

INCYTE CORPORATION



11 β HSD1 INHIBITOR PROGRAM

***NOVEL ORALLY-ADMINISTERED THERAPEUTICS FOR
TYPE 2 DIABETES***



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Opportunity Overview

Over 20 million Americans, approximately 7% of the US population, have type 2 diabetes mellitus. The disease frequently leads to serious long-term microvascular complications including blindness, kidney failure, amputations and nerve damage. Most people with type 2 diabetes have additional macrovascular risk factors, including dyslipidemia and high blood pressure, which significantly increase their risk for heart attacks and stroke. Ultimately, the successful treatment of hyperglycemia, as well as the associated cardiovascular risk factors, is required to achieve clinical benefit in patients with the disease.

Glucocorticoids play a fundamental role in controlling physiologic homeostasis and, when present in excess, can have a detrimental impact on glucose control, blood pressure and lipid levels. Cortisol, the primary glucocorticoid in man, acts as a functional antagonist of insulin action in multiple tissue types, including liver, adipose, skeletal muscle, and pancreas. This activity is mediated by its ability to bind and activate the glucocorticoid receptor (GR), an intracellular ligand-dependent transcription factor. Cortisol has been proposed to play a central role in the many metabolic sequelae observed in type 2 diabetes. A well-tolerated treatment that effectively abrogates cortisol's antagonistic actions toward insulin thus has the potential to deliver significant therapeutic benefit across the broad range of pathologies present in human type 2 diabetes.

The enzyme 11 β -hydroxysteroid dehydrogenase type 1, or 11 β HSD1, catalyzes the intracellular conversion of functionally inert cortisone to biologically-active cortisol. This activity is distinct from the process of adrenal cortisol biosynthesis which occurs in an 11 β HSD1-independent manner under the control of the hypothalamic-pituitary-adrenal axis. The level of 11 β HSD1 activity, therefore, provides a means whereby specific cell types can generate locally high intracellular concentrations of cortisol in a manner that is independent of plasma cortisol exposures. Given that the enzyme is abundantly expressed in metabolically important tissues, such as adipose, muscle, and liver, that become resistant to insulin action in type 2 diabetes, inhibition of 11 β HSD1 offers the potential to restore the metabolic action of insulin in these tissues.

Multiple lines of evidence indicate that 11 β HSD1-mediated intracellular cortisol production may have a pathogenic role in type 2 diabetes and its co-morbidities. Furthermore, lowering of intracellular glucocorticoid concentrations through a variety of means, including administration of small molecule 11 β HSD1 inhibitors, significantly attenuates the signs and symptoms of disease in preclinical animal models of diabetes/metabolic syndrome.

Incyte has discovered novel, potent, orally-available inhibitors of the 11 β HSD1 enzyme. These compounds are highly selective, demonstrate pharmacologic activity in metabolically important tissues, and display excellent drug-like properties. They represent multiple distinct chemical series and, with the accompanying intellectual



property, increase the overall likelihood of success of the program and offer numerous compounds for pursuit across multiple potential indications.

Incyte's lead compound, INCB13739, has completed single and multiple dose Phase I clinical trials in healthy volunteers, a Phase IIa pharmacodynamic activity study in obese insulin resistant subjects and a 28 day Phase IIa two-step insulin clamp study in patients with type 2 diabetes. The compound has been very well tolerated in all studies to date. Results from the 28 day clamp study have demonstrated improvements in glucose control, including clamp-based measures of hepatic glucose production and plasma LDL- and total-cholesterol levels. Additionally, trends for improvement were observed in clamp-based measures of peripheral glucose uptake, in plasma glucose and triglycerides, and in blood pressure. These results suggest that inhibition of the 11 β HSD1 enzyme by INCB13739 has the potential to produce clinically meaningful benefit on macrovascular risk in patients with type 2 diabetes.

Therapeutic Rationale

Local Tissue-Specific Reactivation of Cortisol by 11 β HSD1

The phenotypic similarities between human metabolic syndrome and Cushing's syndrome ¹ have led to the provocative hypothesis that the metabolic consequences of obesity and insulin resistance may be driven by cortisol action. Paradoxically, however, circulating cortisol levels are invariably normal in the former ². It was not until the discovery of the cortisol-generating enzyme 11 β -hydroxysteroid dehydrogenase type 1 (11 β HSD1) that a mechanistic rationale for this similarity could be proposed.

A number of studies have demonstrated substantial 11 β HSD1 enzymatic activity in metabolically important tissues:

- (1) The liver possesses a significant capacity for cortisone reactivation, where orally administered cortisone is rapidly converted to cortisol by way of first pass metabolism by 11 β HSD1. ³
- (2) Using hepatic vein catheterization and systemic infusion of isotopically labeled cortisol, the contribution of extra-hepatic tissues, primarily visceral adipose tissue, to total splanchnic cortisol production has been shown to equal or exceed the relative contribution by the liver⁴, and as a whole, the splanchnic bed has been shown to produce up to 30% as much cortisol as is produced by adrenal biosynthesis.
- (3) Both *in vitro* and *ex vivo* studies using human and rodent tissues have illustrated the capacity of skeletal muscle and pancreatic beta-cells to reactivate corticosteroids by way of 11 β HSD1 activity. ^{5,6}



Adipose Tissue 11 β HSD1 Activity and Type 2 Diabetes

The activity of 11 β HSD1 provides a mechanism for specific cell types to leverage the relatively large but inactive circulating cortisone pool for intracellular cortisol production. Specifically, 11 β HSD1 activity in metabolically active tissues enables glucocorticoid-mediated antagonism of insulin action in a manner that is independent of circulating hormone levels.

