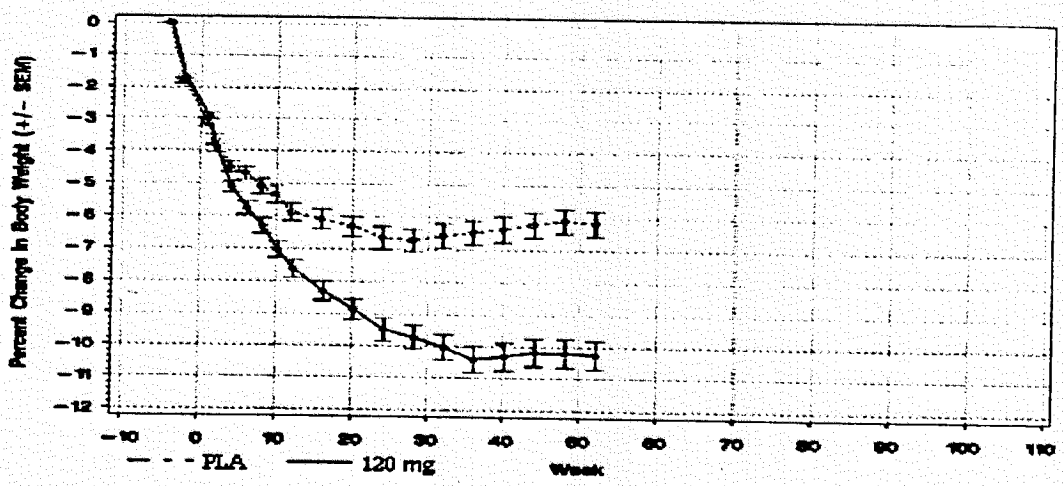
EFFICACY ENDPOINT OUTCOMES

Weight Loss

One-Year Data

Analysis of the Means

Following 52 weeks of treatment the orlistat group had a mean weight loss of 6.68 kg and the placebo group lost 2.45 kg ($p<0.001$). As shown in the figure below, the mean percent change in body weight from baseline (Day 1) to Week 52 was approximately -7% in the orlistat group and -3% in the placebo group ($p<0.05$).



Categorical Analysis

Approximately 66% of the orlistat patients lost greater than 5% of initial body weight, whereas 33% percent of the placebo patients met this criterion ($p<0.01$). It is of interest to note that the greater than 10% weight loss category was responsible for the statistically significant difference between the two groups with respect to greater than 5% weight loss. There was a higher percentage of patients in the placebo group that lost greater than 5% but less than 10% compared to the orlistat group, 36% vs 30%, respectively. However, 29% of the orlistat subjects and 7% of the placebo subjects lost greater than or equal to 10% of baseline body weight ($p<0.01$).

Second-Year Data

In general, the continued use of orlistat 120mg tid during the second year of the study while consuming a eucaloric diet was associated with a smaller amount of regained weight. At the end of 104 weeks of treatment the 120/120 group regained 3.0 kg and the pla/pla group regained 5.7 kg of the weight lost during the first year of double-blind treatment. At the completion of the 2-year study the average weight loss in the placebo/placebo group was 1.5 kg and 4.7 kg in the 120/120 group ($p=0.004$). Forty-seven

percent of the orlistat subjects and 25% of the placebo subjects lost at least 5% of baseline body weight after two years of treatment (p=0.002).

Secondary Efficacy Parameters (Completers data)

One-Year Data

Lipoprotein Lipids

Following 52 weeks of treatment, the orlistat group had a mean percent change in total cholesterol (TC) of -0.20% and the placebo group had a mean percent change of 5.3% (p<0.001). Similarly, the levels of LDL-C were reduced by 1.3% in the active-treatment group and increased by 6.5% in the placebo group (p<0.001). There were no significant differences between the two groups in the mean percent change in levels of HDL-C, TG, or lipoprotein (a) [Lp(a)].

Blood Pressure

There were small but statistically significant reductions in both SBP and DBP in the orlistat subjects compared to the changes in the placebo group (SBP: -1.25 vs 1.51 mmHg, p=0.02 and DBP: -1.90 vs -0.26 mmHg, p=0.02, orlistat vs placebo, respectively).

Fasting Plasma Glucose and Insulin

The mean change in fasting glucose was -0.24 mmol/L (-4.3 mg/dl) in the orlistat group and -0.03 mmol/L (-0.5 mg/dl) in the placebo group (p=0.004) after 52 weeks of treatment. There were no statistically significant differences between groups in the change in fasting insulin levels.

