

Effects of an 11 β -hydroxysteroid dehydrogenase type 1 inhibitor, MK-0916, in patients with type 2 diabetes mellitus and metabolic syndrome

P. U. Feig¹, S. Shah¹, A. Hermanowski-Vosatka¹, D. Plotkin², M. S. Springer¹, S. Donahue³, C. Thach⁴, E. J. Klein⁵, E. Lai¹ & K. D. Kaufman¹

¹Merck Sharp & Dohme Corp., Rahway, NJ, USA

²Clinical Development, ActivX Biosciences, Inc., La Jolla, CA, USA

³Ore Pharmaceuticals, Cambridge, MA, USA

⁴Chau Thach, Inc., Parkland, FL, USA

⁵Capital Clinical Research Center, Olympia, WA, USA

Aim: We examined the effects of the 11 β -hydroxysteroid dehydrogenase type 1 (HSD1) inhibitor, MK-0916, on the multiple components of the metabolic syndrome (MetS) in patients with type 2 diabetes (T2DM) and MetS.

Methods: This was a 12-week, multicentre, randomized, double-blind, placebo-controlled study. Patients with T2DM (mean baseline A1C: 7.3%) and National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III)-defined MetS were randomized 1 : 1 : 1 : 1 to 0.5, 2 or 6 mg/day MK-0916 or placebo. The primary efficacy endpoint was a change from baseline at week 12 in fasting plasma glucose (FPG). Secondary endpoints included glycosylated haemoglobin A_{1c} (A1C), 2-h postprandial glucose (2-h PPG), body weight, waist circumference, blood pressure and lipid profile.

Results: Treatment with MK-0916 had no significant effect relative to placebo on FPG at week 12. Compared to placebo, 6 mg MK-0916 produced a modest, significant ($p = 0.049$) reduction in A1C of 0.3% at week 12, but no significant difference was observed in 2-h PPG. Six milligram MK-0916 increased LDL-C relative to placebo by 10.4% ($p = 0.041$). Treatment with MK-0916 led to modest dose-dependent decreases in blood pressure and body weight. Overall, MK-0916 was generally well tolerated. MK-0916 produced mechanism-based activation of the hypothalamic–pituitary–adrenal axis, resulting in mean increases in adrenal androgen levels that remained within the normal range at all doses tested.

Conclusions: Inhibition of HSD1 with MK-0916 was generally well tolerated in patients with T2DM and MetS. Although no significant improvement in FPG was observed with MK-0916 compared to placebo, modest improvements in A1C, body weight and blood pressure were observed.

Keywords: 11 β -hydroxysteroid dehydrogenase type 1 inhibitor, metabolic syndrome, type 2 diabetes mellitus

Date submitted 21 September 2010; date of first decision 4 November 2010; date of final acceptance 24 December 2010

Introduction

The metabolic syndrome (MetS) comprises a cluster of cardiovascular risk factors including visceral adiposity, insulin resistance, hypertension and dyslipidaemia (1). Cushing's syndrome, which involves an elevation in circulating cortisol levels, is characterized by a constellation of cardiovascular risk factors similar to that observed in MetS patients (2). Bjorntorp et al. (3) proposed that subtle alterations in the hypothalamic–pituitary–adrenal axis (HPA) and cortisol homeostasis may link the pathogenesis and metabolic consequences of visceral adiposity. While the similarity between Cushing's and MetS has been noted, circulating glucocorticoid levels are typically not elevated in patients with MetS. These findings led to the hypothesis that MetS, at least in part, is caused by functional hypercortisolism through increased levels of intracellular glucocorticoids.

Glucocorticoid levels are modulated at the cellular level by the 11 β -hydroxysteroid dehydrogenase (HSD) enzymes, HSD1 and HSD2. In humans, HSD1 is ubiquitously expressed, with the highest levels being found in the liver and adipose tissue, and catalyses the intracellular conversion of inactive cortisone into active cortisol (4). HSD2 is found primarily in the kidneys and colon and catalyses the reverse reaction (4).

There is some evidence that HSD1-mediated intracellular production of cortisol may play a role in the pathogenesis of MetS (5–7). For example, mice in which the gene for HSD1 was deleted were shown to be resistant to developing multiple components of MetS (8–10). Inhibition of HSD1 was shown to improve multiple components of MetS in diet-induced obese mice and to decrease plaque progression in a mouse model of atherosclerosis (11). Additionally, mice in which the HSD1 gene was transgenically overexpressed in either adipose tissue or the liver exhibited a MetS-like phenotype (12). A positive correlation was reported for HSD1 mRNA expression and enzyme activity levels with body mass index, fasting insulin levels and percent body fat in Pima Indians

Correspondence to: Dr. Peter U. Feig, Merck Research Laboratories, Merck Sharp & Dohme Corp., RY34A-200, 126 East Lincoln Avenue, Rahway, NJ 07065, USA.
E-mail: peter_feig@merck.com

and Caucasians (13). Taken together, these results support the hypothesis that it is the intracellular, not the systemic, levels of glucocorticoids that regulate metabolic parameters and that elevated intracellular cortisol levels contribute to the pathogenesis of MetS. Moreover, these data raise the possibility that lowering of intracellular cortisol levels through inhibition of HSD1 could have a beneficial effect on components of MetS.

