SAFETY DATA

8.3.7 Deaths

One patient died during the study. This patient — who was in the 120mg group — was a 55-year-old male with a history of hypertension. He died of an acute MI on Day 317 of treatment.

Symptom-Related Adverse Events

By far, adverse events related to the GI tract were reported more frequently in all groups, and to a greater extent in the orlistat groups compared with the placebo group. The more common complaints included fecal urgency, oily spotting, flatus with discharge, abdominal pain, liquid stools, and oily evacuation. Most of these adverse events were recorded as mild to moderate. In the orlistat groups, the most common reasons for withdrawal from the study were GI-related adverse events. The relatively low incidence of serious adverse events precludes a valid assessment of causality, this will be discussed in the ISS.

Special Laboratory Assessments

Urinary Oxalate

There were no significant differences between the placebo and orlistat groups in the levels of 24-hour urinary oxalate following one or two years of treatment. The largest absolute difference was between the placebo and the 120mg group: 8.0 mg/dL (p=0.26). Three placebo patients and ten orlistat (120mg) patients had markedly high levels of urinary oxalate (>1111.0 umol/d) during the study (p=0.05 for ITT, and p=0.15 for completers). Of interest, two patients in the 60mg group who had elevated levels of urinary oxalate developed nephrolithiasis during the trial. One of these patients had a history of previous renal calculi, whereas the other patient had no history of renal problems.

Serum Calcium and PTH

There were no significant changes in the mean levels of serum calcium (total and ionized) or PTH (intact) after one and two years of treatment (table below).

Levels of Ionized Calcium (1.12-1.4 mmol/L) and Intact PTH (13.3-60.2 ng/L)

	Placebo	60mg	120mg
Ionized Calcium mmol/L			
Baseline	1.24 (212)	1.24 (213)	1.23 (209)
Week 52	1.23 (110)	1.22 (145)	1.22 (143)
Week 104	1.24 (90)	1.24 (115)	1.23 (112)
PTH ng/L			
Baseline	33.5 (212)	32.3 (213)	33.2 (210)
Week 52	31.9 (112)	29.8 (146)	31.6 (144)
Week 104	34.1 (91)	31.5 (116)	33.2 (117)

More importantly, there were no differences among the groups in the proportion of patients with normal baseline PTH values who developed abnormally elevated levels of intact PTH (>60 ng/L) at any time during the first or second year of treatment (table below).

Shift Table of Normal Baseline PTH to Abnormally Elevated PTH (>60ng/L) at End of Year 1

	Follow-up		
	Normal	Abnormal	P-value
Placebo	168	2	0.7+
120mg	170	4	

+Two-tailed Fisher's Exact Test

The results for Year 2 were similar to the Year 1 results.

Phospholipid Fatty Acids

There were also no significant changes in the levels of phospholipid fatty acids in the orlistat groups compared to the placebo group (see table below). In addition, the ratio of triene/tetraene — a sensitive indicator of essential fatty acid deficiency — was not significantly altered following 104 weeks of treatment with orlistat.

CHANGES IN FATTY ACIDS FROM BASELINE TO WEEK 104

Fatty Acid	Orlistat	Placebo	P Value
Total n-6 Fatty Acid	-2.88%	-2.12%	0.50
Linoleic Acid	-0.84%	0.76%	0.09
Gamma-Linolenic Acid	-0.92%	-0.81%	0.50
Arachidonic Acid	-0.34%	-1.20%	0.18
Triene/Tetraene	0.01%	0.01%	1.00

Plasma Fat-Soluble Vitamin Levels

At the completion of the first year, all groups had a decrease from baseline in the mean level of vitamin D. The reduction was significantly greater in the 120mg group compared to the placebo group (-11 vs -6 nmol/L, p=0.005). The mean levels of β-carotene also decreased from baseline in all the groups. The two active-treatment groups had a mean reduction of 0.09 umol/L, while the placebo group had a mean reduction of 0.04 umol/L (p=0.004, 60mg vs placebo and p=0.001, 120mg vs placebo). Of patients with normal baseline vitamin and β-carotene levels (93%), a greater percentage of orlistat-treated patients compared to placebo patients had two or more consecutive low values. The greatest differences in incidence between groups were seen with vitamin D (2.0%, 3.8%, and 2.5% in the placebo, 60mg, and