8.1.7 SAFETY DATA

Adverse Events

Deaths

There were two deaths reported during this study. A 61-year-old man in the 120/120 group died of a cardiac arrest after 707 days of treatment. The second patient was a 40-year-old woman in the 120/pla group who died in a car accident seven days after she completed the study.

Symptom-Related Adverse Events

As one might expect there was a greater incidence of GI adverse events in the orlistat group compared to the placebo group. These events included fatty/oily stools, increased defecation, oily spotting, soft stools, liquid stools, fecal urgency, flatulence, fecal incontinence, and oily evacuation. The majority of these complaints were recorded as mild to moderate in intensity. There did not appear to be any striking differences between the various groups in the incidence of serious adverse events, particularly those related to the GI tract. However, this issue will be more appropriately addressed in the ISS where the total exposure population is examined.

Plasma Fat-Soluble Vitamin Levels

There is reason to believe, based on the action of orlistat in the GI tract and the results from preclinical studies, that the drug impairs the absorption of fat-soluble vitamins and β-carotene. And indeed, subjects taking orlistat had mean reductions in plasma levels of vitamins D, E, and β-carotene. Vitamin K status was assessed by measuring prothrombin time (PT), and this parameter did not change significantly in the orlistat group.

As shown in the table below, at the end of the first year of treatment there were statistically significant reductions in the levels of vitamins D, E, and β-carotene in the orlistat group compared to the placebo group. Significant differences between the placebo and orlistat groups in the mean levels of vitamins D, E, and β-carotene persisted at the end of second year of treatment.

Mean Change in Vitamin Levels from Baseline to Week 52

	Orlistat	Placebo	p value
Vitamin D (nmol/L)	-11	-2	<0.001
Vitamin E (umol/L)	-1.3	1.3	<0.001
β-carotene (umol/L)	-0.14	0.0	<0.001

In addition to reductions in the mean level of vitamins D, E, and β-carotene following 1-year of treatment with orlistat, a larger percentage of drug-treated patients had low vitamin D and E and β-carotene levels on two or more consecutive visits. Approximately 5% of orlstat-treated patients had a low level of vitamin D on two or more consecutive visits compared with 0.6% of placebo-treated patients. Similarly, nearly 5% of subjects in the orlistat group had low levels of vitamin E on two or more consecutive visits compared with 1% of placebo subjects. Only 1.2% of orlistat patients and 0.3% of placebo patients had low values for β-carotene on two or more consecutive visits; however, 3.6% of orlistat-treated patients vs 0.3% of placebo-treated subjects had a low β-carotene level at the last visit. These patterns persisted during the second year of treatment.

Thirty-three subjects (placebo and orlistat) were instructed to take vitamin supplements during the study because of low levels determined at two consecutive visits. The Sponsor did not preform an analysis of the efficacy of the supplementation because different methods of supplementation were used.

Ultrasounds of the Gallbladder and Kidney

Because of orlistat's effect on CCK and bile acid synthesis/release/excretion and its potential effects on calcium and phosphorus metabolism, patients were examined at baseline, Year 1, and Year 2 for the presence of gallbladder and kidney abnormalities via ultrasound. After one year of treatment, five placebo and seven orlistat patients developed gallbladder stones. After two years of treatment, six placebo and nine orlistat patients developed stones. Regarding kidney stones, after Year 1, none of the placebo and two of the orlistat-treated patients developed kidney stones. One patient in the 120/120 groups developed a stone by the completion of Year 2; none of the placebo subjects developed a stone during the second year of treatment.

SPONSOR'S CONCLUSIONS

Orlistat administered at a dose of 120mg tid with a hypocaloric diet, produced a statistically significant and clinically meaningful reduction in body weight after one year of treatment compared to placebo treatment. A significantly greater amount of weight loss was maintained for longer periods over two years of orlistat treatment. Orlistat also prevented much of the regain of body weight that inevitable occurs after a patient initially losses weight, especially when the patients' diet changes after initial weight loss.

In addition to the effect on body weight, treatment with orlistat produced meaningful improvements in secondary efficacy parameters associated with potential increased risk of increased morbidity or early mortality. Especially significant are long term improvements of total cholesterol, LDL cholesterol, the LDL/HDL ratio, fasting glucose, fasting insulin and diastolic blood pressure. In patients with a pre-existing higher risk, the effects are even greater. In general orlistat treatment was well tolerated during chronic treatment. In addition, when compared to placebo there were overall improvements in many aspects of patients quality of life.