We conducted a 12-week, Phase IIa, proof of concept study to evaluate the safety and efficacy of an HSD1-selective inhibitor, MK-0916, in patients with type 2 diabetes (T2DM) and MetS. The primary efficacy endpoint was fasting plasma glucose (FPG), with secondary efficacy endpoints of A1C, 2-h postprandial glucose (2-h PPG), body weight, waist circumference, lipids and blood pressure.

Methods

Patients

Patients between the ages of 18 and 65 years were eligible for enrollment in the study if they had T2DM, defined as FPG ≥ 7 mmol/l and met two of the following four National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) criteria for MetS (1): (i) waist circumference > 102 cm for men or > 88 cm for women; (ii) HDL-C < 1.0 mmol/l for men or < 1.3 mmol/l for women; (iii) triglycerides (TG) ≥ 1.7 mmol/l; and (iv) treatment with an antihypertensive agent or blood pressure $\geq 130/85$ mmHg.

Exclusion Criteria

Patients were excluded if they were chronically taking any of the following medication(s) at the screening visit: > 2 oral antihyperglycaemic agents (AHAs), non-statin lipid-modifying medication (e.g. bile acid sequestrant, ezetimibe, fibrate or niacin), high dose of a statin (defined as statin with potency > 40 mg/day simvastatin), systemic glucocorticoids or androgen-containing medications, cyclical oestrogen medications, potent inhibitors of CYP3A4 (e.g. clarithromycin, ketoconazole) or thiazolidinediones within 8 weeks prior to screening. Other exclusion criteria included a history of type 1 diabetes mellitus or ketoacidosis, active liver disease (except steatohepatitis), other endocrine abnormalities including, but not limited to, Cushing's syndrome, Addison's disease, congenital adrenal hyperplasia, abnormal virilization or history of polycystic ovary syndrome; history of severe peripheral vascular disease; uncontrolled hypertension ($> 160/95$ mmHg); or NYHA Class III or IV congestive heart failure. Premenopausal women were allowed to enroll if they were surgically sterilized or highly unlikely to conceive. Other laboratory exclusion criteria included: FPG > 12.2 mmol/l, TG > 6.8 mmol/l; aspartate transaminase or alanine transaminase > 2 times the upper limit of normal, or serum creatinine > 159.1 μ mol/l.

Patients received counselling from a dietitian or qualified health personnel concerning diet and exercise consistent with recommendations from the American Heart Association (or other similar guidelines). Patients who were taking a statin and/or antihypertensive medication(s) were expected to

maintain a stable dose regimen throughout the study unless a change in dose or medication was medically necessary. Patients provided written informed consent. The protocol was reviewed and approved by the appropriate committees and authorities and performed in accordance with the Declaration of Helsinki.

Study Design and Procedures

This was a 12-week, multicentre, randomized, double-blind, placebo-controlled study. Patients on AHA(s) underwent a 5-week washout period that included a 2-week placebo run-in, whereas patients naïve to AHAs entered a 2-week placebo run-in prior to randomization. Eligible patients were randomized to 0.5, 2 or 6 mg MK-0916 or placebo (1 : 1 : 1 : 1) daily for 12 weeks. The three doses of MK-0916 used in this study were selected based on different levels of hepatic HSD1 inhibition, determined *in vivo* in Phase I pharmacokinetic/pharmacodynamic studies involving measurement of the conversion of stable isotope labelled cortisone acetate to cortisol following treatment with MK-0916; 0.5, 2 and 6 mg MK-0916 produce ~ 45 , ~ 74 and $\sim 85\%$ hepatic HSD1 inhibition, respectively (unpublished data). The study also included a 3-week, post-treatment, reversibility phase. Patients were stratified based on whether they were naïve or not naïve to AHA therapy for at least 6 months prior to screening and whether they were taking a statin or not. Enrollment of patients treated with a statin was limited to a maximum of 25% of the total cohort in order to evaluate the effects of MK-0916 on lipids in the absence of statin. Efficacy and safety measures were assessed at weeks 2, 4, 8, 12 and 15.

Efficacy Assessments

The primary efficacy endpoint was a change from baseline at week 12 in FPG. Secondary efficacy endpoints included the change from baseline at week 12 in A1C, 2-h PPG, fasting and postprandial serum insulin, sitting systolic and diastolic blood pressure, plasma lipids in statin-naïve patients, waist circumference and body weight. Sitting trough blood pressure was measured with automated blood pressure monitor [LifeSource™ UA-787 (A&D Engineering, Inc., San Jose, CA, USA)] in triplicate such that none of the consecutive three measurements were discrepant by > 5 mmHg relative to the calculated average of the three readings. Waist circumference was measured in duplicate using a standardized procedure across all sites. Body weight was measured using a standardized Tanita BWB-800-AS scale (Tanita Corporation, Tokyo, Japan) at all sites.

