

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

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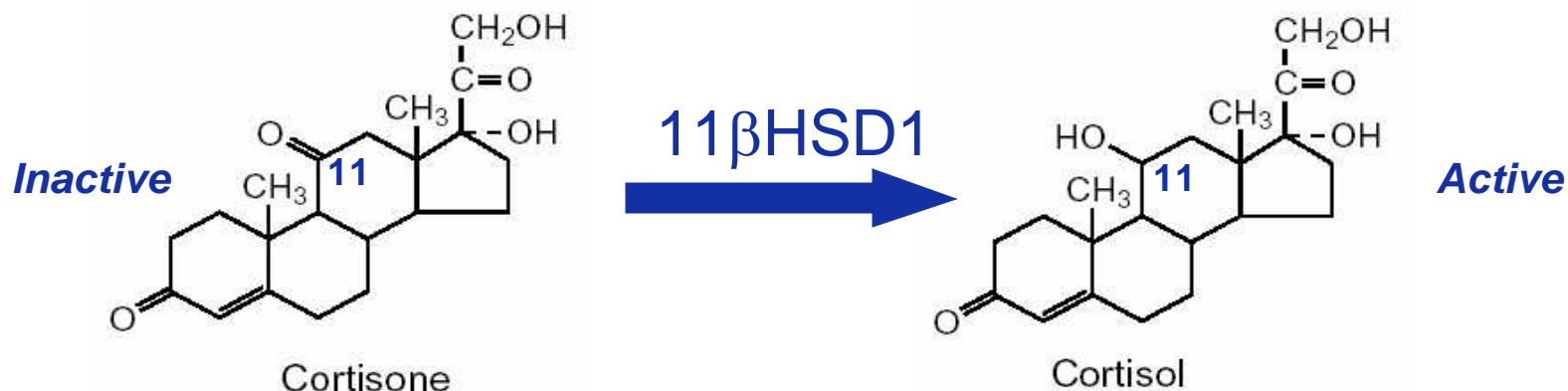
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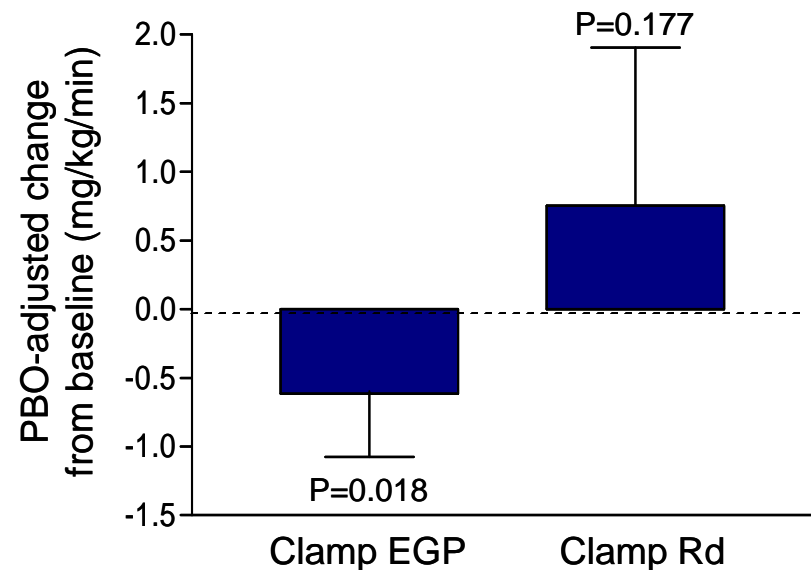
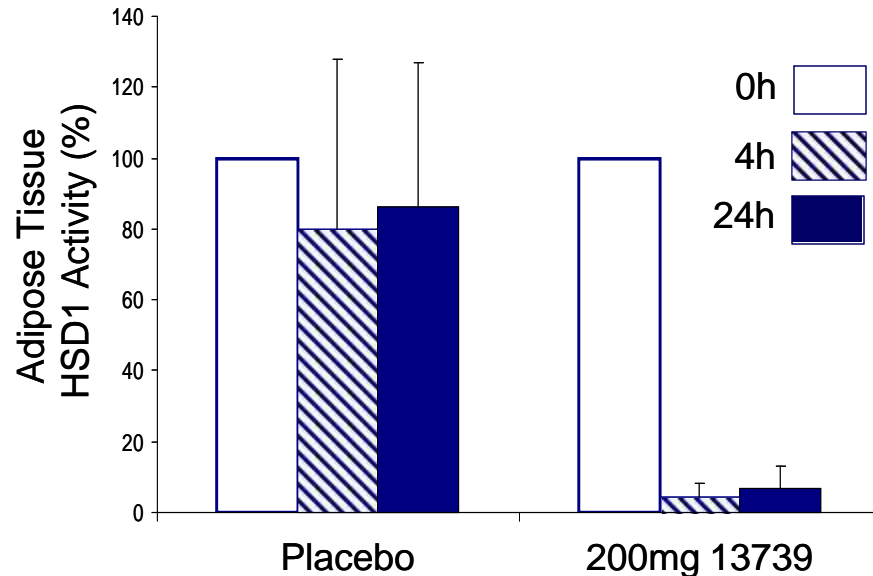
11 β HSD1 as an Intervention Point in T2D

