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Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Serial Number: 21-887 Original
(Rx to OTC switch)

Drug Name: Orlistat 60 mg Capsules

Indication(s): Weight Loss Aid

Applicant: GlaxoSmithKline

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1. EXECUTIVE SUMMARY OF STATISTICAL FINDINGS

With NDA 21-887, orlistat is being studied as an OTC weight loss product for short-term use (the applicant suggests 6 months of treatment). The 120 mg tid dose of orlistat is approved for prescription weight loss. A dose of 60 mg tid is being proposed for OTC weight loss (perhaps in addition to the 120 mg dose).

The results of three clinical trials were submitted to support the efficacy and safety of the 60 mg tid dose of orlistat. These trials differed in length and subject population demographics (see Table 2.2.1 on page 6 and Table 3.1.1.1 on page 8). Each trial showed that the 60 mg dose decreased weight statistically significantly more than placebo (both groups included diet and exercise modification) after 6 months of treatment in two trials and after 4 months of treatment in the third trial. Subjects on either dose of orlistat on average can expect to experience a weight loss of about 3 to 4 kg after 4 months of treatment and about 4 to 6 kg after 6 months of treatment. The weight loss beyond the loss seen with diet and exercise alone would likely be only about an average of 2-3 kgs. Less than 10% of the orlistat-treated subjects lose 10% or more of their weight; about 1/3 lose 5% or more of their weight.

The effect of dietary counseling was evident by the large placebo effects in two of the trials. In the one trial where no monitoring of diet diaries was performed, the mean placebo effect was essentially null and the treatment effect was the largest (see Study NM14161 in Table 3.1.3.1.1 on page 15 and Appendix 6.3); however, the observed mean weight loss on orlistat 60 mg in that study was only 3.6 kg after 6 months of treatment compared to 4.9 kg in a study with intensive monitoring (see Table 3.1.3.1.1).

The relationship between diet and the efficacy of orlistat has not been examined well in the studies presented. In all three studies, patients were to maintain a diet of 30% fat. In only one study did the investigators compile and analyze the diet data and that study (BM14149) showed that subjects increased calories and fat intake with time in both treatment groups. There is no evidence that orlistat teaches subjects to modify their diet. Long-term data submitted with the original NDA for prescription orlistat showed that subjects will lose statistically significantly more weight on orlistat but the weight loss is not maintained (see Appendix 6.6). So at best, there is a small weight loss on orlistat that is only short-term. There appears to be no long-term modification to diet that enables the subject to maintain the weight loss afforded in the short-term.

It is not clear to this reviewer what benefit a consumer purchasing orlistat OTC can possibly reap from 6 months of OTC use. The probability of even a modest weight loss of 2 pounds a month for 6 months is low with only about half the patients achieving that much loss or more; subtracting off the effect of diet and exercise, 30% or less of subjects (dependent on the monitoring of diet) get a modest benefit from orlistat.

This reviewer concludes that though a statistically significant weight loss for orlistat 60 mg compared to placebo is seen, there is no evidence presented that the modest, transient weight loss due to orlistat will afford any long-term clinical benefit through either a change in behavior or a reduced risk of serious clinical diseases manifested by being overweight.

2. Introduction

2.1 Background

Orlistat is an inhibitor of lipases which are required for the absorption of dietary triglycerides. Approximately 25-30% of ingested fat is not absorbed in the gastrointestinal tract with the use of orlistat 120 mg. The 120 mg dose of orlistat was approved April 23, 1999 (NDA 20-766 submitted by Hoffman-La-Roche) for the treatment of obese patients ($BMI \geq 30 \text{ kg/m}^2$) and overweight patients ($BMI \geq 27 \text{ kg/m}^2$) with co-morbidities (hypertension, diabetes, dyslipidemia). The NDA under review here is for orlistat 60 mg administered three times a day as an Over-The-Counter (OTC) weight loss aid in overweight adults (BMI of 25 to $<28 \text{ kg/m}^2$). The 60 mg dose was tested along with the 120 mg dose in the original clinical trials of orlistat. The studies, however, were in an obese/overweight population and did not include the population being considered for OTC use. In this application, the results of a clinical trial (NM17247) in subjects proposed for OTC use (BMI of 25 to $<28 \text{ kg/m}^2$) are presented. This trial assessed only the 60 mg dose of orlistat against placebo. A large part of this review is devoted to examining this study.

The criterion for efficacy based on an FDA guidance on weight loss products is a treatment effect above placebo of at least 5% and/or a significantly higher number of patients achieving a 5% weight loss on the new drug compared to placebo. This guidance was written for prescription weight loss products studied for at least one year. It is not clear at this writing whether this guidance would apply to an OTC product for weight loss.

2.2 Brief Overview of Clinical Studies

Three Phase 3 clinical trials have been conducted using the proposed OTC dose of 60 mg tid; Studies NM14161, BM14149 and NM17247 (Table 2.2.1 on next page). The results of Studies NM14161 and BM14149 were submitted with the original NDA for prescription orlistat; these studies were reviewed by FDA statistical reviewer Dr. Lee Pian. Study NM17247 was conducted several years later apparently to obtain further data on the 60 mg dose. All three trials were randomized, double blind, placebo-controlled studies. The treatment period in the earlier studies was 52 weeks while in the last study, it was only 16 weeks. About 200 patients were randomized in each treatment arm of each study.

Studies NM14161 and NM17247 were conducted in the USA in primary care centers. Study BM14149 was conducted in Europe in special obesity and nutrition centers. The entry criteria for these studies only varied with regard to BMI as shown in the table on the next page. It is

interesting to note that drug-treated diabetics and patients with uncontrolled hypertension were not treated in these trials, even though prescription orlistat is indicated for overweight patients with risk factors such as hypertension, diabetes and dyslipidemia.

