

Statistical Review and Evaluation

NDA#: 20-766/Class 1S APR 30 1997
Applicant: Hoffmann-La Roche Inc.
Name of Drug: XENICAL (Orlistat) capsules
Indication: Antiobesity
Documents Reviewed: Vols. 1.1, 1.152-467
Submission dated November 27, 1996

Background

Orlistat (tetrahydrolipstatin, THL) is an inhibitor of lipases. It targets the lipases in the stomach and the small intestine by forming a covalent bond with the active serine site of gastric and pancreatic lipases. The inactivated enzymes are thus unavailable to digest the dietary fat which can be absorbed only after breaking down into its constituents. The body produces the said enzymes in such quantity that no more than 1/3 of the ingested amount of fat is lost.

Controlled Studies

There were 6 placebo-controlled studies. For regulatory reasons, Protocol BM14119A has been split into Protocols BM14119B which referred to the one-year study in the U.K., and BM14119C which referred to the 2-year study in continental Europe. There were three two-year studies, NM14185 (US), BM14149 (European), and NM14161 (US) and two one-year U.S. studies in special populations, NM14336 (NIDDM), and NM14302 (weight loss on 24-week diet lead-in).

Efficacy data from three time intervals of year 1 (day 1 to week 52), year 2 (week 52 to week 104) and 2 years (day 1 to week 104) can be analyzed depending on the study. Four populations were defined for the three analysis intervals (identical population for year 2 and 2 years). These populations are defined as below:

Year One

a. Intent-to-Treat Analysis Population (ITT) - included all patients who received at least one dose of study medication during double-blind treatment and had body weight measurements before and after randomization. The ITT population for Quality of Life (QoL) was a subset of the ITT population. It included only patients who had a baseline QoL assessment and at least one follow-up assessment on either day 169 or day 365.

b. Intent-to-Treat 12 Week Analysis Population (ITT_{12wk}) - included all patients who met the criteria for the ITT population and had at least one efficacy assessment after 12 weeks of double-blind treatment.

c. Standard Analysis Population (Standard) - included all patients who completed at least 12 weeks of double-blind treatment and did not: violate any inclusion or exclusion criteria, violate any of the randomization criteria, refuse to comply with the regimen of study medication, use drugs during the study for periods in excess of 28 contiguous days that were prohibited by the protocol and thought to alter body weight (e.g., cold medications containing phenylpropanolamine), or change smoking habits (starting or stopping) during the study.

d. Completers Analysis Population (Completers_{1yr}) - included all patients in the standard analysis population who completed at least 50 weeks of double blind treatment.

Note that each population is a subset of the prior population and the "completers" population excluded patients due to protocol violations and noncompliance.

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Year Two

Intent-to-Treat 52 Week Analysis Population (ITT_{52wk}) - included all patients who completed the first year of double-blind treatment, received at least one dose of the second-year treatment and had a subsequent body weight measurement. The ITT population for QoL included patients who had a baseline QoL assessment and follow-up assessments on at least days 365 and 729.

Intent-to-Treat 60 Week Analysis Population (ITT_{60wk}) - included all patients who entered the second year of the study and completed at least 8 weeks of the second year of double-blind treatment, the minimum duration of treatment for effects on weight regain to be identified.

Standard Analysis Population (Standard) - included all patients who entered the second year of the study, completed at least 8 weeks of second-year double-blind treatment, and met the criteria for Standard population analysis specified under Year One.

Completers Analysis Population (Completers_{2yrs}) - included all patients in the year two standard population who completed at least 60 weeks of the second year of double-blind treatment.

The same populations analyzed for year 2 of treatment were

analyzed for 2 years of treatment.

The protocol described two other populations to be included in the intent-to-treat analysis: analysis at week 52 for patients who completed at least 24 weeks of treatment and analysis at week 104 for patients who completed at least 76 weeks of treatment. The sponsor decided that these analyses were too restrictive and therefore were not performed.

The term "initial values" described measurements made at the start of the placebo lead-in period (day -28) and "values at the start of double-blind treatment" described measurements made at the start of double-blind (day 1, baseline).

The Sponsor's Primary Efficacy Parameters

The primary efficacy measurements were the changes from baseline in body weight at weeks 56 (year 1) and 108 (year 2). The weight changes at weeks 28 and 80 were also evaluated. The testing hypothesis for year one was:

H_0 : The expected mean weight change after 52 weeks of double-blind treatment is the same for the placebo tid and orlistat tid treatment groups. The testing hypotheses for the year two and the two years analyses depended on the study design.

