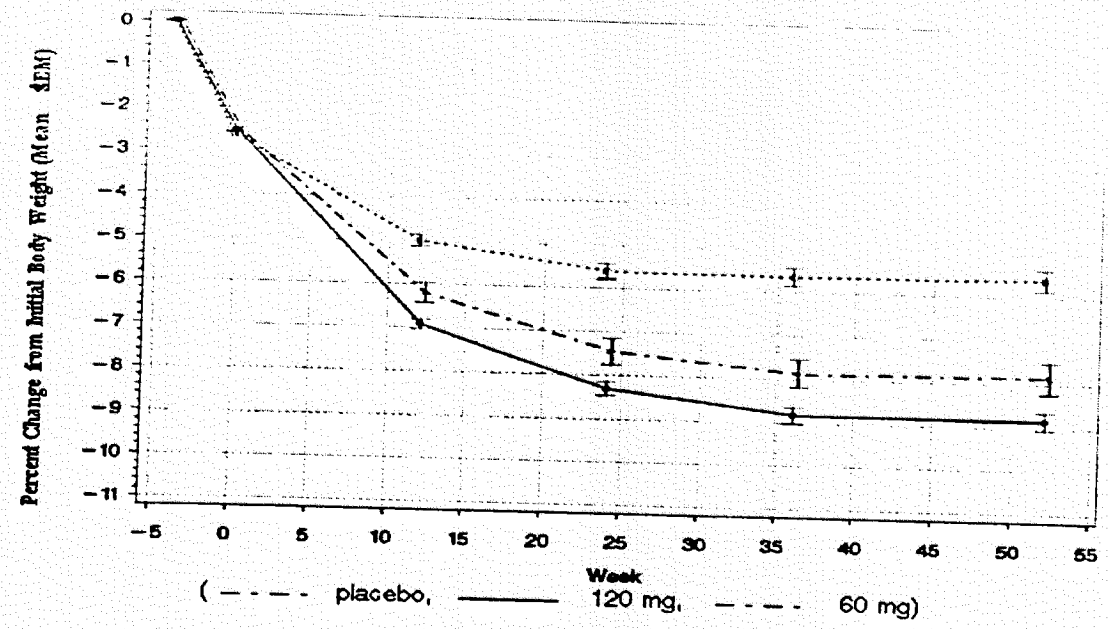
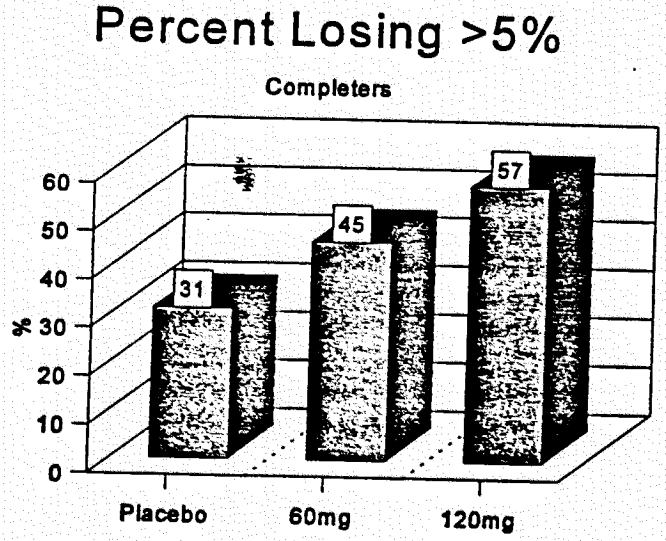
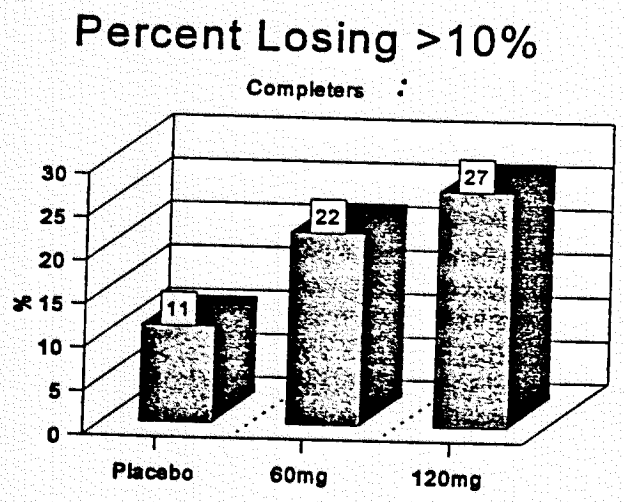


In terms of absolute weight loss from baseline, the difference from placebo was -2.56 kg for the 60mg group ($p<0.001$) and -3.21 for the 120mg group ($p<0.001$). The difference between the 60mg and 120mg groups was -0.57 kg ($p=0.1$). In the completers analysis the difference between the 60mg and 120mg groups was -1.05 kg ($p=0.03$).

Categorical Analysis

A statistically significantly ($p<0.01$) larger percentage of patients in the 60mg and 120mg groups compared with the placebo group lost >5% and >10% of baseline body weight as shown in the figures below. There were no significant differences between the two active-treatment groups.