Table 2.2.1 Clinical Trials

Study (# of centers) Completion Date	Treatment groups (# randomized)	Key entry criteria	Diet	Duration of treatment
NM14161 primary care (17 USA) 2/95	Placebo (214) ORL 60 mg tid (214) ORL 120 mg tid (214)	BMI 30-43 No GI disorders No drug- treated diabetes	Diet counseling at screening only Encouraged to exercise at each visit Hypocaloric 30% fat 50% carbo 20% protein Wt<90kg⇒1200kcal/day Wt≥90kg⇒1500kcal/day	4-wk placebo lead-in 52-week trt period followed by 52-wk maintenance
BM14149 Obesity and nutritional centers (14 Europe) 2/96	Placebo (243) ORL 60 mg tid (242) ORL 120 mg tid (244)	BMI 28-<43 No GI disorders No drug- treated diabetes	Intensive counseling by dietitians Hypocaloric 30% fat 50% carbo 20% protein 1200kcal/day	4-wk placebo lead-in 52-week trt period followed by 52-wk maintenance
NM17247 primary care (20 USA) 10/03	Placebo (195) ORL 60 mg tid (196)	BMI 25-<28 No GI disorders No drug- treated diabetes	Diet counseling at each visit Hypocaloric 30% fat 50% carbo 20% protein Wt<90kg⇒ 1200kcal/day for women 1400kcal/day for men Wt≥90kg⇒ 1400kcal/day for women 1600kcal/day for men	No run-in 16-week trt period

The diets in the 3 studies were similar, the monitoring of the diets, however, differed appreciably. In Study NM14161, patient diaries were only reviewed during screening while in Study NM17247, diaries were reviewed at each visit. The special obesity and nutritional centers in the European study (BM14149) had intensive monitoring of diet by dietitians.

Two additional studies were done by the applicant to test the use of orlistat in an OTC setting. These two studies (RCH-ORL-002 and NM17285) are only briefly mentioned in this review (see Appendix 6.8).

The applicant presented the pooled results of Studies BM14149 and NM14161 and the results of Study NM17285 in the Integrated Summary of Efficacy of the NDA. This reviewer presents the results for these studies separately because of the differing placebo responses in these studies. The results for Studies RCH-ORL-002 (orlistat in a naturalistic setting) and NM17285 (an actual use study) are reviewed by the FDA OTC staff. This reviewer does describe the baseline characteristics of the populations of all 5 studies side-by-side and summarizes the weight loss results for all 3 clinical trials to illustrate how the results of Study NM17285 fit in to the overall clinical program for OTC orlistat 60 mg TID.

2.3 Data Sources

Study reports and data were accessed from the CDER electronic document room (EDR) at \\CDSESUB1\N21887\N_000\2005-06-06.

NDA 20-766 for Xenical was cross referenced by the applicant and the reviewer for study results and reviews relevant to this submission.

All tables and graphs in this review were created by this reviewer unless otherwise noted.

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3. Statistical Evaluation

3.1 Evaluation of Efficacy

3.1.1 Baseline demographics for 3 Phase 3 clinical trials and 2 OTC trials

To appreciate the commonalties and differences among the patient populations in the 5 trials presented to support the efficacy of 60 mg orlistat as an OTC drug, the baseline characteristics of the enrolled patients are summarized in the table on the following page. Note that there were no notable treatment differences at baseline so the data is presented with the treatment groups

combined. With regard to age, race and gender, the five study populations are similar with the majority of the patients being Caucasian women between the approximate ages of 35 and 55. (See Appendix 6.1 for histograms of the age distribution.) It is interesting that only the actual use study (NM17285) enrolled notable numbers of elderly with about 8% (Table 3.1.1.1).

Only in Study NM17247 are there sizable numbers of patients in the proposed OTC BMI range (25 to <28). So generalizing results from the other studies to an OTC population may be difficult if BMI is related to treatment efficacy or safety. For graphs of the BMI distribution, see Appendix 6.2.

Table 3.1.1.1 Baseline characteristics of ITT (eligible) subjects in five trials of Orlistat

	Clinical Trials			Actual Use/OTC Studies	
	NM17247 (N=378)	BM14149 (N=716)	NM14161 (N=635)	RCH-ORL-002 (N=162)	NM17285 (N=262)
Age (yrs)					
Mean (SD)	46 (11)	44 (11)	42 (10)	37 (12)	45 (14)
Median	46	45	42	36	45
Min-Max	19-80	18-74	18-78	18-73	18-80
% ≥65	5.1%	2.4%	2.4%	1.2%	8.4%
Gender					
% female	94%	82%	78%	84%	85%
Race					
% white	89%	99%	91%	71%	82%
% black	8%	0.6%	7%	13%	3%
BMI (kg/m ²)					
Mean (SD)	27 (1)	34 (4)	35 (4)	35 (6)	32 (6)
Min-Max	24-29	27-46	28-43	27-57	21-55
<25	9 (2%)	0 (0%)	0 (0%)	0 (0%)	20 (8%)
25 to <28	328 (87%)	18 (3%)	0 (0%)	3 (1.8%)	50 (19%)
28 to <30	41 (11%)	95 (13%)	46 (7%)	28 (17%)	35 (13%)
≥30	0 (0%)	603 (84%)	589 (93%)	131 (81%)	157 (60%)
Weight (kg)					
Mean (SD)	73 (7)	95 (14)	98 (14)	96 (18)	89 (20)
Median	72	94	97	91	86
Min-Max	56-102	66-151	67-143	68-179	54-160
Waist Circum (cm)	(N=378)	(N=709)	(N=631)	NA	NA
Mean (SD)	85 (7)	103 (12)	103 (12)		
Median	85	103	102		
Min-Max	69-107	72-148	70-139		
Men>102;Women>88	27%	88%	87%		
Waist-Hip Ratio				NA	NA
Mean (SD)	0.82 (0.07)	0.88 (0.09)	0.87 (0.1)		
Median	0.82	0.88	0.86		
Min-Max	0.65-1.18	0.66-1.26	0.66-1.15		
Men≥0.9;Women≥.85	31%	62%	51%		

NA=Not available because it was not measured in the trial.

Men with a waist circumference greater than 102 cm (40 inches) and/or a waist-hip ratio of 0.90 or greater and women with a waist greater than 88 cm (35 inches) and/or a waist-hip ratio of 0.85 or greater are generally considered at increased risk for heart disease. Since these parameters are related to BMI, it is clear that the patients at greatest risk would be the obese and overweight patients in Studies BM14149 and NM14161; less than one-third of the patients

in Study NM17247 fall into this risk group.