- Patients with Cushing's syndrome – circulating cortisol excess – closely resemble patients with T2D
 - Insulin resistant, glucose intolerant, obese and hypertensive
- 11 β HSD1 catalyzes the intracellular conversion of inactive cortisone to active cortisol in metabolic tissues
 - Adipose, liver, skeletal muscle, and the pancreas
- Adipose 11 β HSD1 activity is upregulated in human obesity and insulin resistance
 - This dysregulation can produce a near complete metabolic syndrome phenotype in rodents



INCB13739: A Potent and Selective Small Molecule Inhibitor of 11β HSD1

- INCB13739 is a selective small molecule inhibitor of 11β HSD1 exhibiting a 1.1 nM IC_{50} in cellular assays
- INCB13739 is orally bioavailable with a half-life of 11 h
- INCB13739 has been shown to inhibit both adipose and liver 11β HSD1 activity in healthy volunteers and improve insulin sensitivity after 28 days of dosing in T2D patients



Study 202 – A 12 Week Trial in T2D Patients

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/m² 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 placebo, 5 mg, 15 mg, 50 mg, 100 mg or 200 mg INCB13739 in addition to their metformin regimen (n=50/arm; n=300 total)

Study Endpoints

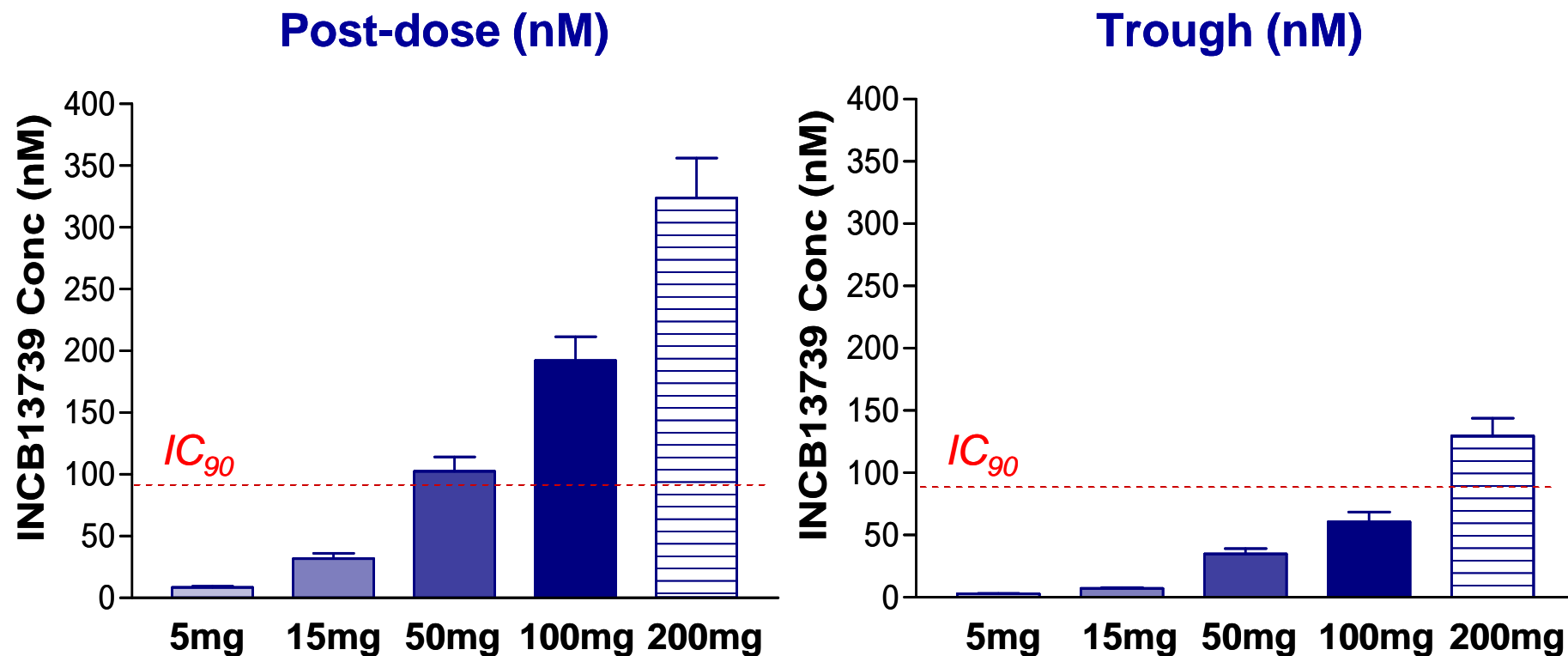
- 1° endpoint: Change from baseline to week 12 in HbA1c.
- 2° endpoints: Change from baseline to week 12/LOCF in FPG, lipids, body weight.

