CENTER FOR DRUG EVALUATION AND RESEARCH

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MEDICAL REVIEW(S)

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MEDICAL OFFICER'S REVIEW OF CLINICAL DATA
for ORLISTAT

Sponsor: Hoffman-La Roche Inc.
Drug: Orlistat (Xenical)
Category: Lipase Inhibitor
Indication: Weight Loss

Contents **Page(s)**

cc. NDA 20-766

/S/ [redacted]
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Animal Toxicology (summarized from Pharmacology review)

Some notable findings in studies of dogs and/or rats treated with orlistat include hypertriglyceridemia, hyperbilirubinemia, decreased liver concentrations of vitamins E and A, and in some cases, reduced plasma levels of vitamins A, E, and D.

There was no evidence of mutagenic potential in several assay systems.

In rat studies employing doses of orlistat at >29 times the human exposure, there was no evidence of carcinogenic potential. In studies of mice using doses at >22 times human exposure there were two hemangiosarcomas detected in high-dose, orlistat-treated animals and none in the placebo-treated animals; this was statistically significant. There was no finding of increased breast carcinomas in orlistat- vs. placebo-treated animals.

Description of Clinical Data

The Sponsor conducted seven primary studies: six in obese patients without a history of drug-treated NIDDM and one in obese patients with NIDDM. Study BM14119C was a 2-year, placebo-controlled study of weight loss and maintenance (year 1) and prevention of weight regain (year 2). Active treatment consisted of 120mg tid of orlistat. Study NM14185 was a 2-year, placebo-controlled study of weight loss and maintenance (year 1) and prevention of weight regain (year 2). Active treatment consisted of 60 or 120mg tid. Studies BM14149 and NM14161 were 2-year, placebo-controlled studies employing 60 or 120mg tid of orlistat. Study BM1419B was a 1-year, placebo-controlled trial comparing placebo to 120mg tid of orlistat along with regular diet counseling. Study NM14302 was a 18-month, placebo-controlled trial in which all subjects received six months of diet therapy followed by one year of either placebo or 30mg, 60mg, or 120mg of orlistat tid. And finally, study NM14336 was a placebo-controlled, one-year study of placebo vs 120mg tid of orlistat in obese patients with NIDDM.

Overview of Efficacy

Because five of the seven phase III studies employed similar study designs and include a homogeneous patient population it is reasonable to pool the data to obtain a more accurate assessment of orlistat's efficacy and safety. The data that are subsequently reviewed represent pooled data from studies BM14119B, BM14119C, NM14161, BM14149, and NM14185.

In this section of the review both intent-to-treat (ITT) and completers datasets were used to assess the effect of orlistat and placebo on weight loss and comorbidities. The ITT population was defined as randomized patients who received at least one dose of study medication and had body weight measurements before and after randomization. Completers were defined as randomized patients who 1) did not have any protocol violations that might affect efficacy evaluation 2) completed at least 50 weeks or 102 weeks of treatment for one-year or two-year analyses, respectively and 3) had efficacy measurements inside the corresponding time window. These definitions are reasonable. In general, the results of the ITT and completers analyses were similar; therefore, for ease of presentation most of the data presented in this overview of efficacy will be from the ITT analyses.

One-Year Data

One-Year Data

Demographics

At baseline there were 1561 patients in the 120mg group, 452 in the 60mg group, and 1119 patients in the placebo group. By and large the groups were well matched. Approximately 81% of the subjects were female, the mean age was 44 years (range 18-78 yrs), nearly 92% were Caucasian, the mean body weight was 97 kg, and the average BMI equaled 35 kg/m^2.

Baseline Risk Factors

The following table illustrates the baseline risk factors for the three groups. In general, this population of obese patients was normotensive and did not have exceedingly high total and LDL cholesterol levels. While some of the baseline values were statistically significantly different among groups, the absolute differences were small. More importantly, the baseline values were included in the statistical model as covariates; thus, any differences at baseline were accounted for statistically.