3.1.2 Study NM17247 (conducted 3/2003 to 10/2003)

3.1.2.1 Design

Study NM17247 is a multicenter, double-blind, randomized, placebo-controlled, parallel group study to establish the efficacy and safety of orlistat 60 mg tid in overweight patients ($25 \leq \text{BMI} < 28 \text{ kg/m}^2$). Qualified patients were randomized to treatment and followed for 16 weeks; there was no run-in period. No rationale for the 16-week treatment duration was provided in the protocol.

All patients were to follow a hypocaloric diet containing:

- 30% kcals fat
- 50% kcals carbohydrates
- 20% kcals protein
- cholesterol $\leq 300 \text{ mg/day}$
- alcohol $\leq 150 \text{ g/week}$
- if weight $< 90 \text{ kg}$, then 1200 kcal/day for women and 1400 for men
- if weight $\geq 90 \text{ kg}$, then 1400 kcal/day for women and 1600 for men

Patients were to complete a food intake diary for the first two weeks of the study and for the week prior to each visit (Weeks 4, 8, 12 and 16). Calories and grams of fat were recorded. Dietary diary monitoring was performed throughout the trial in a primary care setting (no dietitians). No data on diet was included in the database and the applicant provided no information on diet compliance.

Entry criteria included (but was not limited to) the following:

- age ≥ 18 men and women (not pregnant nor lactating)
- no weight loss of 3kg or more in the 3 months prior to screening
- $25 \leq \text{BMI} < 28 \text{ kg/m}^2$
- no active GI disorders

All patients were given a multivitamin to be taken daily at least 2 hours before or after taking orlistat.

The primary efficacy variable is weight change from baseline (kgs). Secondary efficacy variables include changes from baseline and % change from baseline in waist and hip circumference, blood pressure, TC, HDL, LDL, LDL/HDL and TG.

3.1.2.2 Patient Disposition

The trial was powered with 186 patients in each arm to detect a treatment difference of 1.4 kgs (SD of 4), assuming a 30% dropout rate. The applicant randomized 195 patients to placebo and 196 patients to orlistat 60 mg (Table 3.1.2.2.1) at 20 centers in the USA.

Table 3.1.2.2.1 Study NM17247 Patient Disposition

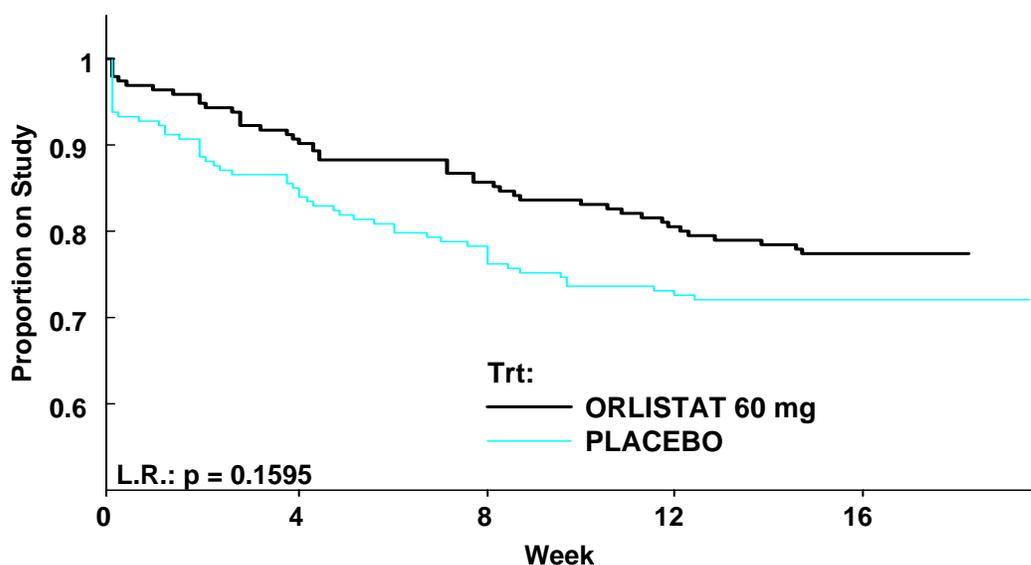
	Placebo	ORL60
Randomized	195	196
Completers	140 (72%)	152 (78%)

ITT	184 (94%)	194 (99%)
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Overall about 25% of the patients discontinued treatment early in this 4-month study; note that this rate is more than double the dropout rate seen at Month 4 in Studies BM14149 and NM14161 (2-year studies) where about 10% discontinued treatment during the first 4 months of treatment.

The proportion of patients on study in each treatment group over time is shown in Figure 3.1.2.2.1. Nearly 5% of the placebo patients dropout in the early days of the trial for various reasons and this early treatment difference holds for the remainder of the trial. These early dropouts did not have any weight measurements on therapy; they were not included in the applicant's analyses and most of this reviewer's analyses.

Figure 3.1.2.2.1 Proportion of patients on study by treatment group



The primary reason for withdrawal in the placebo group was patient request while the primary reason in the orlistat group was adverse event (ADE, Table 3.1.2.2.2). Of the 14 orlistat patients withdrawing for an ADE, 10 were due to gastrointestinal (GI) events with 8 of the 10 withdrawing during the first month of therapy.

Table 3.1.2.2.2 Study NM17247 Reasons for discontinuation

	Placebo (n=195)	ORL60 (n=196)
ADE	6 (3%)	14 (7%)
Pt Request	30 (15%)	11 (6%)
Lost to Follow-up	16 (8%)	12 (6%)
Protocol Violation	2 (1%)	4 (2%)
Other	1 (0.5%)	3 (1.5%)

3.1.2.3 Baseline Demographics

The treatment groups in Study NM17247 were well-balanced for baseline demographics (Table 3.1.2.3.1). Patients ranged in age from 19 to 80 with half the patients below 46 years. Most patients were women (94%) and Caucasian (89%). All patients had a BMI under 30 (no patients were considered obese) with a mean and median of 27. Note that 9 patients with normal BMI's (under 25) were enrolled in the trial. Additional displays of the baseline data from this study along with the data from Studies BM14149 and NM14161 are provided in Section 3.1.1 on pages 6 to 7 of this review.