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)

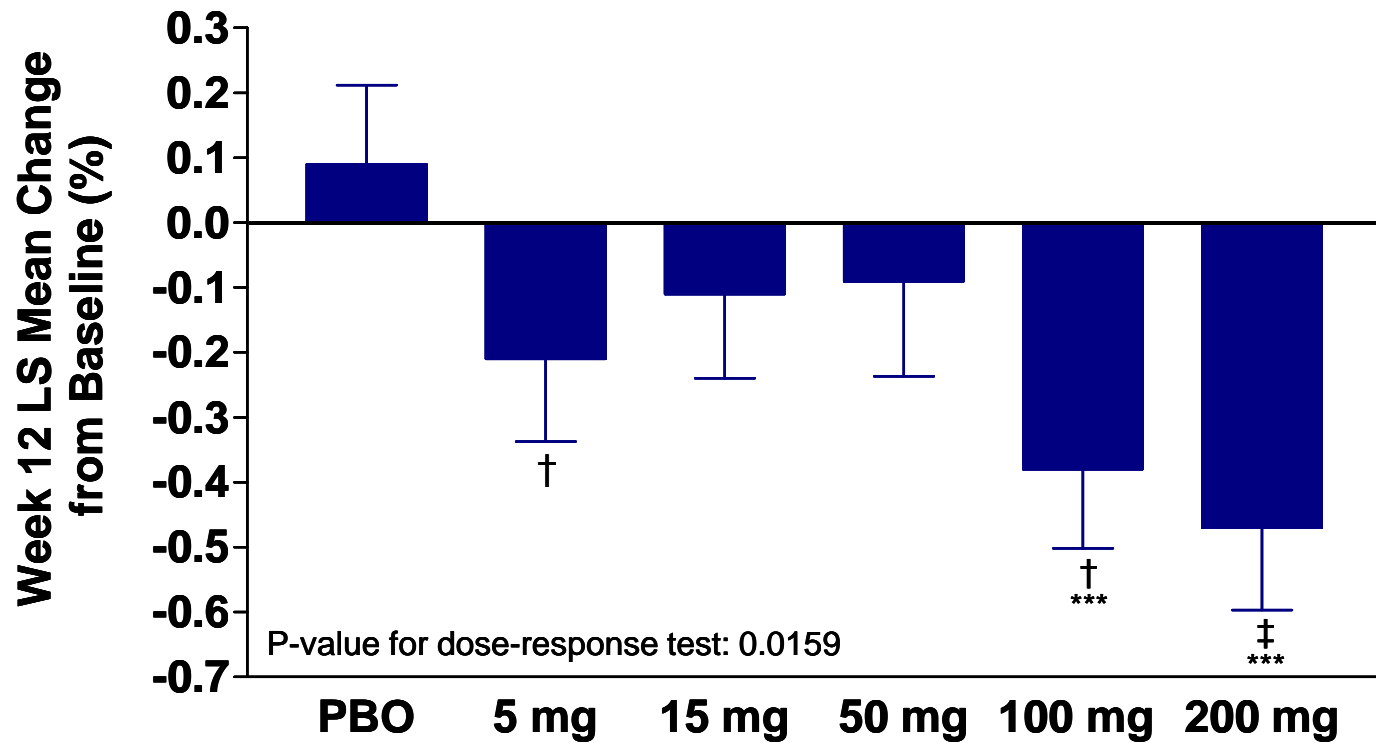
*Mean ± STD unless otherwise specified

Post-dose and Trough Concentrations Achieved Relative to IC90



HbA1c Efficacy at Endpoint

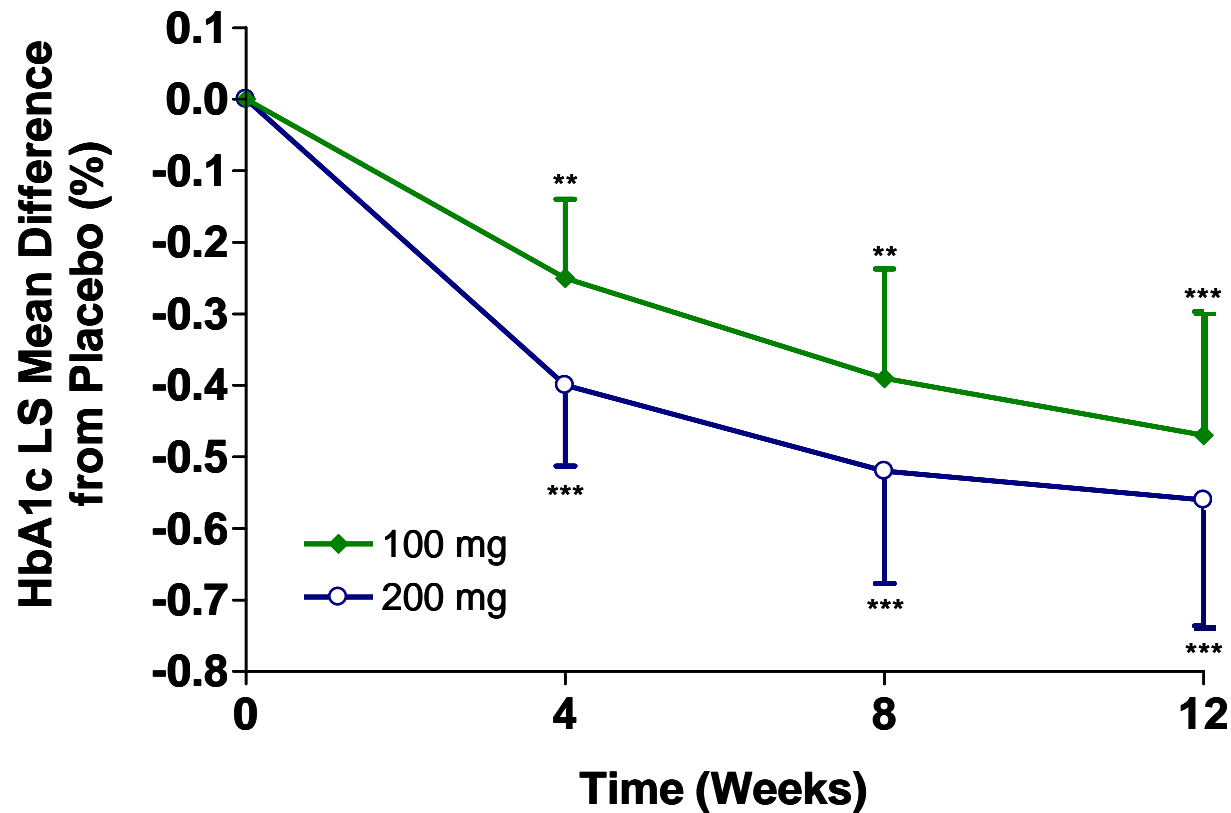
Week 12 Change from Baseline in HbA1c



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

HbA1c Efficacy by Visit

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

Summary of Glycemia-Related Endpoints

LS Mean Change (\pm SE) from Baseline

	PBO	5 mg	15 mg	50 mg	100 mg	200 mg
HbA1c, %	0.09 \pm 0.1	-0.21 \pm 0.1*	-0.11 \pm 0.1	-0.09 \pm 0.2	-0.38 \pm 0.1***	-0.47 \pm 0.1***
8% at Baseline	-0.10 \pm 0.2	-0.39 \pm 0.2	-0.24 \pm 0.2	-0.65 \pm 0.3	-0.72 \pm 0.2**	-0.65 \pm 0.2*
n for 8% Subgroup	23	23	18	11	16	19
FPG, mg/dL	12.6 \pm 6.1	6.0 \pm 6.3	2.3 \pm 6.4	-4.7 \pm 7.2*	-1.6 \pm 6.1*	-11.5 \pm 6.2***
C-peptide, pmol/L	-9.48 \pm 40	-9.84 \pm 41	-14.0 \pm 41	-39.6 \pm 45	-32.2 \pm 39	-47.4 \pm 40
HOMA-IR	0.25 \pm 0.4	-0.29 \pm 0.4	0.33 \pm 0.4	-0.42 \pm 0.5	-0.51 \pm 0.4	-1.06 \pm 0.4**