<u>Lipoprotein Lipids</u> (ITT)

Active treatment vs placebo

The baseline values for triglycerides and VLDL-cholesterol were higher in the 60mg group than in the placebo and 120mg groups, and baseline Lp(a) values were lower in the 60mg group than in the placebo and 120mg groups; these differences were accounted for in the statistical model. In general, the levels of total, LDL, and HDL cholesterol increased from baseline to Week 52 in the placebo group, despite a reduction in body weight. Conversely, in the 60mg and 120mg groups, the levels of total and LDL cholesterol decreased and HDL increased slightly from baseline to Week 52. The mean differences from placebo in the 60mg and 120mg groups were -4% ($p<0.001$) and -6% ($p<0.001$), respectively for total cholesterol; -7% ($p<0.001$), and -8% ($p<0.001$), respectively for LDL-cholesterol; and -2% ($p=0.05$), and -3% ($p<0.001$), respectively for HDL-cholesterol. There were no significant differences between the orlistat groups compared to the placebo group in the mean changes from baseline to Week 52 in the levels of triglycerides, VLDL, or Lp(a).

Orlistat 120mg vs 60mg

Following 52 weeks of treatment, the changes in the levels of total cholesterol were statistically significantly different between the 120mg and 60mg groups, although the magnitude of the difference was only -1.8%. As for the levels of LDL-C, the difference between the two active-treatment groups was significant in the completers dataset only ($p<0.03$). However, again, the magnitude of the difference was only -3.4%. The 60mg and 120mg groups did not differ significantly from one another with respect to the changes in the levels of HDL-C. There were no significant differences between the two groups in the changes from baseline in levels of triglyceride, VLDL, or Lp(a).

Subgroup Analysis

In as subgroup analysis of patients with a baseline LDL-C level >3.36 mmol/L (>130mg/dl), the patients in the 120mg group had an 8% reduction in LDL-C relative to the change in the placebo group ($p<0.001$); there was no difference between the orlistat 60mg and 120mg groups however. In addition, there were no differences between placebo and orlistat groups in the changes in HDL-C or triglyceride levels in the subgroups with low baseline levels of HDL-C or elevated levels of triglycerides.

Blood Pressure (IVT)

Active Treatment vs Placebo

Systolic blood pressure increased from baseline to Week 52 by 0.6 mmHg in the placebo group and decreased by -0.9 mmHg in the 60mg group (p=ns vs placebo) and by -1.0 mmHg in the 120mg group (p=0.02, vs placebo). Diastolic blood pressure increased from baseline to Week 52 by 0.5 mmHg in the placebo group and decreased by -1.5 mmHg in the 60mg group (p=0.01 vs placebo) and by -1.2 mmHg in the 120mg group ($p<0.001$ vs placebo).

Orlistat 120mg vs 60mg

There were no significant differences between the two active-dose groups in the changes in levels of systolic or diastolic blood pressure.

Subgroup Analysis

Among the patients with a baseline diastolic blood pressure >90 mmHg there were no significant differences between the placebo and orlistat groups in the change in diastolic blood pressure from baseline to Week 52. Among patients with a baseline systolic blood pressure >140 mmHg and a diastolic blood pressure <90 mmHg, there was a -7.0 mmHg difference ($p<0.05$) between the placebo and 120mg orlistat groups in the change from baseline to Week 52 in systolic blood pressure.

Fasting Glucose (ITT)

The difference in the change in fasting glucose levels from baseline to Week 52 between the placebo and 60mg groups was -0.10 mmol/L (1.8 mg/dl) ($p=0.003$) and between the placebo and 120mg groups it was -0.07 mmol/L (1.3 mg/dl) ($p=0.001$), both in favor of orlistat treatment. The changes in fasting glucose levels did not differ significantly between the two active-treatment groups.

Fasting Insulin (ITT)

Only the non-US studies (120mg orlistat only) measured fasting insulin levels at baseline and Week 52. At the completion of the 52-week treatment period the fasting insulin levels were reduced relative to baseline in both the placebo and 120mg groups. The insulin levels in the 120mg group were reduced relative to placebo by -10.0 pmol/L ($p=0.002$).

OGTT Parameters (ITT)

The reduction in the glucose AUC in the 120mg group relative to the placebo group was -42 mmol/L•min ($p<0.001$). The reduction in the insulin AUC in the 120mg group relative to the placeob group was -8010 pmol/L•min ($p<0.001$). And the reduction in the C-peptide AUC in the 60mg and 120mg groups relative to placebo were -24nmol/L•min ($p=0.008$) and -15 nmol/L•min ($p=0.01$), respectively.

Insulin Resistance Index

The Sponsor has defined insulin resistance as the product of the glucose concentration x the insulin concentration/ 22.5 (Insulin Resistance = glucose x insulin/22.5). This equation was cited by Duncan et al. as a simple means to estimate insulin resistance in a short correspondence published in the July 8, 1995 issue of *The Lancet*. Until this technique is validated in a large sample of patients using glucose clamps, it seems premature to make too much of these data. With this caveat in mind, the change in the insulin resistance index was 0.51lower in the 120mg group relative to the placebo group ($p=0.003$). There was no significant difference in the change in the insulin resistance index between the 60mg and 120mg groups.

