

## Conclusions by the researchers

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.

## Key messages

- The rise of obesity is evident worldwide
- Obesity is clearly established as a major risk factor for cardiovascular disease and cerebrovascular disease, type 2 diabetes, gallstones, respiratory dysfunction, several forms of cancer and premature death
- Modest weight loss significantly improves risk factors for cardiovascular disease which have led to the suggestion that a goal of obesity treatment should be sustained, moderate weight loss rather than attainment of a ideal weight
- 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
- Weight management programmes based on restricted dietary intake alone have a limited efficacy and, consequently, a number of pharmacological agents have been used in combination with dietary intervention
- 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 ( $p < 0.05$ )
- Similarly, 31.2% ( $p$  value was less than 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% ( $p < 0.005$ ) of patients receiving placebo, orlistat 60 mg and 120 mg respectively
- 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
- In contrast, changes in these parameters were much smaller and not significant in the placebo group
- GI events were the most common side effect associated with premature withdrawal in all three groups with 2 (0.08%), 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
- 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;  $p < 0.05$ )
- 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)
- 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 programme is likely to be high, as a diet of the type developed in this programme is more palatable and acceptable over prolonged periods than a more restrictive hypocaloric diet.

## Weight Loss, Weight Management, and Improved Cardiovascular Risk factors after 2 Years of Treatment with Orlistat for Obesity



## Published

Obesity Research Vol 8, No 1, January 2000

## Author

Stephan Rossner, Lori Sjostrom, Rudolf Noack, A. Edo Meinders and Giorgio Nosedà on behalf of the European Orlistat Obesity Study Group



alli is a registered trademark of the GlaxoSmithKline group of companies

## Aims of the study

- To determine the weight loss effect of orlistat 60 mg or 120 mg 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
- To assess the long term effects of treatment on cardiovascular risk factors and quality of life.

## Treatments being studied

60 and 120 mg orlistat TID

## Treatment period

2 Years

## Design of the study

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 randomized at baseline (Day 1)
- For randomization and entry into the double-blind treatment period, subjects must have shown at least 75% compliance to treatment, assessed by the proportion of orlistat capsules taken.

## Primary endpoint

Change in body weight over time.

## Secondary endpoint

- 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 levels
- Waist circumference.

## Number of patients in the study

783 subjects were enrolled in the placebo run-in study. (Men and women aged 18 years of age and older with a body mass index of 28 to 43 kg/m<sup>2</sup>) 54 subjects dropped out

729 patients were randomized to double blind treatment with placebo, orlistat 60 mg and orlistat 120 mg

## Inclusion/exclusion criteria & demographics

Men and women (aged 18 years of age and older) with a body mass index of 28 to 43 kg/m<sup>2</sup>

### Exclusions:

- Women who were pregnant, lactating or of childbearing potential and not taking contraceptive measures.

Other patients **excluded** from the study were those who:

- Had any clinically significant condition, other than obesity, that might affect the outcome of the study
- Had weight loss of more than 4 kg during the previous three months
- Stopped smoking in the last six months
- Had undergone gastrointestinal surgery for weight-reducing purposes
- Had a history of post-surgical adhesions or of bulimia or laxative abuse
- Had taken any drug that might influence body weight or serum lipids during 8 weeks before screening
- Had uncontrolled hypertension, drug-treated diabetes mellitus, or history or presence of symptomatic cholelithiasis

## Main results

- Within two weeks of the start of the double-blind treatment, the body weight of the placebo and the orlistat groups began to diverge. In the ITT (intent to treat) 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 ( $p < 0.001$ )
- During the second year of treatment, when patients were switched to a 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 ( $p < 0.05$ )
- 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% ( $p < 0.005$ ) of patients receiving placebo, orlistat 60 mg and 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  $p$  value was less than 0.05 )
- After randomization, orlistat treatment was associated with a further decrease in serum levels of total cholesterol (  $p$  value was less than 0.001 ) LDL cholesterol ( $p < 0.001$ ) and the LDL/HDL ratio ( $p < 0.002$ ) during both years of treatment
- The decrease in lipoprotein [a] at the end of years 1 and 2 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
- 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;  $p < 0.05$ )
- 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).