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

Summary of Lipid Endpoints

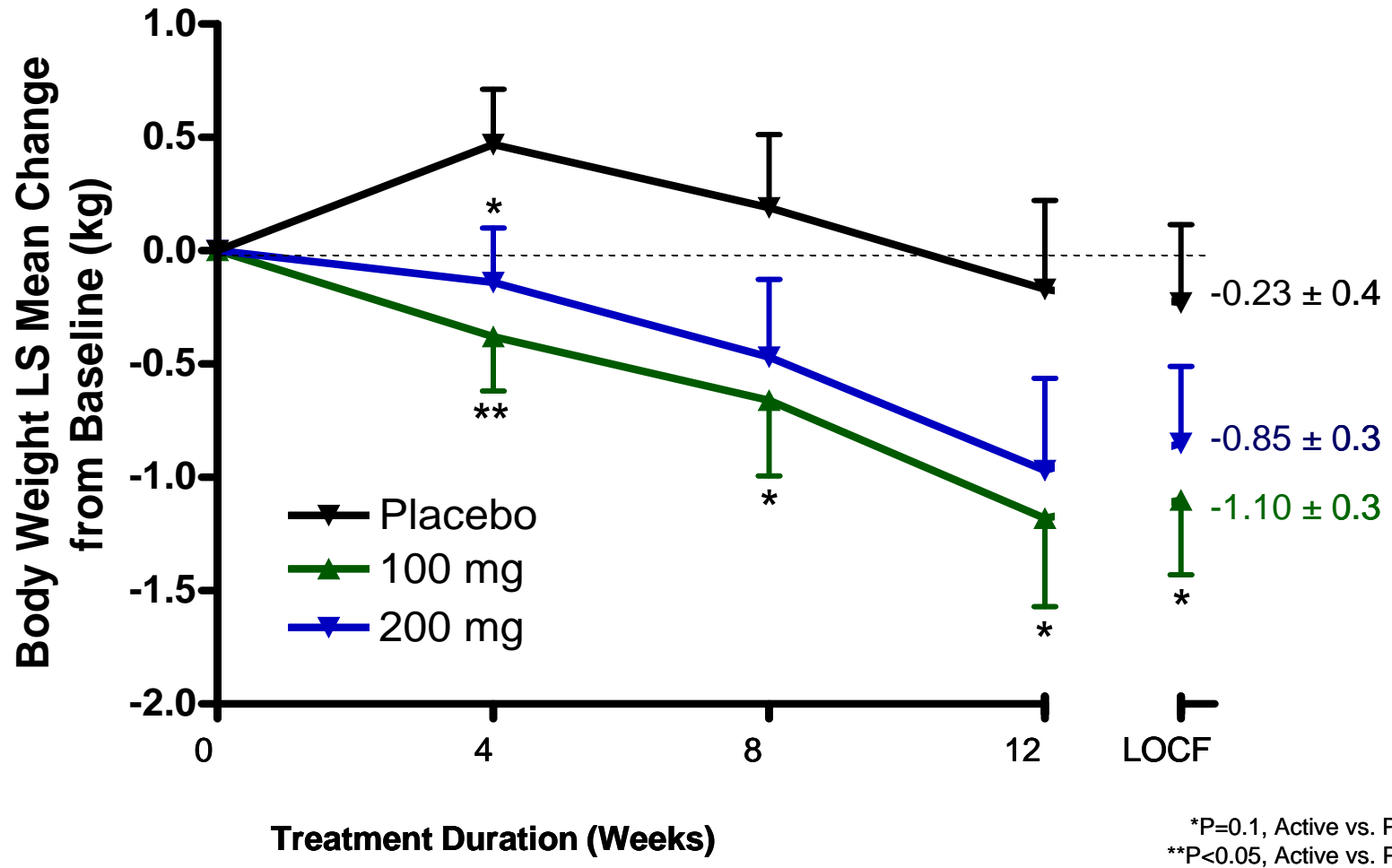
LS Mean Change (\pm SE) from Baseline

	PBO	5 mg	15 mg	50 mg	100 mg	200 mg
Cholesterol (mg/dL)						
Avg at baseline	197 \pm 7	190 \pm 6	177 \pm 1	193 \pm 8	205 \pm 6	194 \pm 5
All subjects	1.2 \pm 4	-0.7 \pm 4	-1.2 \pm 4	-3.9 \pm 4	-6.6 \pm 4*	-7.3 \pm 4*
200 mg/dL	-10.0 \pm 6	-11.6 \pm 5	-12.4 \pm 7	1.5 \pm 7	-16.2 \pm 5**	-18.5 \pm 6*
n in subgroup	19	22	14	12	28	20
LDL-C (mg/dL)						
Avg at baseline	112 \pm 0.5	107 \pm 5	99 \pm 5	111 \pm 7	121 \pm 5	110 \pm 4
All subjects	2.3 \pm 4	-1.2 \pm 4	0.4 \pm 4	-7.0 \pm 4*	-4.6 \pm 3*	-4.3 \pm 3
130 mg/dL	-8.5 \pm 8	-19.3 \pm 8	-9.7 \pm 9	-8.5 \pm 13	-17.0 \pm 6**	-14.3 \pm 8
n in subgroup	12	10	9	6	18	12
Triglycerides (mg/dL)						
Avg at baseline	188 \pm 15	189 \pm 17	196 \pm 21	188 \pm 18	187 \pm 13	195 \pm 18
All subjects	0.0 \pm 12	-4.4 \pm 12	-27.4 \pm 5	-12.4 \pm 13	-11.5 \pm 12	-10.6 \pm 12
200 mg/dL	-19.5 \pm 28	-3.5 \pm 28	-105.3 \pm 31	-57.5 \pm 29	-74.3 \pm 27**	-55.8 \pm 29
n in subgroup	16	17	13	15	18	15