Waist Circumference

Waist circumference is a crude index of visceral fat content. All groups had a reduction in mean waist circumference. The difference between the 120mg and the placebo group in the reduction in waist circumference was -2.22 cm ($p<0.001$). And the difference between the 60mg group and the placebo group in the reduction in waist circumference was -1.1 cm ($p=0.02$).

Quality of Life

Overweight Distress - There was a statistically significant ($p=0.003$) difference, in favor of orlistat, between placebo and 120mg treatment in the mean change in overweight distress, but not between placebo and 60mg treatment.

Depression - There was no statistically significant (p=0.07) difference between placebo and 120mg treatment in the mean change in depression. In the patients with a baseline depression score of ≥ 16, there was a statistically significant (p=0.04) difference between placebo and 120mg treatment in the change in the mean change in depression following 1 year of treatment.

Satisfaction with Treatment Index - There were statistically significant (p<0.05) differences between the placebo and the 60mg and 120mg groups for the satisfaction with treatment index.

There were no significant differences between the 120mg and the 60mg groups in any of the above parameters. It should be noted that while there were statistically significant differences between the active-treatment and placebo groups, the clinical relevance of these relative changes is difficult to assess.

One-Year Data - The Prevention of Weight Regain

Three studies, NM14302, NM14185, and BM14119C included assessments of the effect of treatment with orlistat on regained weight following a change from a hypo to a eucaloric diet. Because of the unique study design of NM14302, the results from that study were not pooled with the results from studies NM14185 and BM14119C. Therefore, the following review is limited to the pooled data from studies NM14185 and BM 14119C.

Demographics

At the start of the second year of double-blind treatment the placebo (n=274), 60mg (n=145), and 120mg (n=280) groups were well matched for demographic characteristics. The mean age was 46 years (range 20-76 yrs), approximately 80% of the subjects were female, 85-90% of the patients were Caucasian, and the mean BMI was 33 kg/m^2.

Percent Regain of Lost Weight (orlistat 120mg vs placebo, ITT)

The placebo group had a mean percent regain of lost weight of 57%, while the 120mg group regained 31% (p<0.001).

Frequency Distribution of Body Weight Regain (ITT)

For those subjects that lost at least 5% of initial body weight during the first year of treatment , 73% of the subjects in the 120mg group regained less than less than or equal to 50% of initial body weight during the second year of treatmet, compared with 60% and 47% of the subjects in the 60mg and placebo groups, respectively. The difference between the 120mg vs the placebo groups was significant at p<0.001. All other comparisons were not statistically significant.

Secondary Efficacy Parameters

Levels of total and LDL cholesterol increased in all three groups during the treatment period. The increases in the 120mg group were approximately 5% lower than the placebo values for both total and LDL cholesterol (p<0.001). The levels of HDL-C increased in all groups; the increase was approximately 3% lower in the 120mg group compared to the placebo group (p=0.03). The changes in the levels of triglyceride were not significantly different between the 120mg and placebo groups.

Both systolic and diastolic blood pressure increased in the placebo, 60mg, and 120mg groups during the treatment period. The increases were small, on the order of 1-3 mmHg, and there were no significant differences among the groups in the magnitude of the changes in systolic or diastolic blood pressure.

The levels of fasting glucose increased in all three groups. The magnitude of the difference between the placebo and 120mg groups was -0.11 mmol/L (p=0.005) in favor of the 120mg group. Fasting insulin level increased in the placebo group, whereas it decreased in the 60mg and 120mg groups. The magnitude of the difference between the placebo and the 120mg groups in the change from baseline in fasting insulin was -9.32 pmol/L (p=0.02) in favor of the orlistat group.

Two-Year Data

The effect of orlistat on body weight during 104 weeks of double-blind treatment in obese patients was evaluated in studies NM14185, NM14161 (US), BM14119C, and BM14149 (non-US).

Demographics

At baseline there were 606 patients in the 120mg group, 328 subjects in the 60mg group, and 516 patients in the placebo group. With the exception of the gender distribution, the three groups were well matched at baseline. There were 81%, 76%, and 84% females in the 120mg, 60mg, and placebo groups, respectively (p=0.01). The mean age was 45 years (range 18-78 yrs), approximately 94% of the subjects were Caucasian, the mean body weight was 96.5 kg, and the mean BMI was 35 kg/m^2.