Safety Assessments

Safety and tolerability were assessed by review of clinical and laboratory adverse experiences, laboratory values, vital signs and electrocardiogram (ECG) data. As cortisol can act as a negative feedback inhibitor of the HPA, activation of the HPA axis was monitored by measuring the production of the adrenal androgens androstenedione, dehydroepiandrosterone (DHEA) and dehydroepiandrosterone sulfate (DHEA-S) in all patients; free testosterone in women; and symptoms of virilization (body

hair growth and acne) in women. Serum androgens and free testosterone were measured by radioimmunoassay. Body hair assessments were performed by the investigator at 11 body sites using the Ferriman–Gallwey method (14). Global assessments of acne were performed by the investigator and by the patient based on visual inspection of the face (15).

Statistical Analysis

Efficacy analyses were based on the all-patients-treated (APT) population, which included all randomized patients who received at least one dose of study treatment and who had both baseline and at least one postbaseline measurement. To address the primary hypothesis, the change from baseline in FPG at week 12 was analysed using an analysis of covariance (ANCOVA) model that included the terms for treatment, statin use at randomization, drug-naïve or treated with AHA(s) and baseline value as covariates. The dose–response relationship in the mean FPG change from baseline for placebo and the three doses of MK-0916 was examined by stepwise linear contrast test based on the ANCOVA model, using a step-down procedure. If a statistically significant result was observed, then the highest dose group (i.e. 6 mg) was deemed significantly different from placebo and was removed from the linear contrast, and the test repeated, proceeding in a stepwise fashion until lack of significance was observed to determine the minimal effective dose that was significantly different from placebo. This process preserved the overall type I error rate for testing the primary efficacy hypothesis. Other pairwise comparisons among the MK-0916 doses were also performed to estimate the treatment differences.

The ANCOVA model was also used to evaluate MK-0916-induced changes from baseline at week 12 for A1C, 2-h PPG, LDL-C and body weight. The baseline value of each parameter was the covariate in the model.

The analyses for all safety outcomes (categorical or continuous measures) used the all-patients-as-treated (APaT) population, which included all randomized patients who received at least one dose of study therapy. For adrenal androgens (androstenedione, DHEA and DHEA-S) and free testosterone (in women), inferential testing using an ANCOVA with model terms of treatment and baseline value, provided statistical significance levels for between-group comparisons.

Results

Demographic and Baseline Clinical Characteristics

A total of 154 patients were randomized. The demographic and baseline clinical characteristics in each of the four treatment groups are provided in Table 1. There were no meaningful differences across the treatment groups in demographic or baseline clinical characteristics.

Effects on Glycaemic Parameters

Compared to placebo, there was no statistically significant effect at week 12 of treatment with any dose of MK-0916 on FPG (primary efficacy endpoint; Table 2). Similarly,

compared to placebo, treatment with MK-0916 produced neither meaningful change in 2-h PPG after 12 weeks of dosing, nor did it have any significant effects on the levels of fasting or postprandial serum insulin (data not shown). However, treatment with 6 mg MK-0916 led to a placebo-adjusted reduction of 0.3% in A1C at week 12 ($p = 0.049$ for between-group difference) (Table 2).

Effects on Body Weight and Waist Circumference

Treatment with 6 mg MK-0916 resulted in a significant ($p < 0.001$) decrease in body weight compared to placebo at week 12 (1.8 kg reduction relative to placebo; Table 2). Consistent with the observed weight loss, there was a trend towards a small decrease in waist circumference (Table 2).

Effects on Blood Pressure

Treatment with MK-0916 led to dose-dependent decreases in both systolic and diastolic blood pressure (Table 2). Compared to placebo, the change from baseline (128.3 mmHg) in systolic blood pressure at 12 weeks with the 6 mg dose was -7.9 mmHg ($p < 0.001$). Similar changes were observed with MK-0916 for diastolic blood pressure. At 12 weeks, the change from baseline (81.1 mmHg) in diastolic blood pressure with the 6 mg dose compared to placebo was -5.4 mmHg ($p = 0.001$). Approximately 60% of patients in the study had a history of hypertension, of which 92% (55% of total study population) were on antihypertensive medications during the study.

Effects on Lipids

In statin-naïve patients, the 6 mg dose of MK-0916 produced modest (10–11%) significant dose-dependent increases in LDL-C and non-HDL-C levels relative to placebo (Table 2). MK-0916 produced numerical, but not statistically significant, increases in TG and decreases in HDL-C levels (Table 2).

Safety and Tolerability

MK-0916 was generally well tolerated, with adverse experiences being reported at a similar incidence across all treatment groups (Table 3). There were no clinically significant changes in other safety measures including laboratory assessments, physical evaluations, vital signs or ECG.