MEDICAL OFFICER'S CONCLUSIONS

This Reviewer agrees with the Sponsor's statement that treatment with orlistat for one year produced a statistically significant reduction in mean body weight when compared to treatment with placebo. In addition, compared to placebo, a significantly greater percentage of orilstat-treated patients lost 5% or more of baseline body weight. Regarding comorbid risk factors, there were minor improvements in the levels of total cholesterol, LDL-C, systolic and diastolic blood pressure, and fasting glucose in the orlistat subjects that completed 1 year of treatment. It should be pointed out that statistical significance was achieved when the changes in the orlistat group were compared to the changes in the placebo group not because of substantial improvement in the active treatment group, but rather because of the increase from baseline in the levels of these risk factors in the placebo group. This worsening of comorbidities despite weight loss in the placebo group is unexpected and without an obvious explanation.

As one might predict, the most commonly reported adverse events associated with orlistat treatment were GI related. Largely, these events were not serious. The use of orlistat was associated with reductions in the plasma levels of vitamins D, E, and β-carotene. If review of the entire NDA data base indicates that a sizable portion of patients experience reductions in these fat-soluble compounds details of monitoring or supplementation will need to be addressed.

STUDY BM14149

OBJECTIVES

8.2.1 The primary objective of this study was to compare the two-year weight-loss efficacy of orlistat 120mg or 60mg tid to placebo when combined with dietary counseling and a hypocaloric diet during the first year and a eucaloric diet during the second year.

PROTOCOL DESIGN

8.2.2 This was a multi-center, double-blind, placebo-controlled, randomized, parallel-group study with a four-week, single-blind lead-in period followed by 104 weeks of double-blind treatment in 729 patients. Following the four-week lead-in period patients were stratified into two weight loss categories based on the weight loss during this lead-in period: ≤2.0 kg or >2.0 kg. The Sponsor's rationale for the stratification was that the drug and placebo groups would be matched in terms of probable success at weight loss with diet alone. Patients were then randomized in equal fashion to either placebo, orlistat 120mg tid, or orlistat 60mg tid.

Patients' diets consisted of three meals a day and contained 30% of calories as fat, 50% carbohydrate, 20% protein, and a maximum of 300 mg/day of cholesterol. Alcohol consumption was limited to no more than 150g per week. During the first year subjects were instructed to maintain a hypocaloric diet (-600kcal/day). After 24 weeks of treatment, to compensate for the expected lower caloric requirements following weight loss, subjects were instructed to reduce their caloric intake an additional 300kcal/day. To promote a stable body weight during the second year of treatment, the daily prescribed caloric intake was recalculated at the end of 52 weeks of double-blind treatment for those patients who lost ≥ 3 kg between Weeks 40 and 52. The caloric intake prescribed equaled the estimated total daily energy expenditure (1.3 x BMR) minus 10% kcal/day. Patients who lost < 3 kg during this period were considered relatively weight stable and had no dietary adjustment. Patients recorded all food and beverages consumed for four consecutive days including two week days and two weekend days during the week preceding each clinic visit and the contents of the diaries were analyzed by a dietitian and used for counseling patients. Only subjects with vitamin levels within the normal range at the beginning of the double-blind phase were allowed to participate in the study. During the trial, if a subject's vitamin level was below the lower limit of normal, the investigator repeated the measurement at the next visit. If the second value was still below the lower limit of normal, the subject was placed on supplementation. If the supplementation did not increase the level to within normal by two months, the dose was increased. If this failed to normalize the level the patient was discontinued.

STUDY POPULATION

8.2.3 Eligible patients included men and women aged 18 years and older with a BMI between 28 and 43 kg/m^2. The major exclusion criteria included:

- Hx or presence of significant cardiac, renal, hepatic, GI, or endocrine disorders
- MI, CABG, or PTCA within six months prior to screening
- SBP ≥165 mmHg or DBP ≥105 mmHg on two consecutive visits
- Episode of nephrolithiasis within 1 year of screening
- Active GI disease
- History of pancreatitis
- Drug-treated diabetes
- Abnormal laboratory tests

Patients were excluded if they were taking or had taken within four weeks of screening the following medications:

- appetite suppressants
- fish oil supplements
- retinoids

- anticoagulants
- digoxin, anti-arrhythmics
- lipid-soluble vitamin supplements
- oral hypoglycemics
- insulin

ENDPOINTS

8.2.4 Body weight was measured at frequent intervals and the average of two measurements was recorded in the CRF. Other efficacy parameters included the waist to hip ratio, serum lipids, fasting serum glucose and insulin, an OGTT (optional), and blood pressure (considered efficacy and safety). A quality of life questionnaire was also administered.

In addition to the standard hematology and chemistry parameters, the levels of plasma retinol, vitamin D, alpha-tocopherol, beta-carotene, TSH, and prothrombin time were measured throughout the study. Hemeoccult, chest x-ray, ECG, and gallbladder and renal ultrasounds were also performed.

