



**SOLVE  
ON.**

## **Incyte's Selective Oral Inhibitor of 11beta-HSD1 Demonstrates Improvements in Insulin Sensitivity and Lowers Cholesterol Levels in Type 2 Diabetics**

June 9, 2008

Results Presented at the American Diabetes Association 68th Scientific Sessions

WILMINGTON, Del.--(BUSINESS WIRE)--June 9, 2008--Incyte Corporation (Nasdaq:INCY) announced clinical results presented today at the American Diabetes Association 68th Scientific Sessions of its Phase IIa trial of INCB13739, an orally bioavailable inhibitor of the 11beta-hydroxysteroid dehydrogenase type 1 (11beta-HSD1) enzyme. These results showed that 28 days of treatment with INCB13739 significantly improved hepatic insulin sensitivity and decreased plasma LDL- and total-cholesterol levels in patients with type 2 diabetes. Results from this double-blind, placebo-controlled trial in 31 subjects diagnosed with type 2 diabetes were presented during an oral session entitled, "New and Novel Treatments for Diabetic Complications" by Meredith Hawkins, M.D., Department of Medicine, Division of Endocrinology, Albert Einstein College of Medicine and Principal Investigator for the trial.

"These findings indicate that inhibition of 11beta-HSD1 can improve insulin sensitivity and plasma cholesterol levels in patients with type 2 diabetes. The insulin sensitivity data obtained after INCB13739 therapy in this trial are comparable to those obtained following pioglitazone treatment for a similar duration. The results from this trial suggest that INCB13739 has the potential to produce clinically meaningful benefit on macrovascular risk in patients with type 2 diabetes mellitus," stated Dr. Hawkins.

### **Summary of Results**

Stepped pancreatic clamp studies were designed to optimally study hepatic and peripheral insulin sensitivity using two distinct levels of insulin. In this trial, INCB13739 treatment resulted in:

- a placebo-adjusted mean 0.614 mg/kg/min decrease in glucose production ( $P = 0.018$ ), indicating markedly enhanced hepatic insulin sensitivity
- a mean 0.752 mg/kg/min trend toward increased insulin-stimulated glucose uptake ( $P = 0.177$ ), an indicator of peripheral insulin sensitivity

Fasting blood tests were used to assess the secondary endpoints of the study, plasma glucose concentrations and lipid profiles. INCB13739 treatment resulted in:

- a trend toward reduced fasting plasma glucose (-19.5 mg/dL), with the treatment effect being of greater magnitude in patients with higher (greater than 160 mg/dL) baseline hyperglycemia (-45.0 mg/dL,  $P = 0.075$ )
- a significant decrease in plasma total cholesterol (-26.9 mg/dL,  $P = 0.007$ ) and LDL-cholesterol (-22.3 mg/dL,  $P = 0.001$ ).

### **Summary of Safety Results**

INCB13739 was safe and very well tolerated over the course of the trial with no serious adverse events noted. The most frequent adverse events occurring in more than one subject were headache, nausea, hyporeflexia, diarrhea and upper respiratory tract infection, all mild to moderate in intensity. Headache, nausea and hyporeflexia were also reported by subjects randomized to the placebo arm. No other adverse trends in vital signs, ECGs, or laboratory parameters were observed. As expected, fasted morning plasma ACTH levels increased after INCB13739 treatment relative to baseline (+9.5 pg/mL), likely reflecting compensatory pharmacology to maintain plasma cortisol levels. In line with this finding and consistent with Phase I data presented from an earlier trial, morning plasma cortisol levels were unchanged after INCB13739 therapy.

### **About the Trial**

This was a 28-day Phase IIa clinical trial in type 2 diabetic patients who were either treatment-naïve or had been withdrawn from other anti-hyperglycemic medication for 14 days. Subjects receiving thiazolidinediones (TZDs), exenatide, or insulin in the three-months prior to screening were excluded. Subjects received either 100 mg INCB13739 BID or placebo. In addition to evaluating the safety and tolerability of INCB13739, several key efficacy measures were assessed including:

- insulin sensitivity as determined by a stepped hyperinsulinemic, euglycemic, pancreatic clamp
- fasting blood glucose
- fasting plasma lipid profiles

### **Current Status of INCB13739**

INCB13739 is currently being evaluated in a randomized, double-blind, placebo-controlled, dose-ranging Phase IIb clinical trial in patients with type 2 diabetes. This is a multi-national trial designed to evaluate the safety and efficacy of multiple once-daily dose regimens of INCB13739 when added to failing metformin monotherapy. The primary endpoint of the trial is the change from baseline to week 12 in hemoglobin A1c, a recognized surrogate endpoint for integrated glycemic control over a 2-3 month period.