MK-0916-induced modest activation of the HPA axis relative to placebo as shown by the mean percent increases observed in androstenedione, DHEA and DHEA-S (Table 4). There was a statistically significant, dose-dependent mean percent increase in androstenedione, with a 21.8% increase at 12 weeks relative to placebo in the 6 mg group ($p = 0.026$), and one of similar magnitude in DHEA (33.5% increase relative to placebo at 6 mg; $p = 0.004$). There was no significant dose-dependent effect on DHEA-S. The levels of DHEA and DHEA-S appeared to reach a maximum with MK-0916 by 4 weeks and stabilized thereafter (data not shown). There were also non-statistically significant mean percent increases in serum testosterone levels of 27.6 and 26.2% in women in the 2 mg and 6 mg dose groups, respectively (Table 4). Increases in androgen levels

Table 1. Baseline demographics and clinical characteristics of patients.

Characteristic	Placebo (n = 39)	MK-0916		
		0.5 mg (n = 37)	2 mg (n = 38)	6 mg (n = 40)
Age (year)*	52.8 ± 8.8	52.9 ± 8.3	52.5 ± 8.5	53.4 ± 8.5
Age range (year)	29–66	27–64	29–65	39–66
Men, no. (%)	22 (56)	18 (49)	20 (53)	23 (58)
Race, no. (%)				
White	26 (67)	26 (70)	29 (76)	26 (65)
Black	3 (8)	5 (14)	3 (8)	3 (8)
Hispanic	8 (20)	6 (16)	5 (13)	10 (25)
Other	2 (5)	0 (0)	1 (3)	0 (0)
Weight (kg)*	91.6	95.6	96.2	91.9
BMI (kg/m ²)*	32.5 ± 4.6	33.1 ± 4.8	32.9 ± 4.7	31.7 ± 4.6
Waist circumference (cm)*	105.6 ± 10.8	109.9 ± 12.1	108.1 ± 12.4	105.3 ± 12.2
Hypertension, no. (%)	16 (41)	28 (76)	21 (55)	27 (67)
Blood pressure (mmHg)*				
Systolic	124.5 ± 14.5	129.1 ± 13.0	122.2 ± 12.2	128.6 ± 12.7
Diastolic	79.2 ± 8.7	80.1 ± 9.5	79.2 ± 8.1	81.1 ± 8.9
On AHTN medication(s), no. (%)	16 (41)	24 (65)	21 (55)	24 (60)
Glycaemic parameters*				
FPG (mmol/l)	8.5 ± 2.0	8.6 ± 2.4	8.4 ± 1.7	8.4 ± 1.9
A1C (%)	7.4 ± 1.0	7.3 ± 0.9	7.3 ± 0.7	7.2 ± 0.7
2-h PPG (mmol/l)	13.2 ± 4.3	13.1 ± 4.9	13.1 ± 3.4	11.4 ± 3.7
Fasting insulin (pmol/l)	112.5 ± 61.8	136.1 ± 81.3	155.6 ± 143.1	145.1 ± 136.8
Naïve to AHAs, no. (%)	16 (41)	16 (43)	17 (45)	18 (45)
Naïve to statin therapy, no. (%)	24 (62)	27 (73)	28 (74)	27 (68)
Lipids (mmol/l)*				
All patients				
LDL-C	3.2 ± 0.9	3.3 ± 0.8	3.1 ± 0.8	3.2 ± 1.0
HDL-C	1.1 ± 0.2	1.2 ± 0.3	1.0 ± 0.2	1.0 ± 0.2
TG	2.3 ± 1.6	2.2 ± 0.9	2.4 ± 1.3	2.0 ± 0.9
Non-HDL-C	4.0 ± 1.0	4.0 ± 0.9	4.0 ± 1.0	3.9 ± 1.1
Statin-naïve patients				
LDL-C	3.2 ± 0.1	3.4 ± 0.8	3.3 ± 0.7	3.4 ± 0.9
HDL-C	1.1 ± 0.2	1.1 ± 0.3	1.0 ± 0.2	1.0 ± 0.2
TG	2.6 ± 1.9	2.2 ± 0.8	2.5 ± 1.3	1.9 ± 0.7
Non-HDL-C	4.1 ± 0.8	4.2 ± 0.9	4.3 ± 0.9	4.2 ± 1.0

A1C, glycosylated haemoglobin; AHA, antihyperglycaemic agent; AHTN, antihypertensive; BMI, body mass index; FPG, fasting plasma glucose; 2-h PPG, 2-h postprandial glucose; TC, total cholesterol; TG, triglycerides; SD, standard deviation.

*Data are mean ± SD.

were generally reversed at week 15, that is, 3 weeks following cessation of treatment with MK-0916 (Table 4).

There were no statistically meaningful changes from baseline at week 12 at any dose in either body hair growth, as measured by the Ferriman–Gallwey method, or acne, as evaluated by investigator and patient global assessments (data not shown).

Discussion

It has been hypothesized that elevated intracellular glucocorticoid levels can contribute to the pathogenesis of the various components of MetS. Inhibition of HSD1, which activates glucocorticoids intracellularly, could therefore be expected to have beneficial effects of the components of MetS. The effect of MK-0916, a specific inhibitor of HSD1, on the components of MetS, is presented here.

