Weight Loss, HbA_{1c} Reduction, and Tolerability of Cetilistat in a Randomized, Placebo-controlled Phase 2 Trial in Obese Diabetics: Comparison With Orlistat (Xenical)

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The objective of this multicenter, randomized, double-blind study was to determine the efficacy and safety of cetilistat and orlistat relative to placebo in obese patients with type 2 diabetes, on metformin. Following a 2-week run-in, patients were randomized to placebo, cetilistat (40, 80, or 120 mg three times daily), or orlistat 120 mg t.i.d., for 12 weeks. The primary endpoint was absolute change in body weight from baseline. Secondary endpoints included other measures of obesity and glycemic control. Similar reductions in body weight were observed in patients receiving cetilistat 80 or 120 mg t.i.d. or 120 mg t.i.d. orlistat; these reductions were significant vs. placebo (3.85 kg, $P = 0.01$; 4.32 kg, $P = 0.0002$; 3.78 kg, $P = 0.008$). In the 40 mg t.i.d. and placebo groups, reductions were 2.94 kg, $P = 0.958$ and 2.86 kg, respectively. Statistically significant reductions in glycosylated hemoglobin (HbA_{1c}) were noted. Cetilistat was well tolerated, and showed fewer discontinuations due to adverse events (AEs) than in the placebo and orlistat groups. Discontinuation in the orlistat group was significantly worse than in the 120 mg cetilistat and placebo groups and was entirely due to gastrointestinal (GI) AEs. Treatment with cetilistat 80 or 120 mg t.i.d., or with orlistat 120 mg t.i.d., significantly reduced body weight and improved glycemic control relative to placebo in obese diabetic patients. Cetilistat was well tolerated with the number of discontinuations due to AEs being similar to placebo.

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INTRODUCTION

Weight control plays an important role in the management of patients with type 2 diabetes and is typically addressed by lifestyle modifications. These focus on a nutritionally balanced, moderately hypocaloric diet, with a reduced intake of saturated fat and an increase in physical activity (1–6). Current pharmacological options for weight management are limited, with only three agents, orlistat (an inhibitor of gastric and pancreatic lipases) (7–10), sibutramine (a combined reuptake inhibitor of both serotonin and norepinephrine) that acts centrally to enhance satiety (11), and phentermine (a sympathomimetic) currently approved in some countries for use in obese patients with or without diabetes (12–15). Rimonabant (a cannabinoid-1 receptor blocker) was recently removed from the market. Cetilistat is a novel, highly lipophilic benzoxazinone inhibitor of gastrointestinal (GI) and pancreatic lipases, which is currently under development for the management of weight loss in obese patients with or without medical complications. In a 12-week, randomized, placebo-controlled, phase 2 clinical study in obese patients without pharmacologically treated comorbidities, administration of 60, 120, or 240 mg cetilistat three times daily (t.i.d.) in combination with a hypocaloric diet produced significantly greater weight loss than placebo at all doses tested (16). In addition, cetilistat was well tolerated, with a similar proportion of discontinuations due to adverse events (AEs) in both the cetilistat and the placebo groups (16). AEs were predominantly GI in nature and mild or moderate in severity.

We report here the results from a randomized, placebo-controlled study investigating the efficacy and tolerability of three cetilistat doses (40, 80, and 120 mg t.i.d.) compared to placebo, in obese patients with type 2 diabetes on metformin. The study also included an active treatment comparator arm, with patients in this group receiving orlistat (120 mg t.i.d.).

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METHODS AND PROCEDURES

Patients

Male and female patients aged between 18 and 65 years of age with type 2 diabetes, a BMI between 28 and 45 kg/m^2, and a glycosylated hemoglobin (HbA_{1c}) of >6 and <10% were eligible for inclusion in this study. The diagnosis of diabetes must have been made >3 months previously and have been controlled by a stable dose of metformin for at least 3 months. Statin treatment was allowed, provided it had been stable for at least 3 months before entry into the study.

