CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

NDA 20-766/S-019

Trade Name: Xenical Capsules

Generic Name: Orlistat

Sponsor: Hoffman LaRoche, Inc.

Approval Date: October 22, 2004

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APPLICATION NUMBER:

20-766/S-019

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APPLICATION NUMBER:

20-766/ S-019

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-766/S-019

Hoffman-LaRoche, Inc.
Attention: Margaret J. Jack
Program Director
340 Kingsland Street
Nutley, New Jersey, 07110-1199

Dear Ms. Jack:

Please refer to your supplemental new drug application dated December 22, 2004, received December 23, 2004, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Xenical (Orlistat) Capsules.

We acknowledge receipt of your submissions dated December 22, 2003, June 22, July 13, August, 17, October 21, 2004.

This supplemental new drug application provides for labeling changes in the package insert to include data from the Xendos Study.

We completed our review of this application, as amended. This application is approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text and with the minor editorial revisions listed below.

- Removed the unnecessary the footnote for Table 6 that reads, "orlistat - placebo"

The final printed labeling (FPL) must be identical, and include the minor editorial revisions indicated, to the enclosed labeling (text for the package insert). These revisions are terms of the approval of this application.

Please submit the FPL electronically according to the guidance for industry titled Providing Regulatory Submissions in Electronic Format – NDA. Please individually mount 15 of the copies on heavy-weight paper or similar material. For administrative purposes, this submissions should be designated "FPL for approved supplement NDA 20-766, S-019." Approval of this submission by FDA is not required before the labeling is used.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We note that you have fulfilled the pediatric study requirement for this application.

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Oluchi Elekwachi, PharmD, MPH, Regulatory Project Manager, at (301) 827-6381.

Sincerely,

{See appended electronic signature page}

David G. Orloff, MD
Director
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure: PI Approved Labeling

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

David Orloff
10/22/04 10:07:30 AM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-766/S-019

APPROVED LABELING

Roche

XENICAL®

(orlistat)

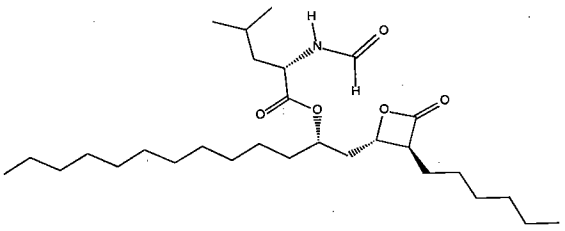
CAPSULES

R_x only

DESCRIPTION

XENICAL (orlistat) is a lipase inhibitor for obesity management that acts by inhibiting the absorption of dietary fats.

Orlistat is (S)-2-formylamino-4-methyl-pentanoic acid (S)-1-[[(2S, 3S)-3-hexyl-4-oxo-2-oxetanyl] methyl]-dodecyl ester. Its empirical formula is $C_{29}H_{53}NO_5$, and its molecular weight is 495.7. It is a single diastereomeric molecule that contains four chiral centers, with a negative optical rotation in ethanol at 529 nm. The structure is:



Orlistat is a white to off-white crystalline powder. Orlistat is practically insoluble in water, freely soluble in chloroform, and very soluble in methanol and ethanol. Orlistat has no pK_a within the physiological pH range.

XENICAL is available for oral administration in dark-blue, hard-gelatin capsules, with light-blue imprinting. Each capsule contains 120 mg of the active ingredient, orlistat. The capsules also contain the inactive ingredients microcrystalline cellulose, sodium starch glycolate, sodium lauryl sulfate, povidone, and talc. Each capsule shell contains gelatin, titanium dioxide, and FD&C Blue No.1, with printing of pharmaceutical glaze NF, titanium dioxide, and FD&C Blue No.1 aluminum lake.

CLINICAL PHARMACOLOGY

Mechanism of Action

Orlistat is a reversible inhibitor of lipases. It exerts its therapeutic activity in the lumen of the stomach and small intestine by forming a covalent bond with the active serine residue site of gastric and pancreatic lipases. The inactivated enzymes are thus unavailable to hydrolyze dietary fat in the form of triglycerides into absorbable free fatty acids and monoglycerides. As undigested triglycerides are not absorbed, the resulting caloric deficit may have a positive effect on weight control. Systemic absorption of the drug is therefore not needed for activity. At the recommended therapeutic dose of 120 mg three times a day, orlistat inhibits dietary fat absorption by approximately 30%.

Pharmacokinetics

Absorption

Systemic exposure to orlistat is minimal. Following oral dosing with 360 mg ^{14}C-orlistat, plasma radioactivity peaked at approximately 8 hours; plasma concentrations of intact orlistat were near the limits of detection (<5 ng/mL). In therapeutic studies involving monitoring of plasma samples, detection of intact orlistat in plasma was sporadic and concentrations were low (<10 ng/mL or 0.02 μM), without evidence of accumulation, and consistent with minimal absorption.

The average absolute bioavailability of intact orlistat was assessed in studies with male rats at oral doses of 150 and 1000 mg/kg/day and in male dogs at oral doses of 100 and 1000 mg/kg/day and found to be 0.12%, 0.59% in rats and 0.7%, 1.9% in dogs, respectively.

Distribution

In vitro orlistat was >99% bound to plasma proteins (lipoproteins and albumin were major binding proteins). Orlistat minimally partitioned into erythrocytes.

Metabolism

Based on animal data, it is likely that the metabolism of orlistat occurs mainly within the gastrointestinal wall. Based on an oral ^{14}C-orlistat mass balance study in obese patients, two metabolites, M1 (4-member lactone ring hydrolyzed) and M3 (M1 with N-formyl leucine moiety cleaved), accounted for approximately 42% of total radioactivity in plasma. M1 and M3 have an open β-lactone ring and extremely weak lipase inhibitory activity (1000- and 2500-fold less than orlistat, respectively). In view of this low inhibitory activity and the low plasma levels at the therapeutic dose (average of 26 ng/mL and 108 ng/mL for M1 and M3, respectively, 2 to 4 hours after a dose), these metabolites are considered pharmacologically inconsequential. The primary metabolite M1 had a short half-life (approximately 3 hours) whereas the secondary metabolite M3 disappeared at a slower rate (half-life approximately 13.5 hours). In obese patients, steady-state plasma levels of M1, but not M3, increased in proportion to orlistat doses.

Elimination

Following a single oral dose of 360 mg ^{14}C-orlistat in both normal weight and obese subjects, fecal excretion of the unabsorbed drug was found to be the major route of elimination. Orlistat and its M1 and M3 metabolites were also subject to biliary excretion. Approximately 97% of the administered radioactivity was excreted in feces; 83% of that was found to be unchanged orlistat. The cumulative renal excretion of total radioactivity was <2% of the given dose of 360 mg ^{14}C-orlistat. The time to reach complete excretion (fecal plus urinary) was 3 to 5 days. The disposition of orlistat appeared to be similar between normal weight and obese subjects. Based on limited data, the half-life of the absorbed orlistat is in the range of 1 to 2 hours.

Special Populations

Because the drug is minimally absorbed, studies in special populations (geriatric, different races, patients with renal and hepatic insufficiency) were not conducted.

Pediatrics

Plasma concentrations of orlistat and its metabolites M1 and M3 were similar to those found in adults at the same dose level. Daily fecal fat excretions were 27% and 7% of dietary intake in orlistat and placebo treatment groups, respectively.

Drug-Drug Interactions

Drug-drug interaction studies indicate that XENICAL had no effect on pharmacokinetics and/or pharmacodynamics of alcohol, digoxin, glyburide, nifedipine (extended-release tablets), oral contraceptives, phenytoin, pravastatin, or warfarin. Alcohol did not affect the pharmacodynamics of orlistat.

Other Short-term Studies

Adults

In several studies of up to 6-weeks duration, the effects of therapeutic doses of XENICAL on gastrointestinal and systemic physiological processes were assessed in normal-weight and obese subjects. Postprandial cholecystokinin plasma concentrations were lowered after multiple doses of XENICAL in two studies but not significantly different from placebo in two other experiments. There were no clinically significant changes observed in gallbladder motility, bile composition or lithogenicity, or colonic cell proliferation rate, and no clinically significant reduction of gastric emptying time or gastric acidity. In addition, no effects on plasma triglyceride levels or systemic lipases were observed with the administration of XENICAL in these studies. In a 3-week study of 28 healthy male volunteers, XENICAL (120 mg three times a day) did not significantly affect the balance of calcium, magnesium, phosphorus, zinc, copper, and iron.

Pediatrics

In a 3-week study of 32 obese adolescents aged 12 to 16 years, XENICAL (120 mg three times a day) did not significantly affect the balance of calcium, magnesium, phosphorus, zinc, or copper. The iron balance was decreased by 64.7 μmole/24 hours and 40.4 μmole/24 hours in orlistat and placebo treatment groups, respectively.

Dose-response Relationship

A simple maximum effect (E_{max}) model was used to define the dose-response curve of the relationship between XENICAL daily dose and fecal fat excretion as representative of gastrointestinal lipase inhibition. The dose-response curve demonstrated a steep portion for doses up to approximately 400 mg daily, followed by a plateau for higher doses. At doses greater than 120 mg three times a day, the percentage increase in effect was minimal.

CLINICAL STUDIES

Observational epidemiologic studies have established a relationship between obesity and visceral fat and the risks for cardiovascular disease, type 2 diabetes, certain forms of cancer, gallstones, certain respiratory disorders, and an increase in overall mortality. These studies suggest that weight loss, if maintained, may produce health benefits for obese patients who have or are at risk of developing weight-related comorbidities. The long-term effects of orlistat on morbidity and mortality associated with obesity have not been established.

The effects of XENICAL on weight loss, weight maintenance, and weight regain and on a number of comorbidities (eg, type 2 diabetes, lipids, blood pressure) were assessed in the 4-year XENDOS study and in seven long-term (1- to 2-years duration) multicenter, double-blind, placebo-controlled clinical trials. During the first year of therapy, the studies of 2-year duration assessed weight loss and weight maintenance. During the second year of therapy, some studies assessed continued weight loss and weight maintenance and others assessed the effect of orlistat on weight regain. These studies included over 2800 patients treated with XENICAL and 1400 patients treated with placebo. The majority of these patients had obesity-related risk factors and comorbidities. In the XENDOS study, which included 3304 patients, the time to onset of type 2 diabetes was assessed in addition to weight management. In all these studies, treatment with XENICAL and placebo designates treatment with XENICAL plus diet and placebo plus diet, respectively.

During the weight loss and weight maintenance period, a well-balanced, reduced-calorie diet that was intended to result in an approximate 20% decrease in caloric intake and provide 30% of calories from fat was recommended to all patients. In addition, all patients were offered nutritional counseling.

One-year Results: Weight Loss, Weight Maintenance, and Risk Factors

Weight loss was observed within 2 weeks of initiation of therapy and continued for 6 to 12 months.

Pooled data from five clinical trials indicated that the overall mean weight loss from randomization to the end of 6 months and 1 year of treatment in the intent-to-treat population were 12.4 lbs and 13.4 lbs in the patients treated with XENICAL and 6.2 lbs and 5.8 lbs in the placebo-treated patients, respectively. During the 4-week placebo lead-in period of the studies, an additional 5 to 6 lb weight loss was also observed in the same patients. Of the patients who completed 1 year of treatment, 57% of the patients treated with XENICAL (120 mg three times a day) and 31% of the placebo-treated patients lost at least 5% of their baseline body weight.

The percentages of patients achieving ≥5% and ≥10% weight loss after 1 year in five large multicenter studies for the intent-to-treat populations are presented in Table 1.

Table 1 **Percentage of Patients Losing ≥5% and ≥10% of Body Weight From Randomization After 1-Year Treatment***

Intent-to-Treat Population†									
	≥5% Weight Loss					≥10% Weight Loss			
Study No.	XENICAL	n	Placebo	n	p-value	XENICAL	n	Placebo	n	p-value
14119B	35.5%	110	21.3%	108	0.021	16.4%	110	6.5%	108	0.022
14119C	54.8%	343	27.4%	340	<0.001	24.8%	343	8.2%	340	<0.001
14149	50.6%	241	26.3%	236	<0.001	22.8%	241	11.9%	236	0.02
14161‡	37.1%	210	16.0%	212	<0.001	19.5%	210	3.8%	212	<0.001
14185	42.6%	657	22.4%	223	<0.001	17.7%	657	9.9%	223	0.006

The diet utilized during year 1 was a reduced-calorie diet.

* Treatment designates XENICAL 120 mg three times a day plus diet or placebo plus diet

† Last observation carried forward

‡ All studies, with the exception of 14161, were conducted at centers specialized in treating obesity and complications of obesity. Study 14161 was conducted with primary care physicians.

The relative changes in risk factors associated with obesity following 1 year of therapy with XENICAL and placebo are presented for the population as a whole and for the population with abnormal values at randomization.

Population as a Whole

The changes in metabolic, cardiovascular and anthropometric risk factors associated with obesity based on pooled data for five clinical studies, regardless of the patient's risk factor status at randomization, are presented in Table 2. One year of therapy with XENICAL resulted in relative improvement in several risk factors.

Table 2 Mean Change in Risk Factors From Randomization Following 1-Year Treatment* Population as a Whole

Risk Factor	XENICAL 120 mg†	Placebo†
Metabolic:		
Total Cholesterol	-2.0%	+5.0%
LDL-Cholesterol	-4.0%	+5.0%
HDL-Cholesterol	+9.3%	+12.8%
LDL/HDL	-0.37	-0.20
Triglycerides	+1.34%	+2.9%
Fasting Glucose, mmol/L	-0.04	+0.0
Fasting Insulin, pmol/L	-6.7	+5.2
Cardiovascular:		
Systolic Blood Pressure, mm Hg	-1.01	+0.58
Diastolic Blood Pressure, mm Hg	-1.19	+0.46
Anthropometric:		
Waist Circumference, cm	-6.45	-4.04
Hip Circumference, cm	-5.31	-2.96

* Treatment designates XENICAL 120 mg three times a day plus diet or placebo plus diet

† Intent-to-treat population at week 52, observed data based on pooled data from 5 studies

Population With Abnormal Risk Factors at Randomization

The changes from randomization following 1-year treatment in the population with abnormal lipid levels (LDL ≥ 130 mg/dL, LDL/HDL ≥ 3.5, HDL <35 mg/dL) were greater for XENICAL compared to placebo with respect to LDL-cholesterol (-7.83% vs +1.14%) and the LDL/HDL ratio (-0.64 vs -0.46). HDL increased in the placebo group by 20.1% and in the XENICAL group by 18.8%. In the population with abnormal blood pressure at baseline (systolic BP ≥ 140 mm Hg), the change in SBP from randomization to 1 year was greater for XENICAL (-10.89 mm Hg) than placebo (-5.07 mm Hg). For patients with a diastolic blood pressure ≥90 mm Hg, XENICAL patients decreased by -7.9 mm Hg while the placebo patients decreased by -5.5 mm Hg. Fasting insulin decreased more for XENICAL than placebo (-39 vs -16 pmol/L) from randomization to 1 year in the population with abnormal baseline values (≥120 pmol/L). A greater reduction in waist circumference for XENICAL vs placebo (-7.29 vs -4.53 cm) was observed in the population with abnormal baseline values (≥100 cm).

Effect on Weight Regain

Three studies were designed to evaluate the effects of XENICAL compared to placebo in reducing weight regain after a previous weight loss achieved following either diet alone (one study, 14302) or prior treatment with XENICAL (two studies, 14119C and 14185). The diet utilized during the 1-year weight regain portion of the studies was a weight-

maintenance diet, rather than a weight-loss diet, and patients received less nutritional counseling than patients in weight-loss studies. For studies 14119C and 14185, patients' previous weight loss was due to 1 year of treatment with XENICAL in conjunction with a mildly hypocaloric diet. Study 14302 was conducted to evaluate the effects of 1 year of treatment with XENICAL on weight regain in patients who had lost 8% or more of their body weight in the previous 6 months on diet alone.

In study 14119C, patients treated with placebo regained 52% of the weight they had previously lost while the patients treated with XENICAL regained 26% of the weight they had previously lost ($p<0.001$). In study 14185, patients treated with placebo regained 63% of the weight they had previously lost while the patients treated with XENICAL regained 35% of the weight they had lost ($p<0.001$). In study 14302, patients treated with placebo regained 53% of the weight they had previously lost while the patients treated with XENICAL regained 32% of the weight that they had lost ($p<0.001$).

Two-year Results: Long-term Weight Control and Risk Factors

The treatment effects of XENICAL were examined for 2 years in four of the five 1-year weight management clinical studies previously discussed (see Table 1). At the end of year 1, the patients' diets were reviewed and changed where necessary. The diet prescribed in the second year was designed to maintain patient's current weight. XENICAL was shown to be more effective than placebo in long-term weight control in four large, multicenter, 2-year double-blind, placebo-controlled studies.

Pooled data from four clinical studies indicate that 40% of all patients treated with 120 mg three times a day of XENICAL and 24% of patients treated with placebo who completed 2 years of the same therapy had ≥5% loss of body weight from randomization. Pooled data from four clinical studies indicate that the relative weight loss advantage between XENICAL 120 mg three times a day and placebo treatment groups was the same after 2 years as for 1 year, indicating that the pharmacologic advantage of XENICAL was maintained over 2 years. In the same studies cited in the **One-year Results** (see Table 1), the percentages of patients achieving a ≥5% and ≥10% weight loss after 2 years are shown in Table 3.

Table 3 **Percentage of Patients Losing ≥5% and ≥10% of Body Weight From Randomization After 2-Year Treatment***

Intent-to-Treat Population†							
	≥5% Weight Loss			≥10% Weight Loss			
Study No.	XENICAL	n	Placebo n	p-value	XENICAL	n	Placebo n	p-value
14119C	45.1%	133	23.6% 123	<0.001	24.8%	133	6.5% 123	<0.001
14149	43.3%	178	27.2% 158	0.002	18.0%	178	9.5% 158	0.025
14161‡	25.0%	148	15.0% 113	0.049	16.9%	148	3.5% 113	0.001
14185	34.0%	147	27.9% 122	0.279	17.7%	147	11.5% 122	0.154

The diet utilized during year 2 was designed for weight maintenance and not weight loss.

* Treatment designates XENICAL 120 mg three times a day plus diet or placebo plus diet

† Last observation carried forward

‡ All studies, with the exception of 14161 were conducted at centers specializing in treating obesity or complications of obesity. Study 14161 was conducted with primary care physicians.

The relative changes in risk factors associated with obesity following 2 years of therapy were also assessed in the population as a whole and the population with abnormal risk factors at randomization.

Population as a Whole

The relative differences in risk factors between treatment with XENICAL and placebo were similar to the results following 1 year of therapy for total cholesterol, LDL-cholesterol, LDL/HDL ratio, triglycerides, fasting glucose, fasting insulin, diastolic blood pressure, waist circumference, and hip circumference. The relative differences between treatment groups for HDL cholesterol and systolic blood pressure were less than that observed in the year one results.

Population With Abnormal Risk Factors at Randomization

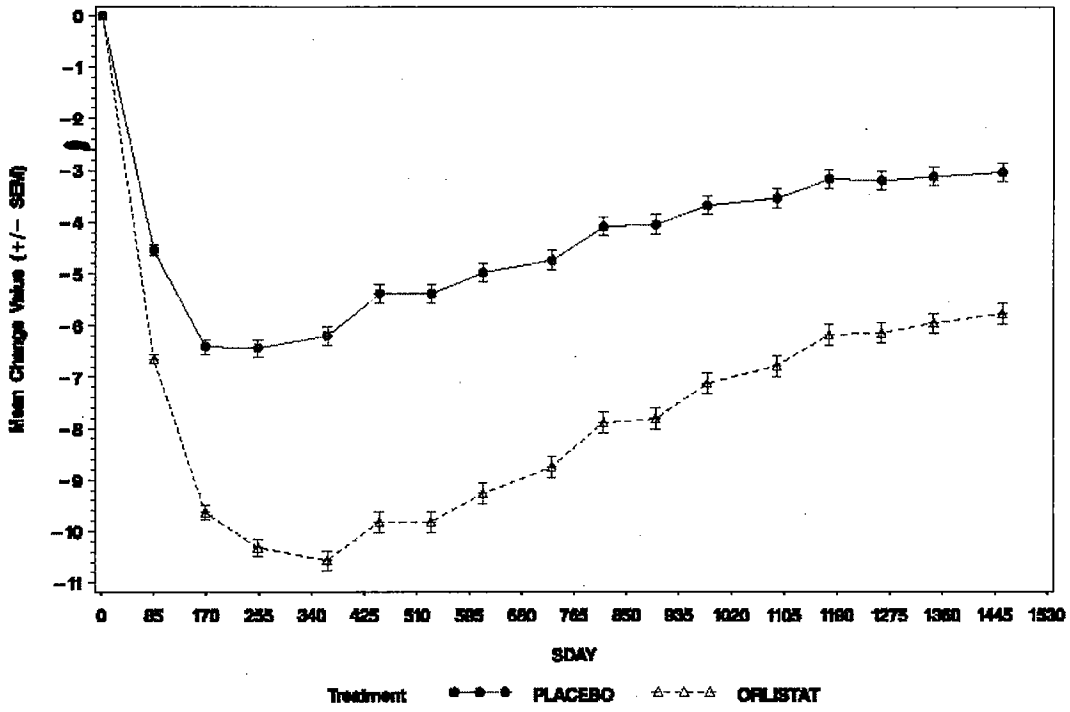
The relative differences in risk factors between treatment with XENICAL and placebo were similar to the results following 1 year of therapy for LDL- and HDL-cholesterol, triglycerides, fasting insulin, diastolic blood pressure, and waist circumference. The relative differences between treatment groups for LDL/HDL ratio and isolated systolic blood pressure were less than that observed in the year one results.

Four-Year Results: Long-term Weight Control and Risk Factors

In the 4-year double-blind, placebo-controlled XENDOS study, the effects of orlistat in delaying the onset of type 2 diabetes and on body weight were compared to placebo in 3304 obese patients who had either normal or impaired glucose tolerance at baseline. Thirty-four percent of the 1655 patients who were randomized to the placebo group and 52% of the 1649 patients who were randomized to the orlistat group completed the 4-year study.

At the end of the study, the mean percent weight loss in the placebo group was -2.75% compared with -5.17% in the orlistat group ($p<0.001$) (see Figure 1). Forty-five percent of the placebo patients and 73% of the orlistat patients lost ≥5% of their baseline body weight, and 21% of the placebo patients and 41% of the orlistat patients lost ≥10% of their baseline body weight following the first year of treatment. Following 4 years of treatment, 28% of the placebo patients and 45% of the orlistat patients lost ≥5% of their baseline body weight and 10% of the placebo patients and 21% of the orlistat patients lost ≥10% of their baseline body weight.

Figure 1 Mean Change from Baseline Body Weight (Kgs) Over Time



The relative changes from baseline in risk factors associated with obesity following 4 years of therapy were assessed in the XENDOS study population (see Table 4).

Table 4 **Mean Change in Risk Factors From Randomization Following 4-Years Treatment***

Risk Factor	XENICAL 120 mg†	Placebo†
Metabolic:		
Total Cholesterol	-7.02%	-2.03%
LDL-Cholesterol	-11.66%	-3.85%
HDL-Cholesterol	+5.92%	+7.01%
LDL/HDL	-0.53	-0.33
Triglycerides	+3.64%	+1.30
Fasting Glucose, mmol/L	+0.12	+0.23
Fasting Insulin, pmol/L	-24.93	-15.71
Cardiovascular:		
Systolic Blood Pressure, mm Hg	-4.12	-2.60
Diastolic Blood Pressure, mm Hg	-1.93	-0.87
Anthropometric:		
Waist Circumference, cm	-5.78	-3.99

*Treatment designates XENICAL 120 mg three times a day plus diet or placebo plus diet

†Intent-to-treat population

Study of Patients With Type 2 Diabetes

A 1-year double-blind, placebo-controlled study in type 2 diabetics (N=321) stabilized on sulfonylureas was conducted. Thirty percent of patients treated with XENICAL achieved at least a 5% or greater reduction in body weight from randomization compared to 13% of the placebo-treated patients ($p<0.001$). Table 5 describes the changes over 1 year of treatment with XENICAL compared to placebo, in sulfonylurea usage and dose reduction as well as in hemoglobin HbA1c, fasting glucose, and insulin.

Table 5 **Mean Changes in Body Weight and Glycemic Control From Randomization Following 1-Year Treatment in Patients With Type 2 Diabetes**

	XENICAL 120 mg* (n=162)	Placebo* (n=159)	Statistical Significance
% patients who discontinued dose of oral sulfonylurea	11.7%	7.5%	†
% patients who decreased dose of oral sulfonylurea	31.5%	21.4%	
Average reduction in sulfonylurea medication dose	-22.8%	-9.1%	†
Body weight change (lbs)	-8.9	-4.2	†
HbA1c	-0.18%	+0.28%	†
Fasting glucose, mmol/L	-0.02	+0.54	†
Fasting insulin, pmol/L	-19.68	-18.02	ns

Statistical significance based on intent-to-treat population, last observation carried forward.

* Treatment designates XENICAL 120 mg three times a day plus diet or placebo plus diet

† Statistically significant ($p \leq 0.05$) based on intent-to-treat, last observation carried forward

ns nonsignificant, $p>0.05$

In addition, XENICAL (n=162) compared to placebo (n=159) was associated with significant lowering for total cholesterol (-1.0% vs +9.0%, $p \leq 0.05$), LDL-cholesterol (-3.0% vs +10.0%, $p \leq 0.05$), LDL/HDL ratio (-0.26 vs -0.02, $p \leq 0.05$) and triglycerides (+2.54% vs +16.2%, $p \leq 0.05$), respectively. For HDL cholesterol, there was a +6.49% increase on XENICAL and +8.6% increase on placebo, $p>0.05$. Systolic blood pressure increased by +0.61 mm Hg on XENICAL and increased by +4.33 mm Hg on placebo, $p>0.05$. Diastolic blood pressure decreased by -0.47 mm Hg for XENICAL and by -0.5 mm Hg for placebo, $p>0.05$.

Glucose Tolerance in Obese Patients

Two-year studies that included oral glucose tolerance tests were conducted in obese patients not previously diagnosed or treated for type 2 diabetes and whose baseline oral glucose tolerance test (OGTT) status at randomization was either normal, impaired, or diabetic.

The progression from a normal OGTT at randomization to a diabetic or impaired OGTT following 2 years of treatment with XENICAL (n=251) or placebo (n=207) were compared. Following treatment with XENICAL, 0.0% and 7.2% of the patients progressed from normal to diabetic and normal to impaired, respectively, compared to 1.9% and 12.6% of the placebo treatment group, respectively.

In patients found to have an impaired OGTT at randomization, the percent of patients improving to normal or deteriorating to diabetic status following 1 and 2 years of treatment with XENICAL compared to placebo are presented. After 1 year of treatment, 45.8% of the placebo patients and 73% of the XENICAL patients had a normal oral glucose tolerance test while 10.4% of the placebo patients and 2.6% of the XENICAL patients became diabetic. After 2 years of treatment, 50% of the placebo patients and 71.7% of the XENICAL patients had a normal oral glucose tolerance test while 7.5% of placebo patients were found to be diabetic and 1.7% of XENICAL patients were found to be diabetic after treatment.

Onset of Type 2 Diabetes in Obese Patients

In the XENDOS trial, in the overall population, orlistat delayed the onset of type 2 diabetes such that at the end of four years of treatment the cumulative incidence rate of diabetes was 8.3% for the placebo group compared to 5.5% for the orlistat group, p=0.01 (see Table 6). This finding was driven by a statistically-significant reduction in the incidence of developing type 2 diabetes in those patients who had impaired glucose tolerance at baseline (Table 6 and Figure 2). Orlistat did not reduce the risk for the development of diabetes in patients with normal glucose tolerance at baseline.

The effect of XENICAL to delay the onset of type 2 diabetes in obese patients with IGT is presumably due to weight loss, and not to any independent effects of the drug on glucose or insulin metabolism. The effect of orlistat on weight loss is adjunctive to diet and exercise.

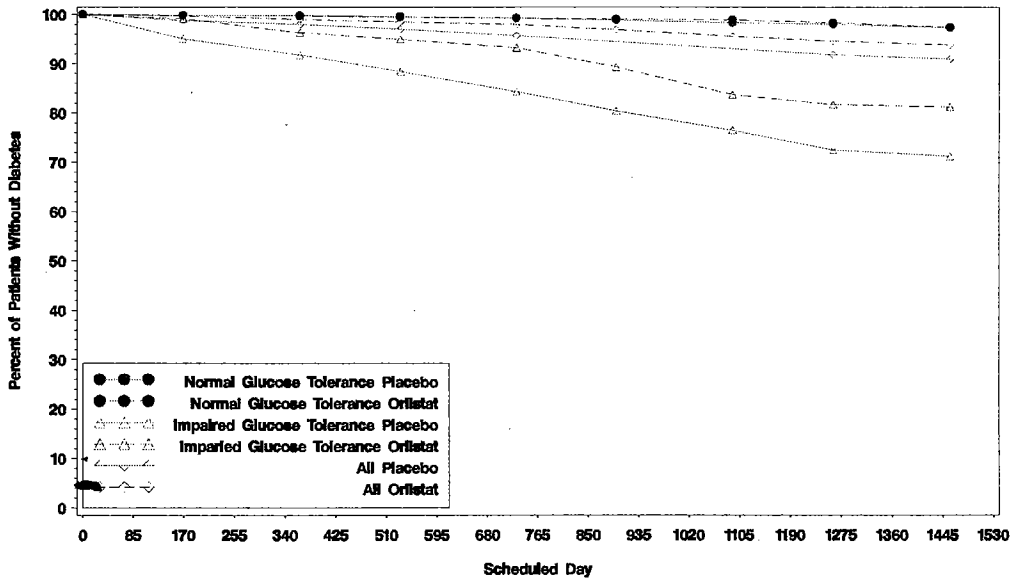
Table 6 Incidence Rate of Diabetes at Year 4 by OGTT Status at Baseline*

OGTT at baseline	**Normal**		**Impaired**		**All**	
Treatment	Placebo	Orlistat	Placebo	Orlistat	Placebo	Orlistat
Number of patients*	1148	1235	324	337	1472	1572
# pts developing diabetes	16	21	62	48	78	69
Life table rate†	2.1%	1.7%	27.2%	18.7%	8.3%	5.5%
Observed percent	1.4%	1.7%	19.1%	14.2%	5.3%	4.4%
Absolute risk reduction§						
Life table	0.4%		8.5%		2.8%	
Observed	-0.3%		4.9%		0.9%	
Relative risk reduction††	8%		42%		34%	
p-value	0.79		<0.01		0.01	

*Based on patients with a baseline and at least one follow-up OGTT measurement
†Rate adjusted for drop outs

†† Computed as (1- hazard ratio)

Figure 2 Percentage of Patients Without Diabetes Over Time



Pediatric Clinical Studies

The effects of XENICAL on body mass index (BMI) and weight loss were assessed in a 54-week multicenter, double-blind, placebo-controlled study in 539 obese adolescents (357 receiving XENICAL 120 mg three times a day, 182 receiving placebo), aged 12 to 16 years. All study participants had a baseline BMI that was 2 units greater than the US weighted mean for the 95th percentile based on age and gender. Body mass index was the primary efficacy parameter because it takes into account changes in height and body weight, which occur in growing children.

During the study, all patients were instructed to take a multivitamin containing fat-soluble vitamins at least 2 hours before or after ingestion of XENICAL. Patients were also maintained on a well-balanced, reduced-calorie diet that was intended to provide 30% of calories from fat. In addition, all patients were placed on a behavior modification program and offered exercise counseling.

Approximately 65% of patients in each treatment group completed the study.

Following one year of treatment, BMI decreased by an average of 0.55 kg/m^2 in the XENICAL-treated patients and increased by an average of 0.31 kg/m^2 in the placebo-treated patients (p=0.001).

The percentages of patients achieving ≥5% and ≥10% reduction in BMI and body weight after 52 weeks of treatment for the intent-to-treat population are presented in Table 7.

Table 7 Percentages of Patients with ≥5% and ≥10% Decrease in Body Mass Index and Body Weight After 1-Year Treatment* (Protocol NM16189)

	Intent-to-Treat Population†			
	≥5% Decrease		≥10% Decrease	
	XENICAL n	Placebo n	XENICAL n	Placebo n
BMI	26.5% 347	15.7% 178	13.3% 347	4.5% 178
Body Weight	19.0% 348	11.7% 180	9.5% 348	3.3% 180

* Treatment designates XENICAL 120 mg three times a day plus diet or placebo plus diet

† Last observation carried forward

INDICATIONS AND USAGE

XENICAL is indicated for obesity management including weight loss and weight maintenance when used in conjunction with a reduced-calorie diet. XENICAL is also indicated to reduce the risk for weight regain after prior weight loss. XENICAL is indicated for obese patients with an initial body mass index (BMI) ≥30 kg/m^2 or ≥27 kg/m^2 in the presence of other risk factors (eg, hypertension, diabetes, dyslipidemia).

Table 8 illustrates body mass index (BMI) according to a variety of weights and heights. The BMI is calculated by dividing weight in kilograms by height in meters squared. For example, a person who weighs 180 lbs and is 5'5" would have a BMI of 30.

Table 8 Body Mass Index (BMI), kg/m^2*

HEIGHT (ft/in)	WEIGHT (lb)																				
	120	130	140	150	160	170	180	190	200	210	220	230	240	250	260	270	280	290	300	310	320
4'10"	25	27	29	31	34	36	38	40	42	44	46	48	50	52	54	57	59	61	63	65	67
4'11"	24	26	28	30	32	34	36	38	40	43	45	47	49	51	53	55	57	59	61	63	65
5'0"	23	25	27	29	31	33	35	37	39	41	43	45	47	49	51	53	55	57	59	61	63
5'1"	23	25	27	28	30	32	34	36	38	40	42	44	45	47	49	51	53	55	57	59	61
5'2"	22	24	26	27	29	31	33	35	37	38	40	42	44	46	48	49	51	53	55	57	59
5'3"	21	23	25	27	28	30	32	34	36	37	39	41	43	44	46	48	50	51	53	55	57
5'4"	21	22	24	26	28	29	31	33	34	36	38	40	41	43	45	46	48	50	52	53	55
5'5"	20	22	23	25	27	28	30	32	33	35	37	38	40	42	43	45	47	48	50	52	53
5'6"	19	21	23	24	26	27	29	31	32	34	36	37	39	40	42	44	45	47	49	50	52
5'7"	19	20	22	24	25	27	28	30	31	33	35	36	38	39	41	42	44	46	47	49	50
5'8"	18	20	21	23	24	26	27	29	30	32	34	35	37	38	40	41	43	44	46	47	49
5'9"	18	19	21	22	24	25	27	28	30	31	33	34	36	37	38	40	41	43	44	46	47
5'10"	17	19	20	22	23	24	26	27	29	30	32	33	35	36	37	39	40	42	43	45	46
5'11"	17	18	20	21	22	24	25	27	28	29	31	32	34	35	36	38	39	41	42	43	45
6'0"	16	18	19	20	22	23	24	26	27	29	30	31	33	34	35	37	38	39	41	42	43
6'1"	16	17	19	20	21	22	24	25	26	28	29	30	32	33	34	36	37	38	40	41	42
6'2"	15	17	18	19	21	22	23	24	26	27	28	30	31	32	33	35	36	37	39	40	41

* Conversion Factors:
Weight in lbs ÷ 2.2 = weight in kilograms (kg)
Height in inches × 0.0254 = height in meters (m)
1 foot = 12 inches

CONTRAINDICATIONS

XENICAL is contraindicated in patients with chronic malabsorption syndrome or cholestasis, and in patients with known hypersensitivity to XENICAL or to any component of this product.

WARNINGS

Miscellaneous

Organic causes of obesity (eg, hypothyroidism) should be excluded before prescribing XENICAL.

Preliminary data from a XENICAL and cyclosporine drug interaction study indicate a reduction in cyclosporine plasma levels when XENICAL was coadministered with cyclosporine. Therefore, XENICAL and cyclosporine should not be coadministered. To reduce the chance of a drug-drug interaction, cyclosporine should be taken at least 2 hours before or after XENICAL in patients taking both drugs. In addition, in those patients whose cyclosporine levels are being measured, more frequent monitoring should be considered.

PRECAUTIONS

General

Patients should be advised to adhere to dietary guidelines (see DOSAGE AND ADMINISTRATION). Gastrointestinal events (see ADVERSE REACTIONS) may increase when XENICAL is taken with a diet high in fat (>30% total daily calories from fat). The daily intake of fat should be distributed over three main meals. If XENICAL is taken with any one meal very high in fat, the possibility of gastrointestinal effects increases.

Patients should be strongly encouraged to take a multivitamin supplement that contains fat-soluble vitamins to ensure adequate nutrition because XENICAL has been shown to reduce the absorption of some fat-soluble vitamins and beta-carotene (see DOSAGE AND ADMINISTRATION). In addition, the levels of vitamin D and beta-carotene may be low in obese patients compared with non-obese subjects. The supplement should be taken once a day at least 2 hours before or after the administration of XENICAL, such as at bedtime.

Table 9 illustrates the percentage of adult patients on XENICAL and placebo who developed a low vitamin level on two or more consecutive visits during 1 and 2 years of therapy in studies in which patients were not previously receiving vitamin supplementation.

Table 9 **Incidence of Low Vitamin Values on Two or More Consecutive Visits (Nonsupplemented Adult Patients With Normal Baseline Values - First and Second Year)**

	Placebo*	XENICAL*
Vitamin A	1.0%	2.2%
Vitamin D	6.6%	12.0%
Vitamin E	1.0%	5.8%
Beta-carotene	1.7%	6.1%

* Treatment designates placebo plus diet or XENICAL plus diet

Table 10 illustrates the percentage of adolescent patients on XENICAL and placebo who developed a low vitamin level on two or more consecutive visits during the 1-year study.

Table 10 **Incidence of Low Vitamin Values on Two or More Consecutive Visits (Pediatric Patients With Normal Baseline Values*)**

	Placebo†	XENICAL†
Vitamin A	0.0%	0.0%
Vitamin D	0.7%	1.4%
Vitamin E	0.0%	0.0%
Beta-carotene	0.8%	1.5%

* All patients were treated with vitamin supplementation throughout the course of the study

† Treatment designates placebo plus diet or XENICAL plus diet

Some patients may develop increased levels of urinary oxalate following treatment with XENICAL. Caution should be exercised when prescribing XENICAL to patients with a history of hyperoxaluria or calcium oxalate nephrolithiasis.

Weight-loss induction by XENICAL may be accompanied by improved metabolic control in diabetics, which might require a reduction in dose of oral hypoglycemic medication (eg, sulfonylureas, metformin) or insulin (see CLINICAL STUDIES).

Misuse Potential

As with any weight-loss agent, the potential exists for misuse of XENICAL in inappropriate patient populations (eg, patients with anorexia nervosa or bulimia). See INDICATIONS AND USAGE for recommended prescribing guidelines.

Information for Patients

Patients should read the Patient Information before starting treatment with XENICAL and each time their prescription is renewed.

Drug Interactions

Alcohol

In a multiple-dose study in 30 normal-weight subjects, coadministration of XENICAL and 40 grams of alcohol (eg, approximately 3 glasses of wine) did not result in alteration of alcohol pharmacokinetics, orlistat pharmacodynamics (fecal fat excretion), or systemic exposure to orlistat.

Cyclosporine

Preliminary data from a XENICAL and cyclosporine drug interaction study indicate a reduction in cyclosporine plasma levels when XENICAL was coadministered with cyclosporine (see WARNINGS).

Digoxin

In 12 normal-weight subjects receiving XENICAL 120 mg three times a day for 6 days, XENICAL did not alter the pharmacokinetics of a single dose of digoxin.

Fat-soluble Vitamin Supplements and Analogues

A pharmacokinetic interaction study showed a 30% reduction in beta-carotene supplement absorption when concomitantly administered with XENICAL. XENICAL inhibited absorption of a vitamin E acetate supplement by approximately 60%. The effect of orlistat on the absorption of supplemental vitamin D, vitamin A, and nutritionally-derived vitamin K is not known at this time.

Glyburide

In 12 normal-weight subjects receiving orlistat 80 mg three times a day for 5 days, orlistat did not alter the pharmacokinetics or pharmacodynamics (blood glucose-lowering) of glyburide.

Nifedipine (extended-release tablets)

In 17 normal-weight subjects receiving XENICAL 120 mg three times a day for 6 days, XENICAL did not alter the bioavailability of nifedipine (extended-release tablets).

Oral Contraceptives

In 20 normal-weight female subjects, the treatment of XENICAL 120 mg three times a day for 23 days resulted in no changes in the ovulation-suppressing action of oral contraceptives.

Phenytoin

In 12 normal-weight subjects receiving XENICAL 120 mg three times a day for 7 days, XENICAL did not alter the pharmacokinetics of a single 300-mg dose of phenytoin.

Pravastatin

In a 2-way crossover study of 24 normal-weight, mildly hypercholesterolemic patients receiving XENICAL 120 mg three times a day for 6 days, XENICAL did not affect the pharmacokinetics of pravastatin.

Warfarin

In 12 normal-weight subjects, administration of XENICAL 120 mg three times a day for 16 days did not result in any change in either warfarin pharmacokinetics (both R- and S-enantiomers) or pharmacodynamics (prothrombin time and serum Factor VII). Although undercarboxylated osteocalcin, a marker of vitamin K nutritional status, was unaltered with XENICAL administration, vitamin K levels tended to decline in subjects taking XENICAL. Therefore, as vitamin K absorption may be decreased with XENICAL, patients on chronic stable doses of warfarin who are prescribed XENICAL should be monitored closely for changes in coagulation parameters.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity studies in rats and mice did not show a carcinogenic potential for orlistat at doses up to 1000 mg/kg/day and 1500 mg/kg/day, respectively. For mice and rats, these doses are 38 and 46 times the daily human dose calculated on an area under concentration vs time curve basis of total drug-related material.

Orlistat had no detectable mutagenic or genotoxic activity as determined by the Ames test, a mammalian forward mutation assay (V79/HPRT), an in vitro clastogenesis assay in peripheral human lymphocytes, an unscheduled DNA synthesis assay (UDS) in rat hepatocytes in culture, and an in vivo mouse micronucleus test.

When given to rats at a dose of 400 mg/kg/day in a fertility and reproduction study, orlistat had no observable adverse effects. This dose is 12 times the daily human dose calculated on a body surface area (mg/m^2) basis.

Pregnancy

Teratogenic Effects: Pregnancy Category B.

Teratogenicity studies were conducted in rats and rabbits at doses up to 800 mg/kg/day. Neither study showed embryotoxicity or teratogenicity. This dose is 23 and 47 times the daily human dose calculated on a body surface area (mg/m^2) basis for rats and rabbits, respectively.

The incidence of dilated cerebral ventricles was increased in the mid- and high-dose groups of the rat teratology study. These doses were 6 and 23 times the daily human dose calculated on a body surface area (mg/m^2) basis for the mid- and high-dose levels, respectively. This finding was not reproduced in two additional rat teratology studies at similar doses.

There are no adequate and well-controlled studies of XENICAL in pregnant women. Because animal reproductive studies are not always predictive of human response, XENICAL is not recommended for use during pregnancy.

Nursing Mothers

It is not known if orlistat is secreted in human milk. Therefore, XENICAL should not be taken by nursing women.

Pediatric Use

The safety and efficacy of XENICAL have been evaluated in obese adolescent patients aged 12 to 16 years. Use of XENICAL in this age group is supported by evidence from adequate and well-controlled studies of XENICAL in adults with additional data from a 54-week efficacy and safety study and a 21-day mineral balance study in obese adolescent patients aged 12 to 16 years. Patients treated with XENICAL had a mean reduction in BMI of 0.55 kg/m^2 compared with an average increase of 0.31 kg/m^2 in placebo-treated patients (p=0.001). In both adolescent studies, adverse effects were generally similar to those described in adults and included fatty/oily stool, oily spotting, and oily evacuation. In a subgroup of 152 orlistat and 77 placebo patients from the 54-week study, changes in body composition measured by DEXA were similar in both treatment groups with the exception of fat mass, which was significantly reduced in patients treated with XENICAL compared to patients treated with placebo (-2.5 kg vs -0.6 kg, p=0.033). Because XENICAL can interfere with the absorption of fat-soluble vitamins, all patients should take a daily multivitamin that contains vitamins A, D, E, K, and beta-carotene. The supplement should be taken at least 2 hours before or after XENICAL (see CLINICAL PHARMACOLOGY: Other Short-term Studies; CLINICAL STUDIES: Pediatric Clinical Studies; ADVERSE REACTIONS: Pediatric Patients). XENICAL has not been studied in pediatric patients below the age of 12 years.

Geriatric Use

Clinical studies of XENICAL did not include sufficient numbers of patients aged 65 years and older to determine whether they respond differently from younger patients.

ADVERSE REACTIONS

Commonly Observed (based on first year and second year data - XENICAL 120 mg three times a day versus placebo):

Gastrointestinal (GI) symptoms were the most commonly observed treatment-emergent adverse events associated with the use of XENICAL in the seven double-blind, placebo-controlled clinical trials and are primarily a manifestation of the mechanism of action. (Commonly observed is defined as an incidence of ≥5% and an incidence in the XENICAL 120 mg group that is at least twice that of placebo.)

Table 11 Commonly Observed Adverse Events

Adverse Event	Year 1		Year 2	
	XENICAL* % Patients (N=1913)	Placebo* % Patients (N=1466)	XENICAL* % Patients (N=613)	Placebo* % Patients (N=524)
Oily Spotting	26.6	1.3	4.4	0.2
Flatus with Discharge	23.9	1.4	2.1	0.2
Fecal Urgency	22.1	6.7	2.8	1.7
Fatty/Oily Stool	20.0	2.9	5.5	0.6
Oily Evacuation	11.9	0.8	2.3	0.2
Increased Defecation	10.8	4.1	2.6	0.8
Fecal Incontinence	7.7	0.9	1.8	0.2

* Treatment designates XENICAL three times a day plus diet or placebo plus diet

These and other commonly observed adverse reactions were generally mild and transient, and they decreased during the second year of treatment. In general, the first occurrence of these events was within 3 months of starting therapy. Overall, approximately 50% of all episodes of GI adverse events associated with orlistat treatment lasted for less than 1 week, and a majority lasted for no more than 4 weeks. However, GI adverse events may occur in some individuals over a period of 6 months or longer.

