



## Isis Pharmaceuticals Reports Final Phase 2 Data on ISIS-GCGR RX Showing Significant Reduction in HbA1c in Patients with Type 2 Diabetes

June 16, 2014

**Up to 2.25 percentage point reduction in HbA1c achieved after only 13 weeks of dosing**  
**Treated patients achieved statistically significant reductions in measures of glucose control**  
**Isis to host an investor event and live webcast at 6:30 a.m. PDT on Monday, June 16 in San Francisco**

CARLSBAD, Calif., June 16, 2014 /PRNewswire/ -- Isis Pharmaceuticals, Inc. (NASDAQ: ISIS) announced today the final results from its Phase 2 study of ISIS-GCGR<sub>RX</sub> in patients with type 2 diabetes uncontrolled on stable metformin therapy. In this study, patients in the per protocol population (PP) treated with ISIS-GCGR<sub>RX</sub> in addition to metformin achieved absolute mean reduction in hemoglobin A1c (HbA1c) of up to 2.25 percentage points from baseline after only 13 weeks of treatment. Patients receiving placebo had an 0.25 percentage point reduction in HbA1c. In this study, more than half of the PP patients achieved an HbA1c level of less than or equal to 7.0 percent. PP patients treated with ISIS-GCGR<sub>RX</sub> in this study also achieved a mean reduction of up to 74.9  $\mu$ mol/L in fructosamine. In addition, in these patients a mean increase in total GLP-1 of up to 19.97 pmol/L was observed.



The full data, including the intent-to-treat analysis, which were similar in all measured endpoints to the PP, were presented as a late-breaking abstract program at the American Diabetes Association 74<sup>th</sup> Scientific Sessions. In conjunction, Isis is hosting an investor event on June 16, 2014 at 6:30 a.m. PDT in San Francisco.

"Diabetes is a worldwide epidemic with more than 366 million patients living with diabetes worldwide. Unfortunately, despite current treatments, the majority of patients with type 2 diabetes will fail one or more therapies and progress in their disease. These patients are unable to achieve adequate glucose control and are at greater risk to develop significant health conditions, including stroke, heart attack and kidney disease. These patients need new therapeutic approaches to help them achieve the recommended glycemic goals. As type 2 diabetes progresses, dysregulated glucagon action becomes a more significant contributor to the disease. As such, the addition of a glucagon receptor-targeted drug that is safe and effective could be a major advance in the treatment of type 2 diabetes," said Robert Henry, M.D., chief, section of diabetes, endocrinology & metabolism; director, center for metabolic research, VA and professor of medicine in residence, University of California, San Diego School of Medicine. "The results from ISIS-GCGR<sub>RX</sub> presented at the ADA suggest that ISIS-GCGR<sub>RX</sub> could be a best-in-class medicine for patients with advanced type 2 diabetes. The potential of ISIS-GCGR<sub>RX</sub> to improve glycemic control without causing any clinically significant increases in weight gain or lipids could offer a significant advantage for both patients and treating physicians. Also, the additional effect on increasing GLP-1 levels means that ISIS-GCGR<sub>RX</sub> treatment could help to preserve pancreatic function and enhance insulin secretion in diabetic patients. If successfully developed, ISIS-GCGR<sub>RX</sub> has the potential to delay the need for or significantly reduce the requirement for insulin and GLP-1 treatments in patients with type 2 diabetes."

**Table 1: ISIS-GCGR<sub>RX</sub> Produced Statistically Significant Reductions in Measures of Glucose Control After Only 13 Weeks of Dosing.**

|  | Per Protocol Population <sup>i</sup> |
|--|--------------------------------------|
|  | Mean                                 |
|  | (SEM)                                |

|                          |                      | Placebo<br>N=24        | 100 mg<br>N=21            | 200 mg<br>(load)<br>N=8   | 200 mg<br>(no load)<br>N=9 |
|--------------------------|----------------------|------------------------|---------------------------|---------------------------|----------------------------|
| HbA1c<br>(%)             | Baseline             | 8.60<br>(0.17)         | 8.55<br>(0.23)            | 9.10<br>(0.31)            | 8.80<br>(0.38)             |
|                          | Change to<br>Week 14 | <b>-0.25</b><br>(0.24) | <b>-1.35***</b><br>(0.16) | <b>-2.25***</b><br>(0.33) | <b>-1.74**</b><br>(0.27)   |
| Fructosamine<br>(μmol/L) | Baseline             | 323.2<br>(9.8)         | 324.4<br>(12.0)           | 309.9<br>(14.1)           | 324.9<br>(16.7)            |
|                          | Change to<br>Week 14 | <b>-7.6</b><br>(10.1)  | <b>-62.3***</b><br>(8.8)  | <b>-74.9**</b><br>(11.7)  | <b>-72.2**</b><br>(12.7)   |
| Total GLP-1<br>(pmol/L)  | Baseline             | 5.09<br>(0.65)         | 6.51<br>(0.75)            | 7.65<br>(1.84)            | 4.55<br>(0.77)             |
|                          | Change to<br>Week 14 | <b>-0.05</b><br>(0.51) | <b>9.13***</b><br>(1.35)  | <b>19.89***</b><br>(2.98) | <b>19.97***</b><br>(3.50)  |

\*\*  $p \leq 0.01$ , \*\*\*  $p \leq 0.001$  vs. placebo

<sup>i</sup>Per protocol population (PP) = patients received at least 11 doses within 70 days (load) or 12 doses within 87 days (no load).