Baseline Risk Factors

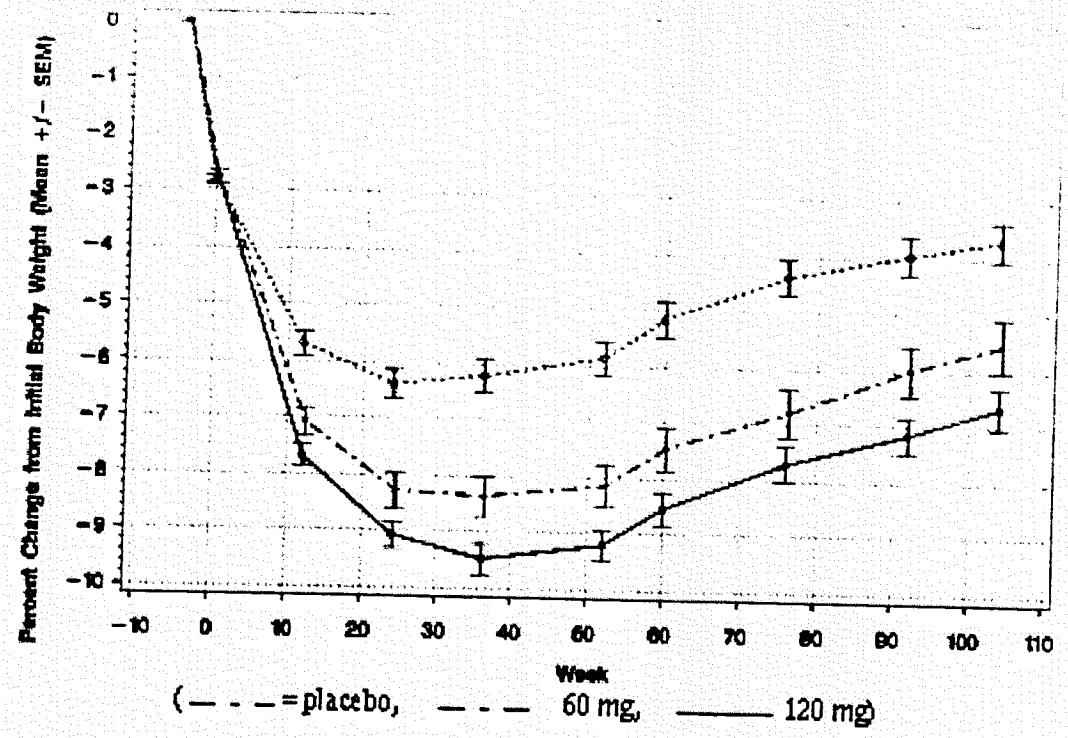
The following table illustrates the baseline risk factors for the 3 groups. While some of the baseline values were statistically significantly different among groups, the absolute differences were small. More importantly, baseline differences were accounted for statistically.

	Orlistat 120mg	Orlistat 60mg	Placebo	P value
SBP (mmHg)	123	126	124	0.04
DBP (mmHg)	79	80	80	0.3
TC (mmol/L)	5.22	5.17	5.23	0.7
LDL (mmol/L)	3.38	3.27	3.41	0.07
HDL (mmol/L)	1.17	1.16	1.17	0.7
TG (mmol/L)	1.58	1.72	1.52	0.04
Fas Gluc (mmol/L)	5.65	5.61	5.67	0.6
Fas Ins (pmol/L)	89	95	96	0.4

Weight Loss

Analysis of the Means

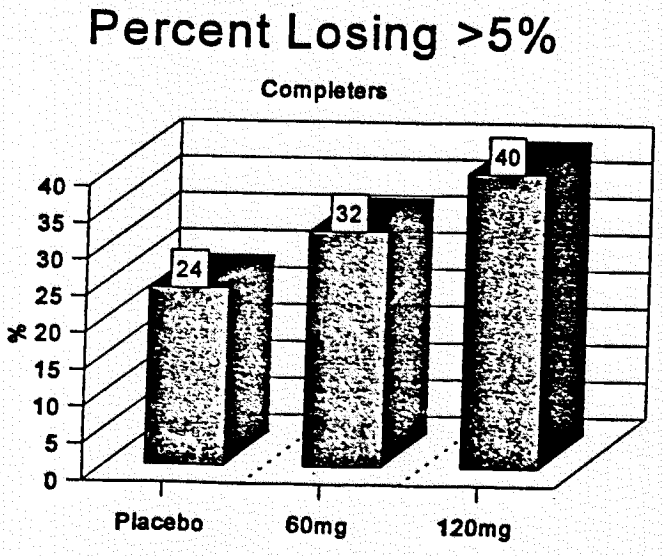
The figure below illustrates the mean percent change in body weight from Week -4 to Week 104 (ITT). All three groups lost nearly 3% of initial weight during the four-week lead-in period. It is evident from the graph that weight loss slowed at Week 40 and then increased up to the completion of the study. After Week 20 the difference in weight loss between the placebo and 120mg groups — approximately 3% — remained fairly constant. Weight gain was evident after subjects were instructed, at the start of the second year, to consume a eucaloric diet.