STATISTICAL CONSIDERATIONS

8.2.5 Two efficacy populations were defined by the Sponsor that are of interest. The first are the completers, which includes all patients who completed at least 52 weeks and 104 weeks of treatment and had a body weight assessment that fell within the time window for study day 365 and 729. And the second are the ITT populations that include all patients who received at least one dose of study medication and who had at least one efficacy assessment after baseline.

For the change in body weight from baseline to Week 52 and Week 104, hypothesis testing was conducted using ANOVA with terms for center, stratum, center by stratum, treatment, center by treatment, and stratum by treatment. In the event that some strata contained no patients an ANCOVA was conduced with weight change during the lead-in phase included as a covariate. Categorical analyses comparing orlistat to placebo were also conduced using the Chi-square test statistic. Five weight change categories were defined: lost more than 10% from start of double-blind treatment, lost more than 5% but less than or equal to 10%, lost more than 0% but less than or equal to 5%, gained more than or equal than 0% but less than or equal to 5%, and gained more than 5%. The baseline values (Day 1) for the secondary efficacy variables (lipids, blood pressure, glucose, and insulin) and vitamin levels were covariates in the ANCOVA models used to assess change from baseline. This technique would take into consideration any significant baseline differences among groups.

Input from the Agency's statistician will be required to determine whether these analyses were appropriate regarding the assumptions of the ANOVA model: normality of the residual error, homogeneity of variance, statistical independence of the residual errors, and linearity of the model.

RESULTS

POPULATIONS ENROLLED/ANALYZED

8.2.6 <u>Patient Disposition</u>

A total of 783 patients were enrolled into the study. Fifty-four patients withdrew during the lead-in phase and therefore 243 subjects were randomized to placebo, 242 to orlistat 60mg tid, and 244 to orlistat 120mg tid. Fifty-six percent, 58%, and 65% of the placebo, 60mg, and 120mg patients, respectively, completed the 2-year study. Approximately 7% of the placebo subjects withdrew from the study because of adverse events, while approximately 25% withdrew from the study because of adverse events in both active-treatment groups.

Baseline Demographics

The baseline demographic characteristics were similar among the three groups. The vast majority of subjects were female, the mean age was 44 years, over 99% were Caucasian, and the mean BMI was 34 kg/m^2.

Concomitant Medications

The most common medications that were being taken at baseline were: thyroid hormones, estrogens, ACE-inhibitors, calcium channel blockers, beta-blockers, and thiazides. Similar percentages of patients were taking these medications among the three groups.

Baseline Risk Factors

The baseline risk factors, which were similar for the three groups, are shown in the table below. There were fewer patients in the 120mg group with hypertension (26%) compared to the percentage in the 60mg group (36%)(p=0.05). Approximately 28% of the placebo subjects were hypertensive at baseline. The percent of patients in the three groups that were receiving antihypertensive medications at baseline was similar (12-19%). Less than 2% of subjects in each group had diet controlled NIDDM. Roughly 2-3% of the patients in each group were taking lipid lowering drugs at baseline.

BASELINE RISK FACTORS (means)

	Orlistat 120mg	Orlistat 60mg	Placebo	P value
SBP (mmHg)	126	128	127	0.1
DBP (mmHg)	80	81	80	0.09
TC (mmol/L)	5.3	5.4	5.4	0.2
LDL (mmol/L)	3.4	3.5	3.6	0.4
HDL (mmol/L)	1.17	1.13	1.17	0.3
TG (mmol/L)	1.53	1.75	1.58	0.08

Patient Daily Diet

The total daily caloric and fat intakes were similar among the three groups and tended to increase throughout the first year.

EFFICACY ENDPOINT OUTCOMES

Weight Loss (Completers)

One-Year Data

Analysis of the Means

Following 52 weeks of treatment the placebo group had a mean weight loss from baseline of 3.7 kg; the orlistat 60mg group had a mean loss of 5.2 kg (p=0.9 vs placebo) and the 120mg group had a loss of 6.2 kg (p=0.002 vs placebo). During the four-week lead-in phase, all groups lost approximately 3% of initial body weight. Thus, at Week 52 the mean percent weight loss from baseline for the placebo, 60mg, and 120mg groups were approximately -3.5%, -5.6%, and -6.9%, respectively.

Categorical Analysis

Approximately 33% of the placebo subjects lost more than 5% of baseline body weight, whereas 52% and 60% of the subjects in the orlistat 60 and 120mg groups, respectively, met this goal (p<0.01, orlistat groups vs placebo). There were also statistically significant differences between the drug and placebo groups in the percentage of patients who lost at least 10% of baseline body weight: 16%, 26%, and 31% for the placebo, 60mg, and 120mg groups, respectively (p=0.04, placebo vs 60mg and p=0.003, placebo vs 120mg).