Compared to placebo, treatment with MK-0916 had no significant effect on FPG (primary efficacy endpoint) or 2-h

Table 2. Effects of MK-0916 on primary and secondary efficacy endpoints at week 12.

	n	Change* from baseline, LS mean	Difference from placebo in change* from baseline, LS mean		p-Value for dose- response
				95% CI for difference	
FPG (mmol/l)					
Placebo	37	0.3	—	—	—
0.5 mg	37	0.5	0.2	−0.7 to 1.0	—
2 mg	38	0.2	−0.07	−0.9 to 0.8	—
6 mg	38	0.04	−0.3	−1.1 to 0.6	0.443
2-h PPG (mmol/l)					
Placebo	33	0.3	—	—	—
0.5 mg	30	−0.3	−0.7	−2.2 to 0.8	—
2 mg	31	−0.6	−0.9	−2.4 to 0.6	—
6 mg	32	−0.4	−0.7	−2.2 to 0.8	0.349

Table 2. Continued.

	n	Change* from baseline, LS mean	Difference from placebo in change* from baseline, LS mean	95% CI for difference	p-Value for dose- response
A1C (%)					
Placebo	35	0.22	—	—	—
0.5 mg	34	0.04	-0.18	-0.49 to 0.13	—
2 mg	34	-0.06	-0.28	-0.59 to 0.03	0.079
6 mg	33	-0.08	-0.30	-0.62 to 0.02	0.049
Body weight (kg)					
Placebo	39	-0.4	—	—	—
0.5 mg	36	-0.3	0.1	-0.9 to 1.1	—
2 mg	38	-1.3	-0.8	-1.8 to 0.2	0.116
6 mg	38	-2.2	-1.8	-2.8 to -0.8	<0.001
Waist circumference (cm)					
Placebo	34	0.1	—	—	—
0.5 mg	32	-1.3	-1.4	-3.0 to 0.2	—
2 mg	31	-1.2	-1.3	-2.9 to 0.3	0.101
6 mg	30	-1.5	-1.6	-3.2 to -0.0	0.064
Systolic BP (mmHg)					
Placebo	39	3.3	—	—	—
0.5 mg	36	4.7	1.4	-3.8 to 6.6	—
2 mg	38	-1.4	-4.7	-9.8 to 0.4	0.071
6 mg	38	-4.6	-7.9	-13.0 to -2.8	<0.001
Diastolic BP (mmHg)					
Placebo	39	2.2	—	—	—
0.5 mg	36	2.8	0.6	-2.9 to 4.1	—
2 mg	38	0.1	-2.1	-5.5 to 1.4	0.238
6 mg	38	-3.1	-5.4	-8.9 to -1.9	0.001
LDL-C (%)†					
Placebo	24	-5.7	—	—	—
0.5 mg	27	-0.6	2.0	-8.0 to 11.9	—
2 mg	28	4.0	3.4	-6.5 to 13.2	0.497
6 mg	27	5.7	10.4	0.5 to 20.4	0.041
HDL-C (%)†					
Placebo	24	6.1	—	—	—
0.5 mg	27	6.0	-0.2	-6.9 to 6.6	—
2 mg	28	5.1	-1.0	-7.7 to 6.6	—
6 mg	27	3.1	-3.0	-9.8 to 3.7	0.355
TG (%)†					
Placebo	24	4.0	—	—	—
0.5 mg	27	10.9	7.0	-20.5 to 34.4	—
2 mg	28	19.8	15.8	-11.2 to 42.9	—
6 mg	27	15.5	11.5	-16.3 to 39.3	0.324
Non-HDL-C (%)†					
Placebo	24	-1.0	—	—	—
0.5 mg	27	1.9	2.9	-5.8 to 11.6	0.512
2 mg	28	7.5	8.5	-0.1 to 17.2	0.054
6 mg	27	10.1	11.1	2.4 to 19.8	0.006

A1C, glycosylated haemoglobin; Diastolic BP, diastolic blood pressure; CI, confidence interval; FPG, fasting plasma glucose; 2-h PPG, 2-h postprandial glucose; SD, standard deviation; Systolic BP, systolic blood pressure; TG, triglycerides; LS, least squares.

*Percent change for LDL-C, HDL-C, TG and non-HDL-C.

†Assessed in statin-naive patients.

PPG in patients with T2DM and MetS. However, treatment with 6 mg MK-0916 led to a significant, but modest, dose-dependent lowering of A1C compared to placebo. Although the absolute A1C reduction observed with 6 mg MK-0916

Table 3. Summary of clinical adverse experiences.

AEs	MK-0916							
	Placebo		0.5 mg		2 mg		6 mg	
	(N = 39)	(N = 37)	(N = 38)	(N = 40)	n	%	n	%
One or more AEs	18	46	18	49	22	58	22	55
Drug-related AEs*	4	10	5	14	3	8	4	10
Serious AEs	1	3	1	3	1	3	0	0
Serious drug-related AEs	0	0	0	0	0	0	0	0
Discontinued because of AEs	0	0	1	3	1	3	0	0

AE, adverse experience.