Discontinuation of Treatment

In controlled clinical trials, 8.8% of patients treated with XENICAL discontinued treatment due to adverse events, compared with 5.0% of placebo-treated patients. For XENICAL, the most common adverse events resulting in discontinuation of treatment were gastrointestinal.

Incidence in Controlled Clinical Trials

The following table lists other treatment-emergent adverse events from seven multicenter, double-blind, placebo-controlled clinical trials that occurred at a frequency of ≥2% among patients treated with XENICAL 120 mg three times a day and with an incidence that was greater than placebo during year 1 and year 2, regardless of relationship to study medication.

Table 12 Other Treatment-Emergent Adverse Events From Seven Placebo-Controlled Clinical Trials

	Year 1		Year 2	
Body System/Adverse Event	**XENICAL* % Patients (N=1913)**	**Placebo* % Patients (N=1466)**	**XENICAL* % Patients (N=613)**	**Placebo* % Patients (N=524)**
Gastrointestinal System				
Abdominal Pain/Discomfort	25.5	21.4	–	–
Nausea	8.1	7.3	3.6	2.7
Infectious Diarrhea	5.3	4.4	–	–
Rectal Pain/Discomfort	5.2	4.0	3.3	1.9
Tooth Disorder	4.3	3.1	2.9	2.3
Gingival Disorder	4.1	2.9	2.0	1.5
Vomiting	3.8	3.5	–	–
Respiratory System				
Influenza	39.7	36.2	–	–
Upper Respiratory Infection	38.1	32.8	26.1	25.8
Lower Respiratory Infection	7.8	6.6	–	–
Ear, Nose & Throat Symptoms	2.0	1.6	–	–
Musculoskeletal System				
Back Pain	13.9	12.1	–	–
Pain Lower Extremities	–	–	10.8	10.3
Arthritis	5.4	4.8	–	–
Myalgia	4.2	3.3	–	–
Joint Disorder	2.3	2.2	–	–
Tendonitis	–	–	2.0	1.9
Central Nervous System				
Headache	30.6	27.6	–	–
Dizziness	5.2	5.0	–	–
Body as a Whole				
Fatigue	7.2	6.4	3.1	1.7
Sleep Disorder	3.9	3.3	–	–
Skin & Appendages				
Rash	4.3	4.0	–	–
Dry Skin	2.1	1.4	–	–
Reproductive, Female				
Menstrual Irregularity	9.8	7.5	–	–
Vaginitis	3.8	3.6	2.6	1.9
Urinary System				
Urinary Tract Infection	7.5	7.3	5.9	4.8
Psychiatric Disorder				
Psychiatric Anxiety	4.7	2.9	2.8	2.1
Depression	–	–	3.4	2.5
Hearing & Vestibular Disorders				
Otitis	4.3	3.4	2.9	2.5
Cardiovascular Disorders				
Pedal Edema	–	–	2.8	1.9

* Treatment designates XENICAL 120 mg three times a day plus diet or placebo plus diet

– None reported at a frequency ≥2% and greater than placebo

In the 4-year XENDOS study, the general pattern of adverse events was similar to that reported for the 1- and 2-year studies with the total incidence of gastrointestinal-related adverse events occurring in year 1 decreasing each year over the 4-year period.

Other Clinical Studies or Postmarketing Surveillance

Rare cases of hypersensitivity have been reported with the use of XENICAL. Signs and symptoms have included pruritus, rash, urticaria, angioedema, and anaphylaxis.

Preliminary data from a XENICAL and cyclosporine drug interaction study indicate a reduction in cyclosporine plasma levels when XENICAL was coadministered with cyclosporine (see WARNINGS).

Pediatric Patients

In clinical trials with XENICAL in adolescent patients ages 12 to 16 years, the profile of adverse reactions was generally similar to that observed in adults.

OVERDOSAGE

Single doses of 800 mg XENICAL and multiple doses of up to 400 mg three times a day for 15 days have been studied in normal weight and obese subjects without significant adverse findings.

Should a significant overdose of XENICAL occur, it is recommended that the patient be observed for 24 hours. Based on human and animal studies, systemic effects attributable to the lipase-inhibiting properties of orlistat should be rapidly reversible.

DOSAGE AND ADMINISTRATION

The recommended dose of XENICAL is one 120-mg capsule three times a day with each main meal containing fat (during or up to 1 hour after the meal).

The patient should be on a nutritionally balanced, reduced-calorie diet that contains approximately 30% of calories from fat. The daily intake of fat, carbohydrate, and protein should be distributed over three main meals. If a meal is occasionally missed or contains no fat, the dose of XENICAL can be omitted.

Because XENICAL has been shown to reduce the absorption of some fat-soluble vitamins and beta-carotene, patients should be counseled to take a multivitamin containing fat-soluble vitamins to ensure adequate nutrition (see PRECAUTIONS: General). The supplement should be taken at least 2 hours before or after the administration of XENICAL, such as at bedtime.

Doses above 120 mg three times a day have not been shown to provide additional benefit.

Based on fecal fat measurements, the effect of XENICAL is seen as soon as 24 to 48 hours after dosing. Upon discontinuation of therapy, fecal fat content usually returns to pretreatment levels within 48 to 72 hours.

The safety and effectiveness of XENICAL beyond 4 years have not been determined at this time.

HOW SUPPLIED

XENICAL is a dark-blue, hard-gelatin capsule containing pellets of powder.

XENICAL 120 mg Capsules: Dark-blue, two-piece, No. 1 opaque hard-gelatin capsule imprinted with Roche and XENICAL 120 in light-blue ink — bottle of 90 (NDC 0004-0256-52).

Storage Conditions

Store at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature]. Keep bottle tightly closed.

XENICAL should not be used after the given expiration date.

Distributed by:

Pharmaceuticals

Roche Laboratories Inc.
340 Kingsland Street
Nutley, New Jersey 07110-1199

xxxxxxxx

Revised: Month Year

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-766/S-019

MEDICAL REVIEW(s)

CLINICAL REVIEW

Application Type	NDA
Submission Number	20-766
Submission Code	SE8

Letter Date	December 22, 2003
PDUFA Goal Date	October 22, 2004
Reviewer Name	Eric Colman
Review Completion Date	September 30, 2004

Established Name	Orlistat
(Proposed) Trade Name	Xenical
Therapeutic Class	Pancreatic Lipase Inhibitor
Applicant	Hoffman-La Roche

Priority Designation	Standard

Formulation	Oral
Dosing Regimen	TID with Meals
Indication	Prevention of Type 2 Diabetes
Intended Population	Obese

Table of Contents

1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

Approve

1.2 Recommendation on Postmarketing Actions

None

1.2.1 Risk Management Activity

None beyond those listed in the currently approved labeling.

1.2.2 Required Phase 4 Commitments

None

1.2.3 Other Phase 4 Requests

None

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

This supplemental NDA is based on the results of one trial referred to as the XENDOS study. This was a randomized, double-blind, placebo-controlled 4-year study of obese (BMI $\geq$ 30 kg/m^2) male and female subjects with normal or impaired glucose tolerance (IGT) living in Sweden. The primary objectives of the study were 1) to determine if orlistat, 120 mg TID with meals, relative to placebo could prevent or delay the development of type 2 diabetes; and 2) to compare the changes in body weight from baseline to Endpoint in orlistat vs. placebo-treated subjects. Patients were randomized (1:1) according to gender and oral glucose tolerance test (OGTT) result strata (normal or impaired) to placebo or orlistat TID. All subjects received lifestyle intervention counseling and were encouraged to increase physical activity.

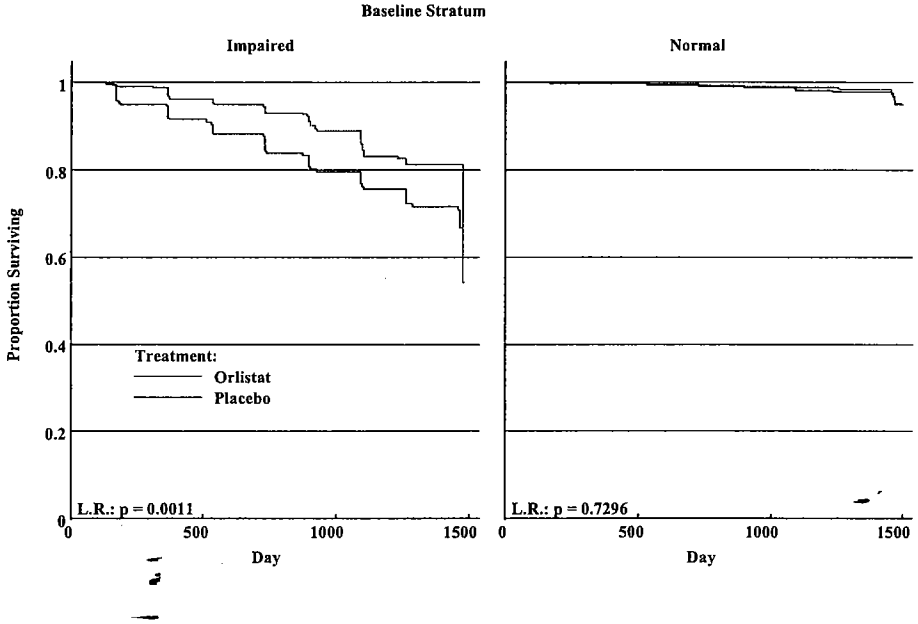
An OGTT was performed at baseline and every 6 months during the trial. Based on the serum glucose value at 2 hours post-OGTT, subjects were classified as having normal glucose tolerance if their value was < 6.7 mmol/L; IGT is their glucose level was 6.7 mmol/L to < 10 mmol/L; or diabetic if their glucose value was $\geq$ 10 mmol/L.

A total of 3304 patients were randomized: 1655 to placebo and 1649 to orlistat. At baseline, the average age was 44 years, the mean BMI was 37 kg/m^2, 55% of the subjects were female, 21%

had IGT, and almost all were Caucasian. Nearly 60% and 78% of placebo and orlistat patients, respectively, completed two years of the study. Approximately 34% of the placebo subjects and 52% of the orlistat subjects completed the 4-year study.

1.3.2 Efficacy

At the completion of the 4-year trial, the adjusted cumulative rates of diabetes in the overall population were approximately 8.3% in the placebo group and 5.5% in the orlistat group (p=0.008). As shown in the following figure, this statistically significant delay in the development of diabetes was driven by the results from patients with IGT at baseline. Of these subjects, the adjusted cumulative rates of diabetes over 4 years were 27.2% in the placebo group and 18.7% in the orlistat group (p=0.005). Of the subjects with normal glucose tolerance at baseline, approximately 1.4% of the placebo patients and 1.7% of the orlistat subjects developed diabetes (p=0.8).



The mean percent reduction in body weight from baseline to Year 4 was -2.8% in the placebo group and -5.2% in the orlistat group (nominal p<0.001). Twenty-eight percent of the placebo subjects and 45% of the orlistat subjects lost at least 5% of their baseline body weight by Year 4 (p<0.001). Ten percent of placebo and 20% of orlistat-treated participants lost at least 10% of their baseline body weight by Year 4 (nominal p<0.001). Waist circumference decreased from baseline to Year 4 by an average of -4.0 cm in the placebo group and -5.8 cm in the orlistat group.

The following changes were noted for serum lipid levels from baseline to Year 4. The mean percent reduction in total cholesterol (TC) was -2.0% in the placebo group and -7.0% in the orlistat group; LDL cholesterol levels decreased by an average of -4.0% and -12.0% in the placebo and orlistat groups, respectively; HDL cholesterol increased by 7.0% in the placebo

group and by 6.0% in the orlistat group; triglyceride (TG) levels increased by an average of 1.3% in the placebo group and by 3.6% in the orlistat group; and Lpa levels increased by an absolute average of 30 ug/L and 38 ug/L in the placebo and orlistat groups, respectively.

The mean fasting glucose levels increased by 0.23 mmol/L in the placebo group and by 0.12 mmol/L in the orlistat group from baseline to Year 4. The mean fasting insulin levels decreased from baseline to Year 4 by -15.7 pmol/L in the placebo group and by -25.0 pmol/L in the orlistat group.

The average levels of systolic and diastolic blood pressure decreased from baseline to Year 4 in both the placebo and orlistat groups. Systolic blood pressure changes were: -2.6 mmHg and -4.1 mmHg (placebo vs. orlistat) and diastolic blood pressure changes were: -0.9 mmHg and -1.9 mmHg (placebo vs. orlistat).

1.3.3 Safety

Seven placebo and 2 orlistat subjects died during or recently following trial participation. One of the orlistat deaths was due to a myocardial infarction and the other was a suicide. Thirteen percent of placebo and 15% of the orlistat subjects reported at least one serious adverse event during the trial. Other than the fact that 9 placebo and 17 orlistat-treated patients developed cholelithiasis that were reported as serious adverse events, there were no meaningful differences between the two groups in the incidence of individual serious adverse events. The most common treatment-emergent adverse events were related to the gastrointestinal tract, with fatty stools, fecal urgency, and flatus with discharge occurring in 43%, 18%, and 11% of orlistat participants, respectively; 5% or less of the placebo subjects experienced any one of these events.

There were no clinically significant changes in standard laboratory parameters, electrocardiograms, or physical examinations between the placebo and orlistat groups. Unlike the recommendation in the approved labeling, patients in XENDOS were not instructed to take a daily multivitamin supplement. This most likely explains why the mean levels of the fat-soluble vitamins decreased by statistically, although probably not clinically, significant amounts in the orlistat compared with the placebo groups.

1.3.4 Dosing Regimen and Administration

One orlistat capsule TID with meals.

1.3.5 Drug-Drug Interactions

As noted in the currently approved labeling, the use of orlistat concomitantly with cyclosporine can lead to significant reductions in the absorption and serum levels of this highly lipophilic anti-rejection medication[1]. If a decision is made to use orlistat in a patient taking cyclosporine, every effort should be made to ensure that the patient takes the cyclosporine at least 2 hours before of after the orlistat. In addition, cyclosporine levels should be carefully monitored to avoid development of subtherapeutic levels.

6 INTEGRATED REVIEW OF EFFICACY

6.1 INDICATION

To delay the development of type 2 diabetes mellitus in obese patients with normal or impaired glucose tolerance.

6.1.1 General Methods

This supplemental NDA is based on a single study, XENDOS, and therefore there was no pooling of data from separate studies.

6.1.2 General Discussion of Study Objectives, Endpoints and Methods

The primary efficacy objectives and parameters presented in this report are: time to onset of type 2 diabetes, and change in body weight from baseline to the end of the study.

An OGTT was performed at baseline and at six-month intervals throughout the study. A fasting blood sample was drawn for glucose and insulin levels, and then the patient drank 75 g of glucose in 400 mL of water within 5 minutes. Additional blood samples were drawn for glucose and insulin analysis at 30, 60, 90, and 120 minutes post-glucose consumption. After the baseline visit, whole blood glucose values at 120 minutes post-glucose consumption were used for diagnosis as follows. Glucose Level at 120 minutes Classification:

<6.7 mmol/L Normal
6.7 mmol/L to <10 mmol/L Impaired
≥ 10 mmol/L Diabetic

The diagnosis of type 2 diabetes was based on a single OGTT result (two hour whole blood glucose value ≥10mmol/L). Once the primary diagnosis of diabetes was made, a repeat OGTT was to be conducted for patients diagnosed after the first six months of the study. As this repeat OGTT was not implemented until six months after study start, patients diagnosed with diabetes at six months may not have had this repeat OGTT performed. For the purposes of safety follow-up, fasting glucose levels were measured at six month intervals for all patients with a change in OGTT status to diabetic. Patients with diabetic blood glucose values during the treatment phase were to remain in the study unless they developed symptoms of frank diabetes and required treatment disallowed by the protocol.

Body weight was recorded at every visit with the patient wearing light indoor clothing and no shoes. Body weight was measured in kilograms (kg) and recorded to the nearest one-tenth of a kg. Electronic scales were supplied by Roche and were calibrated and serviced yearly.

To estimate the proportion of total and visceral adipose tissue (AT), computerized tomography (CT) and Dual energy X-ray Absorptiometry (DEXA) were performed in two centers

and total body potassium (TBK) was performed in one center ( ). These procedures were performed at the randomization visit and were repeated yearly through the end of the study. This measurement technique has been calibrated against a multi-scan computerized tomography (CT) technique. Weight divided by height predicts total adipose volume and sagittal trunk diameter predicts visceral adipose tissue. By using the mean density of adipose tissue (0.923) to convert AT into mass, a series of equations can be used to estimate body compartments:

For males: Total AT (kg) = 0.923 x (1.36W/H - 42)
Visceral AT = 0.923 x (0.731D - 11.5) Where W = weight (kg); H = height (m); and D = sagittal trunk diameter

For females:
Total AT (kg) = 0.923 x (1.61 W/H - 38.3)
Visceral AT = 0.923 x (0.370D - 4.85)
For both: Lean mass = W - AT
Subcutaneous AT = Total AT - visceral AT

DEXA examinations result in body compartmentalization at the molecular level according to the following equation:

Weight = body fat + "lean" + bone mineral content where all compartments are given in kg. Lean plus bone mineral content is equal to fat-free mass (FFM). All are measured directly and none are calculated. Mass measurements performed by DEXA can be compared to body weights actually measured by conventional means. DEXA also reports total body fat and body fat of trunk, legs, and arms, but does not provide separate data on visceral AT. CT examinations allow for body composition determinations at the thigh, L4, and C4 levels. Determinations at the thigh level include dense bone area, muscles plus other non-AT, intramuscular AT, subcutaneous AT, and skin. Determinations at the L4 level include dense bone area, visceral organs including non-calcified aorta, calcified aorta, visceral AT, muscles, subcutaneous AT, and skin. Determinations at the C4 level include dense bone area, muscles plus non-AT, calcified carotid area left and right side, intramuscular AT, subcutaneous AT, and skin.

Due to limitations of the equipment used, DEXA and CT could not be performed on patients who weighed more than 110 kg and 130 kg respectively. In addition, to examine body fat and FFM, total body potassium (TBK) measurements were performed at ( ) TBK is used to estimate lean body mass since the ratio of body potassium is relatively constant in humans. Ninety-eight percent of body potassium is intracellular and present primarily in non-adipose tissue. The method assumes that the naturally occurring isotope, 40K, constitutes a constant proportion (approximately 0.0012%) of all potassium. 40K emits gamma rays that are quantitated in a total body counter. Calculation of FFM from measurement of TBK is based on the assumption of potassium content in FFM that is constant at 60 mmol/kg for women and 66 mmol/kg for men.

Secondary efficacy parameters, including fasting glucose, insulin, total cholesterol, LDL-cholesterol, HDL-cholesterol, TG, and Lpa were measured at regular intervals throughout the study, as were fibrinogen and PAI-I.

Safety parameters included adverse events, serious adverse events, clinical laboratory tests (hematology, fasting chemistry, PT, fat soluble plasma vitamin levels), vital signs, physical examination, 12-lead electrocardiograms (ECGs), mammography, and bone mineralization as measured by dual energy X-ray absorptiometry (DEXA).

Routine hematology and chemistry parameters, including serum chemistry including glucose and insulin from the OGTT, creatinine, alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin, gamma glutamyl transferase, alkaline phosphatase, total protein, albumin, urea, sodium, potassium, calcium, uric acid, thyroxine, thyroid stimulating hormone (TSH), vitamin A, vitamin D, and vitamin E, were measured at regular intervals throughout the study,

Additional laboratory parameters measured at 7 centers included the following:
· Serum 1,25-dihydroxy-vitamin D3 + D2
· Serum ionized calcium
· Urine N-telopeptide (creatinine corrected)
· Plasma vitamin K1
· Plasma parathyroid hormone
· Total serum osteocalcin
· Serum under-carboxylated osteocalcin.

6.1.3 Study Design

This was a four year multi-center, randomized, double-blind, parallel-group, placebo-controlled study conducted in obese patients (Body mass index [BMI], ≥ 30 kg/m2 in males and females) who had either normal or impaired glucose tolerance (IGT). A total of 3304 patients were derived from 22 Swedish centers. The study consisted of a prescreening and screening phase (days -90 to -28), a baseline phase (days -21 to -14), and a treatment phase (days 1 to 1457). At least 45% of the patients enrolled were to be male and at least 10% were to have IGT. Two weeks after the baseline visit, patients were randomized (day 1) according to sex and oral glucose tolerance test (OGTT) result strata to one of two treatment groups: placebo orally tid or orlistat 120 mg orally tid in a 1:1 ratio During the baseline visit, and for the duration of the study, all patients received lifestyle intervention counseling that consisted of two components: a nutritionally-balanced, hypocaloric diet, and encouragement to increase physical activity.

Baseline examinations occurred between 21 to 14 days prior to randomization and treatment day 1. Procedures during this visit, included calculation of BMI, fasting laboratory tests (including OGTT, hematology and chemistry), electrocardiogram (ECG), serum pregnancy test (females only), and mammogram (females only). Also, patients completed a diet questionnaire and were instructed to maintain their usual eating patterns. Results obtained during this visit represent baseline values for analysis. As a result of baseline assessments, the following patients were excluded from randomization: patients with mammographic findings of possible, probable or

confirmed malignancy; diabetic patients; patients experiencing a weight loss of > 2 kg between screen and baseline visits.

As part of the lifestyle intervention counseling, patients met with a dietitian on treatment day 1 at which time their diet was reviewed. Patients were maintained on a nutritionally balanced, hypocaloric (approximately 800 kcal deficit) diet containing approximately 30% of calories as fat (optimally as 10% saturated + unsaturated, 5%-10% polyunsaturated, and 10%-15% monounsaturated), 50%-55% as carbohydrate, 15%-20% as protein, and a maximum of 300 mg cholesterol per day starting at day 1 of the treatment phase. Patients were prescribed a diet based upon an estimate of their initial maintenance needs. The diet was designed to promote a weight loss of 0.25 to 0.5 kg per week. The diet included three meals and, if desired, two to three low-fat snacks each day. Alcohol consumption was not to exceed 150 grams of alcohol (approximately 10 drinks) per week. Every six months during the treatment phase, the prescribed diet was readjusted to account for any weight lost during the preceding months. Patients were required to consume a minimum of 1400 kcal per day. Diet counseling occurred during every study visit.

During lifestyle intervention counseling, patients were encouraged to walk at least one extra kilometer per day over and above their usual physical activity. Patients recorded the number of extra kilometers walked each day in a physical activity diary, and the sum of kilometers per week was entered on the CRF.

Due to the potential for fat soluble vitamin levels to decrease during the study, a procedure was developed to provide appropriate supplementation to patients who had low levels of these vitamins at study entry or experienced a decrease in these vitamin levels during treatment. Prothrombin activity was measured as an assessment of vitamin K levels. Any patient with a vitamin A, D or E level below the lower limit of the reference range, or a decrease in PT, had the test repeated at the next scheduled visit. If the value was below the lower limit of the reference range on the repeat test, vitamin supplementation was prescribed for the remainder of the study and vitamin levels were measured at each subsequent visit. Multivitamins as well as vitamins A, D, E and K supplements were prescribed if needed. Vitamins supplied to each site included: [redacted] (multivitamin) [redacted] (vitamin A) [redacted] (vitamin E), [redacted] (vitamin D), and [redacted] (vitamin K). On [redacted] began using a [redacted] that contained a different reagent. Since the new reagent created a slightly different normal range for vitamin D values, a regression formula was used to convert all results obtained from specimens that were tested with the [redacted]

During the initial Phase III studies of orlistat, there was an observed imbalance in the number of cases of breast cancer in orlistat and placebo treatment groups. Therefore, detailed assessments to detect breast abnormalities were undertaken in this study. Mammograms were performed on female patients during the baseline visit, and repeated annually for the duration of the study. Women aged 30-39 years had one projection performed, and women aged 40-60 years had two projections performed. Radiologists were required to record baseline and annual mammography results on a Mammography Report Form page (Module II). Female patients with a code 3, 4 or 5 result at the baseline mammography were excluded from the study.

Prohibited medications during the study were: Appetite suppressants, Resins for lipid lowering, and Fish oil supplements.

After successful completion of screening, patients were randomized according to gender and OGTT result strata to receive either placebo or orlistat in a 1:1 ratio using a centralized randomization procedure and a randomization schedule generated by Roche. To ensure treatment group balance with respect to gender, a separate randomization schedule was used for males versus females.

Patients were instructed to take one capsule of study medication with breakfast, lunch, and dinner. If a meal was not consumed, patients were to take study medication at the time they would usually have consumed a meal.

Protocol Amendments: The protocol was amended three times, on July 31, 1997, August 20, 1998 and July 31, 1999. Complete Amendment histories are located Module II of this report. Summaries of noteworthy changes for each protocol amendment are listed below.

Amendment 1
Safety

- Addition of mammographies, to be performed at baseline and annually for the duration of the study
- Seven additional laboratory parameters were to be measured in the seven teaching hospitals. These additional laboratory parameters were: serum 1,25-dihydroxy-vitamin D3 + D2, serum ionized calcium, urine N-telopeptide (creatinine corrected), plasma Vitamin K1, plasma parathyroid hormone (PTH), serum osteocalcin total and serum under-carboxylated osteocalcin.

Administrative

- Study screening and baseline visit timelines were extended from November 1997 to December 1997
- Randomization code lists and procedures were changed to meet stratification requirements

Analytical

- Addition of the type of descriptive analysis of mammographies comparing changes observed between exams. Treatments were to be compared with respect to the incidences of new abnormalities that occurred by treatment end.

Amendment 2
Safety

- After the diagnosis of diabetes was made, fasting glucose rather than Oral Glucose Tolerance Test (OGTT) would be measured at six month intervals
- Addition to exclusion criteria: female patients with known or suspected breast cancer were excluded from the trial

- Clarification on medications that would exclude patients from participating in the trial due to safety and efficacy

Administrative
- NIDDM was changed to "type 2 diabetes" throughout the protocol to be consistent with the newer classification and to avoid possible confusion

Analytical
- Clarification that glucose measurements would be from whole blood and that the criteria for IGT based on an OGTT at baseline would be a fasting glucose < 6.7 mmol/L and 120 minutes ≥ 6.7 mmol/L but < 10.0 mmol/L. The subsequent diagnosis of IGT or type 2 diabetes would be based on the 120 minute OGTT glucose value, and defined as: whole blood glucose ≥6.7 mmol/L but < 10.0 mmol/L diagnostic of IGT, and whole blood glucose ≥10.0 mmol/L diagnostic of type 2 diabetes.
- Addition of a single repeat OGTT within four weeks of diagnosis of diabetes.
- Study to be extended from duration of 104 weeks until 95 primary cases of type 2 diabetes were observed, with at least 72 of which had a repeat positive follow-up finding diagnostic of diabetes.
- Study would not continue beyond four years.

Amendment 3
Safety
- Updated procedures implemented for reporting pregnancy in female patients or female partners of male patients

Analytical
- Addition of a separate exploratory analysis involving patients diagnosed with diabetes by an OGTT value, and having a repeat positive finding diagnostic of diabetes.

Study Population: Patients were considered eligible for the study if they provided written informed consent and met the following criteria:
- Age: 30 to 60 years;
- BMI: ≥ 30 kg/m2;
- Gender: Male or female. Women of childbearing potential must have had a negative serum pregnancy test at baseline and be using contraception. Post-menopausal women must have been amenorrheic for at least one year; and
- OGTT: Normal Oral Glucose Tolerance or Impaired Glucose Tolerance.

Patients meeting any of the following criteria were excluded from the study:
- Weight loss >2 kg between screening and baseline examination;
- History or presence of significant medical disorders;
- Myocardial infarction, coronary artery bypass graft, or angioplasty within the six months prior to screening;

• Uncontrolled hypertension (systolic blood pressure >165 mmHg or diastolic blood pressure >105 mmHg on two consecutive visits) at screening and baseline;
• Presence of symptomatic cholelithiasis;
• Gastrointestinal surgery for weight reducing purposes or for peptic ulcer including vagotomy;
• History of post-surgical adhesions;
• Active GI disorders such as peptic ulcer disease or malabsorption syndromes;
• Pancreatic disease defined as either a pancreatic enzyme deficiency, or history or current presence of pancreatitis;
• Drug-treated diabetes mellitus;
• History or presence of cancer except for successfully resected basal cell carcinoma of the skin;
• Psychiatric or neurologic disorders requiring chronic medications or which could interfere with the patient's protocol compliance;
· History or current presence of bulimia or laxative abuse;
· Abnormal laboratory test results of clinical significance;
· Excessive alcohol intake defined as >75 hard liquor equivalents per week;
· Smoking cessation within past six months;
· Lactating female;
· Use of any substances of abuse;
· Unable or unwilling to comply with the protocol requirements or was considered by the investigator to be unfit for the study;
· Participation in a clinical trial within 30 days prior to study entry; or
· Previous participation in a clinical trial of orlistat

Patients receiving the following medications during the screening period were excluded from study entry:
· Appetite suppressants;
· Serotonin-specific-reuptake inhibitors such as Prozac, Fontex, Cipramil, Seroxat,, Zoloft, Fevarin;
· Chronically used psychotropic drugs;
· Medications increasing appetite such as cyproheptadine (Periactin®);
· Resins for lipid lowering;
· Fish oil supplements;
· Systemic steroids other than for sex-hormones replacement or oral contraceptives
· Anticoagulants, except for low dose Acetyl salicylic acid(ASA) treatment

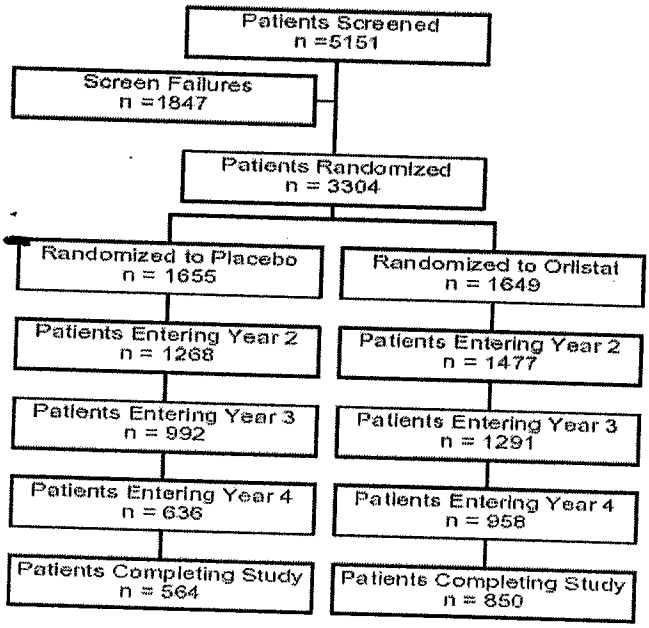
6.1.4 Efficacy Findings

Patient Disposition

A total of 3304 patients were randomized at 22 centers in Sweden. Of these 3304 patients, 1655 were randomized to the placebo treatment group and 1649 were randomized to the orlistat treatment group (Figure below). Approximately equal numbers of patients were randomized to each treatment group at each study center. The most common reasons for screen failures were

inability to meet inclusion/exclusion criteria, abnormal laboratory values and administrative reasons (i.e., scheduling).

Overall, approximately 34% of placebo patients and 52% of orlistat patients completed the 4-year study. Approximately 60% of placebo and 78% of orlistat-treated patients completed two years of treatment.



Throughout the study, at each yearly time point, the number of orlistat patients remaining in the study exceeded the number of placebo patients that remained in the study.

More of the placebo-treated patients (66%) than orlistat-treated patients (48%) withdrew prematurely from the study (Table below). The majority of premature treatment withdrawals were because of non-safety reasons. The most common reasons for premature withdrawals in both treatment groups were: insufficient therapeutic response, refusal of treatment and other reasons. The most predominant other reasons in both treatment groups were: work schedule, lack of time, inability to comply with study schedule and family problems. There were more premature withdrawals in the placebo-treated group than the orlistat-treated group for each of these reasons. A higher percentage of orlistat-treated (8%) compared to placebo-treated patients (4%) discontinued treatment prematurely due to safety reasons. The majority of these safety reasons were adverse events.

Reasons for Patient Withdrawals		
Reason for Withdrawal	Placebo (n=1655)	Orlistat (n=1649)
Lab abnormality	1	0
AE	67	125
Death	4	2
Lack of effect	309	130
Protocol violation	29	26
Refused treatment	332	226
Failure to return	107	111
Other	242	179

Reviewer Comment: The high rate of premature withdrawal from the study underscores the difficulty of doing long-term trials with today's obesity drugs. Use of orlistat is associated with a significant increase in unpleasant side effects, such as fatty/oily stools, and the average weight loss observed in the placebo group was not large. Both of these factors contribute to the problem of high drop out rates.

1.1.1 Baseline Demographics

The placebo and orlistat treatment groups were well-balanced for all of the demographic parameters collected at baseline (Table below). Patients were predominantly Caucasian with a mean BMI of approximately ≥ 37 kg/m^2. Slightly more women than men were enrolled in both treatment groups, but the protocol defined target of at least 45% males was achieved. Twenty one percent (21%) of patients in both treatment groups entered the study with IGT. Therefore, this general population of obese patients consisted of 21% with IGT and 79% of patients with normal OGTT results at baseline.

Baseline Demographic Characteristics		
Characteristic	Placebo	Orlistat
% Female	55%	55%
% IGT	21%	21%
% Normal GT	79%	79%
% Caucasian	99%	99%
Age (years)	44	43
BMI (kg/m^2)	37	37

Reviewer Comment: As expected in a large trial, the two groups were well-matched for baseline demographic characteristics.

Baseline Concomitant Medications

The reported baseline treatments were those that the patients were taking at baseline or within 28 days of the baseline visit. Similar proportions of placebo and orlistat treated patients reported treatment for all groups of concomitant treatments. The most frequent classes of concomitant treatments at baseline reported for both treatment groups were mild analgesics (placebo, 23%; orlistat, 22%), anti-rheumatic and anti-inflammatory agents (placebo, 11%; orlistat 10%) and steroidal agents (placebo and orlistat, 9%). Appendix summarizes all concomitant treatments initiated after the start of randomized treatment and includes those treatments taken for adverse events. The two most commonly reported concomitant treatments in both treatment groups were mild analgesics (placebo, 75%; orlistat, 79%) and anti rheumatic and anti-inflammatory agents (placebo, 45%; orlistat, 51%).

Previous and Concurrent Illness

At least 73% of all patients had at least one previous or concurrent disease at baseline, and the percentage of patients with each disease was similar between treatment groups. The two most frequently reported previous or concurrent diseases were musculoskeletal, connective tissue and bone disorders (placebo, 29%; orlistat, 25%), and infections and infestations (placebo, 20%; orlistat, 22%).

Primary Efficacy Outcome

Time to Onset of Type 2 Diabetes Mellitus

Patients were diagnosed as having type 2 diabetes if their 2-hour whole blood glucose after a single OGTT was > 10 mmol/L.

The average baseline fasting glucose and insulin levels were 4.6 mmol/L and approximately 85 pmol/L, respectively, in both groups.

Orlistat plus lifestyle interventions delayed the time to onset of diabetes (first diagnostic OGTT) compared to placebo plus lifestyle interventions. The Table below provides the cumulative rate for time to onset of diabetes mellitus for each treatment group, the number of OGTT tests at each time point, the number of diabetic cases, and the percentage of cases (relative to the number of patients having an OGTT test). Starting at six months of treatment, a greater proportion of placebo-treated patients developed diabetes than did orlistat-treated patients (1.22% versus 0.32%, respectively). At each subsequent time point, the proportion of placebo-treated patients converting to diabetes mellitus was greater than that of orlistat-treated patients. As a consequence, the cumulative rate of conversion to diabetes mellitus continued to diverge over the entire four-year treatment period. Therefore, at the end of four years, the adjusted cumulative rate for the development of diabetes was approximately 9.0% for placebo and 6.0% for Orlistat (logrank $p < 0.01$).

Cumulative Incidence of Diabetic Cases by Time to First Occurrence - ITT						
Time interval of occurrence	Placebo			Orlistat		
	# patients	# cases	Cumul rate	# patients	# cases	Cumul rate
Day 1	1655			1649		
169	1472	18	.0122	1572	5	.0032
365	1271	10	.0200	1483	10	.0099
533	1106	11	.0297	1362	7	.0150
729	956	13	.0429	1257	7	.0205
897	749	10	.0557	1118	12	.0310
1093	672	10	.0698	1008	14	.0445
1261	551	7	.0816	859	8	.0534
1457	521	5	.0904	810	7	.0615

Time to Onset of a Repeat Diagnostic Diabetes Test.

As pertains to this section of the review, a repeat positive test result for diabetes was included if a patient's next OGTT measurement at 2 hours was >10 mmol/L or if their whole blood fasting glucose (Time 0) was ≥ 6.1 mmol/L. Alternatively, a repeat positive test result for diabetes could have been identified by two consecutive subsequent fasting measurements of ≥ 6.1 mmol/L.

Cumulative Incidence of Repeat Diabetic Cases by Time to First Occurrence						
Time interval of occurrence	Placebo			Orlistat		
	# patients	# cases	Cumul rate	# patients	# cases	Cumul rate
Day 1	1655			1649		
169	1472	1	.0007	1572	1	.0006
365	1285	12	.0100	1486	5	.0040
533	1116	6	.0153	1368	3	.0062
729	968	8	.0234	1267	5	.0101
897	761	5	.0210	1125	10	.0189
1093	686	6	.0384	1015	5	.0237
1261	566	6	.0486	874	6	.0304
1457	537	3	.0539	826	3	.0340

Because the protocol allowed for the diagnosis of DM based on the results of a single OGTT, Roche was asked to provide an analysis limited to only those cases of DM that were confirmed by a second OGTT. The results of that analysis are shown in the following table.

Cumulative Incidence of Diabetic Cases by Time to First Occurrence and Confirmed by a Second OGTT- ITT

Time interval of occurrence	Placebo			Orlistat		
	# patients	# cases	Cumul rate	# patients	# cases	Cumul rate
Day 1	1655			1649		
169	1472	1	0.0007	1572	1	0.0006
365	1271	12	0.010	1483	5	0.004
533	1106	5	0.014	1362	3	0.006
729	956	8	0.023	1257	4	0.009
897	749	5	0.029	1118	8	0.016
1093	672	6	0.038	1008	4	0.020
1261	551	6	0.048	859	5	0.026
1457	521	1	0.049	810	3	0.029

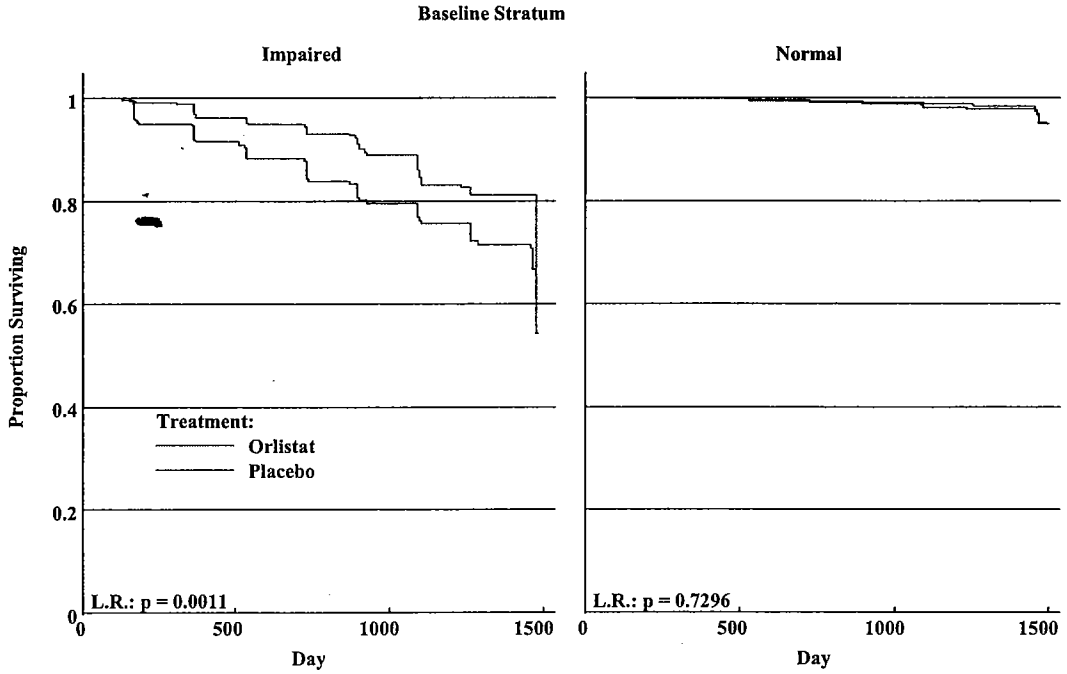
Reviewer Comment: It is clear that elimination of the cases of DM that were based on the results of only one OGTT reduces quite dramatically the total number of patients who were diagnosed with DM in both treatment groups. Nonetheless, as pointed out by the company, the lower cumulative incidence of DM based on two consecutive OGTTs in the orlistat vs. the placebo groups was still of nominal statistical significance ($p < 0.05$).

Reviewer Comment: Of the 5 orlistat patients who had a diagnosis of type 2 diabetes determined from the results of an OGTT at Month 6 and did not have a second confirmatory OGTT, one patient discontinued before subsequent glucose values were taken. Of the remaining 4 patients, all had subsequent whole blood glucose values of 6.1 mmol/L or greater confirming the diagnosis of type 2 diabetes.

Of the 18 placebo patients who had a diagnosis of type 2 diabetes determined from the results of an OGTT at Month 6, seven either did not have a subsequent glucose value or did not have a fasting glucose level of 6.1 mmol/L or greater at subsequent measurements. Therefore 11 of the 18 placebo patients who had a diabetic OGTT at Month 6, had evidence of diabetes at a subsequent time point.

Development of Diabetes in Subgroups who had Normal or Impaired Glucose Tolerance at Baseline

The following survival curve for the development of diabetes illustrate that the statistically and clinically significant results observed in the overall population of subjects were driven by the 20% of patients who had IGT at baseline.



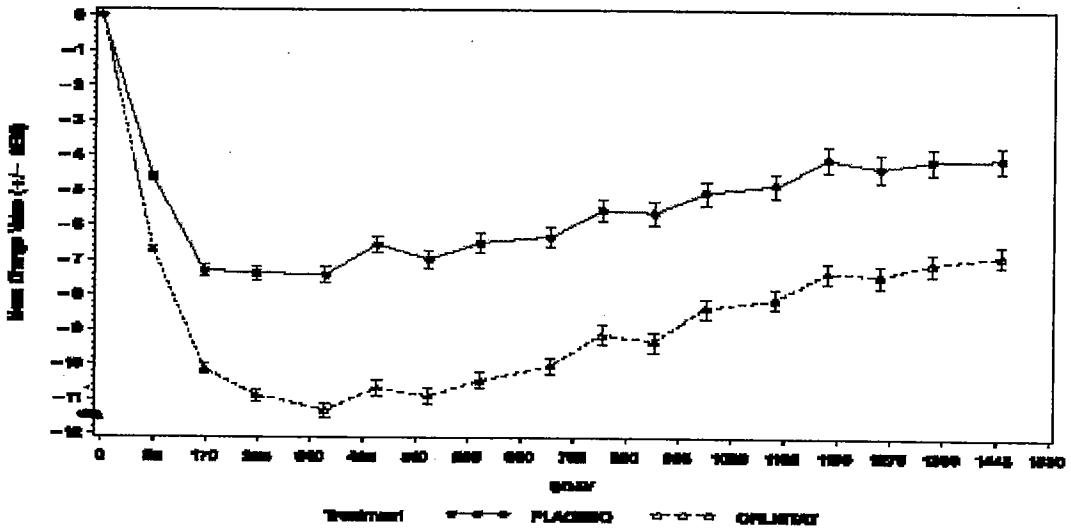
There were 3044 patients with baseline and follow-up 2-hour OGTT values. The baseline characteristics of the 154 patients developing diabetes were as follows: 14 were female with normal baseline OGTT, 23 were males with normal baseline OGTT, 52 were females with impaired baseline OGTT, and 65 were males with impaired baseline OGTT.

Therefore, a large proportion of patients converting to diabetes began the study with impaired glucose tolerance. The remaining 94.94% of patients completed the study without evidence of diabetes.

Secondary Efficacy Outcome

Changes in Body Weight

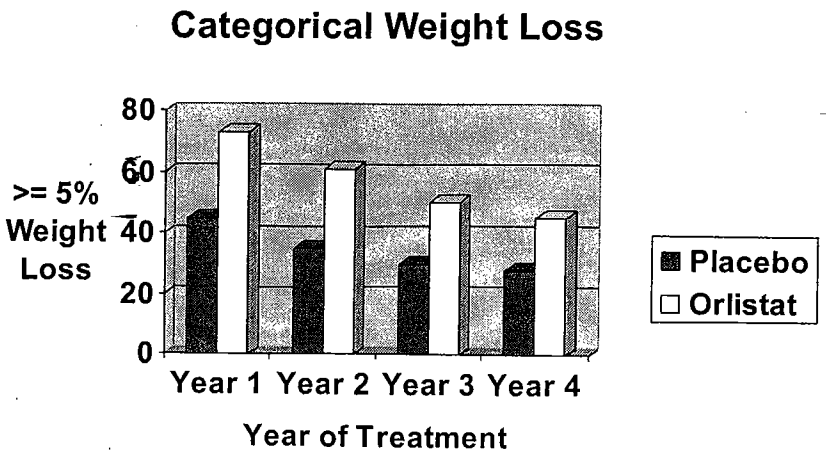
In the ITT observed population, by the end of the first year of treatment, the mean change in body weight was -7.46 kg for the placebo treatment group compared to -11.37 kg for the orlistat treatment group (nominal $p < 0.001$)(Figure below). After four years, the mean change in body weight was -4.09 kg for the placebo treatment group compared to -6.90 kg for the orlistat treatment group (nominal $p < 0.001$). Similar results were observed for the ITT (LOCF) and the Completers datasets.