Table 3.1.2.3.1 Study NM17247 Baseline Demographics

	Placebo (n=195)	ORL60 (n=196)
Age		
Mean (SD)	47 (11)	46 (12)
Median	47	45
Min-Max	19-72	20-80
Gender		
% female	94%	94%
Race		
% white	89%	89%
% black	7%	9%
BMI		
Mean (SD)	27 (1)	27
Median	27	27
Min-Max	24-29	24.5-29
Waist Circum (cm)		
Mean (SD)	86 (7)	85 (7)
Median	85	84
Min-Max	69-107	70-105
Waist-Hip Ratio		
Mean (SD)	0.82 (0.07)	0.82 (0.07)
Median	0.82	0.81
Min-Max	0.66-1.18	0.65-0.99

The treatment groups were also well-balanced with respect to blood pressure, pulse, glucose, lipids and previous/concomitant medications.

3.1.2.4 Statistical Methods

Study NM17247 was completed on October 20, 2003 and the Statistical Analysis Plan (SAP) was dated November 10, 2003, approximately 3 weeks after the completion of the trial. The completion of SAP's after completion of the trials is always of concern to the FDA because of the potential for changes in the analysis plans based on observing the data. In the original protocol, the ANCOVA model is defined and it is stated that the primary efficacy measure of weight loss will be assessed at Day 113. The SAP details the treatment window as Days 99 to 126 (the target day \pm 13 days) and the last observation in the window as the analysis data point. Note that the applicant also applied the criterion of last observation within a window to their reanalysis of Studies BM14149 and NM14161, however for those studies the treatment window was much wider with observations within 42 days (Weeks 12 and 24) of the target timepoint eligible for inclusion in the analysis. For all analyses, the applicant used the last observation in

each window. So the value closest to the named study week (or scheduled day) was not necessarily used. Since characterizing the treatment effects at specific times is important in understanding the efficacy of the two doses of orlistat across the three main clinical trials, this reviewer analyzed measures closest in time to the pre-specified analysis timepoint. Also, this reviewer used windows of target day \pm 13 days to identify LOCF data for all the studies; that is, a value more than 13 days before a timepoint was considered carried forward from an earlier week. Note that since the emphasis here is on the LOCF data, the latter analysis criterion does not impact the number of patients included in the analyses.

An intent-to-treat (ITT) population included patients who received at least one dose of drug and who had at least one post-baseline efficacy measure. Completers included patients who completed 16 weeks on study or discontinued early due to attaining a BMI less than 20 [no patients achieved a BMI of 20]. The applicant analyzed the LOCF data and observed cases data for the ITT population (2 separate analyses) and observed cases (OC) data for the completer population. This reviewer only analyzed the ITT-LOCF data and the completer-OC data.

For their ISE report, the applicant excluded site 12327 of Study NM14161 from their analyses. Following the ITT principle, this reviewer included this site in all analyses as did the FDA statistical reviewer of the original submission.

The protocol-defined analysis model for the primary efficacy variable was ANCOVA with terms for center, treatment, treatment by center interaction and baseline body weight. This reviewer dropped the interaction term if it was not statistically significant at an alpha level of 0.10 or less.

3.1.2.5 Primary Efficacy Results: Weight Loss

Sponsor's results

The primary efficacy variable was weight change from baseline (kg) at endpoint. The sponsor's analyses of both the ITT population LOCF data and the observed data for completers yielded statistically significant treatment differences with the orlistat group showing a larger decrease by about 1 kg. No statistically significant treatment difference in percentage of patients with a 5% or more decrease in weight is seen for the ITT population nor the completers (Table 3.1.2.5.1 on the following page) with only an 8% treatment difference.

Table 3.1.2.5.1 Weight change from baseline (kg) results for ITT, LOCF population and for completers (sponsor's results) Month 4

	Placebo (n=195)	ORL60 (n=196)
ITT, LOCF		
N	184	194
Mean (SD) kg	-1.96 (3.2)	-3.11 (3.0)
p-value vs. placebo		0.0002
% pts with ≥5% decrease in wt	28% (52/184)	36% (70/194)
p-value versus placebo		0.10
Completers		
N	140	152
Mean (SD) kg	-2.41 (3.4)	-3.68 (3.1)
p-value vs. placebo		0.0003
% pts with ≥5% decrease in wt	35% (49/140)	43% (66/152)
p-value versus placebo		0.14

Reviewer's results

As mentioned above with the statistical methods, this reviewer analyzed observations that occurred closest to the preplanned intended time of analysis while the applicant analyzed the last datapoint for a patient within the time window of day \pm 13 days. There are no appreciable differences between this reviewer's results and the applicant's results for Study NM17247.

There is approximately a 1.1 kg weight loss over placebo for orlistat and the confidence interval suggests that treatment effects only as large as 1.7 kg could be expected if we were to repeat this trial. So over a 4-month time period, patients can only expect to lose approximately 1 to 2 kg over diet and exercise alone with the use of orlistat 60 mg tid.

Table 3.1.2.5.2 Mean weight change from baseline and % change for ITT, LOCF population and for completers (reviewer's results) Month 4

	Placebo (n=195) Mean (SD)	ORL60 (n=196) Mean (SD)	LS* MeanTrt Diff (95% CI)
ITT, LOCF			
N	184	194	
Baseline	72.8 (6.6)	72.8 (7.0)	
Change (kg)	-2.0 (3.2)	-3.1 (3.0)	-1.1 (-1.7, -0.53)
% Change	-2.7% (4.4)	-4.2% (4.1)	-1.5% (-2.3%, -0.7%)
% of pts w/ ≥5% loss	29% (53/184)	37% (71/194)	CMH** p=0.10
% of pts w/ ≥10% loss	5% (10/184)	10% (20/194)	CMH p=0.37
Completers			
N	138	154	
Baseline	72.7 (6.8)	72.4 (6.7)	
Change (kg)	-2.5 (3.4)	-3.6 (3.1)	-1.2 (-1.9, -0.5)
% Change	-3.4% (4.7)	-5.0% (4.2%)	-1.6% (-2.6%, -0.6%)
% of pts w/ ≥5% loss	37% (51/138)	44% (68/154)	CMH p=0.25
% of pts w/ ≥10% loss	7% (10/138)	13% (20/154)	CMH p=0.70

* LS mean difference based on ANCOVA model with baseline weight as a covariate. A negative value favors Orlistat.

