

Orlistat, a lipase inhibitor, for weight maintenance after conventional dieting: a 1-y study<sup>1-3</sup>

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## ABSTRACT

**Background:** Long-term maintenance of weight loss remains a therapeutic challenge in obesity treatment.

**Objective:** This multicenter, double-blind, placebo-controlled study was designed to test the hypothesis that orlistat, a gastrointestinal lipase inhibitor, is significantly more effective than a placebo in preventing weight regain.

**Design:** Obese subjects who lost  $\geq 8\%$  of their initial body weight during a 6-mo lead-in of a prescribed hypoenergetic diet (4180-kJ/d deficit) with no adjunctive pharmacotherapy were randomly assigned to receive placebo, 30 mg orlistat, 60 mg orlistat, or 120 mg orlistat 3 times daily for 1 y in combination with a maintenance diet to help prevent weight regain. Of 1313 recruited subjects [body mass index (in kg/m<sup>2</sup>): 28–43], 729 subjects lost  $\geq 8\%$  of their initial body weight during the 6-mo weight-loss lead-in period and were enrolled in the double-blind phase.

**Results:** After 1 y, subjects treated with 120 mg orlistat 3 times daily regained less weight than did placebo-treated subjects ( $32.8 \pm 4.5\%$  compared with  $58.7 \pm 5.8\%$  regain of lost weight;  $P < 0.001$ ). Moreover, more subjects in the 120-mg orlistat group than in the placebo group regained  $\leq 25\%$  of lost weight (47.5% of subjects compared with 29.9%). In addition, orlistat treatment (120 mg 3 times daily) was associated with significantly greater reductions in total and LDL-cholesterol concentrations than was placebo ( $P < 0.001$ ).

**Conclusion:** The use of orlistat during periods of attempted weight maintenance minimizes weight readjustment and facilitates long-term improvement in obesity-related disease risk factors. *Am J Clin Nutr* 1999;69:1108–16.

**KEY WORDS** Obesity, orlistat, lipase inhibition, weight loss, lipids, cardiovascular disease risk factors, weight maintenance, humans

## INTRODUCTION

The prevalence of obesity has increased substantially in the United States during the past decade and continues to rise (1). Obesity is a chronic disease and a major independent risk factor for cardiovascular disease (2). A weight loss of 5–10% of initial body weight improves obesity-related risk factors, including lipid concentrations, blood pressure, and glycemic control (3–5).

See corresponding editorials on pages 1059 and 1061.

However, even with the most rigorous weight-loss interventions, which include behavioral modification, nutrition counseling, social support, and physical activity, these effects dissipate when weight loss is not maintained (6, 7). According to a recent review of long-term weight-loss outcomes after lifestyle interventions alone, individuals regained  $\approx 60\%$  of the weight they had originally lost after 1 y and by the end of 2 y most had regained almost all of their lost weight (8).

Several factors contribute to the extremely high recidivism after weight loss; these include loss of motivation and physiologic adaptations that tend to return formerly obese persons to a higher weight. Homeostatic mechanisms that decrease total daily energy expenditure, which are in part a function of reduced body weight and a loss of metabolically active lean tissue, produce added difficulties in the maintenance of a new lower weight (9). In addition, long-term weight maintenance is dependent on sustained changes in lifestyle involving dietary modification and regular physical activity. Accordingly, long-term prevention of relapse after intentional weight loss remains a therapeutic challenge. Adjunctive drug therapy may facilitate long-term weight maintenance for many individuals. One potential approach to preventing weight regain is to alter the absorption of energy-containing nutrients. Orlistat (Xenical; Hoffmann-La Roche, Nutley, NJ), a new antiobesity agent, works in the gastrointestinal tract to reduce dietary fat absorption. Its mechanism of action is inhibition of the activity of gastrointestinal lipases, predominantly pancreatic lipase, thereby decreasing the hydrolysis and subsequent absorption of ingested fat by  $\approx 30\%$  (10). Initial studies showed that orlistat is minimally ( $< 1\%$ ) absorbed from the

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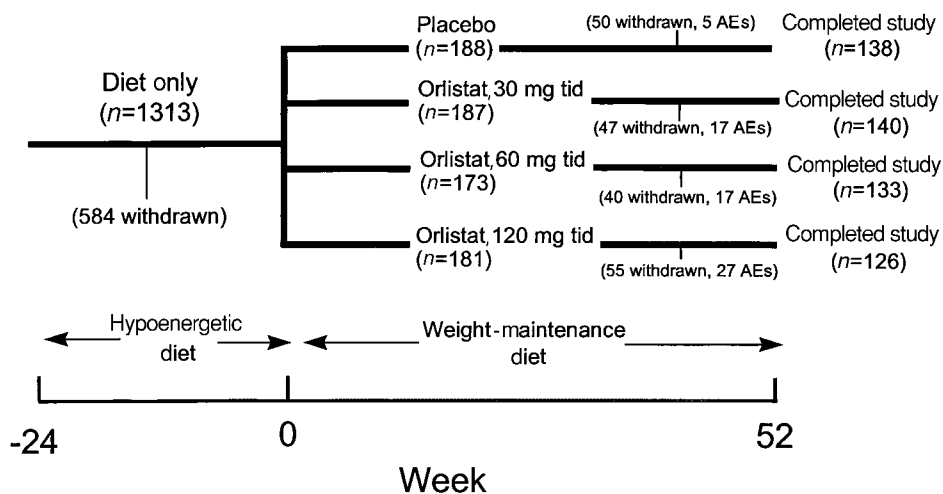


FIGURE 1. Study design and assignment of subjects. AE, adverse event; tid, 3 times daily.

gastrointestinal tract, promotes significant weight loss when used in conjunction with a mildly hypoenergetic diet, and lowers blood lipid concentrations (11–13).