Several lines of evidence indicate that adipose 11 β HSD1 and intracellular glucocorticoid concentrations represent a primary driver of insulin resistance and type 2 diabetes:

- 11 β HSD1 is upregulated 3-5 fold within the subcutaneous adipose tissue of obese humans. In this population, adipose tissue 11 β HSD1 activity exhibits a close positive correlation with body mass index (BMI) and measures of insulin resistance.^{7,8}
- Adipose-specific overexpression of 11 β HSD1 by 2-3 fold in a transgenic mouse produces a phenotype closely resembling that of human type 2 diabetes, including visceral obesity, insulin-resistant hyperglycemia, hyperlipidemia, hyperphagia, and hypertension. As in the human disease, circulating glucocorticoid levels are normal in these animals.^{9,10}
- Reduction of intracellular glucocorticoid levels in the mouse as a result either of 11 β HSD1 deletion by homologous recombination^{11,12,13} or of adipose tissue overexpression of the glucocorticoid-inactivating enzyme, 11 β HSD2¹⁴, is sufficient to promote resistance to weight gain on high-fat diets, correct dyslipidemic profiles, improve glucose tolerance, and heighten insulin sensitivity. All of these changes occur in the presence of normal circulating glucocorticoid levels.

Properties of Incyte 11 β HSD1 Inhibitors

Effective small molecule inhibitors of 11 β HSD1 must strike a balance between potency, selectivity, and appropriate pharmacokinetic and distribution properties, all while avoiding hERG and cytochrome p450 induction liabilities. Incyte has identified multiple chemically-distinct series of compounds with all of these characteristics, increasing the probability of success of the overall program and offering the opportunity to progress distinct compounds for different indications.

Our most advanced oral 11 β HSD1 inhibitor, INCB13739, has shown the following properties:



- low nanomolar potency in biochemical and cellular assays
- greater than 1,000-fold selectivity against 11 β HSD2 in biochemical assays
- greater than 1,000-fold selectivity against the mineralocorticoid and glucocorticoid receptors in binding and functional assays
- high selectivity against a panel of relevant GPCRs, enzymes, and ion channels
- high selectivity against hERG in patch clamp assays
- no significant induction or inhibition of cytochrome p450 enzymes
- excellent preclinical pharmacokinetic profile
- pharmacodynamic activity in adipose tissue of non-human primates

Clinical Results with INCB13739

Single and multiple dose Phase I studies in healthy volunteers have been completed with INCB13739 (Study INCB 13739-101), as has a Phase 2a pharmacodynamic activity study where INCB13739 was shown to achieve prolonged inhibition of 11 β HSD1 in both adipose and liver of obese insulin resistant individuals after oral dosing (Study INCB 13739-103). A one-month Phase 2a hyperinsulinemic clamp study in 31 type 2 diabetic patients has recently been completed (Study INCB 13739-201) in which the effect of INCB13739 on multiple disease parameters, including insulin sensitivity, glycemia and lipemia were evaluated.

In all of these studies, INCB013739 was safe and very well tolerated. There have been no serious adverse events noted to date, nor has there been any dose relationship to the frequency or severity of adverse events. No trends have emerged in an analysis of vital signs, ECGs, or laboratory parameters.

In the proof-of-concept Phase 2a study, INCB 13739-201, a stepped hyperinsulinemic, euglycemic, pancreatic clamp technique was used to assess the two primary endpoints of the study, hepatic and peripheral insulin sensitivity, under fixed hormonal conditions. The first step of the clamp measures endogenous glucose production (EGP) in the liver under physiologic insulin levels and, as can be seen in Figure 1, INCB013739 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. The second step of the clamp measures glucose uptake under pharmacologic insulin levels. INCB013739 treatment resulted in a mean 0.752 mg/kg/min trend toward increased insulin-stimulated glucose uptake ($P = 0.177$), an indicator of peripheral insulin sensitivity.