BASELINE RISK FACTORS (means)

	Orlistat 120mg	Orlistat 60mg	Placebo	P value
SBP (mmHg)	123	125	124	0.01
DBP (mmHg)	79	80	79	0.2
TC (mmol/L)	5.10	5.21	5.21	0.02
LDL (mmol/L)	3.28	3.31	3.38	0.01
HDL (mmol/L)	1.17	1.17	1.16	0.8
TG (mmol/L)	1.54	1.71	1.55	0.007
Fas Gluc (mmol/L)	5.63	5.60	5.70	0.03
Fas Ins (pmol/L)	94	92	95	0.8

Dietary Intake Data

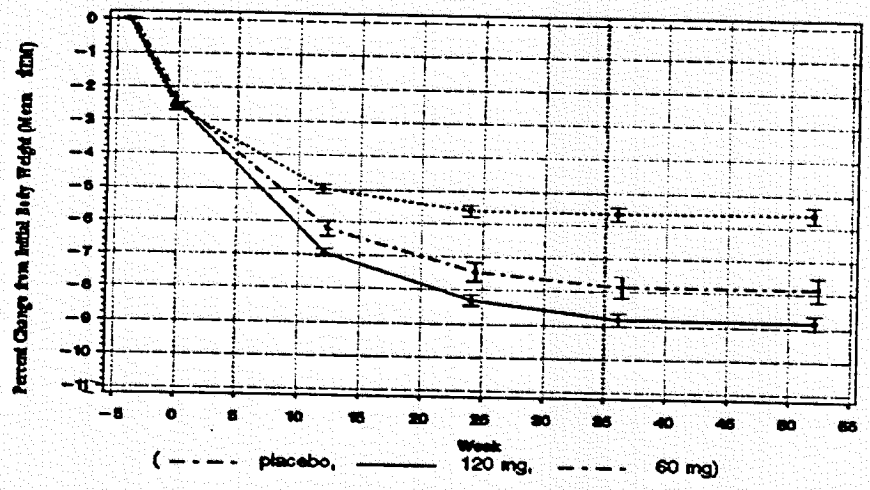
The daily intake of calories, fat, carbohydrate, and protein did not change significantly from baseline to Week 52 for the placebo or 120mg groups. There were statistically, but not clinically significant differences between the two groups for the change in the intake of some dietary parameters. For example, in the US studies the orlistat group had an increase in total daily calorie intake of 79 kcal when compared with placebo. When reviewing dietary intake data derived from patient records it should be kept in mind that this method is notoriously inaccurate.

Weight Loss (a reminder that initial body weight refers to Week -4 and baseline weight refers to Day 1

of double-blind treatment)

Analysis of the Means

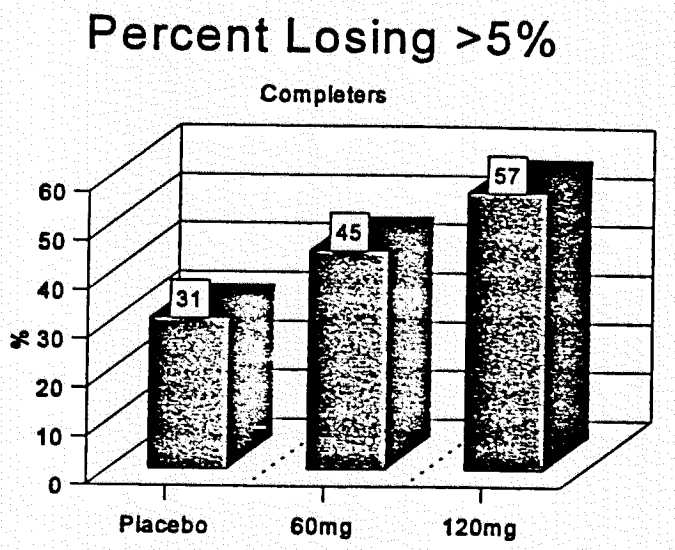
The figure below illustrates the mean percent change in body weight from Week -4 to Week 52 (ITT dataset). All three groups lost approximately 2.5% of initial body weight during the four-week lead-in period. While weight loss platued at Week 25 in the placebo group a steady state did not appear until Week 35 in the orlistat 120mg group. The placebo-subtracted mean percent weight loss from baseline to Week 52 was approximately 3% for the orlistat 120mg group.