Categorical Weight Loss

In the ITT observed population, at 4 years, 53% of orlistat patients vs. 37% of placebo patients achieved at least a 5% reduction in baseline body weight. In the same population, at 4 years, 26% vs. 16% of orlistat and placebo-treated patients, respectively, lost at lease 10% of baseline body weight. Very similar results were observed for the Completers.

The Figure below provides the percentage of patients in the placebo and orlistat groups who lost at least 5% of their baseline body weight at Years 1 – 4.



Reviewer Comment: Not surprisingly, the average percent weight loss in the subjects who developed either IGT or DM was less that the average weight loss in those subjects who did not develop IGT or DM. Of those who did develop IGT or DM, the mean percent weight loss from baseline to Year 4 was -0.87% in the placebo group and -3.4% in the orlistat group; of those who did not develop IGT or DM, the mean percent weight loss in the placebo group was -3.5% and -5.8% in the orlistat group.

Serum Lipids

Total Cholesterol: Baseline TC levels were 5.8 mmol/L in both groups. After 4 years, the mean percent change in TC from baseline was -2.0% in the placebo group and -7.0% in the orlistat group (nominal $p<0.001$).

LDL Cholesterol: Baseline LDL levels were approximately 3.7 mmol/L in both groups. After 4 years, the mean percent change in LDL from baseline was -3.9% and -11.7% in the placebo and orlistat groups, respectively (nominal $p<0.001$).

HDL Cholesterol: Baseline HCL levels were 1.20 mmol/L in both groups. At 4 years the mean percent change in HDL from baseline was 7.1% in the placebo group and 6.0% in the orlistat group (nominal $p=0.06$).

Triglycerides: Baseline TG levels were 1.9 mmol/L in both groups. At 4 years, the mean percent change in TG levels from baseline was 1.3% and 3.6% in the placebo and orlistat groups, respectively (nominal $p=0.08$).

Lipoprotein a: Baseline Lpa levels were about 253 ug/L in both groups. At 4 years, the mean percent change in Lpa levels from baseline were 16.0% and 17.0% in the placebo and orlistat groups (nominal $p=0.03$).

Patients with Baseline Lipid Abnormalities

A priori, Roche defined the following cutoff values for baseline lipid abnormalities:

LDL > 3.36 mmol/L
HDL < 0.91 mmol/L
TG > 2.54 mmol/L

LDL: The mean baseline LDL values in this subgroup was approximately 4.2 mmol/L in each group. The mean percent change from baseline to Year 4 was -7.3% in the placebo group and -14.9% in the orlistat group (nominal $p<0.001$).

HDL: The mean baseline HDL values in this subgroup was 0.85 mmol/L in each group. The mean percent change from baseline to Year 4 was 12.9% in the placebo group and 11.6% in the orlistat group (nominal $p=0.3$).

TG: The mean baseline TG levels in this subgroup was 3.7 mmol/L in the placebo group and 3.6 mmol/L in the orlistat group. The mean percent change from baseline to Year 4 was -13.9% and -15.6% in the placebo and orlistat groups, respectively (nominal p=0.5).

Fasting Insulin and Glucose

Insulin: Baseline fasting insulin levels were 83.6 pmol/L in the placebo group and 86.1 pmol/L in the orlistat group. The mean change from baseline to Year 4 was -15.7 pmol/L in the placebo group and -24.9 pmol/L in the orlistat group (nominal p<0.001).

For those subjects with baseline fasting insulin levels > 90 pmol/L, the mean changes from baseline to Year 4 were -37.5 pmol/L and -47.0 pmol/L in the placebo and orlistat groups, respectively (nominal p=0.002).

Glucose: Baseline fasting glucose levels were 4.6 mmol/L in both groups. The mean changes from baseline to Year 4 were 0.23 mmol/L and 0.12 mmol/L in the placebo and orlistat groups, respectively (nominal p<0.001).

Blood Pressure

Systolic Blood Pressure: The baseline SBP values were 130 mmHg in each group. The mean change from baseline to Year 4 was -2.6 mmHg in the placebo group and -4.1 mmHg in the orlistat group (nominal p<0.001).

Diastolic Blood Pressure: The baseline DBP values were 82 mmHg in each group. The mean change from baseline to Year4 was -0.9 mmHg and -1.9 mmHg in the placebo and orlistat groups, respectively (nominal p<0.001).

For those patients with baseline SBP values > 140 mmHg, the mean changes from baseline to Year 4 were -8.7 mmHg in the placebo group and -11.4 mmHg in the orlistat group (nominal p=0.002).

For those patients with baseline DBP values > 90 mmHg, the mean changes from baseline to Year 4 were -6.3 mmHg in the placebo group and -8.0 mmHg in the orlistat group (p=0.006).

Pulse: The mean baseline pulse rates in the placebo and orlistat groups were 75 bpm. The average change from baseline to Year 4 was -5.3 bpm in the placebo group and -6.5 bpm in the orlistat group (nominal p<0.001).

Waist Circumference: The average baseline waist circumference was 115 cm in both groups. The mean change from baseline to Year 4 was -4.0 cm in the placebo group and -5.8 cm in the orlistat group (nominal p<0.001).

Development of Impaired Glucose Tolerance in Patients with Normal Glucose Tolerance at Baseline

Although the incidence of the development of impaired glucose tolerance in patients with normal glucose tolerance at baseline was lower in the orlistat compared with the placebo group the difference was not statistically significant (nominal p=0.2).

Cumulative Incidence of IGT in Patients with Normal Glucose Tolerance at Baseline by Time to First Occurrence - ITT

Time interval of occurrence	Placebo			Orlistat		
	# patients	# cases	Cumul rate	# patients	# cases	Cumul rate
Day 1	1310			1297		
169	1148	65	0.057	1235	74	0.060
365	939	53	0.110	1098	38	0.092
533	771	30	0.145	973	36	0.126
729	636	24	0.177	867	20	0.146
897	483	19	0.210	755	32	0.182
1093	425	18	0.242	659	30	0.220
1261	336	15	0.276	537	23	0.253
1457	306	12	0.305	488	15	0.276

Development of Diabetes in Patients with Impaired Glucose Tolerance at Baseline

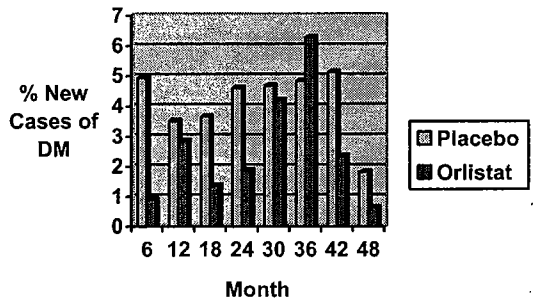
As shown in the table below, there were about 16 more cases of diabetes mellitus in the placebo group than would be expected under the null hypothesis of equal survival distributions (logrank p <0.01). The odds ration for the development of diabetes in the orlistat group was 0.55 (0.38, 0.80).

Cumulative Incidence of Diabetes n Patients with IGT at Baseline by Time to First Occurrence - ITT

Time interval of occurrence	Placebo			Orlistat		
	# patients	# cases	Cumul rate	# patients	# cases	Cumul rate
Day 1	345			352		
169	324	16	0.049	337	3	0.009
365	285	10	0.083	316	9	0.037
533	246	9	0.116	293	4	0.050
729	217	10	0.157	268	5	0.068
897	171	8	0.196	238	10	0.107

Cumulative Incidence of Diabetes n Patients with IGT at Baseline by Time to First Occurrence - ITT						
Time interval of occurrence	Placebo			Orlistat		
	# patients	# cases	Cumul rate	# patients	# cases	Cumul rate
1093	145	7	0.235	207	13	0.163
1261	117	6	0.274	171	4	0.183
1457	110	2	0.288	160	1	0.188

The following figure provide the percent of new cases of diabetes by 6-month interval in those patients who had IGT at baseline. The largest difference between groups in the percentage of new cases of diabetes occurred during the first 6 months of the study.



6.1.5 Clinical Microbiology

N/A

6.1.6 Efficacy Conclusions

Treatment with orlistat 120 mg TID reduces the risk of developing type 2 diabetes in patients with impaired, but not normal, glucose tolerance.

7 INTEGRATED REVIEW OF SAFETY

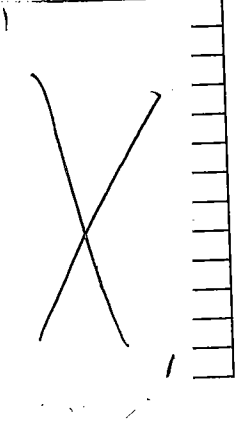
7.1 METHODS AND FINDINGS

7.1.1 Deaths

Seven placebo and 2 orlistat-treated patients died during or recently following trial participation. Two additional placebo patients died after study participation. The following table provides details about these deaths.

Listing of Patient Deaths

Placebo	Cause of Death	Last Trial Day	Day of Death
54 year old male	Ruptured AAA	1093	
40 year old male	Pancreatitis	542	
48 year old female	MI	284	
45 year old female	MI	980	
51 year old male	Renal Cell Carcinoma	1319	
52 year old male	MI	1059	
54 year old female	MI	387	
Orlistat			
53 year old male	MI	502	
45 year old male	Suicide	82	



7.1.2 Other Serious Adverse Events

Thirteen percent of placebo and 15% of orlistat patients reported at least one serious adverse event during the course of the 4-year study. Of note, 9 placebo and 17 orlistat subjects reportedly developed cholelithiasis (7 subjects in each group developed cholecystitis). There were no imbalances between groups for reports of pancreatitis or renal stones.

7.1.3 Dropouts and Other Significant Adverse Events

7.1.3.1 Overall profile of dropouts

Of the dropouts that were related to safety, 125 orlistat and 67 placebo subjects discontinued treatment prematurely because of an adverse event.

7.1.3.2 Adverse events associated with dropouts

The difference between groups in the number of dropouts due to an adverse events was due almost entirely to events related to the GI tract, such as fatty/oily stools, abdominal pain, and fecal incontinence.

7.1.3.3 Other significant adverse events

None

7.1.4 Other Search Strategies

None

7.1.5 Common Adverse Events

By far and not surprisingly, the most comment adverse events were related to the GI tract (See Table in Appendix). The following events were reported during the first year of the study by at least 5% of subjects in the orlistat group and at least double the incidence of that in the placebo group: Fatty stool (43% vs. 5%), fecal urgency (18% vs. 5%), flatus with discharge (11% vs. 1%), oily evacuation (9% vs. 0.4%), and oily discharge (7% vs. 0.1%). The incidence of these events decreased as a function of the trial duration.

7.1.5.1 Eliciting adverse events data in the development program

It is known from previous experience in clinical trials with orlistat that there is a relatively high incidence of adverse events reported within the gastrointestinal (GI) system. To ensure consistency across study centers in identifying those GI adverse events thought to be potentially related to orlistat, Roche formulated a dictionary of standard terms. Each investigator received this dictionary within the protocol appendices to be used when reporting an adverse event related to bowel habit (Table below). Items marked with an asterisk (*) in this dictionary were always considered to be adverse events and appear in this list in decreasing order of clinical significance. Unasterisked items may represent variations in normal defecation patterns and therefore were considered to be adverse events only when described as bothersome by the patient. The following are rules the investigators used when recording defecation patterns that occurred as a complex (i.e., more than one defecation pattern occurring at the same time):

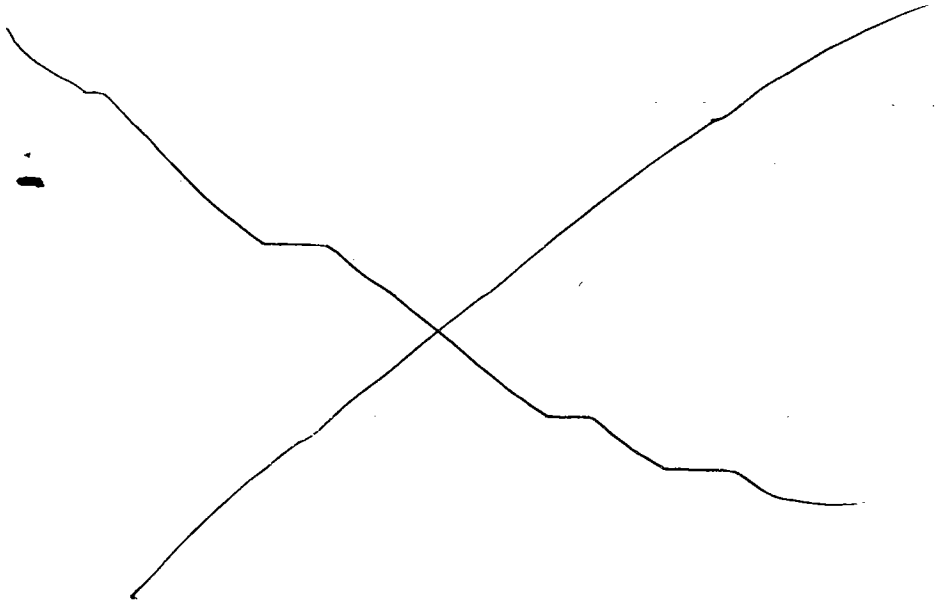
1. If the most descriptive term for the complex was any asterisked (*) term, this single term was to be recorded as the adverse event.

2. If the most descriptive term was not an asterisked (*) term, and any term(s) marked with (*) occurred as part of the complex, the most descriptive term was to be recorded as a separate adverse event. All of the asterisked (and any remaining unasterisked term(s)) were listed on a single adverse event entry line. The term on this line that appeared highest on the list in the Table below was chosen as the preferred term by the sponsor.

3. If it was not possible to choose one term as the most descriptive, then each symptom that occurred as part of the complex was recorded on the same adverse event entry line of the CRF. The term that appeared highest on the list in the Table below was later chosen as the preferred term by the sponsor.

Any symptom not in this dictionary that occurred simultaneously with a defecation pattern symptom or symptoms was to be recorded as a separate adverse event. Investigators were discouraged from using the terms "constipation" or "diarrhea" in describing defecation patterns.

Preferred Term	Definition



7.1.5.2 Appropriateness of adverse event categorization and preferred terms

The sponsor's adverse event categorization and use of preferred terms were appropriate.

7.1.5.3 Incidence of common adverse events

By far and not surprisingly, the most comment adverse events were related to the GI tract (See Table in Appendix). The following events were reported during the first year of the study by at least 5% of subjects in the orlistat group and at least double the incidence of that in the placebo group: Fatty stool (43% vs. 5%), fecal urgency (18% vs. 5%), flatus with discharge (11% vs. 1%), oily evacuation (9% vs. 0.4%), and oily discharge (7% vs. 0.1%). The incidence of these events decreased as a function of the trial duration.

7.1.5.4 Common adverse event tables

The table below provides the common (> 2% incidence in the orlistat group) adverse events during the first year of the trial.

Adverse Event	Placebo (N=1655)	Orlistat (N=1649)
GASTROINTESTINAL DISORDERS		
FATTY/OILY STOOL	85 (5.1)	716 (43.4)
STOOLS SOFT	272 (16.4)	499 (30.3)
FLATULENCE	327 (19.8)	400 (24.3)
INCREASED DEFECATION	279 (16.9)	362 (22.0)
FECAL URGENCY	87 (5.3)	301 (18.3)
LIQUID STOOLS	149 (9.0)	273 (16.6)
ABDOMINAL PAIN NOS	188 (11.4)	235 (14.3)
FLATUS WITH DISCHARGE	16 (1.0)	188 (11.4)
ABDOMINAL PAIN UPPER	157 (9.5)	160 (9.7)
OILY EVACUATION	6 (0.4)	143 (8.7)
OILY SPOTTING	2 (0.1)	109 (6.6)
GASTRITIS NOS	82 (5.0)	83 (5.0)
FECAL INCONTINENCE	4 (0.2)	60 (3.6)
SORE THROAT NOS	45 (2.7)	52 (3.2)
FAECES DISCOLOURED	4 (0.2)	40 (2.4)
HAEMORRHOIDS	16 (1.0)	38 (2.3)
INFECTIONS AND INFESTATIONS		
INFLUENZA	296 (17.9)	318 (19.3)
SINUSITIS NOS	55 (3.3)	71 (4.3)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS		
RHINITIS SEASONAL	22 (1.3)	41 (2.5)
COUGH	27 (1.6)	35 (2.1)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS		
PYREXIA	47 (2.8)	53 (3.2)
PSYCHIATRIC DISORDERS		
DEPRESSION NEC	34 (2.1)	44 (2.7)
INJURY AND POISONING		
JOINT SPRAIN	42 (2.5)	43 (2.6)
MUSCULOSKELETAL, CONNECTIVE TISSUE AND BONE DISORDERS		
SCIATICA	37 (2.2)	38 (2.3)

See Appendix for a complete listing of all adverse events.

7.1.5.5 Identifying common and drug-related adverse events

Given its pharmacodynamic mode of action to inhibit breakdown and absorption of dietary fat, GI adverse events such as flatulence, cramping, loose stools are common orlistat-related adverse events.

7.1.5.6 Additional analyses and explorations

In orlistat-treated patients, the most frequent gastrointestinal adverse event (also the most frequent adverse event) that was possibly and probably treatment-related was fatty/oily stool during each year of treatment. The incidence of possibly and probably treatment-related fatty/oily stool in orlistat-treated patients was 38% and 5% in year 1, 21% and 5% in year 2, 13% and 2% in year 3, and 7% and 2% in year 4. Other common gastrointestinal adverse events that were possibly or probably treatment-related included stools soft, flatulence, increased defecation, abdominal pain, liquid stools, and gastritis for different years of treatment.

7.1.6 Less Common Adverse Events

There were no other adverse events that appeared to be drug-related.

7.1.7 Laboratory Findings

7.1.7.1 Overview of laboratory testing in the development program

Fasting blood samples were collected from each patient for laboratory assessments. Samples were obtained prior to taking study medication for that day. All laboratory work was analyzed by a qualified central laboratory [redacted] that provided each study center with standard operating instructions for sampling, handling, and dispatch of laboratory specimens.

7.1.7.2 Selection of studies and analyses for drug-control comparisons of laboratory values

N/A

7.1.7.3 Standard analyses and explorations of laboratory data

7.1.7.3.1 Analyses focused on measures of central tendency

The following section provides the mean changes from baseline to Endpoint for various standard laboratory parameters.

Hematocrit: The average hematocrit value did not change in the placebo group and decreased by 0.01 in the orlistat group.

Platelets: The average platelet values changed by approximately 20 x 10^9/L.

ALT: The mean ALT value decreased by 3.3 U/L in the placebo group and 4.3 U/L in the orlistat group.

AST: The mean AST value decreased by 0.6 U/L in the placebo group and 0.3 U/L in the orlistat group.

GGT: The average GGT value decreased by 0.3 U/L in the placebo group and 3.0 in the orlistat group.

Calcium: The average calcium level did not change in either group.

BUN: The average levels of BUN decreased by 0.01 mmol/L in the placebo group and 0.01 in the orlistat group.

Creatinine: The average creatinine level increase by 1.7 umol/L in the placebo group and decreased by 0.3 umol/L in the orlistat group.

7.1.7.3.2 Analyses focused on outliers or shifts from normal to abnormal

Levels of lymphocytes were markedly low (< 1.0 x 10^9/L) more often in the orlistat than the placebo group, throughout the 4 year study. The incidence rates for Years 1, 2, 3, and 4 were 1.3% and 0.8%; 1.5% and 0.8%; 1.9% and 1.2%; and 3.3% and 2.7%, (orlistat vs. placebo) respectively.

Levels of GGT were markedly high (> 120 U/L) more often in the orlistat than the placebo group during the first 3 years of the trial. The incidence rates for Years 1, 2, and 3 were 2.4% and 1.3%; 2.5% and 1.8%; and 2.2% and 1.9% (orlistat vs. placebo) respectively. The incidence rates for Year 4 were 1.8% and 2.4% for orlistat and placebo.

7.1.7.4 Additional analyses and explorations

None

7.1.7.5 Special assessments

Based on its pharmacodynamic mechanism of action, orlistat is known to inhibit the absorption of fat-soluble vitamins and beta-carotene. Therefore, the following analyses of vitamin levels was performed.

The mean changes in serum vitamin A levels from baseline to Year 4 were -0.19 umol/L in the placebo group and -0.23 umol/L in the orlistat group (p=0.02).

The mean changes in serum 25(OH)D levels from baseline to Year 4 were -13.1 nmol/mL in the placebo group and -17.1 nmol/mL in the orlistat group (p<0.001).

The mean changes in serum vitamin E levels from baseline to Year 4 were 0.35 umol/L in the placebo group and -2.8 umol/L in the orlistat group (p<0.001).

The mean changes in serum vitamin K levels from baseline to Year 4 were 0.06 ug/L in the placebo group and -0.09 ug/L in the orlistat group (p<0.001). The mean values for prothrombin time (normalized ratio) did not change in the placebo group and decreased by 0.04 in the orlistat group.

The following figures apply to those patients who had normal fat-soluble vitamin levels at baseline.

Approximately 4% of placebo and 5% of orlistat subjects had two or more consecutive low vitamin A levels during the trial.

None of the placebo and 0.2% of the orlistat patients had two or more consecutive low 25(OH)D levels during the trial.

Half of one percent of the placebo subjects and 3% of the orlistat patients had two or more consecutive low vitamin E levels during the study.

No patient in either group developed a low serum vitamin K level during the study.

Reviewer Comment: Although the reference ranges for serum 25OHD vary depending on the assay used, many laboratories consider vitamin D levels above 10 nmol/L as normal. Emerging data, however, suggests that 25OHD levels below 50 nmol/L are associated with suboptimal levels of serum iPTH and some investigators consider 25OHD levels below 50 nmol/L as representing vitamin D insufficiency[1].

At baseline, 832 placebo subjects and 888 orlistat subjects had baseline 25OHD levels > 50 nmol/L. During the trial, 454 (55%) of the placebo subjects and 684 (77%) of the orlistat subjects developed two or more consecutive 25OHD values < 50 nmol/L.

Given the this study was conduced in Sweden, it is not surprising that more than 40% of the subjects had baseline serum 25OHD levels below 50 nmol/L.

That more orlistat-treated compared with placebo-treated subjects developed levels of 25OHD below 50 nmol/L is not unexpected based on the pharmacodynamic action of orlistat and the results of previous studies. The approved labeling appropriately recommends that all patients who take orlistat receive a daily supplement that contains fat-soluble vitamins.

Note: subjects in XENDOS did not receive universal vitamin supplementation.

The following special laboratory assessments were made, as they relate to the possibility that orlistat could interfere with absorption of calcium and/or vitamin D, and therefore affect PTH and bone metabolism.

Serum Osteocalcin: The mean levels of serum Osteocalcin, a marker of bone resorption, increased by 0.4 ug/L in the placebo group and 0.3 ug/L in the orlistat group.

PTH: The mean levels of PTH increased by 12 and 15 ng/L in the placebo and orlistat groups, respectively.

Body Composition was assessed by computed tomography in a subset of patients from two clinical sites. Of greatest interest is the change in visceral fat content, measured at the level of L4.

At baseline the mean visceral fat content was 183 cm^2 in the placebo group and 196 cm^2 in the orlistat group. The mean changes from baseline to Year 4 were -15 cm^2 and -31 cm^2 in the placebo and orlistat groups, respectively. The mean percent weight loss in these two groups from baseline to Year 4 were -2.8% in the placebo group and -5.4% in the orlistat group.

1 Holick MF. Redefining vitamin D insufficiency. 1998 *The Lancet* 351: 805-806.

7.1.8 Vital Signs

7.1.8.1 Overview of vital signs testing in the development program

Vital signs were obtained at baseline and every 6 months thereafter.

7.1.8.2 Selection of studies and analyses for overall drug-control comparisons

N/A

7.1.8.3 Standard analyses and explorations of vital signs data

7.1.8.3.1 Analyses focused on measures of central tendencies

The baseline SBP values were 130 mmHg in each group. The mean change from baseline to Year 4 was -2.6 mmHg in the placebo group and -4.1 mmHg in the orlistat group (nominal $p<0.001$).

The baseline DBP values were 82 mmHg in each group. The mean change from baseline to Year4 was -0.9 mmHg and -1.9 mmHg in the placebo and orlistat groups, respectively (nominal $p<0.001$).

For those patients with baseline SBP values > 140 mmHg, the mean changes from baseline to Year 4 were -8.7 mmHg in the placebo group and -11.4 mmHg in the orlistat group (nominal $p=0.002$).

For those patients with baseline DBP values > 90 mmHg, the mean changes from baseline to Year 4 were -6.3 mmHg in the placebo group and -8.0 mmHg in the orlistat group (nominal $p=0.006$).

The mean baseline pulse rates in the placebo and orlistat groups were 75 bpm. The average change from baseline to Year 4 was -5.3 bpm in the placebo group and -6.5 bpm in the orlistat group (nominal $p<0.001$).

7.1.8.3.2 Analyses focused on outliers or shifts from normal to abnormal

Of the patients who had normal baseline vital signs, 1 orlistat patient and none of the placebo subjects developed a pulse rate of > 100 bpm on two or more consecutive visits. Nineteen (1.2%) of the orlistat subjects and 35 (2.3%) of the placebo patients developed a SBP > 160 mmHg on two or more consecutive visits. Twenty-five (1.6%) of orlistat subjects and 35 (2.3%) of the placebo patients developed a DBP > 100 mmHg on two or more consecutive visits.

7.1.8.3.3 Marked outliers and dropouts for vital sign abnormalities

See above section, 7.1.8.3.2

7.1.8.4 Additional analyses and explorations

None

7.1.9 Electrocardiograms (ECGs)

7.1.9.1 Overview of ECG testing in the development program, including brief review of preclinical results

There were no signals from the preclinical development of orlistat to suggest that the drug would affect cardiac conductivity.

7.1.9.2 Selection of studies and analyses for overall drug-control comparisons

ECG were performed at baseline and Years 2, 3, and 4.

7.1.9.3 Standard analyses and explorations of ECG data

7.1.9.3.1 Analyses focused on measures of central tendency

See below

7.1.9.3.2 Analyses focused on outliers or shifts from normal to abnormal

Approximately 4.3% of placebo-treated patients and 4.5% of orlistat-treated patients with a normal baseline ECG result had an abnormal ECG finding at the end of treatment, and over 60% of both the placebo-treated and orlistat-treated patients with an abnormal baseline ECG result had a normal ECG finding at the end of treatment.

Number of Subjects with Newly Developed ECG Abnormalities

	Placebo	Orlistat
ECG Abnormality[a]	**n = 1118**	**n = 1334**
Abnormal rhythm	11 (1.0)	17 (1.3)
Ventricular/Supraventricular contractions	3 (0.3)	4 (0.3)
ST segment and/or T wave changes	19 (1.7)	19 (1.4)
Atrioventricular block	4 (0.4)	6 (0.4)
Left bundle branch block	2 (0.2)	4 (0.3)

Number of Subjects with Newly Developed ECG Abnormalities		
Right bundle branch block	2 (0.2)	5 (0.4)
Q waves/evidence of old myocardial	4 (0.4)	8 (0.7)
Infarction		
Prolonged QT interval	1 (0.1)	1 (0.1)
Left ventricular hypertrophy	4 (0.4)	5 (0.4)
Axis deviation	1 (0.1)	1 (0.1)
Intraventricular conduction delay	1 (0.1)	5 (0.4)
Others	3 (0.3)	2 (0.1)

7.1.9.3.3 Marked outliers and dropouts for ECG abnormalities

None

7.1.9.4 Additional analyses and explorations

None

7.1.10 Immunogenicity

N/A

7.1.11 Human Carcinogenicity

An imbalance was noted in the number of women who were diagnosed with breast cancer in the orlistat vs. the placebo groups from studies submitted with the original NDA in 1996. Subsequent data, largely from the then ongoing XENDOS trial, failed to confirm an imbalance in this adverse event.

A total of 4 placebo and 1 orlistat-treated patient was diagnosed with breast cancer during this trial. One orlistat and none of the placebo patients was diagnosed with carcinoma in situ.

7.1.12 Special Safety Studies

None

7.1.13 Withdrawal Phenomena and/or Abuse Potential

Based on the low bioavailability and the mechanism of action, there is no reason to believe that orlistat would be associated with physical abuse or withdrawal phenomena.

A case report of a woman with bulimia nervosa who abused orlistat as a laxative was recently published[2].

7.1.14 Human Reproduction and Pregnancy Data

In animal reproductive studies, no embryotoxic or teratogenic effects were observed with orlistat. In absence of a teratogenic effect in animals, no malformative effect is expected in human beings. However, orlistat is not recommended for use during pregnancy in the absence of clinical data. The secretion of orlistat in human breast milk has not been investigated.

Up until January 31, 2004, a total of 496 single pregnancy cases were reported on maternal exposure). No cases on paternal exposure were reported.

Of these cases, there were 12 reports of birth defects (2.4% of all cases of exposure), 45 cases were lost to follow up, 131 cases were reported as normal babies, 2 as normal fetuses, 24 as "other" disorders, 181 as ongoing pregnancies, and 101 cases as "unknown".

The types of birth defects reported were quite different and did not suggest a pattern of any kind.

7.1.15 Assessment of Effect on Growth

In a study of approximately 500 obese adolescent males and females (this study was the basis for granting orlistat 6-months exclusivity and adding data to the Pediatric Use subsection of the labeling), one year of treatment with 120 mg TID orlistat or placebo was associated with an average height increase of about 1.0 cm.

7.1.16 Overdose Experience

Since the bioavailability of orlistat is very low, systemic reactions to "overdose" are not expected. Roche reports that there are 16 cases of "overdose" in their database from spontaneous Postmarketing reports, and 7 cases of "overdose" in their controlled trial database. In most of these cases, Roche reports that the outcomes are unknown. The largest acute ingestion of orlistat was in a 13-year-old who took 52 capsules of orlistat in a suicide attempt. There was no information regarding the outcome.

7.1.17 Postmarketing Experience

As part of an assessment for another approved obesity drug, the Office of Drug Safety analyzed the total number of fatalities that have been submitted to the Agency's Adverse Event Reporting System. The following table provides these data during the time period of initial marketing in the spring of 1999 through 18 March 2002.

ORLISTAT FATAL CASES BY CAUSE OF DEATH

Reported Cause of Death	Number of Cases
Cardiac (i.e., myocardial infarction, cardiomyopathy, congestive heart failure)	14
Pulmonary embolism	1
Pneumonia	1

ORLISTAT FATAL CASES BY CAUSE OF DEATH	
Reported Cause of Death	**Number of Cases**
Gastrointestinal hemorrhage	1
Intestinal perforation	1
Retroperitoneal fibrosis	1
Liver failure	1
Drug Interaction*	1
Splenic infarction	1
Pancreatitis	2
Unknown	5

7.2 Adequacy of Patient Exposure and Safety Assessments

7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

7.2.1.1 Study type and design/patient enumeration

See section 6 of this review

7.2.1.2 Demographics

See section 6 of this review.

7.2.1.3 Extent of exposure (dose/duration)

See section 6 of this review.

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

7.2.2.1 Other studies

None

7.2.2.2 Postmarketing experience

See section 7.1.17 of this review.

7.2.2.3 Literature

Results of XENDOS have been published in the January 2004 issue of *Diabetes Care*[3]. This reviewer has read and analyzed this publication.

7.2.3 Adequacy of Overall Clinical Experience

XENDOS was a very large, long-term randomized, controlled trial. Relative to most studies submitted in support of regulatory approval, this trial provides an adequate assessment of orlistat's efficacy and safety.

7.2.4 Adequacy of Special Animal and/or In Vitro Testing

Given the extremely low bioavailability of orlistat, it would not be worthwhile to conduct special animal or in vitro assessments of the drug's affect on cardiac repolarization.

7.2.5 Adequacy of Routine Clinical Testing

The sponsor's testing of routine clinical parameters in this trial was adequate.

7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

See review of the original NDA, submitted in 1996.

7.2.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

Although the sponsor adequately assessed the effect of orlistat on serum levels of vitamin A, D, and E, more sensitive measures of vitamin K status than prothrombin time could have been conducted. One of the more sensitive measures of vitamin K status is the level of undercarboxylated osteocalcin.

7.2.8 Assessment of Quality and Completeness of Data

In general, this reviewer believes that the quality of the submitted XENDOS data is good.

7.2.9 Additional Submissions, Including Safety Update

None

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

Gastrointestinal adverse events are the most common drug-related adverse events associated with orlistat's use. In particular, fatty/oily stool was reported by 38% of orlistat treated subjects and 5% of placebo subjects during Year 1. Of note, the incidence of fatty/oily stool decreased progressively in the orlistat group during each successive year of the trial, such that the incidence was 7% in the orlistat group during Year 4.

7.4 General Methodology

7.4.1 Pooling Data Across Studies to Estimate and Compare Incidence

7.4.1.1 Pooled data vs. individual study data

This review is based on the results of a single study.

7.4.1.2 Combining data

N/A

7.4.2 Explorations for Predictive Factors

7.4.2.1 Explorations for dose dependency for adverse findings

N/A – there was only one dosing regimen used in XENDOS

7.4.2.2 Explorations for time dependency for adverse findings

In general, the incidence of GI-adverse events declined with continued exposure to orlistat.

7.4.2.3 Explorations for drug-demographic interactions

There were no meaningful differences in the incidence rates of GI adverse events in males vs. females, or in those subjects who were < 38 years, 38-48 years, or > 48 years or age.

7.4.2.4 Explorations for drug-disease interactions

None

7.4.2.5 Explorations for drug-drug interactions

None

9 OVERALL ASSESSMENT

9.1 Conclusions

The results of XENDOS indicate that treatment with 120 mg tid orlistat reduces the incidence of developing type 2 diabetes in obese patients with impaired glucose tolerance from approximately

27% to 19% over a 4-year period. Treatment with orlistat had no effect on the occurrence of type 2 diabetes in obese subjects with normal glucose tolerance. No new safety issues emerged from the XENDOS trial.

9.2 Recommendation on Regulatory Action

Approve

9.3 Recommendation on Postmarketing Actions

None

9.3.1 Risk Management Activity

None

9.3.2 Required Phase 4 Commitments

None

9.3.3 Other Phase 4 Requests

None

9.4 Labeling Review

See below

9.5 Financial Disclosure

According to information submitted by the company, none of the investigators for the XENDOS trial engaged in any of the following financial relationships.

1. Compensation made to the investigator in which the value of compensation could be affected by study outcome.

2. A proprietary interest in the tested product, including, but not limited to, a patent, trademark, copyright or licensing agreement.

3. Any equity interest in the sponsor of a covered study, i.e., any ownership interest, stock options, or other financial interest whose value cannot be readily determined through reference to public prices.

4. Any equity interest in a publicly held company that exceeds $50,000 in value.

5. Significant payments of other sorts, which are payments that have a cumulative monetary value of $25,000 or more made by the sponsor of a covered study to the investigator or the investigators' institution to support activities of the investigator exclusive of the costs of conducting the clinical study or other clinical studies, (e.g., a grant to fund ongoing research, compensation in the form of equipment or retainers for ongoing consultation or honoraria) during the time the clinical investigator is carrying out the study and for 1 year following completion of the study.

23 Page(s) Withheld

_____ § 552(b)(4) Trade Secret / Confidential

✓ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

Withheld Track Number: Medical- 20-766 5019

Common Adverse Events

Summary of Adverse Events by Body System and Trial Treatment
All Adverse Events
Protocol(s): BM15421
Analysis: ALL PATIENTS Center: ALL CENTERS

Body System/ Adverse Event	PLACEBO N = 1655 No. (%)	ORLISTAT N = 1649 No. (%)
ALL BODY SYSTEMS		
Total Pts with at Least one AE	1596 (96)	1634 (99)
Total Number of AEs	12081	15563
INFECTIONS AND INFESTATIONS		
Total Pts With at Least one AE	1443 (87)	1514 (92)
NASOPHARYNGITIS	1217 (74)	1283 (78)
INFLUENZA	548 (33)	639 (39)
GASTROENTERITIS NOS	358 (22)	409 (25)
UPPER RESPIRATORY TRACT INFECTION NOS	138 (8)	173 (10)
TONSILLITIS NOS	135 (8)	166 (10)
SINUSITIS NOS	115 (7)	173 (10)
GASTROENTERITIS VIRAL NOS	117 (7)	121 (7)
BRONCHITIS NOS	79 (5)	87 (5)
URINARY TRACT INFECTION NOS	67 (4)	65 (4)
PNEUMONIA NOS	60 (4)	68 (4)
CYSTITIS NOS	39 (2)	44 (3)
EAR INFECTION NOS	35 (2)	48 (3)
TOOTH ABSCESS	35 (2)	44 (3)
LOCALISED INFECTION	37 (2)	32 (2)
ERYSIPELAS	21 (1)	31 (2)
OTITIS EXTERNA (EXC BOIL OF MEATUS) NOS	19 (1)	29 (2)
PERIODONTITIS	18 (1)	25 (2)
HERPES SIMPLEX	17 (1)	23 (1)
BACTERIAL INFECTION NOS	14 (<1)	21 (1)
EYE INFECTION NOS	18 (1)	17 (1)
VIRAL INFECTION NOS	14 (<1)	17 (1)
OTITIS MEDIA NOS	10 (<1)	20 (1)
VAGINAL CANDIDIASIS	14 (<1)	16 (<1)
HERPES ZOSTER	9 (<1)	16 (<1)
LARYNGITIS NOS	15 (<1)	10 (<1)
PHARYNGITIS NOS	10 (<1)	14 (<1)
FUNGAL INFECTION NOS	12 (<1)	11 (<1)
SKIN FUNGAL INFECTION NOS	10 (<1)	8 (<1)
VAGINITIS	9 (<1)	7 (<1)

(body system continuing ...)

Percentages are based on N. Percentages not calculated if N < 10.
Multiple occurrences of the same adverse event in one individual counted only once.

ae11 Summary of Adverse Events by Body System and Trial Treatment
All Adverse Events
Protocol(s): BM15421
Analysis: ALL PATIENTS Center: ALL CENTERS

Body System/ Adverse Event	PLACEBO N = 1655 No. (%)	ORLISTAT N = 1649 No. (%)
(... body system continuing)		
BRONCHITIS ACUTE NOS	5 (<1)	10 (<1)
SKIN INFECTION NOS	3 (<1)	12 (<1)
TONSILLITIS ACUTE NOS	5 (<1)	9 (<1)
FURUNCLE (EXC GENITAL)	4 (<1)	9 (<1)
ENDOMETRITIS NOS	4 (<1)	8 (<1)
FOLLICULITIS	6 (<1)	6 (<1)
SKIN & SUBCUTANEOUS TISSUE ABSCESS	7 (<1)	5 (<1)
SKIN PAPILLOMA	5 (<1)	7 (<1)
ABSCESS NOS	8 (<1)	3 (<1)
PYELONEPHRITIS NOS	4 (<1)	7 (<1)
WOUND INFECTION NEC	6 (<1)	5 (<1)
CARBUNCLE (EXC GENITAL) NOS	5 (<1)	5 (<1)
PHARYNGITIS STREPTOCOCCAL	4 (<1)	6 (<1)
TOOTH CARIES NOS	3 (<1)	6 (<1)
EPIDIDYMITIS NOS	4 (<1)	4 (<1)
GASTROENTERITIS HELICOBACTER	4 (<1)	4 (<1)
STYE	3 (<1)	5 (<1)
GENITAL INFECTION FUNGAL NOS	5 (<1)	2 (<1)
IMPETIGO NOS	3 (<1)	4 (<1)
SALPINGITIS NOS	-	7 (<1)
SINUSITIS ACUTE NOS	5 (<1)	2 (<1)
ENTEROBIASIS	2 (<1)	4 (<1)
LOWER RESPIRATORY TRACT INFECTION NOS	4 (<1)	2 (<1)
OTITIS MEDIA ACUTE NOS	3 (<1)	3 (<1)
PANOPHTHALMITIS	3 (<1)	3 (<1)
PERITONSILLAR ABSCESS NOS	1 (<1)	5 (<1)
UPPER RESPIRATORY TRACT INFECTION VIRAL NOS	2 (<1)	4 (<1)
CHICKENPOX	3 (<1)	2 (<1)
CHLAMYDIAL INFECTION NOS	2 (<1)	3 (<1)
HERPES SIMPLEX AGGRAVATED	2 (<1)	3 (<1)
IRITIS	3 (<1)	2 (<1)
ORAL CANDIDIASIS	4 (<1)	1 (<1)
PNEUMONIA MYCOPLASMAL	3 (<1)	2 (<1)
(body system continuing ...)		

Percentages are based on N. Percentages not calculated if N < 10.
Multiple occurrences of the same adverse event in one individual counted only once.
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ae11 Summary of Adverse Events by Body System and Trial Treatment
All Adverse Events
Protocol(s): BM15421
Analysis: ALL PATIENTS Center: ALL CENTERS

Body System/ Adverse Event	PLACEBO N = 1655 No. (%)	ORLISTAT N = 1649 No. (%)
(... body system continuing)		
TINEA NOS	3 (<1)	2 (<1)
VAGINAL INFECTION NOS	3 (<1)	2 (<1)
CANDIDA NOS	1 (<1)	3 (<1)
CERVICITIS NEC	1 (<1)	3 (<1)
CONJUNCTIVITIS (INFECTIVE) NEC	2 (<1)	2 (<1)
DIARRHOEA INFECTIOUS	2 (<1)	2 (<1)
EXTERNAL EAR INFECTION NOS	2 (<1)	2 (<1)
GASTROENTERITIS SALMONELLA	2 (<1)	2 (<1)
HERPES VIRAL INFECTION NOS	2 (<1)	2 (<1)
MOLLUSCUM CONTAGIOSUM	1 (<1)	3 (<1)
MYCOPLASMA INFECTION NOS	1 (<1)	3 (<1)
NAIL BED INFECTION NOS	3 (<1)	1 (<1)
NAIL FUNGAL INFECTION NOS	2 (<1)	2 (<1)
PERIANAL ABSCESS	2 (<1)	2 (<1)
SKIN CANDIDA NOS	1 (<1)	3 (<1)
URETHRITIS NON-SPECIFIC	3 (<1)	1 (<1)
BLEPHARITIS	-	3 (<1)
BRONCHITIS CHRONIC NOS	2 (<1)	1 (<1)
GASTROINTESTINAL INFECTION NOS	1 (<1)	2 (<1)
GENITAL CANDIDIASIS	-	3 (<1)
INFECTED SKIN ULCER	1 (<1)	2 (<1)
PAROTITIS	1 (<1)	2 (<1)
RICKETTSIOSIS NOS	1 (<1)	2 (<1)
SIALOADENITIS NOS	2 (<1)	1 (<1)
TINEA CRURIS	-	3 (<1)
TINEA PEDIS	1 (<1)	2 (<1)
VAGINOSIS FUNGAL NOS	-	3 (<1)
BODY TINEA	-	2 (<1)
BREAST INFECTION NOS	2 (<1)	-
BRONCHOPNEUMONIA NOS	-	2 (<1)
CHOLECYSTITIS ACUTE NOS	2 (<1)	-
CONJUNCTIVITIS AGGRAVATED	1 (<1)	1 (<1)
GINGIVITIS INFECTION NOS	1 (<1)	1 (<1)
HAEMORRHAGIC FEVER NOS	-	2 (<1)
HAND FOOT & MOUTH DISEASE	1 (<1)	1 (<1)
(body system continuing ...)		

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Multiple occurrences of the same adverse event in one individual counted only once.
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ae11 Summary of Adverse Events by Body System and Trial Treatment
All Adverse Events
Protocol(s): BM15421
Analysis: ALL PATIENTS Center: ALL CENTERS

Body System/ Adverse Event	PLACEBO N = 1655 No. (%)	ORLISTAT N = 1649 No. (%)
(... body system continuing)		
OTITIS MEDIA SEROUS CHRONIC NOS	1 (<1)	1 (<1)
PYELONEPHRITIS ACUTE NOS	1 (<1)	1 (<1)
STAPHYLOCOCCAL INFECTION NOS	1 (<1)	1 (<1)
STREPTOCOCCAL INFECTION NOS	-	2 (<1)
VAGINITIS BACTERIAL NOS	1 (<1)	1 (<1)
VULVAL ABSCESS	-	2 (<1)
VULVITIS	1 (<1)	1 (<1)
ACUTE EXACERBATION OF CHRONIC BRONCHITIS NOS	1 (<1)	-
ANO-RECTAL INFECTION NOS	-	1 (<1)
BLADDER INFECTION NOS	1 (<1)	-
CELLULITIS	-	1 (<1)
EMPYEMA NOS	1 (<1)	-
EPIGLOTTITIS NOS	-	1 (<1)
EYE ABSCESS	1 (<1)	-
EYE INFECTION BACTERIAL NOS	1 (<1)	-
FOOT AND MOUTH DISEASE	1 (<1)	-
GASTROENTERITIS BACTERIAL NOS	1 (<1)	-
GIARDIASIS	1 (<1)	-
HEPATITIS B	-	1 (<1)
INFECTION NOS	1 (<1)	-
INFECTIOUS MONONUCLEOSIS	-	1 (<1)
KERATITIS HERPETIC	1 (<1)	-
KERATOCONJUNCTIVITIS	1 (<1)	-
LARYNGITIS VIRAL NOS	-	1 (<1)
LARYNGOTRACHEITIS NOS	-	1 (<1)
LYME DISEASE	1 (<1)	-
MENINGITIS BACTERIAL NOS	-	1 (<1)
MENINGITIS NOS	1 (<1)	-
MENINGITIS VIRAL NEC	-	1 (<1)
MUMPS	-	1 (<1)
NAIL TINEA	-	1 (<1)
NIPPLE INFECTION	-	1 (<1)
OESOPHAGEAL CANDIDIASIS	1 (<1)	-
ORAL INFECTION NEC	1 (<1)	-
(body system continuing ...)		