Figure 1. Primary clamp endpoints in Study INCB 13739-201

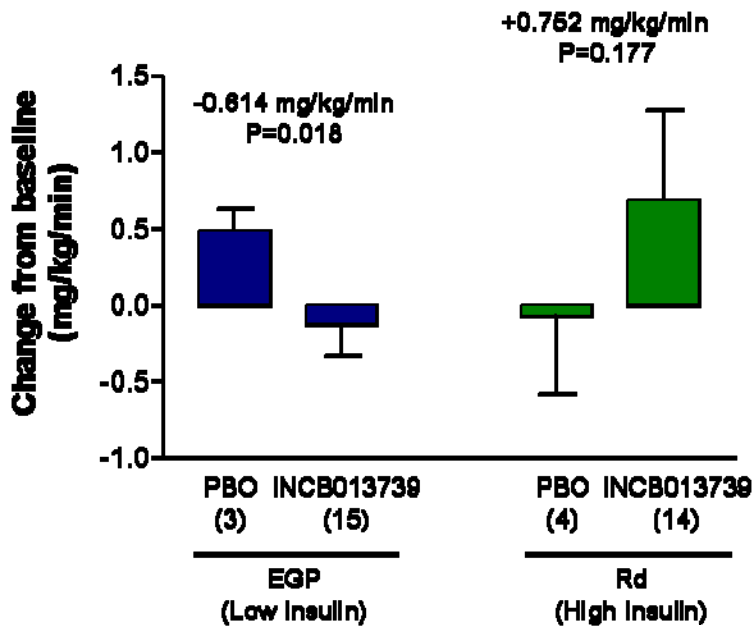
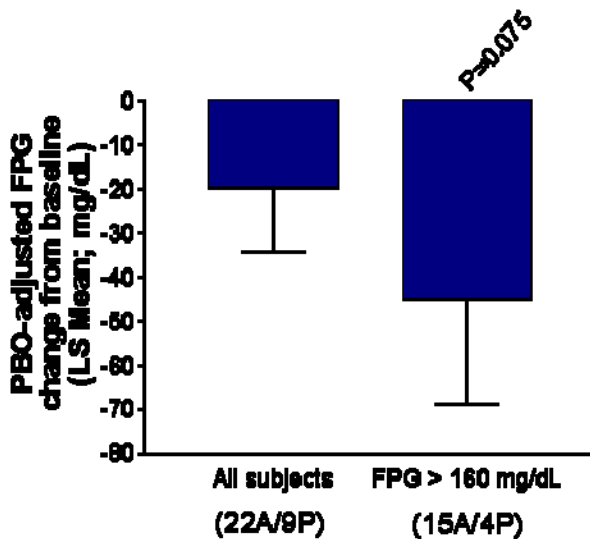


Figure 2 shows the fasting plasma glucose data from this study, a secondary endpoint. INCB013739 treatment resulted in a trend toward reduced fasting plasma glucose (-19.5 mg/dL), with the treatment effect being of greater magnitude in patients with higher (>160 mg/dL) baseline hyperglycemia (-45.0 mg/dL, P = 0.075).

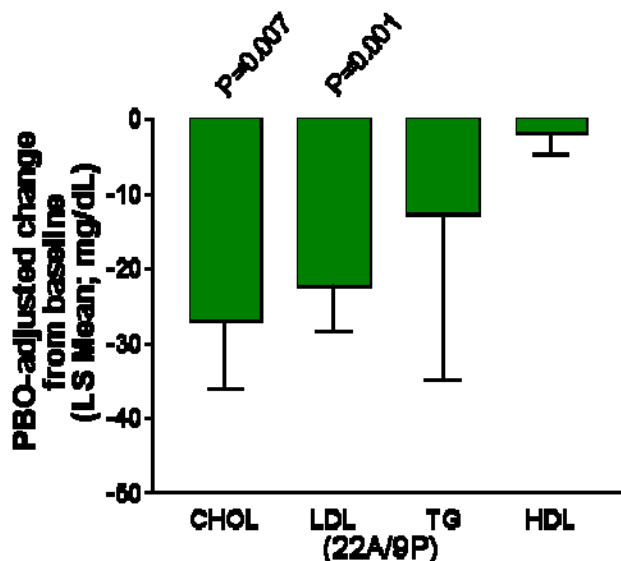
Figure 2. Fasting plasma glucose levels in Study INCB 13739-201.





Lipid profiles were also examined as a secondary endpoint in this study. As shown in Figure 3, 28 days of treatment with INCB013739 resulted in a significant decrease in plasma LDL (-22.3 mg/dL, P = 0.001) and total cholesterol (-26.9 mg/dL, P = 0.007). A trend toward improvement in triglyceride levels was also observed.

Figure 3. Plasma lipid profiles in Study INCB 13739-201



Based on these results, INCB13739 has advanced into a 3 month dose ranging study in patients with type 2 diabetes. This study, INCB 13739-202, was initiated on May 30, 2008 and will enroll a total of 300 subjects who are poorly controlled on metformin monotherapy. INCB13739 at one of 5 dose levels or placebo will be added on to the patients' stable dose metformin regimen for a total duration of 12 weeks. The primary endpoint of the study will be the change from baseline in HbA1c.

Summary

Incyte has discovered multiple distinct chemical series of potent, selective, and orally available 11 β HSD1 inhibitors, which have potential as novel therapies for type 2 diabetes (with uniquely positive effects on cardiovascular co-morbid risk factors), dyslipidemia, hypertension, and metabolic syndrome, amongst other disorders. The most advanced of these, INCB013739, has demonstrated positive effects on glycemic control and plasma cholesterol in a 1 month study in Type 2 diabetics, and is currently in a 3 month Phase 2b study in this disease. The preclinical and clinical safety profile of INCB013739 to date has been excellent.



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