Study design

This was a 12-week multicenter, randomized, double-blind, placebo-controlled parallel group study, comprising an initial 2-week run-in phase, 12-week double-blind treatment phase, and a further 4-week follow-up period. During the 2-week run-in phase, patients discontinued all prohibited medications and were advised to maintain a diet that was deficient by ~500 calories per day, with ~30% of calories derived from fat. Prohibited medications included any anorectant medications, appetite suppressants, immunosuppressants, dietary supplements, e.g., vitamins, anticoagulants, and steroids (except topical or inhaled). The calorie requirement was calculated according to the revised World Health Organization equation for estimating basal metabolic rate. Patients who met the inclusion/exclusion criteria following the run-in period and whose body weight had not increased by >0.1 kg were randomized to treatment with cetilistat (40, 80, or 120 mg t.i.d.), orlistat (120 mg t.i.d.) or matching placebo in a 1:1:1:1:1 ratio, stratified on the basis of the dose of metformin (≤ or >1,500 mg/day), for 12 weeks. The medication was taken three times daily with meals.

Patients were scheduled for clinic visits at screening, baseline (week 0), weeks 4, 8, and 12 during treatment, and at week 16 (end of 4-week follow-up period). Patients were also contacted via telephone at weeks 3, 6, and 11, for AE recording and further dietary advice.

This study was conducted in accordance with the International Conference on Harmonisation guidelines on Good Clinical Practice and was approved by an independent ethics committees of each country and as appropriate, each site. Written informed consent was obtained from each patient before enrollment in the study.

Assessments

Assessments were made at each four weekly visit. The primary outcome was the absolute change in body weight at week 12, last observation carried forward from baseline. Secondary endpoints included the proportion of patients achieving weight loss within predefined limits (≥0% (increase), and >0% and <5%, 5–10%, and >10% (all decrease)), change in waist circumference from baseline, change in lipid profiles, fasting blood glucose, insulin level, and HbA_{1c} at week 12. All patients were given the option of collecting a stool sample for assessment of fecal fat. Approximately 30% of patients (n = 32–44 per group) provided stool samples at baseline and at the end of treatment. Patients provided stool samples rather than the total stool passed; fat excretion was therefore determined as the percentage of fat within the sample. Safety was assessed by means of AE reporting, GI symptoms reporting, vital signs, electrocardiogram, and clinical laboratory variables including fat soluble vitamins (A, E, and K).

The intensity (severity) of AEs was classified as follows:

Mild: aware of sign or symptoms, easily tolerated
Moderate: sign or symptom causes discomfort but does not interfere with normal activities
Severe: sign or symptom is of sufficient intensity to interfere with normal activities.

These were defined in the protocol, together with GI symptom terminology, to ensure as far as possible uniform standards across centers.

Statistical analysis

All efficacy analyses were performed using the intention-to-treat group. This comprised all patients who were randomized and received at least one dose of study medication and had at least one postbaseline weight assessment. Missing data were imputed using the last observation carried forward method and so all patients with at least one postbaseline assessment were included in the analysis.

Analyses of weight change data were performed by analysis of covariance using weight change as the response. Treatment and country were used as fixed effects, while baseline weight, metformin dose, screening weight change, baseline BMI, and HMG-CoA reductase inhibitor (statin) use were used as covariates. Least-square mean values with 95% confidence intervals for the least-square mean difference were also calculated and used to determine the placebo-adjusted effect of cetilistat. Based on the analysis of covariance results, Dunnett's post hoc test for multiple comparisons was used to compare differences between the cetilistat treatment groups and the placebo group. Secondary analyses were performed using analysis of covariance.

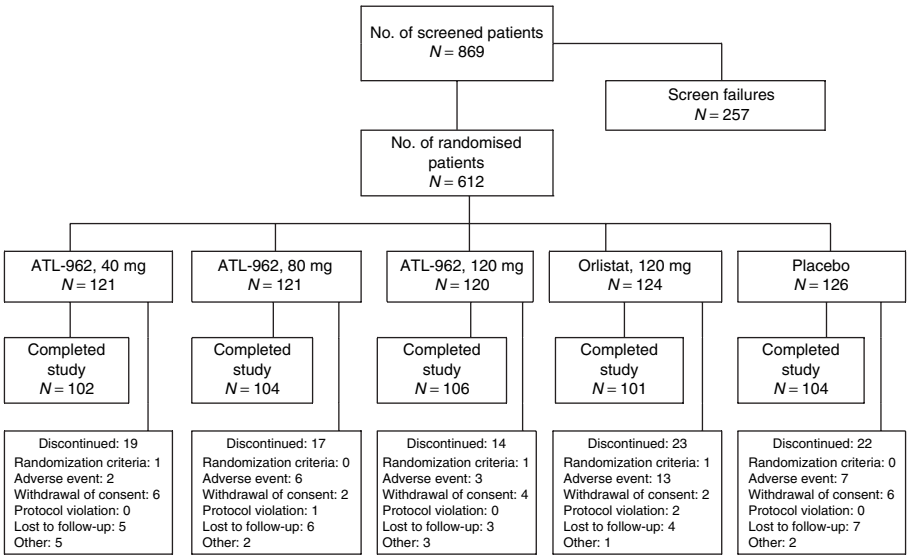

Figure 1 Patient disposition.