The purpose of the present study was to test the hypothesis that orlistat therapy, combined with appropriate dietary and behavioral counseling, effectively diminishes the weight regain that generally occurs after a period of conventional hypoenergetic dieting. The secondary purpose of the study was to evaluate the long-term effects of orlistat on obesity-related cardiovascular disease risk factors.

## SUBJECTS AND METHODS

### Subjects

Adult men and women aged  $\geq 18$  y with a body mass index (in  $\text{kg}/\text{m}^2$ ) between 28 and 43 were recruited into the study at 17 clinical research centers in the United States. All subjects provided written, informed consent. The study was conducted according to the principles of the Declaration of Helsinki and was approved by the institutional review board at each study center. Patients were excluded if they ever had significant medical disorders, uncontrolled hypertension, recurrent nephrolithiasis, symptomatic cholelithiasis, active gastrointestinal disorders, type 2 diabetes, pancreatic disease, or cancer or if they were pregnant or lactating. Other exclusion criteria were a history or presence of substance abuse, eating disorders, excessive alcohol intake, significantly abnormal laboratory test results, and previous gastrointestinal surgery for weight reduction or a history of postsurgical adhesions. Subjects had not taken any medications known to influence body weight, appetite, or lipid concentrations during the 8 wk before screening. All vitamin supplements taken previously were discontinued and subjects were provided with standard multivitamin-multimineral tablets (Centrum, 1 tablet daily; Lederle, Madison, NJ) from the start of the 6-mo lead-in weight-loss period.

### Dietary intervention

For the first 6 mo of the study, subjects received a nutritionally balanced, hypoenergetic diet (deficit of 4180 kJ/d) with no pharmacologic intervention to produce weight loss. The standard energy deficit prescribed was based on estimated energy expendi-

ture, calculated from each individual's calculated basal metabolic rate, taking into account sex, age, and weight (14). Individuals were given a daily energy intake equivalent to their basal metabolic rate multiplied by a correction factor of 1.3. The calculated energy requirement was reduced by 4180 kJ/d to produce a weight loss of 0.5–1.0 kg/wk. The diet contained 30% of energy as fat, 50% as carbohydrate, and 20% as protein. Subjects received dietary counseling throughout the 6-mo lead-in weight-loss period, attended a 4-session behavioral modification program (University of Minnesota's Wise Weighs), and were encouraged to increase their physical activity (brisk walking for 20–30 min 5 times/wk).

The overall study design is shown in **Figure 1**. Only persons who lost  $\geq 8\%$  of their initial body weight during the 6-mo lead-in weight-loss period were included in the 1-y, double-blind treatment phase of the study. These patients were stratified according to their degree of weight loss ( $\leq 10\%$  or  $> 10\%$  of initial body weight) to ensure balanced distribution among treatment groups. The patients were then randomly assigned to receive 120 mg orlistat, 60 mg orlistat, 30 mg orlistat, or placebo 3 times daily for 1 y. Before the randomization step, the subjects' energy requirements were reassessed according to the body weight recorded at week 22 of the 6-mo lead-in weight-loss period and an increase in energy intake was prescribed to match anticipated metabolic requirements over the ensuing 1-y treatment period. If patients gained weight during this period, however, a hypoenergetic diet was not initiated; rather, these patients were encouraged to maintain this higher weight. Dietary and behavioral counseling was provided throughout the 1-y treatment period to help subjects maintain their body weights. Patients were instructed to keep a comprehensive dietary record of food and beverage intakes for 3 consecutive days at 7 time points during the 6-mo lead-in weight-loss period and at 4 time points during the 1-y treatment period. Compliance was assessed by counting the number of capsules returned by the patients at specified clinic visits and by calculating the number of capsules that had been consumed each day. Patients whose compliance was  $< 70\%$  were only excluded from the completers analysis.

### Measurements

Clinic visits were scheduled weekly for the first 2 mo of the 6-mo lead-in weight-loss period and every 2 wk thereafter. During the

**TABLE 1**  
Patient characteristics at study entry (start of the 6-mo lead-in weight-loss period)<sup>1</sup>

	Placebo group (n = 28 M, 156 F)	Orlistat treatment groups		
		30 mg tid (n = 29 M, 157 F)	60 mg tid (n = 35 M, 136 F)	120 mg tid (n = 23 M, 156 F)
Age (y)	46.4 ± 0.7 <sup>2</sup>	46.8 ± 0.8	46.1 ± 0.7	45.9 ± 0.7
Race				
White	164	164	155	153
Black	9	14	10	9
Hispanic	8	5	5	17
Other	3	3	1	0
Weight (kg)	90.8 ± 0.9	89.3 ± 0.9	92.4 ± 0.9 <sup>3</sup>	89.7 ± 0.9
Height (cm)	166.1 ± 0.6	165.3 ± 0.6	167.4 ± 0.6	165.2 ± 0.6
BMI (kg/m <sup>2</sup> )	32.8 ± 0.2	32.6 ± 0.2	32.9 ± 0.2	32.8 ± 0.2

<sup>1</sup>tid, 3 times daily.

