DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF BIOSTATISTICS

Statistical Review and Evaluation

CLINICAL STUDIES

NDA:	20766/SE5-018
Name of drug:	Xenical® (orlistat) capsules
Applicant:	Hoffmann-La Roche, Inc.
Indication:	Weight management of obese pediatric patients
Documents reviewed:	Location of the sNDA in EDR (electronic documents room): \\CDSESUB1\N20766\S_018 and amendments dated 7-31-03, 8-19-03, and 8-26-03.
Project manager:	Oluchi Elekwachi, Pharm.D. (HFD-510)
Clinical reviewer:	Theresa Kehoe, M.D. (HFD-510)
Dates:	Submitted 6/23/03
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Keywords: NDA review, clinical studies, pediatric exclusivity

Contents:

1 EXECUTIVE SUMMARY OF STATISTICAL FINDINGS

1.1 CONCLUSIONS AND RECOMMENDATIONS

Study NM16189 has provided statistical evidence in favor of orlistat with respect to the primary efficacy variable change from baseline to the end of the study for BMI.

1.2 OVERVIEW OF CLINICAL PROGRAM AND STUDIES REVIEWED

The applicant has submitted this Prior-Approval (i.e., already approved for adults) Efficacy Supplement for pediatric exclusivity. In support of this, it has provided results from the following clinical trial:

Protocol No.	Location of Synopsis (Module 2) Location of Report (Module 5)	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage regimen; Route of Admin.	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
5.3.5 Efficacy and Safety Studies								
NM16189		1. Efficacy and safety 2. Changes in obesity related risk factors	Multicenter, randomized, double-blind, placebo-controlled, parallel study	120 mg capsules oral tid	539	Obese adolescent patients	52 weeks of treatment	Complete Full

Note: tid = three times daily.

1.3 PRINCIPAL FINDINGS

Study NM16189 has provided statistical evidence in favor of orlistat with respect to the primary efficacy variable change from baseline to the end of the study for BMI.

Some discussion on subgroup results is at the end of the Section 2.3.3.1.5 Efficacy Results (Sponsor's Analyses).

2 STATISTICAL REVIEW AND EVALUATION OF EVIDENCE

2.1 INTRODUCTION AND BACKGROUND

Specific Indication: 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 (e.g., hypertension, diabetes, dyslipidemia).

Note: New Drug Application is abbreviated by NDA. Except where specifically mentioned otherwise (as notes, reviewer's comments, conclusions, etc.), all other results and statements in this document are the sponsor's. The reviewer's silence does not imply his agreement with the sponsor's statements. Whatever the reviewer has verified and believes to be true is specifically stated so. In particular, the material in Sections 2.1 to 2.3.2 (indented) is almost verbatim from the sponsor's submission. Elsewhere, sponsor's statements may be slightly changed for brevity or for clarity.

Parts of the synopsis provided by the sponsor follow.

TITLE OF THE STUDY / REPORT No. / DATE OF REPORT - A double-blind, placebo- controlled, 54- week study of the efficacy and safety of Xenical (orlistat) in the weight management of obese pediatric patients. Research report 1011426/ June 6, 2003.

INVESTIGATORS / CENTERS AND COUNTRIES - This was a multicenter trial in the US and Canada. A complete list of investigators is provided in the Study Documentation section of this report.

PERIOD OF TRIAL - August 8, 2000 to September 12, 2002

CLINICAL PHASE - IV

OBJECTIVES - The primary objectives of this study were to characterize the efficacy of orlistat as an adjunct to diet in the treatment of obese pediatric patients and to characterize the safety profile of orlistat in obese pediatric patients, using the following endpoints: gastrointestinal tolerability; linear growth and Tanner pubertal stage assessment; bone mineral content and body composition; fat-soluble vitamins, beta-carotene, PTH, and serum calcium levels; gall bladder and renal ultrasound.

The secondary objective of this study was to characterize changes in obesity related risk factors including total cholesterol, LDL cholesterol, HDL cholesterol, LDL/ HDL ratio, blood pressure, triglycerides, waist circumference, and glucose and insulin responses to an oral glucose challenge.

STUDY DESIGN - This was a multicenter, randomized, double-blind, placebo-controlled, parallel study of obese adolescents. Following a 2-week placebo lead-in period, patients were randomized to receive either orlistat or placebo in a 2: 1 ratio as an adjunct to a hypocaloric diet for 52 weeks. All patients received nutritional guidance, behavioral modification, and exercise counseling throughout the study. All patients began multivitamin supplementation at the time of randomization.

NUMBER OF SUBJECTS - 539 randomized

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION - Males and females between 12 and 16 years of age with a body mass index (BMI) at the time of screening that was 2 units greater than the US weighted mean for the 95th percentile based on age and gender were eligible for study entry.

DOSE / ROUTE / REGIMEN / DURATION - 120 mg/oral/tid/52 weeks

CRITERIA FOR EFFICACY EVALUATION - The primary efficacy parameter was change in BMI from baseline to the end of the study. The secondary efficacy parameters were change in body weight, total cholesterol, LDL cholesterol, HDL cholesterol, LDL/HDL ratio, triglycerides, diastolic and systolic blood pressure, waist circumference, and glucose and insulin responses to an oral glucose challenge. In addition, hip circumference and categorical changes in BMI and body weight were analyzed for the report.

STATISTICAL METHODS - Efficacy was analyzed for all patients who had baseline efficacy assessments and at least one post-baseline efficacy measurement (ITT population). Primary and secondary efficacy endpoints were also analyzed for all patients who completed a final visit at week 52 (Completers population). All efficacy endpoints were derived using the last-observation-carried-forward (LOCF) data set. Change from baseline to week 52 in BMI was analyzed using an analysis of covariance model (ANCOVA) that included change from baseline value as the response, and treatment, center, and treatment-by-center, and baseline stratification terms.

METHODOLOGY: Patients meeting the inclusion criteria were entered into the study and, after a 2-week placebo lead-in period, were randomized to receive either orlistat or placebo in a 2:1 ratio. Patients were instructed to take their study medication 3 times a day with meals and a multivitamin once a day 2 hours after a meal or at bedtime. All patients were maintained on a nutritionally balanced

hypopcaloric diet and provided with behavioral modification and exercise counseling.

EFFICACY RESULTS: Least squares mean (LSM) difference from placebo for the orlistat treatment group for BMI was -0.86 kg/m^2 at week 52. This difference between treatment groups was statistically significant (p= 0.001). The LSM difference from placebo for the orlistat treatment group for body weight was -2.61 kg at week 52 and this was also statistically significant (p= 0.001). Overall, 26.5% of orlistat-treated patients and 15.7% of placebo-treated patients had a 5% reduction of their baseline BMI and 13. 3% of orlistat-treated patients and 4.5% of placebo-treated patients had a 10% reduction of their baseline BMI. The difference between treatment groups for both BMI categories was statistically significant (p = 0.005 and p = 0.002, respectively). Similarly, significantly more patients treated with orlistat had 5% (19%) and a 10% (9.5%) reduction in baseline body weight than patients treated with placebo (11.7% of patients had a 5% weight loss and 3.3% of patients had a 10% weight loss; p-value for difference from orlistat-treated patients is 0.032 and 0.011, respectively). Since very few patients in this study had abnormalities in serum lipid values at baseline, it was not unexpected that there were no significant improvements by the end of the study and no significant differences between orlistat-treated and placebo-treated patients. Similarly, most of the patients in this study had normal glucose tolerance at baseline and patients in both treatment groups had similar decreases in mean 0 minute and 120 minute glucose values by the end of the study. Patients in both treatment groups also had large decreases in baseline insulin levels at the end of the study and there was no statistical difference between the treatment groups. Patients treated with orlistat had statistically significant reductions in both waist circumference (p= 0.008) and hip circumference (p= 0.013) compared with patients treated with placebo.