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Multiple occurrences of the same adverse event in one individual counted only once.
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ae11 Summary of Adverse Events by Body System and Trial Treatment
All Adverse Events
Protocol(s): BM15421
Analysis: ALL PATIENTS Center: ALL CENTERS

Body System/ Adverse Event	PLACEBO N = 1655 No. (%)	ORLISTAT N = 1649 No. (%)
(... body system continuing)		
OTITIS MEDIA SEROUS NOS	1 (<1)	-
OVARIAN ABSCESS	1 (<1)	-
PERIANAL FUNGAL INFECTION NOS	-	1 (<1)
PHARYNGITIS VIRAL NOS	-	1 (<1)
PNEUMONIA STREPTOCOCCAL	1 (<1)	-
SCABIES INFESTATION	-	1 (<1)
SCARLET FEVER	1 (<1)	-
SCLERITIS NOS	-	1 (<1)
SEPSIS NOS	1 (<1)	-
SINUSITIS CHRONIC NOS	-	1 (<1)
STAPHYLOCOCCAL ABSCESS	-	1 (<1)
SWEATING FEVER	1 (<1)	-
TUBERCULOSIS NOS	1 (<1)	-
VIRAL LABYRINTHITIS	-	1 (<1)
VULVOVAGINITIS NOS	-	1 (<1)
Total Number of AEs	3389	3874

Percentages are based on N. Percentages not calculated if N < 10.
Multiple occurrences of the same adverse event in one individual counted only once.
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ae11 Summary of Adverse Events by Body System and Trial Treatment
All Adverse Events
Protocol(s): BM15421
Analysis: ALL PATIENTS Center: ALL CENTERS

Body System/ Adverse Event	PLACEBO N = 1655 No. (%)	ORLISTAT N = 1649 No. (%)
GASTROINTESTINAL DISORDERS		
Total Pts With at Least one AE	1183 (71)	1540 (93)
FATTY/OILY STOOL	92 (6)	760 (46)
STOOLS SOFT	309 (19)	540 (33)
FLATULENCE	349 (21)	431 (26)
INCREASED DEFECATION	296 (18)	381 (23)
LIQUID STOOLS	209 (13)	344 (21)
ABDOMINAL PAIN NOS	220 (13)	297 (18)
ABDOMINAL PAIN UPPER	205 (12)	235 (14)
FECAL URGENCY	98 (6)	321 (19)
GASTRITIS NOS	157 (9)	192 (12)
NAUSEA	173 (10)	161 (10)
DECREASED DEFECATION	181 (11)	151 (9)
FLATUS WITH DISCHARGE	18 (1)	194 (12)
SORE THROAT NOS	80 (5)	118 (7)
FAECES HARD	95 (6)	93 (6)
OILY EVACUATION	7 (<1)	171 (10)
TOOTHACHE	72 (4)	70 (4)
OILY SPOTTING	3 (<1)	125 (8)
DYSPEPSIA	56 (3)	64 (4)
PELLETS	65 (4)	44 (3)
VOMITING NOS	52 (3)	45 (3)
HAEMORRHOIDS	29 (2)	53 (3)
FECAL INCONTINENCE	7 (<1)	70 (4)
FAECES DISCOLOURED	4 (<1)	43 (3)
DRY MOUTH	17 (1)	22 (1)
OESOPHAGITIS NOS	15 (<1)	19 (1)
FAECES PALE	4 (<1)	27 (2)
FOOD POISONING NOS	11 (<1)	17 (1)
RECTAL BLEEDING	11 (<1)	17 (1)
GINGIVITIS	8 (<1)	18 (1)
ABDOMINAL DISTENSION	10 (<1)	15 (<1)
INTESTINAL HYPERMOTILITY	15 (<1)	9 (<1)
DIVERTICULITIS NOS	8 (<1)	15 (<1)
PULPITIS DENTAL	8 (<1)	15 (<1)
GASTRITIS AGGRAVATED	12 (<1)	10 (<1)
ABDOMINAL PAIN LOWER	6 (<1)	14 (<1)

(body system continuing ...)

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Multiple occurrences of the same adverse event in one individual counted only once.
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ae11 Summary of Adverse Events by Body System and Trial Treatment
All Adverse Events
Protocol(s): BM15421
Analysis: ALL PATIENTS Center: ALL CENTERS

Body System/ Adverse Event	PLACEBO N = 1655 No. (%)	ORLISTAT N = 1649 No. (%)
(... body system continuing)		
ENTERITIS	8 (<1)	9 (<1)
PRURITUS ANI	3 (<1)	12 (<1)
LIP ULCERATION	10 (<1)	4 (<1)
GASTRO-OESOPHAGEAL REFLUX DISEASE	5 (<1)	8 (<1)
INGUINAL HERNIA NOS	7 (<1)	6 (<1)
BOWEL SOUNDS ABNORMAL	5 (<1)	6 (<1)
ERUCTATION	6 (<1)	5 (<1)
DIVERTICULUM NOS	2 (<1)	7 (<1)
GASTRIC ULCER	6 (<1)	3 (<1)
ANAL FISSURE	3 (<1)	5 (<1)
APPENDICITIS	4 (<1)	4 (<1)
HIATUS HERNIA	3 (<1)	5 (<1)
MOUTH ULCERATION	2 (<1)	6 (<1)
ORAL MUCOSAL BLISTERING	2 (<1)	6 (<1)
FAECAL ABNORMALITY NOS	3 (<1)	4 (<1)
OESOPHAGEAL REFLUX	3 (<1)	4 (<1)
PANCREATITIS NOS	4 (<1)	3 (<1)
IRRITABLE BOWEL SYNDROME	4 (<1)	2 (<1)
PROCTALGIA	3 (<1)	3 (<1)
TENESMUS	4 (<1)	2 (<1)
UMBILICAL HERNIA NOS	4 (<1)	2 (<1)
DYSPEPSIA AGGRAVATED	1 (<1)	4 (<1)
GLOSSODYNIA	2 (<1)	3 (<1)
HALITOSIS	1 (<1)	4 (<1)
INCISIONAL HERNIA NOS	3 (<1)	2 (<1)
ANAL FISTULA	-	4 (<1)
GASTROINTESTINAL HAEMORRHAGE NOS	1 (<1)	3 (<1)
HAEMORRHOIDS AGGRAVATED	1 (<1)	3 (<1)
STOMATITIS	3 (<1)	1 (<1)
TOOTH DISORDER NOS	1 (<1)	3 (<1)
ABDOMINAL PAIN AGGRAVATED	1 (<1)	2 (<1)
CHEILITIS	1 (<1)	2 (<1)
DYSPHAGIA	1 (<1)	2 (<1)
GASTROINTESTINAL PAIN NOS	1 (<1)	2 (<1)
(body system continuing ...)		

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Multiple occurrences of the same adverse event in one individual counted only once.
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ae11 Summary of Adverse Events by Body System and Trial Treatment
All Adverse Events
Protocol(s): BM15421

Analysis: ALL PATIENTS Center: ALL CENTERS

Body System/ Adverse Event	PLACEBO N = 1655 No. (%)	ORLISTAT N = 1649 No. (%)
(... body system continuing)		
ILEUS	1 (<1)	2 (<1)
TONGUE BLISTERING	1 (<1)	2 (<1)
ABDOMINAL HERNIA NOS	1 (<1)	1 (<1)
ABDOMINAL TENDERNESS	-	2 (<1)
COLITIS NOS	2 (<1)	-
COLONIC POLYP	1 (<1)	1 (<1)
DIVERTICULITIS AGGRAVATED	1 (<1)	1 (<1)
DIVERTICULUM INTESTINAL	1 (<1)	1 (<1)
DRY THROAT	1 (<1)	1 (<1)
DUODENAL ULCER	2 (<1)	-
DYSPHAGIA AGGRAVATED	1 (<1)	1 (<1)
GASTROINTESTINAL DISORDER NOS	-	2 (<1)
GINGIVAL BLEEDING	2 (<1)	-
MELAENA	2 (<1)	-
MOUTH CYST	-	2 (<1)
OESOPHAGEAL REFLUX AGGRAVATED	2 (<1)	-
OESOPHAGEAL SPASM	1 (<1)	1 (<1)
PANCREATITIS ACUTE	1 (<1)	1 (<1)
PROCTITIS NOS	-	2 (<1)
RECTAL POLYP	2 (<1)	-
SALIVARY GLAND CALCULUS	1 (<1)	1 (<1)
SWALLOWING PAINFUL	1 (<1)	1 (<1)
TOOTH LOSS	1 (<1)	1 (<1)
APPENDICITIS PERFORATED	1 (<1)	-
COLITIS ULCERATIVE	-	1 (<1)
DEFECATION DESIRE	-	1 (<1)
DUODENAL ULCER AGGRAVATED	1 (<1)	-
DUODENITIS	1 (<1)	-
EPIGASTRIC HERNIA	1 (<1)	-
GASTRITIS HAEMORRHAGIC	1 (<1)	-
HICCUPS	-	1 (<1)
LIP DRY	1 (<1)	-
MOUTH HAEMORRHAGE	1 (<1)	-
OESOPHAGEAL DISORDER NOS	-	1 (<1)
OESOPHAGEAL PAIN	-	1 (<1)
OESOPHAGITIS AGGRAVATED	1 (<1)	-
(body system continuing ...)		

Percentages are based on N. Percentages not calculated if N < 10.
Multiple occurrences of the same adverse event in one individual counted only once.
AE11 30MAY2002:08:15:37 (8 of 44)

ae11 Summary of Adverse Events by Body System and Trial Treatment
All Adverse Events
Protocol(s): BM15421
Analysis: ALL PATIENTS Center: ALL CENTERS

Body System/ Adverse Event	PLACEBO N = 1655 No. (%)	ORLISTAT N = 1649 No. (%)
(... body system continuing)		
ORAL DISCOMFORT	-	1 (<1)
ORAL LICHEN PLANUS	1 (<1)	-
ORAL NEOPLASM NOS	-	1 (<1)
ORAL PAIN	1 (<1)	-
PEPTIC ULCER	-	1 (<1)
PROCTITIS HAEMORRHAGIC	-	1 (<1)
RECTAL DISORDER NOS	-	1 (<1)
RECTAL PROLAPSE	-	1 (<1)
REGURGITATION OF FOOD	-	1 (<1)
SALIVARY GLAND PAIN	-	1 (<1)
STOOLS WATERY	1 (<1)	-
THROAT IRRITATION	1 (<1)	-
TOOTH DEPOSIT	-	1 (<1)
Total Number of AEs	3047	5279

Percentages are based on N. Percentages not calculated if N < 10.
Multiple occurrences of the same adverse event in one individual counted only once.

ae11 Summary of Adverse Events by Body System and Trial Treatment
All Adverse Events
Protocol(s): BM15421
Analysis: ALL PATIENTS Center: ALL CENTERS

Body System/ Adverse Event	PLACEBO N = 1655 No. (%)	ORLISTAT N = 1649 No. (%)
MUSCULOSKELETAL, CONNECTIVE TISSUE AND BONE DISORDERS		
Total Pts With at Least one AE	980 (59)	1016 (62)
BACK PAIN	371 (22)	438 (27)
ARTHRALGIA	368 (22)	412 (25)
PAIN IN LIMB	210 (13)	211 (13)
SCIATICA	88 (5)	92 (6)
TENDONITIS	81 (5)	93 (6)
ARTHRALGIA AGGRAVATED	64 (4)	54 (3)
MYALGIA	56 (3)	62 (4)
NECK PAIN	42 (3)	57 (3)
BACK PAIN AGGRAVATED	53 (3)	44 (3)
MYOSITIS	35 (2)	43 (3)
ARTHRITIS NOS	29 (2)	41 (2)
CHEST WALL PAIN	29 (2)	37 (2)
BONE SPUR	30 (2)	26 (2)
LOCALISED OSTEOARTHRITIS	24 (1)	28 (2)
BURSITIS	23 (1)	13 (<1)
OSTEOARTHRITIS AGGRAVATED	13 (<1)	18 (1)
INTERVERTEBRAL DISC PROLAPSE	13 (<1)	17 (1)
MUSCLE CRAMPS	10 (<1)	17 (1)
PLANTAR FASCIITIS	14 (<1)	13 (<1)
FIBROMYALGIA	21 (1)	5 (<1)
ARTHROSIS NOS	7 (<1)	16 (<1)
BONE PAIN	7 (<1)	9 (<1)
PERIOSTITIS	4 (<1)	11 (<1)
HYPERTONIA	8 (<1)	6 (<1)
JOINT SWELLING	8 (<1)	6 (<1)
MUSCULOSKELETAL PAIN	7 (<1)	7 (<1)
MUSCLE SPASMS	5 (<1)	8 (<1)
SCIATICA AGGRAVATED	5 (<1)	8 (<1)
SPONDYLOSIS	4 (<1)	8 (<1)
TOE DEFORMITIES NOS	3 (<1)	8 (<1)
ENTHESOPATHY	6 (<1)	4 (<1)
GANGLION	3 (<1)	7 (<1)
COSTAL PAIN	4 (<1)	5 (<1)
TENDON DISORDER NOS	7 (<1)	2 (<1)

(body system continuing ...)

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AE11 30MAY2002:08:15:37 (10 of 44)

ae11 Summary of Adverse Events by Body System and Trial Treatment
All Adverse Events
Protocol(s): BM15421
Analysis: ALL PATIENTS Center: ALL CENTERS

Body System/ Adverse Event	PLACEBO N = 1655 No. (%)	ORLISTAT N = 1649 No. (%)
(... body system continuing)		
MYALGIA AGGRAVATED	2 (<1)	6 (<1)
OSTEOARTHRITIS NOS	5 (<1)	3 (<1)
TENDONITIS EXACERBATED	1 (<1)	7 (<1)
TENOSYNOVITIS	3 (<1)	5 (<1)
COSTOCHONDRITIS	3 (<1)	3 (<1)
JOINT STIFFNESS	2 (<1)	4 (<1)
MUSCLE WEAKNESS NOS	2 (<1)	4 (<1)
PAIN IN JAW	3 (<1)	3 (<1)
SYNOVITIS	3 (<1)	3 (<1)
INTERVERTEBRAL DISC DISPLACEMENT	5 (<1)	-
PSORIATIC ARTHROPATHY AGGRAVATED	3 (<1)	2 (<1)
RHEUMATOID ARTHRITIS AGGRAVATED	2 (<1)	3 (<1)
SHOULDER BLADE PAIN	3 (<1)	2 (<1)
CARTILAGE DISORDER NOS	-	4 (<1)
JOINT DISORDER NOS	2 (<1)	2 (<1)
RHEUMATOID ARTHRITIS	1 (<1)	3 (<1)
BAKER'S CYST	1 (<1)	2 (<1)
EXOSTOSIS	1 (<1)	2 (<1)
JAW INFLAMMATION	-	3 (<1)
JOINT EFFUSION	1 (<1)	2 (<1)
LIGAMENT DISORDER NOS	1 (<1)	2 (<1)
ROTATOR CUFF SYNDROME	3 (<1)	-
ANKYLOSING SPONDYLITIS	1 (<1)	1 (<1)
GOUTY ARTHRITIS	1 (<1)	1 (<1)
INTERVERTEBRAL DISC DISORDER NOS	1 (<1)	1 (<1)
METATARSALGIA	-	2 (<1)
MUSCLE TWITCHING	1 (<1)	1 (<1)
NECK STIFFNESS	1 (<1)	1 (<1)
OSTEOCHONDROSIS	1 (<1)	1 (<1)
OSTEOPOROSIS NOS	1 (<1)	1 (<1)
PELVIC DEFORMITY NOS	1 (<1)	1 (<1)
POLYARTHRITIS	1 (<1)	1 (<1)
(body system continuing ...)		

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ae11 Summary of Adverse Events by Body System and Trial Treatment
All Adverse Events
Protocol(s): BM15421
Analysis: ALL PATIENTS Center: ALL CENTERS

Body System/ Adverse Event	PLACEBO N = 1655 No. (%)	ORLISTAT N = 1649 No. (%)
(... body system continuing)		
POLYMYALGIA RHEUMATICA	1 (<1)	1 (<1)
PSORIATIC ARTHROPATHY	2 (<1)	-
SCOLIOSIS	1 (<1)	1 (<1)
SJOGREN'S SYNDROME	2 (<1)	-
SPINAL OSTEOARTHRITIS	1 (<1)	1 (<1)
SPONDYLITIS ANKYLOSING AGGRAVATED	1 (<1)	1 (<1)
ARTHRITIS NOS AGGRAVATED	1 (<1)	-
BONE CYST NOS	1 (<1)	-
BONE PAIN AGGRAVATED	1 (<1)	-
CHONDRITIS	1 (<1)	-
CHONDROMALACIA NOS	-	1 (<1)
CHONDROMALACIA PATELLAE	-	1 (<1)
COCCYDYNIA	1 (<1)	-
FIBROSITIS	1 (<1)	-
FLAT FEET	1 (<1)	-
INTERCOSTAL PAIN	-	1 (<1)
INTERVERTEBRAL DISC DEGENERATION NOS	-	1 (<1)
JAW CYST	1 (<1)	-
JUVENILE RHEUMATOID ARTHRITIS	1 (<1)	-
MUSCLE DISORDER NOS	1 (<1)	-
MUSCLE STIFFNESS	1 (<1)	-
MUSCULOSKELETAL DISORDER NOS	1 (<1)	-
MYALGIA INTERCOSTAL	-	1 (<1)
NODAL OSTEOARTHRITIS	-	1 (<1)
NODULE ON FINGER	1 (<1)	-
OSTEONECROSIS	1 (<1)	-
POLYARTHRALGIA	-	1 (<1)
SACROILIITIS	-	1 (<1)
SPONDYLITIS NOS	-	1 (<1)
SYSTEMIC LUPUS ERYTHEMATOSUS SYNDROME AGGRAVATED	1 (<1)	-
Total Number of AEs	1731	1915

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AE11 30MAY2002:08:15:37 (12 of 44)

ae11 Summary of Adverse Events by Body System and Trial Treatment
All Adverse Events
Protocol(s): BM15421
Analysis: ALL PATIENTS Center: ALL CENTERS

Body System/ Adverse Event	PLACEBO N = 1655 No. (%)	ORLISTAT N = 1649 No. (%)
NERVOUS SYSTEM DISORDERS		
Total Pts With at Least one AE	645 (39)	691 (42)
HEADACHE NOS	436 (26)	449 (27)
DIZZINESS (EXC VERTIGO)	122 (7)	137 (8)
MIGRAINE NOS	48 (3)	43 (3)
INSOMNIA NEC	35 (2)	35 (2)
HYPOAESTHESIA	29 (2)	37 (2)
TORTICOLLIS	28 (2)	34 (2)
SYNCOPE	14 (<1)	28 (2)
PARAESTHESIA NEC	18 (1)	18 (1)
CARPAL TUNNEL SYNDROME	17 (1)	16 (<1)
MIGRAINE AGGRAVATED	10 (<1)	23 (1)
SLEEP APNOEA SYNDROME	20 (1)	9 (<1)
TASTE DISTURBANCE	10 (<1)	5 (<1)
TENSION HEADACHES	6 (<1)	9 (<1)
HEADACHE NOS AGGRAVATED	3 (<1)	9 (<1)
FACIAL PALSY	4 (<1)	6 (<1)
MENTAL IMPAIRMENT NOS	3 (<1)	4 (<1)
BURNING SENSATION NOS	3 (<1)	2 (<1)
CEREBROVASCULAR ACCIDENT NOS	1 (<1)	3 (<1)
EPILEPSY NOS	2 (<1)	2 (<1)
DISTURBANCE IN ATTENTION NEC	-	3 (<1)
INITIAL INSOMNIA	-	3 (<1)
INSOMNIA EXACERBATED	2 (<1)	1 (<1)
LOSS OF CONSCIOUSNESS NEC	1 (<1)	2 (<1)
MEMORY IMPAIRMENT	1 (<1)	2 (<1)
MULTIPLE SCLEROSIS AGGRAVATED	2 (<1)	1 (<1)
NERVE COMPRESSION	1 (<1)	2 (<1)
OBSTRUCTIVE SLEEP APNOEA SYNDROME	2 (<1)	1 (<1)
RESTLESS LEG SYNDROME	-	3 (<1)
SOMNOLENCE	-	3 (<1)
SPINAL STENOSIS NOS	2 (<1)	1 (<1)
VISUAL FIELD DEFECT NOS	1 (<1)	2 (<1)
CERVICAL ROOT PAIN	-	2 (<1)
CLUSTER HEADACHES	1 (<1)	1 (<1)
CONVULSIONS NOS	-	2 (<1)

(body system continuing ...)

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AE11 30MAY2002:08:15:37 (13 of 44)

ae11 Summary of Adverse Events by Body System and Trial Treatment
All Adverse Events
Protocol(s): BM15421
Analysis: ALL PATIENTS Center: ALL CENTERS

Body System/ Adverse Event	PLACEBO N = 1655 No. (%)	ORLISTAT N = 1649 No. (%)
(... body system continuing)		
DIZZINESS AGGRAVATED	1 (<1)	1 (<1)
DIZZINESS POSTURAL	-	2 (<1)
MULTIPLE SCLEROSIS	2 (<1)	-
MUSCLE CONTRACTIONS INVOLUNTARY	2 (<1)	-
AMNESIA NEC	1 (<1)	-
ANOSMIA	-	1 (<1)
BRACHIAL PLEXUS LESION	-	1 (<1)
ENTRAPMENT NEUROPATHY	1 (<1)	-
HAEMORRHAGIC STROKE	-	1 (<1)
HYPERAESTHESIA	-	1 (<1)
HYPOTONIA	-	1 (<1)
INCREASED ACTIVITY	1 (<1)	-
NEURITIS NOS	-	1 (<1)
PERIPHERAL NEUROPATHY AGGRAVATED	-	1 (<1)
PERIPHERAL NEUROPATHY NEC	-	1 (<1)
PERONEAL NERVE PALSY	-	1 (<1)
POLYNEUROPATHY NOS	1 (<1)	-
POST-TRAUMATIC HEADACHE	1 (<1)	-
RADIAL NERVE PALSY	-	1 (<1)
SENSORY LOSS	1 (<1)	-
SPINAL CORD COMPRESSION	-	1 (<1)
TASTE LOSS	1 (<1)	-
TREMOR NEC	-	1 (<1)
VASOVAGAL ATTACK	-	1 (<1)
Total Number of AEs	834	914

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AE11 30MAY2002:08:15:37 (14 of 44)

ae11 Summary of Adverse Events by Body System and Trial Treatment
All Adverse Events
Protocol(s): BM15421
Analysis: ALL PATIENTS Center: ALL CENTERS

Body System/ Adverse Event	PLACEBO N = 1655 No. (%)	ORLISTAT N = 1649 No. (%)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS		
Total Pts With at Least one AE	420 (25)	457 (28)
FATIGUE	124 (7)	114 (7)
PYREXIA	80 (5)	95 (6)
CHEST PAIN NEC	61 (4)	66 (4)
FALL	59 (4)	62 (4)
INFLUENZA LIKE ILLNESS	39 (2)	64 (4)
PAIN NOS	30 (2)	25 (2)
INFLAMMATION LOCALISED	26 (2)	23 (1)
FEELING COLD	14 (<1)	18 (1)
SWELLING NOS	17 (1)	13 (<1)
GROIN PAIN	17 (1)	11 (<1)
MALAISE	11 (<1)	2 (<1)
SHIVERING	7 (<1)	6 (<1)
LETHARGY	3 (<1)	8 (<1)
THIRST	4 (<1)	7 (<1)
PAIN EXACERBATED	5 (<1)	5 (<1)
WEAKNESS	5 (<1)	5 (<1)
MUCOSAL VESICLE NOS	5 (<1)	2 (<1)
FEELING HOT	3 (<1)	2 (<1)
PAIN TRAUMA ACTIVATED	4 (<1)	1 (<1)
ASTHENIA	3 (<1)	1 (<1)
HAEMORRHAGE NOS	2 (<1)	2 (<1)
NECK OEDEMA	1 (<1)	3 (<1)
SICKNESS	2 (<1)	2 (<1)
DISCOMFORT NOS	3 (<1)	-
INJECTION SITE PAIN	1 (<1)	2 (<1)
FEELING DRUNK	2 (<1)	-
NEURALGIA NOS	-	2 (<1)
PAIN IN FACE	-	2 (<1)
TENDERNESS NOS	1 (<1)	1 (<1)
UPPER EXTREMITY MASS	1 (<1)	1 (<1)
ABDOMINAL MASS NOS	-	1 (<1)
ANALGESIA	-	1 (<1)
CHRONIC FATIGUE SYNDROME	-	1 (<1)
COLD INTOLERANCE	1 (<1)	-

(body system continuing ...)

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AE11 30MAY2002:08:15:37 (15 of 44)

ae11 Summary of Adverse Events by Body System and Trial Treatment
All Adverse Events
Protocol(s): BM15421
Analysis: ALL PATIENTS Center: ALL CENTERS

Body System/ Adverse Event	PLACEBO N = 1655 No. (%)	ORLISTAT N = 1649 No. (%)
(... body system continuing)		
DRUG WITHDRAWAL SYNDROME	-	1 (<1)
FEELING HOT AND COLD	1 (<1)	-
HERNIA NOS	-	1 (<1)
INFLAMMATION NOS	1 (<1)	-
INJECTION SITE ERYTHEMA	1 (<1)	-
INJECTION SITE REACTION NOS	-	1 (<1)
LIMB DISCOMFORT NOS	-	1 (<1)
MUCOSAL SWELLING NOS	1 (<1)	-
MUCOUS MEMBRANE DISORDER NOS	-	1 (<1)
NONSPECIFIC REACTION	-	1 (<1)
PELVIC MASS	-	1 (<1)
RIGORS	-	1 (<1)
ULCER NOS	1 (<1)	-
Total Number of AEs	536	556

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AE11 30MAY2002:08:15:37 (16 of 44)

ae11 Summary of Adverse Events by Body System and Trial Treatment
All Adverse Events
Protocol(s): BM15421
Analysis: ALL PATIENTS Center: ALL CENTERS

Body System/ Adverse Event	PLACEBO N = 1655 No. (%)	ORLISTAT N = 1649 No. (%)
INJURY AND POISONING		
Total Pts With at Least one AE	368 (22)	440 (27)
JOINT SPRAIN	80 (5)	116 (7)
LIMB INJURY NOS	71 (4)	64 (4)
TENDON INJURY	22 (1)	39 (2)
LACERATION	24 (1)	28 (2)
ROAD TRAFFIC ACCIDENT	20 (1)	23 (1)
MUSCLE RUPTURE	22 (1)	20 (1)
INJURY NOS	18 (1)	22 (1)
MUSCLE SPRAIN	17 (1)	13 (<1)
RIB FRACTURE	7 (<1)	23 (1)
FOOT FRACTURE	13 (<1)	12 (<1)
ARTHROPOD BITE	11 (<1)	12 (<1)
JOINT DISLOCATION NEC	8 (<1)	15 (<1)
LIGAMENT SPRAIN	7 (<1)	14 (<1)
CONCUSSION	6 (<1)	10 (<1)
WHIPLASH INJURY	8 (<1)	7 (<1)
ANIMAL BITE	7 (<1)	7 (<1)
CARTILAGE INJURY	4 (<1)	10 (<1)
BACK INJURY NOS	6 (<1)	7 (<1)
HAND FRACTURE	5 (<1)	8 (<1)
FOREIGN BODY TRAUMA	8 (<1)	4 (<1)
TRAUMATIC CHEST INJURY NOS	5 (<1)	6 (<1)
ACCIDENT NOS	6 (<1)	4 (<1)
TENDON RUPTURE	2 (<1)	8 (<1)
TOOTH INJURY	4 (<1)	6 (<1)
BLISTER	4 (<1)	5 (<1)
BURNS NOS	4 (<1)	5 (<1)
LEG FRACTURE	3 (<1)	6 (<1)
UPPER LIMB FRACTURE NOS	5 (<1)	4 (<1)
ARTHROPOD STING	-	8 (<1)
WRIST FRACTURE	3 (<1)	5 (<1)
HEAD INJURY	1 (<1)	6 (<1)
MUSCLE INJURY NOS	5 (<1)	1 (<1)
ANKLE FRACTURE	2 (<1)	3 (<1)
HUMERUS FRACTURE	2 (<1)	2 (<1)
RADIUS FRACTURE	2 (<1)	2 (<1)

(body system continuing ...)

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AE11 30MAY2002:08:15:37 (17 of 44)

ae11 Summary of Adverse Events by Body System and Trial Treatment
All Adverse Events
Protocol(s): BM15421
Analysis: ALL PATIENTS Center: ALL CENTERS

Body System/ Adverse Event	PLACEBO N = 1655 No. (%)	ORLISTAT N = 1649 No. (%)
(... body system continuing)		
SKELETAL INJURY NOS	4 (<1)	-
TRAUMATIC HAEMATOMA	2 (<1)	2 (<1)
ABRASION NOS	3 (<1)	-
ACCIDENT AT WORK	1 (<1)	2 (<1)
ALCOHOL POISONING	3 (<1)	-
ELECTRIC SHOCK	-	3 (<1)
FIBULA FRACTURE	1 (<1)	2 (<1)
FINGER CRUSHING	1 (<1)	2 (<1)
PERIPHERAL NERVE INJURY	-	3 (<1)
SPORTS INJURY	-	3 (<1)
BURNS FIRST DEGREE	-	2 (<1)
BURNS SECOND DEGREE	-	2 (<1)
EAR DRUM PERFORATION	2 (<1)	-
FACIAL BONES FRACTURE	-	2 (<1)
FINGER TRAUMATIC AMPUTATION	2 (<1)	-
FOREARM FRACTURE	1 (<1)	1 (<1)
NON-ACCIDENTAL INJURY	1 (<1)	1 (<1)
SCRATCH	-	2 (<1)
SOFT TISSUE INJURY NOS	2 (<1)	-
ABDOMEN CRUSHING	1 (<1)	-
CLAVICLE FRACTURE	1 (<1)	-
CORNEAL PERFORATION	1 (<1)	-
DRUG TOXICITY NOS	-	1 (<1)
EYE BURNS	1 (<1)	-
FOOT CRUSHING	1 (<1)	-
GAS POISONING	-	1 (<1)
HAND CRUSHING	1 (<1)	-
HEAT EXHAUSTION	1 (<1)	-
HUMAN BITE	1 (<1)	-
JAW FRACTURE	1 (<1)	-
MALLET FINGER	-	1 (<1)
MEDICATION ERROR	-	1 (<1)
METAL POISONING	1 (<1)	-
MULTIPLE FRACTURES	-	1 (<1)
MULTIPLE INJURIES	-	1 (<1)
OVERDOSE NOS	-	1 (<1)
(body system continuing ...)		

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ae11 Summary of Adverse Events by Body System and Trial Treatment
All Adverse Events
Protocol(s): BM15421
Analysis: ALL PATIENTS Center: ALL CENTERS

Body System/ Adverse Event	PLACEBO N = 1655 No. (%)	ORLISTAT N = 1649 No. (%)
(... body system continuing)		
PATELLA FRACTURE	-	1 (<1)
PNEUMOTHORAX TRAUMATIC	1 (<1)	-
POST-TRAUMATIC STRESS DISORDER	-	1 (<1)
SCAR	1 (<1)	-
SKIN INJURY NOS	1 (<1)	-
SPINAL COMPRESSION FRACTURE	-	1 (<1)
SPINAL FRACTURE NOS	1 (<1)	-
SPLINTER	-	1 (<1)
STRESS FRACTURE	1 (<1)	-
SUBCUTANEOUS HAEMATOMA	-	1 (<1)
SUNBURN	1 (<1)	-
TIBIA FRACTURE	1 (<1)	-
TOE CRUSHING	1 (<1)	-
TRAUMATIC TORTICOLLIS	-	1 (<1)
ULNA FRACTURE	-	1 (<1)
Total Number of AEs	453	566

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AE11 30MAY2002:08:15:37 (19 of 44)

ae11 Summary of Adverse Events by Body System and Trial Treatment
All Adverse Events
Protocol(s): BM15421
Analysis: ALL PATIENTS Center: ALL CENTERS

Body System/ Adverse Event	PLACEBO N = 1655 No. (%)	ORLISTAT N = 1649 No. (%)
SKIN & SUBCUTANEOUS TISSUE DISORDERS		
Total Pts With at Least one AE	303 (18)	370 (22)
ECZEMA NOS	60 (4)	53 (3)
DERMATITIS NOS	48 (3)	58 (4)
PRURITUS NOS	35 (2)	42 (3)
URTICARIA NOS	19 (1)	33 (2)
ALOPECIA	18 (1)	31 (2)
DRY SKIN	8 (<1)	26 (2)
ACNE NOS	13 (<1)	16 (<1)
ECCHYMOSIS	13 (<1)	13 (<1)
SWEATING INCREASED	8 (<1)	16 (<1)
PSORIASIS AGGRAVATED	10 (<1)	10 (<1)
DERMATITIS ALLERGIC	9 (<1)	7 (<1)
ECZEMA EXACERBATED	5 (<1)	10 (<1)
INGROWING NAIL	10 (<1)	5 (<1)
SKIN FISSURES	5 (<1)	9 (<1)
ROSACEA	3 (<1)	10 (<1)
PSORIASIS	8 (<1)	4 (<1)
BRITTLE NAILS	4 (<1)	7 (<1)
FACE OEDEMA	7 (<1)	3 (<1)
ERYTHEMA NEC	5 (<1)	4 (<1)
HIDRADENITIS	6 (<1)	3 (<1)
CLAMMINESS	4 (<1)	4 (<1)
ECZEMA SEBORRHOEIC	3 (<1)	5 (<1)
NAIL DISORDER NOS	2 (<1)	5 (<1)
PARONYCHIA	4 (<1)	3 (<1)
RASH PRURITIC	4 (<1)	3 (<1)
ANGIONEUROTIC OEDEMA	3 (<1)	3 (<1)
EYELID OEDEMA	4 (<1)	2 (<1)
RASH PAPULAR	1 (<1)	5 (<1)
GENITAL PRURITUS FEMALE	3 (<1)	2 (<1)
SEBACEOUS GLAND DISORDER NOS	4 (<1)	1 (<1)
SKIN NODULE	3 (<1)	2 (<1)
DERMATITIS EYELID	2 (<1)	2 (<1)
HAIR TEXTURE ABNORMAL	1 (<1)	3 (<1)
LEG ULCER (EXC VARICOSE)	3 (<1)	1 (<1)

(body system continuing ...)

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AE11 30MAY2002:08:15:37 (20 of 44)

ae11 Summary of Adverse Events by Body System and Trial Treatment
All Adverse Events
Protocol(s): BM15421
Analysis: ALL PATIENTS Center: ALL CENTERS

Body System/ Adverse Event	PLACEBO N = 1655 No. (%)	ORLISTAT N = 1649 No. (%)
(... body system continuing)		
RASH ERYTHEMATOUS	3 (<1)	1 (<1)
RASH PUSTULAR	2 (<1)	2 (<1)
SKIN IRRITATION	3 (<1)	1 (<1)
SKIN LESION NOS	2 (<1)	2 (<1)
CALLUS	1 (<1)	2 (<1)
DERMATITIS NOS AGGRAVATED	2 (<1)	1 (<1)
ECZEMA INFECTED	1 (<1)	2 (<1)
ERYTHEMA NODOSUM	1 (<1)	2 (<1)
PHOTOSENSITIVITY REACTION NOS	-	3 (<1)
RASH VESICULAR	2 (<1)	1 (<1)
SEBACEOUS CYST	2 (<1)	1 (<1)
SKIN CHAPPED	2 (<1)	1 (<1)
ACNE AGGRAVATED	-	2 (<1)
ALOPECIA AREATA	1 (<1)	1 (<1)
DERMATITIS ATOPIC AGGRAVATED	-	2 (<1)
DERMATITIS EXFOLIATIVE NOS	-	2 (<1)
FOOT ULCER	1 (<1)	1 (<1)
HYPERKERATOSIS	-	2 (<1)
INTERTRIGO	2 (<1)	-
PHOTOSENSITIVE RASH	1 (<1)	1 (<1)
SKIN ODOUR ABNORMAL	1 (<1)	1 (<1)
SKIN ULCER NOS	1 (<1)	1 (<1)
SUBCUTANEOUS NODULE	-	2 (<1)
URTICARIA AGGRAVATED	1 (<1)	1 (<1)
ADIPOSIS DOLOROSA	-	1 (<1)
DERMATITIS CONTACT	-	1 (<1)
ECZEMA GRAVITATIONAL	-	1 (<1)
ERYTHEMA MULTIFORME	1 (<1)	-
GENITAL PRURITUS MALE	1 (<1)	-
GRANULOMA ANNULARE	-	1 (<1)
HAIR GROWTH ABNORMAL	-	1 (<1)
INCREASED TENDENCY TO BRUISE	1 (<1)	-
LICHEN PLANUS	-	1 (<1)
LICHEN SCLEROSUS	-	1 (<1)
NETTLE RASH	-	1 (<1)
NIGHT SWEATS	1 (<1)	-
(body system continuing ...)		

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AE11 30MAY2002:08:15:37 (21 of 44)

ae11 Summary of Adverse Events by Body System and Trial Treatment
All Adverse Events
Protocol(s): BM15421
Analysis: ALL PATIENTS Center: ALL CENTERS

Body System/ Adverse Event	PLACEBO N = 1655 No. (%)	ORLISTAT N = 1649 No. (%)
(... body system continuing)		
PARAPSORIASIS	1 (<1)	-
PETECHIAE	1 (<1)	-
PIGMENTATION DISORDER NOS	-	1 (<1)
RASH GENERALISED	-	1 (<1)
SCALP TENDERNESS	1 (<1)	-
SKIN HYPERPIGMENTATION	1 (<1)	-
TONGUE OEDEMA	-	1 (<1)
URTICARIA COLD	-	1 (<1)
YELLOW SKIN	-	1 (<1)
Total Number of AEs	372	449

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AE11 30MAY2002:08:15:37 (22 of 44)

ae11 Summary of Adverse Events by Body System and Trial Treatment
All Adverse Events
Protocol(s): BM15421
Analysis: ALL PATIENTS Center: ALL CENTERS

Body System/ Adverse Event	PLACEBO N = 1655 No. (%)	ORLISTAT N = 1649 No. (%)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS		
Total Pts With at Least one AE	259 (16)	330 (20)
COUGH	70 (4)	105 (6)
RHINITIS SEASONAL	35 (2)	65 (4)
ASTHMA AGGRAVATED	31 (2)	30 (2)
ASTHMA NOS	28 (2)	29 (2)
RHINITIS ALLERGIC NOS	20 (1)	36 (2)
EPISTAXIS	28 (2)	23 (1)
RHINITIS NOS	22 (1)	16 (<1)
DYSPNOEA NOS	17 (1)	12 (<1)
HOARSENESS	14 (<1)	13 (<1)
NASAL CONGESTION	7 (<1)	14 (<1)
PLEURISY	5 (<1)	8 (<1)
VOCAL CORD DISORDER NOS	1 (<1)	4 (<1)
AIRWAY OBSTRUCTION NOS	1 (<1)	2 (<1)
CHRONIC OBSTRUCTIVE AIRWAYS DISEASE EXACERBATED	-	3 (<1)
DYSPNOEA EXERTIONAL	3 (<1)	-
NASAL PASSAGE IRRITATION	1 (<1)	2 (<1)
NASAL POLYPS	2 (<1)	1 (<1)
NASAL ULCER	2 (<1)	1 (<1)
OBSTRUCTIVE AIRWAYS DISORDER NOS	1 (<1)	2 (<1)
SNORING	1 (<1)	2 (<1)
CHOKING SENSATION	1 (<1)	1 (<1)
HAEMOPTYSIS	2 (<1)	-
SPUTUM INCREASED	-	2 (<1)
THROAT OEDEMA	1 (<1)	1 (<1)
VOCAL CORD POLYP	-	2 (<1)
ASTHMA EXERCISE INDUCED	1 (<1)	-
CATARRH	-	1 (<1)
CHEST TIGHTNESS	-	1 (<1)
CHRONIC OBSTRUCTIVE AIRWAYS DISEASE	-	1 (<1)
DIAPHRAGMATIC DISORDER NOS	-	1 (<1)
DIAPHRAGMATIC HERNIA NOS	1 (<1)	-

(body system continuing ...)

Percentages are based on N. Percentages not calculated if N < 10.
Multiple occurrences of the same adverse event in one individual counted only once.
AE11 30MAY2002:08:15:37 (23 of 44)

ae11 Summary of Adverse Events by Body System and Trial Treatment
All Adverse Events
Protocol(s): BM15421
Analysis: ALL PATIENTS Center: ALL CENTERS

Body System/ Adverse Event	PLACEBO N = 1655 No. (%)	ORLISTAT N = 1649 No. (%)
(... body system continuing)		
EMPHYSEMA	1 (<1)	-
HYPERVENTILATION	1 (<1)	-
LARYNGEAL PAIN	-	1 (<1)
NASAL OBSTRUCTION	-	1 (<1)
OROPHARYNGEAL SWELLING	-	1 (<1)
PLEURAL EFFUSION	1 (<1)	-
PNEUMONITIS NOS	1 (<1)	-
PNEUMOTHORAX NOS	-	1 (<1)
RESPIRATORY DISORDER NOS	-	1 (<1)
RESPIRATORY FAILURE (EXC NEONATAL)	-	1 (<1)
RESPIRATORY OBSTRUCTION UNSPECIFIED	1 (<1)	-
RHINITIS NOS EXACERBATED	-	1 (<1)
RHINORRHOEA	1 (<1)	-
SINUS CONGESTION	1 (<1)	-
VOCAL CORD THICKENING	1 (<1)	-
Total Number of AEs	303	385

Percentages are based on N. Percentages not calculated if N < 10.
Multiple occurrences of the same adverse event in one individual counted only once.
AE11 30MAY2002:08:15:37 (24 of 44)

ae11 Summary of Adverse Events by Body System and Trial Treatment
All Adverse Events
Protocol(s): BM15421
Analysis: ALL PATIENTS Center: ALL CENTERS

Body System/ Adverse Event	PLACEBO N = 1655 No. (%)	ORLISTAT N = 1649 No. (%)
REPRODUCTIVE SYSTEM AND BREAST DISORDERS		
Total Pts With at Least one AE	191 (12)	238 (14)
MENORRHAGIA	41 (2)	49 (3)
MENSTRUATION IRREGULAR	20 (1)	29 (2)
DYSMENORRHOEA	25 (2)	23 (1)
MENOPAUSAL SYMPTOMS	19 (1)	18 (1)
MENOMETRORRHAGIA	11 (<1)	20 (1)
PROSTATITIS	8 (<1)	12 (<1)
VAGINAL HAEMORRHAGE	11 (<1)	9 (<1)
BREAST PAIN	7 (<1)	8 (<1)
MENOPAUSE	7 (<1)	7 (<1)
AMENORRHOEA NOS	5 (<1)	8 (<1)
INTERMENSTRUAL BLEEDING	3 (<1)	10 (<1)
POST-MENOPAUSAL BLEEDING	5 (<1)	7 (<1)
OVARIAN CYST	4 (<1)	7 (<1)
MENSES DELAYED	3 (<1)	7 (<1)
IMPOTENCE	5 (<1)	4 (<1)
BREAST TENDERNESS	3 (<1)	5 (<1)
BENIGN PROSTATIC HYPERPLASIA	4 (<1)	3 (<1)
BREAST ENGORGEMENT	3 (<1)	4 (<1)
ENDOMETRIOSIS	3 (<1)	3 (<1)
PREMENSTRUAL SYNDROME	4 (<1)	2 (<1)
VAGINAL DISCHARGE	4 (<1)	2 (<1)
UTERINE PROLAPSE	1 (<1)	4 (<1)
GENITAL INFECTION	2 (<1)	2 (<1)
MASTITIS	-	4 (<1)
POLYMENORRHOEA	2 (<1)	2 (<1)
CERVICAL DYSPLASIA	1 (<1)	2 (<1)
ERECTILE DISTURBANCE	2 (<1)	1 (<1)
MENSTRUAL DISORDER NOS	2 (<1)	1 (<1)
PROSTATISM	2 (<1)	1 (<1)
UTERINE INFLAMMATION NOS	-	3 (<1)
UTERINE POLYP NOS	1 (<1)	2 (<1)
BARTHOLINITIS	1 (<1)	1 (<1)
BREAST CALCIFICATIONS	-	2 (<1)
BREAST DISCHARGE	-	2 (<1)

(body system continuing ...)