<sup>2</sup> $\bar{x} \pm \text{SEM}$ .

<sup>3</sup>Significantly different from all other groups,  $P < 0.05$ .

1-y treatment period, subjects were seen on day 1, at 2-wk intervals during month 1, every month between months 1 and 5, and every 2 mo thereafter. Body weight was measured at every clinic visit. Serum lipids (total cholesterol, LDL cholesterol, VLDL cholesterol, HDL cholesterol, triacylglycerol, and the ratio of LDL to HDL) were measured at the start and end of month 2 of the 6-mo lead-in weight-loss period (weeks -24 and -8) and on day 1 and at months 1, 5, and 12 of the 1-y treatment period. Fasting serum glucose and insulin concentrations were also measured at these visits, with one additional measurement during both the 6-mo lead-in weight-loss period and the 1-y treatment period. Other assessments included waist circumference, vital signs, blood pressure, and standard laboratory analyses (hematology, clinical chemistry, and urinalysis), including measurement of fat-soluble vitamin and  $\beta$ -carotene concentrations.

The pharmacodynamic effect of orlistat was assessed by measuring fecal fat content. This measurement was undertaken  $\approx 2$  wk before randomization and after 44 wk of double-blind treatment. Fecal collections were analyzed by Medi-Lab Bioprofil, Copenhagen.

All clinical complaints during the 6-mo lead-in weight-loss period and adverse events during the 1-y treatment period were recorded. To ensure consistency of gastrointestinal event reporting between study centers, a dictionary of standard terms was used to describe changes in defecation patterns.

### Statistical analysis

Efficacy analyses were performed on the intent-to-treat population, which consisted of subjects who received at least one dose of study medication during the 1-y treatment phase and for whom at least one body weight measurement was taken before and after random assignment. The safety analysis population included all subjects who had received at least one dose of medication in a double-blind fashion and had at least one follow-up safety evaluation.

For statistical analysis, both observed and derived (last observation carried forward) data were used. However, all reported data were actual observed rather than derived values, whereas the technique of carrying forward the last observation was applied only for analyses of statistical significance. The significance of between-group differences for percentage regain of lost weight was tested by applying analysis of covariance (ANCOVA) to the

1-y treatment period (15). The analysis was applied to the change in body weight during the 1-y treatment period, expressed as a percentage of the weight lost during the 6-mo lead-in weight-loss period, and weight-loss during the 6-mo lead-in weight-loss period was used as the covariate. Placebo-adjusted treatment differences and 95% CIs were based on least-squares mean values. Significant treatment effects from the analysis of variance (ANOVA) were followed by comparisons between treatment groups with the Bonferroni adjustment for multiple comparisons (15). ANCOVAs were applied to vitamin and  $\beta$ -carotene concentrations. Comparisons between groups in changes in risk factor variables over time were performed by ANOVA and ANCOVA, with change in body weight used as the covariate. Changes in the self-reported energy and macronutrient intake data over time were analyzed by ANOVA. Categorical analysis of the frequency distributions were tested for statistical significance with use of the chi-square statistic (15). The 0.05 level of significance was used for all analyses.

### RESULTS

A total of 1313 subjects were enrolled in the study and entered the 6-mo lead-in weight-loss period. The main reasons for withdrawal during the weight-loss period were failure to meet the 8% weight-loss goal (35%), lost to follow-up (27%), failure to keep appointments (14%), noncooperation (9%), and protocol violation (9%). An 8% reduction in initial body weight was achieved by 729 (56%) subjects who were subsequently stratified by weight loss and randomly assigned to receive 120 mg orlistat ( $n = 181$ ), 60 mg orlistat ( $n = 173$ ), 30 mg orlistat ( $n = 187$ ), or placebo ( $n = 188$ ) 3 times daily for 1 y. A total of 537 (74%) subjects completed the 1-y treatment phase of the study (120 mg orlistat,  $n = 126$ ; 60 mg orlistat,  $n = 133$ ; 30 mg orlistat,  $n = 140$ ; placebo,  $n = 138$ ). Seven subjects were excluded from the safety analysis because of no follow-up assessment and 2 subjects were excluded from the intent-to-treat population because of no follow-up efficacy assessments.

