Weight Loss, Weight Maintenance, and Improved Cardiovascular Risk Factors after 2 Years Treatment with Orlistat for Obesity

Stephan Rössner, Lars Sjöström,† Rudolf Noack,‡ A. Edo Meinders,¶ and Giorgio Noseda‖ on behalf of the European Orlistat Obesity Study Group*[1]

Abstract

RÖSSNER, STEPHAN, LARS SJÖSTRÖM, RUDOLF NOACK, A. EDO MEINDERS, AND GIORGIO NOSEDA ON BEHALF OF THE EUROPEAN ORLISTAT OBESITY STUDY GROUP. Weight loss, weight maintenance, and improved cardiovascular risk factors after 2 years treatment with orlistat for obesity. *Obes Res.* 2000:8:49–61.

Objective: To determine the effect of orlistat, a new lipase inhibitor, on long-term weight loss, to determine the extent to which orlistat treatment minimizes weight regain in a second year of treatment, and to assess the effects of orlistat on obesity-related risk factors.

Research Methods and Procedures: This was a 2-year, multicenter, randomized, double-blind, placebo-controlled study. Obese patients (body mass index 28 to 43 kg/m^2) were randomized to placebo or orlistat (60 or 120 mg) three times a day, combined with a hypocaloric diet during the first year and a weight maintenance diet in the second year of treatment to prevent weight regain. Changes in body weight, lipid profile, glycemic control, blood pressure, quality of life, safety, and tolerability were measured.

Results: Orlistat-treated patients lost significantly more weight ($p < 0.001$) than placebo-treated patients after Year 1 (6.6%, 8.6%, and 9.7% for the placebo, and orlistat 60 mg and 120 mg groups, respectively). During the second year, orlistat therapy produced less weight regain than placebo ($p = 0.005$ for orlistat 60 mg; $p < 0.001$ for orlistat 120 mg). Several obesity-related risk factors improved significantly more with orlistat treatment than with placebo. Orlistat was generally well tolerated and only 6% of orlistat-treated patients withdrew because of adverse events. Orlistat leads to predictable gastrointestinal effects related to its mode of action, which were generally mild, transient, and self-limiting and usually occurred early during treatment.

Discussion: Orlistat administered for 2 years promotes weight loss and minimizes weight regain. Additionally, orlistat therapy improves lipid profile, blood pressure, and quality of life.

Key words: orlistat, lipase-inhibition, weight loss, cardiovascular risk factors, quality-of-life

Introduction

The rising prevalence of obesity is evident worldwide. In the Unites States, 20% of men and 25% of women are considered obese (body mass index $\geq$ 30 kg/m^2), and similar rates of obesity are observed in Europe (1,2). Obesity is clearly established as a major risk factor for cardiovascular disease and is associated with an increased risk of cerebrovascular disease, type 2 diabetes, gallstones, respiratory dysfunction, several forms of cancer, and premature death (3,4).

Modest weight loss significantly improves risk factors for cardiovascular disease (5,6), which have led to the suggestion that a goal of obesity treatment should be sustained moderate weight loss rather than attainment of ideal weight. Weight management programs based on restricted dietary intake alone have limited long-term efficacy (7), and, consequently, a number of pharmacological agents have been used in combination with dietary intervention. This paper describes the efficacy and tolerability of orlistat (Xenical;

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From the *Obesity Unit, Huddinge Hospital, Stockholm, Sweden; †Medicin I SOS-Sekretariatet, Sahlgrenska Sjukhuset, Goeteborg, Sweden; ‡Deutsches Institut für Ernaehrungsforschung, Bergholz-Rehbruecke, Germany; ¶Department of General Internal Medicine, Leiden University Medical Center, Leiden, The Netherlands; and ‖Medicina Interna, Ospedale della Beata Vergine, Mendrisio, Switzerland.
[1]The other investigators in the Study Group are: J.-R. Attali, Hopital Jean Verfier, France; P. Drouin, Hopital Jeanne D'Arc, France; K. Irsigler, Drankenh D. Stadt Wien-Lain, Austria; H. Kaffarnik, Klinikum der Philipps Universität, Germany; R. Lebmeier, private practice, Bechhofen, Germany; F. Lindgärde, Allmänna Hospital, Sweden; Magometschnigg D., Gesellschaft Für Klinische Pharmakologi, Austria; E. M. H. MathusVliegen, Academisch Medisch Centrum, The Netherlands; and M. Uusitupa, Kuopio University, Finland.
Address correspondence to Professor Stephan Rössner, Obesity Unit, Huddinge Hospital, S-14186 Stockholm, Sweden. E-mail: stephan.rossner@medhs.ki.se