Post hoc analyses of the proportion of patients with AEs and GI AEs together with those that discontinued as a result of such events were performed using the Cochran Mantel–Haenszel test controlling for country. These statistical comparisons focused on the highest dose of cetilistat (120 mg) vs. 120 mg orlistat. In addition to the analyses of the proportion of patients affected, the number of AEs per patient was analyzed.

A sample size of 115 evaluable patients per treatment arm was estimated to provide 80% power to detect treatment differences in body weight of 1.3 kg from baseline. This assumed a 5% significance level using Dunnett's procedure for comparison of the three active cetilistat doses to placebo and a standard deviation in change in weight from baseline of 3.0 kg. A sample size of 120 patients per treatment arm was randomized assuming that ~3% of subjects would be non-evaluable.

RESULTS

Patients

Of 869 patients screened for entry into the study, 612 were randomized to receive placebo (N = 126), orlistat (N = 124), or cetilistat (40 mg t.i.d.: N = 121; 80 mg t.i.d.: N = 121; 120 mg t.i.d.: N = 120) (see **Figure 1**). The baseline characteristics of the randomized patients are listed in **Table 1** and were similar across the treatment groups. The mean age of the randomized patients was 53.4 years and 50.4% were men.

During the run-in period, 95 patients used medications that were discontinued before randomization. There was no clinically significant difference in the type of medications that were used by the patients in each arm, except for the number of patients taking serum lipid reducing agents, which was higher in the orlistat group (9 patients vs. 2 or 3 patients in the other treatment groups).

For the concomitant medications, cardiovascular medications including antihypertensive and lipid reducing medications were used by 78% of patients and antithrombotic agents by 36%. Overall, 53% of patients were receiving lipid-lowering therapy, mostly HMG-CoA reductase inhibitors. In all cases, medical treatments were essentially balanced across the groups.

The double-blind treatment phase was completed by 87% of patients and 85% completed the follow-up phase. The primary reasons for discontinuation were AEs (31/612; 5.1%; 2, 6, 3, 13, and 7 patients in the 40, 80, and 120 mg cetilistat, 120 mg orlistat and placebo groups, respectively) (see **Figure 1**). Patients lost to follow-up comprise (25/612; 4.1%; 5, 6, 3, 4, and 7 patients in the 40, 80, and 120 mg cetilistat, 120 mg orlistat and placebo groups, respectively) (see **Figure 1**). The intention-to-treat analysis group consisted of patients who took at least 1 dose of study medication and had 1 postbaseline weight assessment and comprised 589 patients (96.2%) (**Figure 1**).

Efficacy endpoints

The change in mean weights between screening and randomization was essentially similar for each of the five groups in this study (~1.5 kg).

Reductions in weight from baseline were observed in all treatment groups including the placebo group at the end of the double-blind treatment phase (week 12; **Figure 2**). Absolute weight loss in the cetilistat 80 and 120 mg t.i.d. dose group was significantly greater than in the placebo group (P = 0.01 and P = 0.0002, respectively), but in the cetilistat 40 mg t.i.d. dose group weight loss was similar to placebo. The weight loss in the group receiving orlistat 120 mg t.i.d. was similar to that with

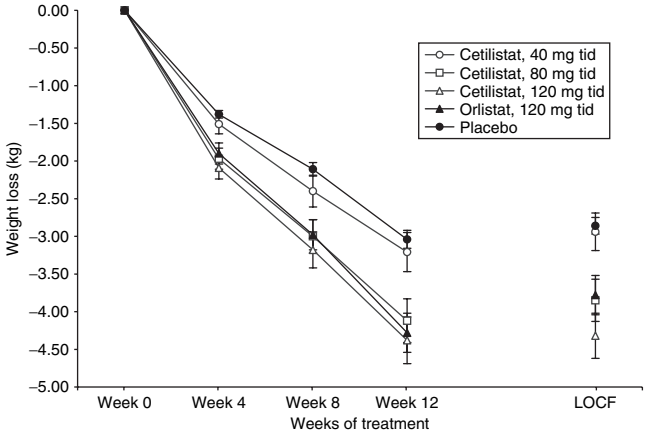

Figure 2 Profile of mean weight loss over time (mean ± s.e.m.). LOCF, last observation carried forward; t.i.d., three times daily.