Percentages are based on N. Percentages not calculated if N < 10.
Multiple occurrences of the same adverse event in one individual counted only once.
AE11 30MAY2002:08:15:37 (25 of 44)

ae11 Summary of Adverse Events by Body System and Trial Treatment
All Adverse Events
Protocol(s): BM15421
Analysis: ALL PATIENTS Center: ALL CENTERS

Body System/ Adverse Event	PLACEBO N = 1655 No. (%)	ORLISTAT N = 1649 No. (%)
(... body system continuing)		
BREAST DISORDER NOS	1 (<1)	1 (<1)
ENDOMETRIAL HYPERPLASIA	1 (<1)	1 (<1)
MENOPAUSAL SYMPTOMS AGGRAVATED	-	2 (<1)
OLIGOMENORRHOEA NOS	-	2 (<1)
UTERINE HAEMORRHAGE	1 (<1)	1 (<1)
VAGINAL DISORDER NOS	-	2 (<1)
VAGINITIS ATROPHIC	-	2 (<1)
BREAST ABSCESS	-	1 (<1)
BREAST FIBROSIS	-	1 (<1)
BREAST HAEMORRHAGE	-	1 (<1)
CERVICAL POLYP	-	1 (<1)
CERVICAL STRICTURE	-	1 (<1)
CYSTOCELE	-	1 (<1)
GENITAL HAEMORRHAGE NOS	1 (<1)	-
GENITAL PAIN NOS	-	1 (<1)
GENITAL RASH	-	1 (<1)
GYNAECOMASTIA	1 (<1)	-
HAEMORRHAGE INTO OVARIAN CYST	-	1 (<1)
HYDROCELE	-	1 (<1)
NIPPLE PAIN	1 (<1)	-
ORCHITIS NOS	-	1 (<1)
OVARIAN DISORDER NOS	1 (<1)	-
OVULATION PAIN	-	1 (<1)
PELVIC PAIN NOS	1 (<1)	-
PERINEAL PAIN NOS	1 (<1)	-
PHIMOSIS	-	1 (<1)
PROSTATISM AGGRAVATED	1 (<1)	-
TESTICULAR DISORDER NOS	-	1 (<1)
TESTICULAR PAIN	-	1 (<1)
TESTICULAR SWELLING	-	1 (<1)
UTEROVAGINAL PROLAPSE	-	1 (<1)
VAGINAL PROLAPSE	-	1 (<1)
VARICOCELE	-	1 (<1)
VULVOVAGINAL DRYNESS	1 (<1)	-
Total Number of AEs	220	294

Percentages are based on N. Percentages not calculated if N < 10.
Multiple occurrences of the same adverse event in one individual counted only once.
AE11 30MAY2002:08:15:37 (26 of 44)

ae11 Summary of Adverse Events by Body System and Trial Treatment
All Adverse Events
Protocol(s): BM15421
Analysis: ALL PATIENTS Center: ALL CENTERS

Body System/ Adverse Event	PLACEBO N = 1655 No. (%)	ORLISTAT N = 1649 No. (%)
PSYCHIATRIC DISORDERS		
Total Pts With at Least one AE	149 (9)	197 (12)
DEPRESSION NEC	62 (4)	98 (6)
STRESS SYMPTOMS	20 (1)	29 (2)
DEPRESSED MOOD	25 (2)	20 (1)
ANXIETY NEC	13 (<1)	16 (<1)
DEPRESSION AGGRAVATED	7 (<1)	5 (<1)
SLEEP DISORDER NOS	3 (<1)	9 (<1)
ALCOHOLISM	3 (<1)	6 (<1)
PANIC REACTION	3 (<1)	3 (<1)
IRRITABILITY	1 (<1)	4 (<1)
LIBIDO DECREASED	4 (<1)	1 (<1)
ANXIETY AGGRAVATED	-	3 (<1)
CONVERSION DISORDER	2 (<1)	1 (<1)
MENTAL DISORDER NEC	1 (<1)	2 (<1)
NIGHTMARE	-	3 (<1)
ABNORMAL DREAMS	-	2 (<1)
ACUTE STRESS DISORDER	-	2 (<1)
ANGER	2 (<1)	-
BEREAVEMENT REACTION	-	2 (<1)
DISTRESS	-	2 (<1)
INSOMNIA RELATED TO ANOTHER MENTAL CONDITION	-	2 (<1)
PANIC DISORDER WITHOUT AGORAPHOBIA	1 (<1)	1 (<1)
AGGRESSION	-	1 (<1)
ALCOHOLIC WITHDRAWAL SYMPTOMS	-	1 (<1)
ANXIETY DISORDER NEC	-	1 (<1)
BIPOLAR DISORDER NEC	1 (<1)	-
BULIMIA NERVOSA	1 (<1)	-
COMPLETED SUICIDE	-	1 (<1)
DISORIENTATION	-	1 (<1)
DYSPHORIA	-	1 (<1)
DYSTHYMIC DISORDER	1 (<1)	-
EARLY MORNING AWAKENING	-	1 (<1)
EMOTIONAL DISTURBANCE NOS	1 (<1)	-
EXACERBATION OF ANXIETY	1 (<1)	-

(body system continuing ...)

Percentages are based on N. Percentages not calculated if N < 10.
Multiple occurrences of the same adverse event in one individual counted only once.
AE11 30MAY2002:08:15:37 (27 of 44)

ae11 Summary of Adverse Events by Body System and Trial Treatment
All Adverse Events
Protocol(s): BM15421
Analysis: ALL PATIENTS Center: ALL CENTERS

Body System/ Adverse Event	PLACEBO N = 1655 No. (%)	ORLISTAT N = 1649 No. (%)
(... body system continuing)		
MOOD ALTERATION NOS	1 (<1)	-
NERVOUSNESS	1 (<1)	-
PANIC ATTACK	1 (<1)	-
PHOBIA OF FLYING	1 (<1)	-
SHIFT-WORK RELATED SLEEP DISTURBANCE	1 (<1)	-
SHORT-TERM MEMORY LOSS	1 (<1)	-
SUICIDE ATTEMPT	1 (<1)	-
Total Number of AEs	159	218

Percentages are based on N. Percentages not calculated if N < 10.
Multiple occurrences of the same adverse event in one individual counted only once.
AE11 30MAY2002:08:15:37 (28 of 44)

ae11 Summary of Adverse Events by Body System and Trial Treatment
All Adverse Events
Protocol(s): BM15421
Analysis: ALL PATIENTS Center: ALL CENTERS

Body System/ Adverse Event	PLACEBO N = 1655 No. (%)	ORLISTAT N = 1649 No. (%)
VASCULAR DISORDERS		
Total Pts With at Least one AE	175 (11)	165 (10)
HYPERTENSION NOS	60 (4)	53 (3)
HYPERTENSION AGGRAVATED	41 (2)	30 (2)
PHLEBITIS NOS	17 (1)	21 (1)
VARICOSE VEINS NOS	8 (<1)	18 (1)
PERIPHERAL COLDNESS	12 (<1)	9 (<1)
HAEMATOMA NOS	8 (<1)	10 (<1)
FLUSHING	3 (<1)	5 (<1)
ATHEROSCLEROSIS	4 (<1)	3 (<1)
VENOUS THROMBOSIS DEEP LIMB	4 (<1)	2 (<1)
HYPOTENSION NOS	3 (<1)	2 (<1)
PERIPHERAL VASCULAR DISEASE NOS	-	5 (<1)
PULMONARY EMBOLISM	4 (<1)	1 (<1)
HOT FLUSHES NOS	3 (<1)	1 (<1)
POSTURAL HYPOTENSION	2 (<1)	2 (<1)
THROMBOPHLEBITIS SUPERFICIAL	2 (<1)	1 (<1)
VENOUS THROMBOSIS NOS LIMB	-	3 (<1)
HYPOTENSION AGGRAVATED	-	2 (<1)
RAYNAUD'S PHENOMENON	2 (<1)	-
THROMBOSIS NOS	1 (<1)	1 (<1)
TRANSIENT ISCHAEMIC ATTACK	2 (<1)	-
VARICOSE ULCERATION	2 (<1)	-
VASCULITIS NOS	1 (<1)	1 (<1)
VENOUS THROMBOSIS SUPERFICIAL LIMB	1 (<1)	1 (<1)
AORTIC ANEURYSM	1 (<1)	-
AORTIC ANEURYSM RUPTURE	1 (<1)	-
AORTO-ILIAC ARTERIAL STENOSIS	-	1 (<1)
CEREBRAL INFARCTION	-	1 (<1)
CRANIAL ARTERITIS	-	1 (<1)
ESSENTIAL HYPERTENSION	-	1 (<1)
HENOCH-SCHONLEIN PURPURA	1 (<1)	-
PALLOR	1 (<1)	-
RAYNAUD'S PHENOMENON AGGRAVATED	1 (<1)	-

(body system continuing ...)

Percentages are based on N. Percentages not calculated if N < 10.
Multiple occurrences of the same adverse event in one individual counted only once.
AE11 30MAY2002:08:15:37 (29 of 44)

ae11 Summary of Adverse Events by Body System and Trial Treatment
All Adverse Events
Protocol(s): BM15421
Analysis: ALL PATIENTS Center: ALL CENTERS

Body System/ Adverse Event	PLACEBO N = 1655 No. (%)	ORLISTAT N = 1649 No. (%)
(... body system continuing)		
SUBARACHNOID HAEMORRHAGE NOS	-	1 (<1)
THROMBOEMBOLISM NOS	1 (<1)	-
THROMBOSED VARICOSE VEIN	-	1 (<1)
VENOUS THROMBOSIS NOS	1 (<1)	-
Total Number of AEs	187	177

Percentages are based on N. Percentages not calculated if N < 10.
Multiple occurrences of the same adverse event in one individual counted only once.
AE11 30MAY2002:08:15:37 (30 of 44)

ae11 Summary of Adverse Events by Body System and Trial Treatment
All Adverse Events
Protocol(s): BM15421
Analysis: ALL PATIENTS Center: ALL CENTERS

Body System/ Adverse Event	PLACEBO N = 1655 No. (%)	ORLISTAT N = 1649 No. (%)
CARDIAC DISORDERS		
Total Pts With at Least one AE	159 (10)	164 (10)
OEDEMA LOWER LIMB	47 (3)	36 (2)
PALPITATIONS	21 (1)	23 (1)
ANGINA PECTORIS	13 (<1)	19 (1)
OEDEMA NOS	11 (<1)	16 (<1)
ATRIAL FIBRILLATION	9 (<1)	14 (<1)
TACHYCARDIA NOS	11 (<1)	11 (<1)
MYOCARDIAL INFARCTION	7 (<1)	10 (<1)
OEDEMA UPPER LIMB	12 (<1)	4 (<1)
OEDEMA PERIPHERAL	9 (<1)	5 (<1)
ANGINA PECTORIS AGGRAVATED	5 (<1)	5 (<1)
ARRHYTHMIA NOS	4 (<1)	5 (<1)
CARDIAC FAILURE NOS	5 (<1)	4 (<1)
BRADYCARDIA NOS	1 (<1)	5 (<1)
CARDIAC MURMUR NOS	2 (<1)	4 (<1)
CHEST PRESSURE SENSATION	3 (<1)	3 (<1)
OEDEMA AGGRAVATED	1 (<1)	4 (<1)
EXTRASYSTOLES NOS	1 (<1)	3 (<1)
MYOCARDITIS NOS	1 (<1)	2 (<1)
ANGINA UNSTABLE	-	2 (<1)
ATRIAL FLUTTER	1 (<1)	1 (<1)
CARDIAC FAILURE AGGRAVATED	2 (<1)	-
MYOCARDIAL ISCHAEMIA	1 (<1)	1 (<1)
PALPITATIONS AGGRAVATED	2 (<1)	-
SUPRAVENTRICULAR EXTRASYSTOLES	1 (<1)	1 (<1)
TACHYCARDIA PAROXYSMAL NOS	-	2 (<1)
AORTIC VALVE DISEASE NOS	-	1 (<1)
AORTIC VALVE STENOSIS	1 (<1)	-
ATRIAL FIBRILLATION AGGRAVATED	-	1 (<1)
ATRIAL TACHYCARDIA	-	1 (<1)
CARDIAC FAILURE CONGESTIVE	1 (<1)	-
CORONARY ARTERY SPASM	1 (<1)	-
ENDOCARDITIS NOS	-	1 (<1)
MITRAL VALVE INCOMPETENCE	-	1 (<1)
NODAL ARRHYTHMIA	-	1 (<1)
PERICARDITIS NOS	-	1 (<1)

(body system continuing ...)

Percentages are based on N. Percentages not calculated if N < 10.
Multiple occurrences of the same adverse event in one individual counted only once.
AE11 30MAY2002:08:15:37 (31 of 44)

ae11 Summary of Adverse Events by Body System and Trial Treatment
All Adverse Events
Protocol(s): BM15421
Analysis: ALL PATIENTS Center: ALL CENTERS

Body System/ Adverse Event	PLACEBO N = 1655 No. (%)	ORLISTAT N = 1649 No. (%)
(... body system continuing)		
SINUS TACHYCARDIA	1 (<1)	-
SUPRAVENTRICULAR TACHYCARDIA	1 (<1)	-
TACHYCARDIA AGGRAVATED	-	1 (<1)
VENTRICULAR EXTRASYSTOLES	1 (<1)	-
VENTRICULAR FIBRILLATION	-	1 (<1)
Total Number of AEs	176	189

Percentages are based on N. Percentages not calculated if N < 10.
Multiple occurrences of the same adverse event in one individual counted only once.
AE11 30MAY2002:08:15:37 (32 of 44)

ae11 Summary of Adverse Events by Body System and Trial Treatment
All Adverse Events
Protocol(s): BM15421
Analysis: ALL PATIENTS Center: ALL CENTERS

Body System/ Adverse Event	PLACEBO N = 1655 No. (%)	ORLISTAT N = 1649 No. (%)
RENAL AND URINARY DISORDERS		
Total Pts With at Least one AE	135 (8)	125 (8)
URINARY FREQUENCY	50 (3)	39 (2)
CALCULUS RENAL NOS	21 (1)	19 (1)
POLYURIA	20 (1)	19 (1)
LOIN PAIN	6 (<1)	11 (<1)
NOCTURIA	6 (<1)	7 (<1)
DYSURIA	6 (<1)	5 (<1)
URINARY INCONTINENCE	5 (<1)	5 (<1)
FLUID RETENTION	3 (<1)	5 (<1)
URINARY TRACT DISORDER NOS	4 (<1)	4 (<1)
RENAL COLIC	1 (<1)	3 (<1)
DIFFICULTY IN MICTURITION	1 (<1)	2 (<1)
BLADDER DISORDER NOS	-	2 (<1)
CALCULUS URETHRAL	1 (<1)	1 (<1)
CYSTITIS HAEMORRHAGIC	-	2 (<1)
GLOMERULONEPHRITIS PROLIFERATIVE	2 (<1)	-
MICTURITION URGENCY	2 (<1)	-
RENAL PAIN	-	2 (<1)
URINARY INCONTINENCE AGGRAVATED	1 (<1)	1 (<1)
URINE ABNORMAL NOS	2 (<1)	-
URINE DISCOLOURATION	1 (<1)	1 (<1)
BLADDER NECK OBSTRUCTION	1 (<1)	-
BLADDER PAIN	1 (<1)	-
BLADDER PROLAPSE	1 (<1)	-
CALCULUS URETERIC	-	1 (<1)
CALCULUS URINARY	1 (<1)	-
GLOMERULONEPHRITIS NOS	-	1 (<1)
NEPHRITIS NOS	1 (<1)	-
NOCTURIA AGGRAVATED	1 (<1)	-
OLIGURIA	1 (<1)	-
URETHRAL DISORDER NOS	-	1 (<1)
URETHRAL PAIN	-	1 (<1)
URETHRAL STRICTURE NOS	-	1 (<1)
URINARY TRACT OBSTRUCTION NOS	-	1 (<1)

(body system continuing ...)

Percentages are based on N. Percentages not calculated if N < 10.
Multiple occurrences of the same adverse event in one individual counted only once.
AE11 30MAY2002:08:15:37 (33 of 44)

ae11 Summary of Adverse Events by Body System and Trial Treatment
All Adverse Events
Protocol(s): BM15421
Analysis: ALL PATIENTS Center: ALL CENTERS

Body System/ Adverse Event	PLACEBO N = 1655 No. (%)	ORLISTAT N = 1649 No. (%)
(... body system continuing)		
URINE ODOUR FOUL	-	1 (<1)
Total Number of AEs	139	135

Percentages are based on N. Percentages not calculated if N < 10.
Multiple occurrences of the same adverse event in one individual counted only once.
AE11 30MAY2002:08:15:37 (34 of 44)

ae11 Summary of Adverse Events by Body System and Trial Treatment
All Adverse Events
Protocol(s): BM15421
Analysis: ALL PATIENTS Center: ALL CENTERS

Body System/ Adverse Event	PLACEBO N = 1655 No. (%)	ORLISTAT N = 1649 No. (%)
EYE DISORDERS		
Total Pts With at Least one AE	101 (6)	113 (7)
CONJUNCTIVITIS NEC	23 (1)	29 (2)
CONJUNCTIVITIS ALLERGIC	21 (1)	19 (1)
ALLERGIC CONJUNCTIVITIS AGGRAVATED	12 (<1)	4 (<1)
EYE INFLAMMATION NOS	10 (<1)	4 (<1)
CONJUNCTIVAL HAEMORRHAGE	5 (<1)	4 (<1)
EYE PAIN	5 (<1)	4 (<1)
EYE HAEMORRHAGE NEC	5 (<1)	3 (<1)
EYE IRRITATION	5 (<1)	3 (<1)
VISION BLURRED	2 (<1)	6 (<1)
CATARACT NEC	1 (<1)	4 (<1)
DIPLOPIA	-	5 (<1)
RED EYE	2 (<1)	3 (<1)
VISUAL ACUITY REDUCED	2 (<1)	3 (<1)
VISUAL DISTURBANCE NOS	-	5 (<1)
EYE INJURY NOS	1 (<1)	2 (<1)
EYELID PTOSIS	2 (<1)	1 (<1)
KERATITIS NEC	1 (<1)	2 (<1)
CATARACT NOS AGGRAVATED	-	2 (<1)
DRY EYE NEC	2 (<1)	-
EPISCLERITIS NOS	1 (<1)	1 (<1)
LACRIMAL DUCT OBSTRUCTION NOS	1 (<1)	1 (<1)
LACRIMAL GLAND ENLARGEMENT	1 (<1)	1 (<1)
PHOTOPSIA	1 (<1)	1 (<1)
VITREOUS DETACHMENT	-	2 (<1)
VITREOUS DISORDER NOS	-	2 (<1)
AMAUROSIS FUGAX	-	1 (<1)
ASTHENOPIA	1 (<1)	-
CORNEAL INJURY NOS	-	1 (<1)
CORNEAL ULCER NEC	1 (<1)	-
DACRYOCANALICULITIS	1 (<1)	-
DACRYOCYSTITIS NEC	1 (<1)	-
ENTROPION NEC	1 (<1)	-
EYE DISCHARGE	-	1 (<1)
EYE DISORDER NOS	-	1 (<1)

(body system continuing ...)

Percentages are based on N. Percentages not calculated if N < 10.
Multiple occurrences of the same adverse event in one individual counted only once.
AE11 30MAY2002:08:15:37 (35 of 44)

ae11 Summary of Adverse Events by Body System and Trial Treatment
All Adverse Events
Protocol(s): BM15421
Analysis: ALL PATIENTS Center: ALL CENTERS

Body System/ Adverse Event	PLACEBO N = 1655 No. (%)	ORLISTAT N = 1649 No. (%)
(... body system continuing)		
IRIDOCYCLITIS	1 (<1)	-
KERATOCONUS	-	1 (<1)
LACRIMATION DECREASED	-	1 (<1)
LACRIMATION INCREASED	-	1 (<1)
PAINFUL RED EYES	-	1 (<1)
PAPILLOEDEMA	1 (<1)	-
POSTERIOR CAPSULE OPACIFICATION	1 (<1)	-
PRESBYOPIA	-	1 (<1)
RETINAL DETACHMENT	1 (<1)	-
RETINITIS NEC	-	1 (<1)
SICCA SYNDROME	-	1 (<1)
STRABISMUS NEC	-	1 (<1)
VISION ABNORMAL NEC	-	1 (<1)
VITREOUS HAEMORRHAGE	1 (<1)	-
Total Number of AEs	113	124

Percentages are based on N. Percentages not calculated if N < 10.
Multiple occurrences of the same adverse event in one individual counted only once.
AE11 30MAY2002:08:15:37 (36 of 44)

ae11 Summary of Adverse Events by Body System and Trial Treatment
All Adverse Events
Protocol(s): BM15421
Analysis: ALL PATIENTS Center: ALL CENTERS

Body System/ Adverse Event	PLACEBO N = 1655 No. (%)	ORLISTAT N = 1649 No. (%)
EAR AND LABYRINTH DISORDERS		
Total Pts With at Least one AE	97 (6)	112 (7)
VERTIGO NEC	65 (4)	81 (5)
TINNITUS	4 (<1)	10 (<1)
EARACHE	6 (<1)	7 (<1)
VESTIBULAR NEURONITIS	6 (<1)	5 (<1)
HEARING IMPAIRED	3 (<1)	3 (<1)
EAR WAX	1 (<1)	3 (<1)
MENIERE'S DISEASE	-	4 (<1)
OTOSALPINGITIS	1 (<1)	3 (<1)
TINNITUS AGGRAVATED	3 (<1)	1 (<1)
VERTIGO AGGRAVATED	2 (<1)	2 (<1)
MOTION SICKNESS	2 (<1)	1 (<1)
DEAFNESS NOS	2 (<1)	-
EAR DISORDER NOS	1 (<1)	-
EAR HAEMORRHAGE	1 (<1)	-
MENIERE'S DISEASE AGGRAVATED	1 (<1)	-
OTORRHOEA	1 (<1)	-
SENSATION OF BLOCK IN EAR	1 (<1)	-
VERTIGO POSITIONAL	1 (<1)	-
Total Number of AEs	101	120
IMMUNE SYSTEM DISORDERS		
Total Pts With at Least one AE	70 (4)	70 (4)
HYPERSENSITIVITY NOS	38 (2)	38 (2)
DRUG HYPERSENSITIVITY	7 (<1)	8 (<1)
FOOD ALLERGY	4 (<1)	9 (<1)
ALLERGY AGGRAVATED	6 (<1)	6 (<1)
ALLERGY TO INSECT STING	8 (<1)	4 (<1)
ANAPHYLACTIC REACTION	2 (<1)	2 (<1)
HOUSE DUST MITE ALLERGY	2 (<1)	2 (<1)
SARCOIDOSIS NOS	2 (<1)	2 (<1)
NICKEL SENSITIVITY	-	3 (<1)
AMYLOIDOSIS NOS	1 (<1)	-
Total Number of AEs	70	74

Percentages are based on N. Percentages not calculated if N < 10.
Multiple occurrences of the same adverse event in one individual counted only once.
AE11 30MAY2002:08:15:37 (37 of 44)

ae11 Summary of Adverse Events by Body System and Trial Treatment
All Adverse Events
Protocol(s): BM15421
Analysis: ALL PATIENTS Center: ALL CENTERS

Body System/ Adverse Event	PLACEBO N = 1655 No. (%)	ORLISTAT N = 1649 No. (%)
NEOPLASMS BENIGN AND MALIGNANT (INCLUDING CYSTS AND POLYPS)		
Total Pts With at Least one AE	58 (4)	69 (4)
FIBROADENOMA OF BREAST	9 (<1)	8 (<1)
BENIGN BREAST NEOPLASM NOS	3 (<1)	12 (<1)
LIPOMA NOS	9 (<1)	2 (<1)
UTERINE FIBROIDS	3 (<1)	6 (<1)
FIBROCYSTIC BREAST DISEASE	4 (<1)	4 (<1)
BASAL CELL CARCINOMA	3 (<1)	4 (<1)
BENIGN NEOPLASM NOS	3 (<1)	1 (<1)
DERMATOFIBROMA	2 (<1)	2 (<1)
MALIGNANT MELANOMA SITE/STAGE UNSPECIFIED	3 (<1)	1 (<1)
SOLAR KERATOSIS	2 (<1)	2 (<1)
DYSPLASTIC NAEVUS SYNDROME	-	3 (<1)
LEIOMYOMA NOS	-	3 (<1)
LIPOMA OF BREAST	1 (<1)	2 (<1)
PROSTATE CANCER NOS	1 (<1)	2 (<1)
UTERINE CANCER NOS	1 (<1)	2 (<1)
BREAST CANCER FEMALE NOS	2 (<1)	-
RENAL CELL CARCINOMA STAGE UNSPECIFIED	1 (<1)	1 (<1)
THYROID ADENOMA NOS	1 (<1)	1 (<1)
BENIGN ANORECTAL NEOPLASM NOS	-	1 (<1)
BENIGN FEMALE REPRODUCTIVE TRACT NEOPLASM NOS	1 (<1)	-
BENIGN LYMPH NODE NEOPLASM NOS	1 (<1)	-
BENIGN RENAL NEOPLASM NOS	-	1 (<1)
BENIGN SKIN NEOPLASM NOS	-	1 (<1)
BRAIN NEOPLASM BENIGN NOS	-	1 (<1)
CERVICAL CANCER STAGE 0	-	1 (<1)
CHRONIC LYMPHOCYTIC LEUKAEMIA NOS	1 (<1)	-
FIBROMA NOS	1 (<1)	-
GALL BLADDER CANCER NOS	1 (<1)	-
GASTRIC CANCER NOS	-	1 (<1)
GRANULOMA NOS	-	1 (<1)

(body system continuing ...)

Percentages are based on N. Percentages not calculated if N < 10.
Multiple occurrences of the same adverse event in one individual counted only once.
AE11 30MAY2002:08:15:37 (38 of 44)

ae11 Summary of Adverse Events by Body System and Trial Treatment
All Adverse Events
Protocol(s): BM15421
Analysis: ALL PATIENTS Center: ALL CENTERS

Body System/ Adverse Event	PLACEBO N = 1655 No. (%)	ORLISTAT N = 1649 No. (%)
(... body system continuing)		
HAEMANGIOMA OF LIVER	1 (<1)	-
HISTIOCYTOMA	1 (<1)	-
HODGKIN'S DISEASE NOS	1 (<1)	-
INTRACRANIAL HAEMANGIOMA	-	1 (<1)
LARYNGEAL NEOPLASM BENIGN	1 (<1)	-
LENTIGO	-	1 (<1)
LYMPHOMA NOS	-	1 (<1)
NEOPLASM NOS	-	1 (<1)
ORAL NEOPLASM BENIGN	1 (<1)	-
OVARIAN CANCER NOS	-	1 (<1)
PHARYNGEAL CYST	1 (<1)	-
RECTAL CANCER NOS	-	1 (<1)
SQUAMOUS CELL CARCINOMA OF THE CERVIX	-	1 (<1)
URETHRAL CANCER NOS	-	1 (<1)
VAGINAL POLYP	1 (<1)	-
Total Number of AEs	60	71
HEPATO-BILIARY DISORDERS		
Total Pts With at Least one AE	45 (3)	62 (4)
CHOLELITHIASIS	30 (2)	47 (3)
CHOLECYSTITIS NOS	10 (<1)	7 (<1)
BILIARY COLIC	8 (<1)	8 (<1)
BILE DUCT STONE	2 (<1)	1 (<1)
CHOLANGITIS NOS	1 (<1)	1 (<1)
BILE DUCT OBSTRUCTION NOS	-	1 (<1)
CHOLESTASIS	1 (<1)	-
GALL BLADDER DISEASE NOS	-	1 (<1)
GALL BLADDER PAIN	-	1 (<1)
HEPATITIS ALCOHOLIC	1 (<1)	-
HEPATOMEGALY	-	1 (<1)
HEPATOTOXICITY NOS	-	1 (<1)
Total Number of AEs	53	69

Percentages are based on N. Percentages not calculated if N < 10.
Multiple occurrences of the same adverse event in one individual counted only once.
AE11 30MAY2002:08:15:37 (39 of 44)

ae11 Summary of Adverse Events by Body System and Trial Treatment
All Adverse Events
Protocol(s): BM15421
Analysis: ALL PATIENTS Center: ALL CENTERS

Body System/ Adverse Event	PLACEBO N = 1655 No. (%)	ORLISTAT N = 1649 No. (%)
METABOLISM AND NUTRITION DISORDERS		
Total Pts With at Least one AE	37 (2)	29 (2)
GOUT	17 (1)	13 (<1)
APPETITE DECREASED NOS	4 (<1)	5 (<1)
GOUT AGGRAVATED	5 (<1)	3 (<1)
HYPOGLYCAEMIA NOS	1 (<1)	2 (<1)
APPETITE DISORDER NOS	1 (<1)	1 (<1)
APPETITE INCREASED NOS	1 (<1)	1 (<1)
CALCINOSIS	2 (<1)	-
EATING DISORDER NEC	2 (<1)	-
CARBOHYDRATE CRAVING	-	1 (<1)
DIABETES MELLITUS AGGRAVATED	-	1 (<1)
DIABETES MELLITUS INSULIN-DEPENDENT	1 (<1)	-
DIABETES MELLITUS NON INSULIN-DEPENDENT	1 (<1)	-
HUNGER	1 (<1)	-
HYPERLIPIDAEMIA NOS	-	1 (<1)
HYPOVITAMINOSIS NOS	1 (<1)	-
LACTOSE INTOLERANCE	1 (<1)	-
VITAMIN B12 DEFICIENCY	-	1 (<1)
Total Number of AEs	38	29

Percentages are based on N. Percentages not calculated if N < 10.
Multiple occurrences of the same adverse event in one individual counted only once.
AE11 30MAY2002:08:15:37 (40 of 44)

ae11 Summary of Adverse Events by Body System and Trial Treatment
All Adverse Events
Protocol(s): BM15421
Analysis: ALL PATIENTS Center: ALL CENTERS

Body System/ Adverse Event	PLACEBO N = 1655 No. (%)	ORLISTAT N = 1649 No. (%)
SURGICAL AND MEDICAL PROCEDURES		
Total Pts With at Least one AE	23 (1)	35 (2)
POST-OPERATIVE WOUND INFECTION	5 (<1)	9 (<1)
POST-OPERATIVE PAIN	6 (<1)	5 (<1)
TOOTH EXTRACTION NOS	4 (<1)	1 (<1)
ABORTION INDUCED NOS	-	4 (<1)
POST-OPERATIVE HAEMORRHAGE	1 (<1)	2 (<1)
APICECTOMY	1 (<1)	1 (<1)
DENTAL IMPLANT FAILED	-	2 (<1)
LIPOMA EXCISION	2 (<1)	-
MOLE EXCISION	1 (<1)	1 (<1)
NEEDLE STICK/PUNCTURE	-	2 (<1)
POST-OPERATIVE COMPLICATIONS NOS	-	2 (<1)
CATARACT EXTRACTION	-	1 (<1)
FINGER AMPUTATION	1 (<1)	-
FINGER REPAIR OPERATION	-	1 (<1)
HAND REPAIR OPERATION	-	1 (<1)
IUCD COMPLICATION	1 (<1)	-
POST VACCINATION SYNDROME	-	1 (<1)
SPINAL DECOMPRESSION	-	1 (<1)
TENOTOMY	1 (<1)	-
THUMB AMPUTATION	-	1 (<1)
VENTRAL HERNIA REPAIR	-	1 (<1)
WART EXCISION	-	1 (<1)
Total Number of AEs	23	37

Percentages are based on N. Percentages not calculated if N < 10.
Multiple occurrences of the same adverse event in one individual counted only once.
AE11 30MAY2002:08:15:37 (41 of 44)

ae11 Summary of Adverse Events by Body System and Trial Treatment
All Adverse Events
Protocol(s): BM15421
Analysis: ALL PATIENTS Center: ALL CENTERS

Body System/ Adverse Event	PLACEBO N = 1655 No. (%)	ORLISTAT N = 1649 No. (%)
BLOOD AND LYMPHATIC SYSTEM DISORDERS		
Total Pts With at Least one AE	23 (1)	27 (2)
ANAEMIA NOS	10 (<1)	11 (<1)
LYMPHADENOPATHY	2 (<1)	8 (<1)
IRON DEFICIENCY ANAEMIA	2 (<1)	2 (<1)
LYMPHADENITIS NOS	2 (<1)	2 (<1)
LYMPHADENITIS SUBMANDIBULAR	3 (<1)	-
ANAEMIA NOS AGGRAVATED	2 (<1)	-
PERNICIOUS ANAEMIA NOS	-	2 (<1)
IDIOPATHIC THROMBOCYTOPENIC PURPURA	-	1 (<1)
LEUCOCYTOSIS NOS	1 (<1)	-
LYMPHADENITIS ACUTE	-	1 (<1)
NEUTROPENIA	1 (<1)	-
SECONDARY ANAEMIA	1 (<1)	-
Total Number of AEs	24	27

Percentages are based on N. Percentages not calculated if N < 10.
Multiple occurrences of the same adverse event in one individual counted only once.
AE11 30MAY2002:08:15:37 (42 of 44)

ae11 Summary of Adverse Events by Body System and Trial Treatment
All Adverse Events
Protocol(s): BM15421
Analysis: ALL PATIENTS Center: ALL CENTERS

Body System/ Adverse Event	PLACEBO N = 1655 No. (%)	ORLISTAT N = 1649 No. (%)
INVESTIGATIONS		
Total Pts With at Least one AE	16 (<1)	26 (2)
HAEMATURIA PRESENT	-	12 (<1)
BLOOD IN STOOL	5 (<1)	2 (<1)
HEART RATE IRREGULAR	-	5 (<1)
BLOOD PRESSURE DIASTOLIC INCREASED	-	3 (<1)
BLOOD TESTOSTERONE DECREASED	1 (<1)	1 (<1)
INTRAOCULAR PRESSURE INCREASED	2 (<1)	-
ARTHROSCOPY	1 (<1)	-
BLOOD CULTURE POSITIVE	1 (<1)	-
BLOOD GLUCOSE ABNORMAL	-	1 (<1)
ELECTROCARDIOGRAM ABNORMAL NOS	-	1 (<1)
HORMONE LEVEL NOS ABNORMAL	1 (<1)	-
LIVER FUNCTION TESTS NOS ABNORMAL	1 (<1)	-
MONOCLONAL IMMUNOGLOBULIN PRESENT	1 (<1)	-
PROTEINURIA AGGRAVATED	1 (<1)	-
SMEAR CERVIX ABNORMAL	-	1 (<1)
TOTAL LUNG CAPACITY DECREASED	1 (<1)	-
X-RAY NOS CHEST	1 (<1)	-
Total Number of AEs	16	26
ENDOCRINE DISORDERS		
Total Pts With at Least one AE	21 (1)	18 (1)
HYPOTHYROIDISM	14 (<1)	8 (<1)
GOITRE	3 (<1)	3 (<1)
THYROIDITIS CHRONIC	2 (<1)	1 (<1)
HYPERPARATHYROIDISM NOS	1 (<1)	1 (<1)
OESTROGEN DEFICIENCY	1 (<1)	1 (<1)
ADRENAL DISORDER NOS	-	1 (<1)
HIRSUTISM	-	1 (<1)
HYPERTHYROIDISM	-	1 (<1)
THYROTOXICOSIS	-	1 (<1)
Total Number of AEs	21	18

Percentages are based on N. Percentages not calculated if N < 10.
Multiple occurrences of the same adverse event in one individual counted only once.
AE11 30MAY2002:08:15:37 (43 of 44)

ae11 Summary of Adverse Events by Body System and Trial Treatment
All Adverse Events
Protocol(s): BM15421
Analysis: ALL PATIENTS Center: ALL CENTERS

Body System/ Adverse Event	PLACEBO N = 1655 No. (%)	ORLISTAT N = 1649 No. (%)
CONGENITAL AND FAMILIAL/GENETIC DISORDERS		
Total Pts With at Least one AE	10 (<1)	8 (<1)
EPIDERMAL NAEVUS	7 (<1)	7 (<1)
BIRTH MARK NOS	-	1 (<1)
EHLERS-DANLOS SYNDROME	1 (<1)	-
EPIDERMOLYSIS BULLOSA	1 (<1)	-
POLYCYSTIC KIDNEY	1 (<1)	-
Total Number of AEs	10	8
SOCIAL CIRCUMSTANCES		
Total Pts With at Least one AE	4 (<1)	4 (<1)
OVERWORK	3 (<1)	1 (<1)
CESSATION OF SMOKING	-	1 (<1)
DRUG ABUSE	-	1 (<1)
JOB DISSATISFACTION	1 (<1)	-
OCCUPATIONAL PHYSICAL PROBLEM NOS	-	1 (<1)
Total Number of AEs	4	4
PREGNANCY, PUERPERIUM AND PERINATAL CONDITIONS		
Total Pts With at Least one AE	2 (<1)	5 (<1)
ABORTION SPONTANEOUS NOS	1 (<1)	4 (<1)
ABORTION NOS	1 (<1)	1 (<1)
Total Number of AEs	2	5

Percentages are based on N. Percentages not calculated if N < 10.
Multiple occurrences of the same adverse event in one individual counted only once.
AE11 30MAY2002:08:15:37 (44 of 44)

REFERENCES

[1] Nagele H, Petersen B, Bonacker U, Rodiger W. Effect of orlistat on blood cyclosporin concentration in an obese heart transplant patient. Eur J Clin Pharmacol. 1999 Nov;55(9):667-9.
[2] Cochrane C el al. Case report of abuse of orlistat. Eating Behaviors. 2002; 3:167-169.
[3] Torgerson J S. Xenical in the prevention of diabetes in obese subjects study. Diabetes Care. 2004 January, 27:155-161.

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/s/

Eric Colman
10/21/04 11:12:12 AM
MEDICAL OFFICER

David Orloff
10/21/04 03:32:23 PM
MEDICAL OFFICER

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

DATE: October 18, 2004

FROM: David G. Orloff, M.D.
Director, Division of Metabolic and Endocrine Drug Products

TO: NDA 20-766/S-019
Xenical (orlistat)
Hoffman La-Roche
Proposed changes to labeling based on results of Xendos

SUBJECT: sNDA review issues and recommended action

Background and study results

Xenical is an non-absorbed pancreatic lipase inhibitor that induces fat malabsorption, fecal fat wasting, and thus caloric wasting and modest weight loss. It is indicated for the treatment of obesity in patients with BMI 27-30 with comorbities and BMI > 30 with or without comorbidities.

This memo will summarize very briefly the results of the Xendos study, reviewed in detail by Dr. Colman, in order to explain the division's interpretation of the significance of the results and our approach to the changes to the product labeling.

Xendos was a 4-year, double-blind, randomized, placebo-controlled trial, conducted in 22 centers in Sweden, of the effect of orlistat on weight and risk of progression to type 2 diabetes (DM2) in some 3300 men and women with BMI $\geq$ 30 kg/m2 with randomization stratified based on normal (80% of patients enrolled) or impaired (20%) glucose tolerance at baseline. Oral glucose tolerance tests (OGTT) were performed at baseline and every six months thereafter, with a protocol-mandated (based on an early amendment) follow-up/confirmatory OGTT within 4 weeks in positive patients required for censoring based on the primary outcome variable of diagnosis of DM. The OGTT diagnostic criterion for DM was 2-hour whole blood glucose of > 10 mmol/L (equivalent to plasma glucose of 200 mg/dL). Among those patients with OGTT 2-hour glucose > 10 mmol/L and not having a confirmatory OGTT, those who had a subsequent fasting whole blood glucose > 6.1 mmol/L were considered in the FDA reviews as having confirmation of diagnosis of DM. Patients diagnosed with DM were maintained in the trial on blinded therapy with further follow up of weight and safety outcomes unless they required treatment for DM. The trial also examined a number of potential, previously identified, or not fully resolved safety issues with orlistat that will not be discussed here as no important findings emerged (see Dr. Colman's review for details).

For placebo and Xenical groups, 34% and 52% of patients, respectively, completed 4 years of study follow up. While this is not unusual for a study of a weight loss drug, the very high dropout rate does impact the reliability of the estimate of effect to reduce the risk of DM based on a life table analysis (as opposed to that based on the observed incidence of DM as a function of the total denominator of patients enrolled in the study and contributing evaluable data).

The primary efficacy data are shown in the figure on page 5 of Dr. Colman's review, depicting the life table (time to first event) results for development of DM by treatment group and, across the two panels, by NGT or IGT at baseline. As is clear, there was no effect of orlistat relative to placebo on the rate of development of DM in patients with NGT as baseline. The statistically significant reduction in the conversion rate to DM for the overall study cohort was driven by the outcome in the group with IGT at baseline. In this group, as summarized by Dr. Colman, the adjusted (for dropouts/number at risk at each 6 month follow up point) cumulative incidence rates for DM were, for the IGT subgroup, approximately 27% and 19% in the placebo and Xenical-treated groups respectively ($p<<0.05$). Among the patients with NGT, the cumulative adjusted rates of DM2 were 1.4% and 1.7% (p=NS), respectively, in placebo and Xenical groups.

Importantly, the overall results paralleled the effects of Xenical vs. placebo on weight loss, regardless of the analysis (mean weight loss, rates of categorical weight loss), consistent with the known effects of Xenical on weight relative to placebo plus hygienic measures alone. Specifically, from Dr. Colman's review, the mean weight loss from baseline to 4 years (LOCF) was 2.8% and 5.2% in placebo and Xenical groups, respectively. Weight loss of at least 5% from baseline to 4 years was achieved in 28% of placebo patients and 45% of Xenical patients. Weight loss of at least 10 % was achieved in 10% of placebo patients and 20% of Xenical patients.

Small effects favoring Xenical over placebo, were observed on blood pressure. Effects on different plasma lipids were mixed with regard to favoring Xenical or placebo, related most likely to the competing effects of weight loss and improvement in insulin sensitivity and alterations in the makeup of the diet between Xenical and placebo groups.

In short, the effect of Xenical compared to placebo on the rate of progression to DM in the subgroup of patients with IGT at baseline was presumably the result of Xenical's superior efficacy with regard to weight loss, with no evidence at all of a direct effect of Xenical on glucose metabolic/insulin sensitivity.

Labeling

With regard to labeling, the results of this study ([redacted] Xenical remains a drug for the treatment of obesity and ([redacted] Labeling in the Clinical Studies section of Clinical Pharmacology will convey that patients with IGT who are prescribed Xenical as an adjunct to diet and exercise to enhance weight loss, can expect, if they do lose weight and maintain significant weight loss, to reduce their risk of progression from IGT to frank DM. Indeed, patients on diet and exercise alone can also expect such salutary health effects. No benefit of Xenical over placebo with regard to progression to DM is expected over 4

years in obese patients with normal glucose tolerance, despite Xenical's overall superior effect on weight relative to placebo.

Labeling will convey results from both the life-table (adjusted based on dropouts—those at risk at each time point) and observed (actual incidence observed in the total randomized cohort with evaluable data) analyses.

Finally, labeling will included a disclaimer statement to the effect that the effect of Xenical to reduce progression to DM is a function of its effects to promote weight loss, and not due to some other "pleiotrophic" effect of the drug.

Recommendation
Pending agreement on final labeling, this supplemental NDA may be approved.

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/s/

David Orloff
10/18/04 04:08:31 PM
MEDICAL OFFICER

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
20-766 /S-019

ENVIRONMENTAL ASSESSMENT

CLAIM FOR CATEGORICAL EXCLUSION FROM THE

ENVIRONMENTAL ASSESSMENT REQUIREMENTS FOR

XENICAL® (ORLISTAT) CAPSULES (120mg)

SUPPLEMENTAL NEW DRUG APPLICATION

Hoffmann-LaRoche Incorporated claims a categorical exclusion from the requirement to prepare an environmental assessment in accordance with 21 CFR 25.31 (b). The proposed action, approval of a Labeling Supplement to include additional clinical information regarding adult obese patients, will not increase the use of the active moiety.

Roche

October 21, 2004

Food and Drug Administration
Division of Metabolic and Endocrine Drug Products, HFD-510
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Fishers Document Control Room
Parklawn Bldg. Room 8B 45
5600 Fishers Lane
Rockville, Maryland 20857-1706

Ladies and Gentlemen:

Re: NDA 20-766/S-019 Xenical® (orlistat) Capsules, 120 mg
Replacement of the Page 10, Claim for Categorical Exclusion from
Environmental Assessment Requirements for S-019

Reference is made to the labeling supplement to NDA 20-766/S-019 submitted December 22, 2003 for the purpose of including data from the XENDOS study in the approved label for Xenical. Reference is also made to a discussion with the Agency on October 21, 2004 during which it was agreed that a replacement for page 10 of the previously mentioned application needs to be submitted to the Agency. This page includes the claim for categorical exclusion from the environmental assessment requirements. The purpose of this submission is to provide the replacement for page 10 of NDA 20-766/S-019.

Please feel free to contact the undersigned if you have any questions regarding these responses.

Sincerely,

HOFFMANN-LA ROCHE INC

Margaret J. Jack
Program Director
(973) 235-4463 (telephone)
(973) 562-3700/3554 (fax)

MJJ/dc
Attachments

HLR No. 2004-10907

Hoffmann-La Roche Inc. 340 Kingsland Street
Nutley, New Jersey 07110-1199

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: October 21, 2004

TO: File

FROM: Mamta Gautam-Basak, Ph.D.
Team Leader, DNDC II, HFD-820

SUBJECT: **Categorical Exclusion**
NDA 20-766/S-019, Xenical (Orlistat) Capsules

The request for a Categorical Exclusion is acceptable.

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/s/

Oluchi Elekwachi
10/21/04 03:09:11 PM
CSO

Mamta Gautam-Basak
10/21/04 03:14:20 PM
CHEMIST

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-766/S-019

STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Pharmacoepidemiology and Statistical Science
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Serial Number:	20-766/ SE8-019
Drug Name:	Xenical (orlistat) Capsules, 120 mg
Indication(s):	Obesity
Applicant:	Hoffmann-La Roche Inc.
Date(s):	December 22, 2003
Review Priority:	Standard
Biometrics Division:	2 (HFD-715)
Statistical Reviewer:	Lee-Ping Pian, Ph.D.
Concurring Reviewers:	Todd Sahlroot, Ph.D.
Medical Division:	Metabolic and Endocrinologic Drug Products (HFD-510)
Clinical Team:	Eric Colman, M.D.
Project Manager:	Oluchi Elekwachi

Keywords: clinical study, NDA review, missing data

Table of Contents

1. EXECUTIVE SUMMARY

Xendos was a diabetes outcome study for a maximum of 4 years to examine weight reducing and type 2 diabetes preventing and or delaying effects of Xenical vs. placebo in obese patients.

The study was conducted in Sweden in 3304 non diabetic obese (BMI≥30) patients 30 to 60 years of age. Patients were stratified at randomization as normal (<6.7 mmol/L) or impaired glucose tolerance (IGT) (≥6.7mmol/L and <10mmol/L) based on the 2-hour OGTT (Oral Glucose Tolerance Test). The primary outcome variable was time to diabetic event (2 hr OGTT >10mmol/L) of 1st occurrence based on the 2 hr OGTT test. Of the 3304 randomized patients, 2383 (78%) were normal and 661 (22%) were IGT. The sponsor indicated that "the mean prevalence of IGT is 6.5% among obese patients with BMI>30."

At the end of 4 years of treatment, 84/1472 (5.7%) placebo patients and 70/1572 (4.5%) orlistat patients were diabetic. The estimator of cumulative failure rate from the sponsor's life table for ½ yearly grouped data was 9% for the placebo group and 6% for the orlistat group. The logrank test showed that orlistat significantly ($p<0.01$) delayed the onset of type 2 diabetes at the end of study.

The logrank test stratified by baseline glucose tolerance showed the p value controlled for strata was 0.0035 favoring Xenical. 76% (117/154) of the total diabetic events occurred in the IGT stratum. Logrank tests on the 2 strata separately showed that the 2 treatment groups were significantly different ($p=0.001$) in the IGT patients ($n=661$) and not significantly different in the normal stratum patients ($p=0.7$, $n=2383$). Table 1 displays the life table statistics and mean weight change statistics by baseline strata. The mean weight changes from a baseline of approximately 111 kg in both strata were similar: -3 kg for the placebo patients and -6 kg for the orlistat patients. Mean weight changes are also shown for subgroups defined by the primary endpoint. These subgroups are determined by response and therefore do not fit the usual definition. The data are exploratory in nature and require caution in interpretation.

