Efficacy and Safety of the 11-beta-HSD1 Inhibitor, INCB13739, Added to Metformin Therapy in Patients with Type 2 Diabetes

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Abstract

INCB13739 (13739) is a selective inhibitor of 11-beta-hydroxysteroid dehydrogenase type 1 (11-β-HSD1) being developed for the treatment of type 2 diabetes (T2DM). This randomized, double-blind, placebo (PBO)-controlled trial assessed the efficacy and safety of 13739 in combination with metformin (MET) in patients with T2DM inadequately controlled by MET monotherapy. The primary endpoint was the change from baseline in HbA1c at week 12. After a 2 week PBO run-in period, patients (n=302; mean BMI=32.4 kg/m2; mean HbA1c=8.3%; mean duration of T2DM=6.2 yr) were assigned to receive 13739 at doses of 5 mg (n=51), 15 mg (51), 50 mg (46), 100 mg (53), 200 mg (51) or PBO (50) once-daily in addition to a stable MET regimen for 12 weeks. Mean changes from baseline in HbA1c were significantly (p<0.01) greater for 13739 100 mg (-0.4%) and 200 mg (-0.5%) vs. PBO (+0.1%) at week 12. Although plasma lipids were well controlled at baseline, 13739 treatment resulted in a dose-dependent reduction from baseline in total cholesterol, with a statistically significant effect observed in the 100 and 200 mg groups (-2 and -3%, P<0.05). The frequency and severity of adverse events following 13739 treatment were similar to those observed in subjects randomized to PBO. 13739 did not affect sex hormone levels or the aldosterone-renin axis. A dose dependent increase in morning plasma ACTH was reached by week 4 and then plateaued (mean = 11.2 pmol/l, in the 200 mg group at week 12; normal range <13.9 pmol/L). Plasma DHEA-s increased in a dose-dependent manner in concert with ACTH, reaching a maximum at week 4 in the 200 mg group (mean = 5.25 umol/L) which was within age and gender-based normal ranges. Plasma morning cortisol, late-night salivary cortisol, and response to Cortrosyn challenge were unchanged from baseline, indicating that the changes in ACTH reflect compensatory HPA axis activity to maintain normal circulating cortisol homeostasis. In summary, 13739 was very well tolerated and is the first 11-β-HSD1 inhibitor to demonstrate improvements in HbA1c and cholesterol in patients with T2DM. *[Abstract updated with final study data]*

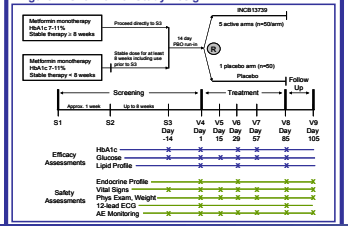
Introduction

- INCB13739 is an inhibitor of 11-β-HSD1 being developed for the management of T2DM.
- 11-β-HSD1 catalyzes the tissue-specific, intracellular conversion of inactive cortisone to active cortisol, thus amplifying local glucocorticoid action (Seckl and Walker 2001).
- Cortisol functionally antagonizes insulin action and evidence from rodents and humans support a key role for increased 11-β-HSD1 in driving insulin resistance and cardiovascular risk.
- Thus, INCB13739 has the potential to reduce hyperglycemia and macrovascular risk in concert in patients with T2DM.

Study Objectives

- Primary objective: evaluate the efficacy, safety and tolerability of adding INCB13739 for 12 weeks to patients with T2DM inadequately-controlled on metformin monotherapy.
- Secondary objective: evaluate the effect of INCB13739 on multiple cardiovascular risk factors in T2DM patients.

Figure 1. Overview of Study Design



Methods

Study Design

- This was a multicenter, double-blind, PBO controlled, randomized Phase 2 study.
- Eligible patients were adults, age 18-75 years with T2DM and a body mass index (BMI) of > 25 and < 45 kg/m^2 who had inadequate glycemic control (HbA1c 7-11%, inclusive) while on stable metformin monotherapy ≥ 10 wks at baseline.
- Patients were equally randomized to once-daily treatment with either placebo, 5 mg, 15 mg, 50 mg, 100 mg or 200 mg INCB13739 in addition to their stable metformin regimen.

Study Endpoints

- 1º endpoint: Change from baseline to week 12 in HbA1c.
- 2º endpoints: Change from baseline to week 12 in FPG, lipids, body weight.