CONCLUSIONS: Orlistat when administered at a dose of 120 mg tid for 52 weeks in conjunction with a reduced calorie diet, exercise, and behavioral modification results in significant improvement in weight management for obese adolescent patients. In addition, orlistat is generally well tolerated in this patient population.

DATA ANALYZED AND SOURCES

Data used by the reviewer are from the electronic document room: electronic documents room): \\ CDSESUB1\N20766\S_018\2003-08-19

STATISTICAL EVALUATION OF EVIDENCE ON EFFICACY

2.3.1 SPONSOR'S RESULTS AND CONCLUSIONS

Note: The sponsor's results and conclusions are following. To re-emphasize, Sections 2.1 to 2.3.2 are almost verbatim from the sponsor's submission. This reviewer's findings have been presented at appropriate places. His silence in Sections 2.1 to 2.3.2 does not imply agreement with the sponsor's statements (his comments, if any, are in italic as notes).

Note: Statistical review and analyses have been done by the reviewer only with respect to the primary efficacy evaluation: Change From Baseline in Body Mass Index (BMI).

Sponsor's Results (Body Mass Index)

The primary efficacy parameter for this study was change from baseline in BMI. During the first 12 weeks of treatment, patients in both groups had a decrease in BMI. During the rest of the treatment period, this decrease stabilized in the orlistat group, but increased to above baseline values in the placebo group (Figure below). By the end of the study, the BMI of patients treated with orlistat had decreased 0.62 kg/m^2 from baseline while the BMI of patients treated with placebo increased 0.17 kg/m^2 from baseline (the Table below the Figure).

Change of BMI (kg/m^2) from Baseline, LOCF Data, ITT Population:

	Within Treatment			Difference from Placebo				
	N	MEAN BASELINE VALUE	LS MEAN CHANGE FROM BASELINE	LS MEAN	SE	95% CI LOWER	95% CI UPPER	P-VALUE*
TREATMENT								
PLACEBO	178	35.49	0.31					
ORLISTAT	347	35.67	-0.55	-0.86	0.25	-1.34	-0.37	0.001

Figure for Mean Percent Change from Baseline BMI, LOFC, ITT:

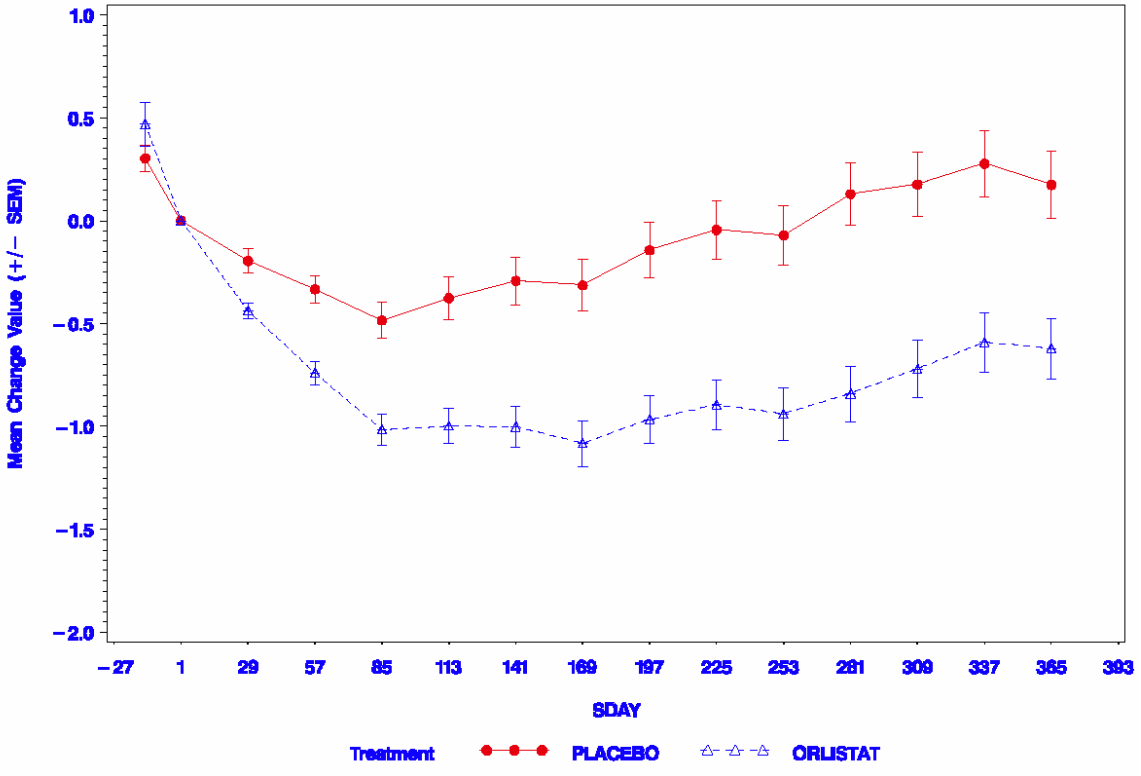


Table for Summary of BMI (kg/m^2), LOCF Data, ITT Population:

		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 -14	179	35.74	3.92	35.20	179	0.30	0.87	0.40	179	0.94	2.48	0.96
	BASELINE	180	35.47	4.07	34.60								
	DAY 29	155	35.35	4.10	34.30	155	-0.20	0.73	-0.10	155	-0.55	2.10	-0.31
	DAY 57	177	35.19	4.22	34.20	177	-0.33	0.89	-0.30	177	-0.97	2.50	-0.98
	DAY 85	178	35.00	4.31	34.20	178	-0.49	1.17	-0.35	178	-1.40	3.31	-1.04
	DAY 113	178	35.11	4.42	34.25	178	-0.38	1.38	-0.30	178	-1.11	3.91	-0.83
	DAY 141	178	35.19	4.41	34.40	178	-0.29	1.55	-0.10	178	-0.85	4.35	-0.28
	DAY 169	178	35.17	4.56	34.40	178	-0.31	1.69	-0.20	178	-0.94	4.76	-0.52
	DAY 197	178	35.34	4.64	34.45	178	-0.14	1.81	0.00	178	-0.47	5.09	0.00
	DAY 225	178	35.44	4.68	34.35	178	-0.05	1.91	0.05	178	-0.19	5.33	0.12
	DAY 253	178	35.42	4.76	34.35	178	-0.07	1.94	0.00	178	-0.28	5.43	0.00
	DAY 281	178	35.62	4.75	34.65	178	0.13	2.01	0.20	178	0.31	5.59	0.64
	DAY 309	178	35.66	4.82	34.45	178	0.18	2.09	0.40	178	0.42	5.79	1.03
	DAY 337	178	35.76	4.86	34.80	178	0.28	2.16	0.35	178	0.71	6.02	0.97
	DAY 365	178	35.66	4.84	34.45	178	0.17	2.18	0.30	178	0.43	6.06	0.88
ORLISTAT	DAY -14	348	36.14	4.22	35.40	348	0.47	2.00	0.40	348	1.47	6.38	1.05
	BASELINE	348	35.68	4.12	35.30								
	DAY 29	321	35.33	4.06	35.00	321	-0.44	0.70	-0.40	321	-1.22	1.99	-1.30
	DAY 57	344	34.94	4.11	34.75	344	-0.74	1.08	-0.70	344	-2.05	3.45	-1.94
	DAY 85	347	34.65	4.25	34.60	347	-1.02	1.38	-0.90	347	-2.85	4.23	-2.59
	DAY 113	347	34.67	4.35	34.60	347	-1.00	1.60	-0.80	347	-2.81	4.85	-2.28
	DAY 141	347	34.67	4.46	34.60	347	-1.00	1.88	-0.80	347	-2.81	5.58	-2.21
	DAY 169	347	34.59	4.55	34.60	347	-1.08	2.05	-0.70	347	-3.05	6.11	-2.21
	DAY 197	347	34.70	4.60	34.60	347	-0.97	2.18	-0.60	347	-2.72	6.46	-1.77
	DAY 225	347	34.77	4.66	34.70	347	-0.90	2.26	-0.60	347	-2.52	6.71	-1.65
	DAY 253	347	34.73	4.75	34.70	347	-0.94	2.39	-0.60	347	-2.66	7.09	-1.60
	DAY 281	347	34.83	4.78	34.80	347	-0.84	2.51	-0.40	347	-2.37	7.42	-1.23
	DAY 309	347	34.95	4.86	34.80	347	-0.72	2.62	-0.40	347	-2.03	7.69	-1.09
	DAY 337	347	35.08	4.90	34.90	347	-0.59	2.66	-0.30	347	-1.68	7.80	-0.88
	DAY 365	347	35.05	4.98	34.70	347	-0.62	2.73	-0.40	347	-1.78	7.99	-1.01

Sponsor's Conclusions

The results of this study indicate that orlistat, when administered at a dose of 120 mg tid for 52 weeks in conjunction with a reduced calorie diet, exercise, and behavioral modification results in a significant improvement in weight management for obese adolescent patients. In addition, orlistat is generally well tolerated in this patient population and no new findings were noted that were not previously identified in the adult population.

2.3.2 STATISTICAL METHODOLOGIES (Stated by the sponsor)

The following summary was based on the study protocol:

Since the body weight at randomization (the end of the lead-in period) and the amount of weight loss during the lead-in period are used to stratify patients within each center, an analysis of variance model will be performed, including the terms stratuml, center, stratum2, treatment, center*treatment, body weight at randomization and weight loss during the lead-in period as covariates. In the event of missing strata, an analysis of covariance will be used with covariates

Note: See Section 2.33.1.5 Efficacy Results (Sponsor's Analyses) for more details.

2.3.3 DETAILED REVIEW OF INDIVIDUAL STUDIES

Only one Phase III study, **Study MA-98-0108** (U.S.), as presented in Tabular form in Section 1.2 "Overview of Clinical Program and Studies Reviewed", has been conducted for this indication.

2.3.3.1 Study NM16189

2.3.3.1.1 Primary Objective

To characterize the efficacy of Xenical administered daily (120 mg TID with meals) as an adjunct to diet in the treatment of obese pediatric patients.

2.3.3.1.2 Disposition of Patients

A total of 539 patients from 32 centers were randomized. Of these 539 patients, 182 were randomized to the placebo group and 357 were randomized to the orlistat group. A similar percentage of patients in each treatment group (placebo, 64%; orlistat 65%) completed the study. A total of 11 patients were excluded from the ITT analysis population because they did not have a follow-up efficacy assessment (Table below). In addition, six patients were excluded from the safety population because they did not have a follow-up safety assessment.

A summary of the percentage of patients in each analysis population is presented in Table below:

	PLACEBO	ORLISTAT
No. of Patients Randomized	182	357
No. Included in ITT	180	348
No. Excluded from ITT	2	9
No. Included in SAFETY	181	352
No. Excluded from SAFETY	1	5

Summary of Reasons for Premature Withdrawal from Study:

Reason for Withdrawal	PLACEBO N = 181 No. (%)	ORLISTAT N = 352 No. (%)
Safety	3 (2)	12 (3)
Abnormality of Laboratory Test	0	0
Adverse Event(a)	3	12
Death	0	0
Nonsafety	61 (34)	108 (31)
Insufficient Therapeutic Response	1	3
Violation of Selection Criteria at Entry	1	1
Other Protocol Violation	3	2
Refused Treatment(b)	31	68
Failure to Return	23	28
Other	2	6
Total	64 (35)	120 (34)

(a)=Including intercurrent illness (b)=Including 'did not co-operate', 'withdrew consent'
Percentages are based on N. Percentages not calculated if N < 10.

"The Failure to Return" rate was much higher in the placebo group.

Figure for Percent of Patients Continuing in the Trial Over Time:

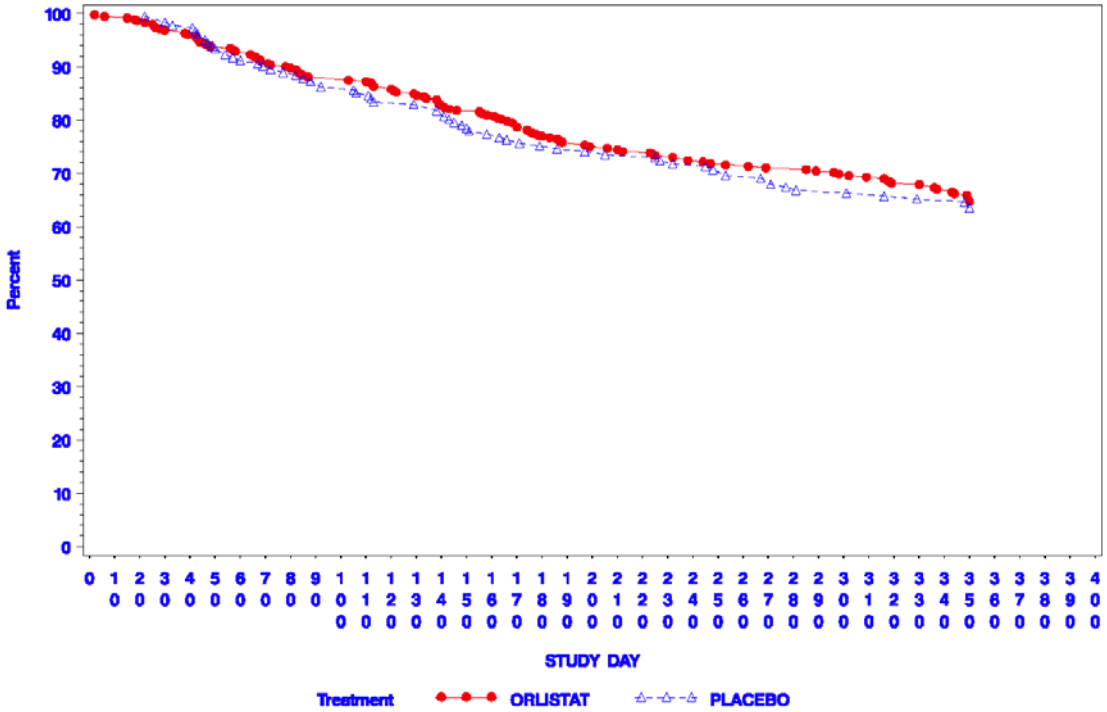
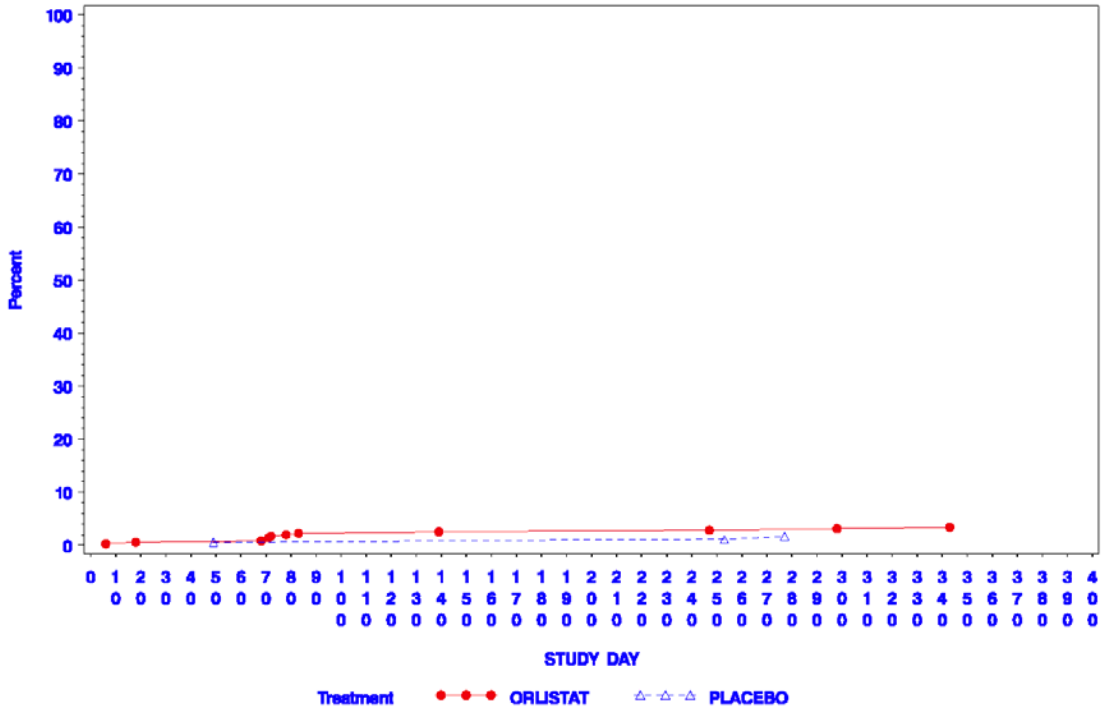


Figure for Percent of Patients Withdrawn from Trial Due to Adverse Events Over Time:



2.3.3.1.3 Demographic and Other Baseline Characteristics

Demographic characteristics were generally similar in the placebo and orlistat treatment groups for all analysis populations (Table below). Most of the patients were Caucasian and there were slightly more girls than boys enrolled in both treatment groups. Patients in both treatment groups were also assigned to a similar diet (2nd Table below).

The patients in the orlistat treatment group had a slightly higher mean body weight than patients in the placebo group. Randomization strata were based on baseline body weight and weight loss during the placebo lead-in period. Although this randomization plan successfully balanced the treatment groups regarding these parameters, overall a larger percentage of patients had a baseline body weight ≥80 kg and the mean number of patients in this body weight group was slightly higher in the orlistat treatment group than in the placebo group.

Although there was a slight difference between treatment groups in body weight, the mean BMI was similar in both groups at approximately 35 kg/m^2. The patients in this study were above the 98th percentile for BMI. These patients are similar to morbidly obese adults who are known to be the most resistant to treatment.

The patients in the orlistat treatment group had a slightly higher mean height and mean waist circumference than patients in the placebo group. Statistical analyses (submission dated August 26, 2003) showed that these and body weight were not significant predictors of response and, therefore, imbalances in them should not be of much concern.

Summary of Demographic Data, ITT Population:

PARAMETER	PLACEBO	ORLISTAT
SEX		
MALE	52 (28.7)	124 (35.2)
FEMALE	129 (71.3)	228 (64.8)
TOTAL	181 (100.0)	352 (100.0)
RACE		
CAUCASIAN	141 (77.9)	264 (75.0)
BLACK	25 (13.8)	66 (18.8)
OTHER	15 (8.3)	22 (6.3)
TOTAL	181 (100.0)	352 (100.0)
BW PRELOSS		
BW PRELOSS <1%	95 (52.5)	166 (47.2)
BW PRELOSS >=1%	86 (47.5)	186 (52.8)
ALL	181 (100.0)	352 (100.0)
BL BW		
BL BW <80 kg	22 (12.2)	36 (10.2)
BL BW >=80 kg	159 (87.8)	316 (89.8)
ALL	181 (100.0)	352 (100.0)
AGE		
N	181	352
MEAN	13.50	13.61
SD	1.24	1.35
MEDIAN	13.00	13.00
MIN,MAX	11.00,16.00	11.00,16.00
95% C.I.	13.32,13.68	13.47,13.76
WEIGHT (kg)		
N	181	352
MEAN	95.11	97.71
SD	14.18	14.96
MEDIAN	93.90	96.85
MIN,MAX	60.60,134.10	58.10,133.00
95% C.I.	93.03,97.19	96.14,99.28
HEIGHT (cm)		
N	181	352
MEAN	163.65	165.16
SD	7.74	8.43
MEDIAN	163.00	165.00
MIN,MAX	143.00,190.00	141.00,191.00
95% C.I.	162.51,164.78	164.28,166.05
BMI (kg/m^2)		
N	181	352
MEAN	35.43	35.72
SD	4.07	4.17
MEDIAN	34.60	35.20
MIN,MAX	27.30,45.40	24.00,46.60
95% C.I.	34.83,36.03	35.28,36.16