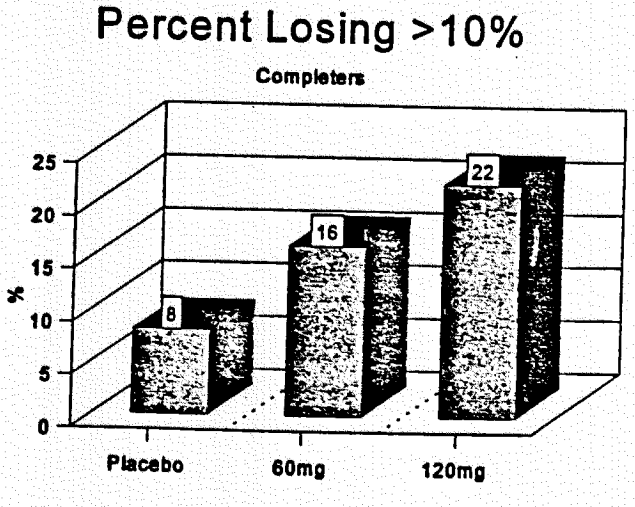


In terms of absolute weight loss, the difference from placebo was -2.42 kg for the 60mg group ($p<0.001$) and -2.93 kg for the 120mg group ($p<0.001$). The difference in weight loss between the 120mg and 60mg groups was not statistically significant.

Categorical Analysis

As shown in the figures below, compared to the placebo group, a significantly larger percentage of patients in the 60mg ($p=0.02$) and the 120mg groups ($p<0.01$) lost 5% of initial body weight following 104 weeks of treatment. Similarly, a larger percentage of patients in the 60mg ($p=0.004$) and the 120mg ($p<0.01$) groups lost greater than 10% of initial body weight compared to the placebo group following 2 years of treatment. There were no differences between the 60mg and the 120mg doses.





Lipoprotein Lipids (ITT)

Active treatment vs placebo

The baseline values for triglycerides and VLDL were higher in the 60mg group than in the placebo and 120mg groups and Lp(a) and Apo B values were higher in the 120mg group compared to the values in the other two groups. The baseline values for the other lipid parameters were similar among the groups. In the placebo group, the levels of total, LDL, and HDL cholesterol increased from baseline (Day 1) to Week 104. In contrast, in the active-treatment groups, the levels of total and LDL cholesterol decreased during the first 12 weeks of the double-blind phase, plataeued up to Week 52, and then tended to increase up to Week 104. The mean percent differences from placebo in the 60mg and 120mg groups were -4% ($p=0.002$) and -5% ($p<0.001$), respectively for total cholesterol; and -7% ($p<0.001$), respectively for LDL-C. The difference in the mean change from baseline in Lp(a) levels between placebo and 120mg treatment was -15.4 mmol/L ($p=0.02$) in favor of the orlistat group; the difference between placebo and 60mg treatment was not significant. There were no significant differences between the orlistat groups compared to the placebo group in the mean changes from baseline to Week 104 in triglycerides or VLDL.

Subgroup Analysis

In a subgroup analysis of subjects with a baseline LDL-C value >3.36 mmol/L (>130mg/dl), patients treated with 120mg or 60mg tid had a mean percent difference from baseline of -3% when compared with placebo treatment ($p<0.001$). There were no significant differences, however, between the orlistat groups and the placebo group in the changes in HDL-C or triglyceride levels in patients with low baseline values of HDL-C or elevated levels of triglycerides.

Blood Pressure (ITT)

Active Treatment vs Placebo

The difference from placebo in the change in mean diastolic blood pressure was -1.1 mmHg ($p<0.03$) for the 120mg group; the difference between placebo and 60mg treatment was not statistically significant. The mean difference from placebo for systolic blood pressure was not statistically significant for either of the orlistat treatment groups.

Subgroup Analysis

There were no significant changes in systolic or diastolic blood pressure in the orlistat groups compared to the placebo group when the subgroups with elevated baseline systolic (≥140 mmHg) or diastolic (≥90 mmHg) blood pressure were analyzed.

Fasting Glucose (ITT)

The mean difference between placebo and 120mg for the change in fasting glucose from baseline to Week 104 was -0.11 mmol/L ($p=0.004$) in favor of orlistat. There were no significant differences between the 60mg group and the placebo or 120mg groups.

Fasting Insulin (ITT)

The mean differences between placebo and 60mg and 120mg for the change in fasting insulin from baseline to Week 104 were -12.4 pmol/L ($p=0.04$) and -15.4 pmol/L ($p<0.001$), respectively. There were no significant differences between the two orlistat groups. In the subgroups with baseline fasting insulin

levels ≥90 or 120 pmol/L the reduction in insulin from baseline to Week 104 was significantly greater in the orlistat 120mg group compared to the placebo group.

OGTT Parameters

The OGTTs were administered in studies BM14149, NM14185, and NM14161. The only parameter that was significantly different between the orlistat and placebo groups was the change in the insulin AUC. The mean difference between placebo and 120mg for the change in insulin AUC from baseline to Week 104 was -5580 pmol/L•min (p=0.03).

Insulin Resistance Index

The mean difference from placebo for insulin resistance was -0.84 (p<0.001) for patients treated with 120mg. There were no significant differences between placebo and 60mg or between the two orlistat groups.

Waist Circumference

The reduction in waist circumference was -1.74 cm greater in the 120mg group compared to the placebo group (p<0.001). There were no significant differences between the placebo and 60mg groups or between the two orlistat groups.