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

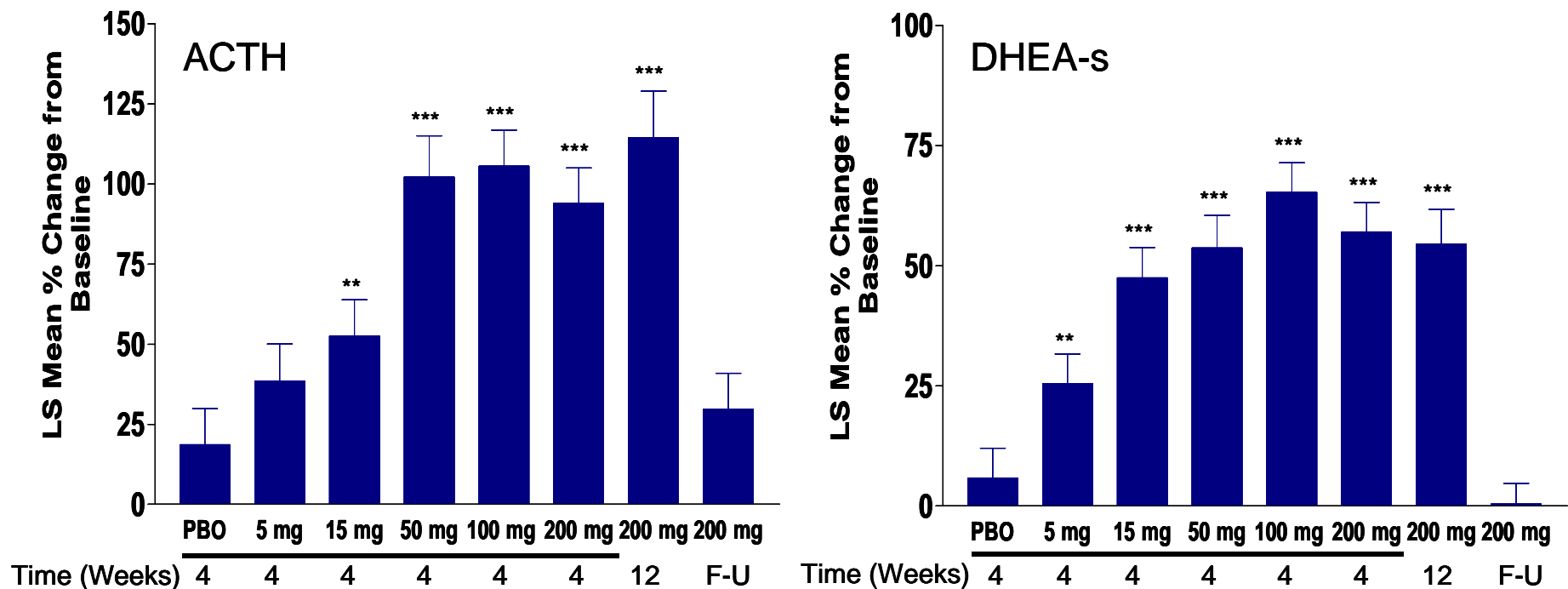
Change in Body Weight

LS Mean Change (\pm SE) from Baseline