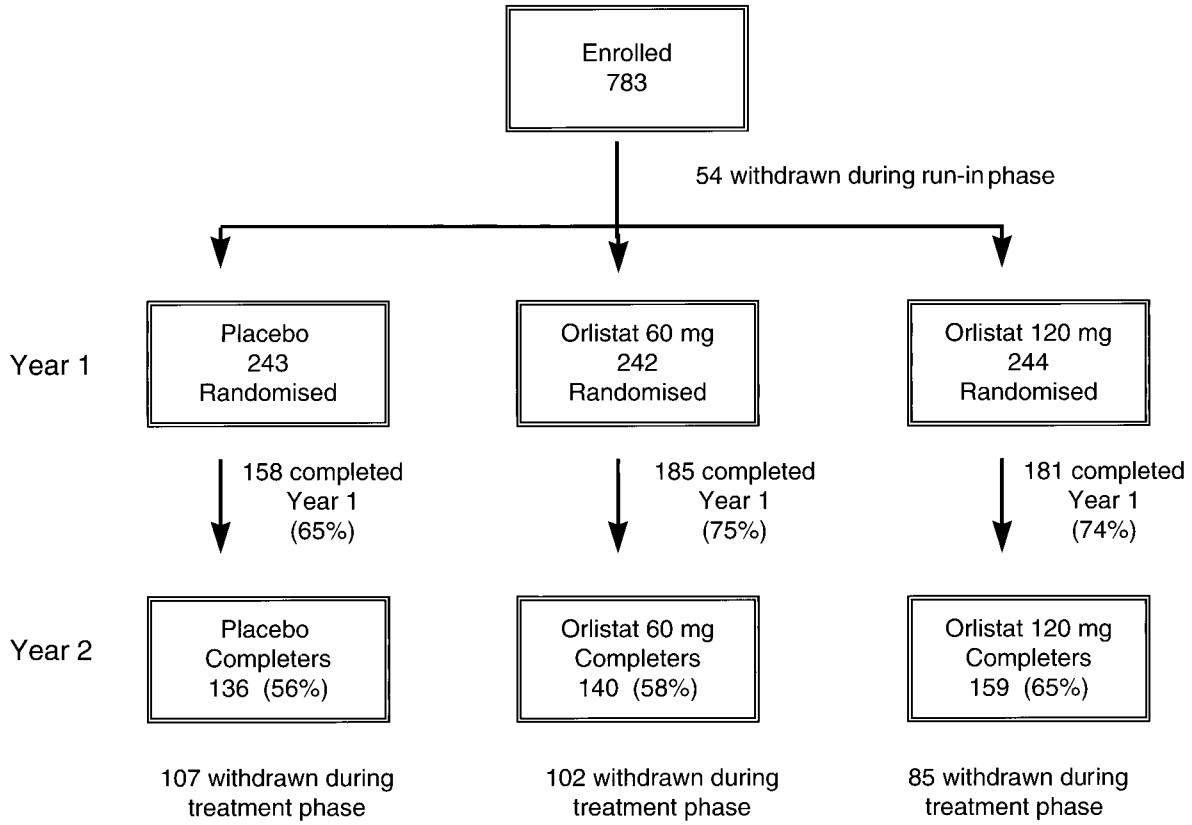

Figure 1: Disposition of subjects entered into the study.

Hoffmann-La Roche, Nutley, NJ), a lipase inhibitor that alters nutrient absorption by inhibiting pancreatic and gastric lipases in the gastrointestinal (GI) tract (8).

Excessive intake of dietary fat, promoted by its palatability and low satiety effect, is a major contributing factor for obesity (9–11). Because up to 40% of energy in the typical western diet is derived from fat, an agent that interferes with the absorption of dietary fat could provide a significant new strategy in the long-term management of obesity. Orlistat limits the digestion and absorption of triglycerides in the GI tract (12) and subsequently causes the excretion of about 30% of ingested fat (13).

Initial, short-term (12 weeks), placebo-controlled studies with orlistat have demonstrated clear additional weight loss above that obtained with diet alone (14,15). Orlistat has also been shown to be safe and effective in a previous 2-year randomized, placebo-controlled study of similar design, in which patients treated with orlistat 120 mg achieved weight loss of 10.2% (vs. 6.1% with placebo; $p < 0.001$) and 8.0% (vs. 4.5% with placebo; $p < 0.001$) after 1 and 2 years of treatment, respectively (16). The aims of the current long-term study were: to determine the weight loss effect of orlistat (60 or 120 mg three times a day [tid]) administered in conjunction with a mildly hypocaloric diet during the first year of treatment; to monitor the effects of orlistat on weight regain during a second year of treatment after switching to a weight maintenance diet; and to assess the long-term effects of treatment on cardiovascular risk factors and quality of life.

Methods

Study Design

This randomized, double-blind, parallel-group, placebo-controlled study was conducted in 14 centers throughout Europe. During a single-blind, run-in period, placebo was given in combination with a nutritionally balanced diet that was designed to cause a 600-kcal daily energy deficit and to supply about 30% of energy as fat. To ensure an even distribution of subjects with rapid or slow weight loss rates between treatment groups, subjects were stratified based upon the amount of weight lost during the 4-week lead-in period and then randomized at baseline (Day 1). For randomization and entry into the double-blind treatment period, subjects must have completed the placebo run-in period and have shown at least 75% compliance to treatment, assessed by the proportion of orlistat capsules taken. At randomization, subjects received placebo, orlistat 60 mg, or orlistat 120 mg tid (i.e., with breakfast, lunch, and dinner) for a further 52 weeks in combination with the same diet.

These doses of orlistat were chosen because dose-ranging studies found that orlistat 60 mg and 120 mg tid resulted in a significant weight loss (120 mg being the optimal dose) compared with placebo (15,17). During the second year of the trial, all subjects continued on the same treatment, but with diet adjusted as follows: for those subjects who had lost ≥3 kg between Weeks 40 and 52, the daily caloric intake was prescribed at a level equivalent to the estimated total daily energy expenditure minus 10% kcal/day, whereas those subjects who lost <3 kg during this period were considered relatively weight stable and no dietary adjustment was made.

Subjects

Men and women (aged ≥18 years) with a body mass index of 28 to 43 kg/m^2 were enrolled in the study. Women who were pregnant, lactating, or of childbearing potential, but not taking adequate contraceptive measures, were excluded. Also excluded were subjects who had any clinically significant condition, other than obesity, that might affect the outcome of the study. Subjects were also excluded if they had lost more than 4 kg during the previous 3 months, stopped smoking in the previous 6 months, undergone GI surgery for weight reducing purposes, had a history of post-surgical adhesions or of bulimia or laxative abuse, or had taken any drug that might influence body weight or serum lipids during 8 weeks before screening. Subjects with uncontrolled hypertension, drug-treated diabetes mellitus, or history or presence of symptomatic cholelithiasis were also excluded. All patients ceased taking vitamin supplements before taking part in the study. The study protocol was approved by each of the centers' regional ethical committees and was conducted in accordance with the revised Declaration of Helsinki. All subjects gave either written or witnessed verbal informed consent.

Assessments

All subjects underwent an initial screening assessment, which comprised a medical history, physical examination and measurement of vital signs, electrocardiogram, laboratory testing, and validated quality-of-life questionnaire. Before randomization, a chest X-ray was taken and renal and gallbladder ultrasound scans were performed. Patients received advice from a dietitian on the dietary requirements of the study and received instructions on the accurate completion of food intake diaries. Baseline assessments performed included a physical examination (including body weight and height, waist and hip circumferences, and vital signs), electrocardiogram, and laboratory parameters. In addition, patients completed quality-of-life questionnaires and 4-day food intake diaries and adverse events were recorded. A similar assessment was repeated at the end of both study years. During double-blind treatment, if vitamin levels or β-carotene levels fell below the clinical reference range for two consecutive measurements, then the laboratory alerted the investigator to provide subjects with appropriate multivitamin supplementation. Body weight, vital signs, and adverse events were assessed at clinic visits every 2 weeks for the

Table 1. Demographic and baseline characteristics and incidence of risk factors at randomization: safety population