Subgroup Analyses of Efficacy

Efficacy (change in body weight from baseline) was examined in several subgroups. These groups included age (<40, >40 but <60, >60), gender, race (Caucasian, Black, Hispanic, other), and BMI (<30, >30<35, >35).

There was no significant age or BMI effect for weight loss efficacy during Year 1. Race and gender, however, were significant. The mean placebo-subtracted weight loss in females was 3.3 kg and 2.6 kg in males. The mean placebo-subtracted weight loss was 3.4 kg in Caucasians, 2.1 kg in Blacks, and 5.1 kg in Hispanics. No significant subgroup effects were observed for Year 2.

Summary of the Changes in Comorbidities by Degree of Weight Loss

The table below summarizes the changes from baseline to Year 1 in the common obesity-related comorbidities for three categories of weight loss: <5%, ≥5% to <10%, and ≥10%.

Change in Risk Factor from Baseline to Year 1 by Degree of Weight Loss (Completers)

Risk Factor	<5%		≥5% to <10%		≥10%	
	Orlistat	Placebo	Orlistat	Placebo	Orlistat	Placebo
ΔTC	0%††	5%	-2%†††	5%	-5%††	1%
ΔLDL	-2%†††	6%	-5%†††	6%	-7%†	-1%
ΔHDL	5%†††	10%	12%†	16%	17%†	23%
ΔTG	14%†	9%	-2%	-4%	-14%	-18%
ΔSBP (mmHg)	2	2	-3	-1	-2	-4

Risk Factor	<5%		≥5% to <10%		≥10%	
	Orlistat	Placebo	Orlistat	Placebo	Orlistat	Placebo
ΔDBP(mmHg)	1	1	-2†	0	-3	-2
ΔG_0 (mg/dl)	0.5	2	-1	-3	-4	-3
ΔIRI (pmol/L)	7	11	-12	-11	-22	-15

†p<0.05, ††p<0.01, †††p<0.001 orlistat vs placebo
G_0=fasting glucose, IRI=fasting insulin

On balance, these data indicate progressive improvements in the comorbid risk factors with increasing amounts of weight loss in the orlistat-treated patients.

EFFECT OF ORLISTAT ON BODY COMPOSITION

The effect of orlistat on body composition was assessed in a subgroup of 240 patients from studies BM14119C and BM14149. The techniques used to measure body composition included DEXA, TBK, anthropometric measurements, and bioelectrical impedance. The majority of the data are the result of anthropometric measurements derived from formulas previously calibrated against CT measurements. Changes as assessed by DEXA were the second most frequent measurements reported. And total body potassium was determined in a small number of patients and only for the first year of treatment.

With few exceptions, there was good agreement among the various methods used to measure body composition. Weight loss associated with orlistat treatment was largely due to a reduction in fat mass. Although loss of fat-free mass occurred in both placebo and orlistat groups following weight loss, the difference between the active-treatment and placebo groups was not clinically significant. These results are in agreement with the expected changes associated with diet-induced weight loss.

10. OVERVIEW OF SAFETY

10.1.1 Exposure

A total of 7072 patients have participated in orlistat's global development program, with 4852 receiving at least one dose of orlistat. Approximately 2847 subjects participated in the phase III studies; 2153 of these patients received at least 1 year of treatment with orlistat and 884 received at least 2 years of treatment. The orlistat dose with the greatest exposure was 120mg; approximately 2038 subjects received 120mg of orlistat for 1 year and 1068 received this dose for over 1 year. A total of 510 patients were treated with 120mg for 2 years.

10.1.2 Demographics

The mean age of the participants was 45 years (range 18-78 yrs), the majority (80%) were female and Caucasian (91%), and the average BMI was 35 kg/m^2 (range 26-47 kg/m^2).

10.1.3 Disposition of Patients

The table below lists the reasons for premature withdrawal during Year 1. Adverse events were the most common reason for premature withdrawal in the orlistat groups, while lost to follow-up was the most common reason for premature withdrawal in the placebo group. A similar pattern was observed during Year 2.

Reason for Dropout	Placebo n=1466	120mg n=1913
Adverse event	4.9%	8.8%
Treatment failure	2.6%	1.0%
Early improvement	0.1%	0.0%
Refused treatment	3.2%	1.5%
Died during study	0.0%	0.1%
Lost to follow-up	9.8%	7.7%
Did not cooperate	6.5%	3.8%
Protocol violation	2.2%	2.0%
Entry violation	0.2%	0.3%
Administrative	5.8%	4.0%
Total no. of withdrawal	35.3%	29.1%

10.2.1 Deaths

There were seven deaths in the phase III studies as shown in the table below.

Treatment	Sex	Age at Death	Day of Death	Cause of Death
Diet lead-in	F	40	-107	MVA
Lead-in	F	48	-8	MVA
Placebo	F	36	637	MVA
120mg/Placebo	F	40	748	MVA
60mg	M	61	449	MI
120mg	M	60	707	Cardiac Arrest
120mg	M	55	317	MI

A review of the summaries of the above deaths does not raise suspicion that orlistat was a causative agent. Four of the subjects were not receiving drug at the time of death and two of the three patients who died from acute myocardial infarction had significant histories of cardiac disease.

