

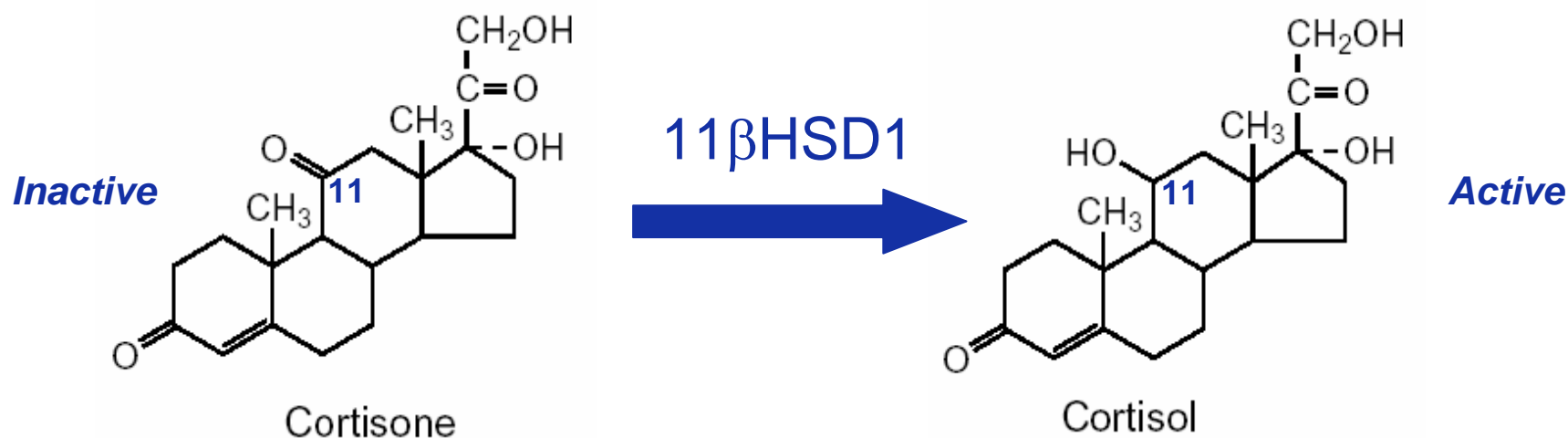
**INCB013739, a Selective Inhibitor of 11 $\beta$ -Hydroxysteroid  
Dehydrogenase Type 1 (11 $\beta$ HSD1), Improves Insulin  
Sensitivity and Lowers Plasma Cholesterol Over 28 Days  
in Patients with Type 2 Diabetes Mellitus**

**Meredith Hawkins<sup>1</sup>, Deborah Hunter<sup>2</sup>, Preeti Kishore<sup>1</sup>, Sherwyn  
Schwartz<sup>3</sup>, Marcus Hompesch<sup>4</sup>, Gregory Hollis<sup>2</sup>, Richard Levy<sup>2</sup>,  
Bill Williams<sup>2</sup>, Reid Huber<sup>2</sup>**

*<sup>1</sup>AECOM, Bronx, NY; <sup>2</sup>Incyte Corporation, Wilmington, DE;  
<sup>3</sup>dgd Research, San Antonio, TX; <sup>4</sup>Profil Institute, San Diego, CA*



## 11 $\beta$ HSD1 Activity Increases Local Cortisol Concentrations in Key Metabolic Tissues



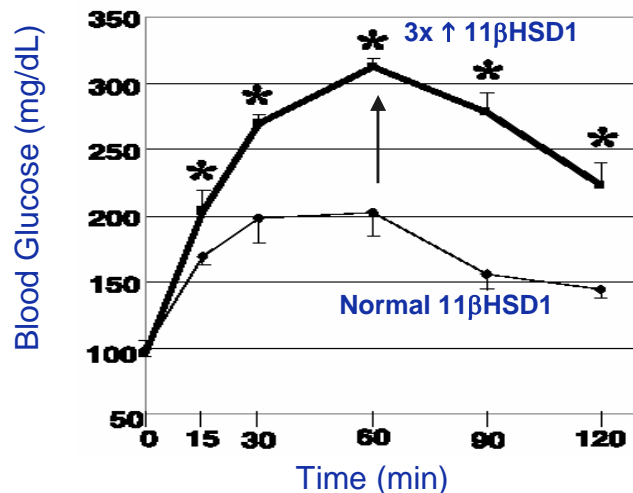
- 11 $\beta$ HSD1 increases local cortisol production in specific tissue types such as adipose, liver, skeletal muscle, and the pancreas
- 11 $\beta$ HSD1 activity within the splanchnic bed produces as much as 30% of the amount of cortisol as is produced by adrenal biosynthesis
- Adipose tissue 11 $\beta$ HSD1 activity has been shown to be upregulated in human obesity and insulin resistance