	Placebo (n = 237)	Orlistat 60 mg, tid (n = 239)	Orlistat 120 mg, tid (n = 242)
Male/female	31/206	56/183	40/202
Mean (±SD) age (years)	44.3 ± 10.8	44.7 ± 10.7	43.6 ± 11.4
Mean (±SD) weight (kg)	97.7 ± 14.6	99.1 ± 14.3	96.7 ± 13.8
Mean BMI (kg/m^2)	35.3 ± 4.1	35.2 ± 3.9	34.7 ± 3.7
Number of patients with risk factors:			
LDL cholesterol ≥ 3.362 mmol/L*	127	131	125
LDL cholesterol < 3.362 mmol/L†	1	2	0
HDL cholesterol < 0.905 mmol/L	45	76	65
Triglycerides ≥ 2.54 mmol/L	24	30	20
Fasting insulin ≥ 90 pmol/L	103	111	93
Diastolic blood pressure ≥ 90 mmHg*	47	63	45
Diastolic blood pressure < 90 mmHg†	20	22	17
Waist circumference ≥ 100 cm	141	145	133

* Untreated or treated; † treated.

Table 2. Summary of reasons for premature withdrawal during double-blind treatment

	Year 1			Years 1 and 2		
Reason for withdrawal	**Placebo (n = 243)**	**Orlistat 60 mg (n = 242)**	**Orlistat 120 mg (n = 244)**	**Placebo (n = 243)**	**Orlistat 60 mg (n = 242)**	**Orlistat 120 mg (n = 244)**
Adverse event	4 (1.6%)	16 (6.6%)	15 (6.1%)	7 (2.9%)	24 (9.9%)	21 (8.6%)
Treatment failure	5 (2.1%)	4 (1.7%)	6 (2.5%)	8 (3.3%)	4 (1.7%)	6 (2.5%)
Refused treatment	24 (9.9%)	12 (5.0%)	20 (8.2%)	33 (13.6%)	25 (10.3%)	23 (9.4%)
Lost to follow-up	21 (8.6%)	12 (5.0%)	6 (2.5%)	23 (9.5%)	16 (6.6%)	11 (4.5%)
Did not co-operate	20 (8.2%)	10 (4.1%)	12 (4.9%)	24 (9.9%)	16 (6.6%)	15 (6.1%)
Protocol violation	5 (2.1%)	2 (0.8%)	2 (0.8%)	6 (2.5%)	4 (1.7%)	4 (1.6%)
Entry violation	1 (0.4%)	0 (0%)	0 (0%)	1 (0.4%)	0 (0%)	0 (0%)
Administrative	5 (2.1%)	4 (1.7%)	2 (0.8%)	5 (2.1%)	12 (5.0%)	5 (2.0%)
Died during study	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0.4%)	0 (0%)
Total withdrawn	85 (35.0%)	60 (24.8%)	63 (25.8%)	107 (44.0%)	102 (42.1%)	85 (34.8%)

first 2 months, monthly up to month 6, and then every 2 months for the remainder of the study. In addition, food intake diaries were assessed by a dietitian at each clinic visit and advice on how to improve compliance with the prescribed diet was given to patients if necessary. Waist circumferences were measured after 24, 52, 80, and 104 weeks and laboratory parameters after 4, 12, 24, 36, 52, 64, 80, 96, and 104 weeks.

Efficacy Measurements

The primary efficacy parameter was change in body weight over time. Subjects were weighed on calibrated scales, which were serviced annually. A record was kept of dates and values of calibration by each center.

Secondary efficacy parameters included determination of serum lipid levels (total cholesterol, low density lipoprotein [LDL] cholesterol, high density lipoprotein [HDL] cholesterol, very low density lipoprotein cholesterol, triglycerides, and lipoprotein [a]). Blood pressure, fasting blood glucose, and insulin were also measured. Secondary efficacy parameters also included waist circumference, measured at the level midway between the lateral lower rib margin and the iliac crest using a calibrated spring-loaded measuring tape, and a 55-item, self-administered quality-of-life questionnaire developed and validated by Technology Assessment Group (San Francisco, CA) (18). It included measurements on both global and disease-specific scales relevant to obesity. Primary measures of outcome were scored on scales assessing obesity distress, depression, and satisfaction with treatment. The satisfaction with treatment index was measured as a combination of three parameters, satisfaction

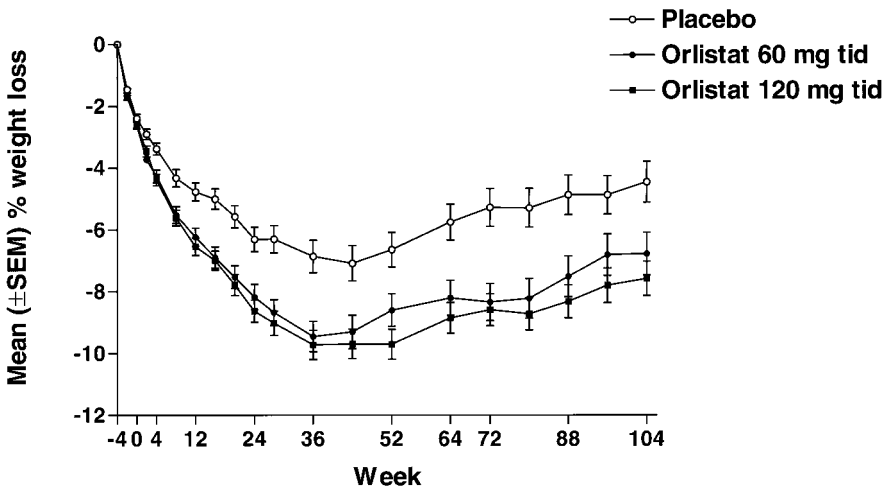

Figure 2: Mean percentage change (±SEM) from initial body weight during 2 years of treatment. ITT population.