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PARAMETER	PLACEBO	ORLISTAT
HEIGHT PERCENTILE*		
N	180	348
MEAN	64.04	66.33
SD	26.29	27.14
MEDIAN	70.28	72.66
MIN,MAX	1.56,99.99	1.55,99.99
95% C.I.	60.17,67.90	63.47,69.19
WEIGHT PERCENTILE*		
N	180	348
MEAN	98.97	99.08
SD	1.21	1.13
MEDIAN	99.31	99.46
MIN,MAX	91.82,99.99	92.29,99.99
95% C.I.	98.79,99.15	98.96,99.20
BMI PERCENTILE*		
N	180	348
MEAN	98.86	98.89
SD	0.72	1.02
MEDIAN	99.07	99.10
MIN,MAX	96.41,99.74	84.53,99.80
95% C.I.	98.76,98.97	98.78,98.99

Summary and Confidence Intervals for Study Caloric Intake Assignment, ITT Population:

Parameter	Treatment Group	Value at Screening Visit					Difference from Placebo 95% Confidence Interval	
		N	Mean	SD	Median	Min	Max	Lower Limit	Upper Limit
Calories from Carbohydrates									
	PLACEBO	180	770	122	800	250	990		
	ORLISTAT	346	793	92	800	260	990	-6.6	28.7
Calories from Fat									
	PLACEBO	180	464	49	450	280	700		
	ORLISTAT	346	470	55	480	280	900	-6.7	10.8
Calories from Protein									
	PLACEBO	180	316	92	300	210	900		
	ORLISTAT	346	314	67	320	180	900	-16.9	12.2
Total Daily Calories									
	PLACEBO	180	1549	145	1500	1200	1810		
	ORLISTAT	346	1577	148	1600	1200	1800	-10.5	32.3

Very few patients in this study had risk factors associated with obesity at baseline other than waist circumference and hyperinsulinemia, and very few patients had impaired glucose tolerance or were diabetic (Table 13 and Table 14 in the sNDA). Almost all of the girls in both the placebo and orlistat treatment groups had a baseline waist

circumference ≥84 cm. A higher percentage of boys in the orlistat treatment group (78%) compared with the placebo treatment group (71%) had a baseline waist circumference ≥102 cm. A slightly higher percentage of orlistat-treated patients (74%) compared with placebo-treated patients (69%) had hyperinsulinemia at baseline.

All of the patients in both treatment groups received concomitant medications during the study (page 180). Mild analgesics were the most frequently reported concomitant medication in both treatment groups with 51% of patients in the placebo group and 60% of patients in the orlistat group reporting taking these medications. This difference is mainly accounted for by the use of paracetamol (orlistat, 52%; placebo 44%). A slightly higher percentage of patients in the orlistat group (55%) reported taking anti-inflammatory agents than patients in the placebo group (49%), with the difference mainly accounted for by the use of ibuprofen (orlistat, 51%; placebo 45%). A patient listing of previous and concomitant medications is available upon request (Study Population Section, see page 1081).

2.3.3.1.4 Measurements of Treatment Compliance and Other Factors That Could Affect Response

Extent of Exposure to Trial Medication:

Overall, 65% of orlistat- treated patients and 63% of placebo- treated patients were treated for 52 weeks (Table below). The calculated compliance based on pill count was 73% in the orlistat treatment group and 72% in the placebo treatment group.

	PLACEBO N = 181 No. (%)	ORLISTAT N = 352 No. (%)
ORLISTAT		
Treatment Duration (days)		
1 - 42	1 (<1)	18 (5)
43 - 70	-	15 (4)
71 - 98	1 (<1)	12 (3)
99 - 140	-	18 (5)
141 - 196	-	26 (7)
197 - 252	-	16 (5)
253 - 316	-	19 (5)
317 - 420	-	228 (65)
Total Cumulative Dose (MG)		
Mean	16200.0	161751.5
SD	21382.91	79961.91
SEM	15120.00	4261.98
Median	16200.0	144720.0
Min	1080	1440
Max	31320	294480
n	2	352

PLACEBO

Treatment Duration (days)		
1 - 42	7 (4)	6 (2)
43 - 70	15 (8)	-
71 - 98	8 (4)	-
99 - 140	4 (2)	-
141 - 196	15 (8)	-
197 - 252	8 (4)	-
253 - 316	10 (6)	-
317 - 420	114 (63)	-

2.3.3.1.5 Efficacy Results (Sponsor's Analyses)

The protocol stated:

> The primary efficacy variable for this study is BMI. Throughout the study, the patient's body weight and height will be recorded at every visit to the clinic (Appendix 3).
>
> Because these adolescent patients may experience linear growth during the study, the actual body weight may remain the same while the BMI may change by the end of the study. Therefore, change from baseline in BMI will be presented.
>
> The primary efficacy parameter will be presented as absolute change and percent (%) change.
>
> Ho: The mean BMI change is the same between patients in both the placebo and Xenical treatment groups.
>
> Descriptive statistics will be provided for all changes in primary and secondary efficacy parameters (mean, median, standard error).
>
> Since the body weight at randomization (the end of the lead-in period) and the amount of weight loss during the lead-in period are used to stratify patients within each center, an analysis of variance model will be performed, including the terms stratuml, center, stratum2, treatment, center*treatment, body weight at randomization and weight loss during the lead-in period as covariates. In the event of missing strata, an analysis of covariance will be used with covariates weight loss during the lead-in period and baseline weight.
>
> For the analysis of primary efficacy, an intent-to-treat (ITT) population consisting of all randomized patients who have received at least one dose of study medication and have a follow-up visit for BMI will be used.

In addition to the last observation carried forward approach, a per-protocol analysis will be provided using patients who have completed the study and have had a measurement of the parameter of interest at week 52.

There was a Statistical Analysis Plan (SAP). However, its purpose is not clear, when it was even less detailed than the protocol. August 26, 2003 submission states that small modifications such as adjustment of time windows, etc. were made. SAP was finalized on Oct. 28, 2002, data base was closed on the same date, and data base was unblinded on Nov. 4, 2002.

A paragraph from the SAP reads, "The primary statistical analysis will use ANCOVA methods with change in BMI as the response variable. The model will be: (b) (4) One strata is based on whether or not a patient weighed 80 kgs, and the other was based on whether or not they lost 1 kg during the two week lead in. In the event of missing strata, baseline body weight, and pre-loss will be treated as quantitative covariates. To avoid estimability complications, centers with missing cells will be collapsed into one center."

§ Results: Primary Efficacy Parameter (Body Mass Index)

The primary efficacy parameter for this study was change from baseline in BMI. During the first 12 weeks of treatment, patients in both groups had a decrease in BMI. During the rest of the treatment period, this decrease stabilized in the orlistat group, but increased to above baseline values in the placebo group (Figure below). By the end of the study, the BMI of patients treated with orlistat had decreased 0.62 kg/m^2 from baseline while the BMI of patients treated with placebo increased 0.17 kg/m^2 from baseline (2nd Table below).