The characteristics of the 4 treatment groups were not significantly different at the start of the 6-mo lead-in weight-loss period (Table 1), with the exception that body weight was higher in the 60-mg orlistat group (although body mass index was not significantly different) than in the other 3 groups. There were more men



**TABLE 2**

Change in body weight from initial values to the end of the 6-mo lead-in weight-loss period (day 1) and after 1 y of double-blind treatment with orlistat or placebo (week 52)<sup>1</sup>

Treatment group and time point	Change from initial value	Percentage change from initial value	LSM percentage regain compared with placebo
	kg	%	
Placebo ( <i>n</i> = 121)			
Day 1	-10.33 ± 0.31	-11.37 ± 0.30	—
Week 52	-5.93 ± 0.69	-6.42 ± 0.70	—
Orlistat, 30 mg tid ( <i>n</i> = 119)			
Day 1	-10.06 ± 0.31	-11.28 ± 0.32	—
Week 52	-5.15 ± 0.55	-5.94 ± 0.60	-10.00 ± 5.73 <sup>2</sup>
Orlistat, 60 mg tid ( <i>n</i> = 116)			
Day 1	-10.00 ± 0.29	-10.83 ± 0.30	—
Week 52	-6.16 ± 0.49	-6.66 ± 0.50	-9.80 ± 5.91
Orlistat, 120 mg tid ( <i>n</i> = 113)			
Day 1	-9.86 ± 0.27	-11.04 ± 0.28	—
Week 52	-7.24 ± 0.52	-8.20 ± 0.50	-27.10 ± 5.79 <sup>2</sup>

<sup>1</sup> $\bar{x} \pm \text{SEM}$ . tid, 3 times daily; LSM, least-squares mean.

<sup>2</sup> $P < 0.001$ .

in the 60-mg orlistat group than in the other 3 groups and this sex distribution accounted for the difference in body weight.

### Weight loss

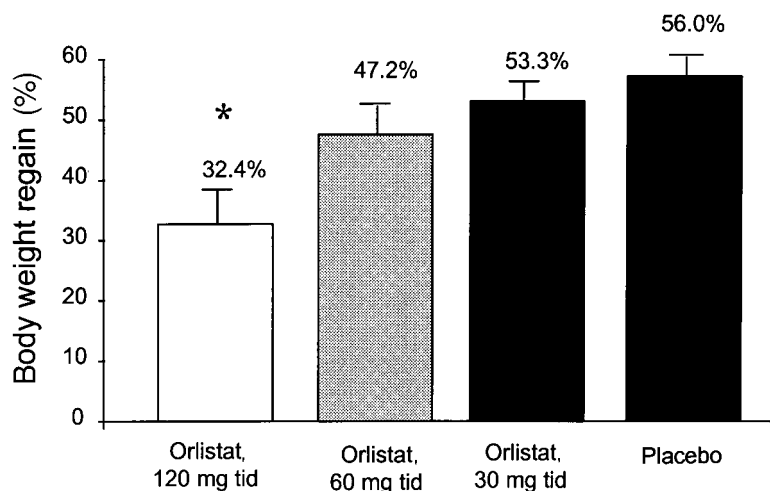
Weight-loss results are presented for the intent-to-treat population. However, the results from the analysis of those who completed the treatment phase were nearly identical. The 4 treatment groups did not differ significantly with respect to weight loss during the 6-mo lead-in weight-loss period: mean weight loss was  $\approx 10$  kg in all 4 groups (Table 2). At the end of the 1-y treatment period, weight loss from initial body weight was greatest with 120 mg orlistat 3 times daily and the least-squares mean difference from placebo was significant only for the 120-mg orlistat group (Table 2).

### Prevention of weight regain

Weight change during the 1-y treatment period was expressed as a percentage of the weight lost during the initial 6 mo lead-in

weight-loss period. These results are shown in Figure 2. Treatment with 120 mg orlistat 3 times daily for 1 y resulted in significantly less weight regain than treatment with placebo. Subjects in the 120-mg orlistat group regained approximately half as much weight as did those in the placebo group.

Categorical analysis of weight regain across 4 percentage weight regain quartiles (Table 3) indicated significant treatment differences between 120 mg orlistat and placebo ( $P < 0.001$ ). A higher percentage of subjects in the 120-mg orlistat group than in any other group regained  $\leq 25\%$  of lost body weight after 1 y. In contrast, the frequency of a large amount of weight regain ( $>75\%$  weight regain) was significantly lower in the 120-mg orlistat group than in the 30-mg orlistat and placebo groups. Further analysis of the subjects who regained  $\leq 25\%$  of lost body weight indicated that 23.5% of subjects who received 120 mg orlistat did not regain any weight or actually continued to lose weight after the randomization step, compared with only 16.3% of subjects in the placebo group. Moreover, at the end of the 1-y



**FIGURE 2.** Mean ( $\pm$ SEM) percentage body weight regain from the time of random assignment to double-blind treatment to the end of 1 y (intent-to-treat population). tid, 3 times daily. \*Significantly different from placebo,  $P < 0.001$ .

**TABLE 3**

Frequency distribution of quartiles of percentage weight regain during the 1-y treatment period<sup>1</sup>

Treatment group	Percentage weight regain			
	≤25	25–50%	50–75%	>75%
	<i>% of subjects</i>			
Placebo ( <i>n</i> = 121)	29.9	22.8	15.2	32.1
Orlistat, 30 mg tid ( <i>n</i> = 119)	32.3	20.4	18.3	29.0
Orlistat, 60 mg tid ( <i>n</i> = 116)	30.4	25.7	25.1	18.7 <sup>2</sup>
Orlistat, 120 mg tid ( <i>n</i> = 113)	47.5 <sup>3</sup>	22.9	17.3	12.3 <sup>2</sup>

<sup>1</sup>Quartile classification is based on weight regain expressed as a percentage of the weight lost during the 6-month lead-in weight-loss period. tid, 3 times daily.