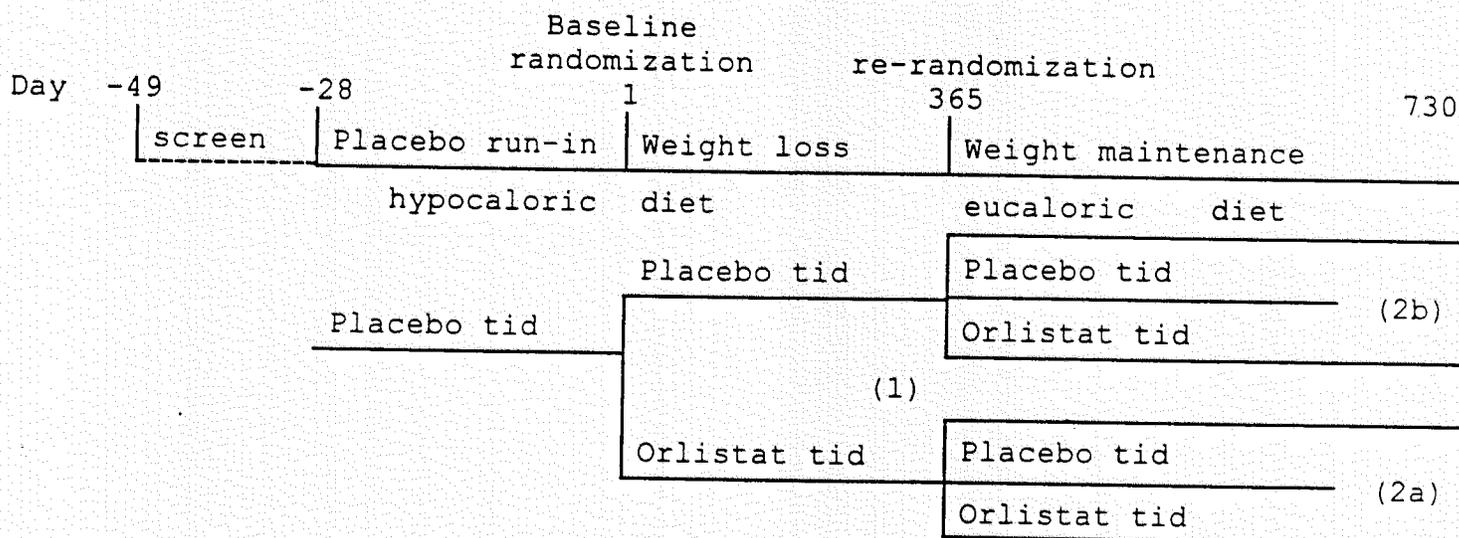
Two additional unplanned categorical analyses were performed which the sponsor indicated comes from the FDA Advisory meeting recommendation. The hypothesis tested was that weight change distribution was the same for patients treated with placebo or orlistat. The five weight change categories were: lost more than 10%, lost more than 5% but less than or equal to 10%, lost more than 0% but less than or equal to 5%, gained between 0% and 5%, and gained more than 5%. A frequency table of percent change from initial body weight at the end of 52 weeks of treatment (LOCF) was used to test the hypothesis by Chi-square with 4 degrees of freedom. The frequency table at the end of week 104 was tested with 12 degrees of freedom $(4-1)*(5-1)$ on the homogeneity of frequency distributions of weight change among treatment groups.

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This reviewer used the last observation carried forward (LOCF) data of the intent-to-treat (ITT) population as the primary analysis population. The binary responder analysis of patients who lost $\geq 5\%$ from baseline weight instead of the sponsor's 5 categorical analyses was employed by this reviewer. In most cases the ITT and "completers" analyses were consistent.

Study BM14119C

This was a two-year study in centers from continental Europe. The study was designed as a randomized, multicenter (15), double-blind, placebo-controlled study with a 4-week single-blind placebo lead-in period, a 52-week double-blind treatment period with either placebo or orlistat plus a hypocaloric diet, a re-randomization on day 365, and a 52-week double-blind treatment period with either placebo or orlistat plus a weight maintenance diet (eucaloric). The design is as follows:



At each study site patients were randomized into orlistat or placebo in two strata based on weight loss between day -28 and baseline. Patient randomization numbers were allocated sequentially. For patients who lost 2.0 kg or less during the placebo run-in, the assignment started with the lowest code at the center in an ascending order and for those who lost more than 2.0 kg the assignment started with the highest code at the center, in a descending order. At both baseline and 52 week randomization, patients had at least 75% compliance of the dosing regimen.

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Study Objectives

In the protocol, the objectives were as follows:

1. To determine the **weight loss** effect of 120 mg orlistat tid compared to placebo tid over a 1 year period when prescribed with a hypocaloric diet.

2 The ability of orlistat to **maintain** body weight was assessed as follows:

2a. In patients treated with **orlistat** and hypocaloric diet for the first year, to determine during the second year, the

effect on body weight change of 120 mg orlistat tid compared to placebo tid when prescribed with a weight maintenance diet.

2b. In patients treated with **placebo** and hypocaloric diet for the first year, to determine during the second year, the effect on body weight change of 120 mg orlistat tid compared to placebo tid when prescribed with a weight maintenance diet.

3. To determine the tolerability of 120 mg orlistat tid administered orally for either 52 or 104 weeks.

In the Analysis Plan, a weight **control** analysis (two years) was added as an exploratory analysis which used the two year data to compare treatment effects between orlistat and placebo treatment for those patients who were in the same treatment for two years.