Table 1 Patient baseline characteristics

Baseline characteristic	Treatment group				
	Placebo	Cetilistat			Orlistat
	0 mg t.i.d. (N = 125)	40 mg t.i.d. (N = 120)	80 mg t.i.d. (N = 121)	120 mg t.i.d. (N = 120)	120 mg t.i.d. (N = 121)
Age (years)[a]	54.4 (7.6)	52.7 (8.0)	52.4 (8.4)	53.5 (7.6)	54.3 (7.8)
Height (cm)[a]	169.0 (9.7)	170.8 (9.4)	170.2 (9.0)	170.7 (9.3)	170.9 (9.0)
Gender (n (%))					
Male	53 (42.4)	57 (47.5)	61 (50.4)	69 (57.5)	66 (54.5)
Female	72 (57.6)	63 (52.5)	60 (49.6)	51 (42.5)	55 (45.5)
Body weight (kg)[a]	98 (15.7)	100 (16.6)	99 (14.6)	103 (15.6)	101 (15.0)
BMI (kg/m^2)[a]	34 (4.1)	34 (4.6)	34 (3.9)	35 (4.4)	35 (4.1)
HbA_{1c} (%)[a]	7.2 (1.0)	7.1 (0.8)	7.2 (1.0)	7.1 (0.9)	7.2 (1.0)

HbA_{1c}, glycosylated hemoglobin; t.i.d., three times daily.
[a]Mean (±s.d.).

Table 2 HbA_{1c} changes based on baseline values

Treatment	Change	Week 12—LOCF mean	HbA_{1c} baseline value		
			<7%	≥7 to <8	≥8%
Placebo t.i.d.	*N*	119	50	31	26
	HbA_{1c} (%)	–0.37	–0.12	–0.52	–0.75
	Weight (kg)	–2.86	–3.05	–3.04	–3.03
Cetilistat 40 mg t.i.d.	*N*	116	52	40	12
	HbA_{1c} (%)	–0.33	–0.14	–0.44	–0.82
	Weight (kg)	–2.94	–3.13	–3.41	–2.77
Cetilistat 80 mg t.i.d.	*N*	119	55	36	17
	HbA_{1c} (%)	–0.54	–0.26	–0.62	–1.39
	Weight (kg)	–3.85	–4.24	–3.58	–4.91
Cetilistat 120 mg t.i.d.	*N*	115	54	38	19
	HbA_{1c} (%)	–0.51	–0.20	–0.72	–1.03
	Weight (kg)	–4.32	–4.35	–4.88	–3.63
Orlistat 120 mg t.i.d.	*N*	120	48	30	25
	HbA_{1c} (%)	–0.53	–0.23	–0.61	–1.19
	Weight (kg)	–3.78	–4.78	–3.61	–4.13

HbA_{1c}, glycosylated hemoglobin; LOCF, last observation carried forward; t.i.d., three times daily.

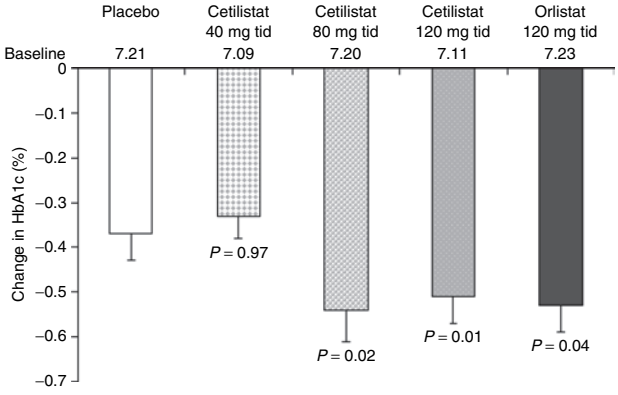

Figure 3 Reduction in HbA_{1c} at week 12—LOCF (ITT population). HbA_{1c}, glycosylated hemoglobin; ITT, intention-to-treat; LOCF, last observation carried forward; t.i.d., three times daily.

cetilistat at 80 and 120 mg t.i.d. and was statistically significant ($P = 0.0075$; Figure 2).