Statistical Methodology

- Two analysis populations were pre-specified:
  1. Completers: all subjects completing 12 weeks of therapy with ≥ 80% medication compliance.
  2. Intent to treat (ITT): all subjects with any missing week 12 data imputed by last observation carried forward (LOCF).
- HbA1c and FPG endpoints were analyzed using the Completers population; all other endpoints were analyzed using the ITT population.
- The study assumes a dose-response curve in the primary endpoint that follows an E_{max} model (Bretz et al. 2005) with a pre-specified ED_{50} = 30 mg.

Figure 2. Patient Disposition

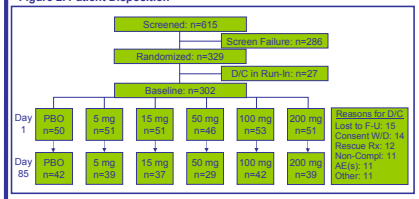


Table 1. Baseline Demographics and Clinical Characteristics

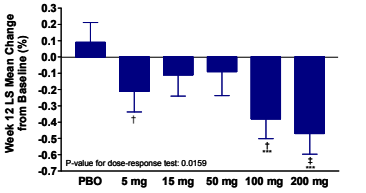
Characteristic*	PBO N=50	5 mg N=51	15 mg N=51	50 mg N=46	100 mg N=53	200 mg N=51
Age, yrs	52 ± 11	55 ± 9	52 ± 10	54 ± 9	54 ± 9	52 ± 10
Sex, n (%)						
Male	25 (50)	30 (59)	24 (47)	22 (48)	28 (53)	21 (41)
Female	25 (50)	21 (41)	27 (53)	24 (52)	25 (47)	30 (59)
BMI, kg/m^2	33.0 ± 5	32.6 ± 6	33.9 ± 5	31.2 ± 4	32.1 ± 5	31.8 ± 5
Avg Duration of T2D, yr	6.7	5.3	6.4	5.8	6.9	6.0
Avg Metformin Dose, mg/d	1462.5	1386.3	1505.0	1436.4	1596.2	1560.0
HbA1c, %	8.3 ± 1	8.2 ± 1	8.3 ± 1	8.3 ± 1	8.2 ± 1	8.2 ± 1
Presence of Met Syn, n (%)	40 (80)	35 (69)	44 (87)	35 (76)	43 (81)	36 (71)
Race, n (%)						
White	40 (80)	40 (78)	47 (92)	40 (87)	45 (85)	44 (86)
Black or African American	6 (12)	7 (14)	3 (6)	5 (11)	5 (9)	4 (8)
Asian	2 (4)	1 (2)	1 (2)	0 (0)	1 (2)	0 (0)
Other	2 (4)	3 (6)	0 (0)	1 (2)	2 (4)	3 (6)
Ethnicity, n (%)						
Hispanic	27 (54)	25 (49)	31 (61)	25 (54)	34 (64)	34 (67)
Non-Hispanic	23 (46)	26 (51)	20 (39)	21 (46)	19 (36)	17 (33)

*Mean ± STD unless otherwise specified

Results

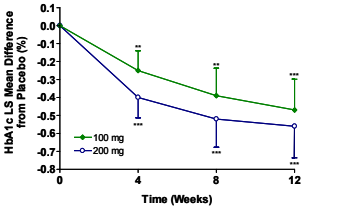
Figure 3. HbA1c Efficacy

A. Week 12 Change from Baseline in HbA1c



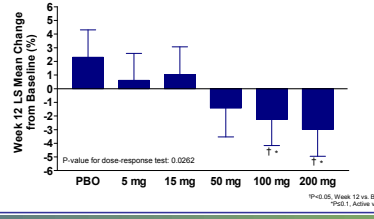
†P<0.05; ‡P<0.01, Week 12 vs. Baseline
***P<0.01, Active vs. PBO

B. Placebo-Adjusted HbA1c Change from Baseline to Week 12 in the 100 mg and 200 mg Treatment Arms



**P<0.05; ***P<0.01, Active vs. PBO

Figure 4. Week 12 Percent Change from Baseline in Cholesterol



†P<0.05, Week 12 vs. Baseline
*P≤0.1, Active vs. PBO

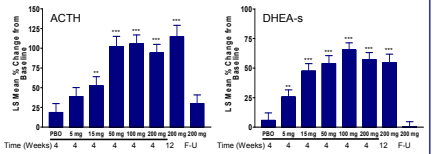
Table 2. LS Mean Change (± SE) from Baseline in 1º and 2º Endpoints