*Determined by the investigator to be possibly, probably or definitely drug related.

compared to placebo was modest (0.3% reduction), the mean baseline A1C level for this study population (7.3%) was relatively low. It is known that the magnitude of A1C reduction produced by other AHAs in general diminishes with lower baseline A1C levels (16). Indeed, a recent study examining the effect of 12 weeks of treatment with the HSD1 inhibitor INCB13739 added to ongoing metformin therapy in T2DM patients with a higher mean baseline A1C (8.3%) showed a significant 0.6% reduction in A1C compared to placebo (17).

Treatment with MK-0916 led to dose-dependent modest weight loss. The 6 mg dose produced a significant ($p < 0.001$) 1.8 kg reduction in body weight relative to placebo at 12 weeks. Consistent with this weight loss, there was a non-significant trend towards a decrease in waist circumference with MK-0916, with the 6 mg dose producing a modest decrease in waist circumference of 1.6 cm relative to placebo at 12 weeks ($p = 0.064$). These findings are consistent with preclinical data showing that HSD1 inhibition can reduce body weight in diet-induced obese mice (11). In addition, HSD1 knockout mice are resistant to weight-gain on high-fat feeding (8). HSD1 inhibition has also been found to reduce body weight in obese rhesus monkeys (unpublished findings). Intracellular glucocorticoid levels have been linked to alterations in adipocyte size and function (18). While there was a trend towards weight loss with the HSD1 inhibitor INCB13739 in T2DM patients at week 12, this effect was not significant compared to placebo (17). Additional studies are needed to assess the body weight-regulating effects of HSD1 inhibition.

Treatment with MK-0916 also led to mean decreases in both systolic and diastolic blood pressures compared to placebo. The 6 mg dose produced significant ($p \leq 0.001$) 7.9 and 5.4 mmHg mean reductions relative to placebo in systolic and diastolic blood pressure, respectively. It is well known that levels of cortisol modulate blood pressure in humans. Patients with Cushing's syndrome have elevated cortisol levels and elevated blood pressure, and the blood pressure elevation in these patients can be at least partially reversed by surgical intervention to decrease cortisol levels. Conversely, patients with Addison's disease have inadequate cortisol secretion and may present with hypotension. A role for HSD1 in blood pressure regulation has also been suggested by several animal model

Table 4. Effect of MK-0916 on adrenal androgens at week 12 (treatment) and week 15 (post-treatment).

Treatment	N	Week 12: percent change from baseline, LS mean	Week 12: difference from placebo in percent change from baseline, LS mean	Week 12: 95% CI for difference	Week 12: p-value for dose-response test	Week 15: percent change from baseline, mean (SD)
Androstenedione						
Placebo	29	4.0	—	—	—	7.7(47.7)
0.5 mg	23	12.4	8.4	−12.6 to 29.5	—	7.1(47.5)
2 mg	27	18.7	14.8	−5.7 to 35.2	0.156	−1.0(38.9)
6 mg	31	25.8	21.8	2.2 to 41.5	0.026	−4.4(37.1)
DHEA-S						
Placebo	30	3.4	—	—	—	7.4(19.4)
0.5 mg	30	21.3	17.9	6.1 to 29.6	—	30.9(82.6)
2 mg	28	14.0	10.6	−1.4 to 22.6	—	6.0(16.6)
6 mg	31	9.1	5.7	−6.0 to 17.4	0.603	7.1(19.5)
DHEA						
Placebo	30	12.2	—	—	—	13.8(41.8)
0.5 mg	30	28.0	15.9	−6.3 to 38.1	—	22.4(57.3)
2 mg	28	30.3	18.1	−4.6 to 40.8	0.117	12.8(35.5)
6 mg	31	45.7	33.5	11.5 to 55.5	0.004	20.7(44.8)
Free testosterone—women only						
Placebo	16	−2.1	—	—	—	−12.7(51.8)
0.5 mg	13	5.5	7.6	−34.2 to 49.4	—	40.5(167.1)
2 mg	12	27.6	29.7	−10.9 to 70.3	—	−20.3(36.6)
6 mg	11	26.2	28.2	−13.4 to 69.8	0.111	0.7(36.4)

DHEA, dehydroepiandrosterone; DHEA-S, dehydroepiandrosterone sulfate; week 12, completion of treatment phase; week 15, completion of 3-week reversal phase; SD, standard deviation; LS, least squares.

studies. Overexpression of HSD1 was observed to cause renin-angiotensin aldosterone system (RAAS) pathway-dependent hypertension, and inhibition of HSD1 in several rodent models of hypertension was observed to lead to a decrease in blood pressure (unpublished findings). In contrast to the blood pressure reduction seen with MK-0916, the HSD1 inhibitor INCB13739 had no significant effect on blood pressure in T2DM patients (17). Full evaluation of the blood pressure-lowering benefit of HSD1 inhibition requires further studies.