The proportion of patients who achieved ≥5% weight loss was greater in the 80 mg and 120 mg t.i.d. cetilistat groups (29%; $P = 0.01$ and 33%; $P = 0.03$) and in the orlistat group (31%; $P = 0.02$) than for the placebo group (19%). The proportion who achieved ≥5% weight loss in the cetilistat 40 mg t.i.d. group (22%) was not significantly different from placebo.

Significant reductions relative to placebo were seen for waist circumference in the cetilistat 80 and 120 mg t.i.d. dose groups (4.3 cm, $P = 0.033$; and 4.5 cm, $P = 0.037$ vs. 3.2 cm) and in the orlistat group (4.4 cm; $P = 0.019$). The reduction in waist circumference (2.9 cm) in the cetilistat 40 mg t.i.d. group was similar to that in the placebo group.

Levels of HbA_{1c} were reduced from baseline in all treatment groups by the end of the randomized treatment period (Figure 3). In the 80 mg and 120 mg cetilistat dose groups, these reductions (ca. 0.5%) were significantly greater than placebo ($P = 0.018$ and $P = 0.015$, respectively). The reduction in HbA_{1c} in the orlistat treatment group was also significant compared to placebo ($P = 0.04$), and was similar to that seen in the cetilistat 80 and 120 mg dose groups; the higher the baseline level of HbA_{1c} the greater the benefit from cetilistat treatment, although weight loss was similar in each of the baseline HbA_{1c} categories (Table 2). A similar, albeit smaller, effect was seen in the placebo group. There were small, but not clinically significant reductions in mean levels of insulin, fasting blood glucose, and fructosamine in all groups (data not shown). No consistent changes in lipid profile from baseline, which were all within the normal range, were seen in any of the treatment groups. This was not surprising given the treatment period and many patients were taking statins as part of their regular therapy.

In the subpopulation of subjects who provided stool samples for determination of fat excretion, the percentage fat in the stool was significantly increased from baseline in all active treatment groups compared to placebo (Table 3). As total stool weight was not recorded it is not possible to determine whether there was a relationship between total fat excreted and weight loss.

Safety

The proportion of patients reporting treatment-emergent AEs, and the number of AEs reported were higher in the cetilistat and orlistat treatment groups compared to placebo (Table 4). The proportion of patients reporting AEs (87–89%) and the number of AEs reported (387–428) were similar in the three cetilistat dose groups. The majority of reported AEs with cetilistat were mild (233–272) or moderate (119–126) in intensity, with few being severe (25–31). The proportion of patients in the orlistat group

reporting AEs (93%) was similar to that in the cetilistat groups ($P = 0.3251$ compared to 120 mg cetilistat group). However, the patients in the orlistat group reported more events (541; $P = 0.0148$ compared to 120 mg cetilistat group), with more being severe (55; $P = 0.0546$ compared to 120 mg cetilistat group), than patients in the cetilistat groups (Table 4). During the study, a total of five serious AEs were reported, one in each treatment group and one in the placebo group. None were considered to be related to the study medication. No deaths were reported.

The most frequently reported AEs were GI (Table 4). In the cetilistat-treated patients, the number of reported GI AEs (282–339) was higher than for placebo (153), but ~30% lower than for the orlistat group (431; $P = 0.0184$ compared to 120 mg cetilistat group). The number of non-GI AEs was similar in all groups including placebo. The number of reported GI AEs in the orlistat-treated patients classified as severe (54) was substantially higher than in the cetilistat groups (17–28) (Table 4). The proportion of patients with AEs (and the number of AEs)

Table 3 Mean fecal fat content, change from baseline to week 12 by treatment group

	Treatment group				
	Placebo	Cetilistat			Orlistat
	0 mg t.i.d.	40 mg t.i.d.	80 mg t.i.d.	120 mg t.i.d.	120 mg t.i.d.
Baseline					
N	54	58	48	56	48
% Fecal fat (s.d.)	8.28 (4.1)	7.98 (3.5)	7.95 (4.5)	8.54 (3.8)	8.90 (3.7)
Week 12[a]					
N	41	47	39	46	36
% Fecal fat (s.d.)	9.05 (4.2)	20.75 (8.4)	18.48 (8.4)	23.27 (8.9)	24.65 (9.3)
Change between baseline and week-12 value[a]					
N	38	44	37	44	32
% Fecal fat (s.d.)	0.96 (4.6)	12.76 (7.1)	10.72 (7.5)	15.26 (9.1)	15.24 (10.5)
95% CI		(8.57, 15.40)	(6.20, 13.34)	(11.16, 18.01)	(11.56, 19.03)
P value		<0.0001	<0.0001	<0.0001	<0.0001
% Increase	9	160	132	172	177