	PBO N=42	5 mg N=39	15 mg N=37	50 mg N=42	100 mg N=42	200 mg N=39
Completers						
HbA1c, %	0.09 ± 0.1	-0.21 ± 0.1*	-0.11 ± 0.1	-0.09 ± 0.2	-0.38 ± 0.1***	-0.47 ± 0.1***
≥ 8% at Baseline	-0.10 ± 0.2	-0.39 ± 0.2	-0.24 ± 0.2	-0.65 ± 0.3	-0.72 ± 0.2**	-0.65 ± 0.2*
n for ≥ 8% Subgroup	23	23	18	11	16	19
FPG, mg/dL	12.6 ± 6.1	6.0 ± 6.3	2.3 ± 6.4	-4.7 ± 7.2*	-1.6 ± 6.1*	-11.5 ± 6.2***
ITT	**N=47**	**N=49**	**N=47**	**N=42**	**N=52**	**N=49**
C-peptide, pmol/L	-9.48 ± 40	-9.84 ± 41	-14.0 ± 41	-39.6 ± 45	-32.2 ± 39	-47.4 ± 40
HOMA-IR	0.25 ± 0.4	-0.29 ± 0.4	0.33 ± 0.4	-0.42 ± 0.5	-0.51 ± 0.4	-1.06 ± 0.4***
Cholesterol, %	2.29 ± 2.0	0.61 ± 2.0	1.03 ± 2.0	-1.40 ± 2.1	-2.24 ± 1.9*	-2.98 ± 2.0*
LDL-C, %	3.32 ± 4.1	2.03 ± 4.1	7.87 ± 4.1	-5.83 ± 4.5	-1.29 ± 3.8	-1.45 ± 4.0
HDL-C, %	2.65 ± 2.7	0.51 ± 2.6	3.93 ± 2.7	4.01 ± 2.9	1.46 ± 2.5	2.32 ± 2.6
Triglycerides, %	4.98 ± 5.3	1.14 ± 5.2	1.39 ± 5.3	2.82 ± 5.7	1.96 ± 5.1	4.62 ± 5.2
Body Weight, kg	-0.23 ± 0.4	-0.48 ± 0.3	-0.58 ± 0.4	-0.01 ± 0.4	-1.10 ± 0.3*	-0.85 ± 0.3

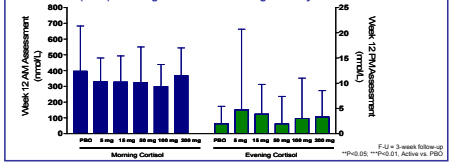
*P≤0.1; **P<0.05; ***P<0.01, Active vs. PBO

