



Isis Pharmaceuticals Reports Positive Phase 2 Data: ISIS 113715 Improves Glucose Control in Patients With Type 2 Diabetes

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Isis Initiates Phase 2 Combination Study of ISIS 113715 in Patients Treated with Currently Marketed Type 2 Diabetes Drugs
Isis to Hold Webcast Presentation on Tuesday, June 13 at 12:00pm E.T.

CARLSBAD, Calif., June 13, 2006 /PRNewswire-FirstCall via COMTEX News Network/ -- Isis Pharmaceuticals, Inc. (Nasdaq: ISIS) announced today positive Phase 2 results in patients with type 2 diabetes treated with ISIS 113715 as a single-agent. An intent-to-treat analysis of all patients enrolled in the trial treated with 200 mg/wk for three months showed statistically significant improvement in multiple measures of glucose control. ISIS 113715 did not cause hypoglycemia (low blood sugar), did not cause weight gain and was well tolerated. ISIS 113715, a second-generation antisense drug, is a novel insulin sensitizer that reduces the expression of protein tyrosine phosphatase-1B (PTP-1B). PTP-1B is a mediator of insulin resistance, one of two main defects in patients with type 2 diabetes.

The randomized, double-blind, placebo-controlled Phase 2 study was conducted in newly diagnosed type 2 diabetic patients with moderate diabetes (average HbA1c approximately 8%, average fasting glucose levels approximately 160 mg/dL). The study was divided into two parts, a dose-escalation portion designed primarily to assess the safety of 6 weeks of dosing with ISIS 113715 at weekly doses of 100, 200, 400 and 600 mg, and a 3 month dosing group at 200 mg/week designed to determine the effects of treatment with ISIS 113715 on several measures of blood glucose control. Because patients in the study were newly diagnosed and had never received drug treatment for diabetes, both placebo and drug treated patients exhibited reductions in glucose levels as a result of improved diet and medical care. However, after 3 months of treatment, patients treated with 200 mg/week of ISIS 113715 showed consistent improvement from baseline in several indices of blood glucose control. Reduction in several of these indices was statistically significant as compared to placebo treated subjects. In addition, patients treated with ISIS 113715 achieved statistically significant reductions in cholesterol levels secondary to reductions in PTP-1B.

ISIS 113715 -3 month efficacy study:

Parameters	Mean Reduction from Baseline		Significance □ vs. placebo
	ISIS 113715 (n=22)	Placebo (n=23)	
Self monitored			
fasting blood glucose	-23 mg/dL	-5 mg/dL	(p=0.03, week 13)
Fasting serum glucose	-24 mg/dL	+5 mg/dL	(p=0.002, week 10)
Hemoglobin A1c	-1.10%	-0.86%	not significant
Total cholesterol	-16 mg/dL	+20 mg/dL	(p=0.002, week 13)
LDL cholesterol	-13 mg/dL	+11 mg/dL	(p=0.03, week 13)

"The results from this study are quite encouraging as ISIS 113715 appears to be effective in improving blood glucose control in patients with type 2 diabetes," said Robert Henry, M.D., Professor of Medicine at the University of California, San Diego and Chief, Section of Diabetes, Endocrinology, and Metabolism at VA San Diego Healthcare System. "If these data are confirmed in larger studies, ISIS 113715 has the potential to be an important new drug for the treatment of patients with type 2 diabetes. Type 2 diabetes represents a rapidly growing population in desperate need of new therapies. With the limitations of current therapies, there is a great need to develop drugs with new mechanisms that can alter the course of the disease or offer multiple metabolic benefits."

In the dose-escalation safety portion of the trial, patients (n=66) were treated for 6 weeks at doses of 100, 200, 400, or 600 mg. The highlights of the safety portion of the study are:

- * No drug related serious adverse events
- * No hypoglycemia, weight gain or metabolic acidosis
- * No clinically significant alterations in kidney or liver function
- * Dose dependent reduction of fasting blood glucose levels (-21mg/dL, p=0.05 at 600 mg/week)

* Dose dependent reduction of LDL cholesterol (-17 mg/dL, p=0.02 at 600 mg/week)

"Having completed the analysis of all the patients in this study through the treatment period, we have shown that reducing PTP-1B expression with ISIS 113715 resulted in significant improvement in glucose control in patients with type 2 diabetes and was well tolerated," said Sanjay Bhanot, M.D., Ph.D., Vice President of Metabolic Diseases Research and Development at Isis Pharmaceuticals. "ISIS 113715 improves glucose control as a single-agent without the side effects observed with existing drugs and also has a favorable effect on cholesterol. In addition to measuring fasting glucose levels, we measured postprandial blood glucose levels in a group of patients. Consistent with our other measurements, we also observed improvements in postprandial glucose control. These benefits make ISIS 113715 a very exciting drug."