Second-Year Data

All three groups tended to regain weight during the second year of treatment while consuming a eucaloric diet. At the completion of Year 2 the mean weight loss in the placebo group was 1.3 kg and the mean weight loss in the orlistat 60mg and 120mg groups were 4.2 kg (p=0.01 compared to placebo) and 5.2 kg (p<0.001 compared to placebo), respectively. Thirty percent of the placebo patients lost >5% of baseline body weight at Week 104, whereas 41% of the 60mg patients and 46% of the 120mg patients lost >5% of initial body weight (p=0.05 60mg vs placebo, and p=0.005, 120mg vs placebo).

Secondary Efficacy Parameters

Lipoprotein Lipids

After one year of treatment the mean percent changes in levels of total cholesterol increased by 0.06% in the placebo group and decreased by 3.0% in the 60mg group (p=0.1 vs placebo) and decreased by 7.0% in the 120mg group (p<0.001 vs placebo). The level of LDL-C decreased by 1.0% in the placebo group and decreased by 7.0% and 11.0% in the 60 (p=0.04 vs placebo) and 120mg (p<0.001 vs placebo) groups, respectively. There were no significant differences among groups in the changes in levels of HDL-C, TG, VLDL, or Lp(a).

After the second year of treatment the mean total cholesterol levels increased from baseline in all three groups. The value in the placebo group increased by 7.6% and by 1.5% in the 60mg group (p=0.003 vs placebo) and by 0.78% in the 120mg group (p<0.001 vs placebo). A similar pattern was observed for the levels of LDL-C. Of note, the level of Lp(a) was reduced by 57 mg/L in the 120mg group, by 53 mg/L in

the 60mg group, and by 31 mg/L in the placebo group. The difference between the 120mg vs the placebo groups was significant at p=0.03. There were no significant differences between the orlistat and placebo groups in the changes in the levels of HDL-C, TG, or VLDL.

Blood Pressure

Blood pressures in the orlistat-treated patients were reduced by a small degree at the end of Year 1, but the differences were not statistically significantly different from placebo. By the end of the second year of treatment the mean blood pressures for all three groups increased by 0.3 to 2 mmHg.

Fasting Glucose and Insulin

The mean values for fasting glucose increased by 0.13 mmol/L (2.3 mg/dl) in the placebo group at Week 52, but decreased by 0.11 mmol/L (2.9 mg/dl) in the 60mg group (p=0.002 vs placebo) and by 0.2 mmol/L (4.0 mg/dl) in the 120mg group (p=0.03 vs placebo). By the completion of the two-year study, there were no clinically or statistically significant differences between the groups in the change from baseline in fasting glucose levels. Regarding fasting insulin levels, following one year of treatment the level increased by 2.8 pmol/L in the placebo group and decreased by 12.3 pmol/L in the 60mg group (p=0.08) and by 17.3 pmol/L in the 120mg group (p=0.01). These differences were not maintained at the completion of the two-year study.

OGTT

About 25% of the patients had OGTTs performed during the first year of the study. There were statistically significant reductions in the AUCs for insulin and C-peptide in the orlistat 120mg group vs the placebo group. By the completion of the two-year study, however, there were no significant differences between the active vs placebo-treated groups in any of the OGTT parameters.

8.2.7 SAFETY DATA

Deaths

One patient in the orlistat 60mg group died on study day 449 from a cardiac arrest. The patient was a 61-year-old white male with a history of coronary artery disease.

Symptom-Related Adverse Events

Adverse events related to the GI system were reported more frequently in the orlistat groups compared to the placebo group. And in general, the incidence of these adverse events were greater in the 120mg group compared to the 60mg group. The majority of these adverse events were mild in nature. It is not clear from the data presented whether the incidence of the GI adverse events decreased with continued use of orlistat. This will be addressed in the ISS.

Plasma Fat-Soluble Vitamin Levels

The mean levels of vitamins D, E, and β-carotene in the orlistat groups were, in general, reduced from baseline and significantly lower than the placebo group at Weeks 52 and 104. Prothrombin time — a

crude indicator of vitamin K status — was not significantly different among the groups after one or two years of treatment.

Fifty-one patients required vitamin supplementation during the study: seven in the placebo group, 19 in the 60mg group, and 25 in the 120mg group. The Sponsor states that because of the differences in the vitamin preparations used for supplementation it was not feasible to accurately analyze the effects of vitamin supplementation.

Ultrasounds of the Gallbladder and Kidney

As assessed by ultrasound, there was no evidence that the risk for developing gallstones or kidney stones was increased by orlistat.

