



ISIS 113715 Improves Glucose Control in Patients With Type 2 Diabetes

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Isis Pharmaceuticals Presents Preliminary Phase 2 Clinical Trial Results at
65th ADA Annual Meeting

CARLSBAD, Calif., June 14 /PRNewswire-FirstCall/ -- Isis Pharmaceuticals, Inc. (Nasdaq: ISIS) announced today that ISIS 113715 reduced HbA1C and plasma glucose after six weeks of dosing. The second-generation antisense drug did not cause any hypoglycemia (low blood sugar) and was well-tolerated. The data reported were from an interim analysis of a randomized, double-blind, placebo-controlled Phase 2 study in diabetic patients. Data were announced in an oral presentation today by Lise Kjems, M.D., Ph.D., Executive Director, Metabolic Drug Development of Isis Pharmaceuticals, at the American Diabetes Association's (ADA) 65th Scientific Sessions in San Diego.

"The results we have reported for ISIS 113715 are encouraging. After just 6 weeks of dosing, we have shown that ISIS 113715 may play an important role in glucose control as evidenced by reductions in HbA1C and fasting glucose," said Mark Wedel, M.D., J.D., Isis' Vice President of Development and Chief Medical Officer. "ISIS 113715 produced these promising results at low weekly doses and without the major side effects associated with other anti-diabetic therapies, such as hypoglycemia, metabolic acidosis, nausea or weight gain. We look forward to results from the two higher dose cohorts in this study and a group of patients dosed for longer periods of time."

The objectives of the double-blind Phase 2 single-agent study are to evaluate the safety, tolerability and pharmacokinetic profile of ISIS 113715 in treatment-naïve type 2 diabetics, establish a dose regimen to support the initiation of studies as an adjunct to oral type 2 diabetes treatments, and to assess the pharmacological effects of the drug in this patient population. In this study, four dose levels are being evaluated: 100, 200, 400 and 600mg per week dosed for six weeks. Patients are then followed for an additional four weeks. Efficacy data from the first two dose cohorts were presented. Dosing and follow-up are continuing in patients in the two higher doses. Results from the two higher dose groups will be reported later this year. Results from patients treated for 12 weeks in another study will be reported early next year.

The principle measures of efficacy were HbA1C levels and fasting blood glucose levels. HbA1C is a measure that reflects the average amount of blood glucose levels over a 3-4 month period, and is the standard measure used by physicians to tell if a patient's blood sugar is under control. The American Diabetes Association has established an HbA1C measurement of 7% or less as the target for effective glucose control.

Study Highlights:

- * ISIS 113715 produced a dose-dependent reduction in HbA1C from placebo at 6 weeks:

- * At 100mg, reduced HbA1C by 0.25%

- * At 200mg, reduced HbA1C by 0.4%

- * ISIS 113715 produced a dose-dependent increase in the percentage of patients who achieved the 7% or lower HbA1C target:

- * 25% of the patients in the placebo group achieved the 7% or lower goal

* 33% of the patients in the 100mg group achieved the 7% or lower goal

* 45% of the patients in the 200mg group achieved the 7% or lower goal

* ISIS 113715 similarly produced a reduction in fasting plasma glucose of about 25mg/dL from placebo

* ISIS 113715 was well-tolerated

* ISIS 113715 resulted in no hypoglycemic events, metabolic acidosis or weight gain.

"HbA1C is a very stable measure, and therefore it is very rare to observe meaningful reductions after only 6 weeks of treatment," said Lise Kjems, M.D., Ph.D., Isis' Executive Director of Metabolic Drug Development. "The patients in this study, who have mild diabetes, had an incoming average baseline value of HbA1C of 8.1%. ISIS 113715 reduced HbA1C on average by 0.4% and increased the percentage of patients who achieved the recommended HbA1C level with just 6 weeks of treatment. To put these results in context, a number of approved anti-diabetic drugs take 26-52 weeks to lower HbA1C by 0.5%. The results presented today are very encouraging as they demonstrate that patients may be able to safely control their glucose levels with ISIS 113715 therapy."

"ISIS 113715 is designed to inhibit an important target for insulin signaling, PTP-1B. This target is a mediator of insulin resistance, one of two main defects in type 2 diabetes. PTP-1B serves as a brake on insulin signaling, thereby reducing cellular responses to insulin. We anticipated that, because of its function, inhibition of PTP-1B would normalize glucose without causing hypoglycemia. Data in animals and now in man confirm that expectation," Dr. Kjems said.

"We are completing the two higher dose cohorts in this study and the additional group of patients being treated with 200mg weekly for 12 weeks is being enrolled now, so we will have important new data on ISIS 113715 later this year and early next year. Additionally, we plan to begin studies in which ISIS 113715 is used in combination with oral anti-diabetic agents later this year," Dr. Kjems added.

About Isis Pharmaceuticals' Metabolic Disease Program

Isis Pharmaceuticals' metabolic disease program has screened inhibitors for more than 100 gene targets that may be involved in diabetes or obesity in animal models of disease. Its most advanced product, ISIS 113715, is currently in phase 2 clinical trials. The compound's antisense mechanism of action may offer new treatment options to patients who do not adequately respond to currently available therapies such as glitazones, sulfonylureas and biguanides.

About Type 2 Diabetes

According to the American Diabetes Association, diabetes affects nearly 17 million people and type 2 diabetes constitutes 90 percent of those cases.

About Isis Pharmaceuticals, Inc.

Isis Pharmaceuticals, Inc. 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 11 antisense drugs in development to treat metabolic, cardiovascular and inflammatory diseases, and cancer. In its Ibis division, Isis is developing and commercializing the TIGER biosensor system, a system that has the potential to revolutionize the identification of infectious organisms. As an innovator in RNA-based drug discovery and development, Isis is the owner or exclusive licensee of more than 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 development, therapeutic potential and safety of ISIS 113715 in treating diabetes. Any statement describing our goals, expectations, 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. Our forward-looking statements also involve assumptions that, if they never materialize or prove correct, could cause our results to differ materially from those expressed or implied by such forward-looking statements. Although our forward-looking statements reflect the good faith judgment of our management, these statements are based only on facts and factors currently known by us. 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 on Form 10-K for the year ended December 31, 2004, and quarterly report on Form 10-Q for the quarter ended March 31, 2005, which are on file with the SEC. Copies of these and other documents are available from the

Company.

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