# 11 $\beta$ HSD1 Activity in Adipose Tissue May Drive Metabolic Disease and Cardiovascular Risk

## Lessons from Rodent Models

3-fold increase in adipose 11 $\beta$ HSD1 as seen in human obesity

### Glucose Intolerance



### 'Metabolic Syndrome'

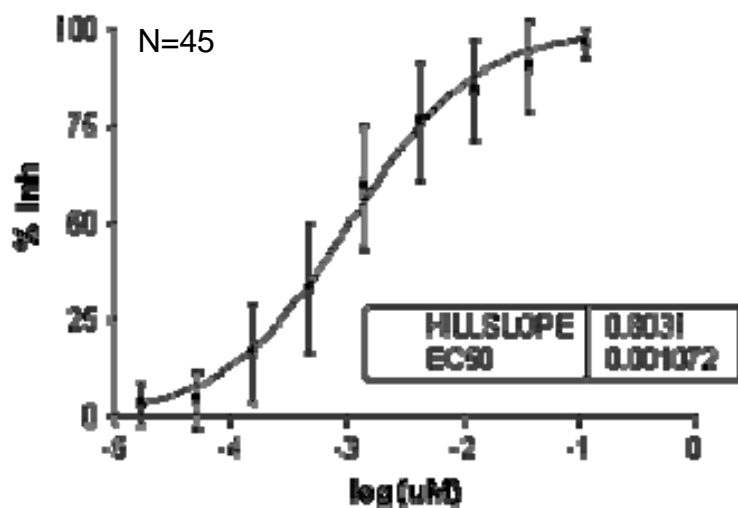
- $\uparrow$  Insulin resistance
- $\uparrow$  Hyperglycemia
- $\uparrow$  Triglycerides
- $\uparrow$  Body weight
- $\uparrow$  Visceral fat mass
- $\uparrow$  Blood pressure

***Could intracellular cortisol production by 11 $\beta$ HSD1 underlie the diverse cardio-metabolic phenotype that associates with obesity?***

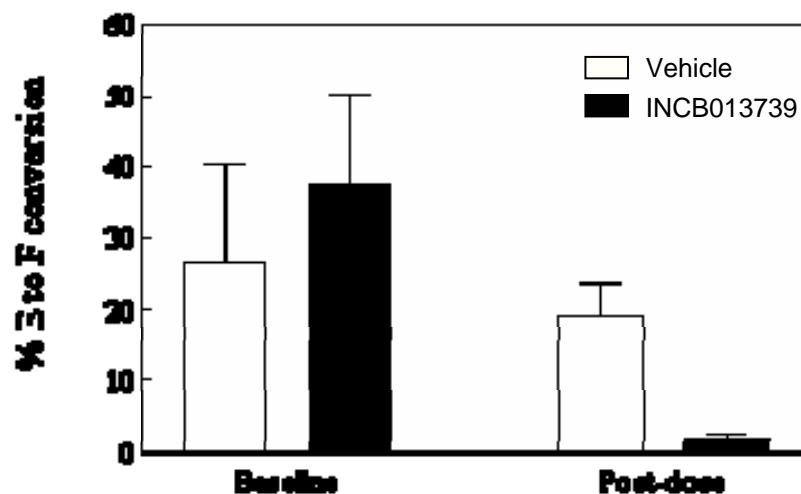
# INCB013739: A Potent and Selective Small Molecule Inhibitor of 11 $\beta$ HSD1

- INCB013739 is a non-steroidal, small molecule inhibitor of 11 $\beta$ HSD1
  - 1.1 nM potency in cellular assays
  - > 1000-fold selective over 11 $\beta$ HSD2, GR, and MR
- INCB013739 is orally bio-available with a plasma  $T_{1/2}$  of 11 h in man
- INCB013739 is pharmacodynamically active in adipose tissue of rhesus monkeys after oral dosing