SPONSOR'S CONCLUSIONS

Orlistat, administered at a dose of 60 or 120 mg tid in conjunction with a mildly hypocaloric diet, produced a statistically significant and clinically meaningful reduction in body weight after one year of treatment compared with placebo treatment, and this significantly greater weight loss was maintained during the second year of continued treatment. In general, 120 mg of orlistat produced a greater response than 60 mg of orlistat. In addition, orlistat was significantly more effective than placebo in reducing levels of total cholesterol, LDL-C, the LDL/HDL ratio, blood pressure, and glucose and attenuated the progressive rise seen in these parameters with continued treatment during the second year of the study. Despite that there was some regain in the orlistat treated group during the second year, changes in risk factors were maintained or improved. Chronic administration of orlistat for up to two years was well tolerated by obese patients in this study.

MEDICAL OFFICER'S CONCLUSIONS

In general, this Reviewer agrees with the Sponsor's assessment of efficacy. However, the statements regarding the improvements in co-morbidities are overly enthusiastic given the magnitude, and in some cases, the direction of the changes in the orlistat groups relative to the placebo group.

For subjects who completed one year of treatment, there was a statistically significantly greater mean weight loss in the 120mg group, but not in the 60mg group, when compared to placebo. By categorical analyses, when compared with placebo, the orlistat groups had a greater percentage of patients who lost >5% of baseline body weight following one and two years of treatment. Though the study was not specifically designed to compare weight loss between the two active treatment groups, the difference in weight loss between the 60mg and 120mg groups was not significant as their 95% confidence intervals overlapped.

Subjects in the orlistat groups had small, but statistically significant improvements in the levels of total cholesterol and LDL-C when compared to placebo. Blood pressures remained fairly stable during the study and there were no clinically meaningful differences between the orlistat and placebo groups. Although not maintained by the end of Year 2, the orlistat groups had clinically and statistically significant reductions in fasting insulin levels in comparison to the placebo group at Week 52.

The levels of vitamins D, E, and β-carotene tended to decrease in the orlistat groups by the completion of

the study. Forty-four orlistat-treated subjects required vitamin supplementation during the study. The clinical significance of minor to moderate reductions in these nutrients that remain within the "normal range" is not clear. However, without question reductions to below "normal" have significant clinical consequence if sustained long term. More thought will be given to the vitamin-depleting effect of orlistat, and to possible approaching of handling the problem in the ISS.

STUDY NM14161

OBJECTIVES

8.3.1 The primary objectives of this study were to compare the efficacy of orlistat 60mg tid and orlistat 120mg tid to placebo in the treatment of obesity when combined with dietary counseling and a hypocaloric diet for one year, and to compare the efficacy between the orlistat and placebo groups when combined with a eucaloric for a second year of treatment.

PROTOCOL DESIGN

8.3.2 This was a multi-center, double-blind, placebo-controlled, randomized, parallel-group study with a four-week, single-blind lead-in period followed by 104 weeks of double-blind treatment in 796 patients. Following the four-week lead-in period patients were stratified into two weight loss categories based on the weight loss during this lead-in period: ≤2.0 kg or >2.0 kg. Patients were then randomized in equal fashion to either placebo, orlistat 120mg tid, or orlistat 60mg tid.

Patients' diets consisted of three meals a day and contained 30% of calories as fat, 50% carbohydrate, 20% protein, and a maximum of 300 mg/day of cholesterol. Alcohol consumption was limited to no more than 10 drinks per week. On Day one patients were assigned to one of two caloric levels depending on their body weight at screening. If the screening body weight was <90 kg, the prescribed caloric level was 1200 kcal/day; if the screening body weight was >90 kg, the prescribed diet was 1500 kcal/day. Patients kept a three-day diary of food and beverage intake at 10 time points during the study. Patients were not given any feedback on their food intakes during the study. At four time points during the first year of the study patients viewed one of four different videos describing behavior modification techniques for weight control. During the second year patients received behavior modification pamphlets that discussed ways to minimized weight regain. And throughout the study patients were encouraged to increase physical activity by walking briskly for 20 to 30 minutes 3-5 times per week.

If during the study a subject's vitamin level was below the lower limit of normal the investigator repeated the measurement at the next visit. If the second value was still below the lower limit of normal the subject was placed on supplementation. If the supplementation did not increase the level to within normal by two months, the dose was increased. If this failed to normalize the level the patient was discontinued.