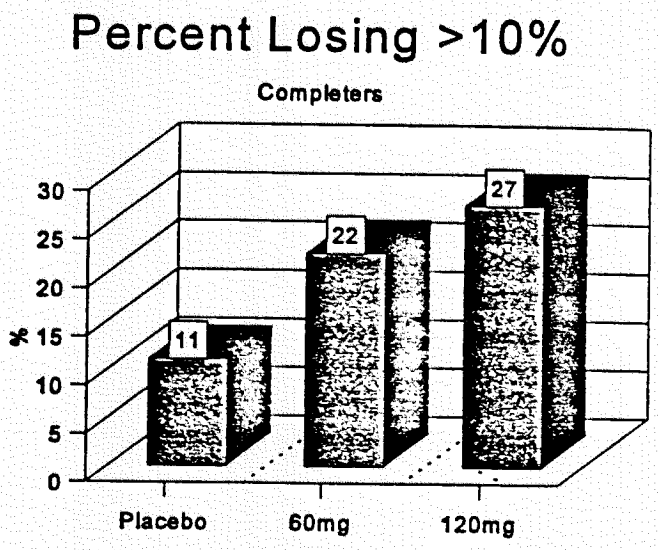


In terms of absolute weight loss from baseline, the difference from placebo was -2.56 kg for the 60mg group ($p<0.001$) and -3.21 for the 120mg group ($p<0.001$). The difference between the 60mg and 120mg groups was -0.57 kg ($p=0.1$). In the completers analysis the difference between the 60mg and 120mg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





Lipoprotein Lipids (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 (ITT)

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 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 favor of the orlistat group) 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 placebo 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 0.51 lower 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 changes is difficult to assess.

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

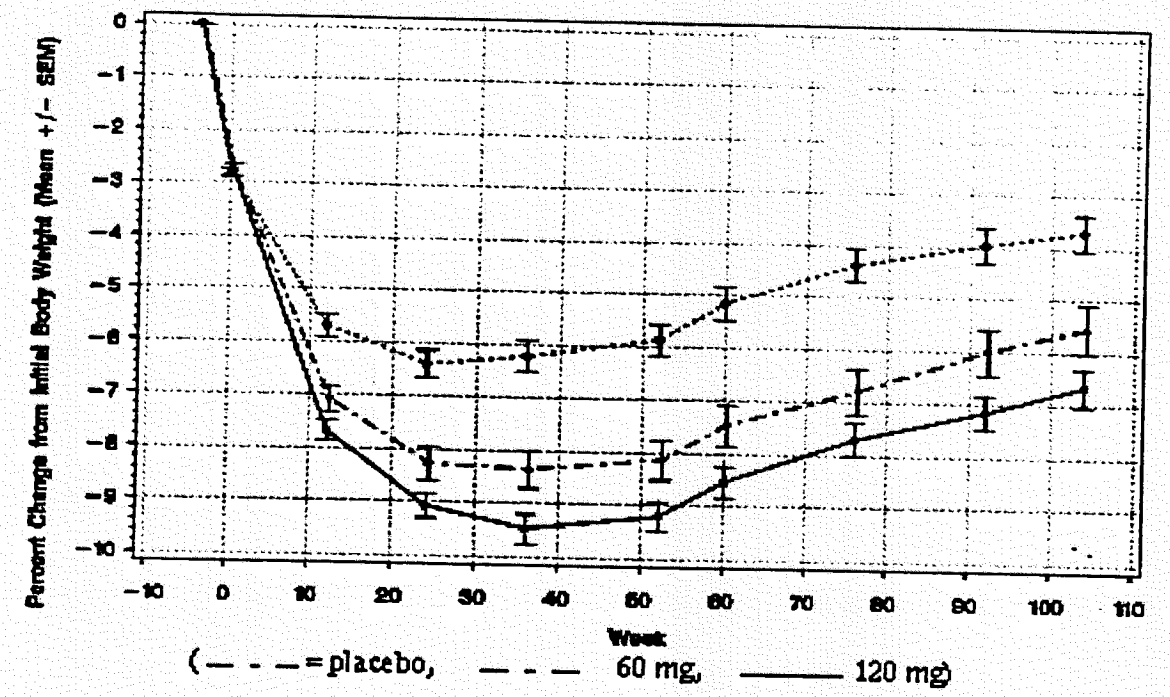
The following table illustrates the baseline risk factors for the 3 groups. While some of the baseline values were statistically significantly different among groups, the absolute differences were small. More importantly, baseline differences were accounted for statistically.

