

Isis Initiates Phase 1 Studies with Isis-GCGRx and Isis-GCCRx to Treat Type 2 Diabetes

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Isis Pharmaceuticals, Inc. (NASDAQ: ISIS) announced today that it has initiated Phase 1 clinical studies for ISIS-GCGRx and ISIS-GCCRx, antisense drugs Isis is developing for the treatment of type 2 diabetes. Isis will develop both ISIS-GCGRx and ISIS-GCCRx to treat a broad population of diabetic patients. The unique mechanism of action of these new drugs could allow each drug to be used in combination with other therapies for type 2 diabetes.

"Type 2 diabetes is a progressive disease. More than half of all diabetic patients cannot reach acceptable glucose control with currently available therapies. Our goal is to develop safe, effective drugs with unique mechanisms of action that can provide significant therapeutic benefit," said B. Lynne Parshall, Chief Operating Officer, Chief Financial Officer and Secretary of Isis. "This year we have made significant progress toward this goal. Our ISIS-GCGRx and ISIS-GCCRx drugs are designed to reduce the activity of two critical hormones that oppose the action of insulin and cause increased glucose levels in diabetic patients. The initial clinical development for both of these drugs will focus on treating diabetic patients with moderate to severe diabetes who cannot achieve adequate glucose control with existing treatments. We believe that each drug could address a significant commercial market by providing long-term disease control in such patients."

ISIS-GCGRx targets the glucagon receptor (GCGR) to reduce the effects of glucagon, a hormone that causes glucose production in the liver. Reducing GCGR also increases the production of active glucagon-like peptide (GLP-1), a hormone that preserves pancreatic function and enhances insulin secretion. "Glucagon plays a particularly significant role in increasing blood glucose levels in patients with advanced diabetes. Therefore ISIS-GCGRx could work very well in those patients in whom most other therapies fail. In our preclinical studies, which were conducted in the most insulin-resistant models of type 2 diabetes, antisense reduction of GCGR produced robust glucose control and resulted in preservation of the pancreas without producing hypoglycemia," said Sanjay Bhanot, M.D., Ph.D., Vice President, Metabolic Disorders and Translational Medicine of Isis. "ISIS-GCGRx has a significant effect in decreasing excessive liver glucagon action in these models. In addition, it increased active GLP-1 thereby improving pancreatic function. Due to this dual-action mechanism, ISIS-GCGRx could be valuable for diabetic patients with severe hyperglycemia who are not controlled with current treatments."

Glucocorticoids are hormones that promote liver glucose production and fat storage. Reduction of the glucocorticoid receptor (GCCR) action specifically in the liver and fat tissues is an attractive therapeutic approach, because it provides the desired effects on glucose and lipid control without causing potential side effects associated with systemic GCCR inhibition. "In preclinical studies, we have demonstrated reduction of GCCR specific to the liver and fat with antisense drugs. These preclinical results were accompanied by robust lowering of blood glucose and lipid levels and a decrease in body fat in obese animals. Therefore ISIS-GCCRx could be used in diabetic patients with moderate to severe hyperglycemia who are also obese and have high levels of lipids," concluded Dr. Bhanot.

ABOUT ISIS PHARMACEUTICALS, INC.

Isis is exploiting its leadership position in antisense technology to discover and develop novel drugs for its product pipeline and for its partners. Isis' broad pipeline consists of 25 drugs to treat a wide variety of diseases with an emphasis on cardiovascular, metabolic and severe and rare/neurodegenerative diseases, and cancer. Isis' partner, Genzyme, plans to commercialize Isis' lead product, mipomersen, following regulatory approval, which is expected in 2012. Isis' patents provide strong and extensive protection for its drugs and technology. Additional information about Isis is available at www.isispharm.com.

ISIS PHARMACEUTICALS' FORWARD-LOOKING STATEMENT

This press release includes forward-looking statements regarding Isis Pharmaceuticals and the discovery, development and potential of ISIS-GCGRx and ISIS-GCCRx for the treatment of type 2 diabetes. Any statement describing Isis' goals, expectations, financial or other projections, intentions or beliefs, including the planned commercialization of mipomersen, 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 drugs. 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, 2010 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., its jointly owned subsidiary.

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