** Cochran-Mantel-Haenszel test adjusting for baseline weight

A little more than one-third of the orlistat patients experience a 5% drop in weight which was not statistically significantly different from placebo. If we assume all the randomized patients who dropped out without any data were non-responders, the percentage of 5% loss responders would be 27% (53/195) for placebo and 36% (71/196) for orlistat ($p=0.065$, Fisher's exact test).

About 10% of the orlistat patients achieve a weight loss of 10% or more, double the placebo rate but not statistically significant ($p=0.37$).

Though the weight loss for orlistat 60 mg tid is statistically significantly larger than the loss for the placebo patients, it is certainly questionable whether a 1 kg treatment effect over 4 months is clinically important (i.e. would it reduce the patient's risk of any morbidities associated with being overweight?) or even whether the loss is of any cosmetic significance to an overweight patient given that only 10% of the patients lose 10% of their weight or more.

More details regarding the treatment effects observed in Study NM17247 are presented with the results of Studies BM14149 and NM14161 in the following section (Section 3.1.3).

3.1.3 Efficacy results in Studies NM17247, BM14149 and NM14161

3.1.3.1 Weight loss at Months 4 and 6

Table 3.1.3.1.1 below shows the Month 4 (Week 16) and Month 6 (Week 24) LOCF results in Studies NM17247, NM14161 and BM14149 computed by this reviewer from observations closest in time to the timepoint of interest. Note that the applicant reported larger orlistat treatment effects for the pooled results (Studies NM14161 and BM14149) using the last observation in a wide treatment window. All the observed data is shown in graphs in Appendix 6.3. From those graphs and from the results in the table below, this reviewer notes the following:

- At Month 4, the treatment effect ranges from about 1 kg to about 2.5 kg regardless of dose or study.
- At Month 6, the treatment effect for orlistat 60 mg tid is 2.4 kg in Study NM14161 and 1.7 kg in Study BM14119.
- At Month 6, the effect for the 120 mg dose is significantly greater than the effect of the 60 mg dose in Study NM14161 but not in Study BM14149.
- The largest placebo effect is seen in Study BM14149; the trial conducted at specialty centers with intense monitoring of diet.

Table 3.1.3.1.1 LS Mean weight change from baseline and % change at Months 4 and 6 LOCF

	Placebo LS Mean (95%CI)	ORL60 LS Mean (95%CI)	ORL120 LS Mean (95%CI)
Weight change (kg)			
Month 4			
Study NM17247	-1.9 (-2.3, -1.5)	-3.0 (-3.5, -2.6)	na
Study NM14161	-1.3 (-1.8, -0.9)	-3.3 (-3.7, -2.8)	-3.8 (-4.2, -3.3)
Study BM14149	-2.2 (-2.6, -1.8)	-3.7 (-4.1, -3.3)	-3.75 (-4.2, -3.3)
Month 6			
Study NM14161	-1.2 (-1.8, -0.6)	-3.6 (-4.2, -3.0)	-4.5 (-5.0, -3.9)
Study BM14149	-2.9 (-3.4, -2.3)	-4.6 (-5.2, -4.1)	-4.9 (-5.5, -4.4)
Weight change (%)			
Month 4			
Study NM17247	-2.6% (-3.2%, -2.0%)	-4.2% (-4.7%, -3.6%)	na
Study NM14161	-1.4% (-1.9%, -0.9%)	-3.3% (-3.8%, -2.9%)	-3.9% (-4.3%, -3.4%)
Study BM14149	-2.3% (-2.8%, -1.9%)	-3.95% (-4.4%, -3.5%)	-3.96% (-4.4%, -3.5%)
Month 6			
Study NM14161	-1.3% (-1.9%, -0.7%)	-3.7% (-4.3%, -3.2%)	-4.6% (-5.2%, -4.0%)
Study BM14149	-3.0% (-3.6%, -2.4%)	-4.9% (-5.5%, -4.4%)	-5.2% (-5.8%, -4.6%)
Month 4			
% pts with ≥5% dec			
Study NM17247	29% (53/184)	37% (71/194)	na
Study NM14161	14% (30/212)	31% (67/213)**	34% (72/210)**
Study BM14149	20% (48/236)	36% (85/239)**	37% (89/241)**
% pts with ≥10% dec			
Study NM17247	5% (10/184)	10% (20/194)	na
Study NM14161	0.5% (1/212)	6% (12/213)**	8% (17/210)**
Study BM14149	4% (10/236)	7% (16/239)	5% (13/241)

* Least squares mean difference based on ANCOVA model with baseline weight as a covariate. A negative value favors Orlistat.

** p<0.05 compared to placebo

The confidence intervals suggest that the largest mean decrease that could be expected in future trials with the 60 mg dose is about 5 kg (5.5% change) and with the 120 mg dose, about

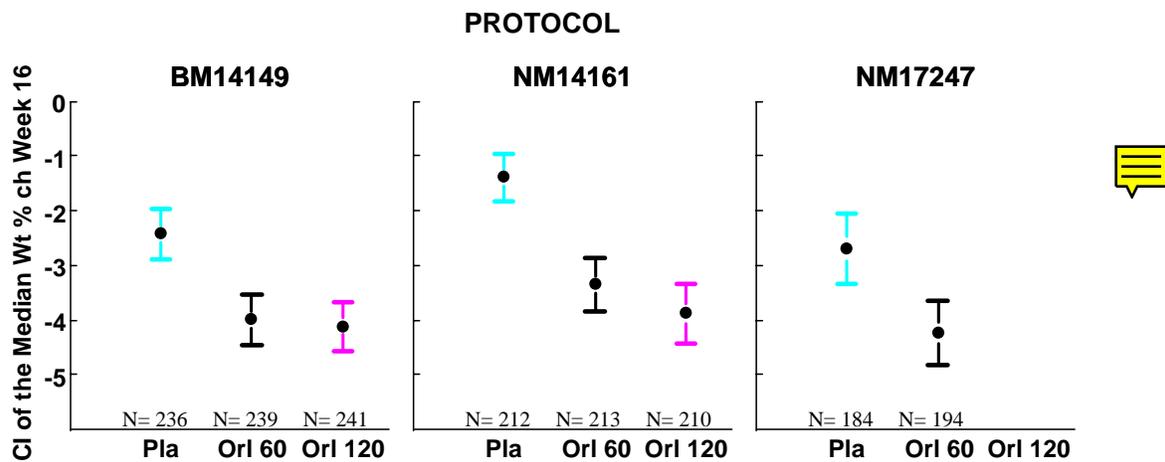
5.5 kg after 6 months of treatment; about half the patients treated, then, can expect to lose 5 kg (about 11 lbs.) or more.