*Cellular INCB013739 Potency*

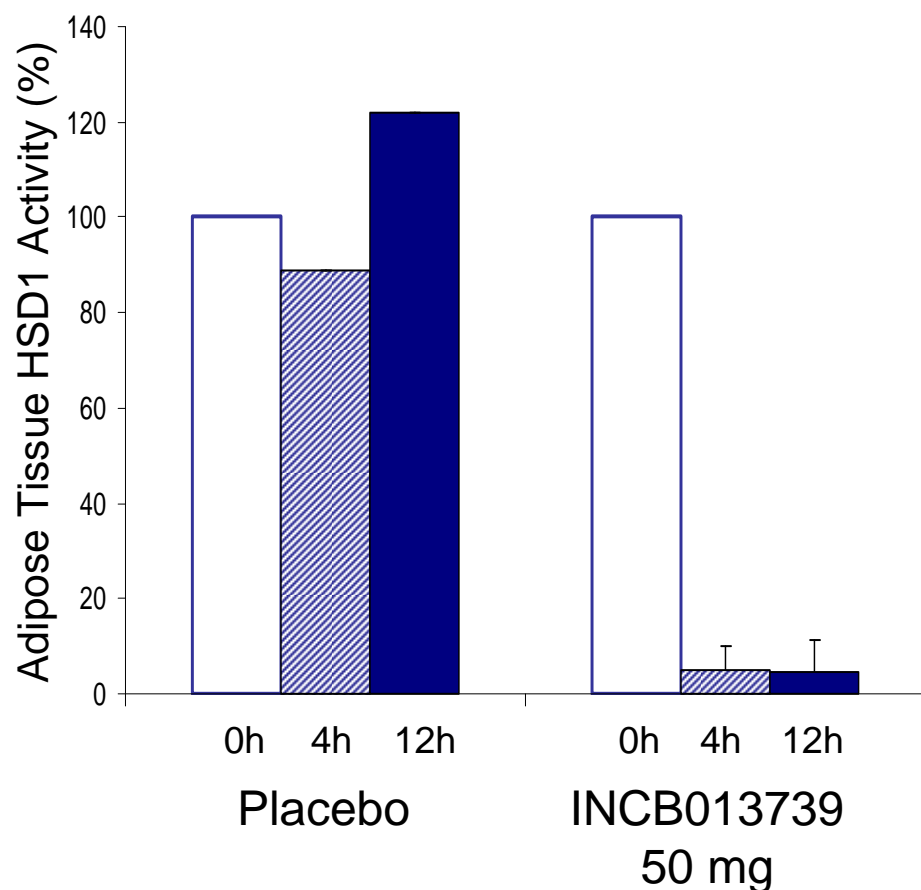


*Rhesus monkey adipose inhibition*

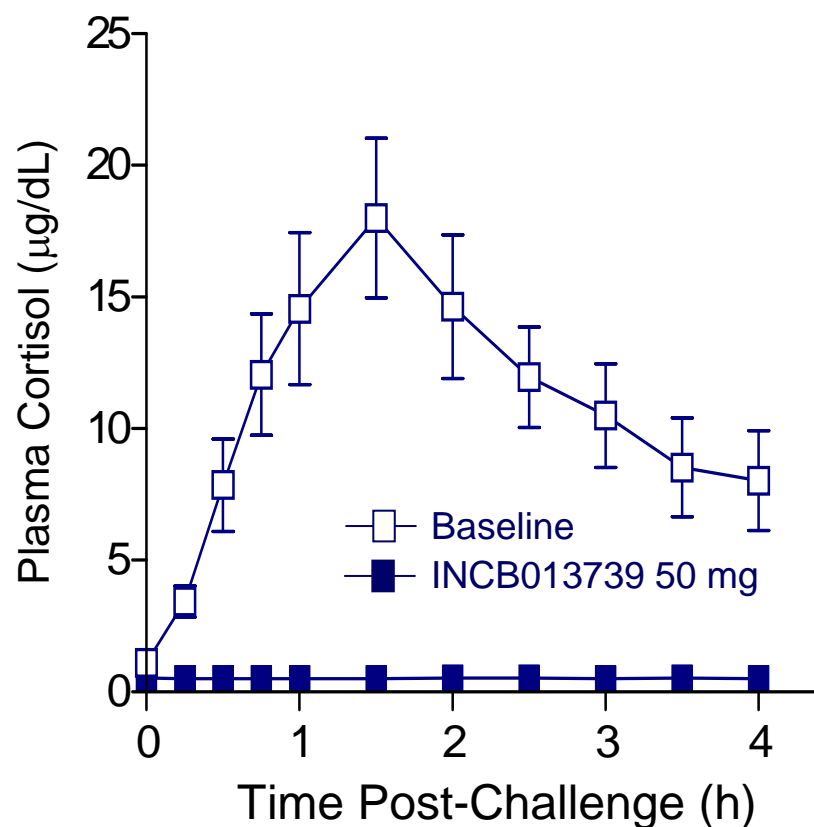


# Adipose Tissue and Liver Pharmacodynamic Activity of INCB013739 After Oral Dosing in Obese Subjects

## Adipose Tissue 11 $\beta$ HSD1 Activity (*ex vivo* whole tissue assay)



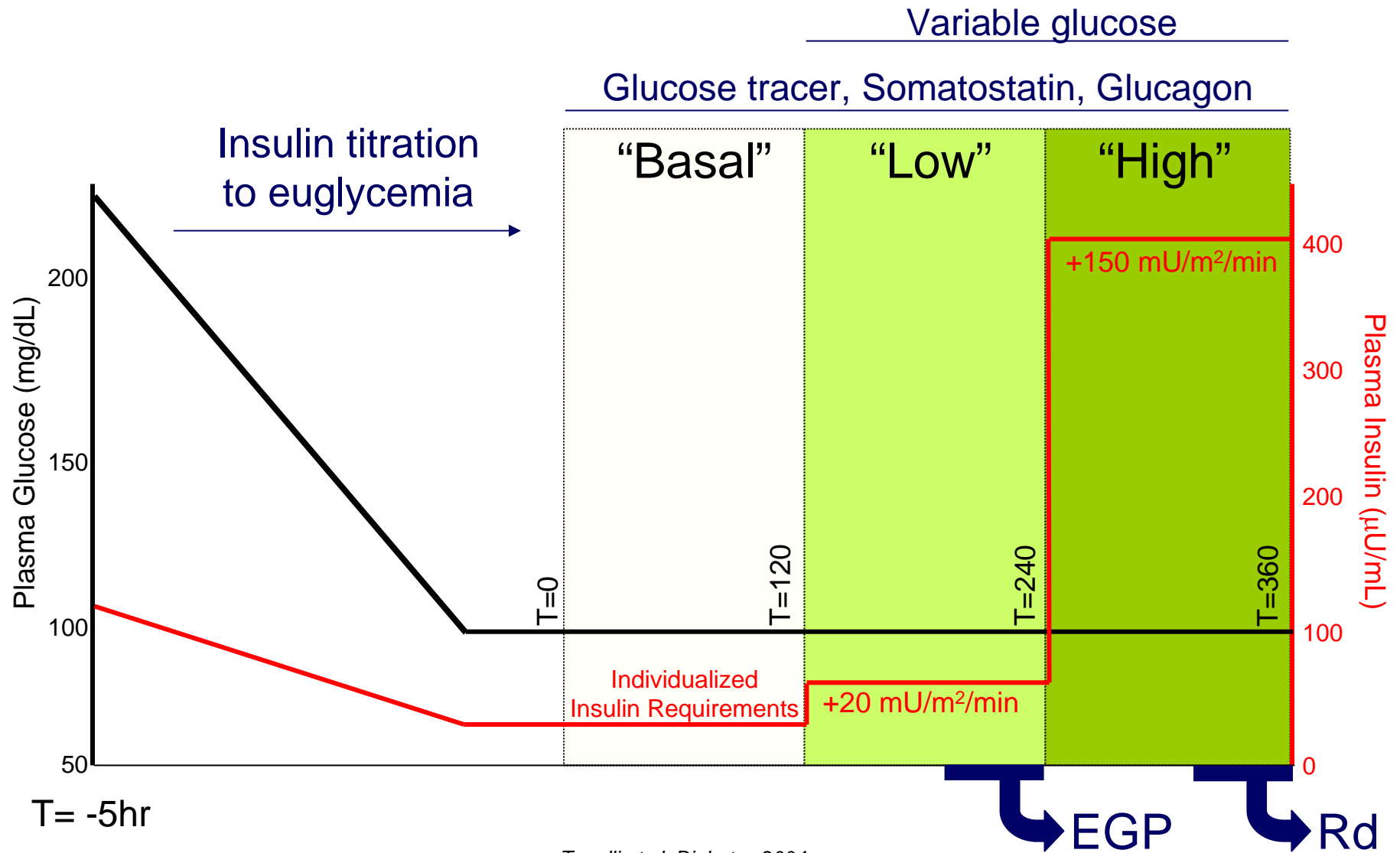
## Liver 11 $\beta$ HSD1 Activity (Oral Cortisone Challenge)



# INCB 13739-201: Phase 2a Evaluation of INCB013739 in Patients with Type 2 Diabetes

- 28-Day Phase IIa study in Type 2 Diabetic patients
  - Eligible subjects were either naïve to treatment or withdrawn from anti-hyperglycemic medication for 14 days (TZDs excluded)
- 100 mg INCB013739 BID vs. Placebo (2:1 randomization)
  - Dose selected to completely inhibit splanchnic 11 $\beta$ HSD1 activity 24/7
- Primary Objectives
  - Safety and tolerability
  - Insulin sensitivity as determined by stepped hyperinsulinemic clamp
- Secondary Objectives
  - Fasting blood glucose
  - Fasting plasma lipid profiles
  - Trough INCB013739 exposures on days 14 and 27