Table 3. Mean (±SD) weight loss from initial body weight (Week −4) (ITT and completers populations)

	Mean ±SD% (mean ±SD kg) reduction in body weight from Week −4					
	Year 1			Year 2		
	Placebo	Orlistat 60 mg*	Orlistat 120 mg*	Placebo	Orlistat 60 mg*	Orlistat 120 mg*
ITT population†	6.6 ± 6.8% (6.4 ± 6.7)	8.6 ± 6.9% (8.5 ± 7.3) $p < 0.001$	9.7 ± 6.3% (9.4 ± 6.4) $p < 0.001$	4.5 ± 7.6% (4.3 ± 7.4)	6.8 ± 8.0% (6.6 ± 8.3) $p = 0.005$	7.6 ± 7.0% (7.4 ± 7.1) $p < 0.001$
Completers population	7.3 ± 6.9% (7.0 ± 6.8)	9.7 ± 6.6% (9.6 ± 7.3) $p =$ NS	10.2 ± 6.1% (9.8 ± 6.3) $p = 0.002$	4.5 ± 7.8% (4.3 ± 7.5)	7.0 ± 8.0% (6.8 ± 8.4) $p = 0.012$	7.8 ± 6.9% (7.6 ± 7.0) $p < 0.001$

* p values are derived from least squares mean differences from placebo from day 1 (baseline) to week 52 or 104.
† ITT weight loss based on last value carried forward.

with losing weight, satisfaction with the medication for weight loss, and satisfaction with the weight loss program.

Safety and Tolerability Measures

All adverse events were recorded regardless of their causality. A preferred term was allocated for each adverse event according to the Ciba-Geigy-modified World Health Organization (WHO) glossary, and then all adverse events were classified by organ system according to standard WHO guidelines. To ensure consistency across centers in identifying GI events, a dictionary of terms was developed to accurately describe defecation patterns. Standard laboratory procedures included hematology, clinical chemistry (including measurements of vitamins A, D, and E and β-carotene), urinalysis, and indirect measurement of vitamin K by prothrombin time.

Statistical Analyses

The following safety and efficacy analyses were conducted. Patients were included in the "safety" analysis if they had received one dose of trial medication after randomization and had a subsequent safety observation. An intent-to-treat (ITT) analysis was conducted in subjects who had received at least one dose of study medication and had a subsequent efficacy observation; the last value-carried-forward technique was employed for 1- and

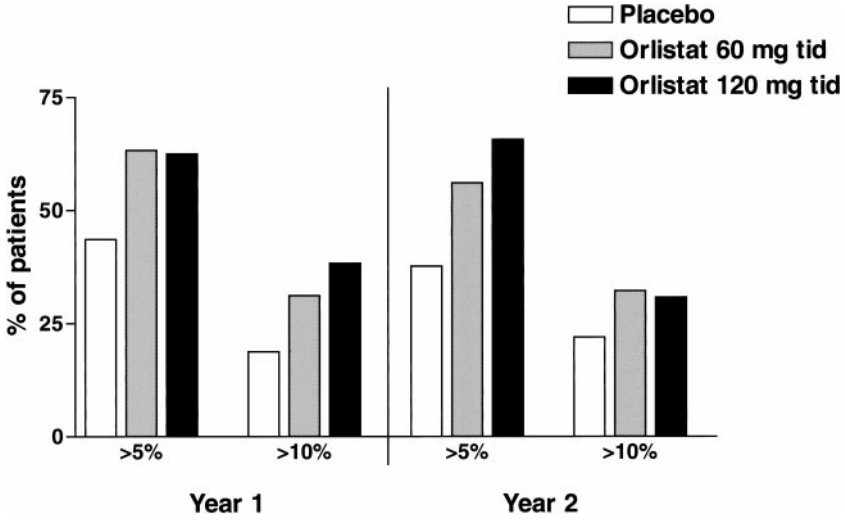

Figure 3: Percentage of patients who lost ≥5% and ≥10% of initial body weight. ITT population.

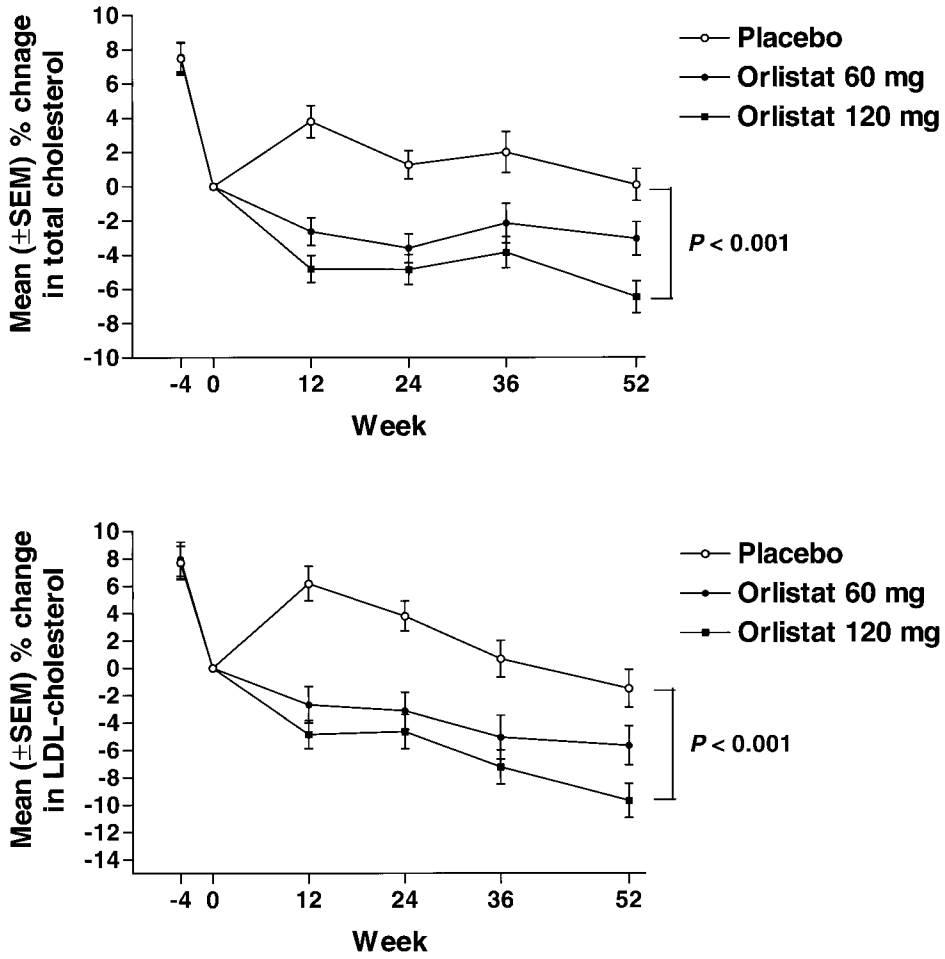

Figure 4: Mean percentage change in serum total and LDL cholesterol during 1 year of treatment. ITT population.