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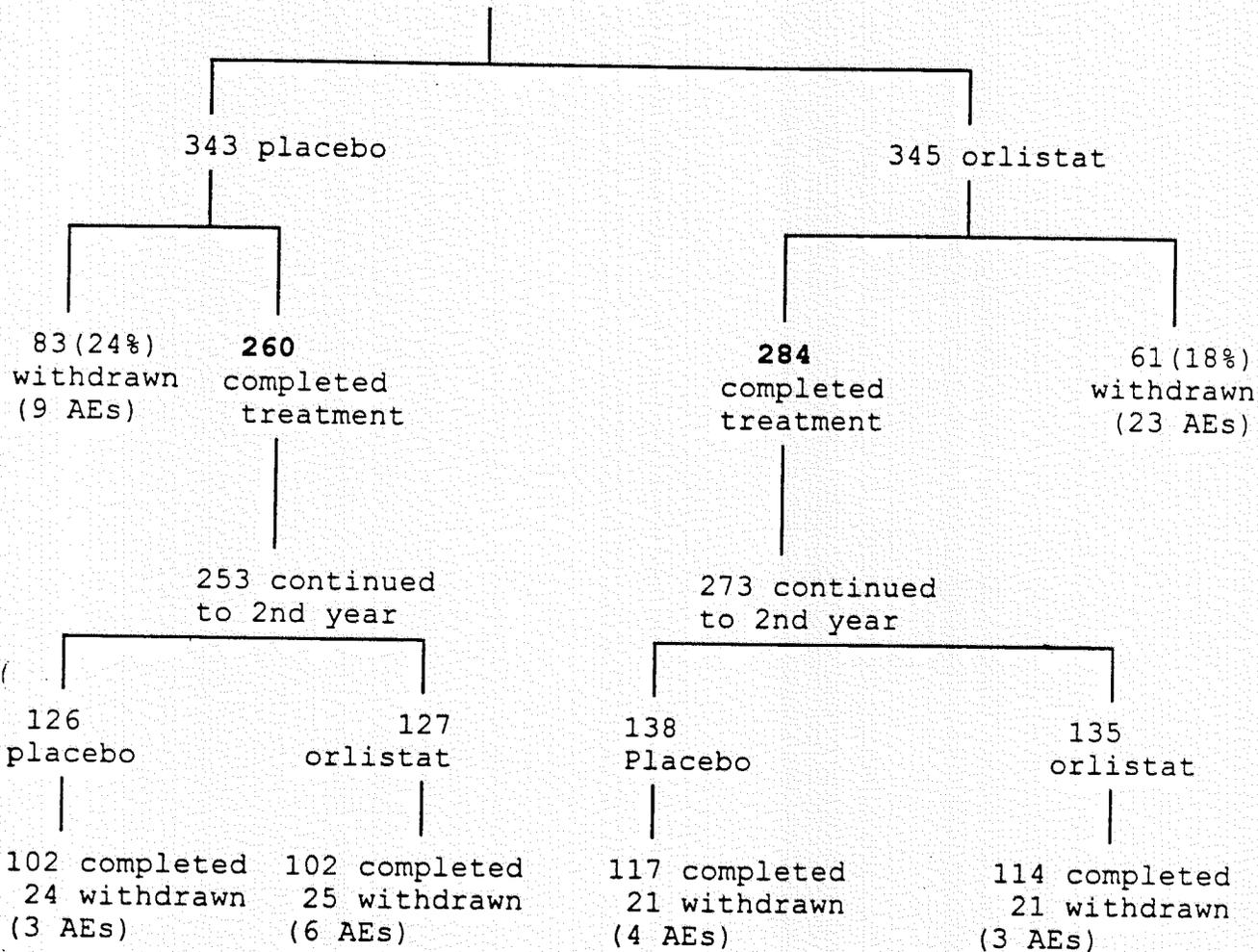
Study Population

The study enrolled patients who were 18 years or older with a body mass index (BMI) between 30 and 43 kg/m². A total of 743 patients entered a four-week placebo run-in period. At baseline, 688 patients who completed the run-in period were grouped into 2 strata based on the weight loss during the run-in period (Stratum 1 ≤ 2.0 kg & Stratum 2 > 2.0 kg) and then randomized to either the orlistat 120 mg tid (345) or placebo tid (343) treatment group for 52 weeks. The 120 mg tid dose was compared to placebo for long-term weight control during the 2-year study period.

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The disposition of patients is as follows:

688 randomized



In the intent-to-treat (or safety) population, there were 683 patients. Of these, 83% (567/683) were female and 99% were Caucasian. At the entry (screening) of the study, patients were on the average 44.8 ± 11.0 years old (range, 18-77) with a weight of 99.4 ± 14.6 kg (range, 61.0-148.6) and a BMI of 36.1 ± 3.8 kg/m² (range, 28.3-47.2).

