Isis Pharmaceuticals Reports Phase 2 Data on ISIS-GCGR Rx Showing Significant Reduction in HbA1c in Patients With Type 2 Diabetes

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Greater than 2 percentage point reduction in HbA1c achieved after only 13 weeks of dosing

CARLSBAD, Calif., May 14, 2014 /PRNewswire/ -- Isis Pharmaceuticals, Inc. (NASDAQ: ISIS) announced today positive data from a Phase 2 study of ISIS-GCGR$_{Rx}$ in patients with type 2 diabetes uncontrolled on stable metformin therapy. In this study, patients in the per protocol efficacy population treated with ISIS-GCGR$_{Rx}$ achieved statistically significant reductions in measures of glucose control. The absolute mean reductions in hemoglobin A1c (HbA1c) were greater than 2 percentage points (p=0.001) and greater than 1 percentage points (p=0.001) in the 200 mg and 100 mg cohorts, respectively, compared to baseline after 13 weeks of treatment. Patients treated with ISIS-GCGR$_{Rx}$ also experienced increased plasma GLP-1 levels. Isis will present additional detail from this study as a late-breaking abstract program at the American Diabetes Association 74th Scientific Sessions. In conjunction, Isis will host an investor event on June 15, 2014 at 7:00 a.m PT.

"These results reported today represent the potential for a major advance in diabetes therapeutics. ISIS-GCGR$_{Rx}$ employs a unique mechanism to treat patients with type 2 diabetes. It is well known that as type 2 diabetes progresses, dysregulated glucagon action becomes a more significant contributor to the disease. The ability of ISIS-GCGR$_{Rx}$ to improve glycemic control without causing any clinically significant increases in blood pressure or lipids offers a significant advantage for both patients and treating physicians," said Robert Henry, M.D., chief, VA endocrinology & metabolism and professor of medicine in residence, University of California, San Diego School of Medicine. "The additional effect on increasing GLP-1 means that ISIS-GCGR$_{Rx}$ treatment could help to preserve pancreatic function and enhance insulin secretion in diabetic patients."

"Glucagon is a hormone that opposes the action of insulin and causes increased glucose production from the liver. In patients with advanced diabetes, uncontrolled glucagon action can lead to a significant increase in blood glucose levels. Therefore, attenuating glucagon action should have a significant glucose lowering effect in patients with severe diabetes," said Sanjay Bhanot, M.D., Ph.D., vice president of clinical development and translational medicine at Isis. "Unlike results with previous small molecule inhibitors of glucagon receptor, patients treated with ISIS-GCGR$_{Rx}$ did not experience significant changes in LDL-C, blood pressure or body weight gain. Additionally, we do not expect ISIS-GCGR$_{Rx}$ to produce drug-drug interactions, which means ISIS-GCGR$_{Rx}$ has the potential to be used in combination with currently available therapies. ISIS-GCGR$_{Rx}$ is a dual acting drug designed to effectively balance reduction of hepatic glucose production and GLP-1 increases. The increases in GLP-1 observed in this study are consistent with our preclinical and Phase 1 experience with ISIS-GCGR$_{Rx}$ and support the dual action of ISIS-GCGR$_{Rx}$. Given the remarkable results we have observed in this 13 week study, we plan to optimize dose and dosing schedules for our longer-term studies of ISIS-GCGR$_{Rx}$ in patients with type 2 diabetes."

This Phase 2 study of ISIS-GCGR$_{Rx}$ was a double-blinded, randomized, placebo-controlled study in 75 patients with type 2 diabetes who had uncontrolled blood sugar despite treatment with stable metformin therapy. Patients received either 100 mg or 200 mg of ISIS-GCGR$_{Rx}$ or placebo for 13 weeks added to their stable doses of metformin. In this study, the average incoming HbA1c level was 8.7 percent. After only 13 weeks of dosing, robust and sustained, dose-dependent, statistically significant mean reductions in HbA1c were achieved in patients treated at both doses. Additional measures of glucose control, including serum fructosamine and fasting plasma glucose levels were also significantly reduced in patients treated with ISIS-GCGR$_{Rx}$. The observed improvement in glucose control was in addition to those achieved with each patient's existing therapeutic regimen of metformin.

ISIS-GCGR$_{Rx}$ was generally well tolerated in the study. The most common adverse event was infrequent injection site reactions, which were predominantly mild and typically resolved rapidly. There were no flu-like symptoms, no abnormalities in renal function, no clinically meaningful changes in other laboratory values and no cases of symptomatic hypoglycemia. As has been observed with small molecule inhibitors of glucagon receptor, liver enzyme elevations that were not associated with elevated bilirubin or other indicators of liver damage were observed. These liver enzyme elevations are consistent with the pharmacology of glucagon receptor inhibition. ISIS-GCGR$_{Rx}$ was not associated with increases in LDL-C, blood pressure or body weight gain (side effects associated with some small molecule inhibitors of glucagon receptor).

ISIS-GCGR$_{Rx}$ is a part of Isis' metabolic franchise that also includes ISIS-PTP1B$_{Rx}$ and ISIS-GCCR$_{Rx}$. Each of these drugs is designed to act through a distinct mechanism to improve insulin sensitivity and/or reduce glucose production in patients with type 2 diabetes. Isis is developing ISIS-GCGR$_{Rx}$ for patients with advanced diabetes whose glucose is uncontrolled with current therapies.

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 32 drugs to treat a wide variety of diseases with an emphasis on cardiovascular, metabolic, severe and rare diseases, including neurological disorders, and cancer. Isis' partner, Genzyme, is commercializing Isis' lead product, KYNAMRO®, in the United States and other countries for the treatment of patients with homozygous FH. 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 the development, activity, therapeutic potential and safety of ISIS-GCGR$_{Rx}$ in treating patients with 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 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, 2013, 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.

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