2-year analyses. In addition, completers analyses were performed for subjects who completed at least 1 and 2 years of treatment.

Summary statistics were used to compare treatment profiles for primary and secondary efficacy parameters. Specific time windows were used to catch the data at each scheduled visit, and the observed value attributed to a scheduled visit was the last value that fell within the specified time window.

The hypothesis that the expected weight change from baseline (Day 1) was the same after 1 and 2 years of double-blind treatment for the placebo and orlistat groups was tested using ANOVA or analysis of covariance (ANCOVA) models. The placebo-adjusted 95% confidence interval of orlistat treatment effect (difference between least square means for orlistat versus placebo treatment groups) was also determined based on the least squares mean (estimated mean after adjustment for covariates). The ANCOVA model was used to test changes for all secondary parameters and included terms for center, treatment, center-by-treatment, and baseline covariate. *p* values and 95% confidence intervals were derived for placebo-adjusted treatment differences. *p* values were not adjusted for multiple comparisons.

Results

A total of 783 subjects were enrolled in the placebo run-in period; 54 subjects dropped out during the 4 weeks, with the two main reasons as "did not cooperate" ($n = 14$) or "entry violation" ($n = 13$) (Figure 1). During the placebo lead-in period, subjects were counseled on their diet and their compliance to treatment assessed. At Day 1, 729 patients were then randomized to double-blind treatment with placebo, orlistat 60 mg, or orlistat 120 mg.

There were no significant differences between the demographic characteristics of the treatment groups and incidence of risk factors at randomization (Table 1). Eleven subjects who had no follow-up assessments were excluded from the safety and efficacy analyses, and two additional subjects, who had a follow-up safety assessment but no efficacy assessment, were excluded from the ITT analysis.

The main reasons for premature withdrawal in the first year were treatment refusal in the placebo (10%) and the orlistat 60 mg and 120 mg groups (5% and 8%, respectively) and adverse events in the placebo, orlistat 60 mg, and 120 mg groups (2%, 7%, and 6%, respectively). Refusal was also the main reason for premature withdrawal in all three treatment groups over the full 2 years of the study (14% in placebo, 10% in orlistat 60 mg, and 9% in orlistat 120 mg). Reasons for premature withdrawal from the study are summarized in Table 2.

Efficacy

Body Weight. The mean percentage reduction in body weight throughout the first and second year of treatment is shown in Figure 2 and Table 3. All three treatment groups showed a similar weight loss during the placebo run-in period. However, within 2 weeks of the start of double-blind treatment, the body weight of the placebo and the orlistat groups began to diverge. In the ITT population, weight loss in both the orlistat 60 mg and orlistat 120 mg groups was significantly greater than that of the placebo group after 1 year ($p < 0.001$). In the completers population, statistically significant greater weight loss than placebo was achieved by the orlistat 120 mg group only ($p = 0.002$). The placebo group achieved a statistically significant decrease in body weight from baseline (Day 1) after 1 year in both the ITT and completers populations ($p < 0.001$).

During the second year of treatment, when patients were switched to a weight maintenance diet and a lower frequency of clinic visits, there was a tendency to regain some of the weight lost during the first year. After 2 years, mean weight loss from Week −4 in the placebo group was statistically significant in the ITT ($p < 0.05$) but not the completers population. However, final weights at the end of the second year were significantly lower in both the orlistat 120 mg ($p < 0.001$) and 60 mg groups compared with placebo ($p < 0.05$). The frequency distribution of percentage change from initial body weight after the first and second years of treatment is shown in Figure 3. Significantly more subjects treated with orlistat 120 mg lost more than 5% of initial body weight after 1 and 2 years of treatment than placebo recipients ($p < 0.001$). Similarly, 31.2% ($p = 0.002$) and 38.3% ($p < 0.001$) of patients in the orlistat 60 mg and 120 mg groups lost more than 10% of their initial body weight after 1 year compared with 18.8% of placebo-treated patients. A weight loss of more than 10% was maintained in the second year by 18.6%, 29.0% ($p < 0.05$), and 28.2% ($p < 0.05$) of patients receiving placebo, orlistat 60 mg, and orlistat 120 mg, respectively.

Treatment with orlistat 60 mg or 120 mg also produced a larger mean decrease in waist circumference (6.0 and 6.2 cm) after 1 year than placebo (4.7 cm), although this did not reach statistical significance. Corresponding values at 2 years were 3.1, 4.7, and 5.1 cm for placebo, orlistat 60 mg, and orlistat 120 mg, respectively (orlistat 120 mg vs. placebo; $p < 0.05$).

Cardiovascular Risk Factors. Both LDL and total cholesterol levels decreased by similar amounts (4% to 6%) in all treatment groups during the 4-week lead-in period. However, after randomization, orlistat treatment was associated with a further decrease in serum levels of total cholesterol ($p < 0.001$), LDL cholesterol ($p < 0.001$), and the LDL/HDL ratio ($p < 0.002$) during both years of treatment (Figure 4 and Table 4). In contrast, changes in these parameters were much smaller and not significant in the placebo group. For HDL cholesterol, there was a gradual and progressive increase in Year 1 in all treatment groups, and these continued to increase during the second year of treatment but statistical significance was only achieved at the end of Year 1 in the orlistat 120 mg group. The decrease in lipoprotein [a] at the end of 1 and 2 years was significantly greater in patients treated with orlistat 120 mg ($p = 0.011$ and $p < 0.001$, respectively). Treatment with orlistat 120 mg was also associated with significant reductions in fasting blood glucose ($p = 0.022$) and diastolic blood pressure ($p = 0.016$) at the end of Year 1 and fasting insulin ($p < 0.05$) at the end of Year 2.

Quality of Life. Patients treated with orlistat reported significantly greater satisfaction with their weight loss medication than did placebo patients after 1 and 2 years ($p < 0.001$ in the orlistat 120 mg group; $p < 0.05$ in the orlistat 60 mg group). Patients taking orlistat 120 mg also expressed greater satisfaction both with losing weight and their weight loss program ($p = 0.011$ and $p = 0.002$, respectively, after 2 years). Overall satisfaction with treatment, as expressed by the treatment index, was significantly greater among patients taking orlistat than placebo recipients after 2 years ($p < 0.001$ and $p < 0.05$ in the orlistat 120 mg and 60 mg groups, respectively).