10.2.2 Serious Adverse Events (SAEs)

Serious adverse events were defined as those which clearly presented or could be expected to present a threat to the well being of the patient. Specifically, this included any event which was fatal or life threatening, permanently disabling, required in-patient hospitalization, or prolongation of hospitalization, caused a congenital anomaly, caused a cancer, or was an overdose.

Approximately 6% of the patients in the placebo and orlistat 30mg, 60mg, and 120mg groups, respectively, reported serious adverse events during Year 1. For patients who received 2 full years of

respectively. During both time periods the most commonly reported SAEs were from the following body systems: reproductive system-female, body as a whole, and gastrointestinal.

Reproductive disorders, female: The overall incidence of SAEs in this category was similar among the placebo and orlistat groups. Approximately 3% of patients in the placebo and orlistat 120mg groups reported one or more SAEs during 2 full years of treatment. Of note, 11 cases of breast cancer were reported; 10 cases occurred in patients randomized to orlistat. Although the number of patients randomized to orlistat was twice that of patients randomized to placebo, the incidence of breast cancer is much higher in the active-treatment groups. Thus, a detailed account of the cases follows in tabular and text form.

ID #	Age	Race	Dose	Duration of Tx	Menopausal Status	ERT	Histology
[redacted]	52	Cauc	120mg	665 days	Post	Yes	Intraductal Lobular
	46	Cauc	120mg	32 days	Pre	No	?
	61	Cauc	120mg	436 days	Post	No	?
	54	Cauc	120mg	709 days	Post	Yes	Infiltrating Ductal
	57	Cauc	120mg	170 days	Post	Yes	Lobular Carcinoma in Situ
	52	Cauc	120mg	55 days	?	No	Infiltrating Lobular
	54	Cauc	Placebo	443 days	Surg. Sterile	Yes	Intraductal
	53	Cauc	120mg	191 days	Post	No	lobular
	47	Cauc	60mg	36 days	Surg. Sterile	No	Ductal Invasive
	55	Cauc	120mg	365 days	Surg. Sterile	No	Ductal
	58	Cauc	120mg	344 days	Post	No	?

To invoke orlistat as a causative agent in these cases of breast cancer one would like to establish biological plausibility. Several factors argue against such plausibility. First, negligible amounts of the drug are absorbed into the systemic circulation. This was verified in patient [redacted] (the only patient in a study that measured plasma drug levels) who had no detectable levels of intact orlistat following six and 24 months of dosing. Second, five of the cases were diagnosed within six months of entering the studies. The absence of carcinogenicity in the long-term animal studies makes it unlikely that, in humans, the drug would initiate or promote breast cancer within six months. And third, in all cases, the plasma levels of vitamin E, and β-carotene — nutrients reported to be associated with a lower risk of breast cancer in some epidemiological studies — remained within normal limits throughout the study.

Orlistat, in all probability, was not a causative agent in these cancers. Yet, because breast cancer is a common source of morbidity and mortality in women — a principal target population for orlistat — a comprehensive evaluation of these cases in warranted. The Sponsor is currently conducting a detailed review of these breast cancer cases.

Body as a whole: Approximately 0.8% to 3.0% of patients reported SAEs in this category. The incidences were not markedly different among the placebo and active-treatment groups. Furthermore, there did not appear to a dose-related effect in the orlistat groups. The majority of the reported cases within this body system were surgical procedures. The most common procedures were hysterectomy (six

Gastrointestinal: There were relatively few SAEs reported in this category and the incidences were similar for the placebo and orlistat groups: 0.5% to 1.3% during Year 1 and 1.5% to 3.0% during 2 years of treatment. One case of a GI neoplasm was reported in the placebo group and in the orlistat 60mg group. Importantly, less than 1% of patients reported SAEs in the liver of biliary systems and the incidences were not significantly different between the placebo and orlistat groups.

10.3.1 Adverse Drug Reactions (ADRs)

The table below summarizes the body system disorders in which at least one treatment group reported an ADR with an incidence of greater than 5%. The most commonly reported ADRs occurred in the GI system in which the incidence was higher for the orlistat groups compared to the placebo group.

Body System Disorder	One Year of Treatment		Two Years of Treatment	
	Placebo n=1466	120mg n=1913	Placebo n=524	120mg n=613
GI system	57%	80%	68%	82%
Respiratory system	40%	46%	61%	60%
Resistance Mech	39%	42%	55%	56%
Musc-Skel System	39%	39%	60%	52%
Nervous System	34%	36%	49%	44%
Body as a Whole	21%	23%	33%	30%
Skin	18%	19%	31%	28%
Female-Reproduct	14%	17%	26%	25%
Urinary System	9%	10%	15%	16%
Psychiatric	7%	9%	13%	14%
Met and Nutr	7%	6%	4%	2%
Hearing	5%	5%	8%	10%
CV	6%	5%	11%	9%
Vision	4%	4%	6%	5%

The Sponsor defined an adverse event as potentially treatment related if the difference in incidence between placebo and drug was at least 3%. Using this definition and excluding GI ADRs, upper respiratory tract infection, influenza syndrome, and headache were reported in active-treated patients with an incidence of approximately 3-4% higher than placebo. There did not appear to be a dose-related increase in the incidences of these events.