120mg orlistat groups, respectively) and vitamin E (0.0%, 4.1%, and 3.6%, respectively). All total, 78 orlistat-patients required vitamin supplementation during the 2-year study compared with 20 placebo subjects.

Ultrasounds of the Gallbladder and Kidney

The number of patients who developed either gallstones or kidney stones was relatively low during both years of the study. As mention above, a more meaningful approach to attempt to answer whether orlistat increases the risk for stone formation is to pool the data from all of the primary studies. This will be discussed in the ISS.

SPONSOR'S CONCLUSIONS

Orlistat administered at a dose of 60 or 120 mg tid in conjunction with a mildly hypocaloric diet in a primary care setting and without the use of extensive dietary or behavioral counseling, 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 addition, orlistat was significantly more effective than placebo in reducing levels of total and LDL cholesterol, fasting insulin and OGTT profiles as well as diastolic blood pressure during the first year of treatment, and attenuated the progressive rise seen in these parameters with continued treatment during the second year of the study. Overall, chronic administration of 60 or 120 mg of orlistat for up to two years was well tolerated by obese patients, however, greater improvement was shown with 120 mg of orlistat.

MEDICAL OFFICER'S CONCLUSIONS

This Reviewer agrees with the Sponsor's conclusion that the 60 and 120mg doses of orlistat produced a statistically significant reduction in body weight after one year of treatment when compared with placebo treatment. However, the changes in the mean percent body weight from baseline to Week 52 were 1.3%, 5.0%, and 5.7% for placebo, 60mg, and 120mg, respectively. The weight loss attributable to orlistat treatment was modest. Nevertheless, this Reviewer believes that a subgroup of patients did derive clinical benefit from orlistat treatment as indicated by the significantly greater percentage of orlistat-treated patients who lost >10% of initial body weight compared to placebo (33% vs 19%, respectively).

The Sponsor's claim that treatment with orlistat was associated with significant improvements in total cholesterol, LDL-C, fasting insulin, OGTT profiles, and diastolic blood pressure is somewhat misleading. In general, when compared to the changes in the placebo group, treatment with orlistat for one year was associated with very small improvements in the individual comorbidities. Yet, this Reviewer does acknowledge that when viewed collectively, the overall risk factor profile improved in a clinically meaningful manner for many patients treated with orlistat.

Some reports in the literature indicate that patients with fat malabsorption may be at risk for developing essential fatty acid deficiency (EFAD)[7,8]. In this study, the concentrations of various phospholipid fatty acid acids were monitored. Compared to placebo there were no significant changes in any of the fatty acid levels in the 120mg orlistat group. In particular, the ratio of triene to tetraene, which is considered a sensitive indicator of EFAD, did not significantly change following two years of treatment with orlistat. Of course, the use of doses higher than recommended or the habitual consumption of a diet low in fat

(<30% of total calories) might lead to EFAD. Prescribing physicians will need to reinforce proper use of the drug

The presence of fatty and bile acids in the colon increases the permeability of the epithelium to dietary oxalate, which may lead to hyperoxaluria and nephrolithiasis[9,10]. In patients that completed two full years of treatment, the mean level of 24-hour urinary oxalate increased by 8 mg/dl in the 120mg group and did not change in the placebo group (p=0.26). Three placebo and ten orlistat (120mg) subjects had abnormally high levels of urinary oxalate during the study (p=0.05 ITT and p=0.15 completers). These results do raise suspicion that the use of 120mg tid of orlistat increases the incidence of hyperoxaluria, and indicate that further study is warrented (the ISS contains a more detailed disucssion of uriniary oxalate and nephrolithiasis).