<sup>2</sup>Significantly different from placebo and 30 mg orlistat, *P* < 0.05.

<sup>3</sup>Significantly different from all other groups, *P* < 0.05.

treatment period, body weight was greater than initial body weight (before the 6-mo lead-in weight-loss period) in 18.3% of placebo-treated patients compared with only 5.4% of orlistat-treated patients. Conversely, 61.8% of the 120-mg orlistat group sustained a weight loss of >5% of initial weight over 1 y compared with 49.8% in the placebo group.

### Obesity-related risk factors

#### *Serum lipid concentrations*

Initial serum lipid concentrations were not significantly different between the 4 treatment groups. After the 6-mo lead-in weight-loss period, total cholesterol and LDL-cholesterol concentrations decreased by 5–8% in all groups. However, at the end of the 1-y treatment period, reductions in total and LDL-cholesterol concentrations from initial values were significantly greater in the 120-mg orlistat group than in the placebo group (Table 4). Reductions in both total and LDL-cholesterol concentrations were also significantly greater after treatment with 30 and 60 mg orlistat than after treatment with placebo. Furthermore, both total and LDL-cholesterol concentrations increased in the placebo group over the 1 y of treatment but decreased further over this time period in the 120-mg orlistat group.

During the 6-mo lead-in weight-loss period, HDL-cholesterol concentrations increased slightly (≈2–4%) in all 4 treatment groups. After 1 y of treatment, however, HDL-cholesterol concentrations decreased slightly (≈1.7%) in the 60- and 120-mg orlistat groups, but these changes were not significant. There were no significant differences between the 4 treatment groups in the decreases in triacylglycerol concentrations (9.5–11.0% of initial value) during the 6-mo lead-in weight-loss period. During the 1-y treatment period, a larger reduction in triacylglycerol was maintained in the 120-mg orlistat group; however, this trend was not significant. Changes in the ratio of LDL to HDL over the 1 y of treatment were significantly different only between the placebo and 30-mg orlistat groups.

#### *Fasting glucose and insulin*

Fasting glucose concentrations decreased slightly (0.02–0.11 mmol/L) in all treatment groups during the 6-mo lead-in weight-loss period. After 1 y of treatment, mean increases of 1–2% above initial values were noted in the placebo and 30-mg orlistat groups compared with slight (≈1%) reductions in the 60- and 120-mg

orlistat groups. Mean fasting insulin concentrations decreased during the 6-mo lead-in weight-loss period in all 4 treatment groups (23.2–28.0 pmol/L). These reductions were sustained throughout the 1-y treatment period: mean (±SEM) reductions were 19.2 ± 8.1, 4.9 ± 8.3, 20.5 ± 6.2, and 18.8 ± 5.2 pmol/L in the placebo, 30-mg orlistat, 60-mg orlistat, and 120-mg orlistat groups, respectively.

#### *Blood pressure*

There were no significant group differences in reductions in systolic and diastolic blood pressure during the 6-mo lead-in weight-loss period (≈3–5 mm Hg). After 1 y of treatment, mean (±SEM) reductions in systolic blood pressure were 2.6 ± 1.2, 0.8 ± 1.1, 0.4 ± 1.2, and 3.0 ± 1.3 mm Hg in the placebo, 30-mg orlistat, 60-mg orlistat, and 120-mg orlistat groups, respectively, and those in diastolic blood pressure ranged from 0.2 to 2.0 mm Hg and did not differ significantly between groups.

#### *Waist circumference*

Waist circumferences were reduced in the 4 treatment groups during the 6-mo lead-in weight-loss period. During the 1-y treatment period, waist circumferences increased slightly in all groups and the resulting mean reductions of 6–8 cm after 1 y of treatment were not significantly different between groups.

#### *Fecal fat content and dietary intake*

Mean fecal fat values increased in a dose-dependent manner in the orlistat groups. Fecal fat content in week 44 of double-blind treatment was 10.06 ± 0.64, 15.01 ± 0.96, and 20.60 ± 1.13 g/d above baseline values in the 30-mg, 60-mg, and 120-mg orlistat groups, respectively. As expected, the increase in fecal fat excretion was minimal in the placebo group (0.50 ± 0.25 g/d).

On initiation of a weight-maintenance diet and the double-blind phase of the study, self-reported energy intake (Figure 3) was increased by ≈1254 kJ/d (300 kcal/d). Thereafter, mean daily energy and fat intakes remained relatively stable in all treatment groups (data shown in Figure 3 for the placebo and 120-mg orlistat groups only). Thus, the lower weight regain in the 120-mg orlistat group than in the placebo group was achieved despite increased energy and dietary fat intakes in all treatment groups.

### Tolerability

During the 1-y treatment period, the percentage of subjects who reported at least one adverse event was ≈7–8% greater in the orlistat-treated groups than in the placebo group. This difference was primarily due to an increased incidence of gastrointestinal events in the orlistat-treated subjects, with similar adverse events for all other body systems across treatment groups. The percentage of subjects reporting gastrointestinal events was 68.1% in the placebo group, 82.3% in the 30-mg orlistat group, 91.8% in the 60-mg orlistat group, and 95.0% in the 120-mg orlistat group. In general, adverse events were mild to moderate in intensity and resolved without intervention.