All treatment differences are cetilistat minus placebo or orlistat minus placebo.
CI, confidence interval.
[a]The fecal fat value for 1 patient was obtained when the patient withdrew from the study rather than at week 12.

Table 4 Adverse event frequency and severity

	Treatment group														
	Placebo			Cetilistat									Orlistat[a]		
	0 mg t.i.d. (*N* = 125)			40 mg t.i.d. (*N* = 120)			80 mg t.i.d. (*N* = 121)			120 mg t.i.d. (*N* = 120)			120 mg t.i.d. (*N* = 121)		
	n	%	AE	*n*	%	AE	*n*	%	AE	*n*	%	AE	*n*	%	AE
Any adverse event	91	(72.8)	280	104	(86.7)**	412	105	(86.8)**	387	107	(89.2)**	428	112	(92.6)	541[†]
Mild	76	(60.8)	180	93	(77.5)	268	93	(76.9)	233	95	(79.2)	272	93	(76.9)	302
Moderate	44	(35.2)	80	58	(48.3)	119	64	(52.9)	126	60	(50.0)	125	74	(61.2)	184
Severe	11	(8.8)	20	16	(13.3)	25	19	(15.7)	28	20	(16.7)	31	28	(23.1)	55
AE leading to discontinuation	8	(6.4)	14	3	(2.5)	8	6	(5.0)	13	3	(2.5)	4	14	(11.6)[††]	47[††]
GI AEs	70	(56.0)	153	94	(78.3)***	294	98	(81.0)***	282	100	(83.3)***	339	106	(87.6)	431[†]
Mild	57	(45.6)	100	83	(69.2)	197	83	(68.6)	178	90	(75.0)	214	88	(72.7)	252
Moderate	28	(22.4)	44	41	(34.2)	80	46	(38.0)	82	52	(43.3)	97	60	(49.6)	125
Severe	6	(4.8)	9	11	(9.2)	17	14	(11.6)	22	17	(14.2)	28	27	(22.3)	54[†]
GI AE leading to discontinuation	5	(4.0)	9	1	(0.8)	4	3	(2.5)	7	2	(1.7)	2	14	(11.6)[††]	46[††]

No statistical analyses were performed on mild or moderate AEs/GI AEs. For severe AEs/GI AEs 120 mg cetilistat was compared to 120 mg orlistat. Orlistat was not compared to placebo.
AE, number of adverse events; GI AE, gastrointestinal adverse events; *N*, no. of patients in the safety population; *n* = no. of patients affected; t.i.d., three times daily.
[a]Orlistat statistical annotations refer to comparison of the highest dose of cetilistat to orlistat; Cochran Mantel–Haenszel test: cetilistat compared to placebo $^{*}P < 0.05$; $^{**}P < 0.01$ $^{***}P < 0.001$ and 120 mg cetilistat compared to 120 mg orlistat $^{\dagger}P < 0.05$; $^{\dagger\dagger}P < 0.01$; $^{\dagger\dagger\dagger}P < 0.001$.

Table 5 Change from baseline to week 12 LOCF in fat soluble vitamins, safety population

Parameter	Treatment group				
	Cetilistat, 40 mg t.i.d.	Cetilistat, 80 mg t.i.d.	Cetilistat, 120 mg t.i.d.	Orlistat, 120 mg t.i.d.	Placebo t.i.d. (*N* = 125)
Vitamin E (μmol/l)					
Baseline values (s.d.)	29.74 (8.04)	29.75 (7.04)	29.19 (8.97)	29.22 (7.70)	29.02 (8.72)
Week 12 LOCF change					
N	116	118	115	115	118
Mean (s.d.)	−0.74 (7.61)	−0.60 (6.28)	−1.21 (5.24)	−1.28 (5.37)	1.43 (6.61)
Median	−1.60	−1.50	−0.70	−1.20	1.40
Min–max	−28.9, 34.5	−22.4, 27.8	−24.0, 10.9	−18.5, 17.5	−18.2, 21.6
Week 12 LOCF change LS mean	−0.49	−0.40	−1.45	−1.45	1.35
Treatment difference					
LS mean	−1.84	−1.75	−2.80	−2.80	
95% CI	(−3.29, −0.39)	(−3.19, −0.30)	(−4.25, −1.35)	(−4.25, −1.35)	
P value	0.0128	0.0177	0.0002	0.0002	