ACTH and DHEA-Sulfate Assessments

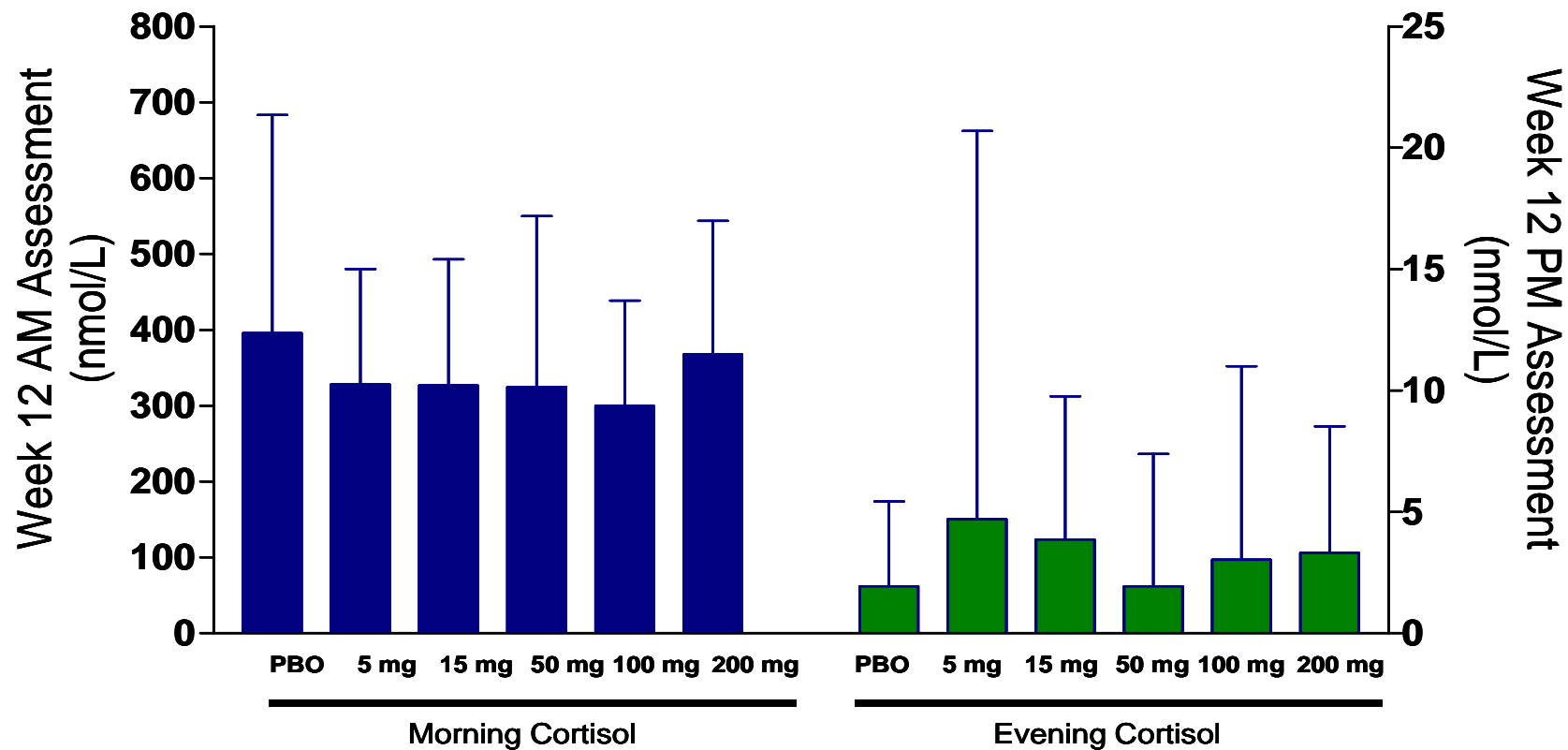
LS Mean (\pm SE) Percent Change from Baseline in ACTH and DHEA-sulfate