Some gastrointestinal events occurred in a greater percentage of patients in the orlistat-treated groups: flatus with discharge (43.9% in the 120-mg orlistat group compared with 4.3% in the placebo group), abdominal pain (41.1% in the 120-mg orlistat group compared with 20.0% in the placebo group), fecal urgency (38.9% in the 120-mg orlistat group compared with 16.8% in the placebo group), and oily spotting (37.2% in the 120-mg orlistat

**TABLE 4**Changes in serum lipid concentrations from initial values to the end of the 6-mo lead-in weight-loss period (day 1) and after 1 y of double-blind treatment with orlistat or placebo (week 52)<sup>1</sup>

Lipid measurement, treatment group, and time point	Change from initial value	Percentage change from initial value	LSM percentage change compared with placebo
	<i>mmol/L</i>	<i>%</i>	
<b>Total cholesterol</b>			
Placebo			
Day 1 ( <i>n</i> = 184)	-0.45 ± 0.06	-7.29 ± 1.04	—
Week 52 ( <i>n</i> = 102)	-0.28 ± 0.08	-3.89 ± 1.33	—
Orlistat, 30 mg tid			
Day 1 ( <i>n</i> = 186)	-0.39 ± 0.05	-6.21 ± 0.88	—
Week 52 ( <i>n</i> = 96)	-0.35 ± 0.08	-5.44 ± 1.31	-3.75 ± 1.39 <sup>2</sup>
Orlistat, 60 mg tid			
Day 1 ( <i>n</i> = 171)	-0.46 ± 0.06	-7.61 ± 0.98	—
Week 52 ( <i>n</i> = 87)	-0.50 ± 0.07	-8.48 ± 1.31	-3.37 ± 1.43 <sup>3</sup>
Orlistat, 120 mg tid			
Day 1 ( <i>n</i> = 179)	-0.39 ± 0.05	-6.47 ± 0.99	—
Week 52 ( <i>n</i> = 87)	-0.47 ± 0.07	-7.99 ± 1.19	-5.27 ± 1.42 <sup>3</sup>
<b>LDL cholesterol</b>			
Placebo			
Day 1 ( <i>n</i> = 184)	-0.33 ± 0.06	-7.89 ± 1.47	—
Week 52 ( <i>n</i> = 102)	-0.21 ± 0.07	-3.67 ± 2.08	—
Orlistat, 30 mg tid			
Day 1 ( <i>n</i> = 186)	-0.28 ± 0.04	-6.03 ± 1.44	—
Week 52 ( <i>n</i> = 96)	-0.38 ± 0.08	-8.28 ± 1.84	-6.54 ± 2.02 <sup>3</sup>
Orlistat, 60 mg tid			
Day 1 ( <i>n</i> = 171)	-0.34 ± 0.06	-8.10 ± 1.38	—
Week 52 ( <i>n</i> = 87)	-0.42 ± 0.07	-10.60 ± 1.85	-5.74 ± 2.08 <sup>4</sup>
Orlistat, 120 mg tid			
Day 1 ( <i>n</i> = 179)	-0.24 ± 0.05	-5.11 ± 1.53	—
Week 52 ( <i>n</i> = 87)	-0.29 ± 0.07	-7.01 ± 1.98	-7.18 ± 2.06 <sup>3</sup>
<b>HDL cholesterol</b>			
Placebo			
Day 1 ( <i>n</i> = 184)	0.01 ± 0.06	2.50 ± 1.47	—
Week 52 ( <i>n</i> = 103)	0.01 ± 0.07	2.18 ± 2.08	—
Orlistat, 30 mg tid			
Day 1 ( <i>n</i> = 186)	0.01 ± 0.04	2.37 ± 1.37	—
Week 52 ( <i>n</i> = 99)	0.01 ± 0.08	1.94 ± 1.91	-0.45 ± 1.87
Orlistat, 60 mg tid			
Day 1 ( <i>n</i> = 171)	0.03 ± 0.06	3.71 ± 1.47	—
Week 52 ( <i>n</i> = 88)	-0.04 ± 0.07	-1.74 ± 2.19	-5.34 ± 1.93 <sup>4</sup>
Orlistat, 120 mg tid			
Day 1 ( <i>n</i> = 179)	0.01 ± 0.05	2.93 ± 1.30	—
Week 52 ( <i>n</i> = 89)	-0.03 ± 0.07	-1.70 ± 1.74	-3.47 ± 1.91
<b>LDL:HDL</b>			
Placebo			
Day 1 ( <i>n</i> = 184)	-0.31 ± 0.06	-11.12 ± 1.64	—
Week 52 ( <i>n</i> = 102)	-0.18 ± 0.08	-3.02 ± 2.68	—
Orlistat, 30 mg tid			
Day 1 ( <i>n</i> = 186)	-0.30 ± 0.05	-5.98 ± 1.61	—
Week 52 ( <i>n</i> = 96)	-0.28 ± 0.07	-7.72 ± 2.3	-6.28 ± 2.61 <sup>5</sup>
Orlistat, 60 mg tid			
Day 1 ( <i>n</i> = 171)	-0.34 ± 0.06	-8.72 ± 1.73	—
Week 52 ( <i>n</i> = 87)	-0.28 ± 0.05	-6.4 ± 2.54	-1.43 ± 2.69
Orlistat, 120 mg tid			
Day 1 ( <i>n</i> = 179)	-0.26 ± 0.05	-5.65 ± 1.76	—
Week 52 ( <i>n</i> = 87)	-0.16 ± 0.07	-2.69 ± 2.74	-4.38 ± 2.67
<b>Triacylglycerol</b>			
Placebo			
Day 1 ( <i>n</i> = 184)	-0.29 ± 0.06	-10.42 ± 2.54	—
Week 52 ( <i>n</i> = 103)	-0.15 ± 0.07	-2.71 ± 5.64	—
Orlistat, 30 mg tid			
Day 1 ( <i>n</i> = 186)	-0.23 ± 0.05	-9.45 ± 2.53	—
Week 52 ( <i>n</i> = 99)	-0.01 ± 0.08	-0.21 ± 3.24	4.96 ± 4.52