The treatment effect seen in NM172147 at Month 4 is similar to the treatment effect seen in Study BM14149. These trials differed in the distribution of BMI (see Appendix 6.2) but in both trials diaries were checked at each visit. However in BM14149, the applicant considered the diet monitoring to be more intensive with dieticians giving advice beyond just checking the diary. Despite this latter difference, a larger placebo effect is seen in Study NM17247.

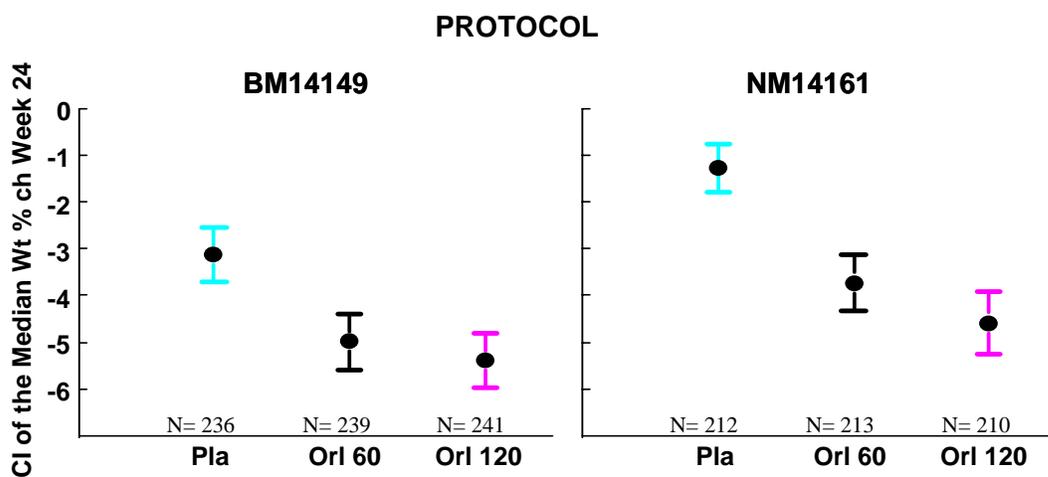
The graph below illustrates the difference in placebo effects seen across the trials. Also it is clearly shown that the largest treatment effect is seen in the study with the least dietary monitoring, Study NM14161. Also in the latter trial a dose response is more readily seen.

Figure 3.1.3.1.1 Median % change from baseline
(See appendix for a graph of change from baseline in kg.)

Month 4 LOCF



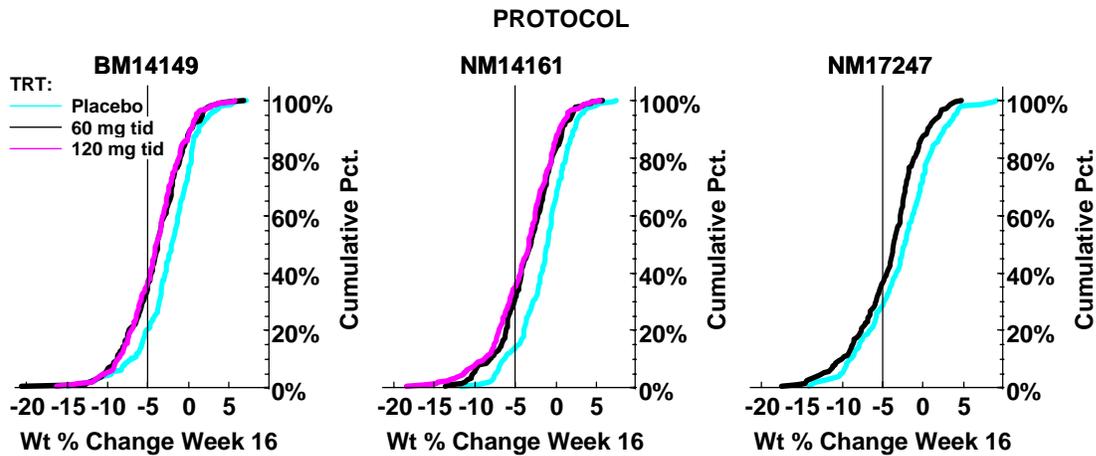
Month 6 LOCF



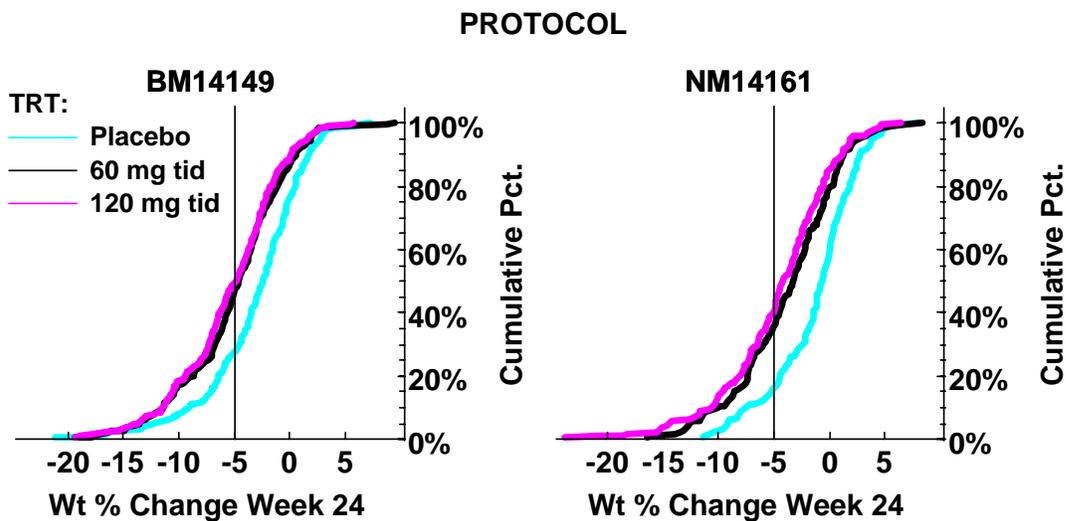
The cumulative distribution plots below show the last response for all ITT patients plotted as % change from baseline. From these plots one can see the percentage of patients having a specific response or better. A reference line is shown at -5%. The steepness of the curves from -5% to 0 illustrates that most patients have some decrease on therapy. Looking at Month 4 and 6, one can see that with time the separation of the orlistat curves from placebo increases.