During the first year, 24% (83/343) of the placebo treated and 18% (61/345) of the orlistat treated patients withdrew from the study. For placebo, the main reason was; did not cooperate (7.3%, 25/343). For orlistat, the main reason for withdrawal was adverse events (6.7%, 23/345) which when compared to the 2.7% placebo rate was statistically significant.

The BMI at inclusion for women and men was $30 \leq \text{BMI} \leq 43$. The BMI range of the safety population at baseline was from 28.3 to 47.2.

Primary Analysis

An analysis of variance with treatment, center, stratum and all 3 interaction terms in the model was performed on the outcomes of change of weight (kg) from

baseline, percent change of weight from baseline and BMI (kg/m²) change from baseline at year 1 for the ITT population with the last observations carried forward. The p-values were statistically significant (p=0.0001) between orlistat and placebo. The interactions were not significant (p>0.2). The least square mean differences of the two treatment groups by stratum are displayed in Table 1.

Table 1. Mean Weight at Baseline and LSM at Year 1 by Stratum

	Stratum 1 n Baseline	Stratum 2 n Baseline	Overall n Baseline
Orlistat	125 94.5 Kg	218 97.3 Kg	343 96.3 Kg
Placebo	122 96.2 Kg	218 97.2 Kg	340 96.8 Kg

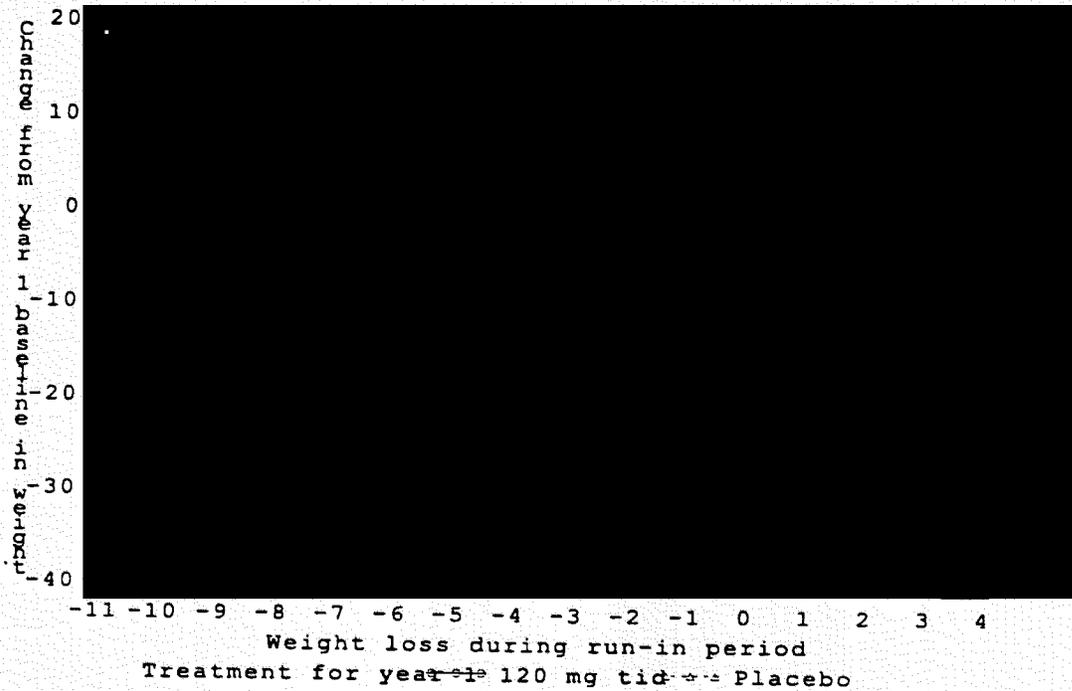
	Stratum	Orlistat	Placebo	Difference from Placebo (95% C.I.)
Kg	1	-4.2	-1.0	-3.3(-4.7, -1.8)
	2	-7.2	-2.7	-4.5(-5.6, -3.4)
	Overall	-5.7	-1.9	-3.9(-4.7, -3.0)
%	1	-4.3%	-1.0%	-3.3%(-4.8%, -1.8%)
	2	-7.5%	-2.9%	-4.5%(-5.7%, -3.4%)
	Overall	-5.9%	-2.0%	-3.9%(-4.8%, -3.0%)
BMI	1	-1.5	-0.4	-1.2(-1.7, -0.6)
	2	-2.6	-1.0	-1.6(-2.0, -1.2)
	Overall	-2.1	-0.7	-1.4(-1.7, -1.1)

When analysis of covariance using run-in weight loss as a covariate was utilized, the treatment-by-covariate interaction was significant (p=0.006). Figure 1 displays the weight loss at year one by the placebo lead-in weight loss.

