INCB013739, a Selective Inhibitor of 11β-Hydroxysteroid Dehydrogenase Type 1 (11βHSD1), Improves Insulin Sensitivity and Lowers Plasma Cholesterol Over 28 Days in Patients with Type 2 Diabetes Mellitus

Meredith Hawkins1, Deborah Hunter2, Preeti Kishore1, Sherwyn Schwartz3, Marcus Hompesch4, Gregory Hollis2, Richard Levy2, Bill Williams2, Reid Huber2

1AECOM, Bronx, NY; 2Incyte Corporation, Wilmington, DE; 3dgd Research, San Antonio, TX; 4Profil Institute, San Diego, CA
11βHSD1 Activity Increases Local Cortisol Concentrations in Key Metabolic Tissues

- 11βHSD1 increases local cortisol production in specific tissue types such as adipose, liver, skeletal muscle, and the pancreas.
- 11βHSD1 activity within the splanchnic bed produces as much as 30% of the amount of cortisol as is produced by adrenal biosynthesis.
- Adipose tissue 11βHSD1 activity has been shown to be upregulated in human obesity and insulin resistance.
11βHSD1 Activity in Adipose Tissue May Drive Metabolic Disease and Cardiovascular Risk

Lessons from Rodent Models
3-fold increase in adipose 11βHSD1 as seen in human obesity

Glucose Intolerance

‘Metabolic Syndrome’

Could intracellular cortisol production by 11βHSD1 underlie the diverse cardio-metabolic phenotype that associates with obesity?

INCB013739: A Potent and Selective Small Molecule Inhibitor of 11βHSD1

- INCB013739 is a non-steroidal, small molecule inhibitor of 11βHSD1
  - 1.1 nM potency in cellular assays
  - > 1000-fold selective over 11βHSD2, 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
Adipose Tissue and Liver Pharmacodynamic Activity of INCB013739 After Oral Dosing in Obese Subjects

Adipose Tissue 11βHSD1 Activity (ex vivo whole tissue assay)

- Placebo
- INCB013739 50 mg

Liver 11βHSD1 Activity (Oral Cortisone Challenge)

Plasma Cortisol (μg/dL)

- Baseline
- INCB013739 50 mg

Time Post-Challenge (h)
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  – Eligible subjects were either naïve to treatment or withdrawn from anti-hyperglycemic medication for 14 days (TZDs excluded)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

Plasma Glucose (mg/dL)

Plasma Insulin (μU/mL)

"Basal"  "Low"  "High"

Variable glucose
Glucose tracer, Somatostatin, Glucagon

Insulin titration to euglycemia

Individualized Insulin Requirements

+20 mU/m²/min

+150 mU/m²/min

Tonelli et al. Diabetes 2004
## INCB 13739-201: Study Demographics
(End-of-study analysis, PP)

### @ Screening Visit:

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n=9)</th>
<th>INCB013739 (n=22)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>53.1 (8.5)</td>
<td>55.7 (7.1)</td>
</tr>
<tr>
<td>Sex</td>
<td>1 female, 8 male</td>
<td>6 female, 16 male</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>34.2 (3.8)</td>
<td>32.0 (3.3)</td>
</tr>
<tr>
<td>A1c (%)</td>
<td>7.2 (0.6)</td>
<td>7.7 (1.1)</td>
</tr>
<tr>
<td>FPG (mg/dL)</td>
<td>134 (26)</td>
<td>156 (36)</td>
</tr>
<tr>
<td>No. on OADs</td>
<td>6 [3M, 1M+S, 2S]</td>
<td>17 [10M, 3M+S, 4S]</td>
</tr>
</tbody>
</table>

### @ Baseline Visit:

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n=9)</th>
<th>INCB013739 (n=22)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FPG (mg/dL)</td>
<td>170 (41)</td>
<td>190 (39)</td>
</tr>
<tr>
<td>LDL (mg/dL)</td>
<td>108 (34)</td>
<td>114 (36)</td>
</tr>
<tr>
<td>HDL (mg/dL)</td>
<td>38 (9)</td>
<td>38 (8)</td>
</tr>
<tr>
<td>Cholesterol (mg/dL)</td>
<td>181 (41)</td>
<td>189 (41)</td>
</tr>
<tr>
<td>Triglyceride (mg/dL)</td>
<td>177 (94)</td>
<td>188 (89)</td>
</tr>
</tbody>
</table>

*Values are mean (SD)*
INCB 13739-201: Morning Trough Exposures of INCB013739

- Phase 1: 100 mg BID
- Day 14 Trough
- Day 27 Trough

IC$_{90}$

IC$_{50}$
• 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

<table>
<thead>
<tr>
<th></th>
<th>Day -2</th>
<th>Day 27</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td></td>
<td></td>
</tr>
<tr>
<td>INCB013739</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Morning Plasma Cortisol

<table>
<thead>
<tr>
<th></th>
<th>Day -2</th>
<th>Day 27</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td></td>
<td></td>
</tr>
<tr>
<td>INCB013739</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

+9.5 pg/mL
P=0.056
INCB 13739-201: Primary Clamp Endpoints
(End-of-study analysis, PP)

Mean change from baseline (mg/kg/min)

-0.614 mg/kg/min
P=0.018

+0.752 mg/kg/min
P=0.177

PBO (3) INCB013739 (15)
EGP (Low Insulin)

PBO (4) INCB013739 (14)
Rd (High Insulin)
INCB 13739-201: Secondary Glucose, Lipid Endpoints (End-of-study analysis, PP)

PBO-adjusted FPG change from baseline (LS Mean; mg/dL)

All subjects: -19.5
FPG > 160 mg/dL: -45.0

P=0.075

PBO-adjusted change from baseline (LS Mean; mg/dL)

CHOL: -26.9
LDL: -22.3
TG: -12.8
HDL: -10.6

P=0.007
P=0.001

(15A/4P)
INCB 13739-201: Exploratory Blood Pressure Evaluation
(End-of-study analysis, PP)

Mean change from baseline (mm Hg)

-6.4 mm Hg

-3.7 mm Hg

Systolic BP

Diastolic BP
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
Acknowledgements

Albert Einstein College of Medicine
Preeti Kishore
Do-Eun Lee
Laura Clintoc
Meredith Hawkins

Profil Institute
Heidi Mueller
Alexa Kollmeier
Linda Morrow
Khin Win
Adalberto Barba
Marcus Hompesch

dgd Research
Sherwyn Schwartz

Yale
Varman Samuel

Incyte Corporation
Bill Williams
Richard Levy
Greg Hollis
Deborah Hunter
Robert Flores
Kevin Hou
William Sun
Swamy Yeleswaram
Xuejun Chen
Reid Huber