STUDY POPULATION

8.3.3 Eligible patients included men and women aged 18 years and older with a BMI between 30 and 43 kg/m^2. The major exclusion criteria included:

- Hx or presence of significant cardiac, renal, hepatic, GI, or endocrine disorders
- MI, CABG, or PTCA within six months prior to screening
- SBP ≥165 mmHg or DBP ≥105 mmHg on two consecutive visits
- Episode of nephrolithiasis within one year of screening
- Active GI disease
- History of pancreatitis
- Drug-treated diabetes
- Abnormal laboratory tests

Patients were excluded if they were taking or had taken within four weeks of screening the following medications:

- appetite suppressants
- fish oil supplements
- retinoids
- anticoagulants
- digoxin, anti-arrhythmics
- lipid-soluble vitamin supplements
- oral hypoglycemics
- insulin
- nicotine replacement
- tricyclic antidepressants
- anticonvulsants
- calcium supplements

ENDPOINTS

8.3.4 Body weight was measured at frequent intervals and the average of two measurements was recorded in the CRF. Other efficacy parameters included the waist to hip ratio, serum lipids, fasting serum glucose and insulin, an OGTT, and blood pressure (considered efficacy and safety). A quality of life questionnaire was also administered.

In addition to the standard hematology and chemistry parameters, the levels of plasma retinol, vitamin D, alpha-tocopherol, beta-carotene, TSH, PTH, and prothrombin time were measured. Hemeoccult, chest x-ray, ECG, and gallbladder and renal ultrasounds were also performed. Other tests included 24-hour urine creatinine, oxalate, calcium, and oxalate:creatinine ratio, and measurement of phospholipid fatty acids. Blood samples were taken at baseline, Week 52, and Week 104 for pharmacokinetic evaluation and 72-hour fecal fat content was measured as well.

STATISTICAL CONSIDERATIONS

8.2.5 For the change in body weight from baseline to Week 52 and Week 104, hypothesis testing was conducted using ANOVA with terms for center, stratum, center by stratum, treatment, center by treatment, and stratum by treatment. In the event that some strata contained no patients an ANCOVA was conduced with weight change during the lead-in phase included as a covariate. Categorical analyses comparing orlistat to placebo were also conduced using the Chi-square test statistic. Five weight change categories were defined: lost more than 10% from start of double-blind treatment, lost more than 5% but

less than or equal to 10%, lost more than 0% but less than or equal to 5%, gained more than or equal than 0% but less than or equal to 5%, and gained more than 5%. The baseline values (Day 1) for the secondary efficacy variables (lipids, blood pressure, glucose, and insulin) and vitamin levels were covariates in the ANCOVA models used to assess change from baseline. This technique would take into consideration any significant baseline differences among groups.

RESULTS

POPULATIONS ENROLLED/ANALYZED

8.3.6 Patient Disposition

A total of 796 patients at 17 centers were enrolled into the study. Six hundred forty-two patients completed the 4-week lead-in phase and were randomly assigned to placebo (n=214), orlistat 60mg (n=214), or orlistat 120mg (n=214). Fifty-seven percent, 72%, and 71% of the patients in the placebo, 60mg, and 120mg groups, respectively, completed one year of treatment. Forty-three percent, 56%, and 55% of placebo, 60mg, and 120mg subjects, respectively, completed two years of treatment. Seven percent, 7%, and 11% of the patients in the placebo, 60mg, and 120mg groups, respectively, withdrew during the two-year study because of an adverse event.

Baseline Demographics

The baseline demographic characteristics were similar for the three groups. Seventy-eight percent of the subjects were female, the mean age was 42 years (range 18-78 years), 90% were Caucasian, and the mean BMI was 35 kg/m^2.

Concomitant Medications

The most common medications at baseline included NSAIDS, ACE-inhibitors, and calcium channel blockers. Four to 9% of the patients were taking thyroid hormone at baseline.

Baseline Risk Factors

The baseline risk factors were similar for the three groups (table below). A similar percentage of patients in each group were hypertensive at baseline (16-23%). Nine percent of the placebo patients and 15% of the active-treatment subjects were being taking antihypertensive medications at baseline (p=0.1). Only one patient had NIDDM at baseline, and this patient was not receiving medication for the condition. Slightly greater than 1% of the patients in each group were receiving lipid altering medications at baseline.

BASELINE RISK FACTORS (means)

	Orlistat 120mg	Orlistat 60mg	Placebo	P value
SBP (mmHg)	121	121	120	0.8
DBP (mmHg)	78	78	78	0.9

BASELINE RISK FACTORS (means)

	Orlistat 120mg	Orlistat 60mg	Placebo	P value
TC (mmol/L)	5.0	5.0	5.0	0.9
LDL (mmol/L)	3.2	3.1	3.2	0.7
HDL (mmol/L)	1.20	1.22	1.17	0.2
TG (mmol/L)	1.55	1.65	1.67	0.4

Patient Daily Diet

The dietary intakes of total calories and fat were similar in the three groups at the start of the double-blind period. When patients were switched to a eucaloric diet during Year two, the mean total caloric intake increased in the two orlistat groups, but decreased in the placebo group from Weeks 52 to 92. In general, total fat intake increased in all groups during the two years. The intake of fat-soluble vitamins, β-carotene, and calcium decreased from baseline in all three groups during Year 1.