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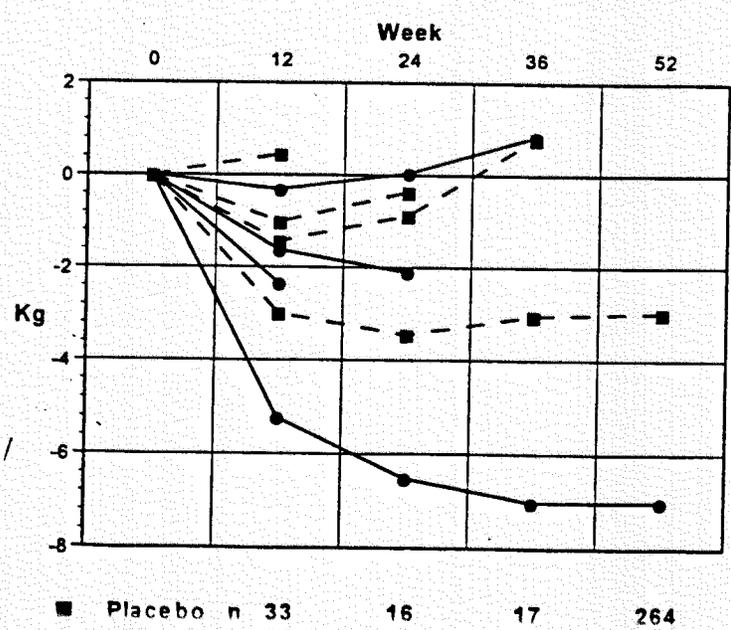
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Figure 1. The Weight Change at Year One by Lead-in Weight Change



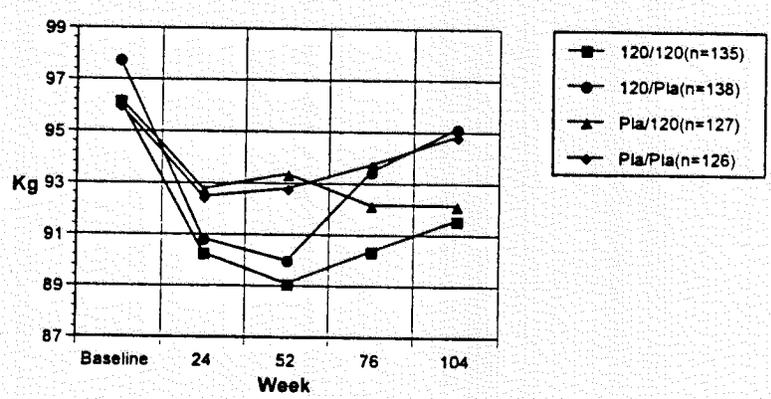
Patients were grouped into cohorts based on the time point of their last observation during year one. Figure 2 displays the mean weight of the four cohorts of patients by treatment group.

Fig 2. SB14119C-Mean Change from Baseline



After the one year treatment of 120 mg tid orlistat or placebo, patients were re-randomized into 120 mg tid orlistat or placebo. The following graph displays the weights of the four treatment groups of 120 mg/120 mg orlistat, 120 mg orlistat/placebo, placebo/120 mg orlistat, and placebo/placebo from baseline to weeks 24, 52, 76 and 104.

Fig. 3. Study 14119C-Weight from Baseline to 2-year, LOCF



120/120(n=135)	96.2	90.3	89.1	90.4	91.6
120/Pla(n=138)	97.8	90.8	90.0	93.5	95.2
Pla/120(n=127)	96.3	92.8	93.4	92.2	92.2
Pla/Pla(n=126)	96.0	92.5	92.8	93.7	94.8

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Mean change of weight from baseline to week 104 and from week 52 baseline to week 104 for the four treatment groups were as follows:

Table 2. Mean Change from Baseline to Year 2 and Year One Baseline to Year 2

Treatment group (yr1/yr2)	N	Mean Baseline (Wk0)	Mean Change (Wk104-Wk0)	Year 1 Baseline (Wk52)	Mean Change (Wk104-Wk52)
120mg/120mg	133	96.22	-4.64	89.05	2.53
120mg/Placebo	138	97.77	-2.62	90.04	5.11
Placebo/120mg	124	96.23	-4.07	93.23	-1.06
Placebo/Placebo	123	95.74	-0.90	92.55	2.29

The prevention of weight regain was assessed using the second year data for patients treated with orlistat or placebo in year one (weight maintenance).

Diet was adjusted to eucaloric to enable the patients to maintain their weight. The sponsor indicated that this increase may have been too great.

The analysis of variance results are in Table 3 for those patients who took orlistat in year one and for those patients who took placebo in year one.