Figure 5. ACTH, DHEA-sulfate and Cortisol Assessments

A. LS Mean (± SE) Percent Change from Baseline in ACTH and DHEA-sulfate



B. LS Mean (± SE) Morning Fasted and Evening Salivary Cortisol at Week 12



F-U = 3-week follow-up
**P<0.05; ***P<0.01, Active vs. PBO

Table 3. LS Mean (± SE) Endocrine Evaluations at Week 12

	Ref. Range	PBO	5 mg	15 mg	50 mg	100 mg	200 mg
ACTH	1.6-13.9 pmol/L	4.9 ± 0.9	8.3 ± 0.9***	7.1 ± 0.9	9.2 ± 1.0***	9.4 ± 0.9***	11.2 ± 0.9***
Aldosterone	111-859 pmol/L	218 ± 23	198 ± 24	208 ± 25	204 ± 28	204 ± 23	276 ± 24
Renin	3.5-65.6 pg/mL	24.9 ± 7.6	26.0 ± 7.5	38.1 ± 7.8	19.8 ± 8.7	18.7 ± 7.3	28.0 ± 7.5
DHEA-s, male	0.14-18.73 umol/L	4.1 ± 0.6	3.7 ± 0.6	5.2 ± 0.6	5.0 ± 0.7	5.4 ± 0.6	6.6 ± 0.7***
DHEA-s, female	0.19-10.61 umol/L	2.3 ± 0.6	3.5 ± 0.7	4.2 ± 0.6**	3.4 ± 0.7	3.5 ± 0.6	4.0 ± 0.6**
A4, male	0.8-2.9 ng/mL	1.7 ± 0.2	1.5 ± 0.1	2.1 ± 0.2	1.7 ± 0.2	2.1 ± 0.2	2.6 ± 0.2***
A4, female	<1.0-4.3 ng/mL	1.1 ± 0.2	1.6 ± 0.3	1.9 ± 0.3**	2.2 ± 0.3***	1.6 ± 0.2	1.8 ± 0.2**
T, male	6.1-27.1 nmol/L	12.7 ± 0.9	11.5 ± 0.8	10.4 ± 0.9	12.0 ± 1.0	11.3 ± 0.9	13.9 ± 0.9
T, female	<0.4-2.6 nmol/L	1.2 (n=2)	1.8 (n=2)			1.2 (n=1)	1.3 (n=3)
SHBG, male	7-70 nmol/L	25.9 ± 3.2	29.9 ± 2.8	20.6 ± 3.1	23.5 ± 3.7	20.8 ± 3.1	29.7 ± 3.4
SHBG, female	15-120 nmol/L	23.0 ± 5.1	27.1 ± 6.1	30.8 ± 5.8	39.9 ± 6.4**	40.0 ± 5.1**	24.9 ± 5.1

**P<0.05; ***P<0.01, Active vs. PBO

Safety

Table 4. Summary of Treatment Emergent Adverse Events (AEs)

	PBO	5 mg	15 mg	50 mg	100 mg	200 mg
≥ 1 AE (all causes)	23	25	22	27	25	20
- Treatment-related	3	8	8	9	4	5
≥ 1 Serious AE	0	1	0	0	1	1
- Treatment-related	0	0	0	0	0	0
D/C due to AE	2	2	2	3	1	1
AEs occurring in ≥ 3% of patients (all severities, related and unrelated)						
Nasopharyngitis	1	4	3	5	3	1
Diarrhea	3	3	1	3	3	1
Upper resp. tract inf.	3	3	2	2	2	1
Headache	3	2	5	1	1	0
Arthralgia	0	7	1	2	0	0
Cough	0	1	2	1	3	2
Nausea	1	2	0	1	1	4

- Three treatment emergent SAEs were seen, cerebrovascular accident (5 mg), prolonged QRS complex (100 mg) and peripheral ischemia (200 mg). All were considered "unlikely" related to treatment.
- 97% of all treatment-emergent AEs were mild or moderate in intensity.
- There were no clinically meaningful changes in vital signs noted among treatment groups.
- There were no clinically meaningful differences between treatment groups in 12-lead ECGs, hematology, serum chemistry or urinalysis.

Summary

- 12 weeks of 200 mg INCB13739 added to failing metformin monotherapy in patients with T2DM resulted in a statistically significant PBO-adjusted reduction in HbA1c of -0.56%.
- Patients receiving 200 mg INCB13739 achieved a statistically significant reduction in FPG, HOMA-insulin resistance and total cholesterol.
- Normal cortisol levels and rhythmicity were maintained by the expected compensatory ACTH response following INCB13739 treatment. ACTH plateaued at week 4 and returned to baseline after cessation of therapy.
- DHEA-s and A4 levels increased in concert with ACTH. Levels plateaued after 4 weeks, reversed after cessation of therapy, and were not associated with increased testosterone or suppression of androgenic target proteins (SHBG).
- INCB13739 was well tolerated at all dose levels.

Conclusions

- Addition of INCB13739 orally once-daily to failing metformin monotherapy significantly improved glycemic control, insulin sensitivity and total cholesterol in patients with T2DM.
- INCB13739 was well tolerated and endocrinologic assessments demonstrated maintenance of normal basal cortisol homeostasis and lack of functional androgen excess.
- Further studies are warranted to explore the safety, anti-hyperglycemic and cardiovascular-risk modifying actions of INCB13739 in patients with T2DM.

References:

1. Seckl JR and Walker BR. Mini-Review: 11beta-Hydroxysteroid Dehydrogenase Type 1 – A Tissue-Specific Amplifier of Glucocorticoid Action. *Endocrinology* 142: 1371-1376 (2001).
2. Bretz et al. Combining Multiple Comparisons and Modeling Techniques in Dose-Response Studies. *Biometrics* 61: 738-748 (2005).

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