Table 1 Diabetic events (time of 1st occurrence) and weight change by randomization stratum

Randomization Stratum	IGT				Normal			
Treatment	Placebo n=324		Orlistat n=337		Placebo n=1148		Orlistat n=1235	
Diabetes 1st event	**Yes**	No	**Yes**	No	**Yes**	No	**Yes**	No
n (cumulative failure or survival rate*)	**68 (29%)**	256 (71%)	**49 (19%)**	288 (81%)	**16 (2%)**	1132 (98%)	**21 (2%)**	1214 (98%)
Mean wt change (kg) (SD)	**-0.9 (5.7)**	-3.7 (6.3)	**-1.6 (6.0)**	-6.6 (7.9)	**-0.4 (11.7)**	-3.3 (7.7)	**3.9 (7.6)**	-6.1 (8.2)
Mean wt change (kg) (SD)	-3.1 (6.3)		-5.8 (7.8)		-3.3 (7.8)		-5.9 (8.3)	

* life table estimates

1.1 Conclusions and Recommendations

The time to 1st occurrence of diabetic event was significantly different in orlistat patients and placebo patients. However, most events were in the baseline IGT stratum (75%). The analysis by baseline glucose tolerance strata showed that only IGT patients were significantly different in the first occurrence of diabetic event between the 2 treatment groups. In the normal stratum, 236 (21%) and 268 (22%) of the placebo patients and orlistat patients, respectively developed IGT. The life table cumulative incidence rates for

time to 1st IGT were 29.2% and 26.2% for the placebo group and the orlistat group, respectively (p=0.1). The overall withdrawal rate was high (57%) and different between the treatment groups (Xenical 48% vs. placebo 66%). The heavy censoring particularly the different censoring rate between treatments was a concern because life table methods assume that censoring is noninformative. That is, those censored at a given time are a representative sample of those at risk. If it can be assumed that these observations are randomly distributed, then they do not bias the estimates. If those censored were having a different risk of failure, the censoring is informative and the estimates may be biased. In this case, the absolute rate of events is preferable.

2. INTRODUCTION

2.1 Overview

Xendos was a multicenter, double blind, placebo-controlled study in non-diabetic obese patients (BMI≥30 aged 30-60 years). Patients were randomized to either orlistat or placebo. Treatment continued for a minimum of two years up to a maximum 4 years, until 95 cases of type 2 diabetes have been observed based on a single OGTT of which 72 should have confirmed diabetic event with a follow-up test.

The objective of the study was to examine whether treatment with orlistat and a hypocaloric diet can prevent obese patients from developing type 2 diabetes to a greater extent than treatment with a placebo and a hypocaloric diet.

3. STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

Study Design and Endpoints

This was a multicenter, double-blind, placebo-controlled, randomized, parallel design study of up to 209 weeks of treatment.

The protocol specified that the target population was to be 45% males and at least 10% IGT patients, however, based on prior studies with orlistat, the mean prevalence of IGT is 6.5% among obese patients with BMI>30. The study included 45% males and 22% IGT patients.

The primary efficacy variables were body weight, time to onset of diabetes response (OGTT≥10 mmol/L) with a repeat OGTT within 4 weeks. Secondary efficacy variables were BMI, the time to onset of IGT in baseline OGTT normal patients, lipids and coagulants, vital signs and pulse, anthropometry, waist/hip ratio.

Patient Disposition, Demographic and Baseline Characteristics

Disposition of Patients

22 centers in Sweden screened 5151 patients and randomized 3304 patients. The rate of completion was just over 40%. The first 3 year withdrawal rate was approximately 20% annually for placebo patients and 10% (first 2 years) and 20% (3rd year) for orlistat patients. The 4th year's withdrawal rate was approximately 5% for both groups. Table 2 and Figure 1 display the number of patients in study versus time. Table 3 and Figure 2 display reasons for withdrawal.

Table 2 Disposition of patients

	Placebo	Orlistat	Total
Year 1 (Randomized)	1655	1649	3304
Year 2	1268 (77%)	1477 (90%)	2745 (83%)
Year 3	992 (60%)	1292 (78%)	2284 (69%)
Year 4	636 (38%)	958 (58%)	1594 (48%)
Completing study	564 (34%)	850 (52%)	1414 (43%)

Figure 1 Number of patients in study versus time

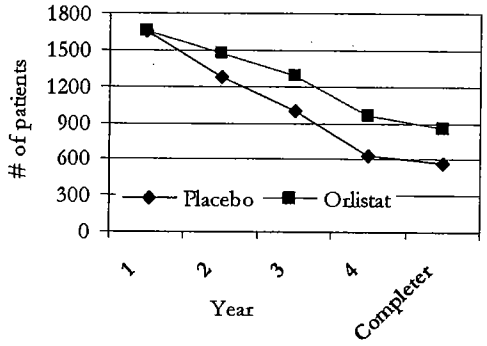
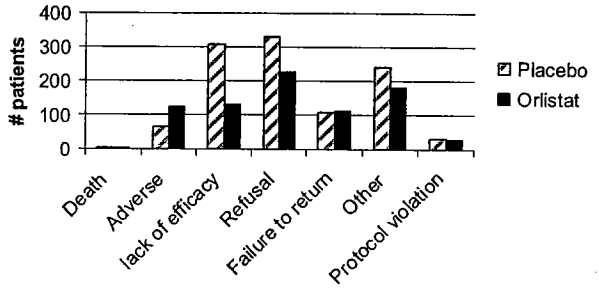


Table 3 Summary of reasons for withdrawal

Reason for withdrawal	Placebo n=1655	Orlistat n=1649
Adverse event	67	125
Death	4	2
Abnormality of lab test	1	0
Insufficient therapeutic response	309	130
Refused treatment	332	226
Failure to return	107	111
Other	242	179
Protocol violation	29	26
Total	1091	799

Figure 2 Number of patients by reason for withdrawal



Patients were predominantly Caucasian (99%). The mean BMI was approximately 37 kg/m^2. 55% of patients were female and 45% were males which was consistent with the protocol enrollment plan. 21% of patients had IGT (the protocol planned >10% with IGT). The demographic characteristics were similar for the 2 treatment groups.
Patients within each stratum were similar in baseline variables between treatment groups. However, baseline values were greater in the impaired stratum than in the normal stratum (Table 4).

Table 4 Mean (SD) for baseline variables

	Impaired		Normal	
	Placebo	Orlistat	Placebo	Orlistat
	n=324	n=337	n=1148	n=1235
2 hr glucose	7.88 (0.90)	7.84 (0.89)	4.84 (1.01)	4.84 (1.03)
glucose	5.04 (0.63)	5.01 (0.65)	4.48 (0.53)	4.51 (0.55)
Insulin	101.1 (57.1)	101.9 (57.9)	78.5 (42.2)	79.5 (46.2)
BMI	38.17 (4.22)	38.49 (4.16)	37.48 (4.36)	37.41 (4.19)

Statistical Methodologies

The primary statistical analysis was survival analysis using the logrank test on the primary events, time to onset of type 2 diabetes. The randomization stratum IGT (impaired or normal) was not a factor in the sponsor's analysis. This reviewer performed stratified logrank test with baseline IGT as a factor. The IGT stratum is highly predictive of the outcome of primary diabetes event. Therefore, the primary analysis and the results should use the covariate of IGT status in order to reduce the confounding, to increase precision and to adjust for the factor imposed by stratification at randomization.
The intent-to-treat population (ITT) for the primary analysis of diabetic incidence included 1472 (89%) placebo patients and 1572 (95%) orlistat patients who had a baseline OGTT measurement and at least one follow-up OGTT measurement.

Results and Conclusions

Efficacy results
The primary efficacy variables were weight change by end of study and time to onset of type 2 diabetes. The onset of diabetes is based on the first diabetic OGTT of 2 hr whole blood glucose value ≥10 mmol/L.

Secondary efficacy variables are change from baseline in BMI, serum lipids, fasting insulin, fasting glucose, blood pressure, pulse rate, cardio-thrombotic markers, anthropometric measurements as well as the time to onset of IGT in patients who were normal at baseline.

The sponsor reported (Table 5) that starting at 6 months of treatment a greater proportion of placebo-treated patients developed diabetes than did orlistat-treated patients (1.22% versus 0.32%, respectively). At the end of 4 years, the cumulative rate for the development of diabetes was 9.04% for placebo and 6.15% for orlistat (p=0.0032).

Table 5 Cumulative incidence of diabetic events by time of 1st occurrence

	Placebo			Orlistat		
Scheduled day	# of pts entering	Events (%)	Cumulative rate	# of pts entering	Events (%)	Cumulative rate
Day 1	1655			1649		
Day 169	1472	18 (1.22)	.01223	1572	5 (0.32)	.00318
Day 365	1271	10 (0.79)	.02000	1483	10 (0.67)	.00990
Day 533	1106	11 (0.99)	.02975	1362	7 (0.51)	.01499
Day 729	956	13 (1.36)	.04294	1257	7 (0.56)	.02048
Day 897	749	10 (1.34)	.05572	1118	12 (1.07)	.03099
Day 1093	672	10 (1.49)	.06977	1008	14 (1.39)	.04445
Day 1261	551	7 (1.27)	.08159	859	8 (0.93)	.05335
Day 1457	521	5 (0.96)	.09040	810	7 (0.86)	.06153

Reviewer's analysis:

The life table method which adjusts the number at risk under an assumption of constant (uniform) censoring to obtain the effective sample size (risk set) is used. The censored cases within an interval are treated as if they were censored at the midpoint of the interval. Half of the censored cases are deducted from the number at risk to produce the effective sample size since they are only considered at risk for half of the interval. Tables 6 and 7 display the life table statistics for placebo group and orlistat group, respectively. The failure rates were 8.7% and 5.6%, respectively.

Table 6 Life table statistics of time to 1st OGTT diabetes - Placebo

	Effective Sample Size	Number Failed	Number Censored	Conditional Probability of Failure	Conditional Probability Standard Error	Survival	Failure
1	1472						
200	1385.5	18	173	0.013	0.00304	1	0
400	1200	10	162	0.00833	0.00262	0.987	0.013
600	1040	11	138	0.0106	0.00317	0.9788	0.0212
800	861	13	198	0.0151	0.00416	0.9684	0.0316
1000	714.5	10	69	0.014	0.00439	0.9538	0.0462
1200	615.5	10	109	0.0162	0.0051	0.9405	0.0595
1400	539	7	24	0.013	0.00488	0.9252	0.0748
1400+	262.5	5	515	0.019	0.00844	0.9132	0.0868

Table 7 Life table statistics of 1st OGTT diabetes - Orlistat

	Effective Sample Size	Number Failed	Number Censored	Conditional Probability of Failure	Conditional Probability Standard Error	Survival	Failure
1	1572						
200	1530.5	5	83	0.00327	0.00146	1	0
400	1429.5	10	109	0.007	0.0022	0.9967	0.00327
600	1315.5	7	99	0.00532	0.00201	0.9898	0.0102
800	1192	7	134	0.00587	0.00221	0.9845	0.0155
1000	1069	12	98	0.0112	0.00322	0.9787	0.0213
1200	940	14	136	0.0149	0.00395	0.9677	0.0323
1400	838	8	40	0.00955	0.00336	0.9533	0.0467
1400+	803	7	408.5	0.0171	0.00642	0.9442	0.0558

The analysis of primary efficacy variable by baseline stratum is presented in Table 8 and in Figure 3. The majority of events (117/156=76%) were in the IGT stratum (n=661, 20%). Treatment groups were significantly different on the primary efficacy variable in patients with IGT at baseline and not significantly different in normal patients at baseline (n=2383, 80%). Tables 9 and 10 display the life table statistics of diabetic cases (1st occurrence) for impaired and normal strata, respectively.

Table 8 Events by IGT stratum - diabetic events (time of 1st occurrence)

Stratum	Impaired		Normal	
Treatment	Placebo	Orlistat	Placebo	Orlistat
n	324	337	1148	1235
Failed (%)	68 (21%)	49 (13%)	16 (1.4%)	21 (1.7%)
Logrank p-value	0.001		0.73	

Figure 3 Kaplan-Meier survival curve for primary diabetes (time of 1st occurrence) by stratum

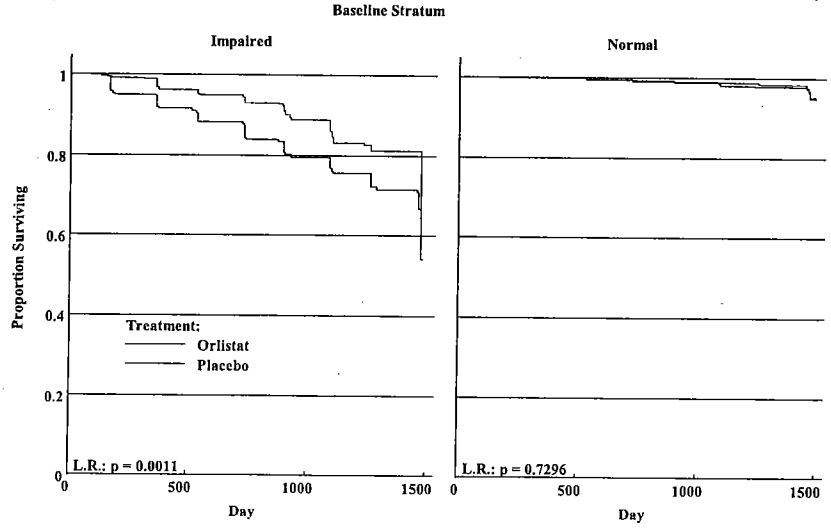


Table 9 Cumulative incidence of diabetic cases by time of 1st occurrence – IGT stratum

		Placebo impaired				Orlistat impaired			
Time interval (days)		# failed	censored	starting #	CFR*	# failed	censored	starting #	CFR
				324				337	
0	200	**16**	23	312.5	0	**3**	18	328	0
200	400	**10**	29	270.5	0.0512	**9**	14	309	0.0092
400	600	**9**	19	236.5	0.0863	**4**	20	283	0.0380
600	800	**10**	37	199.5	0.1210	**5**	26	256	0.0516
800	1000	**8**	18	162	0.1651	**10**	21	227.5	0.0701
1000	1200	**7**	21	134.5	0.2063	**13**	23	195.5	0.1110
1200	1400	**6**	1	116.5	0.2476	**4**	7	167.5	0.1701
1400	.	**2**	108	56	0.2864	**1**	159	80.5	0.1899

* CFR cumulative failure rate

Table 10 Cumulative incidence of diabetic cases by time of 1st occurrence – Normal stratum

		Placebo normal				Orlistat normal			
Time interval (days)		# failed	censored	starting #	CFR*	# failed	censored	starting #	CFR
				1148				1235	
0	200	**2**	150	1073	0.00000	**2**	65	1202.5	0
200	400	**0**	133	929.5	0.00186	**1**	95	1120.5	0.00166
400	600	**2**	119	803.5	0.00186	**3**	79	1032.5	0.00255
600	800	**3**	161	661.5	0.00435	**2**	108	936	0.00545
800	1000	**2**	51	552.5	0.00886	**2**	77	841.5	0.00758
1000	1200	**3**	88	481	0.01250	**1**	113	744.5	0.00994
1200	1400	**1**	23	422.5	0.01860	**4**	33	670.5	0.01130
1400	.	**3**	407	206.5	0.02090	**6**	644	328	0.01720

* CFR cumulative failure rate

Figures 4 and 5 display number of patients censored by time for the normal stratum and the IGT stratum, respectively.

Figure 4 Number of patients censored versus time – Normal stratum

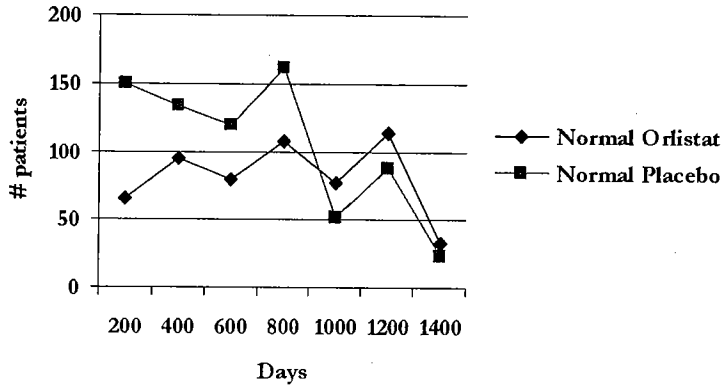


Figure 5 Number of patients censored versus time – Impaired stratum

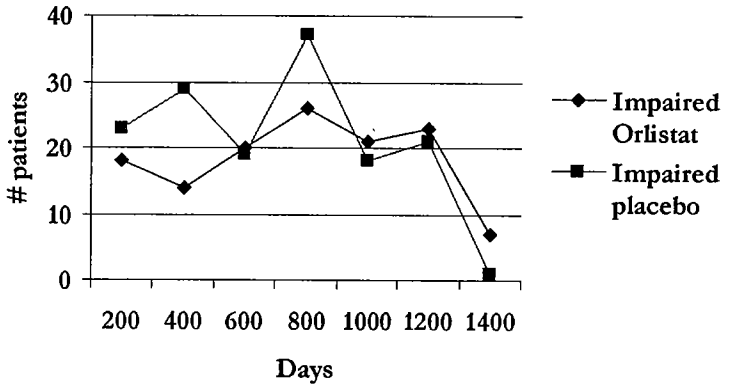
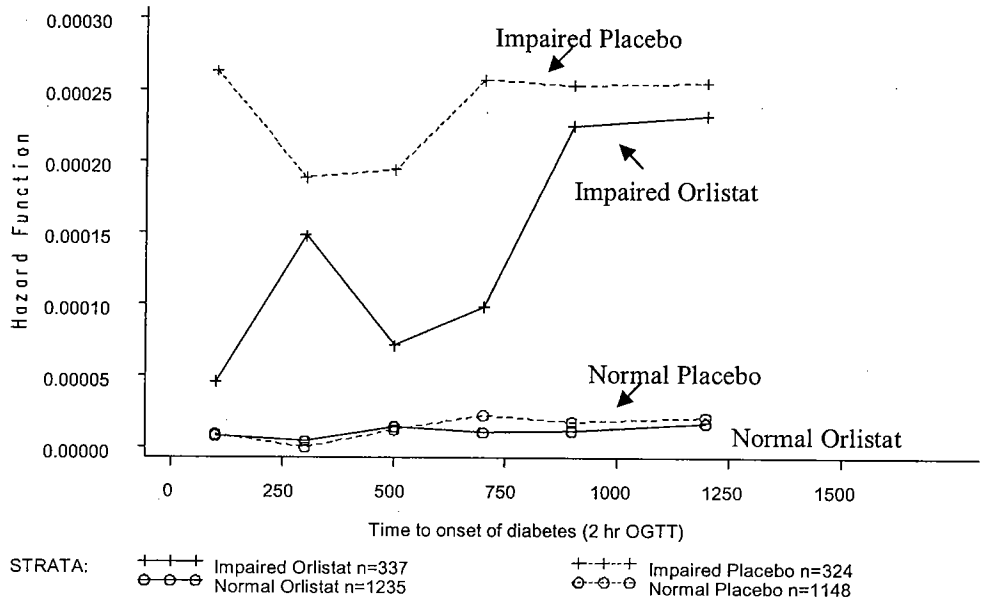


Figure 6 displays the hazard function by treatment group and stratum. The hazard rate is the rate at which events occur. The hazard for patients with normal baseline OGTT was low compared to the baseline IGT patients. The impaired placebo patients experience a greater hazard rate than the impaired orlistat patients. However, the hazard rate increased for the orlistat patients while there was no change for the placebo group. Censored observations deflate the hazard rate by slowing down the decrease in the survival rate which is the denominator of the hazard rate.

Figure 6 Hazard function versus survival time



Medical Officer, Dr. Colman further censored 7 cases of diabetes (6, placebo & 1, orlistat) because those early cases were not followed by a second confirmatory OGTT.

Table 11 displays the failure estimates for all patients and Tables 12 & 13 by stratum for the confirmed cases of diabetes. Figure 7 displays the percent of non diabetics versus survival time. The p values for all patients and IGT and normal GT at baseline were 0.01, 0.006 and 0.79, respectively.

Table 11 Life table statistics by treatment

		Normal Placebo				Normal Orlistat			
Time interval	(Days)	# Failed	# Censored	Effective n	CFR	# Failed	# Censored	Effective n	CFR
0	1	0	0	1472	0	0	0	1572	0
1	200	12	179	1382.5	0	4	84	1530	0
200	400	10	162	1200	0.00868	10	109	1429.5	0.00261
400	600	11	138	1040	0.0169	7	99	1315.5	0.00959
600	800	13	198	861	0.0273	7	134	1192	0.0149
800	1000	10	69	714.5	0.042	12	98	1069	0.0206
1000	1200	10	109	615.5	0.0554	14	136	940	0.0316
1200	1400	7	24	539	0.0708	8	40	838	0.0461
1400	.	5	515	262.5	0.0828	7	803	408.5	0.0552

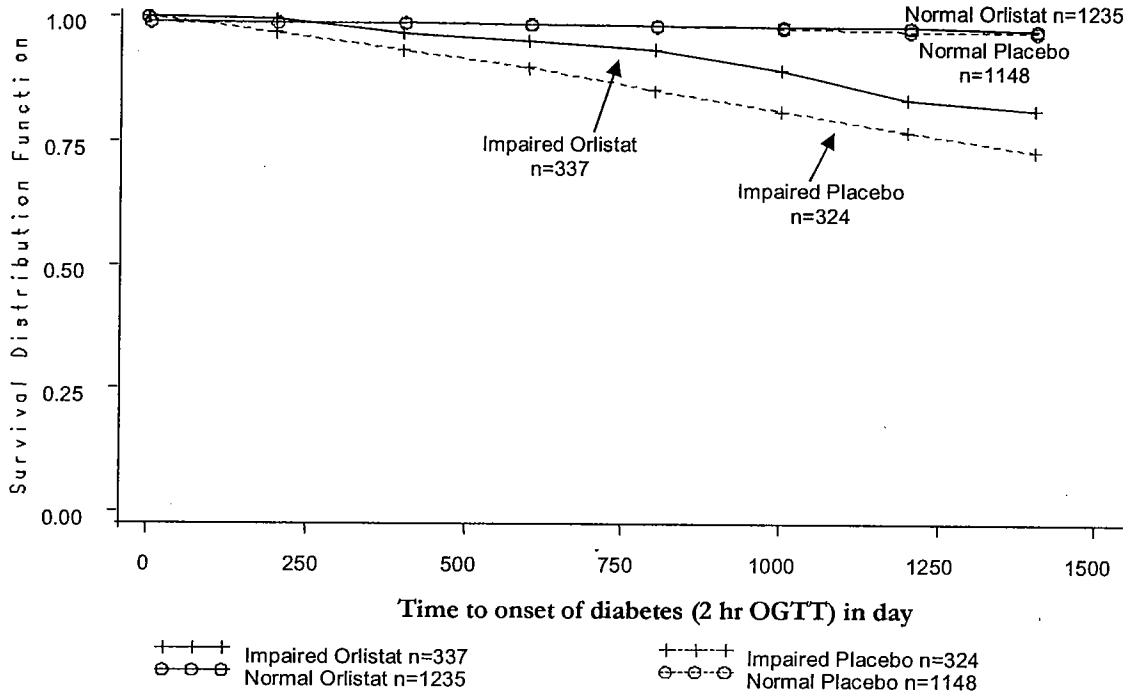
Table 12 Life table statistics by treatment – Normal stratum

		Normal Placebo				Normal Orlistat			
Time interval	(Days)	# Failed	# Censored	Effective n	CFR	# Failed	# Censored	Effective n	CFR
				1148				1235	
1	200	2	150	1073	0	2	65	1202.5	
200	400	0	133	929.5	0.00186	1	95	1120.5	0.00166
400	600	2	119	803.5	0.00186	3	79	1032.5	0.00255
600	800	3	161	661.5	0.00435	2	108	936	0.00545
800	1000	2	51	552.5	0.00886	2	77	841.5	0.00758
1000	1200	3	88	481	0.0125	1	113	744.5	0.00994
1200	1400	1	23	422.5	0.0186	4	33	670.5	0.0113
1400	.	3	407	206.5	0.0209	6	644	328	0.0172

Table 13 Life table statistics by treatment – Impaired stratum

		Impaired Placebo				Impaired Orlistat			
Time interval	(Days)	# Failed	# Censored	Effective n	CFR	# Failed	# Censored	Effective n	CFR
				324				337	0
1	200	10	29	309.5	0	2	19	327.5	0
200	400	10	29	270.5	0.0323	9	14	309	0.00611
400	600	9	19	236.5	0.0681	4	20	283	0.0351
600	800	10	37	199.5	0.1035	5	26	256	0.0487
800	1000	8	18	162	0.1485	10	21	227.5	0.0673
1000	1200	7	21	134.5	0.1905	13	23	195.5	0.1083
1200	1400	6	1	116.5	0.2327	4	7	167.5	0.1676
1400	.	2	108	56	0.2722	1	159	80.5	0.1874

Figure 7 Percent of non diabetics versus survival time



The Cox regression model with treatment as the independent variable was performed. Table 14 summarizes the regression coefficient and its 95% confidence interval.

Table 14 Analysis summary of Cox regression of proportional hazard

Stratum	Impaired		Normal		All	
Treatment	Placebo	Orlistat	Placebo	Orlistat	Placebo	Orlistat
n	324	337	1148	1235	1472	1572
Failed (%)	16	21	62	48	78	69
Regression estimate, ß	-0.54 (0.19)		-0.087 (0.333)		-0.42 (0.17)	
Hazard ratio, $e^{ß}$ (95% CI)	0.58 (0.40, 0.85)		0.92 (0.48, 1.76)		0.66 (0.47, 0.91)	
p-value	0.006		0.79		0.01	

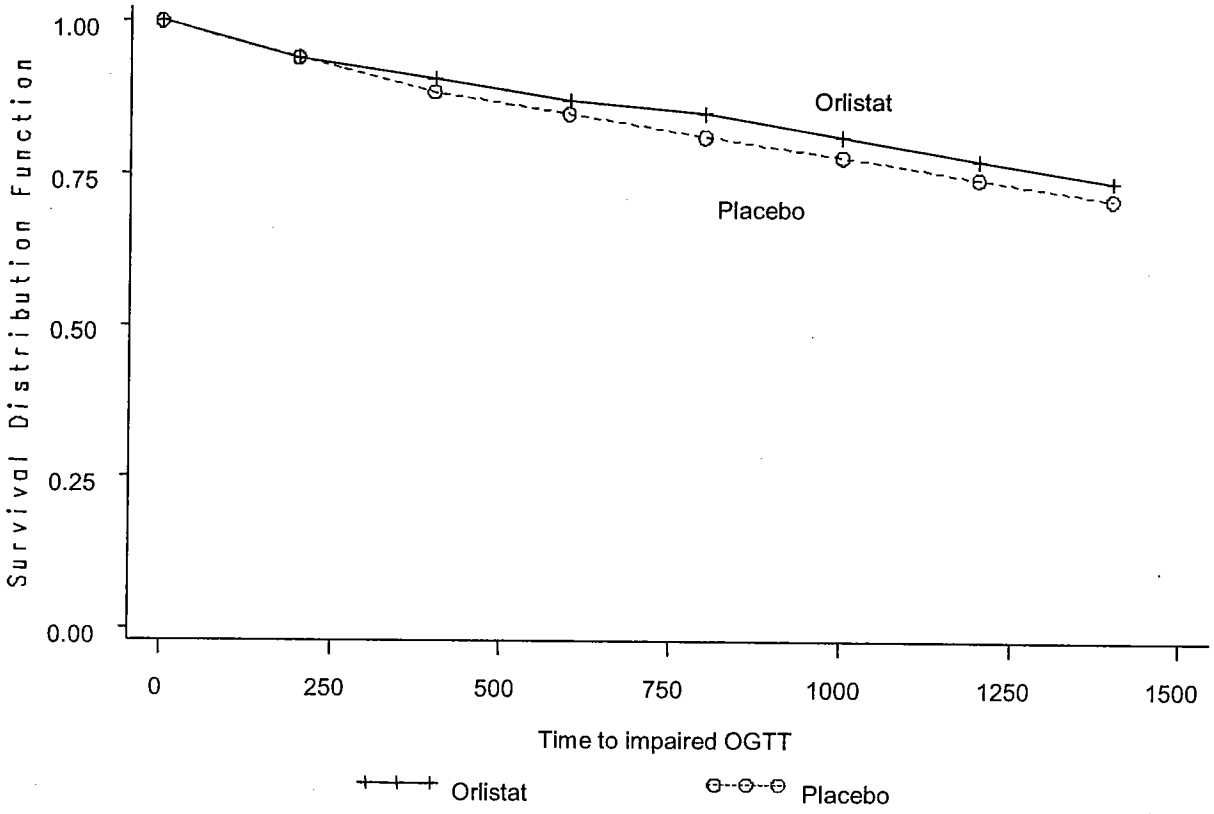
Logrank test was performed in OGTT normal patients at baseline on first time to IGT event (Table 15). The treatment groups were not significantly different in time to IGT (p=0.09).

Table 15 Percentage of IGT patients in baseline OGTT normal patients

Treatment	n	# Failed (Observed failure rate)	Cumulative failure rate	Censored (%)
Placebo	1148	236 (21%)	29%	912 (79%)
Orlistat	1235	268 (22%)	26%	967 (78%)

Figure 8 displays percent of OGTT normal patients over time for the OGTT normal stratum.

Figure 8 Percent of non diabetic patients versus time

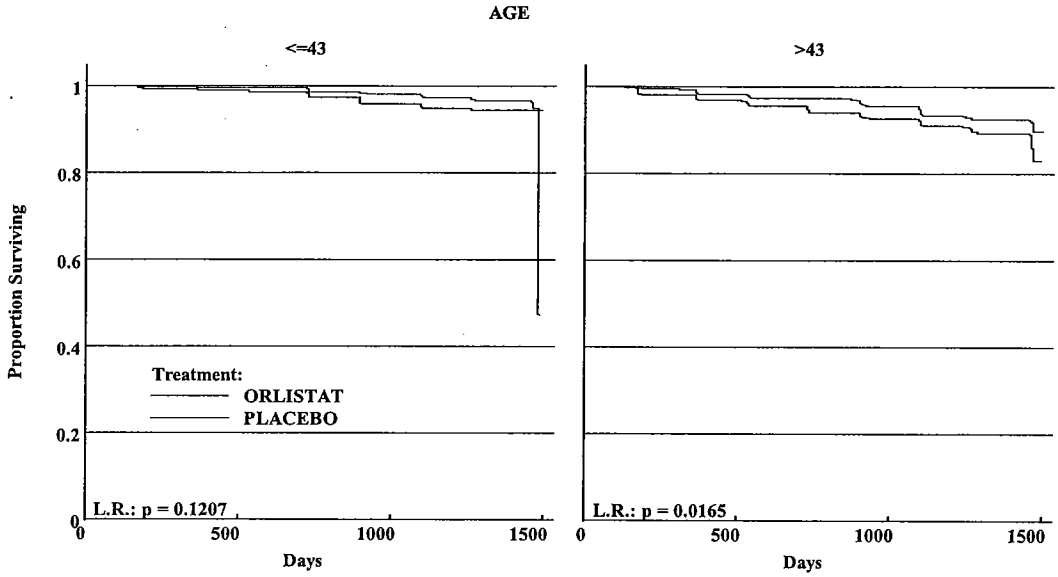


4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Age

The inclusion criterion for age was 30 to 60 years with a median age of 43 years. Patients in the >43 years group experienced more events (73%) than patients in the ≤43 years group (27%). The 2 treatment groups were significantly different in the >43 years age group (Fig. 9).

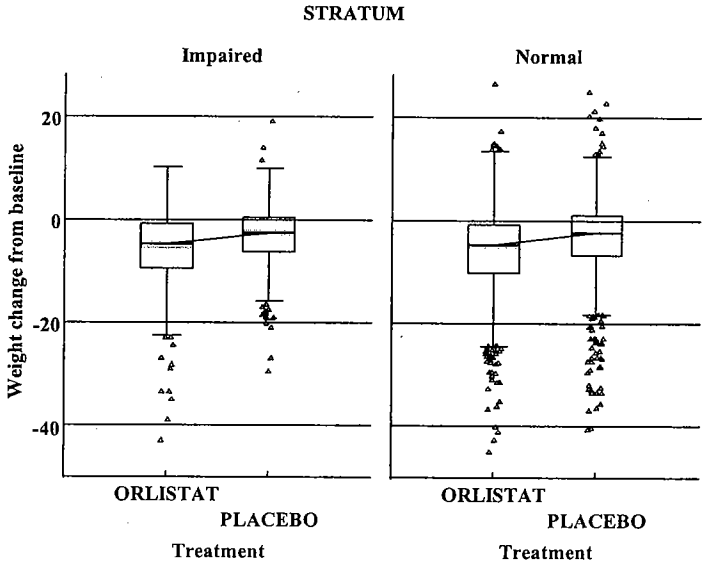
Figure 9 Time to 1st occurrence of diabetic event by age groups



Weight change by stratum

Weight changes from baseline were similar in the 2 strata. Median weight change was -4.8 kg in the orlistat group for both strata. For placebo, the median change was -2.5 for the impaired patients and -2.3 kg for the normal patients (Fig 10).

Figure 10 Median weight changes from baseline at endpoint



Patients with a diabetic event lost less weight than patients who were normal at the end of treatment (Figure 11 and Table 16).
Note that weight change and diabetes event were both outcome variables. Subgroups defined by a diabetic event (yes/no) are not subgroups in the usual sense; therefore caution should be used in interpreting the results.

Figure 11 Median weight change from baseline for diabetic and normal patients at endpoint

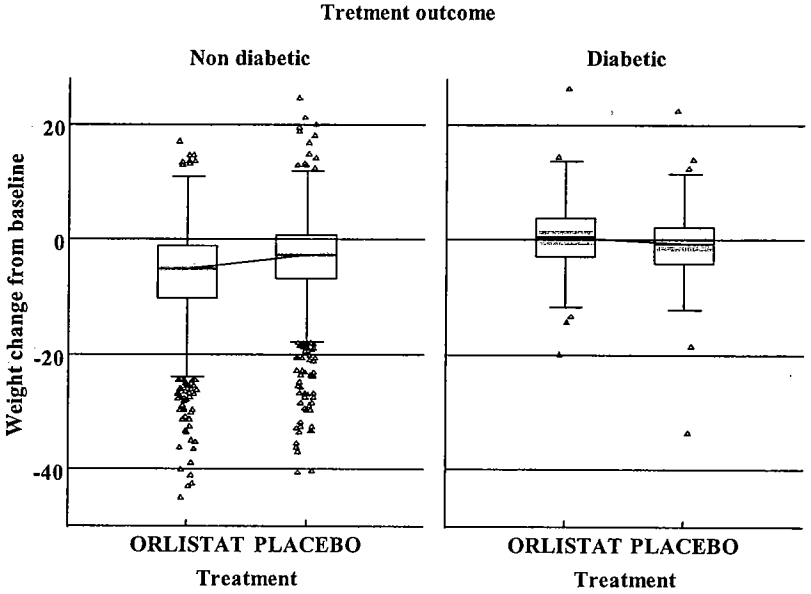


Table 16 Median weight loss by diabetic status at endpoint

	Non diabetic		Diabetic	
	Placebo	Orlistat	Placebo	Orlistat
	n=1388	n=1502	n=84	n=70
Weight loss (kg)	-2.5	-5	-0.55	0.45

5. Labeling Comment:

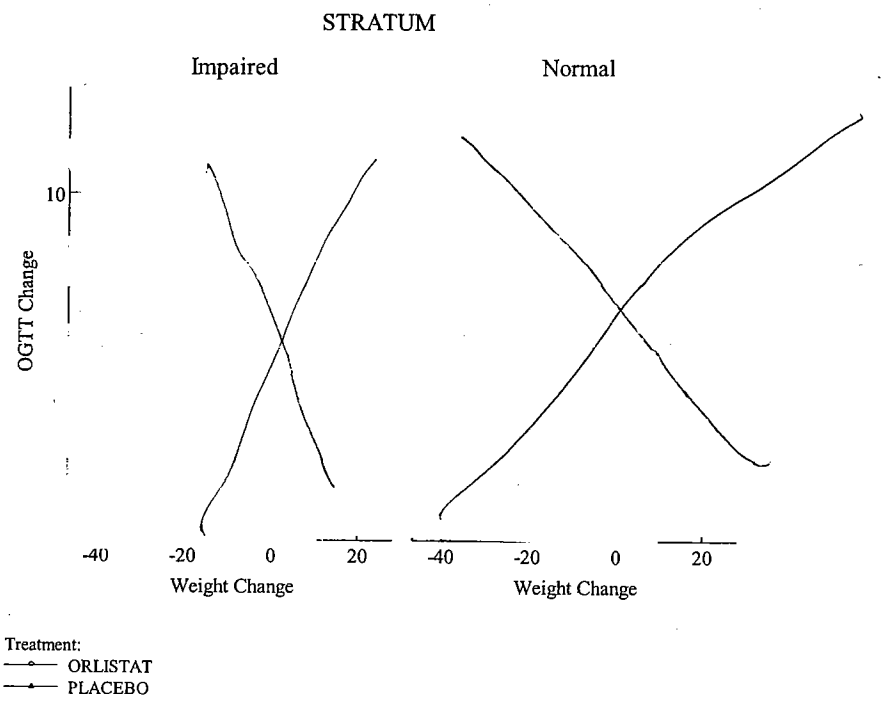
The sponsor presented cumulative rates of diabetes in patients with IGT at baseline but did not present comparable data for patients who were normal at baseline. displays the labeled table with the unconfirmed diabetes events censored.

Incidence Rate of Diabetes at Year 4 by OGTT Status at Baseline

OGTT at baseline	normal		Impaired		All	
Treatment	Placebo	Orlistat	Placebo	Orlistat	Placebo	Orlistat
Number of patients	1148	1235	324	337	1472	1572
# of diabetes	16	21	62	48	78	69
Life table rate	2.1%	1.7%	27.2%	18.7%	8.3%	5.5%
Observed rate	1.4%	1.7%	19.1%	14.2%	5.3%	4.4%
Absolute risk reduction						
Life table	0.4%		8.5%		2.8%	
Observed	-0.3%		4.9%		0.9%	
Relative risk reduction	8%		42%		34%	
p-value	0.79				0.01	

APPENDIX

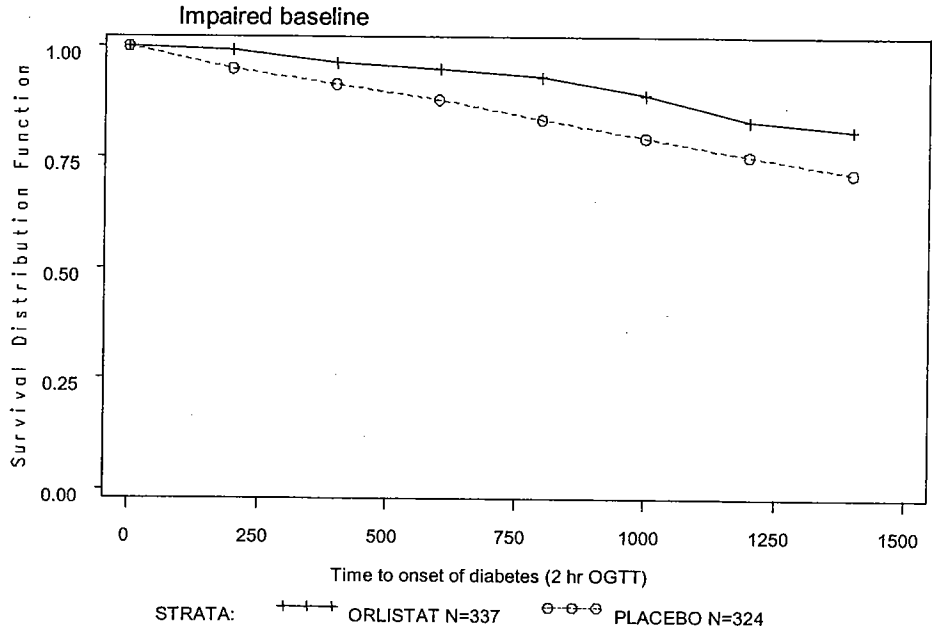
Figure 1 Regression of 2 hr OGTT change by weight change at endpoint

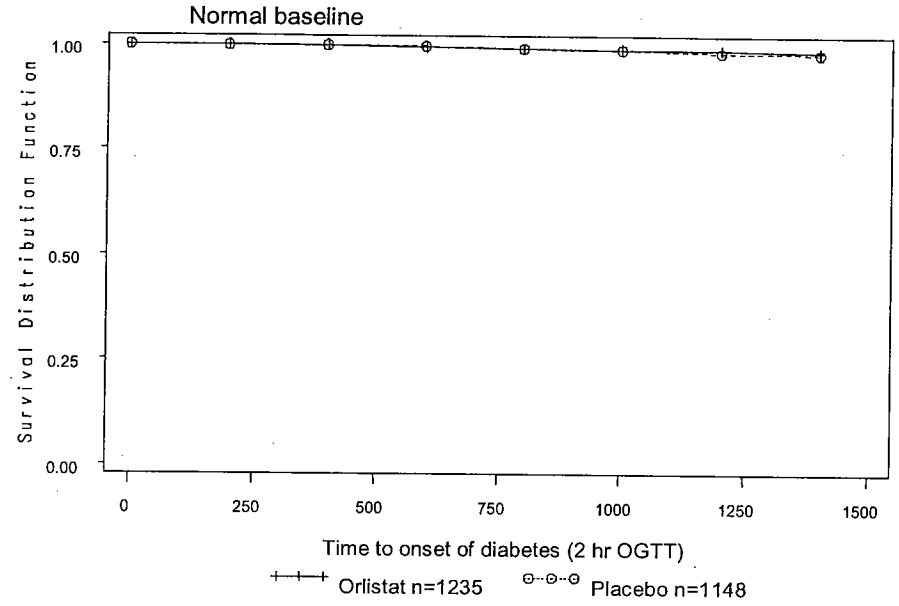


Regression statistics of 2 hr OGTT change (mmol/L) from baseline by weight change (kg) from baseline

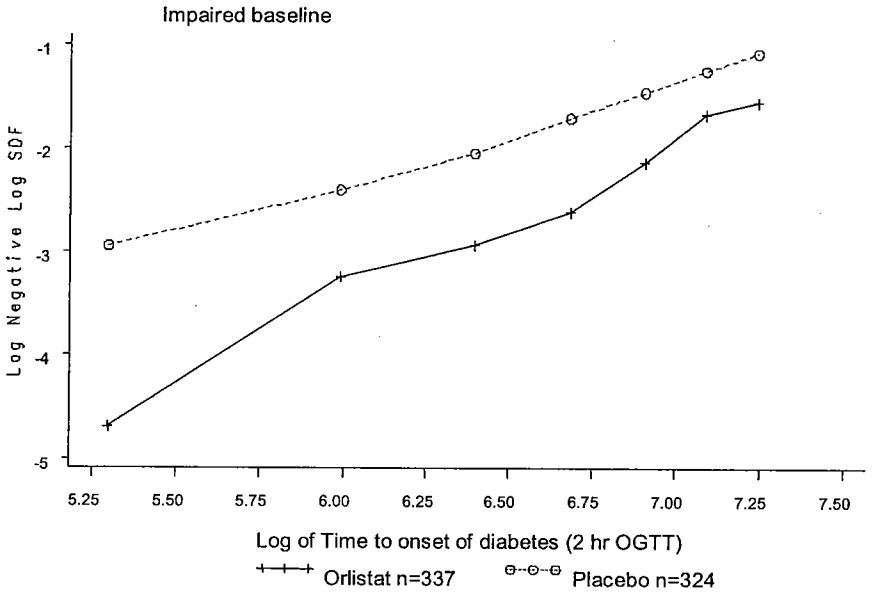
Stratum Treatment	Impaired Orlistat	Impaired Placebo	Normal Orlistat	Normal Placebo
n	337	324	1235	1148
Intercept (mmol/L)	-0.626	-0.423	0.220	0.228
slope	0.106	0.105	0.042	0.043
r-square	0.16	0.09	0.06	0.06

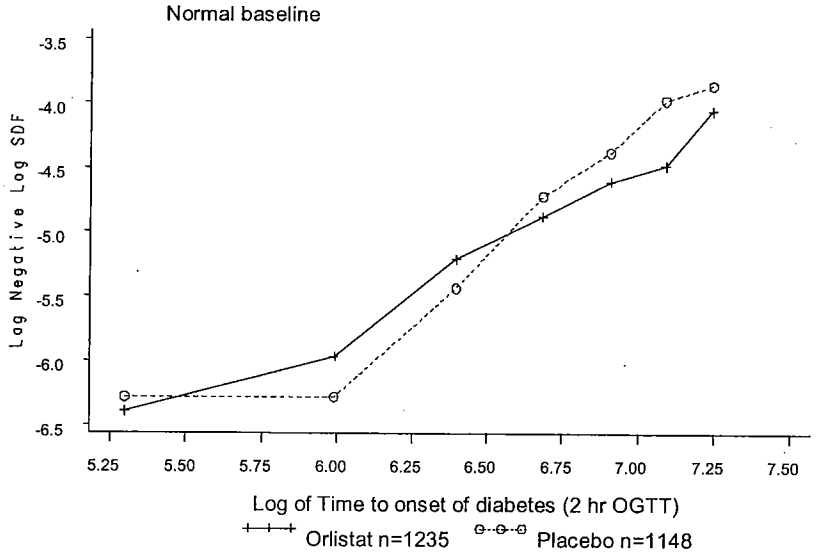
Figure 2 Life table survivor function estimates versus time





The log-log survivor curves in the impaired stratum are approximately linear and parallel which suggests that the assumption of proportional hazards is reasonable.