Table 3. LSM Change in Weight (kg) from the Second Year Baseline to the End of Week 104: Patients Who Took Orlistat or Placebo in Year One

Treatment Group	LSM Change from 2nd Year Baseline	LSM difference from Placebo (C.I.)	P-value
Orlistat/Placebo	4.95 n=138		
Orlistat/Orlistat	2.56 n=133	-2.39 (-3.49, -1.29)	<0.0005
Placebo/Placebo	2.24 n=123		
Placebo/Orlistat	-1.33 n=124	-3.57 (-4.7, -2.45)	<0.0005

The long-term weight control analysis is as follows:

Table 4. LSM Weight Change (kg) from Baseline to the End of Week 104: Two Years of the Same Treatment

Treatment Group	LSM Change from Baseline	LSM difference from Placebo (C.I.)	P-value
Placebo/Placebo	-0.72 n=123		
Orlistat/Orlistat	-4.57 n=133	-3.85 (-5.60, -2.10)	0.000

Responder Analysis:

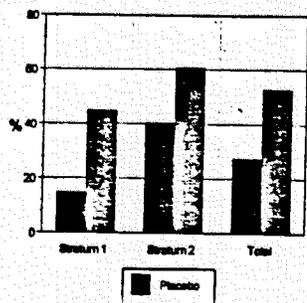
At year one, the percentage of patients who lost 5% or more from baseline weight was compared within each stratum of weight loss during the placebo run-in phase (≤ 2 Kg, stratum 1, > 2 Kg, stratum 2). The analyses on the ITT population and the sponsor's completers population are as follows:

Table 5. Percentage of Patients who lost $\geq 5\%$ and $\geq 10\%$ from Baseline by Stratum - ITT Population

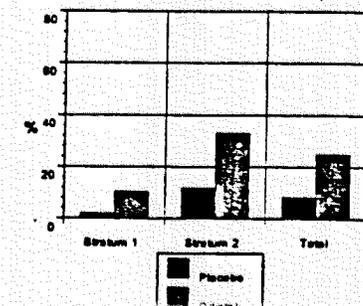
	Placebo 5%	Orlistat 5%	Placebo 10%	Orlistat 10%
Stratum 1 (lead-in ≤ 2 Kg)	14.8% (18/122)	44.8% (56/125)	2.0% (2/122)	10.4% (13/125)
Stratum 2 (lead-in > 2 Kg)	40.4% (75/218)	60.6% (132/218)	11.9% (26/218)	33.0% (72/218)
Total	27.4% (93/340)	54.8% (188/343)	8.2% (28/340)	24.8% (85/343)

Figure 4. Percentage of Patients with $\geq 5\%$ and $\geq 10\%$ Weight Loss

BM14119C- Proportion of 5% Responder, ITT



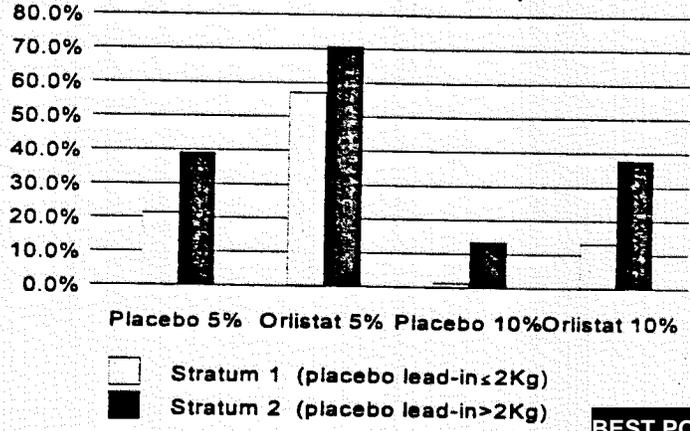
BM14119C- Proportion of 10% Responder, ITT



For the "completers" the percentages are displayed in Table 6 and figure 5.
 Table 6. Percentage of Patients who lost $\geq 5\%$ and $\geq 10\%$ from Baseline
 by Stratum - Completers Population

	Placebo 5%	Orlistat 5%	Placebo 10%	Orlistat 10%
Stratum 1 (placebo lead-in \leq 2Kg)	21.3% (17/80)	57.1% (52/91)	1.3% (1/30)	13.2% (12/91)
Stratum 2 (placebo lead-in $>$ 2Kg)	39.1% (66/169)	70.6% (127/180)	13.6% (23/169)	37.8% (68/180)
Overall	33.3% (83/249)	66.1% (179/271)	9.6% (24/249)	29.5% (80/271)

**Fig 5. Percentages of Responders (5% or 10%)
 Study BM14119C - Completers Population**



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In both populations the Cochran-Mantel-Haenszel X^2 were highly significant (P=0.001) and the Breslow-Day test for homogeneity of the odds ratios was not significant (p $>$ 0.1) which can be interpreted as the two strata are homogeneous.

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The lipid profile after one year of treatment is as follows:

Table 7. LSM Change in Lipids at Week 52, ITT

mmol/L	n	Baseline	LSM %Change from Baseline (Difference from Placebo)	P-value
Total Cholesterol				
Placebo	336	5.33	4.91	
Orlistat	339	5.43	-0.36 (-5.26)	<0.0005
LDL				
Placebo	337	3.51	5.18	
Orlistat	339	3.58	-1.15 (-6.33)	<0.0005
HDL				
Placebo	337	1.15	10.97	
Orlistat	339	1.16	9.82 (-1.15)	0.379
Triglycerides				
Placebo	337	1.56	4.99	
Orlistat	339	1.58	4.02 (-0.97)	0.745

Safety

Safety parameters included the adverse experiences, laboratory tests (including fat-soluble vitamin levels A, D and E and β -carotene), vital signs, electrocardiograms and renal and gallbladder ultrasound. The differences in the percentage of patients reporting adverse events between orlistat and placebo were significant in the gastrointestinal system (p=0.001), resistance mechanism system (0.019), respiratory system (0.012), and urinary system (0.086).