# Stepped Hyperinsulinemic, Euglycemic, Pancreatic Clamp to Assess Hepatic and Peripheral Insulin Sensitivity



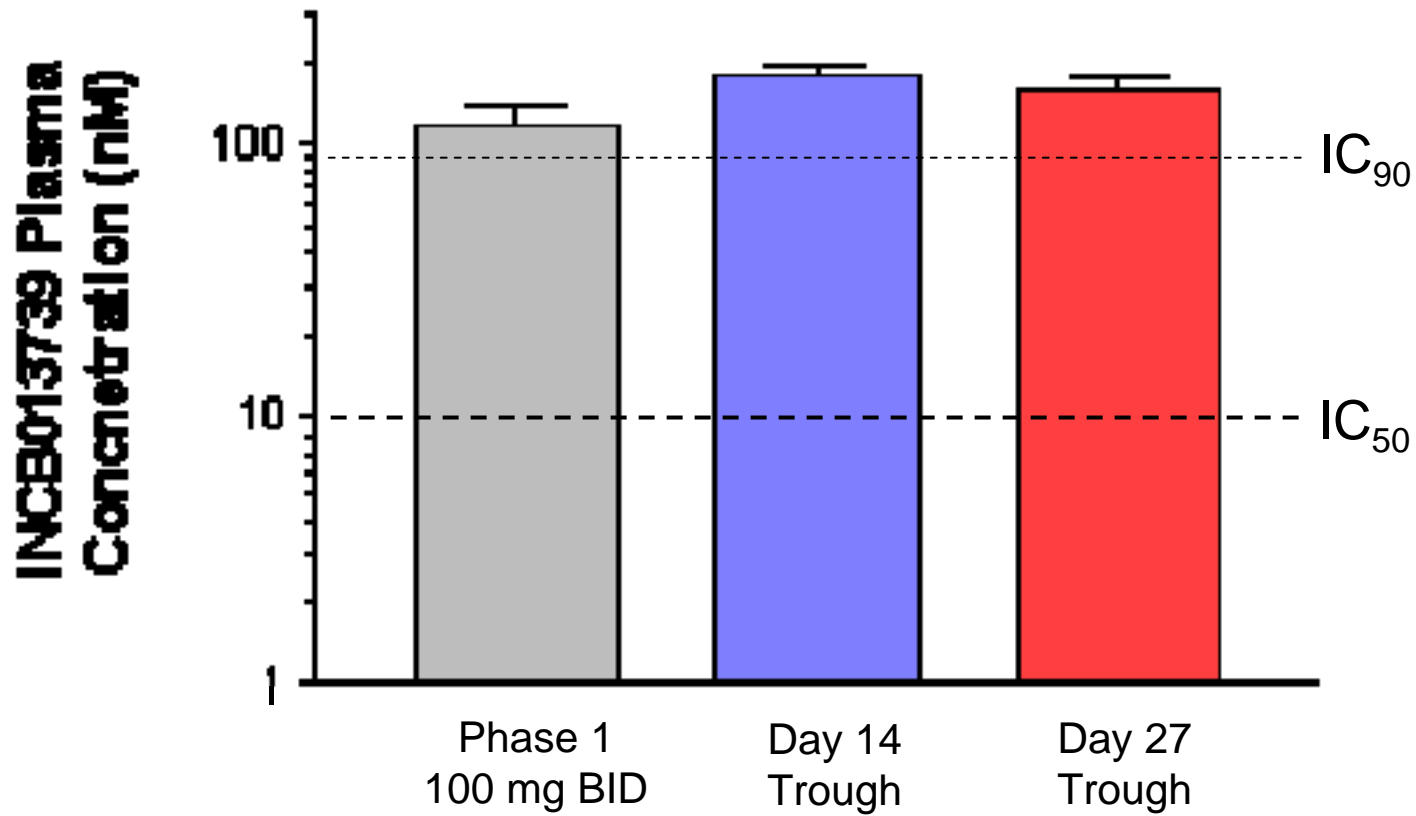
# INCB 13739-201: Study Demographics

(End-of-study analysis, PP)

<b>@ Screening Visit:</b>	<b>Placebo (n=9)</b>	<b>INCB013739 (n=22)</b>
<b>Age (yr)</b>	<b>53.1 (8.5)</b>	<b>55.7 (7.1)</b>
<b>Sex</b>	<b>1 female, 8 male</b>	<b>6 female, 16 male</b>
<b>BMI (kg/m<sup>2</sup>)</b>	<b>34.2 (3.8)</b>	<b>32.0 (3.3)</b>
<b>A1c (%)</b>	<b>7.2 (0.6)</b>	<b>7.7 (1.1)</b>
<b>FPG (mg/dL)</b>	<b>134 (26)</b>	<b>156 (36)</b>
<b>No. on OADs</b>	<b>6 [3M, 1M+S, 2S]</b>	<b>17 [10M, 3M+S, 4S]</b>
<b>@ Baseline Visit:</b>		
<b>FPG (mg/dL)</b>	<b>170 (41)</b>	<b>190 (39)</b>
<b>LDL (mg/dL)</b>	<b>108 (34)</b>	<b>114 (36)</b>
<b>HDL (mg/dL)</b>	<b>38 (9)</b>	<b>38 (8)</b>
<b>Cholesterol (mg/dL)</b>	<b>181 (41)</b>	<b>189 (41)</b>
<b>Triglyceride (mg/dL)</b>	<b>177 (94)</b>	<b>188 (89)</b>