All treatment differences are cetilistat minus placebo or orlistat minus placebo.
CI, confidence interval; LS, least square; LOCF, last observation carried forward.
[a]Safety population defined as all patients who had taken at least one dose of study medication.

leading to discontinuation in the cetilistat-treated groups was 2.5% (8), 5.0% (13), and 2.5% (4) for the 40, 80, and 120 mg t.i.d. groups, respectively, compared to 6.4% (14) in the placebo group ($P > 0.05$) and a higher proportion (11.6%; 46 events) in the orlistat group, all of which were GI (**Figure 4a**). Statistically significantly more patients discontinued due to AEs ($P = 0.0053$) and GI AEs ($P = 0.0019$) in the orlistat-treated group than in the cetilistat-treated groups (*P* values relate to comparison of 120 mg cetilistat and 120 mg orlistat).

The most common GI AEs with orlistat leading to discontinuation were abdominal pain, defecation urgency, diarrhea, fecal incontinence, and oily stool. The frequency of discontinuations due to each of these AEs was considerably higher in the orlistat treatment group compared with the cetilistat groups (**Table 4**; **Figure 4b**).

No clinically significant changes in routine laboratory parameters, vital signs, or electrocardiogram readings were observed during treatment. The active treatment groups for both cetilistat and orlistat had significantly reduced vitamin E values compared to the placebo group. Mean baseline values ranged from 29.19 to 29.75 μmol/l in the active treatment groups, and was 29.02 μmol/l in the placebo group. Mean levels fell in all the active groups (range −0.60 to −1.28 μmol/l), approximately a 2–4% fall relative to baseline, compared to an increase of about 5% in the placebo group (**Table 5**). However, none of the changes in level was reported as an AE.

DISCUSSION

In this randomized, placebo-controlled, double-blind study, treatment with cetilistat (80 and 120 mg t.i.d.) or orlistat (120 mg t.i.d.) for 12 weeks, combined with a hypocaloric, moderate fat diet, produced significant reductions in body weight compared to placebo in obese patients with type 2 diabetes who were being treated with metformin. This was accompanied by improved glycemic control as evidenced by significant reductions (ca. 0.5%) in plasma HbA_{1c} levels. There were also significant reductions in waist circumference, a risk factor for cardiovascular disease (17) in the cetilistat (80 and 120 mg t.i.d.) and orlistat (120 mg t.i.d.) dose groups.

These results are also comparable to those observed in a previous study of orlistat in metformin-treated obese patients with type 2 diabetes (9). They are also similar to those reported for sibutramine and rimonabant (18) indicating that the peripheral mechanism of action of cetilistat has potential for management of patients with type 2 diabetes.

Fat excretion, measured as percentage fat in stool, was increased in all active treatment groups, with the highest values in the 120 mg and orlistat groups, but this was not quantitatively directly related to weight loss. This discrepancy may be attributable to the fat excretion value being a single point sample, whereas weight loss occurs over an extended period of time.

Lipids were essentially normal at baseline in this population and no clinically significant changes in low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, and total cholesterol levels were observed in any of the treatment groups despite the reductions in body weight. The lack of change in lipid levels may be because many patients were on prestudy statin therapy. There were also minor, clinically nonsignificant reductions in both insulin levels and fasting plasma glucose.