Orlistat-treated patients also reported less overweight distress than patients receiving placebo and this became statistically significant in the orlistat 120 mg group after 2 years ($p < 0.05$). There were no significant differences between treatment groups in depression scores after either 1 or 2 years.

Safety and Tolerability

With the predictable exception of more frequent GI events following orlistat treatment, the adverse event profiles were similar in all three treatment groups throughout the study and were generally mild to moderate and resolved spontaneously.

The increased incidence of GI events observed in the orlistat treatment groups is summarized in Table 5. The majority of these events occurred early during treatment, were mild to moderate in intensity, resolved spontaneously,

Table 4. Summary of mean ±SD risk factor values (mean ±SD percentage change from start of double-blind treatment) (ITT population)

Parameter	Study week	Placebo, tid	Orlistat 60 mg, tid*	Orlistat 120 mg, tid*
Total cholesterol (mmol/L)	−4	5.79 ± 1.08	5.73 ± 1.05	5.60 ± 1.07
	Day 1	5.43 ± 1.14	5.39 ± 1.10	5.26 ± 0.97
	52	5.38 ± 1.04	5.15 ± 1.17	4.91 ± 0.93
		(0.11 ± 11.25%)	(−3.04 ± 12.33%)*	(−6.45 ± 11.90%)*
	104	5.74 ± 1.04	5.42 ± 1.06	5.29 ± 0.96
		(6.14 ± 13.41%)	(2.04 ± 15.38%)*	(0.29 ± 12.79%)*
LDL cholesterol (mmol/L)	−4	3.80 ± 0.98	3.69 ± 0.87	3.65 ± 0.97
	Day 1	3.55 ± 0.98	3.49 ± 0.86	3.44 ± 0.86
	52	3.49 ± 0.92	3.18 ± 0.82	3.11 ± 0.78
		(−1.48 ± 16.67%)	(−5.65 ± 17.88%)*	(−9.68 ± 16.08%)*
	104	3.83 ± 0.91	3.42 ± 0.85	3.48 ± 0.87
		(7.70 ± 18.10%)	(1.28 ± 21.53%)*	(0.17 ± 18.47%)*
HDL cholesterol (mmol/L)	−4	1.25 ± 0.31	1.23 ± 0.34	1.25 ± 0.33
	Day 1	1.17 ± 0.36	1.13 ± 0.31	1.17 ± 0.30
	52	1.32 ± 0.35	1.26 ± 0.33	1.25 ± 0.30
		(14.03 ± 18.25%)	(14.60 ± 18.69%)	(10.75 ± 17.83%)†
	104	1.33 ± 0.34	1.29 ± 0.36	1.29 ± 0.32
		(14.59 ± 20.39%)	(16.99 ± 22.26%)	(14.12 ± 21.03%)
LDL/HDL ratio	−4	3.23 ± 1.15	3.22 ± 1.10	3.13 ± 1.16
	Day 1	3.24 ± 1.16	3.28 ± 1.11	3.12 ± 1.07
	52	2.81 ± 1.00	2.70 ± 0.95*	2.64 ± 0.94†
	104	3.06 ± 1.01	2.82 ± 0.94*	2.87 ± 1.05*
Triglycerides (mmol/L)	−4	1.70 ± 0.88	1.93 ± 1.73	1.71 ± 1.53
	Day 1	1.58 ± 0.89	1.75 ± 1.46	1.53 ± 0.97
	52	1.50 ± 0.79	1.77 ± 1.95	1.44 ± 0.91
		(1.31 ± 35.37%)	(−0.82 ± 34.25%)	(−1.87 ± 35.82%)
	104	1.53 ± 0.81	1.89 ± 1.83	1.43 ± 0.85
		(5.51 ± 37.68%)	(8.13 ± 77.64%)	(1.47 ± 40.80%)
VLDL cholesterol (mmol/L)	−4	0.76 ± 0.50	0.82 ± 0.81	0.72 ± 0.66
	Day 1	0.72 ± 0.46	0.78 ± 0.71	0.67 ± 0.46
	52104	0.58 ± 0.37	0.72 ± 0.74	0.56 ± 0.41
		0.59 ± 0.37	0.72 ± 0.74	0.53 ± 0.39
Lipoprotein [a] (mg/L)	−4	277.78 ± 351.19	276.07 ± 333.75	329.66 ± 421.44
	Day 1	284.14 ± 357.93	280.22 ± 346.07	328.54 ± 409.07
	52104	296.84 ± 389.03	266.15 ± 337.33	257.36 ± 316.79†
		284.29 ± 340.52	209.31 ± 259.77	233.14 ± 291.71*

Table 4. Continued

Parameter	Study week	Placebo, tid	Orlistat 60 mg, tid*	Orlistat 120 mg, tid*
Diastolic blood pressure (mmHg)	−4	83.9 ± 11.1	84.7 ± 10.1	82.5 ± 10.1
	Day 1	81.2 ± 9.8	81.5 ± 10.3	79.5 ± 9.4
	52	79.9 ± 11.0	79.5 ± 10.0	78.6 ± 10.2†
	104	81.2 ± 9.9	81.7 ± 10.3	79.9 ± 9.5
Systolic blood pressure (mmHg)	−4	133.6 ± 17.7	133.9 ± 16.0	131.0 ± 15.5
	Day 1	127.3 ± 16.1	128.4 ± 14.5	125.5 ± 14.9
	52	125.4 ± 18.6	125.7 ± 15.9	122.8 ± 16.0
	104	128.5 ± 17.5	129.6 ± 16.7	124.9 ± 16.5
Fasting glucose (mmol/L)	−4	5.68 ± 0.95	5.74 ± 0.95	5.58 ± 0.79
	Day 1	5.56 ± 0.95	5.62 ± 1.06	5.47 ± 0.68
	52	5.66 ± 1.01	5.57 ± 0.96	5.48 ± 0.86
		(2.23 ± 7.45%)	(−0.41 ± 8.94%)†	(0.33 ± 7.62%)†
	104	5.54 ± 0.68	5.57 ± 1.18	5.51 ± 1.29
		(1.89 ± 8.76%)	(−0.53 ± 9.87%)	(−0.01 ± 12.32%)
Fasting insulin (mmol/L)	−4	107.61 ± 68.69	114.89 ± 75.55	102.94 ± 51.47
	Day 1	97.09 ± 62.85	97.53 ± 63.50	87.49 ± 41.69
	52	83.08 ± 74.28	80.96 ± 47.60	71.82 ± 53.55
		(−1.63 ± 63.98%)	(−6.42 ± 49.16%)	(−11.39 ± 54.78%)
	104	87.92 ± 65.24	84.24 ± 48.87	82.21 ± 46.28
		(10.72 ± 68.97%)	(3.22 ± 55.48%)†	(6.29 ± 61.11%)†