Serum calcium levels are tightly regulated. As a result, one would not expect hypocalcemia to develop even if orlistat impaired calcium and/or vitamin D absorption.● And in reality, the levels of serum calcium did not change significantly in the drug-treated groups throughout 2 years of treatment. One of the first compensatory mechanisms triggered by lowered serum calcium levels is an increased secretion of PTH. One could reason that if orlistat significantly reduced the absorption of dietary calcium and/or vitamin D, the levels of plasma PTH should increase. To the extent that PTH values below 60ng/L reflect normal calcium homeostasis, there were very few patients in the placebo or drug-treated groups that developed elevated PTH levels at any time during this study (PTH measured at baseline, 6,12, and 24 months), and even fewer that had sustained elevations of this hormone. These results provide some evidence that long-term treatment with orlistat does not lead to significant aberrations in calcium metabolism. The results of the soon-to-be submitted mineral balance study will provide complimentary data essential in the assessment of orlistat's effect on calcium homeostasis.

Treatment with orlistat was associated with the expected increase in GI tract-related adverse events. These complaints do not, in general, raise concern about the drug's safety; rather, they represent inconveniences that the patients may or may not find troubling enough to discontinue drug use. The effects of orlistat on fat-soluble vitamin and β-carotene levels were consistent with the results from the previously reviewed studies and point toward the need to provide a multivitamin to all treated patients.

STUDY BM14119B

OBJECTIVES

8.4.1 The objective of this study was to compare the weight loss efficacy of 120mg tid of orlistat to placebo in obese patients on a hypocaloric diet for one year.

PROTOCOL DESIGN

8.4.2 This was a multi-center, double-blind, placebo-controlled, randomized, parallel-group study with a four-week, single-blind lead-in period followed by 52 weeks of double-blind treatment in 267 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 or orlistat 120mg tid.

●Hypocalcemia might develop if calcium and/or vitamin D aborption were severly impaired for a prolonged period of time.

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.

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. A diet diary was kept by each patient for four consecutive days. The contents of the diaries were analyzed by a dietician. Unlike the previous protocols, β-carotene was not provided as a supplement because a lower limit of normal was not defined.

STUDY POPULATION

8.4.3 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
- tricyclic antidepressants
- resins for lowering lipids

ENDPOINTS

8.4.4 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, insulin, 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. Hemeoccult, chest x-ray,

ECG, and gallbladder and renal ultrasounds were also performed. Blood samples were taken at baseline, Week 24, and Week 52 for pharmacokinetic evaluation.

STATISTICAL CONSIDERATION

8.4.5 For the change in body weight from baseline to Week 52, 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 and 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

8.4.6 Patient Disposition

A total of 267 patients were enrolled into the study. Thirty-nine subjects withdrew during the four-week lead-in phase and thus 228 patients were randomized: 114 to each group. Fifty-eight percent of placebo subjects completed the study and 64% of the orlistat subjects completed the trial. Adverse events were recorded as the reason for withdrawal in 6% of placebo and 8% of orlistat patients.

Baseline Demographics

The baseline characteristics were similar for the two groups. Eighty-eight percent of the subjects were female, the mean age was 42 years (range 19-71 yrs), the majority of subjects were Caucasian, and the mean BMI was 36 kg/m^2.

Baseline Medications

The most common medications taken at baseline in the orlistat group were estrogens (9%), corticosteroids (8%), and β_2-adrenoceptor agonists (8%), and in the placebo group they were anilides (10%), thiazides (6%), and estrogens (6%).

Baseline Risk Factors

The risk factor profiles for the two groups are shown below. The percentage of subjects in each group with hypertension at baseline was not statistically significantly different (22 vs 30%, orlistat vs placebo, p=0.2). However, 14% of the placebo subjects and only 5% of the orlistat subjects were taking antihypertensive medications at baseline (p=0.02). There were six placebo patients with untreated

NIDDM at baseline compared to only 1 orlistat-treated patient (p=0.05). Three placebo subjects and one orlistat subject were taking lipid lowering medication at baseline (p=0.3).