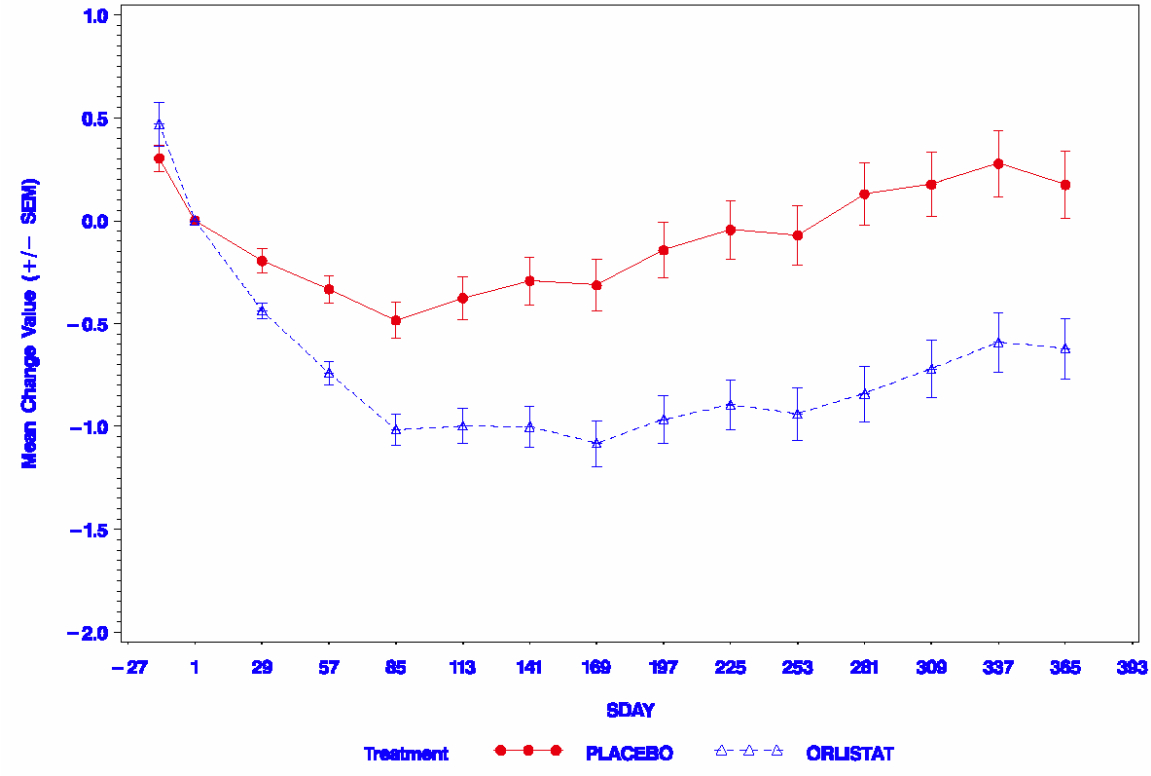
Table for Summary of BMI (kg/m^2), LOCF Data, ITT Population:

	Within Treatment			Difference from Placebo				
	N	MEAN BASELINE VALUE	LS MEAN CHANGE FROM BASELINE	LS MEAN	SE	95% CI LOWER	95% CI UPPER	P-VALUE*
TREATMENT								
PLACEBO	178	35.49	0.31					
ORLISTAT	347	35.67	-0.55	-0.86	0.25	-1.34	-0.37	0.001

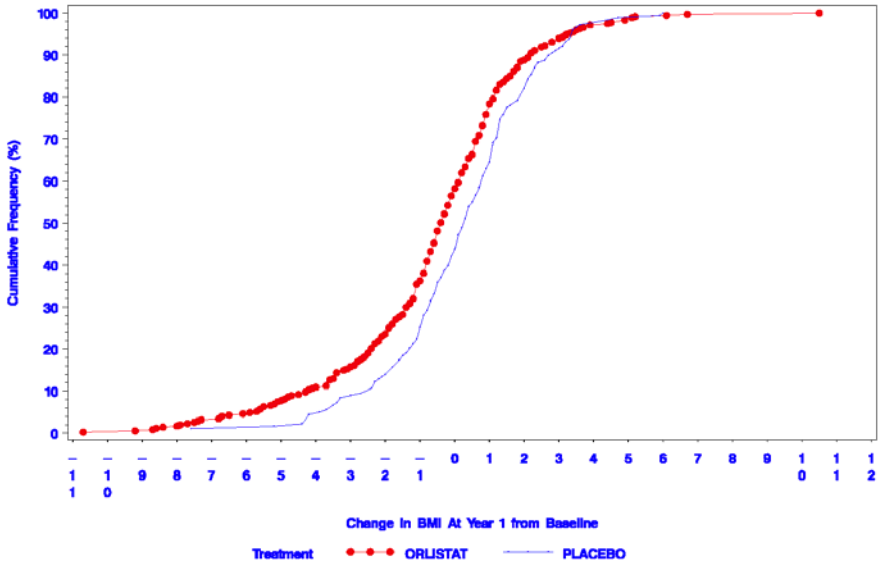
Change of BMI (kg/m^2) from Baseline, LOCF Data, ITT Population:

		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 -14	179	35.74	3.92	35.20	179	0.30	0.87	0.40	179	0.94	2.48	0.96
	BASELINE	180	35.47	4.07	34.60								
	DAY 29	155	35.35	4.10	34.30	155	-0.20	0.73	-0.10	155	-0.55	2.10	-0.31
	DAY 57	177	35.19	4.22	34.20	177	-0.33	0.89	-0.30	177	-0.97	2.50	-0.98
	DAY 85	178	35.00	4.31	34.20	178	-0.49	1.17	-0.35	178	-1.40	3.31	-1.04
	DAY 113	178	35.11	4.42	34.25	178	-0.38	1.38	-0.30	178	-1.11	3.91	-0.83
	DAY 141	178	35.19	4.41	34.40	178	-0.29	1.55	-0.10	178	-0.85	4.35	-0.28
	DAY 169	178	35.17	4.56	34.40	178	-0.31	1.69	-0.20	178	-0.94	4.76	-0.52
	DAY 197	178	35.34	4.64	34.45	178	-0.14	1.81	0.00	178	-0.47	5.09	0.00
	DAY 225	178	35.44	4.68	34.35	178	-0.05	1.91	0.05	178	-0.19	5.33	0.12
	DAY 253	178	35.42	4.76	34.35	178	-0.07	1.94	0.00	178	-0.28	5.43	0.00
	DAY 281	178	35.62	4.75	34.65	178	0.13	2.01	0.20	178	0.31	5.59	0.64
	DAY 309	178	35.66	4.82	34.45	178	0.18	2.09	0.40	178	0.42	5.79	1.03
	DAY 337	178	35.76	4.86	34.80	178	0.28	2.16	0.35	178	0.71	6.02	0.97
	DAY 365	178	35.66	4.84	34.45	178	0.17	2.18	0.30	178	0.43	6.06	0.88
ORLISTAT	DAY -14	348	36.14	4.22	35.40	348	0.47	2.00	0.40	348	1.47	6.38	1.05
	BASELINE	348	35.68	4.12	35.30								
	DAY 29	321	35.33	4.06	35.00	321	-0.44	0.70	-0.40	321	-1.22	1.99	-1.30
	DAY 57	344	34.94	4.11	34.75	344	-0.74	1.08	-0.70	344	-2.05	3.45	-1.94
	DAY 85	347	34.65	4.25	34.60	347	-1.02	1.38	-0.90	347	-2.85	4.23	-2.59
	DAY 113	347	34.67	4.35	34.60	347	-1.00	1.60	-0.80	347	-2.81	4.85	-2.28
	DAY 141	347	34.67	4.46	34.60	347	-1.00	1.88	-0.80	347	-2.81	5.58	-2.21
	DAY 169	347	34.59	4.55	34.60	347	-1.08	2.05	-0.70	347	-3.05	6.11	-2.21
	DAY 197	347	34.70	4.60	34.60	347	-0.97	2.18	-0.60	347	-2.72	6.46	-1.77
	DAY 225	347	34.77	4.66	34.70	347	-0.90	2.26	-0.60	347	-2.52	6.71	-1.65
	DAY 253	347	34.73	4.75	34.70	347	-0.94	2.39	-0.60	347	-2.66	7.09	-1.60
	DAY 281	347	34.83	4.78	34.80	347	-0.84	2.51	-0.40	347	-2.37	7.42	-1.23
	DAY 309	347	34.95	4.86	34.80	347	-0.72	2.62	-0.40	347	-2.03	7.69	-1.09
	DAY 337	347	35.08	4.90	34.90	347	-0.59	2.66	-0.30	347	-1.68	7.80	-0.88
	DAY 365	347	35.05	4.98	34.70	347	-0.62	2.73	-0.40	347	-1.78	7.99	-1.01