	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

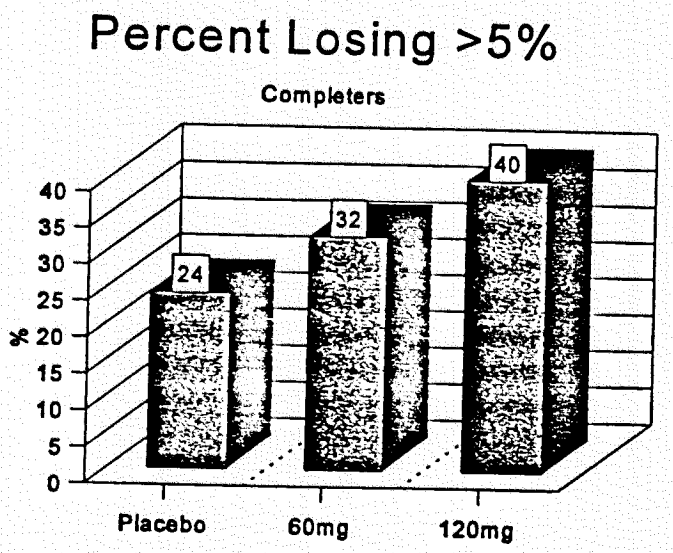
The figure below illustrates the mean percent change in body weight from Week -4 to Week 104 (ITT). All three groups lost nearly 3% of initial weight during the four-week lead-in period. It is evident from the graph that weight loss slowed at Week 40 and then increased up to the completion of the study. 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.

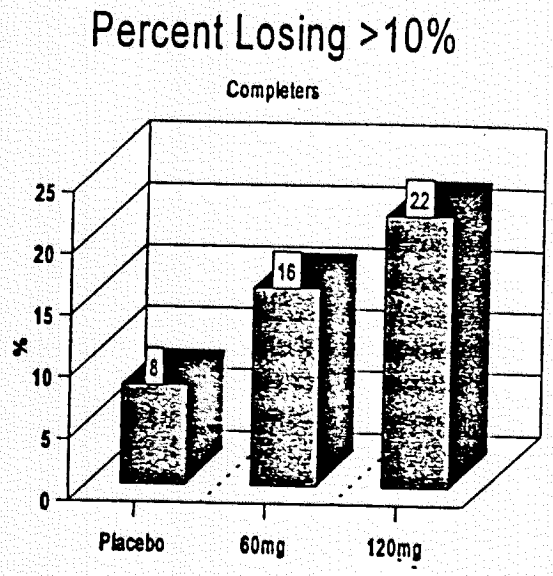


In terms of absolute weight loss, the difference from placebo was -2.42 kg for the 60mg group ($p<0.001$) and -2.93 kg for the 120mg group ($p<0.001$). The difference in weight loss between the 120mg and 60mg groups was not statistically significant.

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.