BASELINE RISK FACTORS (means)

	Orlistat n=343	Placebo n=340	P value
SBP (mmHg)	121	119	0.6
DBP (mmHg)	78	77	0.6
TC (mmol/L)	5.22	5.17	0.7
LDL (mmol/L)	3.44	3.46	0.9
HDL (mmol/l)	1.11	1.08	0.4
TG (mmol/L)	1.51	1.46	0.6

EFFICACY ENDPOINT OUTCOMES

Weight Loss (Completers)

Analysis of the Means

Both groups lost approximately 3 kg (3%) during the four-week lead-in period. At the completion of the study the placebo group had a mean weight loss of 1.8 kg and the orlistat group had a weight loss of 4.3 kg (p=0.09). The change in the mean percent weight loss from baseline was -2.5% and -5.8% in the placebo and orlistat groups, respectively (statistical comparison not provided).

Categorical Analysis

Although the percentage of patients in each group that lost at least 5% of baseline body weight was not statistically significantly different between the placebo and 120mg groups (28% vs 44%, p=0.06), 27% of orlistat-treated patients and 8% of placebo subjects lost at least 10% of baseline body weight after one year of treatment (p=0.006).

Secondary Efficacy Parameters

The only secondary efficacy parameters that changed in a statistically significant manner (although of marginal clinical significance) were total and LDL cholesterol. At Week 52 the levels of total cholesterol increased 7.5% in the placebo group and decreased by 0.3% in the orlistat group (p=0.002); and the levels of LDL-C increased 8% in placebo subjects and decreased by 2.3% in the orlistat group (p=0.001).

Pharmacokinetic Data

Blood samples were collected at baseline, Week 24, and Week 52 for analysis of orlistat concentrations. No orlistat was detected in the placebo subjects. In 5.6% of orlistat-treated patients small quantities of

the drug (0.26-0.35 ng/ml) were detected at Week 24, but not at Week 52.

SAFETY DATA

8.4.7 Deaths

No deaths were reported during or within four weeks of completion of the study.

Symptom-Related Adverse Events

Eighty-two percent of the orlistat subjects and 56% of the placebo subjects reported at least one complaint coded as a GI systems disorder. The symptoms reported with a greater frequency in the orlistat compared to the placebo group were fatty stool, liquid stools, oily evacuation, increased defecation, soft stools, and fecal urgency. The majority of the adverse events were recorded as mild. Only three orlistat subjects were withdrawn from the study because of GI-related complaints.

Plasma Fat-Soluble Vitamin Levels

Although the mean plasma levels of vitamins D, E, and β-carotene in the orlistat group decreased relative to the changes in the placebo group, only the reduction in β-carotene was statistically significant (-0.11 vs 0.0 umol/L, $p<0.001$). As observed in the previous studies, more of the orlistat-treated individuals had two or more consecutive low values for vitamins A, D, and E compared to the placebo-treated subjects. The largest difference was observed for vitamin E: 8% vs 0%: orlistat vs placebo.

Ultrasounds of the Gallbladder and Kidney

There was no evidence that orlistat led to an increased risk for developing either gallstones or kidney stones.

SPONSOR'S CONCLUSIONS

Orlistat administered in a dose of 120 mg tid in conjunction with a hypocaloric diet, produced a statistically significant and clinically meaningful reduction in body weight during 52 weeks of treatment compared with placebo treatment. In addition, in the orlistat-treated patients there was a statistically significant reduction in total cholesterol, LDL-C, and LDL/HDL ratio compared with placebo, as well as a statistically significant difference in satisfaction with treatment favoring the orlistat-treated group compared with the placebo-treated group. There were positive trends in changes in fasting insulin and blood pressure. In general, orlistat was well tolerated by the obese patients in this study.