"The results from this study support our enthusiasm about our recently initiated study to examine ISIS 113715 in combination with other antidiabetic drugs," Dr. Bhanot added. "We continue to be encouraged by the data from our cardiovascular and metabolic programs, including the recently reported Phase 2 data from our cholesterol lowering drug, ISIS 301012. These data reinforce our excitement about our pipeline and the value of our antisense platform."

ABOUT MEASURES OF BLOOD GLUCOSE CONTROL

The measures of blood glucose control in this Phase 2 study were HbA1c levels, fasting glucose levels (both self-monitored with a glucometer and those measured by the treating physicians) and postprandial glucose levels (glucose testing after meals). HbA1c is a measure that reflects the average blood glucose levels over a 3 month period, and is one of the standard measures used by physicians to tell if a patient's blood sugar is under control. The American Diabetes Association has established a HbA1c measurement of 7% or less as the target for effective glucose control.

ABOUT ISIS 113715

ISIS 113715, a second-generation antisense drug, inhibits PTP-1B, an enzyme that is a key mediator of insulin resistance. Insulin resistance is one of two main defects in patients with type 2 diabetes. The inhibition of PTP-1B may allow insulin receptors to stay active longer, allowing for more sugar uptake into cells, and thereby lowering blood sugar levels in the bloodstream. ISIS 113715 may offer new treatment to patients who do not respond adequately to currently available therapies such as glitazones, sulfonylureas, and biguanides.

Data from the single-agent Phase 2 study reported today in newly-diagnosed diabetic patients validate PTP-1B as a target for the treatment of type 2 diabetes that may also have ancillary therapeutic benefits of value to these diabetic patients. ISIS 113715 was well-tolerated. These data support the safety and efficacy for continued development of ISIS 113715 for patients with type 2 diabetes.

Isis recently initiated a combination study of ISIS 113715 in patients with type 2 diabetes. The Phase 2 dose-escalation study will evaluate the safety and activity of ISIS 113715 in combination with oral antidiabetic drugs. In this study, ISIS 113715 will be administered in patients with type 2 diabetes being treated with sulfonylurea or with sulfonylurea and metformin over a 13 week treatment period. In addition, Isis is conducting a Phase 2 study of ISIS 113715 in patients with type 2 diabetes at Yale University to further assess the effects of ISIS 113715 on insulin sensitivity, fasting and postprandial glucose control and lipid metabolism.

In Phase 1 trials, ISIS 113715 increased insulin sensitivity in healthy volunteers. In preclinical studies, ISIS 113715 normalized blood sugar levels in multiple rodent models and improved glucose tolerance in normal and obese primates. ISIS 113715 has not produced hypoglycemia or weight gain, characteristics of many other type 2 diabetes treatments in animals and in human clinical studies to date.

ABOUT TYPE 2 DIABETES

Type 2 diabetes is the most common form of diabetes. In type 2 diabetes, either the body does not produce enough insulin or the cells do not respond to insulin. Insulin is necessary for the body to be able to use sugar. Sugar is the basic fuel for the cells in the body, and insulin takes the sugar from the blood into the cells. When glucose builds up in the blood instead of going into cells, it can cause two problems: cells may be starved for energy or over time, high blood glucose levels may affect the eyes, kidneys, nerves or heart. According to the American Diabetes Association, diabetes affects nearly 17 million people and type 2 diabetes constitutes 90 percent of those cases.

WEBCAST PRESENTATION INFORMATION

Isis will conduct a live webcast presentation with slides to discuss this press release Tuesday, June 13 at 12:00 pm Eastern time. To participate over the Internet go to <http://www.investorcalendar.com/ClientPage.asp?ID=105099> or <http://www.isispharm.com>. A replay of the webcast will be available at these addresses for a limited time.

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 15 drugs in development. Isis' drug development programs are aimed at treating cardiovascular, metabolic and inflammatory diseases. Isis' partners are focused in disease areas such as inflammatory, ocular, viral and neurodegenerative diseases, and cancer. In its Ibis division, Isis is

developing and commercializing the IBIS biosensor system, a revolutionary system to identify infectious organisms. As an innovator in RNA-based drug discovery and development, Isis is the owner or exclusive licensee of approximately 1,500 issued patents worldwide. Additional information about Isis is available at www.isispharm.com.

This press release includes forward-looking statements regarding the therapeutic and commercial potential of ISIS 113715 for the treatment of type 2 diabetes. Any statement describing Isis' 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. 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, 2005, and its quarterly report on Form 10-Q for the quarter ended March 31, 2006, which are on file with the SEC. Copies of these and other documents are available from the Company.

SOURCE Isis Pharmaceuticals, Inc.

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