### **About INCB13739**

INCB13739 is a potent, selective, non-steroidal small molecule inhibitor of 11beta-HSD1 with 1.1 nM potency in cellular assays. The compound is greater than 1000-fold selective over 11beta-HSD2, glucocorticoid receptor, and mineralocorticoid receptor and exhibits good oral pharmacokinetics

with an estimated half-life of 11 hours.

Data from prior clinical trials indicates that the dose level of INCB13739 selected for this study achieves complete inhibition of adipose tissue and liver 11beta-HSD1 activity throughout the dosing interval.

#### About 11beta-HSD1

11beta-HSD1 is an enzyme that converts inactive cortisone into the potent biologically active hormone cortisol. This conversion occurs within cells of key metabolic tissues including liver, adipose, muscle and pancreas. Importantly, preclinical studies have shown that the enzyme does not significantly affect neuroendocrine control of glucocorticoid biosynthesis in the adrenal gland, but rather provides a mechanism to specifically increase local glucocorticoid exposure within cells in a tissue-specific manner. Unlike the hormone insulin, which is produced by beta-cells in the pancreas and maintains normal blood glucose levels, cortisol elevates blood glucose levels by driving glucose production in the liver, and inhibiting the uptake and disposal of glucose in muscle and adipose. Thus, cortisol acts as an antagonist of insulin action, and 11beta-HSD1 mediated production of cortisol has been hypothesized to contribute to human insulin resistance, type 2 diabetes, and the often-associated cardiovascular comorbidities.

Current treatments for type 2 diabetes typically address individual components of the disease, and few therapies target the multiple risk factors that lead to the elevated cardiovascular risk associated with this condition. By selectively inhibiting 11beta-HSD1 and reducing the level of cortisol in key metabolic tissues, INCB13739 has the potential to simultaneously target multiple cardiovascular risk factors in patients with type 2 diabetes.

#### About Type 2 Diabetes

According to the Centers for Disease Control and Prevention (CDC), nearly 21 million Americans have diabetes. The majority of these patients have type 2 diabetes. The CDC also reports that 41 million people are estimated to have pre-diabetes, a pre-disposing condition that occurs before the onset of type 2 diabetes.

#### About Incyte

Incyte Corporation is a Wilmington, Delaware-based drug discovery and development company focused on developing proprietary small molecule drugs to treat serious unmet medical needs. Incyte's pipeline includes multiple compounds in Phase I and Phase II development for oncology, inflammation and diabetes. For additional information on Incyte, visit the Company's web site at [www.incyte.com](http://www.incyte.com).

#### Forward Looking Statements

Except for the historical information contained herein, the matters set forth in this press release, including statements with respect to the potential for INCB13739 to produce clinically meaningful benefit on macrovascular risk in patients with type 2 diabetes mellitus and to simultaneously target multiple cardiovascular risk factors in patients with type 2 diabetes, are all forward-looking statements within the meaning of the "safe harbor" provisions of the Private Securities Litigation Reform Act of 1995. These forward-looking statements are subject to risks and uncertainties that may cause actual results to differ materially, including the high degree of risk associated with drug development and clinical trials, the uncertainty of the FDA approval process, results of further research and development, the impact of competition and of technological advances and the ability of Incyte to compete against parties with greater financial or other resources, Incyte's ability to enroll a sufficient number of patients for its clinical trials, and other risks detailed from time to time in Incyte's filings with the Securities and Exchange Commission, including its Quarterly Report on Form 10-Q for the quarter ended March 31, 2008. Incyte disclaims any intent or obligation to update these forward-looking statements.

#### CONTACT:

Incyte Corporation  
Pamela M. Murphy  
Vice President, Investor Relations/Corporate  
Communications  
302/498-6944

SOURCE: Incyte Corporation