EFFICACY ENDPOINT OUTCOMES

Weight Loss (Completers)

Analysis of the Means

The average weight loss during the lead-in period was approx. 3.0 kg (3%) for the three groups. Following 52 weeks of treatment the placebo group had a mean weight loss from baseline of 1.1 kg; the orlistat 60mg group had a mean loss of 4.8 kg ($p<0.001$ vs placebo); and the 120mg group had a mean loss of 5.1 kg ($p<0.001$ vs placebo). At Week 52, the mean percent weight loss from initial body weight for the placebo, 60mg, and 120mg groups were 4.3%, 8.0%, and 8.7%, respectively (1.3%, 5%, and 5.7%, respectively for change from baseline).

Categorical Analysis

A statistically significantly greater percentage of patients in the orlistat groups lost >5% of baseline body weight after one year of treatment: 25% of placebo patients, 36% of 60mg subjects, and 47% of 120mg subjects ($p<0.05$ orlistat vs placebo). Similarly, a significantly greater percentage of patients in the orlistat groups lost > 10% of baseline body weight after one year of treatment: 7% of placebo patients, 17% of 60mg subjects, and 25% of 120mg subjects ($p<0.01$ orlistat vs placebo).

Second-Year Data

The weights in all three groups gradually increased during the second year of the study and a plateauing was not evident by Week 104. At the completion of the study, the placebo group had a mean weight loss from baseline of 1.3 kg, while the 60mg group had a mean reduction in weight of 2.0 kg ($p=0.004$ vs placebo) and the 120mg group had a 2.2 kg loss ($p=0.001$ vs placebo). Only 11% of placebo patients lost

>5% of initial body weight after two years of treatment compared to 23% of 60mg subjects (p=0.03) and to 25% of 120mg subjects (p=0.009). Of greatest relevance, however, was the difference among the groups in the percentage of patients who lost >10% of initial body weight. Eighteen percent of 120mg subjects, 10% of 60mg subjects, and 1% of placebo subjects achieved this mark at the end of the two-year study (p <0.01, placebo vs drug).

Secondary Efficacy Parameters

Lipoprotein Lipids

Following one year of treatment, the mean percent change from baseline in total cholesterol levels was 3.7% in the placebo group and 0.3% in the 60mg group (p=0.05 vs placebo) and -1.0% in the 120mg group (p=0.007 vs placebo). The levels of LDL-C increased by 7% in the placebo group and by 0.5% in the 60mg group (p=0.02 vs placebo), whereas they decreased by 2.5% in the 120mg group (p=0.001 vs placebo). The levels of Apo B increased in all three groups, but the increase was significantly less in the 120mg group vs placebo (12 vs 58 mg/L, p=0.04). There were no other significant lipid changes noted among the groups.

At the completion of the two-year study, there were no significant differences between the drug-treated vs placebo-treated subjects in any of the lipid parameters . What is more, in all three groups most of the lipid parameters had increased from baseline to Week 104.

Blood Pressure

During the first year of treatment, blood pressures did not change significantly in any of the groups. At the completion of Year 2, the increase from baseline in diastolic blood pressure was significantly less in the 120mg group (0.18 mmHg) compared to placebo group (3.1 mmHg)(p=0.01).

Fasting Glucose and Insulin and OGTT

There were no significant differences among the groups in the levels of fasting glucose or insulin or in any of the OGTT parameters after one or two years of treatment.

Pharmacokinetic Data

Small quantities (0.2 - 5.1 ng/ml) of orlistat were detected in 25% of subjects in the 60mg group and in 50% of the 120mg subjects. The percent of subjects with detectable levels did not increase with time. The mean values for M1 averaged 15.5 ng/ml in the 60mg group and 20 ng/ml in the 120mg group. The mean values for M3 averaged 84.5 ng/ml in the 60mg group and ranged from 51-104 ng/ml in the 120mg group. The mean levels of these metabolites did not increase with time.

Pharmacodynamic Data

72-hour fecal fat content was determined at baseline and at Weeks, 20, 48, and 100. Fat content remained fairly stable across sampling times. As expected, the change from baseline to Week 100 in the mean levels of fecal fat were approximately 0.90 grams in the placebo group, 16 grams in the 60mg group, and 21 grams in the 120mg group.