Although good glycemic control (HbA_{1c} of <7%) can be achieved initially through monotherapy with sulfonylureas or metformin, sustained control with these agents fails in 50% of patients after 3 years (ref. 19). Weight reduction treatments

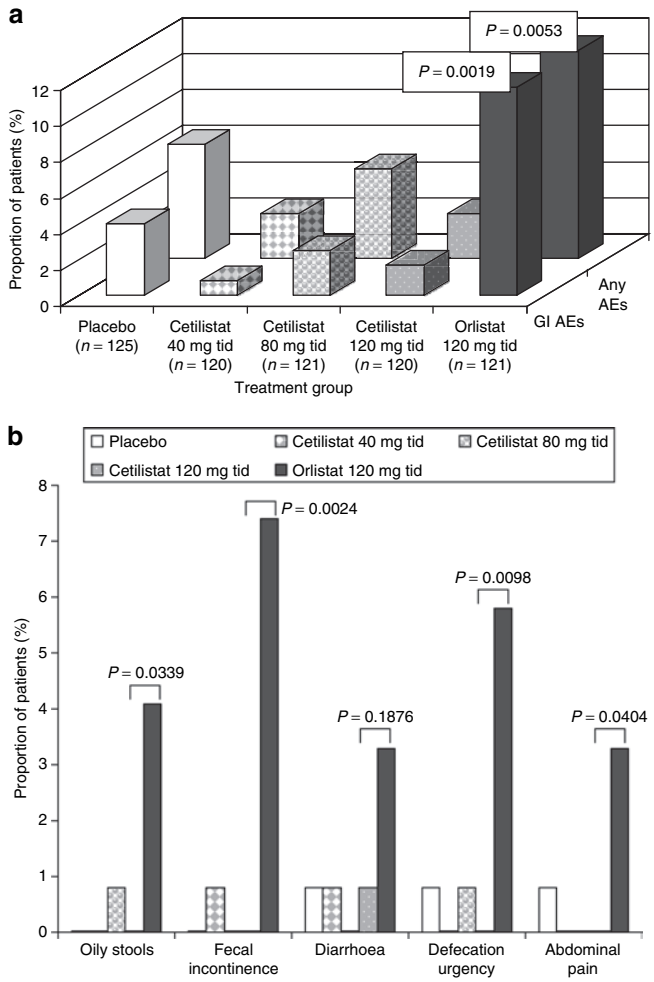

Figure 4 Participant discontinuation from study. (**a**) Proportion of participants discontinuing for adverse events. (**b**) Frequency of adverse event by type resulting in participant discontinuation. AE, adverse events; GI, gastrointestinal; t.i.d., three times daily.

such as cetilistat may therefore play an important role in future combination therapies for diabetes.

Cetilistat was generally well tolerated. The most common AEs observed involved the GI system. However, most of these AEs were rated as being mild or moderate in intensity. The increased frequency of GI AE reporting in the cetilistat groups did not lead to an increase in discontinuations. In fact, the frequency of discontinuations due to GI AEs was lower in all three cetilistat groups vs. placebo.

A higher proportion of patients in the orlistat group reported a greater number of GI AEs compared to the cetilistat groups. In addition, the number of GI AEs in the orlistat-treated patients classified as severe was substantially higher than in the cetilistat groups. The orlistat group also had the highest frequency of discontinuations arising from AEs, more than double that of the cetilistat 80 mg t.i.d. group and almost five times that in the cetilistat 120 mg t.i.d. group. Furthermore, GI AEs, primarily fecal incontinence, defecation urgency, steatorrhea (oily stool), and diarrhea, were responsible for all of the AE-related discontinuations in the orlistat group.

A previous study with orlistat suggested that the incidence of GI AEs was correlated with increased fecal fat content and that this increase may be a class effect (20). However, the lower frequency of these AEs in the cetilistat treatment arms, despite similar fecal fat excretion in this study in the cetilistat and orlistat groups, coupled with the results from phase 1 studies of cetilistat showing no relationship between fecal fat content and GI AEs (21), would indicate that there is no direct correlation between lipase inhibition and the nature and frequency of GI AEs. This would support the notion that it is the physical form of the fat in the intestine, which is important in terms of tolerability. The difference in AEs between cetilistat and orlistat could be attributable to structural differences between the two molecules. Although both molecules are lipase inhibitors, the chemical structural differences, in terms of hydrophilic and lipidophilic components, may influence the way in which the molecules interact with fat micelles in the intestine. Thus orlistat, unlike cetilistat, may promote coalescence of micelles, leading to oils and increased GI AEs.

In conclusion, 12 weeks of treatment with cetilistat 80 or 120 mg t.i.d. significantly reduced body weight and improved glycemic control in obese patients with type 2 diabetes managed with metformin. Cetilistat was well tolerated, with withdrawals due to AEs being similar to placebo and substantially fewer than with orlistat. The high level of tolerability of cetilistat in this patient group, with the consequent increase in compliance, could be clinically significant in the management of this patient population.

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DISCLOSURE

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