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The percentages of the incidence of these adverse events at year 1 were as follows:

Table 8. Summary of Adverse Events at End of Week 52

Adverse Event (p.192 vol. 179)	Placebo n=340		Orlistat 120 mg n=343	
	No.	%	No.	%
Gastrointestinal system	177	52.1%	269	78.4%
Fatty/Oily stool	17	5.0%	106	30.9%
Increased defecation	25	7.4%	70	20.4%
Oily spotting	4	1.2%	60	17.5%
Resistance mechanism disorder	122	35.9%	154	44.9%
Influenza syndrome	100	29.4%	122	35.6%
Respiratory system disorders	75	22.1%	105	30.6%
Bronchitis	15	4.4%	22	6.4%
Pharyngitis	12	3.5%	21	6.1%
Upper respiratory tract infection	10	2.9%	17	5.0%
Rhinitis	5	1.5%	16	4.7%
Urinary system disorders	16	4.7%	28	8.2%
Urinary tract infection	8	2.4%	15	4.4%
cystitis	2	0.6%	9	2.6%

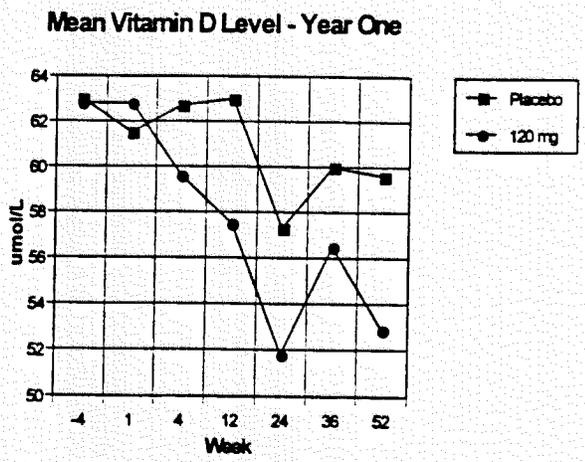
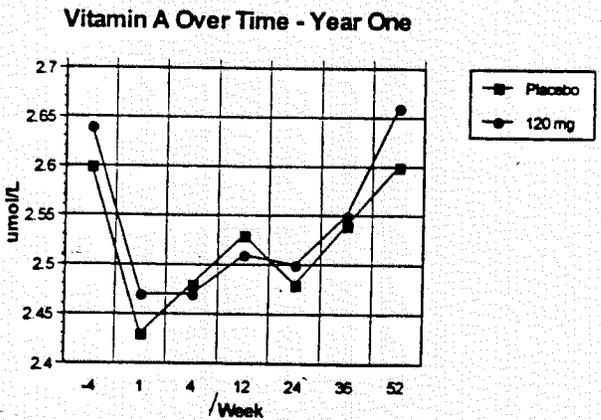
Vitamins

Vitamins A, D, and E, β -carotene, and vitamin K (assessed indirectly by prothrombin times) were evaluated in this study. Patients were instructed to increase their vitamin intake if two values were below the reference level. A total of 33 patients required vitamins during the study.

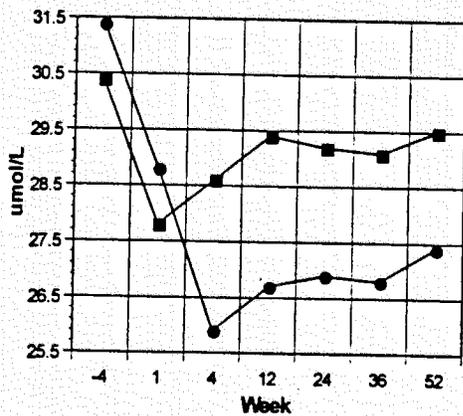
The observed data of the vitamin levels in safety population at year one is displayed in the following figure.

Figure 6. Serum Vitamin Levels at End of Week 52

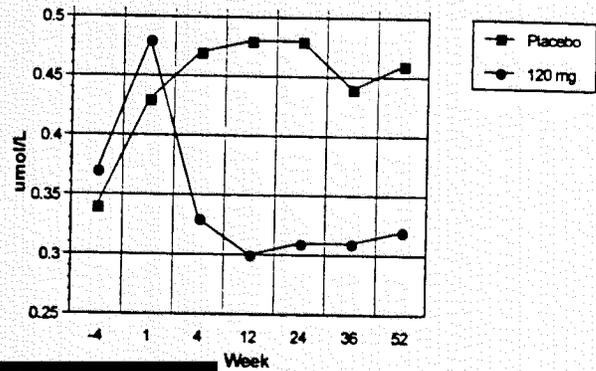
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Mean Vitamin E Level - Year One



Mean Beta Carotene Level - Year One



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The LSM change in vitamin levels at end of week 52 is displayed in Table 9.