MEDICAL OFFICER'S CONCLUSIONS

The Sponsor claims that treatment with 120mg tid of orlistat for one year produced clinically meaningful weight loss compared with placebo treatment. This is true for some of the patients. Although the difference in absolute weight loss between the two groups was not statistically significant (1.8 vs 4.3 kg, $p=0.09$), 27% of the orlistat patients compared with 8% of placebo patients lost at least 10% of baseline body weight ($p=0.006$). This difference speaks to the benefit of the drug for some individuals. Regarding comorbidities, as noted previously, the magnitude of the change in the individual risk factors in the

orlistat-treated subjects was of modest clinical value; nonetheless, collectively they represent a tangible improvement in the overall risk factor profile.

STUDY NM14185

OBJECTIVES

8.5.1 The objectives of this study were as follows: To evaluate the long-term weight control effect of orlistat combined with appropriate dietary counseling among patients receiving the following drug regimens tid:

1. Two years of placebo
2. Two years of orlistat 120mg
3. One year of orlistat 120mg, followed by a second year of orlistat 60mg
4. One year of orlistat 120mg, followed by a second year of placebo

PROTOCOL DESIGN

8.5.2 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 1187 obese 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. Six hundred sixty-eight patients were then randomized to 120mg tid of orlistat and 224 were randomized to placebo for one year. At the completion of one year of treatment subjects assigned to placebo during Year 1 remained on placebo and the subjects who were randomized to 120mg tid of orlistat during the first year were randomized to one of three groups for the second year: (1) continue on 120mg tid; (2) orlistat 60mg tid; or (3) placebo tid. Subjects were instructed to consume a diet that consisted of 30% fat, 50% carbohydrate, and 20% protein. Throughout the study patients recorded their dietary intakes in a three-day food diary and met with dietitians periodically to discuss the appropriate food choices. During the first year patients received a mildly hypocaloric diet (-500-800 kcal/day). During the second year of the study patients were maintained on a eucaloric diet. Patients were also encouraged to attend behavior modification groups and to engage in brisk walking for 20 to 30 minutes three-to-five times per week.

With respect to the monitoring and supplementation of fat-soluble vitamin and β-carotene, these parameters were measured regularly and if a subject had a plasma level below normal on two consecutive visits the patient was started on vitamin supplementation. The actual vitamin was not disclosed to the investigator or the patient. If during the first year a supplemented patient had a low level after two months of supplementation the dose was doubled; in the event that the low level persisted for another two months the patient was withdrawn from the study. All vitamin supplementation was discontinued at the beginning of Year 2 and the above supplementation procedure was then followed.

STUDY POPULATION

8.5.3 Eligible patients included men and women aged 18 years and older with a BMI between 31 and 43 kg/m^2 (men) and between 30 and 43 kg/m^2 (women). 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
- tricyclic antidepressants
- resins for lowering lipids
- nicotine replacement

ENDPOINTS

8.5.4 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 insulin and glucose, 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, and prothrombin time were measured. Hemeoccult, chest x-ray, ECG, and gallbladder and renal ultrasounds were also performed.

STATISTICAL CONSIDERATIONS

8.5.5 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. During the second year of the study an ANCOVA with weight loss during the first year as a covariate was used to test the hypothesis that the expected mean weight change between Week 52 and Week 104 in patients treated with 120mg tid of orlistat in Year 1 is the same when these patients are treated with 120mg tid, 60mg tid, or with placebo during Year 2. Following Year one and two, categorical analyses comparing the various groups 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%. Regarding secondary efficacy parameters, 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.