* $p < 0.001$; † $p < 0.05$; values are derived from least squares mean differences from placebo from Day 1 (baseline) to Weeks 52 or 104.

and were limited to only one or two episodes per patient. There were 49 severe GI events reported during the 2 years of the study: placebo, $n = 8$; orlistat 60 mg, $n = 16$; and orlistat 120 mg, $n = 25$. The majority of severe GI events ($n = 38$) occurred during the first year of the study.

During the 2 years of this study, two serious adverse events were considered to be at least possibly related to orlistat treatment; one a case of cholelithiasis and one a case of diverticulitis. However, neither resulted in discontinuation of study medication. A total of six (2.5%) patients in the placebo group, 23 (9.6%) in the orlistat 60 mg group, and 19 (7.9%) in the orlistat 120 mg group withdrew from the study prematurely due to adverse events. GI events were the most common side effect associated with premature withdrawal in all three groups with 2 (0.8%), 12 (5%), and 9 (3.7%) subjects from the placebo, orlistat 60 mg, and orlistat 120 mg groups, respectively, discontinuing the study in 2 years.

Five patients were diagnosed with breast cancer during the 2-year study. One patient in the orlistat 60 mg group was diagnosed 36 days after randomized treatment. Four other cases occurred in postmenopausal women (one in the placebo group and three in the orlistat 120 mg group).

No clinically significant changes were observed in any laboratory parameters. The changes that were noted were sporadic, resolved spontaneously, and occurred with similar frequencies in all treatment groups. Mean plasma levels of vitamins A, D (measured as 25-OH vitamin D), E, and K (determined indirectly from prothrombin time) and β-carotene remained within reference ranges in all three groups over the 2 years of treatment and no patients were withdrawn because of low vitamin values. For most patients dietary advice and/or vitamin supplementation were sufficient to restore vitamin levels to pretreatment values and during the study. A total of 27 subjects required vitamin supplementation because of low vitamin values (placebo, $n = 1$; orlistat 60 mg, $n = 14$; orlistat 120 mg, $n = 12$). The majority (73%) of these incidences occurred in Year 1. Differences in mean plasma values for vitamins D and E and β-carotene between orlistat-treated patients and patients taking placebo were, however, statistically significant ($p < 0.001$; Table 6). The vitamin E:LDL cholesterol ratio in-

Table 5. Percentage of commonly observed GI effects (with percentage of associated withdrawals) during the 2-year study

	% Affected (% withdrawn)		
GI effect	**Placebo [*n* = 237]**	**Orlistat 60 mg, tid [*n* = 239]**	**Orlistat 120 mg, tid [*n* = 242]**
Fatty/oily stool	4.6 (0)	24.2 (0)	31.7 (0.4)
Fecal urgency	5.4 (0.4)	10.0 (1.3)	14.4 (0)
Oily spotting	0.8 (0)	13.3 (0)	14.5 (0.4)
Increased defecation	2.9 (0)	7.9 (0.4)	8.2 (0)
Fecal incontinence	1.3 (0)	3.1 (1.3)	7.4 (0.4)
Flatus with discharge	0.8 (−)*	6.2 (−)	4.9 (−)
Oily evacuation	0.4 (−)	3.7 (−)	4.7 (−)

* (−), data not available.

creased during the study, indicating that there was no loss of vitamin E protection against LDL-induced atherogenesis during treatment with orlistat.

Treatment with orlistat had no clinically significant effects on pulse rate or ECG results.

Discussion

Weight loss of 5% or more in obese individuals is often sufficient to ameliorate comorbid risk factors of obesity, such as hyperlipidemia, hyperinsulinemia, hypertension, and type 2 diabetes (5). However, it is important that weight loss is maintained over the long term.

Initial studies with orlistat have indicated that this treatment is effective and well tolerated and may thus provide long-term benefits in the management of weight loss in obese individuals (15,16,17).

The results of our 2-year study are consistent with those reported in previous trials and indicate that treatment with orlistat in conjunction with a mildly hypocaloric diet results in a significantly greater weight loss than placebo in the first year of treatment. In addition, patients treated with orlistat 120 mg experienced significantly greater improvements in cardiovascular risk factors, particularly total cholesterol, LDL cholesterol, LDL:HDL ratio, lipoprotein [a], and fasting insulin than placebo patients.

The significantly greater weight loss in the orlistat groups observed throughout the first year of treatment was maintained through the second year of therapy. Patients in all groups regained some weight in the second year following the intentional switch from a hypocaloric to a weight maintenance diet. However, the significant difference between orlistat treatment and placebo was sustained throughout Year 2. The percentage of patients who sustained a weight loss of more than 5% of their initial body weight over 2 years was again particularly noticeable in patients receiving orlistat 120 mg. This finding is important as the potential benefits to the obese individual increase the longer the weight reduction can be maintained (19).

Table 6. Summary statistics for vitamins A, D, and E and β-carotene: ITT population

	Mean (±SD) vitamin level						
	Week −4		Week 52		Week 104		
	Placebo	**Orlistat 120 mg**	**Placebo**	**Orlistat 120 mg**	**Placebo**	**Orlistat 120 mg**	**Reference range**
Vitamin A (μmol/L)	2.69 ± 0.66	2.58 ± 0.63	2.62 ± 0.80	2.60 ± 0.64	2.21 ± 0.60	2.13 ± 0.52	1.58–3.97
Vitamin D (nmol/L)	61.97 ± 24.60	60.88 ± 24.92	74.42 ± 28.61	59.55 ± 25.45	61.24 ± 16.57	52.43 ± 19.73	18–121
Vitamin E (μmol/L)	30.12 ± 8.19	29.81 ± 8.78	28.64 ± 6.37	26.04 ± 6.10	30.19 ± 6.30	27.49 ± 6.37	18.1–50.6
β-Carotene (μmol/L)	0.34 ± 0.25	0.36 ± 0.24	0.42 ± 0.40	0.28 ± 0.27	0.46 ± 0.38	0.33 ± 0.35	0.09–1.06

No direct statistical comparison was made between the efficacy of the two different doses of orlistat used in this study. However, analysis of pooled data from this and four other phase III orlistat trials with an essentially similar study design has indicated that treatment with orlistat 120 mg is associated with greater weight loss and improvement in cardiovascular risk factors than orlistat 60 mg (Hoffmann-La Roche, data on file). Moreover, a previous dose-ranging study indicated that the reduction in body weight achieved with orlistat is dose-dependent (16).