Figure 3.1.3.1.2 Cumulative distribution plot of weight % change from baseline

Month 4 LOCF



Month 6 LOCF



This reviewer also looked at the relationship between the Month 4 and Month 6 responses in Studies BM14149 and NM14161. A regression analysis suggests that a 3% decrease at Month 4 is associated with about a 4-5% decrease at Month 6 (see Appendix 6.5).

3.1.3.2 Waist and hip changes

A recent publication of an epidemiological study (the INTERHEART case-control study) of 27,098 subjects showed that the waist to hip ratio was a better predictor of myocardial infarction than BMI (Lancet 2005; 366: 1640-49). They found that a greater waist-to-hip ratio of about

0.085 resulted in an increase in risk by 37% (OR 1.37 95% CI 1.34-1.41); for BMI, a difference of 4.15 was associated with an OR of 1.10 (95% CI 1.07-1.13).

For Study NM17247, waist and hip measurements decreased by approximately the same amount (about 3-4cm for the orlistat 60 group and about 2.5 cm in the placebo group) with a small statistically significant treatment effect of about 1 cm. There was no difference between the groups for waist/hip ratio. None of the clinical trials showed a significant effect for orlistat (120 mg or 60 mg) on the waist/hip ratio.

3.1.3.3 Lipid changes

The lipid changes in Study NM17247 after 4 months of therapy were small (decrease of 5.9% in LDL) and not clinically relevant according to the usual standards for lipid lowering drugs (a change of about 15% is usually expected for a minimally effective drug). To determine if longer term treatment resulted in greater effects, this reviewer summarized the total cholesterol (TC) and LDL changes at Week 52 in 4 trials conducted by the applicant. LDL treatment effects in these studies ranged from 6.4% to 8.4% more lowering for orlistat 120 mg tid than placebo (Table 3.1.3.4.1).

Table 3.1.3.4.1 Endpoint (LOCF) LSM %change from baseline in total cholesterol and LDL

	Placebo	Orlistat 60	Orlistat 120
TC			
Study NM17247 Wk16	-0.1%	-3.8%	NA
Study NM14161 Wk52	+4.2%	+0.2%	-0.3%
Study BM14149 Wk52	+0.1%	-3.0%	-6.5%
Study BM14119 Wk52*	+4.9%	NA	-0.4%
Study NM14185 Wk52*	+6.0%	NA	-1.7%
LDL			
Study NM17247 Wk16	-0.5%	-5.9%	NA
Study NM14161 Wk52	+6.2%	+0.3%	-1.8%
Study BM14149 Wk52	-1.5%	-5.7%	-9.7%
Study BM14119 Wk52*	+5.2%	NA	-1.2%
Study NM14185 Wk52*	+3.8%	NA	-4.6%

*Studies BM14119 and NM14185 were studies with 1-year weight loss assessment of the Orlistat 120 mg only that were reviewed in the original submission. The numbers for Studies 14161, 14119 and 14185 here were extracted from Dr. Pian's FDA statistical review. The remaining numbers were extracted from the applicant's study reports.

Overall orlistat significantly lowers TC and LDL compared to placebo, however, the decreases are half the effect that is seen for the lowest approved doses of LDL lowering drugs so the clinical benefit is questionable.

3.2 Evaluation of Safety

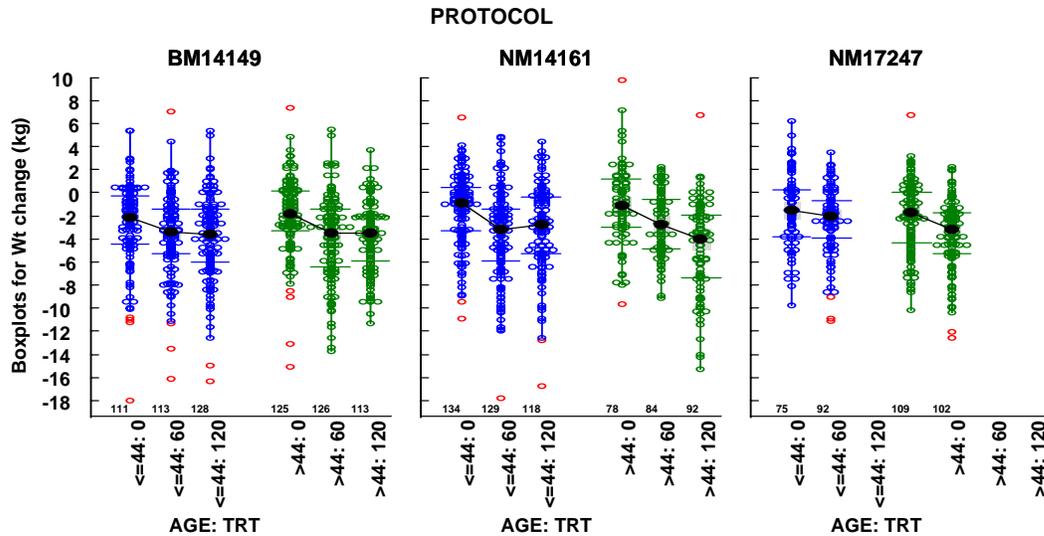
Safety was evaluated by the FDA medical reviewer, Dr. Golden. The only significant adverse events seen in Study NM17247 are gastrointestinal side effects. GI events are a major reason for dropout (about 5% of patients); however, in general, these events tended to be transient and tolerated by the patients with most of the subjects having only one GI adverse event over the course of the trial.