*Values are mean (SD)*

# INCB 13739-201: Morning Trough Exposures of INCB013739

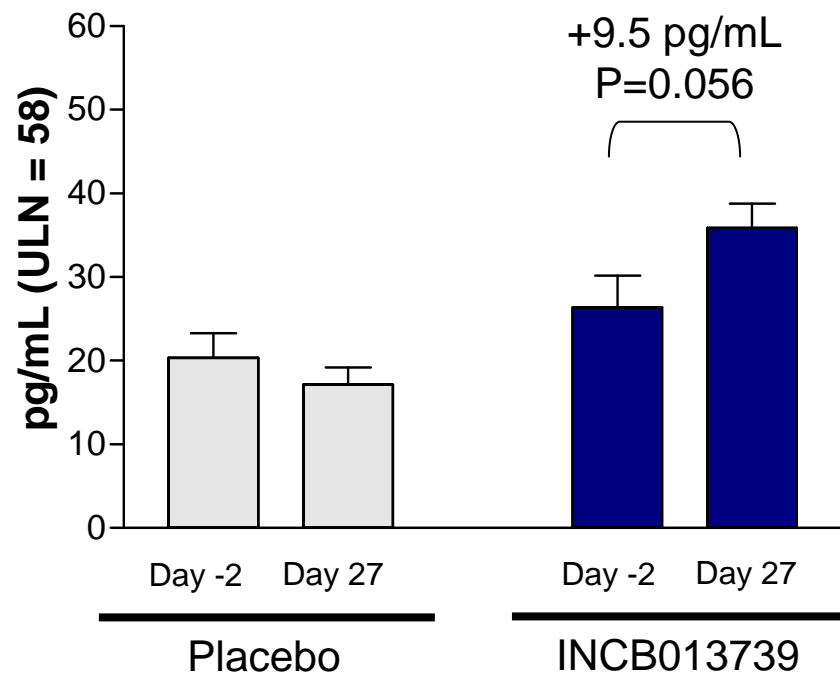


## INCB 13739-201: Safety and Tolerability Summary

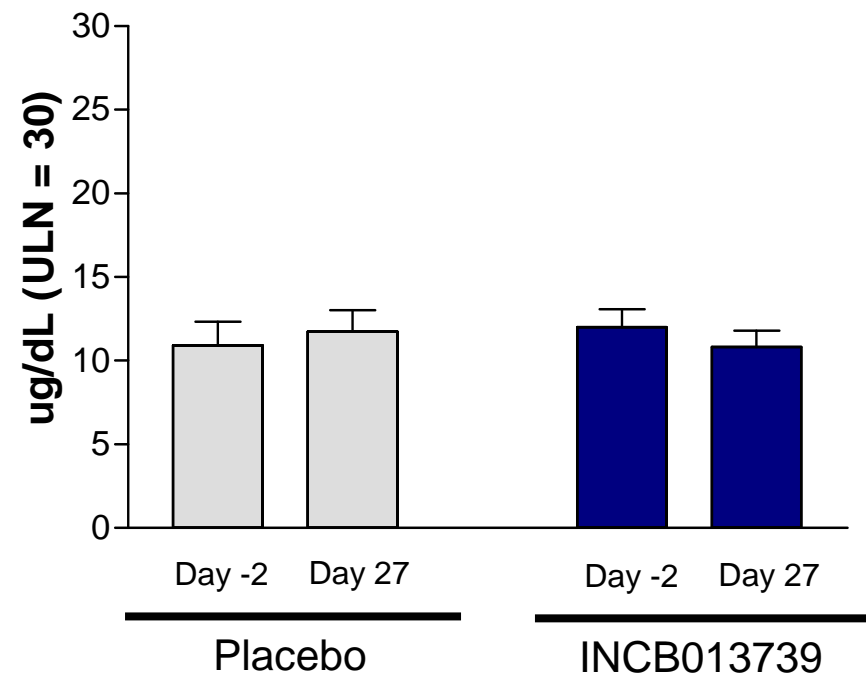
- 100 mg INCB013739 BID was safe and very well tolerated
- No serious adverse events
- Most frequent AEs occurring in more than one subject: headache (6), nausea (4), hyporeflexia (2), diarrhea (2), upper respiratory tract infection (2); all mild to moderate in intensity
  - headache, nausea, and hyporeflexia also reported in PBO arm
- No LFT abnormalities observed
- No incidences of hypoglycemia observed
- No other trends in vital signs, ECGs, or laboratory parameters observed