The dose-dependent increases in LDL-C and non-HDL-C produced by MK-0916 and observed in statin-naïve patients were unexpected. This may have been a compound-specific rather than an HSD1 mechanism-related response. Three lines of evidence suggest that, first, this effect is not in agreement with the known LDL-C-raising effect of glucocorticoids (19). Second, preclinical studies in obese rhesus monkeys with another HSD1 inhibitor lowered LDL-C levels by 20–25% (unpublished findings). Third, treatment with the HSD1 inhibitor INCB13739 was shown to lead to a decrease from baseline in LDL-C in T2DM patients (17). Thus, while the mechanism by which MK-0916 produced increases in LDL-C is unclear, it may be unrelated to HSD1 inhibition. One potential mechanism for this finding is that MK-0916 induces expression of CYP3A4 (unpublished findings); inducers of CYP-3A4 have been shown previously to increase LDL-C (20).

HSD1 inhibition with MK-0916 resulted in modest activation of the HPA axis as evidenced by increases in circulating adrenal androgens. While the levels of androstenedione, DHEA, DHEA-S and of free testosterone in women, were elevated at week 12 with MK-0916 treatment relative to placebo, these elevations were generally modest (mean increases from baseline

of ~20–30%) and consistent with changes reported with the HSD1 inhibitor INCB13739 in T2DM patients (17). Additionally, treatment with MK-0916 over 12 weeks did not lead to clinically-apparent virilization in women, as evidenced by the lack of changes in facial acne or hirsutism index.

Limitations

The following caveats apply when interpreting the results of the secondary efficacy endpoints in this study: (i) the sample size per treatment group was insufficient to provide for adequate statistical power for evaluation of secondary endpoints; (ii) the inferential test results presented, with the exception of those for the primary efficacy endpoint, FPG, were not adjusted for multiplicity in the statistical analyses; (iii) patients on AHAs at screening were washed off their AHA for 5 weeks, which may not have allowed enough time for the baseline A1C level to stabilize prior to randomization; and (iv) while approximately 60% of patients were hypertensive, the majority of them were on antihypertensive medication(s) such that baseline blood pressure was within the normal range.

Conclusions

In summary, this study failed to show efficacy of MK-0916 in patients with T2DM and MetS on the primary efficacy endpoint, FPG. Data from other efficacy endpoints suggest that decreases in intracellular cortisol may have led to the modest decreases observed in A1C, body weight and blood pressure. The dose-dependent increases in LDL-C and non-HDL-C observed with MK-0916 may be a compound-specific rather

than a mechanism-related effect. Treatment with MK-0916 was generally well tolerated, with no clinically meaningful effects of the drug on the HPA axis over 12 weeks. Future confirmatory studies (registered on clinicaltrials.gov as NCT00274716 and NCT00806585) will further assess the effects of HSD1 inhibition on blood pressure and A1C in patients with hypertension with or without diabetes.

Acknowledgements

The authors wish to thank Nicholas Ryan and Alan Meehan (Merck Research Laboratories) for their editorial assistance with this paper. A list of investigators is provided in the Appendix.

Conflict of Interest

E. J. K. has received research grants from Merck. P. U. F., S. S., A. H. V., D. P., M. S. S., S. D., C. T., E. L. and K. D. K. are or were employees of Merck and may hold stock/stock options in the company.

E. J. K. has contributed to the design, conduct/data collection and writing of the manuscript. P. U. F., S. S., A. H. V., D. P., M. S. S., S. D., C. T., E. L. and K. D. K. have all assisted in the design, conduct/data collection, analysis and writing of the manuscript.