(Continued)

TABLE 4 (Continued)

Lipid measurement, treatment group, and time point	Change from initial value	Percentage change from initial value	LSM percentage change compared with placebo
	<i>mmol/L</i>	<i>%</i>	
Triacylglycerol			
Orlistat, 60 mg tid			
Day 1 ( <i>n</i> = 171)	-0.34 ± 0.06	-10.45 ± 2.64	—
Week 52 ( <i>n</i> = 88)	-0.08 ± 0.08	-1.54 ± 3.86	9.55 ± 4.66 <sup>6</sup>
Orlistat, 120 mg tid			
Day 1 ( <i>n</i> = 179)	-0.29 ± 0.05	-10.94 ± 2.71	—
Week 52 ( <i>n</i> = 89)	-0.27 ± 0.06	-11.32 ± 3.38	-3.21 ± 4.63

<sup>1</sup> $\bar{x} \pm \text{SEM}$ . tid, 3 times daily; LSM, least-squares mean.

<sup>2</sup>*P* = 0.007.

<sup>3</sup>*P* = 0.001.

<sup>4</sup>*P* = 0.006.

<sup>5</sup>*P* = 0.02.

<sup>6</sup>*P* = 0.041.

group compared with 2.2% in the placebo group) were the most common. However, most subjects experienced only 1 or 2 episodes and most gastrointestinal events were mild to moderate in intensity, occurred early during treatment, and resolved spontaneously. Withdrawals from the study related to gastrointestinal events were 0.5% in the placebo group, 5.4% in the 30-mg orlistat group, 7.0% in the 60-mg orlistat group, and 11.7% in the 120-mg orlistat group.

Patients received standard vitamin supplements throughout the 1-y treatment phase of the trial; accordingly, mean concentrations of vitamins A, D, and E and of  $\beta$ -carotene remained within the reference ranges, although vitamin E and  $\beta$ -carotene were significantly lower in the orlistat treatment groups than in the placebo group at the end of the study (*P* < 0.001). Few subjects (<4%) met the criteria for additional vitamin supplementation during the study and those who did receive supplementation had normal values at the end of the study.

## DISCUSSION

The present study was designed to evaluate the efficacy of orlistat for body weight maintenance in obese subjects who had lost weight through hypoenergetic dieting alone. The main finding of this study was that orlistat therapy combined with a weight-maintenance diet helped subjects to minimize weight regain and to sustain improvements in cardiovascular disease risk factors.

This randomized, double-blind, placebo-controlled, 1-y study confirmed the hypothesis that partial inhibition of dietary fat absorption with use of the gastrointestinal lipase inhibitor orlistat improves long-term weight maintenance. Although the role of dietary fat in the etiology of obesity remains controversial (16, 17), several lines of evidence suggest that dietary fat is an appropriate target for pharmacologic interventions that are not centrally acting. High-fat diets promote passive overconsumption of total energy (18). Storage of dietary fat in adipose tissue may be more efficient in reduced-obese individuals owing to reduced fat oxida-