Sustained long-term weight loss appears difficult to achieve with current management programs (20). A 2-year comparison of weight loss trends in subjects undergoing weight control interventions showed that a program of dieting alone was associated with weight regain (21) and within 2 or 3 years most dieters regain all of their lost weight (22). The fact that orlistat is effective when given in combination with either a mildly hypocaloric or weight maintenance diet means that compliance with a weight management program is likely to be high, as a diet of the type developed in this program is more palatable and acceptable over prolonged periods than a more restrictive hypocaloric diet.

Only a very limited number of studies with other anti-obesity agents have provided similar findings with regard to weight loss over the initial 12-month period (23). The longest study of an anti-obesity agent has been a 2.5-year study of sibutramine which examined weight loss and weight regain (24). However, the study was relatively small ($n = 122$) and had an 85% drop-out rate compared with a 35% drop-out rate for 85 of 244 patients treated with orlistat 120 mg in the present study (24).

In addition to the reductions in body weight, orlistat was significantly more effective than placebo in affecting several cardiovascular risk factors, including total cholesterol, LDL cholesterol, LDL/HDL ratio, lipoprotein [a], and blood pressure. These advantages were maintained after the full 2 years of treatment. Thus, these results confirm those of a previous short-term study, which showed that orlistat had marked beneficial effects on serum lipid levels in normal weight patients suffering from primary hyperlipidemia (25). Minor, although statistically significant, improvements were observed in fasting blood glucose, insulin, and diastolic blood pressure during treatment.

Central adiposity is a well known cardiovascular risk factor (26). Recent studies have shown that changes in waist circumference correlate well with changes in visceral adipose tissue and thus changes in risk factors (27,28). The marked 4% to 5% reduction in waist circumference observed with orlistat treatment in the current study, after 1 and 2 years of treatment, suggests that orlistat-related weight loss is probably accompanied by a decrease in visceral fat.

The burden of obesity profoundly affects patients' quality of life. This issue was addressed in the study by a comprehensive, validated questionnaire and several quality-of-life criteria were shown to improve with orlistat therapy, in particular, patients' satisfaction with treatment, despite adverse GI events, and the level of distress caused by being overweight.

Both doses of orlistat were well tolerated. Predictably, in view of its pharmacology and mechanism of action, some GI events were more common following orlistat treatment. However, these were generally of mild to moderate intensity, were limited to only one or two episodes per patient, and occurred shortly after the initiation of treatment. A multiple-dose study of orlistat demonstrated that its tolerability is related to the dietary fat content (15). Thus, patients consuming more than the prescribed dietary fat allowance experience a greater frequency and intensity of GI events than patients who comply with the dietary regimen. This produces a "compliance reinforcing" effect for orlistat, whereby the patient is discouraged from straying from the prescribed diet by the likelihood of side effects.

The number of patients prematurely discontinued from the study during Year 1 because of GI events was low, only 3.8% (nine) and 3.3% (eight) in the orlistat 60 mg and 120 mg groups compared with 0.8% (two) in the placebo group. The percentage of patients withdrawn during Year 1 because of adverse events in any body system was 1.7%, 6.7%, and 5.4% in placebo, orlistat 60 mg, and 120 mg groups, respectively. In a 1-year study of dexfenfluramine, a 10% withdrawal of drug and placebo recipients because of adverse events was reported (23). Orlistat did not increase the risk of gallstones or renal stones, which may have resulted from changes in cholesterol/phospholipid/bile salt ratios and calcium soap formation.

During the study, five patients were identified as having breast cancer (placebo, $n = 1$; orlistat 60 mg, $n = 1$; orlistat 120 mg, $n = 3$). This finding was unexpected because genotoxicity and carcinogenicity studies in animals showed no evidence that orlistat caused or stimulated the growth of any type of tumor. Furthermore, systemic absorption of orlistat is minimal ($<1\%$) and no increase in estrogen levels has been observed in clinical studies. Comprehensive reviews of all clinical, histological, and radiographic data from these patients were performed. Two of the three patients on orlistat 120 mg had mammographic evidence of a pre-existing breast cancer. One of the patients was already in the process of being evaluated with sonogram and biopsy follow-up before entering into the study. It was also concluded that none of the cases could have occurred due to the study drug treatment because the tumors were identified too early and were too large to have developed during the study (ranging from 36 to 370 study days for the orlistat patients and 443 days for the placebo patient).

Most significantly, no cases of breast cancer were observed in another parallel multicenter, European study of similar size and design (16). It was concluded that the most likely explanation for these findings was a chance occurrence.

Theoretically, the inhibition of dietary fat absorption induced by orlistat may reduce the efficiency of the absorption of fat-soluble vitamins (29,30). In the present study, plasma levels of vitamins A, D, and E and β-carotene remained within the clinical reference ranges in all three groups throughout the entire study, and there were no symptoms of vitamin deficiency, although levels of vitamins D and E and β-carotene were slightly, but significantly, lower in both orlistat groups than in the placebo group. The dietitians recommended that more fruit and vegetables be consumed to increase vitamin concentrations and no subjects were withdrawn because of low vitamin values. These findings are similar to those previously reported with short-term orlistat treatment (29,30). The mean vitamin D level fluctuation over the 2 years of the study in all three groups may have been related to a seasonal variation in vitamin D levels, rather than to a specific study treatment. In general, reductions in vitamin levels following orlistat treatment tended to be more marked during the first 3 months of treatment, after which levels stabilized and in some cases even increased.

In conclusion, this study demonstrates that orlistat promotes long-term weight loss and prevents weight regain compared with placebo, the optimal effect being achieved at a dose of 120 mg tid. In addition, orlistat was well tolerated and produced beneficial effects with respect to lipid parameters, blood pressure, and quality of life.

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