Figure for Mean Percent Change from Baseline BMI, LOFC, ITT:



Following is the cumulative distribution graph for BMI Change from Baseline, at Year 1, ITT, LOCF:

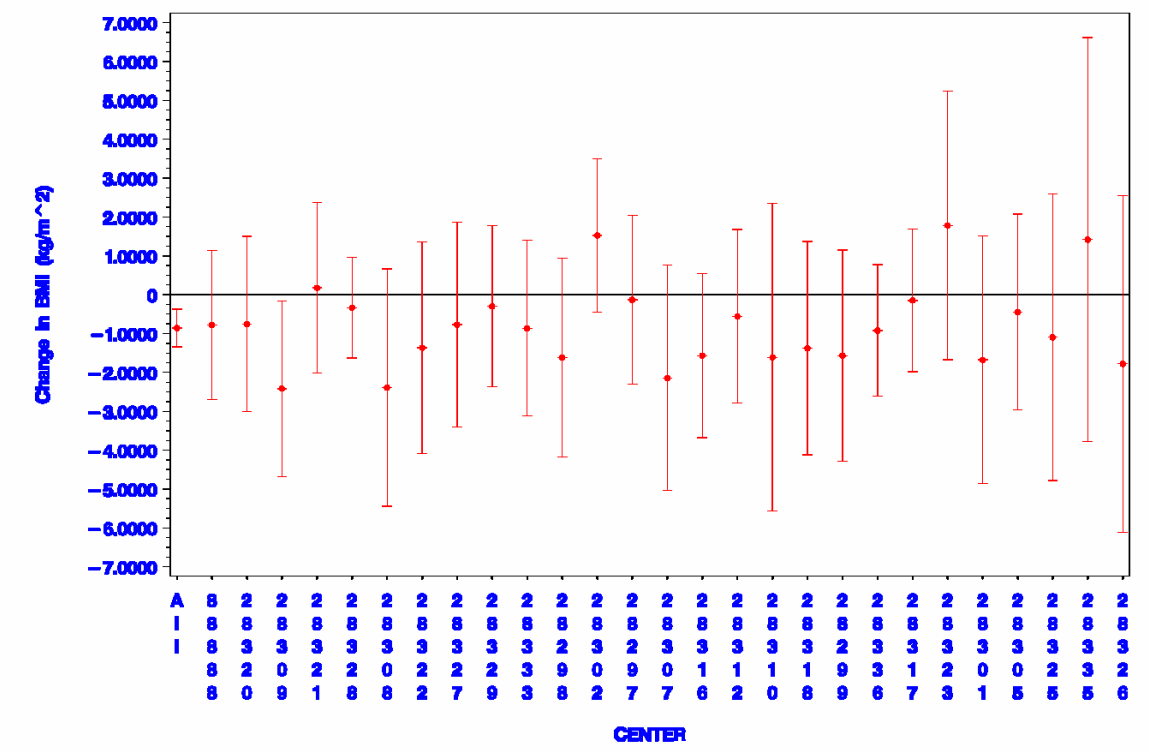


From this, percent of patients (y-axis value) with a value of Change from Baseline, smaller than or equal to a value on the x-axis can be read. For example, roughly 45% of the placebo patients had a ≤0 change from baseline compared with roughly 60% of patients in the orlistat group with that change. The median for placebo was .3 compared with -.4 for orlistat.

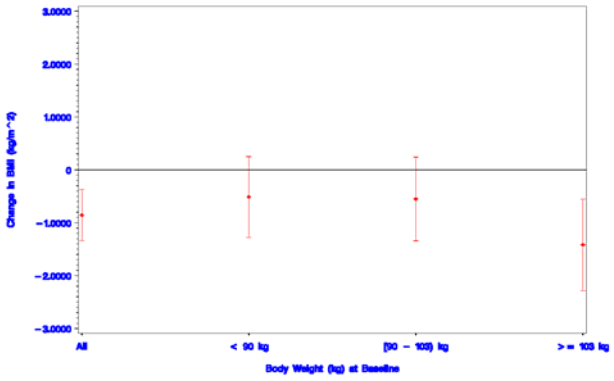
§ The sponsor stated (page 52), "Using SAS Proc Mixed, the results for BMI differed marginally by center (p = 0.0862) and significantly by treatment (p = 0.0006) (Table 16 in the sNDA). However, there was no center by treatment interaction indicating that treatment behaved the same across centers (interaction p = 0.8191). In addition, baseline body weight and body weight pre-loss did not significantly effect the change in BMI."

The corresponding 95% confidence intervals follow, where we see that in four out of 27 centers (one is formed by combining small centers) placebo did better than orlistat. However, this did not lead to a significant center by treatment interaction as mentioned before.

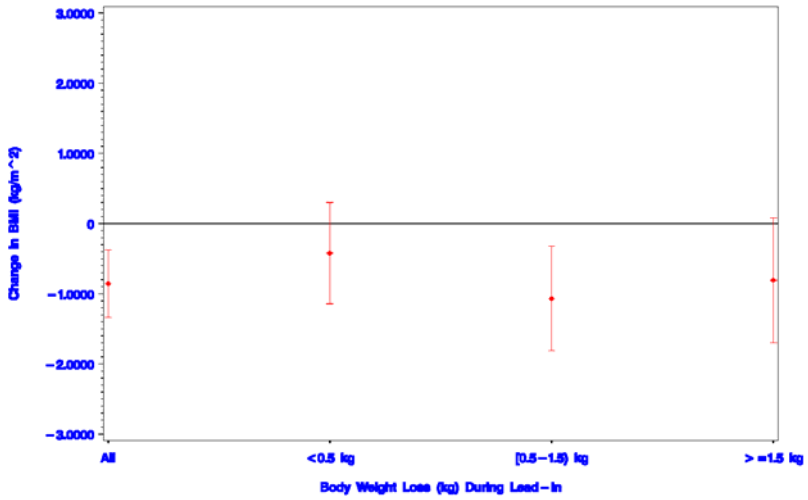
95% Confidence Intervals for difference from Placebo in LSMs by Center



95% Confidence Intervals for difference from Placebo in LSMs, by Body Weight at Baseline



95% Confidence Intervals for difference from Placebo in LSMs, by Body Weight Loss during Placebo Lead-In Period



§ The LSM change from baseline to end of treatment was –0.38 kg/m^2 for female patients treated with orlistat and 0.19 kg/m^2 for female patients treated with placebo and this difference was statistically significant (p = 0.048).

