement in blood glucose levels and reduced liver glucose production following the glucagon challenge at a dose of 400 mg/week
- No clinically significant adverse events or observations of hypoglycemia. The most common adverse event was mild injection site reactions.

"In our Phase 1 study of ISIS-GCGRRx we achieved reductions in blood glucose following a glucagon challenge. This result supports the therapeutic potential of inhibiting the glucagon receptor. Glucagon is thought to play a greater role in increasing blood glucose in patients with advanced diabetes, so a glucagon receptor inhibitor should work very well in these patients. Based on the positive data from this Phase 1 study and the therapeutic potential of a GCGR inhibitor, we are moving the program forward with a more potent GCGR antisense inhibitor," continued Dr. Bhanot.

"Both ISIS 113715 and ISIS-GCGRRx highlight the multifaceted approach Isis employs to develop novel new drugs to treat type 2 diabetes. We now have four drugs in our metabolic pipeline, each with a unique approach to the treatment of type 2 diabetes," added Dr. Bhanot.

Isis scientists presented new data from the Company's obesity drug discovery program, a part of Isis' metabolic disease franchise. Isis previously reported that antisense reduction of fibroblast growth factor receptor 4 (FGFR4) lowered body weight and improved insulin sensitivity in mice, indicating that FGFR4 plays a role in the regulation of energy expenditure and body weight. In this study, an antisense inhibitor to FGFR4 and rimonabant, an appetite-suppressing drug, were administered separately and in combination in animal models of obesity. The study showed that antisense inhibition of FGFR4 was complementary to the CNS-based treatment, rimonabant, suggesting that the peripheral inhibition of FGFR4 in combination with other types of anti-obesity drugs could be a unique therapeutic approach for the treatment of obesity and related metabolic disorders.

"We have made substantial progress in our anti-obesity efforts over the last couple of years and are moving promising compounds closer to development. We have adopted a unique approach in this program. We believe that an anti-obesity drug that works in peripheral tissues, such as fat and liver, and not in the central nervous system could provide significant therapeutic benefit without the side effects that are associated with CNS-acting agents. We look forward to moving a drug into our development pipeline soon," concluded Dr. Bhanot.

In total Isis' antisense drugs were highlighted in seven presentations, including three oral and four poster presentations. In addition to the oral presentations on ISIS 113715 and ISIS-GCGRRx, Isis and collaborators highlighted data from antisense inhibitors to a number of metabolic targets in a variety of animal models showing that antisense inhibition provided therapeutic benefit including reductions in fat mass and body weight and improved glucose metabolism. Complete abstracts for the presentations can be found on the ADA Web site at http://www.diabetes.org/.

ISIS 113715, a Novel PTP-1B Antisense Inhibitor, Improves Glycemic Control and Dyslipidemia and Increases Adiponectin Levels in T2DM Subjects Uncontrolled on Stable Sulfonylurea Therapy (Oral Presentation)

Authors: T. A. Brandt, S. T. Crooke, E. J. Ackermann, S. Xia, E. S. Morgan, Q. Liu, R. S. Geary, S. Bhanot.

First Proof of Pharmacology of a Novel Glucagon Receptor Antisense Drug in Humans (Oral Presentation)

Authors: E. S. Morgan, T. A. Brandt, M. G. J. Van Dongen, B. F. Geerts, J. Burggraaf, J. A. Romjin, A. F. Cohen, T. A. Watanabe, R. S. Geary, S. Bhanot.

FGFR4 Antisense Oligonucleotide Potentiates the Anti-Obesity Effect of Rimonabant in Diet-Induced Obese Mice

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

Antisense Reduction of DGAT2 Reduces Body Weight and Improves Dyslipidemia in High-Fat High-Cholesterol Diet Fed LDLr Knockout Mice

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

Reduced Adiposity and Improved Metabolic Profile after Antisense Reduction of GPAT1 Expression in Mouse Models of Obesity

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

Knockdown of Nicotinamide N-Methyltransferase (NNMT) Reverses Diet-Induced Obesity

Authors: D. Kraus, Q. Yang, T. C. Pulinilkunnil, J. T. Rodgers, B. P. Monia, S. Bhanot, T. C. Becker, O. D. Peroni, P. Puigserver, B. B. Kahn.

Evidence for a Key Role of Hepatic PEPCK-M in Glucose Homeostasis *In Vivo* (Oral Presentation)

Authors: R. Stark, C. N. Feriod, X. Zhao, J. Dong, M. Roden, S. Bhanot, G. I. Shulman, R. G. Kibbey.

ISIS' METABOLIC FRANCHISE

Isis is pursuing the discovery and development of antisense drugs to treat metabolic diseases, such as diabetes and obesity. According to the Centers for Disease Control and Prevention, diabetes affects more than 20 million people in the U.S. Isis has four drugs in its pipeline to treat type 2 diabetes, each of which acts upon targets in the liver, fat tissue or the kidney through distinct mechanisms to improve insulin sensitivity, reduce glucose production, or affect other metabolic aspects of metabolic disease. Isis is developing other drugs aimed at other types of metabolic diseases, including obesity where a peripherally acting anti-obesity drug could provide a unique therapeutic approach for the treatment of obesity and related metabolic disorders.

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 22 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 approximately 1,600 issued patents worldwide. Additional information about Isis is available at http://www.isispharm.com/.

This press release includes forward-looking statements regarding Isis' discovery and development of drugs for metabolic diseases, including the development, activity, therapeutic potential and safety of ISIS 113715 and ISIS-GCGRRx in the treatment of type 2 diabetes. 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, 2009 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.