# INCB 13739-201: Plasma ACTH and Cortisol (End-of-study analysis, PP)

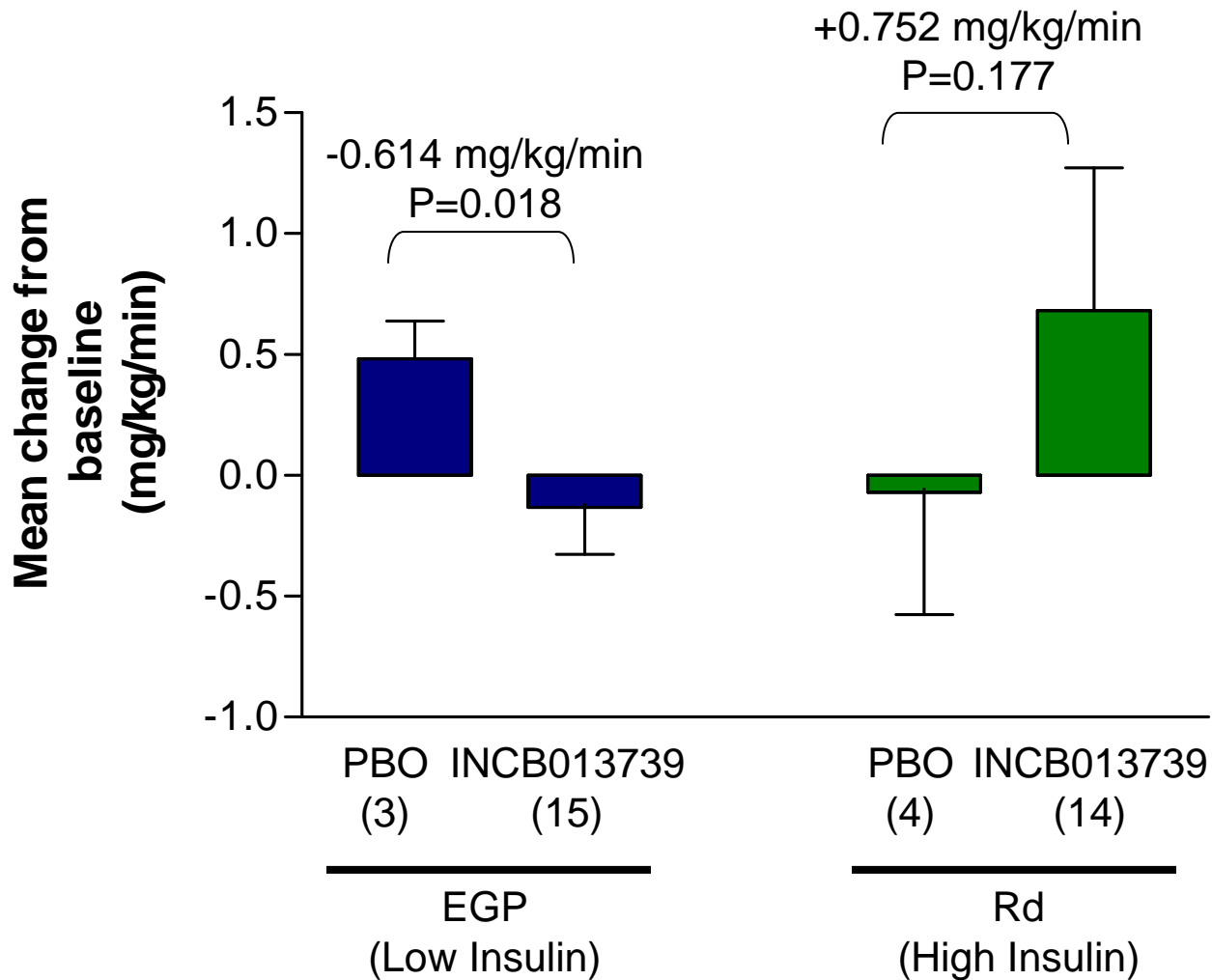
## Morning Plasma ACTH



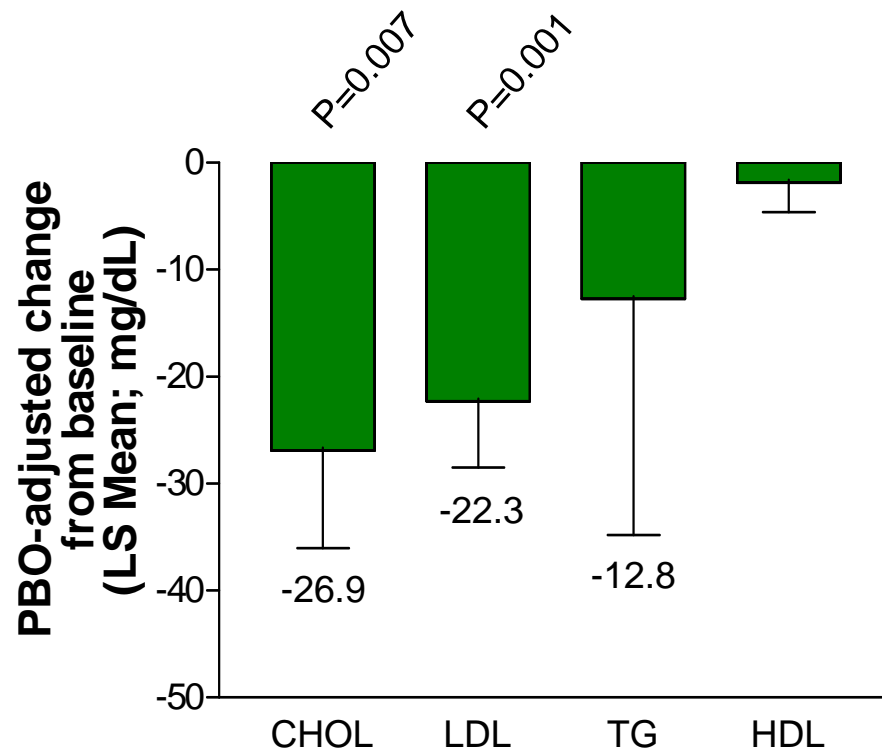
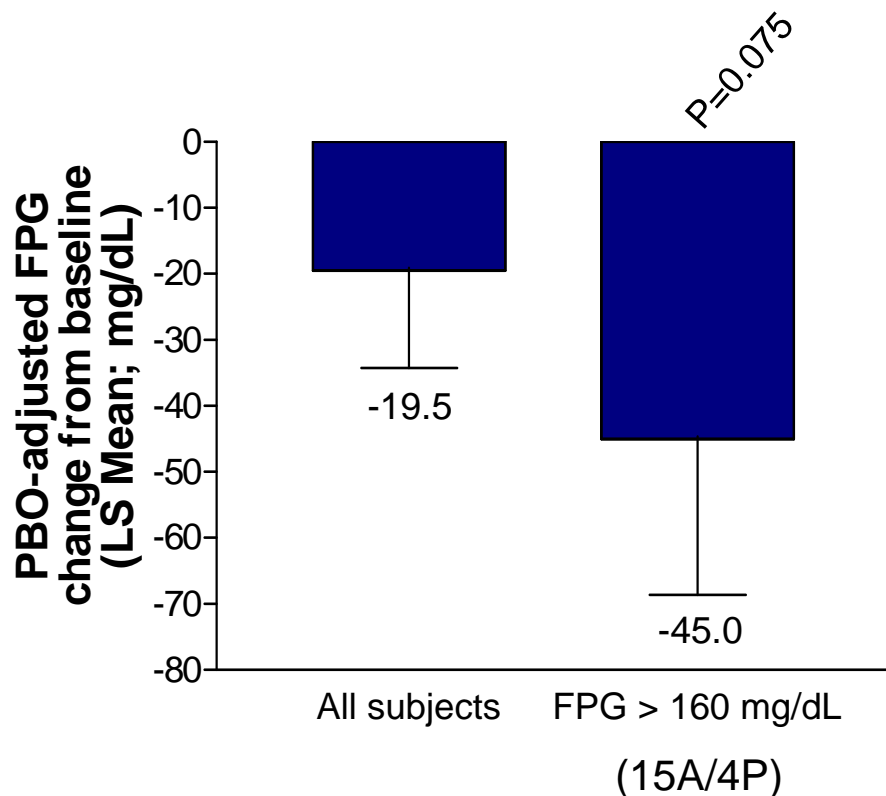
## Morning Plasma Cortisol