"Glucagon is a hormone that opposes the action of insulin and causes increased glucose production from the liver. As such, 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 advanced type 2 diabetes. In the current study we observed significant, dose-dependent reductions of fasting plasma glucose, HbA1c and other measures of glucose control in patients treated with ISIS-GCGR<sub>Rx</sub>, with the added benefit of a significant increase in GLP-1 levels. Because increased GLP-1 levels have the potential to improve pancreatic function, the combination of robust glucose lowering due to antagonism of hepatic glucagon action coupled with an increase in GLP-1 levels could potentially result in significant therapeutic benefit in this patient population," said Sanjay Bhanot, M.D., Ph.D., vice president of clinical development and translational medicine at Isis.

This Phase 2 study of ISIS-GCGR<sub>Rx</sub> 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<sub>Rx</sub> or placebo for 13 weeks added to their stable doses of metformin. Patients in the 100 mg cohort received a loading dose of three 100 mg doses within the first seven days of the study and a weekly 100 mg dose every week thereafter for 12 weeks. Patients in the 200 mg cohort received either a loading dose of three 200 mg doses within the first seven days of the study and a weekly 200 mg dose every week thereafter for 12 weeks or a weekly dose of 200 mg every week for 13 weeks. 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<sub>Rx</sub>. The observed improvement in glucose control was in addition to that achieved with each patient's existing therapeutic regimen of metformin.

"Unlike results with previous small molecule inhibitors of the glucagon receptor, patients treated with ISIS-GCGR<sub>Rx</sub> did not experience significant changes in LDL-C, blood pressure or body weight gain. Additionally, despite the significant increases in GLP-1 levels, patients treated with ISIS-GCGR<sub>Rx</sub> did not experience nausea or vomiting, a side effect associated with GLP-1 agonists. Similar to other glucagon receptor inhibitors and consistent with the pharmacology of glucagon receptor inhibition, we observed dose-dependent liver enzyme elevations that were not associated with elevated bilirubin or other indicators of liver damage. Given the robust glucose lowering we observed with both doses in only 13 weeks, we plan to conduct additional studies to identify the optimal dose and schedule to achieve glucose control with manageable glucagon receptor-related liver enzyme elevations," concluded Dr. Bhanot.

ISIS-GCGR<sub>Rx</sub> 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 and no cases of symptomatic hypoglycemia. ISIS-GCGR<sub>Rx</sub> was not associated with clinically meaningful increases in LDL-C, triglycerides, blood pressure or body weight gain (side effects associated with some small molecule inhibitors of glucagon receptor). As has been observed with small molecule inhibitors of glucagon receptor and consistent with the pharmacology of glucagon receptor inhibition, liver enzyme elevations that were neither associated with elevated bilirubin nor other indicators of liver damage were observed. In this study, mean alanine aminotransferase (ALT) elevations were 1.6 and 2.7 times the upper limit of normal in the 100 mg and 200 mg cohorts, respectively. Liver enzyme elevations were much less frequent and lower in the 100 mg dose cohort compared to the 200 mg dose cohort and declined after dosing was discontinued. There were no clinically meaningful changes in other laboratory values.

ISIS-GCGR<sub>Rx</sub> is a part of Isis' metabolic franchise that also includes ISIS-PTP1B<sub>Rx</sub> and ISIS-GCCR<sub>Rx</sub>. 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<sub>Rx</sub> for patients with advanced diabetes whose glucose is uncontrolled with current therapies.

#### Investor Event

At 6:30 a.m. Pacific Daylight Time Monday, June 16, 2014, Isis will host an investor event and live webcast to discuss

ISIS-GCGR<sub>Rx</sub> data presented at the ADA. A live audio webcast of the presentation will be available on the "Investors & Media" section of the Company's website, [www.isispharm.com](http://www.isispharm.com). A replay will be available for a limited time. The slides presented at the ADA meeting are available on Isis' website at [www.isispharm.com](http://www.isispharm.com).

#### **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<sup>®</sup>, 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](http://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<sub>Rx</sub> 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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D. Wade Walke, Ph.D., Vice President, Corporate Communications and Investor Relations, 760-603-2741; Amy Blackley, Ph.D., Associate Director, Corporate Communications, 760-603-2772