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

Cortisol Assessments

LS Mean (\pm SE) Morning Fasted and Evening Salivary Cortisol at Week 12



Summary of Endocrine Labs at Endpoint

LS Mean (\pm 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 \pm 0.9	8.3 \pm 0.9 ^{***}	7.1 \pm 0.9	9.2 \pm 1.0 ^{***}	9.4 \pm 0.9 ^{***}	11.2 \pm 0.9 ^{***}
Aldosterone	111-859 pmol/L	218 \pm 23	198 \pm 24	208 \pm 25	204 \pm 28	204 \pm 23	276 \pm 24
Renin	3.5-65.6 pg/mL	24.9 \pm 7.6	26.0 \pm 7.5	38.1 \pm 7.8	19.8 \pm 8.7	18.7 \pm 7.3	28.0 \pm 7.5
DHEA-s, male	0.14-18.73 umol/L	4.1 \pm 0.6	3.7 \pm 0.6	5.2 \pm 0.6	5.0 \pm 0.7	5.4 \pm 0.6	6.6 \pm 0.7 ^{***}
DHEA-s, female	0.19-10.61 umol/L	2.3 \pm 0.6	3.5 \pm 0.7	4.2 \pm 0.6 ^{**}	3.4 \pm 0.7	3.5 \pm 0.6	4.0 \pm 0.6 ^{**}
A4, male	0.8-2.9 ng/mL	1.7 \pm 0.2	1.5 \pm 0.1	2.1 \pm 0.2	1.7 \pm 0.2	2.1 \pm 0.2	2.6 \pm 0.2 ^{***}
A4, female	<1.0-4.3 ng/mL	1.1 \pm 0.2	1.6 \pm 0.3	1.9 \pm 0.3 ^{**}	2.2 \pm 0.3 ^{***}	1.6 \pm 0.2	1.8 \pm 0.2 ^{**}
T, male	6.1-27.1 nmol/L	12.7 \pm 0.9	11.5 \pm 0.8	10.4 \pm 0.9	12.0 \pm 1.0	11.3 \pm 0.9	13.9 \pm 0.9
T, female [#]	<0.4-2.6 nmol/L	1.3 \pm 0.4	1.5 \pm 0.3	1.7 \pm 0.8 ^{**}	1.6 \pm 0.5	1.6 \pm 0.6	1.8 \pm 0.8 ^{**}
SHBG, male	7-70 nmol/L	25.9 \pm 3.2	29.9 \pm 2.8	20.6 \pm 3.1	23.5 \pm 3.7	20.8 \pm 3.1	29.7 \pm 3.4
SHBG, female	15-120 nmol/L	23.0 \pm 5.1	27.1 \pm 6.1	30.8 \pm 5.8	39.9 \pm 6.4 ^{**}	40.0 \pm 5.1 ^{**}	24.9 \pm 5.1
FAI, male	na	63.9 \pm 5.8	43.5 \pm 5.0	60.2 \pm 5.5	55.8 \pm 6.6	62.7 \pm 5.7	53.3 \pm 6.2
FAI, female [#]	na	6.9 \pm 1.1	7.9 \pm 1.3	8.2 \pm 1.2	5.7 \pm 1.4	7.2 \pm 1.1	7.9 \pm 1.1

[#] week 8 testosterone levels in females

P<0.05; *P<0.01, Active vs. PBO at Week 12[#]

Summary of Treatment Emergent Adverse Events and Safety

	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, 12-lead ECGs, hematology, serum chemistry or urinalysis noted among treatment groups.

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%.
 - 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 altered free androgen index.
- INCB13739 was well tolerated at all dose levels.
- 11 β HSD1 inhibition by INCB13739 offers a novel approach to T2D therapy and warrants further investigation.

Acknowledgements

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