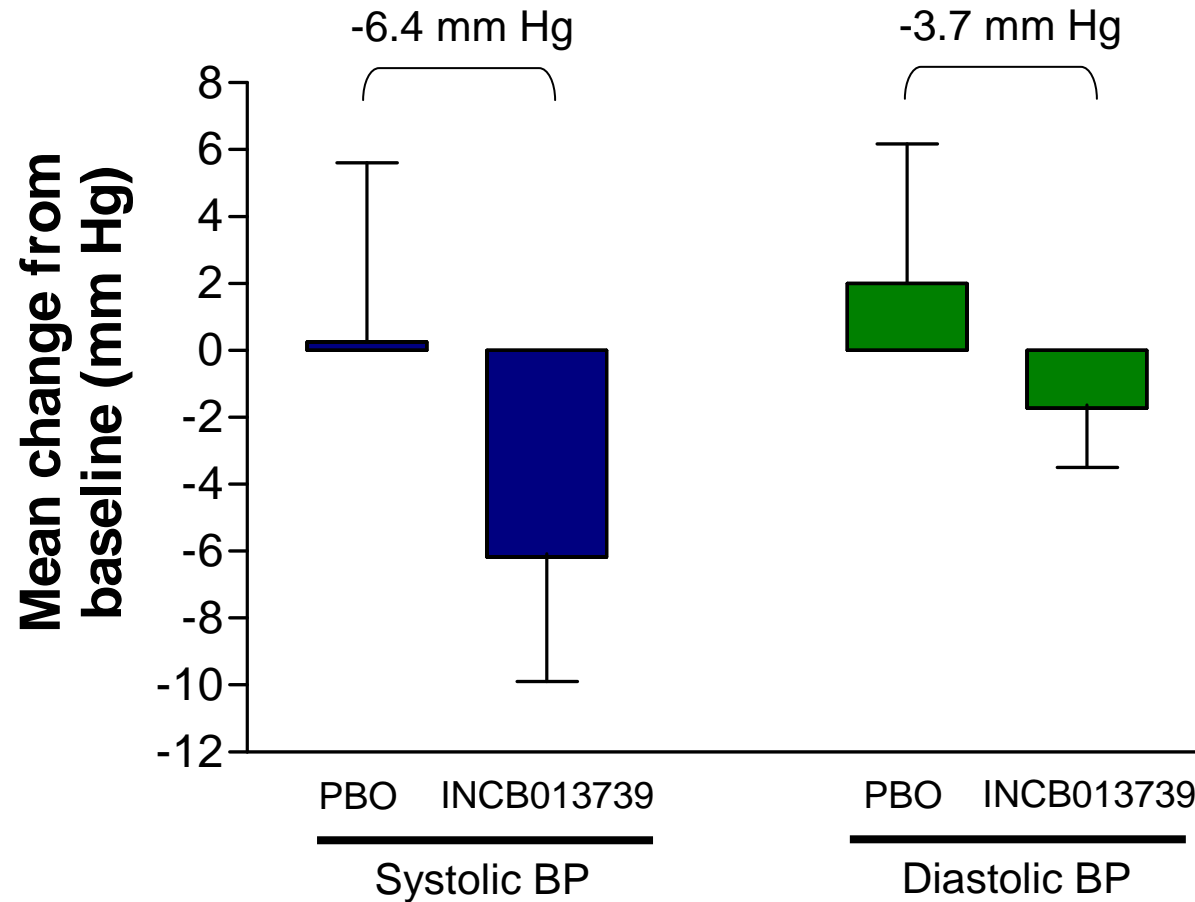
# INCB 13739-201: Primary Clamp Endpoints (End-of-study analysis, PP)



# INCB 13739-201: Secondary Glucose, Lipid Endpoints (End-of-study analysis, PP)



# INCB 13739-201: Exploratory Blood Pressure Evaluation (End-of-study analysis, PP)



## Summary and Conclusions

- 100 mg INCB013739 BID was safe and very well tolerated over 28 days in patients with type 2 diabetes mellitus
- Compensatory ACTH pharmacology with normal cortisol levels observed following INCB013739 therapy
- INCB013739 therapy led to statistically significant improvements in:
  - hepatic insulin sensitivity
  - plasma LDL-cholesterol
  - plasma total-cholesterol
- Trends for improvements also observed in fasting plasma glucose, peripheral insulin sensitivity, plasma triglycerides, blood pressure
- INCB013739 has the potential to target multiple macrovascular risk factors in concert in patients with type 2 diabetes mellitus
- INCB013739 is currently being studied in a dose-ranging Phase 2b study in T2D patients whose glucose levels are not adequately controlled by metformin monotherapy

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