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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-766/ S-019

ADMINISTRATIVE DOCUMENTS AND CORRESPONDENCE

MEMORANDUM OF TELECON

DATE: October 22, 2004

APPLICATION NUMBER: NDA 20-766/S-019, Xenical (Orlistat) Capsules

BETWEEN:

Name: Margart Jack, Program Director, Regulatory Affairs
Phone: 973-235-4463
Representing: Hoffman-La Roche

AND

Name: Oluchi Elekwachi, Pharm.D., M.P.H., Regulatory Health Project Manager
Division of Metabolic and Endocrine Drug Products, HFD-510

SUBJECT: Promotional Materials following Xendos supplement approval

On October 22, 2004, DMEDP approved the Xendos labeling supplement which provided for an expansion in the clinical trials section of the label to include language regarding Xenical's ability to delay the onset of type 2 diabetes. Subsequent to the approval, I spoke with Ms. Jack to remind her of the Division request' for a copy of any promotional material that will result from this approval. Also, I reminded her of the agreement between Roche and the Division that weight loss [redacted] She informed me that the product is not currently promoted and that other than a press release, there is no intention of promoting it. I asked that she provide me with a copy of the press release when it is available and that if in the future they decide to promote it that we would also require a copy of that promotional material. Ms. Jack agreed and assured me that she would comply with our request.

Oluchi Elekwachi, Pharm.D., M.P.H.
Regulatory Health Project Manager

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/s/

Oluchi Elekwachi
10/25/04 10:16:06 AM
CSO

Division of Metabolic and Endocrine Drug Products

REGULATORY PROJECT MANAGER REVIEW

Application Number: N20-766/S-019

Name of Drug: Xenical (orlistat) Capsules 120 mg

Applicant: HLR Technologies (Roche)

Material Reviewed: Draft Package Insert (PI)

Submission Date(s): December 22, 2003, June 22, July 13, August, 17, October 21, 2004

Receipt Date(s): December 23, 2003, June 23, July 15, August 18, October 22, 2004

Background and Summary

On January 2, 2003, the sponsor, Hoffmann- La Roche Inc., requested a meeting to discuss proposed labeling from the completed XENDOS study (a double blind, multi- center, randomized, parallel group design trial to assess whether weight loss with Xenical could delay or prevent the development of type 2 diabetes compared to a placebo group. The meeting was deemed unnecessary, and, in a letter dated February 4, 2003, the firm requested to submit any proposed labeling revision in the form of a prior approval supplement.

On June 30, 2003, the sponsor formally requested reconsideration of its meeting request to discuss the XENDOS study in accordance with the Agency's Guidance for Industry – Formal Dispute Resolutions: Appeals above the Division Level. The meeting was granted July 14, 2003.

As a result of dispute resolution, on September 26, 2003 Roche had a meeting with the Division of Endocrinologic and Metabolic Drug Products to discuss this supplement originally Roche

evidence presented. Roche submitted a supplemental New Drug Application (sNDA) for Xenical (orlistat) Capsules with revised labeling based on the results of the XENDOS Study.

The XENDOS study, which is the basis of this application, is a multi-center, double-blind, placebo controlled, randomized parallel group design study of 4 years duration conducted in obese patients (BMI >30). The objectives of the study were to determine if treatment with orlistat, compared to placebo could delay the onset of type 2 diabetes, to determine the effect of treatment of orlistat compared to placebo on long-term weight control and to determine the effect of long-term treatment on other obesity related risk factors.

Review

The PI was compared to the currently approved version of the PI, Approved with Supplement 20 (Identifier 27898691, Rev. December 2003). The labeling submitted is identical that which was modified and agreed upon by the Division. The labeling will be attached to the approval letter.

Conclusions

An approval letter will issue.

Oluchi Elekwachi, PharmD, MPH
Regulatory Project Manager

Drafted: OElekwachi/10-21-04
Revised/Initialed:
Finalized:
Filename: C:\Data\Obesity\N20766\S019 LabRev.doc

CSO LABELING REVIEW

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Oluchi Elekwachi
10/22/04 09:26:07 AM
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ORIGINAL

Roche

SE8 019 B2
NDA SUPPL AMENDMENT

August 17, 2004

RECEIVED
AUG 18 2004
CDR/CDER

Food and Drug Administration
Division of Metabolic and Endocrine Drug Products, HFD-510
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Fishers Document Control Room
Parklawn Bldg. Room 8B 45
5600 Fishers Lane
Rockville, Maryland 20857-1706

RECEIVED
AUG 18 2004
FDR/CDER

Ladies and Gentlemen:

Re: NDA 20-766/S-019 Xenical® (orlistat) Capsules, 120 mg
Response to Agency's Review Questions Included in Fax dated July 23, 2004
And Response to Agency's Follow-Up Questions
Re: Xendos Data Included in S-019

Reference is made to the labeling supplement to NDA 20-766/S-019 submitted December 22, 2003 for the purpose of including data from the XENDOS study in the approved label for Xenical. Reference is also made to the Agency's fax dated July 23, 2004 which included twelve review questions regarding this labeling supplement. Reference is also made to a follow-up question from Dr. Eric Colman e-mailed to the Sponsor on August 3, 2004 regarding Roche's response to a question in a fax dated June 22, 2004. Reference is also made to a telephone conversation with Dr. T. Sahlroot on August 3, 2004 requesting additional information on treatment failures in S-019. All responses to these questions have been previously e-mailed to the Agency informally. The purpose of this submission is to provide formal responses to all the questions included in the above mentioned fax, e-mail and provided during the August 3rd telephone call.

This submission consists of 3 major sections:

- Responses to the twelve questions included in the July 23rd Fax. This response also includes five Appendices of supporting data
- Response to Dr. Colman's follow-up question included in FDA's June 22, 2004 fax
- Response to Dr. T. Sahlroot's question regarding treatment failures

For ease of review of each section, each question is repeated and the Roche response with supporting documentation is provided.

Please note that in response to question 10 of the July 23rd fax, Roche has just confirmed that two cases of "Birth Defect" are in actuality one case. Appendices 2 and 3 have not been updated in this submission to reflect this new information. In the future MedWatches MCN 246819 and 330406 will be merged into MCN 330406.

Hoffmann-La Roche Inc. 340 Kingsland Street
Nutley, New Jersey 07110-1199

Please feel free to contact the undersigned if you have any questions regarding these responses.

Sincerely,

HOFFMANN-LA ROCHE INC

Margaret J Jack

Margaret J. Jack
Program Director
(973) 235-4463 (telephone)
(973) 562-3700/3554 (fax)

MJJ/dc
Attachments

HLR No. 2004-10146

Desk Copies: Dr. Eric Colman
Dr. Todd Sahlroot

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE II

FACSIMILE TRANSMITTAL SHEET

DATE: July 23, 2004

To: Margaret J. Jack	**From:** Oluchi Elekwachi, Pharm.D., M.P.H.
Company: Hoffmann-LaRoche	Division of Metabolic and Endocrine Drug Products
Fax number: 973-562-3700	**Fax number:** 301-443-9282
Phone number: (973)235-4463	**Phone number:** 301-827-6381

Subject: Discipline Review Information Request

Total no. of pages including cover: 32

Comments:

Document to be mailed: ☑ YES ☐ NO

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-766

DISCIPLINE REVIEW LETTER

7/23/04

Hoffmann-LaRoche
Attention: Margaret J. Jack
Program Director, Drug Regulatory Affairs
340 Kingsland Street
Nutley, NJ 07110

Dear Ms. Jack:

Please refer to your December 22, 2003 supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Xenical (Orlistat).

We also refer to your submission dated June 22, and July 13, 2004.

Our review of the Clinical section of your submission is complete, and we have identified the following deficiencies:

1. Please provide the table of all adverse events that is provided in Appendix 813 in Word format.
2. Please provide a tabular summary of protocol violations, by individual violation, for both treatment groups.
3. Please refer to Table 87 (Summary of Marked Lab Abnormalities). Please provide your interpretation of the data on the incidence of low lymphocyte counts.
4. Was any subject in either treatment group withdrawn from the study due to an abnormal laboratory parameter?
5. Please provide the number (%) of patients in each treatment group who developed two or more consecutive systolic blood pressure readings > 160 mmHg; or two or more consecutive diastolic blood pressure readings > 100 mmHg; or two or more consecutive pulse rates > 100 bpm at any time during the study.
6. Was any study subject withdrawn from the study due to an abnormal value for blood pressure or pulse?
7. At what intervals were ECGs performed?
8. Was any subject from either treatment group withdrawn from the study due to an ECG abnormality?
9. Did any subject in either treatment group develop a QTc > 500 msec at any time during the trial?
10. Please provide a summary of all available data (from clinical trail database and spontaneous post-marketing reports) on pregnancy outcomes in women who received orlistat during pregnancy.
11. Please provide a summary of all available data on the overdose experience with orlistat.
12. Please provide the number (%) of patients in the placebo and orlistat groups who reported fatty/oily stool, by year, for the following subgroups:
    - Male vs. female
    - Age divided into tertiles

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may not be able to consider your response before we take an action on your application during this review cycle.

For administrative purposes, we have enclosed the questions along with your responses to our previous request for information regarding this supplement.

If you have any questions, call, me at 301-827-6381.

Sincerely,

{See appended electronic signature page}

Oluchi Elekwachi, Pharm.D., M.P.H.
Regulatory Health Project Manager
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Q1 Please reference the section of the NDA that contains the information on protocol violations.

The protocol violations are provided in Table 9 "Summary of Patients Withdrawn from Trial Treatment by Trial Treatment" and in Module 1 of the Xendos final study report (CTD Module 5, Volume 1) and in the "Listing of Treatment Withdrawals by Trial Treatment and CRTN/Pat. No." located in the 2nd volume of CTD Module 5, starting on page 326.

Q2 For each treatment group, please provide the number of patients who had one diabetic OGTT that was not confirmed by the results of a second OGTT.

In the Xendos study, there were 154 cases of diabetes (84 pl and 70 orl) based on the results of a single 2hr OGTT (CSR: Table 18). Of these cases, 85 (47 pl and 38 orl) were confirmed based on either the next subsequent fasting or OGTT glucose value, or if not from the next subsequent test then 2 subsequent sequentially fasting values (CSR: Table 15). Of these 85 confirmed cases, 77 (44 pl, 33 orl) have come from the next subsequent test in comparison to only 7 which came from two consecutive additional fasting measurements which where not from the very next test after the original OGTT. Therefore, of the 84 initial cases of type 2 diabetes in the placebo group, 40 were not confirmed by a repeat OGTT and of the 70 cases of type 2 diabetes in the orlistat group, 37 were not confirmed by a repeat OGTT. For comparison purposes, the standard life table analysis provided below is based on the subset of the original those 77 cases whose primary diagnosis of diabetes is immediately confirmed. The log rank test assessing treatment differences remained highly significant ($p < .01$).

Cumulative Incidence of Cases by Time of first Occurrence
Confirmed - Immediate 2 Hr >=10 or 0 hr >= 6.1,

Report Date: 06/25/04

Time Interval of Occurrence (Scheduled Day)	PLACEBO			ORLISTAT		
	Number Pts Entering Interval	Number Pts with Cases n (%)	Cumulative Rate	Number Pts Entering Interval	Number Pts with Cases n (%)	Cumulative Rate
Day 1	1655			1649		
Day 169	1472	1 (0.07)	.00068	1572	1 (0.06)	.00064
Day 365	1285	12 (0.93)	.01001	1486	5 (0.34)	.00400
Day 533	1116	5 (0.45)	.01445	1368	3 (0.22)	.00618
Day 729	968	8 (0.83)	.02259	1267	4 (0.32)	.00932
Day 897	761	5 (0.66)	.02901	1126	8 (0.71)	.01636
Day 1093	686	6 (0.87)	.03751	1017	4 (0.39)	.02023
Day 1261	566	6 (1.06)	.04771	877	5 (0.57)	.02581
Day 1457	537	1 (0.19)	.04948	829	3 (0.36)	.02934

Q3 For each treatment group, please provide the mean percent change in Lpa from baseline to Year 4.

CSR Table 39 has been provided and now includes percent changes from baseline as well as values at each visit and changes from baseline at each visit in Lpa, for each treatment group separately.

ETLLPA_C1000000 Summary of Lipoprotein a (ug/L)
LOCF Data
Intent-to-Treat

		Value at Scheduled Visit				Change from Baseline				% Change from Baseline			
PARAMETER	VISIT	N	MEAN	SD	MEDIAN	N	MEAN	SD	MEDIAN	N	MEAN	SD	MEDIAN
PLACEBO	DAY 1	1637	253.01	315.81	113.00								
	DAY 169	1485	290.46	346.67	144.00	1485	37.46	94.21	10.00	1485	21.80	47.69	6.78
	DAY 365	1487	279.82	339.97	132.00	1487	27.02	92.18	4.00	1487	15.26	41.73	2.15
	DAY 533	1487	279.94	341.56	128.00	1487	27.14	95.99	1.00	1487	15.31	42.54	0.61
	DAY 729	1487	283.79	347.37	128.00	1487	31.00	102.38	3.00	1487	15.92	41.14	2.63
	DAY 897	1487	283.68	349.55	129.00	1487	30.88	96.25	3.00	1487	15.77	42.05	2.35
	DAY 1093	1487	289.38	350.61	136.00	1487	36.59	106.93	9.00	1487	19.83	44.63	5.82
	DAY 1261	1487	279.40	342.52	127.00	1487	26.61	96.59	2.00	1487	14.32	40.63	1.46
	DAY 1457	1487	283.07	345.80	128.00	1487	30.27	97.77	3.00	1487	15.53	40.26	3.23
ORLISTAT	DAY 1	1640	252.28	305.70	109.50								
	DAY 169	1575	294.12	346.76	136.00	1575	41.64	111.26	11.00	1575	19.77	35.18	8.05
	DAY 365	1575	285.37	347.18	131.00	1575	32.89	102.22	4.00	1575	14.21	32.99	1.89
	DAY 533	1575	285.26	346.22	128.00	1575	32.77	105.10	1.00	1575	14.55	35.34	0.60
	DAY 729	1575	292.31	353.89	129.00	1575	39.82	109.34	4.00	1575	16.30	36.25	2.02
	DAY 897	1575	289.72	354.08	129.00	1575	37.23	103.82	4.00	1575	15.34	33.46	2.13
	DAY 1093	1575	296.89	355.29	139.00	1575	44.41	108.91	13.00	1575	20.71	38.82	8.68
	DAY 1261	1575	284.29	341.36	129.00	1575	31.81	100.01	0.00	1575	14.09	34.03	0.00
	DAY 1457	1575	290.54	348.25	130.00	1575	38.05	103.50	6.00	1575	16.99	36.25	4.05

Q4 For each treatment group, please provide the number and percentage of patients with baseline 25OHD values >50nmol/L who subsequently developed two or more consecutive 25OHD levels <50nmol/L.

Below please find the original vitamin analysis updated to reflect a different criteria (Vitamin D: 25OHD) for entry into the table, as well as different criteria for classification of follow-up values. In addition to 50nmol/L being well within the reference range for Vitamin 25OHD in our population of Swedish patients, as you can see from the table below that approximately 44% in each treatment group had values below 50 nmol at baseline. Patients were not receiving multivitamin supplementation until they had two consecutive values below the reference range.

stvitdabnbs50 Incidence of Low Vitamin Values among Patients with Baseline Vitamin D_25OH <50 nmol/L

Population Included in the Safety Analysis

	All Patients				Supplemented			
	PLACEBO		ORLISTAT		PLACEBO		ORLISTAT	
	N	(%)	N	(%)	N	(%)	N	(%)
Number of evaluable patients	1488		1576					
Vitamin D_25 Hydroxy Normal Range = (10 -127 nmol/L) Baseline value - low	656	(44.1)	688	(43.7)	69	(4.6)	107	(6.8)
Low follow-up value# Two or more consecutive	533	(81.3)	637	(92.6)	58	(84.1)	103	(96.3)
Last Value Low	446		572		50		95	
Normal	18		11		3		2	
Missing	69		54		5		6	

Xendos: Generated by $HOME/cdp01276/bm15421/vtm50abn.sas,Created: 29JUN2004 at 8:54
% calculated based on number of patients with normal baseline values
* A low follow-up is based on 50 nmol/L

stvitdnormbs50 Incidence of Low Vitamin Values among Patients with Baseline Vitamin D_25OH >=50 nmol/L
Population Included in the Safety Analysis

	All Patients				Supplemented			
	PLACEBO		ORLISTAT		PLACEBO		ORLISTAT	
	N	(%)	N	(%)	N	(%)	N	(%)
Number of evaluable patients	1488		1576					
Vitamin D_25 Hydroxy								
Normal Range = (10 -127 nmol/L)								
Baseline value - normal	832	(55.9)	888	(56.3)	50	(3.4)	112	(7.1)
Low follow-up value#								
Two or more consecutive	454	(54.6)	684	(77.0)	35	(70.0)	87	(77.7)
Last Value Low	307		529		26		70	
Normal	76		86		7		10	
Missing	71		69		2		7	

Xendos: Generated by $HOME/cdp01276/bm15421/vtm_50bs.sas,Created: 29JUN2004 at 8:53
% calculated based on number of patients with normal baseline values
* A low follow-up is based on 50 nmol/L

Q5 Regarding the measurement of visceral fat with CT, for each treatment group, please provide the mean baseline body weights and the mean percent change in body weight from baseline to endpoint.

Changes from baseline in body weight have been provided using the same cohort of patients who had Visceral Adipose Tissue measurements. While these measurements were taken at specific centers, the efficacy parameter body weight at these centers behaved in comparable fashion to the other centers in aggregate without any notable differences.

ETBW_C0009000 Summary of Body Weight (kg)
LOCF Data
Safety Population
Patients who have visceral fat measurments with CT

PARAMETER	VISIT	Value at Scheduled Visit				Change from Baseline				% Change from Baseline			
		N	MEAN	SD	MEDIAN	N	MEAN	SD	MEDIAN	N	MEAN	SD	MEDIAN
PLACEBO	DAY 1	144	111.00	13.85	109.10								
	DAY 85	143	107.08	13.96	106.00	143	-4.00	4.00	-3.20	143	-3.61	3.53	-2.91
	DAY 169	143	105.18	14.51	104.30	143	-5.90	6.20	-4.40	143	-5.30	5.58	-3.86
	DAY 253	143	104.88	15.08	104.10	143	-6.20	7.44	-4.40	143	-5.58	6.70	-4.04
	DAY 365	143	105.18	15.88	103.90	143	-5.90	8.44	-3.50	143	-5.33	7.71	-3.37
	DAY 449	143	106.05	16.53	104.60	143	-5.02	8.78	-2.90	143	-4.59	8.11	-2.55
	DAY 533	143	105.97	16.78	104.60	143	-5.10	8.99	-2.90	143	-4.67	8.33	-2.63
	DAY 617	143	106.40	16.85	105.20	143	-4.68	9.02	-2.50	143	-4.29	8.27	-2.25
	DAY 729	143	106.56	16.87	105.00	143	-4.52	9.01	-2.80	143	-4.15	8.29	-2.58
	DAY 813	143	107.15	16.58	106.50	143	-3.93	8.84	-2.20	143	-3.59	8.16	-2.22
	DAY 897	143	106.83	16.42	106.50	143	-4.25	9.49	-2.50	143	-3.83	8.51	-2.25
	DAY 981	143	107.06	16.47	106.30	143	-4.02	9.44	-2.00	143	-3.64	8.48	-1.84
	DAY 1093	143	107.28	16.45	107.30	143	-3.80	9.17	-2.20	143	-3.45	8.26	-2.09
	DAY 1177	143	107.95	16.53	107.80	143	-3.13	9.12	-1.60	143	-2.85	8.20	-1.58
	DAY 1261	143	108.08	16.39	107.80	143	-3.00	8.98	-1.50	143	-2.72	8.06	-1.40
	DAY 1345	143	107.92	16.21	106.90	143	-3.16	8.85	-1.50	143	-2.86	7.97	-1.38
	DAY 1457	143	107.98	16.28	106.60	143	-3.10	8.86	-1.60	143	-2.81	7.99	-1.40
ORLISTAT	DAY 1	157	112.43	14.45	112.10								
	DAY 85	156	106.31	14.13	107.05	156	-6.13	3.56	-5.60	156	-5.45	3.12	-5.00
	DAY 169	156	103.19	14.67	104.20	156	-9.25	5.10	-8.45	156	-8.28	4.58	-7.54
	DAY 253	156	102.46	14.88	103.05	156	-9.98	5.71	-9.20	156	-8.94	5.14	-8.82
	DAY 365	156	101.90	15.05	102.05	156	-10.54	6.66	-9.50	156	-9.43	5.91	-8.76
	DAY 449	156	102.71	15.35	103.05	156	-9.73	6.83	-8.50	156	-8.72	6.13	-7.75
	DAY 533	156	102.78	15.85	102.90	156	-9.67	7.24	-8.60	156	-8.70	6.53	-7.87
	DAY 617	156	103.49	15.66	103.20	156	-8.95	7.43	-7.70	156	-8.02	6.63	-6.87
	DAY 729	156	103.63	15.94	103.85	156	-8.81	7.69	-7.60	156	-7.91	6.94	-6.90
	DAY 813	156	104.54	15.98	105.40	156	-7.90	7.58	-6.65	156	-7.10	6.82	-5.89
	DAY 897	156	104.59	16.06	105.65	156	-7.86	8.08	-6.50	156	-7.03	7.24	-5.79
	DAY 981	156	105.34	16.24	106.05	156	-7.10	7.88	-6.10	156	-6.39	7.09	-5.45
	DAY 1093	156	105.51	16.28	106.10	156	-6.94	7.79	-5.15	156	-6.24	7.01	-5.15
	DAY 1177	156	106.27	16.33	106.20	156	-6.18	7.69	-4.70	156	-5.56	6.89	-4.42
	DAY 1261	156	106.07	16.22	106.25	156	-6.37	7.81	-4.80	156	-5.72	6.97	-4.55
	DAY 1345	156	106.28	16.11	106.80	156	-6.16	7.84	-5.20	156	-5.51	7.00	-5.01
	DAY 1457	156	106.42	16.16	106.75	156	-6.02	7.90	-5.30	156	-5.39	7.04	-5.04

Generated by /opt/BIOSTAT/home/xiab/cdp01276/bm15421/tsum_bx_fda.sas at 11:48 on 24JUN2004

Q6 For Completers who lost and maintained at least a 5% reduction in baseline body weight, please provide the mean absolute and percent changes from baseline to Year 4 for the placebo and orlistat groups in the following parameters: Total Cholesterol, LDL, HDL, TG, Lpa, Fasting glucose, Fasting insulin, SBP, and DBP. Please also provide the mean absolute and percent changes in weight from baseline to Year 4 for the two treatment groups.

The sponsor has provided the following summary tables of secondary efficacy parameters using the completer population, and only for those patients who have lost at least 5% from their baseline body weight at the end of year 4 in both the placebo and the orlistat group. Although it is not unexpected that the magnitude of the mean improvements in these obesity related parameters would be generally comparable in each of the two groups since the amount of weight loss is comparable, it is very notable that over twice as many orlistat patients meet this responder criteria for weight loss.

ETBW_C3000030 Summary of Body Weight (kg)
LOCF Data
Completer
Percent BW Loss at DAY 1457 from BL > 5% (LOCF)

		Value at Scheduled Visit				Change from Baseline				% Change from Baseline			
PARAMETER	VISIT	N	MEAN	SD	MEDIAN	N	MEAN	SD	MEDIAN	N	MEAN	SD	MEDIAN
PLACEBO	DAY 1	210	111.63	15.39	110.75								
	DAY 85	210	104.54	15.44	104.10	210	-7.09	4.24	-6.70	210	-6.39	3.72	-6.25
	DAY 169	210	100.47	15.72	100.50	210	-11.16	6.28	-10.30	210	-10.05	5.57	-9.69
	DAY 253	210	98.70	16.55	97.80	210	-12.92	7.70	-11.70	210	-11.68	6.86	-11.54
	DAY 365	210	97.35	16.72	97.65	210	-14.28	8.90	-13.05	210	-12.86	7.88	-12.23
	DAY 449	210	97.90	17.40	98.80	210	-13.72	9.76	-12.30	210	-12.39	8.68	-11.24
	DAY 533	210	97.21	17.19	97.95	210	-14.42	9.87	-12.65	210	-12.99	8.74	-11.69
	DAY 617	210	97.24	17.28	98.20	210	-14.38	10.14	-12.10	210	-12.95	8.86	-11.44
	DAY 729	210	97.27	17.03	97.80	210	-14.36	10.15	-12.25	210	-12.90	8.76	-11.37
	DAY 813	210	98.27	16.58	99.00	210	-13.36	9.95	-11.30	210	-11.96	8.58	-10.54
	DAY 897	210	98.04	16.32	98.50	210	-13.59	10.00	-11.15	210	-12.12	8.56	-10.44
	DAY 981	210	98.51	15.89	99.25	210	-13.12	9.49	-11.10	210	-11.68	8.11	-10.17
	DAY 1093	210	98.64	15.71	98.65	210	-12.98	9.03	-10.55	210	-11.57	7.71	-9.72
	DAY 1177	210	99.67	15.51	99.85	210	-11.96	8.65	-9.60	210	-10.64	7.40	-9.12
	DAY 1261	210	99.27	15.26	99.65	210	-12.36	8.24	-10.25	210	-11.00	7.02	-9.30
	DAY 1345	210	99.12	15.15	99.60	210	-12.50	7.90	-10.15	210	-11.13	6.74	-9.40
	DAY 1457	210	99.02	14.88	99.90	210	-12.61	7.55	-9.80	210	-11.22	6.39	-8.97
ORLISTAT	DAY 1	450	111.41	15.34	110.25								
	DAY 85	450	102.99	14.63	102.40	450	-8.42	3.77	-8.20	450	-7.55	3.18	-7.46
	DAY 169	450	98.47	14.53	97.30	450	-12.93	5.63	-12.35	450	-11.60	4.71	-11.22
	DAY 253	450	96.64	14.93	95.20	450	-14.76	7.00	-13.95	450	-13.25	5.93	-12.68
	DAY 365	450	95.35	14.92	93.85	450	-16.06	7.97	-15.55	450	-14.39	6.69	-13.88
	DAY 449	450	95.56	15.01	94.05	450	-15.85	8.34	-15.05	450	-14.19	6.93	-13.33
	DAY 533	450	94.97	14.99	93.50	450	-16.44	8.51	-15.45	450	-14.72	7.02	-14.07
	DAY 617	450	95.24	14.86	93.90	450	-16.17	8.73	-15.00	450	-14.44	7.10	-13.47
	DAY 729	450	95.51	14.68	94.20	450	-15.89	8.61	-14.60	450	-14.18	6.98	-13.27
	DAY 813	450	96.47	14.83	95.05	450	-14.94	8.60	-13.75	450	-13.32	7.00	-12.48
	DAY 897	450	96.32	14.60	94.50	450	-15.09	8.35	-14.10	450	-13.45	6.74	-12.61
	DAY 981	450	97.24	14.71	95.65	450	-14.17	8.07	-12.85	450	-12.63	6.63	-11.53
	DAY 1093	450	97.49	14.60	95.95	450	-13.92	7.79	-12.45	450	-12.40	6.37	-11.21
	DAY 1177	450	98.45	14.68	97.35	450	-12.96	7.67	-11.20	450	-11.54	6.30	-10.09
	DAY 1261	450	98.33	14.54	97.00	450	-13.08	7.30	-11.80	450	-11.65	6.04	-10.58
	DAY 1345	450	98.54	14.61	97.15	450	-12.87	7.15	-11.50	450	-11.48	5.91	-9.90
	DAY 1457	450	98.43	14.59	97.70	450	-12.98	6.94	-11.05	450	-11.59	5.76	-9.99

ETBMI_C3000030 Summary of BMI(kg/m^2)
LOCF Data
Completer
Percent BW Loss at DAY 1457 from BL > 5% (LOCF)

		Value at Scheduled Visit				Change from Baseline				% Change from Baseline			
PARAMETER	VISIT	N	MEAN	SD	MEDIAN	N	MEAN	SD	MEDIAN	N	MEAN	SD	MEDIAN
PLACEBO	DAY 1	210	37.26	3.97	36.60								
	DAY 85	210	34.88	4.05	34.20	210	-2.38	1.44	-2.20	210	-6.40	3.72	-6.28
	DAY 169	210	33.52	4.17	32.70	210	-3.75	2.16	-3.50	210	-10.04	5.56	-9.68
	DAY 253	210	32.91	4.48	32.15	210	-4.35	2.68	-4.10	210	-11.69	6.87	-11.59
	DAY 365	210	32.46	4.65	31.75	210	-4.80	3.10	-4.50	210	-12.86	7.87	-12.26
	DAY 449	210	32.63	4.88	32.00	210	-4.63	3.43	-4.20	210	-12.39	8.67	-11.42
	DAY 533	210	32.40	4.86	32.00	210	-4.86	3.47	-4.30	210	-12.99	8.74	-11.75
	DAY 617	210	32.42	4.91	31.85	210	-4.84	3.55	-4.20	210	-12.95	8.86	-11.48
	DAY 729	210	32.42	4.81	31.80	210	-4.84	3.55	-4.10	210	-12.90	8.76	-11.39
	DAY 813	210	32.76	4.56	32.25	210	-4.50	3.43	-3.80	210	-11.95	8.58	-10.51
	DAY 897	210	32.69	4.42	32.20	210	-4.57	3.43	-3.80	210	-12.11	8.57	-10.46
	DAY 981	210	32.85	4.24	32.20	210	-4.41	3.25	-3.65	210	-11.68	8.10	-10.17
	DAY 1093	210	32.89	4.12	32.55	210	-4.38	3.09	-3.55	210	-11.57	7.71	-9.73
	DAY 1177	210	33.23	4.06	32.80	210	-4.03	2.97	-3.30	210	-10.64	7.40	-9.04
	DAY 1261	210	33.11	4.04	32.60	210	-4.15	2.81	-3.60	210	-10.99	7.01	-9.31
	DAY 1345	210	33.07	4.00	32.70	210	-4.20	2.71	-3.40	210	-11.13	6.73	-9.35
	DAY 1457	210	33.03	3.87	32.50	210	-4.23	2.62	-3.35	210	-11.22	6.40	-8.88
ORLISTAT	DAY 1	450	37.61	4.03	37.20								
	DAY 85	450	34.76	3.89	34.25	450	-2.84	1.24	-2.80	450	-7.55	3.18	-7.55
	DAY 169	450	33.23	3.92	32.60	450	-4.37	1.86	-4.20	450	-11.60	4.70	-11.29
	DAY 253	450	32.60	4.06	32.00	450	-5.00	2.36	-4.70	450	-13.26	5.93	-12.66
	DAY 365	450	32.17	4.13	31.60	450	-5.43	2.69	-5.20	450	-14.39	6.69	-13.82
	DAY 449	450	32.24	4.14	31.70	450	-5.37	2.81	-5.05	450	-14.19	6.93	-13.36
	DAY 533	450	32.04	4.15	31.70	450	-5.57	2.86	-5.25	450	-14.72	7.03	-14.05
	DAY 617	450	32.14	4.13	31.70	450	-5.47	2.92	-5.10	450	-14.44	7.10	-13.46
	DAY 729	450	32.23	4.07	31.90	450	-5.37	2.87	-5.10	450	-14.18	6.98	-13.26
	DAY 813	450	32.55	4.05	32.10	450	-5.06	2.88	-4.65	450	-13.33	7.00	-12.50
	DAY 897	450	32.51	4.02	32.00	450	-5.10	2.79	-4.80	450	-13.45	6.75	-12.59
	DAY 981	450	32.82	4.04	32.40	450	-4.79	2.70	-4.30	450	-12.62	6.65	-11.55
	DAY 1093	450	32.91	4.01	32.60	450	-4.70	2.59	-4.20	450	-12.40	6.38	-11.21
	DAY 1177	450	33.23	4.03	32.80	450	-4.38	2.54	-3.80	450	-11.54	6.31	-10.09
	DAY 1261	450	33.20	4.04	32.70	450	-4.41	2.40	-3.90	450	-11.65	6.04	-10.59
	DAY 1345	450	33.27	4.06	32.60	450	-4.34	2.35	-3.80	450	-11.47	5.92	-9.95
	DAY 1457	450	33.23	4.04	32.70	450	-4.38	2.28	-3.80	450	-11.59	5.76	-10.02

Generated by /opt/BIOSTAT/home/xiab/cdp01276/bm15421/tsum_bx_fda.sas at 10:14 on 24JUN2004

ETLTC_C3000030 Summary of Total Cholesterol (mmol/L)
LOCF Data
Completer
Percent BW Loss at DAY 1457 from BL > 5% (LOCF)

		Value at Scheduled Visit				Change from Baseline				% Change from Baseline			
PARAMETER	VISIT	N	MEAN	SD	MEDIAN	N	MEAN	SD	MEDIAN	N	MEAN	SD	MEDIAN
PLACEBO	DAY 1	210	5.85	0.94	5.80								
	DAY 169	210	5.46	1.03	5.30	210	-0.39	0.68	-0.40	210	-6.32	11.58	-6.06
	DAY 365	210	5.60	1.02	5.50	210	-0.25	0.67	-0.20	210	-3.97	11.55	-3.54
	DAY 533	210	5.46	1.02	5.40	210	-0.39	0.64	-0.30	210	-6.48	10.94	-5.45
	DAY 729	210	5.42	1.01	5.30	210	-0.44	0.72	-0.50	210	-7.06	12.05	-7.83
	DAY 897	210	5.46	0.96	5.40	210	-0.39	0.74	-0.30	210	-6.07	12.15	-6.12
	DAY 1093	210	5.56	0.97	5.45	210	-0.29	0.74	-0.30	210	-4.36	12.10	-4.59
	DAY 1261	210	5.51	1.01	5.40	210	-0.34	0.83	-0.25	210	-5.15	13.31	-4.35
	DAY 1457	210	5.52	0.98	5.50	210	-0.33	0.77	-0.30	210	-5.01	12.71	-4.51
ORLISTAT	DAY 1	450	5.81	0.97	5.80								
	DAY 169	450	5.07	0.95	5.00	450	-0.74	0.68	-0.70	450	-12.30	11.15	-12.75
	DAY 365	450	5.09	0.96	5.00	450	-0.71	0.71	-0.70	450	-11.83	11.65	-11.86
	DAY 533	450	5.04	0.94	5.00	450	-0.77	0.74	-0.70	450	-12.68	11.90	-12.79
	DAY 729	450	5.07	0.93	5.00	450	-0.73	0.76	-0.70	450	-11.99	12.33	-12.60
	DAY 897	450	5.08	0.91	5.00	450	-0.73	0.76	-0.70	450	-11.92	12.13	-12.39
	DAY 1093	450	5.21	0.91	5.20	450	-0.60	0.79	-0.60	450	-9.46	12.66	-9.93
	DAY 1261	450	5.25	0.94	5.20	450	-0.56	0.81	-0.50	450	-8.85	12.96	-8.67
	DAY 1457	450	5.20	0.94	5.10	450	-0.61	0.77	-0.60	450	-9.80	12.22	-10.19

Generated by /opt/BIOSTAT/home/xiab/cdp01276/bm15421/tsum_bx_fda.sas at 10:14 on 24JUN2004

ETLLDL_C3000030 Summary of LDL Cholesterol (mmol/L)
LOCF Data
Completer
Percent BW Loss at DAY 1457 from BL > 5% (LOCF)

		Value at Scheduled Visit				Change from Baseline				% Change from Baseline			
PARAMETER	VISIT	N	MEAN	SD	MEDIAN	N	MEAN	SD	MEDIAN	N	MEAN	SD	MEDIAN
PLACEBO	DAY 1	207	3.80	0.83	3.70								
	DAY 169	209	3.57	0.92	3.40	207	-0.24	0.62	-0.20	207	-5.50	16.83	-6.67
	DAY 365	209	3.62	0.90	3.60	207	-0.19	0.62	-0.10	207	-4.19	17.10	-3.45
	DAY 533	209	3.46	0.91	3.40	207	-0.35	0.61	-0.30	207	-8.80	16.27	-7.89
	DAY 729	210	3.41	0.89	3.30	207	-0.39	0.66	-0.40	207	-9.68	17.46	-9.68
	DAY 897	210	3.35	0.84	3.30	207	-0.45	0.70	-0.40	207	-10.68	17.79	-10.53
	DAY 1093	210	3.48	0.86	3.40	207	-0.32	0.67	-0.30	207	-7.50	17.20	-7.14
	DAY 1261	210	3.40	0.91	3.30	207	-0.40	0.75	-0.30	207	-9.44	18.50	-8.00
	DAY 1457	210	3.45	0.87	3.40	207	-0.35	0.72	-0.30	207	-8.08	18.44	-8.00
ORLISTAT	DAY 1	440	3.72	0.88	3.70								
	DAY 169	447	3.19	0.82	3.20	440	-0.53	0.62	-0.50	440	-13.16	17.00	-13.89
	DAY 365	449	3.15	0.82	3.10	440	-0.57	0.63	-0.50	440	-14.18	17.25	-14.71
	DAY 533	449	3.08	0.85	3.10	440	-0.64	0.64	-0.60	440	-16.33	17.10	-17.05
	DAY 729	449	3.08	0.81	3.10	440	-0.64	0.69	-0.60	440	-15.97	18.94	-17.19
	DAY 897	449	3.04	0.81	3.00	440	-0.68	0.66	-0.70	440	-17.06	17.68	-18.63
	DAY 1093	449	3.16	0.84	3.20	440	-0.56	0.71	-0.50	440	-13.60	19.56	-15.18
	DAY 1261	449	3.14	0.81	3.10	440	-0.58	0.68	-0.50	440	-14.14	17.83	-15.08
	DAY 1457	449	3.13	0.83	3.10	440	-0.59	0.69	-0.60	440	-14.73	18.68	-16.50

ETLHDL_C3000030 Summary of HDL Cholesterol (mmol/L)
LOCF Data
Completer
Percent BW Loss at DAY 1457 from BL > 5% (LOCF)

		Value at Scheduled Visit				Change from Baseline				% Change from Baseline			
PARAMETER	VISIT	N	MEAN	SD	MEDIAN	N	MEAN	SD	MEDIAN	N	MEAN	SD	MEDIAN
PLACEBO	DAY 1	210	1.20	0.29	1.10								
	DAY 169	210	1.19	0.27	1.20	210	-0.01	0.18	0.00	210	0.28	14.42	0.00
	DAY 365	210	1.32	0.31	1.30	210	0.13	0.20	0.10	210	11.98	17.85	9.09
	DAY 533	210	1.33	0.34	1.30	210	0.13	0.22	0.10	210	12.23	18.30	10.00
	DAY 729	210	1.36	0.35	1.30	210	0.17	0.20	0.20	210	14.62	16.75	12.50
	DAY 897	210	1.39	0.37	1.30	210	0.20	0.23	0.20	210	17.08	18.86	16.67
	DAY 1093	210	1.35	0.35	1.30	210	0.15	0.20	0.10	210	13.38	17.10	11.11
	DAY 1261	210	1.40	0.36	1.30	210	0.20	0.21	0.20	210	17.97	18.59	16.23
	DAY 1457	210	1.36	0.35	1.30	210	0.17	0.21	0.20	210	14.68	16.84	12.50
ORLISTAT	DAY 1	450	1.21	0.30	1.20								
	DAY 169	450	1.12	0.26	1.10	450	-0.09	0.18	-0.10	450	-6.19	13.43	-8.33
	DAY 365	450	1.24	0.29	1.20	450	0.03	0.19	0.00	450	3.67	14.85	0.00
	DAY 533	450	1.26	0.30	1.20	450	0.05	0.19	0.00	450	5.15	15.66	0.00
	DAY 729	450	1.29	0.32	1.30	450	0.08	0.20	0.10	450	7.52	17.11	7.42
	DAY 897	450	1.32	0.32	1.30	450	0.11	0.20	0.10	450	9.96	17.09	9.09
	DAY 1093	450	1.30	0.32	1.30	450	0.09	0.20	0.10	450	8.13	16.59	7.69
	DAY 1261	450	1.36	0.36	1.30	450	0.15	0.23	0.10	450	13.35	18.82	11.11
	DAY 1457	450	1.32	0.34	1.30	450	0.11	0.22	0.10	450	9.77	17.69	8.33

Generated by /opt/BIOSTAT/home/xiab/cdp01276/bm15421/tsum_bx_fda.sas at 10:14 on 24JUN2004

ETLTRG_C3000030 Summary of Triglycerides (mmol/L)
LOCF Data
Completer
Percent BW Loss at DAY 1457 from BL > 5% (LOCF)

		Value at Scheduled Visit				Change from Baseline				% Change from Baseline			
PARAMETER	VISIT	N	MEAN	SD	MEDIAN	N	MEAN	SD	MEDIAN	N	MEAN	SD	MEDIAN
PLACEBO	DAY 1	210	1.87	0.99	1.70								
	DAY 169	210	1.52	0.83	1.30	210	-0.35	0.77	-0.30	210	-12.72	36.75	-19.14
	DAY 365	210	1.41	0.70	1.20	210	-0.46	0.76	-0.30	210	-18.00	32.91	-24.40
	DAY 533	210	1.44	0.74	1.20	210	-0.43	0.74	-0.30	210	-17.05	30.83	-20.53
	DAY 729	210	1.39	0.68	1.30	210	-0.48	0.73	-0.40	210	-20.17	28.65	-23.08
	DAY 897	210	1.55	0.82	1.40	210	-0.33	0.82	-0.30	210	-12.28	35.07	-19.37
	DAY 1093	210	1.57	0.78	1.40	210	-0.31	0.75	-0.20	210	-11.27	30.79	-16.59
	DAY 1261	210	1.55	0.88	1.40	210	-0.32	0.86	-0.30	210	-12.18	34.18	-17.75
	DAY 1457	210	1.52	0.71	1.40	210	-0.35	0.71	-0.30	210	-12.78	31.20	-18.90
ORLISTAT	DAY 1	450	1.91	1.05	1.70								
	DAY 169	450	1.62	0.83	1.40	450	-0.29	0.78	-0.20	450	-7.31	38.46	-11.76
	DAY 365	450	1.53	0.94	1.30	450	-0.37	0.89	-0.30	450	-13.72	35.06	-18.83
	DAY 533	450	1.55	0.88	1.40	450	-0.36	0.86	-0.30	450	-11.96	38.36	-17.65
	DAY 729	450	1.53	0.90	1.30	450	-0.38	0.87	-0.30	450	-12.61	39.94	-20.00
	DAY 897	450	1.55	0.84	1.40	450	-0.36	0.87	-0.30	450	-11.48	37.43	-20.00
	DAY 1093	450	1.63	0.91	1.40	450	-0.27	0.88	-0.20	450	-6.48	37.54	-9.76
	DAY 1261	450	1.62	0.87	1.40	450	-0.29	0.83	-0.20	450	-8.07	35.65	-11.11
	DAY 1457	450	1.64	0.88	1.40	450	-0.26	0.81	-0.20	450	-6.63	36.55	-12.25

Generated by /opt/BIOSTAT/home/xiab/cdp01276/bm15421/tsum_bx_fda.sas at 10:14 on 24JUN2004

ETLLPA_C3000030 Summary of Lipoprotein a (ug/L)
LOCF Data
Completer
Percent BW Loss at DAY 1457 from BL > 5% (LOCF)

		Value at Scheduled Visit				Change from Baseline				% Change from Baseline			
PARAMETER	VISIT	N	MEAN	SD	MEDIAN	N	MEAN	SD	MEDIAN	N	MEAN	SD	MEDIAN
PLACEBO	DAY 1	210	204.99	269.35	95.50								
	DAY 169	210	243.60	294.13	144.50	210	38.62	87.49	10.00	210	29.91	52.40	7.07
	DAY 365	210	236.85	294.55	132.00	210	31.86	78.60	6.00	210	22.11	42.90	5.03
	DAY 533	210	237.50	293.58	131.00	210	32.52	76.15	10.50	210	24.22	49.25	6.64
	DAY 729	210	237.88	291.24	134.50	210	32.89	98.90	7.00	210	23.39	43.17	5.08
	DAY 897	210	243.11	307.53	130.00	210	38.12	80.02	7.00	210	22.23	39.57	5.08
	DAY 1093	210	250.30	291.06	143.00	210	45.32	95.89	22.50	210	31.55	45.76	16.34
	DAY 1261	210	236.68	300.91	112.00	210	31.70	84.02	0.00	210	18.63	40.74	0.00
	DAY 1457	210	246.04	320.56	120.00	210	41.06	90.38	5.50	210	22.11	39.66	5.72
ORLISTAT	DAY 1	450	241.45	280.05	108.50								
	DAY 169	450	295.45	328.80	146.00	450	53.99	109.84	17.00	450	25.45	40.08	12.61
	DAY 365	450	285.66	327.95	138.50	450	44.21	107.72	8.00	450	20.30	38.86	6.10
	DAY 533	450	284.76	329.81	139.00	450	43.31	119.34	6.50	450	20.35	43.43	3.52
	DAY 729	450	291.02	337.91	136.00	450	49.56	117.32	8.50	450	21.16	40.98	5.53
	DAY 897	450	293.31	346.86	139.00	450	51.86	114.40	11.50	450	20.99	37.97	9.02
	DAY 1093	450	302.91	341.11	160.00	450	61.46	108.75	27.00	450	29.60	45.71	15.46
	DAY 1261	450	282.44	321.84	139.00	450	40.99	93.29	2.00	450	17.99	40.25	1.44
	DAY 1457	450	293.84	339.21	142.50	450	52.39	115.40	14.50	450	23.60	41.69	8.66

ETGLU_C3000030 Summary of Glucose at 0 Minute (mmol/L)
LOCF Data
Completer
Percent BW Loss at DAY 1457 from BL > 5% (LOCF)