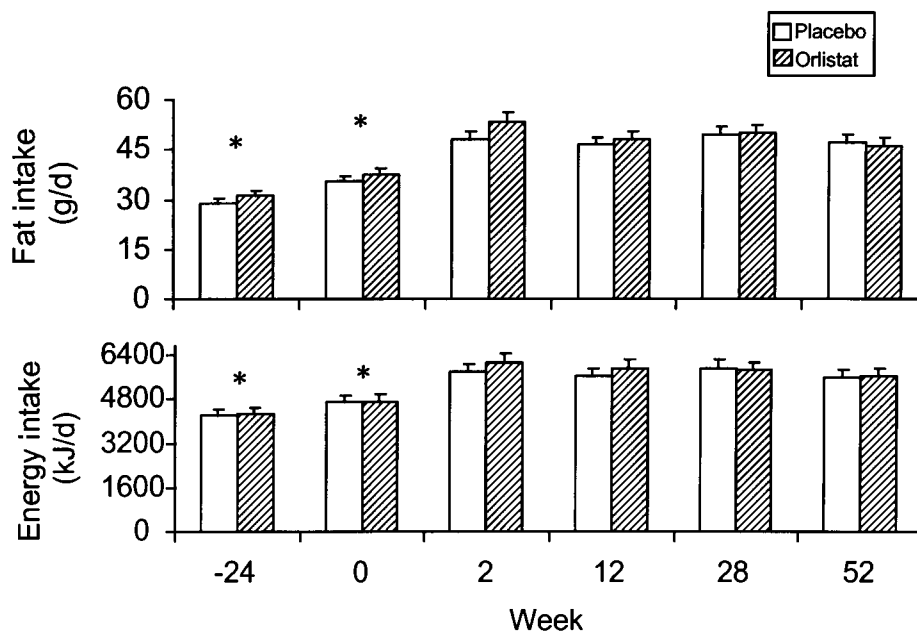


FIGURE 3. Mean ( $\pm$ SEM) self-reported dietary fat and total energy intakes over time during the 6-mo lead-in weight-loss period (weeks -24 to 0) and the 1-y double-blind treatment period (intent-to-treat population) with placebo or 120 mg orlistat 3 times daily. \*Significantly different from the 1-y treatment period, *P* < 0.001. There were no significant differences between treatment groups at any time point.

tion (19, 20). Thus, reduction of dietary fat intake, inhibition of fat absorption, or both may be particularly useful in this population.

### Prevention of weight regain

This is the first double-blind pharmacologic intervention for the prevention of relapse after weight loss to evaluate adjunctive pharmacotherapy based on altering nutrient absorption rather than modifying food intake through appetite suppression. Conventional weight management in obese subjects has relied on reduced energy intake, sometimes in combination with behavioral modification, counseling, and moderate exercise.

The hypoenergetic diet produced an average weight loss of 10 kg during the 6-mo lead-in weight-loss period. However, the large number of subjects who did not meet the weight-loss goal for enrollment in the orlistat treatment period of  $\geq 8\%$  of body weight reflects the difficulty that obese subjects experience in achieving even modest weight loss. After 1 y of treatment, 120 mg orlistat 3 times daily was the most effective dose for preventing weight regain: subjects in this treatment group regained approximately half as much weight as did those in the placebo group. Furthermore, nearly one-quarter of the patients treated with 120 mg orlistat 3 times daily regained no weight at all or even continued to lose weight. Thus, at this recommended dose, orlistat provided a clear improvement over standard care. The enhanced weight maintenance provided by 120 mg orlistat 3 times daily could not be attributed to variations in energy intake or food constituents between groups after they were switched to a weight-maintenance diet. After the increase in energy intake with initiation of the orlistat treatment phase of the study, self-reported energy and dietary fat intakes remained stable throughout the remainder of the study (Figure 3). Taking into consideration the limitations of self-reported dietary intake data, the absence of significant differences in total energy and dietary fat intakes between the placebo and 120-mg orlistat groups during the 1-y treatment period suggests that the difference between the groups in body weight change during this 1-y period can be attributed to the partial inhibition by orlistat of the absorption of energy derived from dietary fat.

### Cardiovascular disease risk factors

The results of the present study show that improvement in obesity-related cardiovascular disease risk factors can be sustained over 1 y after modest weight loss. The 6-mo lead-in weight-loss period of a hypoenergetic diet was associated with improvements in several of these risk factors, eg, serum lipids, blood glucose, blood pressure, and waist circumference. However, treatment with orlistat (60 and 120 mg 3 times daily) resulted in further improvements in total and LDL-cholesterol concentrations relative to initial values. The significantly greater sustained reductions in total and LDL-cholesterol concentrations over 1 y in the 120-mg orlistat group than in the placebo group persisted even after adjustment for the greater percentage of weight loss sustained in the 120-mg orlistat group and were probably related to the mechanism of action of orlistat on the absorption of dietary fat, assuming that much of the dietary fat consumed was saturated.

### Tolerability


Orlistat acts within the intestinal lumen on gastrointestinal lipases and has only minimal systemic absorption; thus, systemic side effects are negligible. This was evidenced in the present

study by the similar adverse event profiles in the placebo and orlistat treatment groups. On the basis of the action of the drug, a higher incidence of gastrointestinal effects was anticipated in the orlistat-treated groups, and these effects generally occurred early during the 1-y treatment period. It is likely that most of these gastrointestinal events occurred in subjects who exceeded the prescribed dietary fat intake. Furthermore, most gastrointestinal events were manageable and resolved spontaneously. The overall withdrawal rate attributable to adverse events is comparable with that in a large 1-y study of dexfenfluramine, in which  $\approx 10\%$  of subjects in both the dexfenfluramine and placebo groups withdrew prematurely because of adverse events (21).

### Study limitations

We anticipated that some readjustment in body weight would occur in most subjects because the prescribed dietary intake was increased by 1254 kJ/d at the time of random assignment. As a result, this study may have underestimated the benefits of orlistat in weight maintenance. Furthermore, subjects who began to gain weight were asked to maintain the higher weight rather than resume a hypoenergetic diet. Under actual clinical practice conditions, subjects would be encouraged to reduce their energy intake for a period of time to decrease their weight.

### Conclusion

In summary, this study showed that partial inhibition of dietary fat absorption enhances long-term weight maintenance after weight loss. Subjects treated with orlistat regained less weight than did those treated with placebo and sustained greater improvements in cardiovascular disease risk factors over 1 y of treatment. These observations indicate that orlistat is a useful adjunctive tool for maintaining significant long-term weight loss and the associated improvements in obesity-related disease risk factors. 

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