RESULTS

POPULATIONS ENROLLED/ANALYZED

8.5.6 Patient Disposition

A total of 1187 patients were enrolled into the study. Two hundred ninety-five subjects withdrew during the lead-in phase and thus 892 patients were randomized to treatment for 1 year: 668 to 120mg tid of orlistat and 224 to placebo. Sixty-nine percent of the individuals in the orlistat group and 62% of the placebo subjects completed the first year. At this point, 443 orlistat patients were randomized for the second year of the study: 138 to placebo, 152 to orlistat 60mg tid, and 153 to orlistat 120mg tid. One hundred thirty-three patients from the first year placebo group continued on placebo during Year 2. Approximately 70% of the subjects randomized into Year 2 completed the study. During the first year 9% of the orlistat subjects and 4% of the placebo subjects withdrew from the study because of an adverse event. During the second year of the study the four groups had similar incidences of adverse event-related withdrawals (3-6%).

Baseline Demographics

There were more females in the placebo group (88%) compared to the orlistat group (83%) ($p=0.05$). The other demographic characteristics were similar between the two groups. The mean age was 43 years (range 20-76 yrs), 80% of the subjects were Caucasian, and the mean BMI was 35.5 kg/m^2.

Baseline Medications

The most common medications at baseline were estrogens (14% placebo and 12% orlistat), NSAIDS (11% placebo and 9% orlistat), and thyroid hormone (9% placebo and 7% orlistat). The distribution between the groups at baseline was similar.

Baseline Risk Factors

The levels of triglycerides were significantly higher in the orlistat group relative to the placebo group; other risk factors at baseline were similar (see table below). Roughly 18% of the subjects in each group were hypertensive at baseline and 12% of the subjects in each group were being treated with antihypertensive medication. There were five subjects in the orlistat group and no subjects in the placebo group with NIDDM at baseline; all were diet-controlled (p=ns). Approximately 1-2% of the patients in the two groups were taking lipid lowering medication.

BASELINE RISK FACTORS (means)

	Orlistat n=343	Placebo n=340	P value
SBP (mmHg)	119	119	0.4
DBP (mmHg)	77	76	0.3
TC (mmol/L)	4.90	4.98	0.3
LDL (mmol/L)	3.08	3.18	0.1
HDL (mmol/l)	1.17	1.21	0.1
TG (mmol/L)	1.53	1.41	0.04

EFFICACY ENPOINT OUTCOMES

Year One

Weight Loss (Completers)

Analysis of the Means

The mean weight loss during the four-week lead-in was 2.3 kg for both groups. The mean weight loss from baseline to Week 52 in the placebo group was 3.5 kg and 6.5 kg in the orlistat group ($p<0.001$). The reduction in the mean percent weight from baseline was approximately 3% in the placebo group and 7% in the orlistat group (no statistics provided).

Categorical Analysis

Fifty-five percent of the orlsitat-treated patients and 33% of placebo subjects lost >5% of baseline body weight during Year 1 ($p<0.01$). In addition, 25% of orlistat subjects and 15% of placebo-treated patients lost > 10% of baseline body weight ($p =0.02$).

Secondary Efficacy Parameters

Total cholesterol levels increased on average by 6% in the placebo group and decreased 3% in the orlistat group ($p<0.001$). Similarly, LDL-C levels increased 5% in the placebo group and decreased 6% in the orlistat-treated individuals ($p<0.001$) and Apo B levels increased by 81 mg/L in the placebo group and decreased by 21 mg/L in the orlistat group ($p<0.001$). The levels of HDL-C increased to a greater extent in the placebo compared to the orlistat group (13 vs 7%, respectively, $p<0.001$). There was a statistically significant difference between the two groups in the change from baseline to Week 52 in diastolic blood pressure (0.8 vs -1.0 mmHg placebo vs orlistat, respectively, $p=0.03$), but not in systolic blood pressure. Although fasting glucose levels were not significantly different between groups there was a trend for a significant difference between groups in fasting insulin levels (22 vs 4 pmol/L placebo vs orlistat, $p=0.07$). In addition, the changes from baseline in mean AUCs for glucose and insulin were reduced by a significantly greater extent in the orlistat compared to the placebo group.