		Value at Scheduled Visit				Change from Baseline				% Change from Baseline			
PARAMETER	VISIT	N	MEAN	SD	MEDIAN	N	MEAN	SD	MEDIAN	N	MEAN	SD	MEDIAN
PLACEBO	DAY 1	210	4.64	0.61	4.60								
	DAY 169	210	4.59	0.59	4.50	210	-0.05	0.63	0.00	210	-0.01	14.03	0.00
	DAY 365	210	4.70	0.59	4.60	210	0.07	0.59	0.00	210	2.34	13.28	0.00
	DAY 533	210	4.68	0.68	4.60	210	0.05	0.68	0.00	210	1.93	15.17	0.00
	DAY 729	210	4.52	0.64	4.40	210	-0.11	0.64	-0.10	210	-1.58	14.08	-2.38
	DAY 897	210	4.68	0.63	4.60	210	0.04	0.61	0.00	210	1.83	13.83	0.00
	DAY 1093	210	4.73	0.61	4.70	210	0.09	0.62	0.10	210	2.95	13.75	1.96
	DAY 1261	210	4.85	0.71	4.70	210	0.21	0.68	0.15	210	5.45	14.96	2.94
	DAY 1457	210	4.63	0.67	4.60	210	-0.01	0.66	0.00	210	0.69	14.15	0.00
ORLISTAT	DAY 1	450	4.66	0.64	4.60								
	DAY 169	449	4.57	0.54	4.50	449	-0.08	0.65	-0.10	449	-0.49	15.48	-2.33
	DAY 365	450	4.66	0.52	4.60	450	0.01	0.59	0.00	450	1.41	13.68	0.00
	DAY 533	450	4.59	0.56	4.50	450	-0.07	0.63	-0.10	450	-0.27	14.25	-1.89
	DAY 729	450	4.51	0.80	4.40	450	-0.14	0.83	-0.20	450	-1.93	16.11	-4.17
	DAY 897	450	4.60	0.54	4.50	450	-0.06	0.63	-0.10	450	0.04	14.05	-1.98
	DAY 1093	450	4.68	0.55	4.60	450	0.02	0.61	0.00	450	1.64	13.70	0.00
	DAY 1261	450	4.72	0.57	4.60	450	0.07	0.63	0.00	450	2.70	14.77	0.00
	DAY 1457	450	4.58	0.60	4.50	450	-0.08	0.63	-0.10	450	-0.65	13.88	-2.17

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ETINS_C3000030 Summary of Insulin (pmol/L)
LOCF Data
Completer
Percent BW Loss at DAY 1457 from BL > 5% (LOCF)

		Value at Scheduled Visit				Change from Baseline				% Change from Baseline			
PARAMETER	VISIT	N	MEAN	SD	MEDIAN	N	MEAN	SD	MEDIAN	N	MEAN	SD	MEDIAN
PLACEBO	DAY 1	209	83.80	47.08	72.00								
	DAY 169	210	52.69	28.92	48.00	209	-31.12	37.81	-24.00	209	-29.76	33.04	-37.50
	DAY 365	210	52.63	33.34	42.00	209	-31.06	40.56	-24.00	209	-29.27	39.52	-37.50
	DAY 533	210	53.11	38.99	42.00	209	-30.57	45.13	-24.00	209	-29.72	41.14	-37.50
	DAY 729	210	49.34	35.15	39.00	209	-34.36	41.01	-30.00	209	-35.09	37.48	-45.45
	DAY 897	210	45.40	33.58	36.88	209	-38.51	38.61	-34.80	209	-42.74	35.86	-50.18
	DAY 1093	210	43.92	36.86	30.57	209	-40.06	39.23	-33.22	209	-45.43	39.42	-54.15
	DAY 1261	210	47.17	33.89	36.88	209	-36.70	38.99	-30.69	209	-40.48	37.26	-49.05
	DAY 1457	210	42.88	31.55	33.73	209	-41.02	41.20	-36.06	209	-44.54	37.66	-53.68
ORLISTAT	DAY 1	450	85.51	51.52	72.00								
	DAY 169	449	50.82	28.89	42.00	449	-34.78	46.59	-30.00	449	-30.19	53.63	-40.00
	DAY 365	450	49.39	28.58	42.00	450	-36.12	44.64	-30.00	450	-33.19	34.26	-41.89
	DAY 533	450	46.59	23.07	42.00	450	-38.92	43.59	-30.00	450	-36.73	31.81	-44.44
	DAY 729	450	45.96	26.19	36.00	450	-39.55	43.93	-36.00	450	-37.36	37.21	-45.80
	DAY 897	450	40.76	27.35	36.88	450	-44.75	43.58	-36.54	450	-46.70	35.84	-55.89
	DAY 1093	450	41.83	29.45	36.88	450	-43.68	42.67	-36.03	450	-46.11	33.74	-53.68
	DAY 1261	450	44.76	30.82	36.88	450	-40.75	46.01	-34.48	450	-41.31	41.64	-49.47
	DAY 1457	450	40.97	32.31	36.88	450	-44.54	45.69	-40.33	450	-47.57	35.62	-54.97

ETVSBP_C3000030 Summary of Systolic Blood Pressure (mmHg)
LOCF Data
Completer
Percent BW Loss at DAY 1457 from BL > 5% (LOCF)

		Value at Scheduled Visit				Change from Baseline				% Change from Baseline			
PARAMETER	VISIT	N	MEAN	SD	MEDIAN	N	MEAN	SD	MEDIAN	N	MEAN	SD	MEDIAN
PLACEBO	DAY 1	210	131.52	16.07	130.00								
	DAY 85	209	126.69	15.38	125.00	209	-4.92	11.15	-5.00	209	-3.35	8.34	-3.79
	DAY 169	210	124.60	15.54	122.00	210	-6.92	13.22	-7.00	210	-4.77	9.79	-5.45
	DAY 253	210	124.83	15.57	123.00	210	-6.69	14.43	-8.00	210	-4.49	10.93	-5.76
	DAY 365	210	123.44	15.03	121.50	210	-8.08	13.78	-8.00	210	-5.59	9.90	-6.10
	DAY 449	210	124.98	15.83	122.50	210	-6.54	13.90	-7.50	210	-4.46	10.53	-5.05
	DAY 533	210	122.54	16.12	120.00	210	-8.98	14.21	-9.00	210	-6.36	10.56	-7.05
	DAY 617	210	124.83	16.58	125.00	210	-6.70	13.57	-6.50	210	-4.66	10.38	-4.72
	DAY 729	210	123.86	15.34	121.00	210	-7.67	14.68	-9.00	210	-5.20	11.12	-6.67
	DAY 813	210	125.74	15.97	125.00	210	-5.78	15.25	-7.00	210	-3.76	11.78	-5.75
	DAY 897	210	123.13	15.41	120.00	210	-8.39	13.04	-9.50	210	-5.90	9.72	-6.87
	DAY 981	210	123.33	15.25	122.00	210	-8.19	14.42	-10.00	210	-5.61	10.87	-7.69
	DAY 1093	210	124.60	16.52	122.00	210	-6.92	14.08	-8.00	210	-4.80	10.76	-6.07
	DAY 1177	210	125.83	16.06	122.00	210	-5.69	13.47	-5.00	210	-3.84	10.22	-4.35
	DAY 1261	210	124.45	15.44	123.00	210	-7.07	15.06	-8.00	210	-4.73	11.36	-6.46
	DAY 1345	210	124.56	14.50	123.50	210	-6.97	14.53	-7.00	210	-4.61	10.91	-5.08
	DAY 1457	210	125.23	14.18	123.00	210	-6.30	14.04	-7.00	210	-4.10	10.63	-5.22
ORLISTAT	DAY 1	450	133.00	15.71	132.50								
	DAY 85	450	127.32	15.15	125.00	450	-5.68	11.26	-5.00	450	-3.91	8.36	-4.18
	DAY 169	450	123.97	14.85	122.00	450	-9.04	12.60	-10.00	450	-6.36	9.15	-7.20
	DAY 253	450	123.48	14.58	121.00	450	-9.52	12.51	-10.00	450	-6.71	9.04	-7.19
	DAY 365	450	123.65	15.34	121.00	450	-9.35	12.78	-10.00	450	-6.62	9.32	-7.41
	DAY 449	450	124.36	15.36	122.00	450	-8.64	13.71	-10.00	450	-6.02	9.91	-7.28
	DAY 533	450	123.40	15.45	120.00	450	-9.60	12.63	-10.00	450	-6.84	9.21	-7.60
	DAY 617	450	123.71	16.04	120.00	450	-9.30	13.94	-10.00	450	-6.56	10.28	-7.49
	DAY 729	450	123.62	16.73	120.00	450	-9.38	13.88	-10.00	450	-6.69	10.14	-7.14
	DAY 813	450	125.80	16.41	123.00	450	-7.20	14.10	-8.00	450	-4.98	10.40	-5.80
	DAY 897	450	123.43	15.81	121.00	450	-9.58	13.67	-10.00	450	-6.78	10.04	-8.13
	DAY 981	450	124.71	16.73	120.00	450	-8.29	14.73	-9.50	450	-5.80	10.77	-6.91
	DAY 1093	450	125.08	16.31	123.00	450	-7.93	13.81	-9.00	450	-5.55	10.06	-6.59
	DAY 1177	450	126.84	16.18	125.00	450	-6.16	13.04	-7.00	450	-4.25	9.65	-5.32
	DAY 1261	450	126.39	16.50	124.00	450	-6.61	14.19	-7.00	450	-4.54	10.39	-5.80
	DAY 1345	450	125.16	16.16	123.00	450	-7.84	13.99	-9.00	450	-5.46	10.18	-6.60
	DAY 1457	450	125.64	15.85	125.00	450	-7.36	14.26	-8.00	450	-5.05	10.43	-6.25

ETVDBP_C3000030 Summary of Diastolic Blood Pressure (mmHg)
LOCF Data
Completer
Percent BW Loss at DAY 1457 from BL > 5% (LOCF)

		Value at Scheduled Visit				Change from Baseline				% Change from Baseline			
PARAMETER	VISIT	N	MEAN	SD	MEDIAN	N	MEAN	SD	MEDIAN	N	MEAN	SD	MEDIAN
PLACEBO	DAY 1	210	82.80	10.05	80.50								
	DAY 85	209	80.09	9.72	80.00	209	-2.75	8.60	-2.00	209	-2.76	10.23	-2.35
	DAY 169	210	78.65	8.87	80.00	210	-4.15	8.50	-4.00	210	-4.37	10.16	-4.55
	DAY 253	210	78.91	9.59	80.00	210	-3.89	9.31	-4.00	210	-4.03	11.24	-4.63
	DAY 365	210	77.80	9.18	78.00	210	-5.00	9.11	-5.00	210	-5.39	10.63	-5.63
	DAY 449	210	78.77	9.80	80.00	210	-4.03	9.30	-3.50	210	-4.27	11.04	-4.73
	DAY 533	210	77.82	9.81	80.00	210	-4.98	9.81	-5.00	210	-5.34	11.67	-6.25
	DAY 617	210	78.36	9.67	80.00	210	-4.44	8.68	-5.00	210	-4.82	10.48	-5.88
	DAY 729	210	77.25	10.08	78.00	210	-5.55	9.55	-5.00	210	-6.12	11.47	-6.67
	DAY 813	210	78.69	9.91	80.00	210	-4.11	9.40	-5.00	210	-4.36	11.11	-5.56
	DAY 897	210	78.56	10.23	80.00	210	-4.24	10.29	-5.00	210	-4.44	12.33	-5.85
	DAY 981	210	78.68	9.83	80.00	210	-4.12	9.49	-5.00	210	-4.33	11.50	-5.68
	DAY 1093	210	78.40	9.86	80.00	210	-4.40	8.70	-5.00	210	-4.79	10.59	-5.26
	DAY 1177	210	79.58	9.90	80.00	210	-3.22	9.01	-4.00	210	-3.34	10.79	-4.32
	DAY 1261	210	78.63	10.09	80.00	210	-4.17	9.75	-4.00	210	-4.40	11.54	-4.81
	DAY 1345	210	78.71	9.34	80.00	210	-4.09	9.58	-5.00	210	-4.23	11.41	-5.56
	DAY 1457	210	78.96	9.22	80.00	210	-3.84	9.93	-3.00	210	-3.85	11.83	-3.18
ORLISTAT	DAY 1	450	83.00	9.97	82.00								
	DAY 85	450	80.27	9.12	80.00	450	-2.73	8.38	-2.00	450	-2.70	10.20	-2.96
	DAY 169	450	77.74	8.91	80.00	450	-5.25	8.65	-5.00	450	-5.71	10.42	-6.67
	DAY 253	450	78.14	9.17	79.00	450	-4.86	8.98	-5.00	450	-5.21	10.91	-6.25
	DAY 365	450	77.59	9.24	78.00	450	-5.40	9.03	-5.00	450	-5.88	10.85	-6.67
	DAY 449	450	78.25	9.24	80.00	450	-4.75	9.47	-5.00	450	-5.04	11.37	-6.25
	DAY 533	450	77.42	9.25	78.00	450	-5.58	9.32	-6.00	450	-6.06	11.14	-7.06
	DAY 617	450	77.61	10.02	78.00	450	-5.39	9.65	-6.00	450	-5.89	11.67	-6.94
	DAY 729	450	77.15	9.70	77.00	450	-5.84	9.39	-5.00	450	-6.43	11.18	-6.67
	DAY 813	450	78.34	9.96	80.00	450	-4.65	9.68	-5.00	450	-4.97	11.83	-5.68
	DAY 897	450	77.77	9.47	78.00	450	-5.22	9.61	-5.00	450	-5.60	11.73	-6.78
	DAY 981	450	78.64	10.20	80.00	450	-4.35	9.92	-5.00	450	-4.62	12.06	-5.88
	DAY 1093	450	78.57	9.66	80.00	450	-4.42	9.61	-5.00	450	-4.66	11.55	-6.25
	DAY 1177	450	79.52	9.98	80.00	450	-3.47	9.47	-4.00	450	-3.58	11.39	-4.76
	DAY 1261	450	79.36	9.67	80.00	450	-3.63	9.57	-4.00	450	-3.72	11.40	-5.00
	DAY 1345	450	78.34	9.70	80.00	450	-4.66	9.80	-5.00	450	-4.95	11.76	-5.88
	DAY 1457	450	78.22	9.37	79.00	450	-4.78	9.52	-5.00	450	-5.09	11.30	-6.25

Q7 For each treatment group, please provide the mean absolute and percent change in baseline body weights for the patients who did vs. those who did not develop either IGT or DM.

As requested, the next two tables provide descriptive statistics for body weight classifying patients separately based on whether they developed either IGT or DM or neither. The first table includes patients who either developed IGT or type 2 diabetes. The placebo patients had a mean weight change after four years of -0.97 kgs while the orlistat group had a mean weight change of -3.8kgs. Furthermore the second table includes those who did not develop either IGT or DM. While on average these patients lost a greater amount of weight (placebo -3.9 kgs vs. orlistat -6.5kgs) then those who developed IGT or DM, the treatment difference in both classification groups is essentially the same.

ETBW_C1000600 Summary of Body Weight (kg)
LOCF Data
Intent-to-Treat
Impaired and/or Diabetic

PARAMETER	VISIT	Value at Scheduled Visit				Change from Baseline				% Change from Baseline			
		N	MEAN	SD	MEDIAN	N	MEAN	SD	MEDIAN	N	MEAN	SD	MEDIAN
PLACEBO	DAY 1	304	113.28	17.41	111.50								
	DAY 85	304	109.40	17.57	107.75	304	-3.88	3.37	-3.70	304	-3.47	3.02	-3.17
	DAY 169	304	107.84	17.66	106.45	304	-5.44	4.85	-5.10	304	-4.84	4.26	-4.69
	DAY 253	304	108.11	18.12	105.75	304	-5.17	5.59	-4.50	304	-4.63	4.93	-4.19
	DAY 365	304	108.68	18.16	105.65	304	-4.60	6.07	-3.60	304	-4.10	5.30	-3.31
	DAY 449	304	109.70	18.38	107.15	304	-3.58	6.17	-2.85	304	-3.20	5.39	-2.50
	DAY 533	304	109.57	18.51	107.00	304	-3.71	6.54	-2.80	304	-3.32	5.69	-2.40
	DAY 617	304	109.88	18.68	107.05	304	-3.39	6.82	-2.15	304	-3.04	5.90	-1.99
	DAY 729	304	110.20	18.70	107.95	304	-3.07	6.89	-1.75	304	-2.75	5.94	-1.64
	DAY 813	304	111.08	18.70	107.70	304	-2.20	6.69	-1.05	304	-1.97	5.78	-0.96
	DAY 897	304	110.98	18.72	108.35	304	-2.30	6.98	-1.10	304	-2.04	5.95	-0.99
	DAY 981	304	111.55	18.79	109.00	304	-1.72	7.08	-0.65	304	-1.53	6.03	-0.55
	DAY 1093	304	111.64	18.78	109.25	304	-1.64	6.98	-1.10	304	-1.46	5.93	-0.93
	DAY 1177	304	112.05	18.75	109.20	304	-1.22	7.09	-0.60	304	-1.08	5.98	-0.52
	DAY 1261	304	112.14	18.83	108.60	304	-1.14	7.14	-0.20	304	-1.00	6.02	-0.18
	DAY 1345	304	112.13	18.86	108.60	304	-1.15	7.16	-0.50	304	-1.02	6.00	-0.47
	DAY 1457	304	112.31	19.02	109.15	304	-0.97	7.19	-0.55	304	-0.87	6.08	-0.50
ORLISTAT	DAY 1	317	110.91	15.98	109.40								
	DAY 85	317	105.02	15.18	103.20	317	-5.89	3.56	-5.40	317	-5.28	2.97	-4.94
	DAY 169	317	102.47	15.53	100.50	317	-8.44	5.53	-7.50	317	-7.60	4.71	-6.95
	DAY 253	317	102.08	15.99	100.60	317	-8.83	6.62	-7.50	317	-7.97	5.76	-7.06
	DAY 365	317	102.02	16.68	100.50	317	-8.89	7.48	-7.70	317	-8.06	6.57	-7.04
	DAY 449	317	103.13	17.18	101.40	317	-7.78	7.86	-6.50	317	-7.08	6.97	-6.11
	DAY 533	317	103.14	17.31	101.50	317	-7.77	8.19	-6.60	317	-7.06	7.23	-5.91
	DAY 617	317	103.77	17.42	102.20	317	-7.14	8.31	-6.00	317	-6.49	7.35	-5.39
	DAY 729	317	104.23	17.57	102.40	317	-6.67	8.35	-5.70	317	-6.07	7.40	-5.22
	DAY 813	317	105.26	17.54	102.80	317	-5.65	8.16	-4.70	317	-5.14	7.29	-4.20
	DAY 897	317	105.25	17.62	102.90	317	-5.66	8.33	-4.60	317	-5.14	7.44	-4.17
	DAY 981	317	106.09	17.71	104.10	317	-4.82	8.06	-3.80	317	-4.40	7.22	-3.44
	DAY 1093	317	106.38	17.77	104.70	317	-4.53	7.96	-3.60	317	-4.15	7.13	-3.27
	DAY 1177	317	107.01	17.55	105.80	317	-3.90	7.78	-2.90	317	-3.55	6.95	-2.64
	DAY 1261	317	106.94	17.56	105.60	317	-3.96	7.85	-2.80	317	-3.61	7.01	-2.77
	DAY 1345	317	107.13	17.68	105.80	317	-3.78	7.97	-2.80	317	-3.44	7.15	-2.57
	DAY 1457	317	107.11	17.57	104.90	317	-3.80	8.31	-2.60	317	-3.42	7.40	-2.51

Generated by /opt/BIOSTAT/home/xiab/cdp01276/bm15421/tsum_bx_fda.sas at 11:48 on 24JUN2004

ETBW_C1000700 Summary of Body Weight (kg)
LOCF Data
Intent-to-Treat
Neither Impaired nor Diabetic

PARAMETER	VISIT	Value at Scheduled Visit				Change from Baseline				% Change from Baseline			
		N	MEAN	SD	MEDIAN	N	MEAN	SD	MEDIAN	N	MEAN	SD	MEDIAN
PLACEBO	DAY 1	1168	110.87	16.20	109.20								
	DAY 85	1168	105.69	15.88	104.25	1168	-5.18	4.02	-4.70	1168	-4.66	3.52	-4.24
	DAY 169	1168	103.46	16.09	102.45	1168	-7.42	5.93	-6.40	1168	-6.67	5.21	-5.96
	DAY 253	1168	103.35	16.70	102.00	1168	-7.52	6.95	-6.35	1168	-6.78	6.19	-5.75
	DAY 365	1168	103.53	17.11	102.05	1168	-7.34	7.64	-6.00	1168	-6.63	6.84	-5.38
	DAY 449	1168	104.41	17.37	103.10	1168	-6.46	7.80	-5.10	1168	-5.85	7.02	-4.57
	DAY 533	1168	104.44	17.56	102.90	1168	-6.43	7.99	-4.80	1168	-5.84	7.17	-4.33
	DAY 617	1168	104.93	17.55	103.60	1168	-5.94	7.96	-4.30	1168	-5.39	7.13	-3.88
	DAY 729	1168	105.18	17.59	103.90	1168	-5.69	7.91	-4.10	1168	-5.16	7.07	-3.70
	DAY 813	1168	105.86	17.51	104.50	1168	-5.01	7.75	-3.70	1168	-4.54	6.92	-3.21
	DAY 897	1168	105.94	17.53	104.95	1168	-4.93	7.85	-3.60	1168	-4.46	6.99	-3.28
	DAY 981	1168	106.31	17.53	104.95	1168	-4.56	7.76	-3.25	1168	-4.13	6.90	-3.00
	DAY 1093	1168	106.49	17.64	105.20	1168	-4.38	7.68	-3.20	1168	-3.98	6.83	-2.91
	DAY 1177	1168	106.90	17.56	105.75	1168	-3.97	7.53	-3.05	1168	-3.60	6.70	-2.70
	DAY 1261	1168	106.83	17.58	105.70	1168	-4.04	7.51	-3.20	1168	-3.67	6.67	-2.84
	DAY 1345	1168	106.94	17.57	105.60	1168	-3.93	7.50	-2.90	1168	-3.56	6.68	-2.66
	DAY 1457	1168	107.01	17.53	105.75	1168	-3.86	7.46	-2.90	1168	-3.49	6.63	-2.63
ORLISTAT	DAY 1	1255	111.63	16.58	109.80								
	DAY 85	1255	104.54	16.05	103.40	1255	-7.09	3.76	-6.70	1255	-6.36	3.22	-6.08
	DAY 169	1255	101.30	16.09	100.00	1255	-10.33	5.61	-9.70	1255	-9.26	4.80	-8.81
	DAY 253	1255	100.51	16.54	98.90	1255	-11.12	6.82	-10.20	1255	-9.98	5.90	-9.38
	DAY 365	1255	100.19	16.72	99.10	1255	-11.44	7.67	-10.40	1255	-10.25	6.64	-9.41
	DAY 449	1255	100.89	16.96	99.90	1255	-10.74	8.05	-9.50	1255	-9.63	6.95	-8.72
	DAY 533	1255	100.90	17.11	99.80	1255	-10.73	8.34	-9.50	1255	-9.62	7.20	-8.84
	DAY 617	1255	101.45	17.10	100.00	1255	-10.18	8.42	-8.70	1255	-9.10	7.22	-7.96
	DAY 729	1255	102.01	17.29	100.50	1255	-9.62	8.45	-8.50	1255	-8.61	7.24	-7.76
	DAY 813	1255	102.87	17.40	101.20	1255	-8.76	8.37	-7.50	1255	-7.84	7.18	-6.76
	DAY 897	1255	102.97	17.26	101.30	1255	-8.66	8.43	-7.40	1255	-7.74	7.22	-6.82
	DAY 981	1255	103.66	17.30	101.90	1255	-7.97	8.27	-6.60	1255	-7.12	7.12	-6.26
	DAY 1093	1255	104.04	17.37	102.10	1255	-7.59	8.20	-6.40	1255	-6.79	7.05	-6.04
	DAY 1177	1255	104.67	17.42	102.90	1255	-6.96	8.10	-5.70	1255	-6.23	6.97	-5.30
	DAY 1261	1255	104.73	17.39	103.00	1255	-6.90	8.04	-5.60	1255	-6.17	6.95	-5.18
	DAY 1345	1255	104.93	17.41	103.40	1255	-6.70	7.99	-5.60	1255	-5.99	6.91	-5.11
	DAY 1457	1255	105.18	17.60	103.50	1255	-6.45	8.06	-5.20	1255	-5.78	7.01	-4.86

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Q8 For those patients with normal glucose tolerance at baseline who were diagnosed with diabetes at Month 6, how many, by treatment group, had a repeat, confirmatory OGTT?

Q9 For those patients with IGT at baseline who were diagnosed with diabetes at Month 6, how many, by treatment group, had a repeat, confirmatory OGTT?

Due to the consequence and timing of the protocol amendment, most patients did not have a repeat OGTT assessment conducted after diagnosis at the 6 month timepoint. More specifically of the 23 patients with a positive OGTT test at 6 months, only five patients had a repeat OGTT and 2 of those patients had a positive confirmation from the repeat OGTT. Broken down by baseline status, 19 (16 pl, and 3 orl) of the patients that developed diabetes at six months had impaired glucose tolerance at baseline, and only one of those patients (placebo) had a repeat confirmed value. Of the 4 (2 pl and 2 orl) patients that were normal at baseline and developed diabetes by six months, only one patient (placebo) confirmed.

To retrospectively assess the robustness of the final results, the 6 month time point was removed and the data reanalyzed using the original methodology. The table below shows the results of removing the 6 month measurements (and treating these cases as dropouts at this time point) in the primary table. Also we are providing the table previously provide in question 2 of the repeat positive confirmed cases, removing the 6m time point. The log rank for both analyses remained significant ($p<0.05$).

Report Date: 06/25/04

Cumulative Incidence of Cases by Time of first Occurrence
Primary - 6 month cases treated as dropouts (noncase) at 6 months

Time Interval of Occurrence (Scheduled Day)	PLACEBO Number Pts Entering Interval	PLACEBO Number Pts with Cases n (%)	PLACEBO Cumulative Rate	ORLISTAT Number Pts Entering Interval	ORLISTAT Number Pts with Cases n (%)	ORLISTAT Cumulative Rate
Day 1	1655			1649		
Day 169	1472	0 (0.00)	.00000	1572	0 (0.00)	.00000
Day 365	1271	10 (0.79)	.00787	1483	10 (0.67)	.00674
Day 533	1106	11 (0.99)	.01774	1362	7 (0.51)	.01185
Day 729	956	13 (1.36)	.03109	1257	7 (0.56)	.01735
Day 897	749	10 (1.34)	.04403	1118	12 (1.07)	.02790
Day 1093	672	10 (1.49)	.05825	1008	14 (1.39)	.04140
Day 1261	551	7 (1.27)	.07022	859	8 (0.93)	.05033
Day 1457	521	5 (0.96)	.07914	810	7 (0.86)	.05853

Treats 6m primary cases as not confirmed
Report Date: 06/25/04
Cumulative Incidence of Cases by Time of first Occurrence
Confirmed - Immediate 2 Hr >=10 or 0 hr >= 6.1,

Time Interval of Occurrence (Scheduled Day)	PLACEBO			ORLISTAT		
	Number Pts Entering Interval	Number Pts with Cases n (%)	Cumulative Rate	Number Pts Entering Interval	Number Pts with Cases n (%)	Cumulative Rate
Day 1	1655			1649		
Day 169	1472	0 (0.00)	.00000	1572	0 (0.00)	.00000
Day 365	1285	4 (0.31)	.00311	1486	2 (0.13)	.00135
Day 533	1116	5 (0.45)	.00758	1368	3 (0.22)	.00354
Day 729	968	8 (0.83)	.01578	1267	4 (0.32)	.00668
Day 897	761	5 (0.66)	.02225	1126	8 (0.71)	.01374
Day 1093	686	6 (0.87)	.03080	1017	4 (0.39)	.01762
Day 1261	566	6 (1.06)	.04107	877	5 (0.57)	.02322
Day 1457	537	1 (0.19)	.04286	829	3 (0.36)	.02675

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/s/

Oluchi Elekwachi
7/23/04 10:47:30 AM

ORIGINAL

Roche

Pharmaceuticals

July 13, 2004

Food and Drug Administration
Division of Metabolic and Endocrine Drug Products, HFD-510
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Fishers Document Control Room
Parklawn Bldg. Room 8B 45
5600 Fishers Lane
Rockville, Maryland 20857-1706

RECEIVED
JUL 15 2004
CDR/CDER

SE6 019 BM

NDA SUPPL AMENDMENT

Ladies and Gentlemen:

Re: NDA 20-766/S-019 Xenical® (orlistat) Capsules, 120 mg
Response to Agency's Review Questions re: Xendos Data Included in S-019

Reference is made to the labeling supplement to NDA 20-766/S-019 submitted December 22, 2003 for the purpose of including data from the XENDOS study in the approved label for Xenical. Reference is also made to the Agency's fax dated June 22, 2004 which included nine review questions regarding the labeling supplement. The purpose of this submission is to provide the responses to those questions.

For ease of review, each question is repeated and the Roche response with supporting documentation is provided, see attached.

Please feel free to contact the undersigned if you have any questions regarding these responses.

RECEIVED
JUL 16 2004
FDR/CDER

Sincerely,

HOFFMANN-LA ROCHE INC

Margaret J Jack

Margaret J. Jack
Program Director
(973) 235-4463 (telephone)
(973) 562-3700/3554 (fax)

MJJ/dc
Attachments

HLR No. 2004-1795

Roche

June 22, 2004

Food and Drug Administration
Division of Metabolism and Endocrine Drug Products, HFD-510
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Fishers Document Room
Parklawn Bldg. Room 8B 45
5600 Fishers Lane
Rockville, Maryland 20857

SE8-019-SL

Re: NDA 20-766/S-019 Xenical® (orlistat) Capsules, 120 mg
Response to FDA's Request for Additional Desk Copies of Previously Submitted Information

Dear Dr. Oluchi Elekwachi:

Reference is made to our telephone conversation on June 22, 2004 during which you requested an additional copy of Module 1, Volume 1.1 and an electronic version of the draft label that was included in the above mentioned application which was submitted December 22, 2003 and received by the Division on December 23, 2003.

Enclosed please find the additional desk copy of Volume 1.1 and well as a disc with the electronic version of the draft label in Word, previously submitted in S-019. The disc with the draft labeling is located immediately following the tab entitled, "Labeling Text – Word Version" in Volume 1.1. Please note we also sent a copy of the draft label to you via e-mail.

In addition we also received a list of questions via e-mail today regarding the above mentioned application entitled "XENDOS Review Questions – June 21, 2004". Responses to these questions are in preparation and be will provided as soon as they are available.

Please feel free to contact the undersigned at the numbers provided if you have any questions regarding this submission or if additional information is needed.

Sincerely,

HOFFMANN-LA ROCHE INC

Margaret J. Jack

Margaret J. Jack
Program Director
(973) 235-4463 (telephone)
(973) 562-3700/3554 (fax)

MJJ/dc
Attachments

Desk Copy: Dr. Oluchi Elekwachi HFD-510
HLR No. 2004-1624

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Rockville, MD 20857

FILING COMMUNICATION

NDA 20-766/S-019

2/23/04

Hoffmann-La Roche
Attn: Margaret Jack
Program Director
340 Kingsland Street
Nutley, New Jersey 07110-1199

Dear Ms. Jack:

Please refer to your December 22, 2003 supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Xenical (Orlistat) Capsules 120 mg.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application will be filed under section 505(b) of the Act on February 21, 2004 in accordance with 21 CFR 314.101(a).

At this time, we have not identified any potential filing review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review.

If you have any questions, call Oluchi Elekwachi, Pharm.D., M.P.H. , Regulatory Project Manager, at (301) 827-6381.

Sincerely,

{See appended electronic signature page}

Enid Galliers
Chief, Project Management Staff
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II

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/s/

Oluchi Elekwachi
2/23/04 02:01:25 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

NDA 20-766/S-019

PRIOR APPROVAL SUPPLEMENT

1/2/04

Hoffman-LaRoche, Inc.
Attention: Margaret J. Jack
Program Director
340 Kingsland Street
Nutley, New Jersey, 07110-1199

Dear Ms. Jack:

We have received your supplemental drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product:	Xenical® (orlistat) Capsules, 120 mg
NDA Number:	20-766
Supplement number:	S-019
Review Priority Classification:	Standard (S)
Date of supplement:	December 22, 2003
Date of receipt:	December 23, 2003

This supplemental application proposes labeling changes in the package insert to include data from the Xendos Study.

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on February 21, 2004, in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be October 23, 2004.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We note that you have not fulfilled the requirement. We are waiving the requirement for pediatric studies for this application.

All communications concerning this supplement should be addressed as follows:

U.S. Postal Service/ Courier/Overnight Mail:

Center for Drug Evaluation and Research
Division of Metabolic and Endocrine Drug Products, HFD-510
Attention: Document Room, Room 8B45
5600 Fishers Lane
Rockville, Maryland 20857

If you have any questions, call Oluchi Elekwachi, Pharm.D., M.P.H., Regulatory Project Manager, at (301) 827-6381.

Sincerely,

{See appended electronic signature page}

Pat Madara, Regulatory Project Manager
Division of Metabolic and Endocrine Drug Products
HFD-510
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Oluchi Elekwachi
1/2/04 01:23:04 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-766

10/24/03

Hoffmann-La Roche Inc.
Attention: Lisa A. Luther
Group Director, Drug Regulatory Affairs
340 Kingsland Street
Nutley, NJ 07110

Dear Ms. Luther:

Please refer to the meeting between representatives of your firm and FDA on September 26, 2003. The purpose of the meeting was to discuss the XENDOS study with the intent to discuss and clearly understand the Agency's policy regarding labeling of obesity drugs, specifically as it relates to XENDOS.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at 301-827-6381.

Sincerely,

{See appended electronic signature page}

Oluchi Elekwachi, Pharm.D., M.P.H.
Regulatory Health Project Manager
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure: Memorandum of Meeting Minutes

MEMORANDUM OF MEETING MINUTES

MEETING DATE: Friday, September 26, 2003
TIME: 10:00AM – 11:00AM
LOCATION: Parklawn Building Conference Room L
APPLICATION: NDA 20-766 Xenical (orlistat) Capsules
TYPE OF MEETING: Dispute Resolution

MEETING CHAIR: Robert Myer, MD

MEETING RECORDER: Oluchi Elekwachi, Pharm.D., M.P.H

FDA ATTENDEES, TITLES, AND OFFICE/DIVISION

Name of FDA Attendee	Title	Division Name & HFD#
Robert Meyer, M.D.	Director	Office of Drug Evaluation II
David Orloff, M.D.	Director	Division of Endocrine and Metabolic Drug Products
Leah Ripper	Associate Director for Regulatory Affairs	Office of Drug Evaluation II
Eric Colman, M.D.	Clinical Team Leader	Division of Endocrine and Metabolic Drug Products
Teresa Kehoe, M.D.	Medical Officer	Division of Endocrine and Metabolic Drug Products
Kati Johnson	Chief, Project Management Staff	Division of Endocrine and Metabolic Drug Products
Oluchi Elekwachi, Pharm.D., M.P.H.	Regulatory Project Manager	Division of Endocrine and Metabolic Drug Products

EXTERNAL CONSTITUENT ATTENDEES AND TITLES:

External Attendee	Title	Sponsor/Firm Name
Dr. Lars Birgerson	VP, Medical Affairs	Hoffmann-La Roche, Inc.
Mr. Mark Boldrin	Biometrics	Hoffmann-La Roche, Inc.
Dr. Paul Brown	Life Cycle Leader	Hoffmann-La Roche, Inc.
Dr. Ralph A. DeFronzo	Consultant, University of Texas	Hoffmann-La Roche, Inc.
Dr. Cynthia Dinella	VP, Regulatory Affairs	Hoffmann-La Roche, Inc.
Dr. Jonathan Hauptman	Clinical Science Leader	Hoffmann-La Roche, Inc.
Ms. Peggy Jack	Regulatory Affairs	Hoffmann-La Roche, Inc.
Ms. Lisa Luther	Group Director, Regulatory Affairs	Hoffmann-La Roche, Inc.
Dr. Rosalind Wilson	International Medical Manager	Hoffmann-La Roche, Inc.

BACKGROUND:

On January 2, 2003, the sponsor, Hoffmann-La Roche Inc., requested a meeting to discuss proposed labeling from the completed XENDOS study (a double blind, multi-center, randomized, parallel

February 4, 2003,

On June 30, 2003, the sponsor formally requested reconsideration of its meeting request to discuss the XENDOS study in accordance with the Agency's Guidance for Industry – Formal Dispute Resolutions: Appeals above the Division Level. The meeting was granted July 14, 2003.

MEETING OBJECTIVES:

1. To obtain a better understanding of the rationale behind the Agency's a priori proposed policy requiring
2. To review the case for the proposed supplement in light of current governmental initiatives focused on the
3. To obtain the Agency's input/advice regarding the proposed submission of a supplement based on the XENDOS data.
4. If a supplemental application is filed to include data from the XENDOS study in the Xenical label, then Roche would like to discuss and obtain agreement on a mutually acceptable communication strategy between the Division and Roche during the review process.

DISCUSSION POINTS :

The firm's specific questions are followed by the Agency response (in bold)

1. Based on the recommendations included in Agency's current draft "Guidance for the clinical Evaluation of Weight-Control Drugs" and the fact that these data are important for physicians in assessing the benefit/risk of treating obese patients for obesity management

FDA Response: Yes we agree, in concept, assuming that the data support the conclusion.

a. Roche is requesting a clear understanding of th

FDA Response:

Based on what we have seen of the XENDOS data, some information from this study may be included in the CLINICAL TRIALS sections.

b. Roche is requesting guidance from the Agency regarding which specific safety and efficacy data from the XENDOS stud

FDA RESPONSE: Submit the study report as a prior approval supplement, including the analyses defined in the protocol. During our review of the data, we may either conduct additional analyses ourselves or request them from the firm.

2. If a supplemental application is filed to include data from the XENDOS study in the Xenical label, then Roche would like to discuss and obtain agreement on a mutually acceptable interactive and transparent communication strategy between the Division and Roche during the review process.

FDA RESPONSE: There are provisions under PDUFA (74-day filing letters, discipline review letters) which stipulate the minimum communication between the sponsor and the firm pertaining to a pending application. Additional communication prior to taking an action on an application will vary according to Divisional resources and the need for additional information. There is a draft guidance on Good Review Principles and we adhere to this guidance. However, it is not possible for the Division to give sponsors advanced notice of impending regulatory action. Unless the application is obviously fatally flawed, due to resource constraints, the regulatory decision is generally reached close to the PDUFA goal date. We attempt, however, to keep an open line of communication.

DECISIONS (AGREEMENTS) REACHED:

1. Based on current Divisional policy, data from the XENDOS / may be placed in the CLINICAL TRIALS section of the package insert. Based on the information available at this time, the Division does not believe that the supplement would meet the criteria for a priority review.

ACTION ITEMS: None

Minutes Preparer: _____

Oluchi Elekwachi, Pharm.D., M.P.H.
Regulatory Project Manager

MEETING MINUTES

2 Page(s) Withheld

_____ § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(4) Draft Labeling

✓ § 552(b)(5) Deliberative Process

Withheld Track Number: Administrative- 20-766
5019

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/s/

Oluchi Elekwachi
10/24/03 10:46:39 AM

December 22, 2003

Food and Drug Administration
Division of Metabolic and Endocrine Drug Products, HFD-510
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Fishers Document Control Room
Parklawn Bldg. Room 8B 45
5600 Fishers Lane
Rockville, Maryland 20857-1706

Ladies and Gentlemen:

Re: NDA 20-766 Xenical® (orlistat) Capsules, 120 mg
Supplemental New Drug Application:
Proposed Labeling Changes to Include Data
from the XENDOS Study in the Xenical Package Insert

In accordance with 21 CFR Section 314.70, Hoffmann La Roche Inc., (Roche) herewith submits a supplemental New Drug Application (sNDA) for Xenical R (orlistat) Capsules with revised labeling based on the results of the XENDOS Study. Reference is made to the meeting between the Division of Endocrinologic and Metabolic Drug Products and Roche which took place September 26, 2003, during which this supplemental application was discussed.

The XENDOS study, which is the basis of this application, is a multicenter, double-blind, placebo controlled, randomized parallel group design study of 4 years duration conducted in obese patients (BMI ≥30). The objectives of the study were to determine if treatment with orlistat, compared to placebo could delay the onset of type 2 diabetes, to determine the effect of treatment of orlistat compared to placebo on long-term weight control and to determine the effect of long-term treatment on other obesity related risk factors. The study was powered to detect treatment differences in time to onset of diabetes mellitus. Changes in body weight from baseline to the end of treatment was also of major interest, while the secondary endpoints of the study were changes from baseline in to the end of treatment in other obesity related risk factors. This study was conducted in Sweden and 3304 patients were randomized. Patients participating in the study were between 30 and 60 years of age with normal or impaired glucose tolerance (IGT) at baseline and could not have a history or presence of type 2 diabetes and could not be drug-treated for type 2 diabetes.

The results of this study indicate that orlistat significantly ($p<0.01$) delayed the onset of type 2 diabetes such that at the end of four years of treatment the cumulative rate of diabetes was 9.04% for the placebo group compared to 6.15% for the orlistat group. The hazard ratio (an estimate of relative risk) indicates that orlistat treatment significantly decreased the hazard of diabetes by 37.3% relative to placebo.

The least square means (LSM) change for body weight from baseline to the end of the first year of treatment for the ITT (LOCF) population was -6.19kg for the placebo treatment group and -10.56kg for the orlistat treatment group. After 4 years of treatment . 44.8% of orlistat-treated and 28.0% of placebo treated patients lost ≥5% of baseline body weight ($p<0.001$).

Hoffmann-La Roche Inc. 340 Kingsland Street
Nutley, New Jersey 07110-1199

Throughout the entire four-treatment period, orlistat-treated compared to placebo-treated patients had statistically significant ($p<0.001$) reductions in several obesity-related risk factors including body mass index, total cholesterol, LDL cholesterol, LDL:HDL ratio, fasting insulin, fasting glucose, systolic blood pressure, diastolic blood bressure, pulse rate, plasminogen activator inhibitor and waist circumference.

On September 26, 2003, Roche met with the Agency to specifically discuss the XENDOS study and the labeling options for the inclusion of data from XENDOS in the labeling of Xenical. Based on these discussions and Agency recommendations provided at that meeting, the Agency agreed that pending the formal review of the supplemental application, some clinical data from the XENDOS study (such as long-term weight loss, reducing the risk of developing diabetes and long-term effects on obesity-related risk factors) may be placed in the CLINICAL Studies section of the Xenical label. Roche is submitting this application in accordance with agreements reached at the September 26th meeting.

No new chemistry, manufacturing or controls information are included in this application nor were there any additional nonclinical studies conducted in support of this application.

This application is being submitted in paper format following the CTD (Common Technical Document) guideline. The overall organization of this sNDA is as follows:

Module 1:

1.1 Comprehensive Table of Contents
1.2 FDA Form 356h
1.3.a Administrative Documents
- Patent Information
- Debarment Certification
- Confidentially Statement
- User Fee Documentation (Form 3397)
- *The User Fee Payment for this sNDA was previously wired to the FDA, with a value date of December 10, 2003. The User Fee I.D. number is 4652*
- Financial Disclosure Information (Form 3455)
- Environmental Assessment/Request for Categorical Exclusion

1.3.b Prescribing Information/Labeling
- Professional Package Insert
  - Proposed Labeling Text (includes patient package)
  - Currently Used Labeling Text
  - Last Approved Labeling Text
- Patient Package Insert
  - Currently Used Labeling Text/Last Approved Labeling Text

1.3.c Annotated Labeling
- Proposed Package Insert - Annotated

Module 2:
2.1 CTD Table of Contents (Modules 2-5)
2.2 CTD Introduction – N/A
2.3 Quality Overall Summary – N/A
2.4 Nonclinical Overview – N/A
2.5 Clinical Overview
2.6 Nonclinical Written and Tabulated Summaries – N/A
2.7 Clinical Summary

Module 3 - Quality - N/A

Module 4 – Non Clinical Study Reports – N/A

Module 5:
5.1 Table of Contents
5.2 Tabular Listings of All Clinical Studies
5.3 Clinical Study Reports
5.3.1 Reports of Biopharmaceutic Studies – N/A
5.3.2 Reports of Studies Pertinent to Pharmacokinetics using Human Biomaterials – N/A
5.3.3 Reports of Human Pharmacokinetic (PK) Studies – N/A
5.3.4 Reports of Human Pharmacodynamic (PD) Studies – N/A
5.3.5 Reports of Efficacy and Safety Studies
5.3.5.1 Study Reports of Controlled Clinical Studies Pertinent to the Claimed Indication
Clinical Study Report – Protocol BM15421D. Weight reducing and type 2 diabetes Preventing effects of Xenical in obese patients (The XENDOS Study).
5.3.5.2 Study Reports of Uncontrolled Clinical Studies – N/A
5.3.5.3 Reports of Analysis of Data from More Than One Study , Including Any Formal Integrated Analyses, Meta-analyses, and Bridging Analyses – N/A
5.3.5.4 Other Clinical Study Reports – N/A
5.3.6 Reports of Postmarketing Experience - N/A
5.3.7 Case Report Forms and Individual Patient Listings
5.3.7.1 Case Report Forms (Available on Request)
5.3.7.2 Case Report Tabulations
5.3.7.2.1 SAS datasets
5.3.7.2.2 Patient Profiles
5.4 References

The datasets and patient profiles portion of this submission is being submitted electronically and is comprised of 2 CDs totaling 1.3GB. The labeltext.doc document is also provided electronically on the CDs. The CDs have been scanned with Norton AntiVirus v.7.61.938 using virus definitions dated 12/10/2003 rev 8, and no viruses were found.

Please feel free to contact the undersigned at the numbers provided if you have any questions regarding this submission or if additional information is needed.

Sincerely,

HOFFMANN-LA ROCHE INC

Margaret J Jack

Margaret J. Jack
Program Director
(973) 235-4463 (telephone)
(973) 562-3700/3554 (fax)

MJJ/dc
Attachments

HLR No. 2003-3658

Debarment Certification

Hoffmann-La Roche Inc. hereby certifies that it did not allow and will not allow use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug and Cosmetic Act in connection with this application.