Isis Highlights Robust Drug Portfolio for Diabetes and Obesity at ADA Conference

June 10, 2008

- Oral presentation on the potent blood glucose lowering effect of SGLT2 antisense inhibitors in multiple preclinical models

- Eight additional presentations highlight significant activity in eight new metabolic disease targets utilizing antisense

SAN FRANCISCO and CARLSBAD, Calif., June 10 /PRNewswire-FirstCall/ -- Isis Pharmaceuticals, Inc. (Nasdaq: ISIS) announced today the presentation of new preclinical data showing that antisense drugs potently reduce levels of sodium dependent glucose transporter type 2 (SGLT2), a key component in controlling glucose re-absorption in the kidney and the target of ISIS 388626. In addition, Isis presented results from eight research programs on novel targets that offer new mechanisms to treat metabolic diseases. The nine presentations (including two late-breaking abstracts) were presented during the American Diabetes Association's (ADA) 68th Scientific Sessions in San Francisco by Isis and its collaborators.

"These data provide further evidence of the power of Isis' antisense technology to discover and develop highly potent and specific molecules targeted against many novel targets to treat a broad spectrum of metabolic diseases," said Robert R. Henry, M.D., Professor of Medicine, University of California at San Diego, and Chief, Section of Diabetes, Endocrinology, and Metabolism at VA San Diego Healthcare System.

The presentation titled "Long Term Safety and Efficacy of ISIS 388626, an Optimized SGLT2 Antisense Inhibitor, in Multiple Diabetic and Euglycemic Species," showed that antisense reduction of SGLT2 produced the following results in preclinical models:

-- Lowered HbA1c, a measure of average blood glucose over time in diabetic animals, and reduced fed and fasted blood glucose levels, while also ameliorating diabetic complications, including slowing progression of cataract formation.
-- Lowered SGLT2 mRNA levels in the kidney by approximately 80% in all species tested, with doses as low as 1-2 mg/kg/week with no effect on SGLT1, a related protein, where levels of activity is desirable.
-- Showed no changes in urinary or plasma markers of renal function and no harmful effects such as low blood glucose.

"In preclinical models, lowering levels of SGLT2 in the kidney by an antisense drug demonstrated very potent reduction in blood glucose that supports the possibility of an infrequent monthly injectable dosing or, potentially, a cost effective oral administration. Furthermore, our SGLT2 inhibitor complements our diabetes drugs in development, and offers a unique and complementary approach to treat diabetes," said Sanjay Bhanot, M.D., Ph.D., Vice President of Metabolic Diseases Research & Development of Isis Pharmaceuticals. "We are moving ISIS 388626, our human antisense SGLT2 inhibitor, toward human clinical proof-of-concept as rapidly as possible, and we look forward to continuing to populate our metabolic disease pipeline with exciting drugs arising from our research program."

As part of Isis' metabolic disease franchise, data from eight additional research programs conducted by Isis and its collaborators were presented at ADA this year, evaluating the effects of antisense drugs against eight promising new targets in a variety of species and models, including diabetic animals. Results of the studies showed that antisense technology reduced mRNA target levels in specific tissues and provided early signs of therapeutic benefit in various models of disease, offering robust and sustained effects for the treatment of obesity, type 2 diabetes and lipid metabolism disorders. Complete abstracts for these presentations can be found on the ADA Web site at http://www.diabetes.org.

"In our metabolic disease franchise we have evaluated more than 130 biological targets and identified more than 20 therapeutic targets that have the potential to offer new approaches to treat diseases, such as obesity and diabetes," said Jeffrey Jonas, M.D., Executive Vice President of Isis Pharmaceuticals. "Our research demonstrates the ability of antisense technology to quickly validate novel targets that provide exciting new approaches to treat metabolic diseases. In particular, obesity is an area where we feel our peripherally acting drugs rather than centrally acting drugs could have a profound impact on the activity and tolerability of anti-obesity therapy. Furthermore, our ongoing clinical studies with other antisense drugs provide evidence for the long-term safety of antisense drugs, making them an attractive possibility for the treatment of chronic diseases."

About SGLT2 and ISIS 388626

The sodium dependent glucose transporter type 2 (SGLT2) is the primary mechanism responsible for 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 preclinical studies, ISIS 388626 and other antisense inhibitors of SGLT2, effectively reduced target mRNA levels in several animal species, increased urinary glucose excretion and consequently lowered blood glucose levels and HbA1c (in hyperglycemic animals) without causing dangerously low levels of blood sugar known as hypoglycemia. These data are consistent with expectations based on human subjects who have mutations in the SGLT2 gene and have increased urine glucose levels but are otherwise asymptomatic. ISIS 388626 effectively and specifically inhibits the production of SGLT2 in the kidney tissue, without having any effect on a related gene product, SGLT1. In addition to being Isis' first antisense drug for a kidney target, ISIS 388626 is also unique due to its 12 nucleotide length rather than the more typical 18 - 21 nucleotide sequences that comprise Isis' other drugs. This attribute simplifies manufacturing and has the potential to substantially reduce related expenses. The short sequence may also contribute to ISIS 388626's unusually high potency; it is among the most potent antisense drugs that Isis has evaluated in preclinical models.

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 18 drugs in development. Isis' drug development programs are focused on treating

cardiovascular and metabolic diseases. Isis' partners are developing antisense drugs invented by Isis to treat a wide variety of diseases. Ibis Biosciences, Inc., Isis' majority-owned subsidiary, is developing and commercializing the Ibis T5000(TM) Biosensor System, a revolutionary system to identify infectious organisms. Isis is a joint owner of Regulus Therapeutics LLC, a joint venture focused on the discovery, development and commercialization of microRNA therapeutics. 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 http://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, 2007, and its quarterly report on Form 10-Q for the quarter ended March 31, 2008, 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" refers to Isis Pharmaceuticals and its subsidiaries.

SOURCE Isis Pharmaceuticals, Inc.
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