The LSM change from baseline to the end of treatment was -1.08 kg/m^2 for male patients treated with orlistat and 0.15 kg/m^2 for male patients treated with placebo (p = 0.004).

The Gender by treatment p-value was non-significant (.1965, 9-25-03 submission).

§ Black patients treated with orlistat had less of an increase in BMI and gained less weight by the end of the study than black patients treated with placebo, although the differences were not statistically significant (25 patients in placebo and 64 patients in orlistat, p=.207). The LSM change from baseline to the end of treatment for BMI was 0.10 kg/m^2 for black patients treated with orlistat and 0.74 kg/m^2 for black patients treated with placebo. For white patients the corresponding LSM change from baseline to the end of treatment for BMI was -0.72 kg/m^2 for patients treated with orlistat and 0.06 kg/m^2 for patients treated with placebo (138 patients in placebo and 261 patients in orlistat, p=.005).

The Race (3 categories, including "Other") by treatment interaction p-value was non-significant (.4089, 9-25-03 submission).

§ For boys and girls in the study who were prepubertal (Tanner stage 1 through 4) at screening, the LSM change from baseline to the end of the study for BMI was -0.76 kg/m^2 for patients treated with orlistat and 0.18 kg/m^2 for patients treated with placebo (p = 0.001; Table 42 of the sNDA). For Tanner stage 5 patients, the corresponding LSM change from baseline to the end of the study for BMI was -0.65 kg/m^2 for patients treated with orlistat and 1.35 kg/m^2 for patients treated with placebo (p=.173, 9-25-03 submission).

The tanner stage by treatment interaction p-value was non-significant (.4686, 9-25-03 submission).

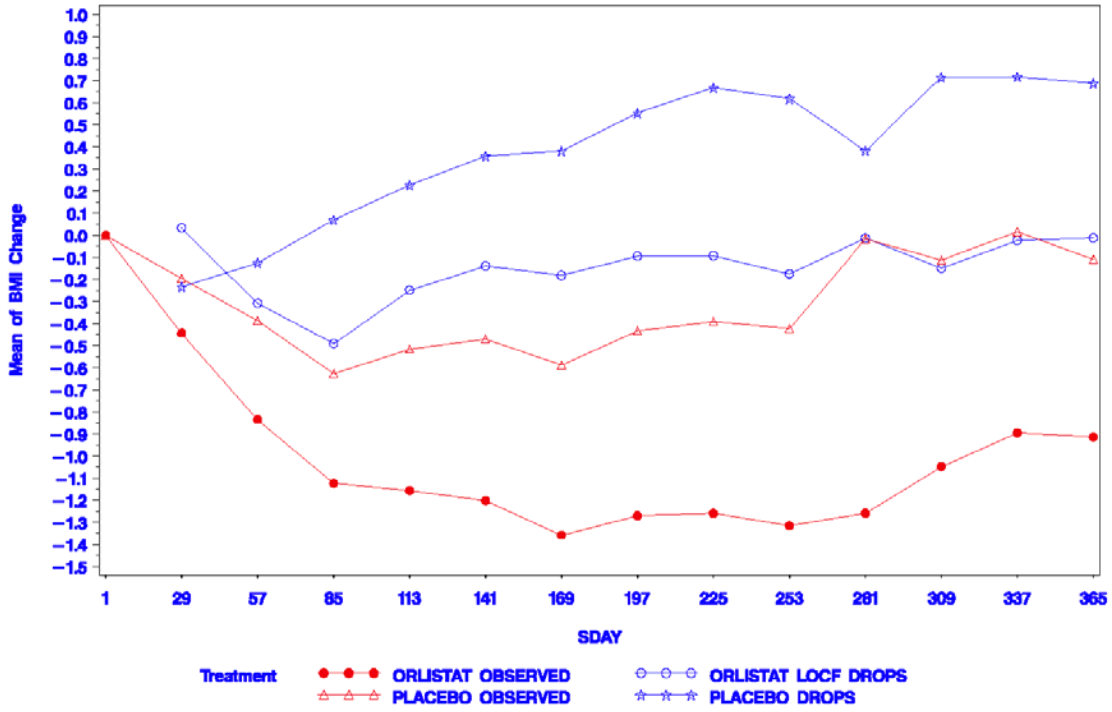
§ For patients aged ≤14 years, the LSM change from baseline to the end of the study for BMI was -0. 59 kg/m^2 for patients treated with orlistat and 0.24 kg/m^2 for patients treated with placebo (p = 0.001; Table 45 of the sNDA). For patients aged >14 years, the corresponding LSM change from baseline to the end of the study for BMI was -0.70 kg/m^2 for patients treated with orlistat and -0.03 kg/m^2 for patients treated with placebo (p= .211 9-25-03 submission).

The age by treatment interaction p-value was non-significant (.7912, 9-25-03 submission).

§ The patients in the orlistat treatment group had a slightly higher mean body weight, height, and waist circumference than patients in the placebo group. Statistical analyses (submission dated August 26, 2003) showed that these were not significant predictors of response and, therefore, marginal imbalances in them should not be of much concern. The sponsor stated, "Note that in every model …, the treatment group was found to be a significant predictor of change in BMI (p<. 001)."

The pre-specified covariates body weight at baseline and weight loss during the lead-in period did not have statistically significant interaction (interaction p-values are .30 and .98, respectively) with treatment.

§ BMI mean change from baseline for (1) observed cases and (2) those of unobserved cases, using the last available observations:



As expected, the adolescents who remained in the study did better on average than those who dropped out. Furthermore, within each of these two cohorts the magnitude of the between group treatment difference was reasonably similar.

2.3.3.1.6 Reviewer's Comments and Conclusions on Study NM16189

Sponsor's analyses and this reviewer's alternative analyses based on data provided on 8-19-03 to the EDR for Study NM16189, have provided statistical evidence in favor of orlistat with respect to the primary efficacy variable change from baseline to the end of the study for BMI.

Japobrata Choudhury, Ph.D.
Mathematical Statistician

Concur: Dr. Sahlroot

CC:
Archival sNDA 20766/SE5-018

HFD-510/Dr. Colman
HFD-510/Dr. Kehoe
HFD-700/ Dr. Anello
HFD-715/Dr. Nevius
HFD-715/Dr. Wilson
HFD-715/Dr. Sahlroot
HFD-715/Dr. Choudhury

J.Choudhury:7-3110: 11/12/03

This review consists of 25 pages of text.

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/s/

Japobrata Choudhury
11/13/03 01:57:23 PM
BIOMETRICS

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