The increased frequency of reported GI ADRs warrants a more detailed review of these events. Seven GI ADRs were identified as being almost exclusively related to orlistat treatment, and occurred with an incidence rate 5% higher and in more than twice as many patients in the 120mg group than in the placebo group (see table below). These ADRs include: oily spotting, flatus with discharge, fecal urgency, fatty/oily stool, oily evacuation, increased defecation, and fecal incontinence.

GI System Disorder	One Year of Treatment		Two Years of Treatment	
	Placebo n=1466	120mg n=1913	Placebo n=524	120mg n=613
Oily Spotting	1%	27%	1%	22%
Flatus with Discharge	1%	24%	1%	17%
Fecal Urgency	7%	22%	7%	22%
Abdominal Pain	16%	21%	245	23%
Fatty/Oily Stool	3%	20%	55	26%
Flatulence	13%	16%	12%	15%
Liquid Stool	11%	16%	18%	19%
Oily Evacuation	1%	12%	1%	10%
Increased Defecation	4%	115	5%	13%
Soft Stools	7%	9%	10%	13%
Nausea	7%	8%	9%	11%
Fecal Incontinence	1%	8%	1%	7%

A larger percentage of patients who received 120mg orlistat compared with placebo experienced two episodes of the GI adverse events listed in the table above. It appeared that the incidence of GI ADRs decreased during the second year of the study suggesting that the intestinal tract may, over time, adjust to effects of orlistat. However, the possibility of bias due to drop outs — those subjects who experienced GI adverse events during the first year dropped out of the study — cannot be dismissed. Although the incidence was only 1.3%, it should be recognized that treatment with the 120mg dose of orlistat was associated with an increased incidence of discolored feces compared with placebo.

As shown in the table below many of the patients reporting GI ADRs that were thought to be related to, or increased with, orlistat treatment had their first occurrence within the first 12 weeks of treatment. Of note, however, was the increased occurrence of abdominal pain and liquid stools over time.

TIME TO EVENT

Adverse Event	120mg Orlistat			
	≤ 1 Wk	≤ 12 Wk	≤ 48 Wk	≥ 96 Wk
Oily Spotting	11%	20%	25%	26%
Flatus with Discharge	11%	19%	23%	23%
Fecal Urgency	9%	17%	21%	22%
Oily Stool	7%	15%	19%	22%
Oily Evacuation	5%	9%	12%	13%
Increased Defecation	4%	8%	11%	12%

Adverse Event	120mg Orlistat			
	≤ 1 Wk	≤ 12 Wk	≤ 48 Wk	≥ 96 Wk
Fecal Incontinence	2%	5%	8%	9%
Abdominal Pain	4%	13%	19%	24%
Liquid Stools	3%	9%	15%	19%

In most cases, a majority of the GI ADRs events in the orlistat treatment group lasted for less than 1 week (see table below). Although some of the events (flatus with discharge, fecal urgency) lasted beyond 24 weeks.

DURATION OF EVENTS

Adverse Event	120mg Orlistat n=1913			
	≤ 1 Wk	>1≤ 4 Wk	> 4 ≤ 24 Wk	> 24 ≤ 96 Wk
Oily Spotting	50%	15%	19%	13%
Flatus with Discharge	38%	15%	24%	18%
Fecal Urgency	33%	18%	26%	18%
Oily Stool	45%	15%	21%	14%
Oily Evacuation	46%	19%	20%	13%
Increased Defecation	39%	24%	21%	12%
Fecal Incontinence	70%	14%	12%	4%
Abdominal Pain	56%	17%	17%	6%
Liquid Stools	74%	14%	9%	25

Subgroup Analysis of GI Adverse Events

The incidence of GI adverse events during Year 1 was examined in several subgroups. These groups included age (<40, >40<60, >60), gender, race (Caucasian and Black), and BMI (<30, >30<35, >35). Because the number of statistical comparisons among groups was so large only those comparisons with a p value of 0.01 or less will be considered here. Several adverse events were reported more frequently by Blacks compared with Caucasians. These include fecal urgency, flatus with discharge, and oily spotting. Other subgroup comparisons were not significant.

10.3.2 **Laboratory Parameters**

Because orlistat has a very low bioavailability one would not anticipate that use of the drug would be associated with clinically significant laboratory or urine abnormalities. Indeed, this is the case. Evaluable laboratory tests were obtained on approximately 1800 patients who received 120mg tid of orlistat for one year and approximately 600 patients who received this treatment for two years. Although the changes in some laboratory and urine parameters led to statistically significantly differences between the orlistat 120mg and placebo groups, none of the changes were large and they were not of clinical significance.