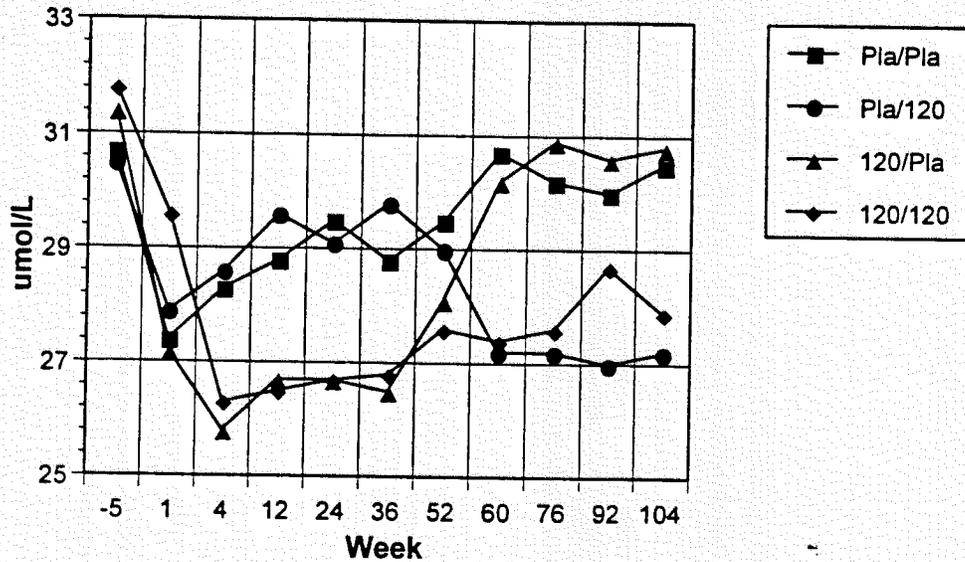
Table 9. LSM Change in Vitamin Levels at Week 52, ITT of the Same Treatment

	n	Baseline	LSM Change from Baseline (Difference from Placebo)	P-value
Vitamin A				
Placebo	336	2.43	0.16	
Orlistat	339	2.47	0.16 (0.00)	0.917
Vitamin D				
Placebo	336	61.54	-1.96	
Orlistat	339	62.99	-10.70 (-8.73)	0.000
Vitamin E				
Placebo	336	27.79	1.28	
Orlistat	339	28.83	-1.27 (-2.55)	0.000
Beta Carotene				
Placebo	336	0.42	-0.00	
Orlistat	339	0.48	-0.14 (-0.14)	0.000

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The vitamin E over time for the four treatment groups is displayed in the following figure.

Fig. 7. Mean Value of Vitamin E over Time



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Subgroup Analysis:

The subgroups in gender, age, and race were examined.

The analysis stratified by gender showed significant treatment effect ($p=0.0001$) without significant treatment by gender interaction ($p=0.84$). The least squares mean of change from baseline to year 1 by treatment and gender is displayed in Table 10.

Table 10. LSM Change from Baseline by Treatment and Gender

Subgroup	Placebo		120 mg		Difference from Placebo		
	n	Baseline LSM Change	n	Baseline LSM Change			
Gender							
Male	57	107.1	-2.40	59	107.2	-6.62	-4.22
Female	283	94.8	-2.17	284	94.0	-6.10	-3.94

There was no treatment-by-age interaction ($p=0.43$). Ninety-nine percent of patients are Caucasian.

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Conclusions of Study BM14119C

The year one ITT population with a last observation carried forward analysis of variance showed that the orlistat 120 mg tid group had a mean weight loss of 5.7 Kg compared to a 1.9 Kg weight loss for the placebo group. The mean difference between groups is 3.9 Kg (C.I. 3, 4.7). Similarly, the percent weight loss had a difference of 3.9% (C.I. 3.0%, 4.8%). The BMI loss is 2.1 Kg/m² for the orlistat 120 mg group and 0.7 for the placebo group. The difference in BMI loss is 1.4 (C.I. 1.1, 1.7). For the responder analysis of percentage of patients who lost 5% or more from baseline, there were ~27% (93/340) of the placebo patients and ~55% (188/343) of the orlistat patients who lost 5% or more. When response was defined as 10% or more weight loss, the percentages in the orlistat and placebo groups were ~25% (85/343) and ~8% (28/340), respectively. The results are summarized as follows:

	Orlistat	Placebo	Difference(CI)	p-value
Weight Loss (Kg)	5.7	1.9	3.9(3.0, 4.7)	0.000
Percent Weight Loss	5.9%	2.0%	3.9(3.0, 4.8)	0.000
BMI Loss (Kg/m ²)	2.1	0.7	1.4(1.1, 1.7)	0.000
Responder	54.8%(188/343)	27.4%(93/340)	27.5%(20%, 35%)	0.002
10% Responder	24.8%(85/343)	8.2%(28/340)	16.6%(11%, 22%)	0.002

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