References

- Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Executive summary of the third report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). *JAMA* 2001; **285**: 2486–2497.
- Bjorntorp P, Rosmond P. Obesity and cortisol. *Nutrition* 2000; **16**: 924–936.
- Bjorntorp P, Holm G, Rosmond R. Hypothalamic arousal, insulin resistance and type 2 diabetes mellitus. *Diabet Med* 1999; **16**: 373–381.
- Edwards CR, Benediktsson R, Lindsay RS, Seckl JR. 11 β -Hydroxysteroid dehydrogenases: key enzymes in determining tissue-specific glucocorticoid effects. *Steroids* 1996; **61**: 263–269.
- Walker BR. Glucocorticoids and cardiovascular disease. *Eur J Endocrinol* 2007; **157**: 545–559.
- Wamil M, Seckl JR. Inhibition of 11 β -hydroxysteroid dehydrogenase type 1 as a promising therapeutic target. *Drug Discov Today* 2007; **12**: 504–520.
- Thieringer R, Hermanowski-Vosatka A. Inhibition of 11 β -HSD1 as a novel treatment for the metabolic syndrome: do glucocorticoids play a role? *Expert Rev Cardiovasc Ther* 2005; **3**: 911–924.
- Kotelevtsev Y, Holmes MC, Burchell A et al. 11 β -hydroxysteroid dehydrogenase type 1 knockout mice show attenuated glucocorticoid-inducible responses and resist hyperglycemia on obesity or stress. *Proc Natl Acad Sci U S A* 1997; **94**: 14924–14929.
- Morton NM, Holmes MC, Fievet C et al. Improved lipid and lipoprotein profile, hepatic insulin sensitivity, and glucose tolerance in 11 β -hydroxysteroid dehydrogenase type 1 null mice. *J Biol Chem* 2001; **276**: 41293–41300.
- Morton NM, Paterson JM, Masuzaki H et al. Novel adipose tissue-mediated resistance to diet-induced visceral obesity in 11 β -hydroxysteroid dehydrogenase type 1-deficient mice. *Diabetes* 2004; **53**: 931–938.
- Hermanowski-Vosatka A, Balkovec JM, Cheng K et al. 11 β -HSD1 inhibition ameliorates metabolic syndrome and prevents progression of atherosclerosis in mice. *J Exp Med* 2005; **202**: 517–527.
- Masuzaki H, Paterson J, Shinyama H et al. A transgenic model of visceral obesity and the metabolic syndrome. *Science* 2001; **294**: 2166–2170.
- Lindsay RS, Wake DJ, Nair S et al. Subcutaneous adipose 11 β -hydroxysteroid dehydrogenase type 1 activity and messenger ribonucleic acid levels are associated with adiposity and insulinemia in Pima Indians and Caucasians. *J Clin Endocrinol Metab* 2003; **88**: 2738–2744.
- Ferriman D, Gallwey JD. Clinical assessment of body hair growth in women. *J Clin Endocrinol Metab* 1961; **21**: 1440–1447.
- Allen BS, Smith JG. Various parameters for grading acne vulgaris. *Arch Dermatol* 1982; **118**: 23–25.
- Bloomgarden ZT, Dodis R, Viscoli CM, Holmboe ES, Inzucchi SE. Lower baseline glycemia reduces apparent oral agent glucose-lowering efficacy: a meta-regression analysis. *Diabetes Care* 2006; **29**: 2137–2139.
- Rosenstock J, Banarer S, Fonseca VA et al. The 11 β -hydroxysteroid dehydrogenase type 1 inhibitor INCB13739 improves hyperglycemia in patients with type 2 diabetes inadequately controlled by metformin monotherapy. *Diabetes Care* 2010; **33**: 1516–1522.
- Morton MN. Obesity and corticosteroids: 11 β -Hydroxysteroid type 1 as a cause and therapeutic target in metabolic disease. *Mol Cell Endocrinol* 2010; **316**: 154–164.
- Sweetman SC. Corticosteroids. In: Martindale-The Complete Drug Reference, 34th edn. London: Pharmaceutical Press, 2005; 1068–1071.
- Mintzer S, Skidmore CT, Abidin CJ et al. Effects of antiepileptic drugs on lipids, homocysteine, and C-reactive protein. *Ann Neurol* 2009; **65**: 448–456.

Appendix

Investigator list

Australia: Bronwym G, Nedlands, WA; Moses R, Wollongong, NSW. *Israel:* Wainstein J, Holon. *New Zealand:* Scott RS, Christchurch. *United States:* Bakhshi V, Montpelier, VA; Bays H, Louisville, KY; Bowling BT, Endwell, NY; Brazg R, Renton, WA; Burton R, Anaheim, CA; Chappel C, Kissimmee, FL; Clark J, Charlottesville, NC; Conard S, Irving, TX; Davidson M, Chicago, IL; Bernstein RI, Greenbrae, CA; Fields H, Houston, TX; Frazer N, Troy, MI; Galitz L, Miami, FL; Gilbert J, Fullerton, CA; Hassman D, Berlin, NJ; Hazan L, Beverly Hills, CA; Herera C, Houston, TX; Hernandez FO, Hialeah, FL; Herring C, Wilmington, NC; Hoekstra J, Richmond, VA; Hollander P, Dallas, TX; Jain RK, Milwaukee, WI; Kerzner B, Baltimore, MD; Kipnes M, San Antonio, TX; Klein EJ, Olympia, WA; Landgarten S, Tulsa, OK; Lerman S, Hollywood, FL; Lewin A, Los Angeles, CA; Littlejohn T, Winston-Salem, NC; Lubin B, Norfold, VA; Miller A, Dunwoody, GA; Niederman A, Fort Lauderdale, FL; Pearson D, St. Louis, MO; Peters P, San Antonio, TX; Pierson M, Overland Park, KS; Poling T, Wichita, KS; Raad G, Charlotte, NC; Rosenstock J, Dallas, TX; Ruoff G, Kalamazoo, MI; Segall N, Atlanta, GA; Serverance RJ, Chandler, AZ; Tonkon MJ, Santa Anna, CA; Toth P, Indianapolis, IN; Turk D, Billingham, WA; Udani J, Northridge, CA; Underberg J, New York, NY; Weerasingh M, Rochester, NY; Weinstein RL, Walnut Creek, CA; Zavoral J, Edina, MN.