4. Findings in Special/Subgroup Populations

4.1 Gender, Race and Age

In the original application, the FDA statistical reviewer found an highly statistically significant interaction for age and treatment in Study NM14161 with older patients showing a larger placebo-subtracted effect on the 120 mg dose than the younger patients; a significant interaction is also seen in Study NM14161 with Month 4 data ($p=0.0007$). No significant interaction was seen in the other studies ($p>0.25$).

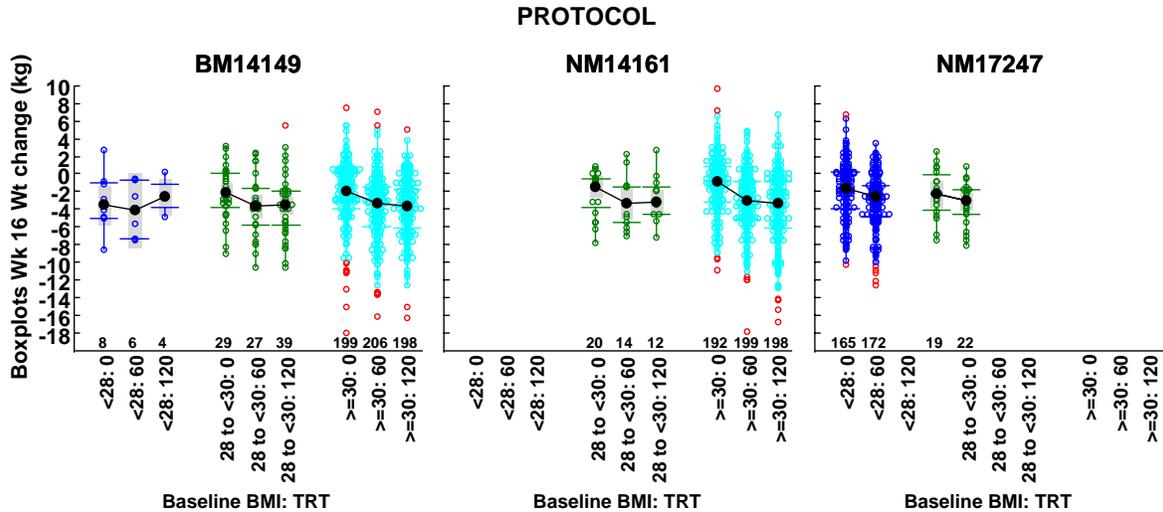
Figure 4.1.1 Boxplots and medians for Month 4 weight change from baseline LOCF by protocol subgrouped by overall median age



4.2 BMI

No relationship between weight loss and baseline BMI was seen in any of the clinical trials. Tests for interaction of treatment by median BMI or by BMI category (Figure 4.2.1) yielded $p>0.20$. Plots of BMI versus weight change suggested no correlation between the measures.

Figure 4.2.1 Boxplots and medians for Month 4 weight change from baseline LOCF by protocol subgrouped by BMI weight categories; OTC overweight population, overweight, and obese



5. Summary and Conclusions

The criterion for efficacy based on an FDA guidance on weight loss products is a treatment effect above placebo of at least 5% and/or a significantly higher number of patients achieving a 5% weight loss on the new drug compared to placebo. [Note that the European Agency for the Evaluation of Medicinal Products states in their guidance that their criterion for efficacy is a 10% drop from baseline which is statistically significantly different from placebo.] In 1982, the FDA released a notice in the Federal Register (21 CFR Part 357) on the establishment of a monograph for OTC weight loss products based on recommendations from an advisory review panel. This panel estimated that a reasonable expected weight loss in a trial that includes dieting would be a mean of about 1 pound in the placebo group and 1.5 pounds in the drug group per week based on averaging over a 12-week period (about a 6 pound or 2.7 kg treatment difference over 12 weeks). The applicability of these guidances and the potentially outdated Federal Register notice to the present application has not been agreed upon by the review team at the time of writing this review and suggests issues that may be discussed at an upcoming advisory committee meeting. Nevertheless it is very clear that the treatment effect of 1.15 kg (95% CI of -1.8, -0.5)¹ after 16 weeks of treatment in Study NM17247, though highly statistically significant, does not meet criterion set in the guidances or in the Federal Register notice so its clinical significance appears to be questionable. Note also that even the maximum mean treatment effect seen after 24 or 52 weeks of treatment with 120 mg in a predominantly obese population was only about 3-4 kg (about 4-5%) though this dose met FDA guidance criteria. For more details regarding the data for orlistat 60 mg and the FDA criteria, see Appendix 6.7.

Greater weight loss was seen for patients whose diet diaries were monitored (Studies NM17247 and BM14149) than for patients not monitored (Study NM14161) regardless of treatment group (see Appendix 6.3). The OTC setting provides obviously even less care and supervision so the expectation might be that a treatment effect less than what was seen in Study NM14161 would be attained. Also, these studies showed that the weight loss could not be maintained (see

1 This estimate is based on the ITT, LOCF analysis (page 50 of the study report). The sponsor presents in their ISE a different estimate of -1.2 which is based on an observed cases dataset (total N of 292) with 86 fewer patients than the ITT, LOCF population.

Appendix 6.6).

The table below shows the percentage of patients in weight loss (lbs. and kgs.) categories at 6 months in predominantly obese patients in the two clinical trials with 6-month data. The difference between orlistat (60 and 120) and placebo is quite evident. The biggest difference between the studies is seen in the percentage of patients able to attain at least a 5 lb. loss.

Table 5.1 Weight loss in categories based on lbs (kgs) after 6 months of treatment in Studies BM14149 and NM14161

Wt loss lbs (kg)	BM14149 (intensive monitoring)			NM14161 (limited monitoring)		
	Placebo (n=241)	ORL60 (n=239)	ORL120 (n=236)	Placebo (n=212)	ORL60 (n=213)	ORL120 (n=210)
< 5 (2.3)	49%	28%	27%	70%	40%	35%
5 (2.3) to <8 (3.2)	15%	15%	16%	6%	13%	14%
8 (3.2) to <11 (4.1)	11%	13%	11%	7%	13%	10%
11 (4.1) to <14 (5)	8%	14%	10%	4%	11%	11%
14 (5) to <17 (5.9)	5%	9%	11%	5%	7%	8%
17 (5.9) to <20 (6.8)	4%	4%	8%	4%	5%	7%
≥20	8%	17%	17%	4%	12%	15%

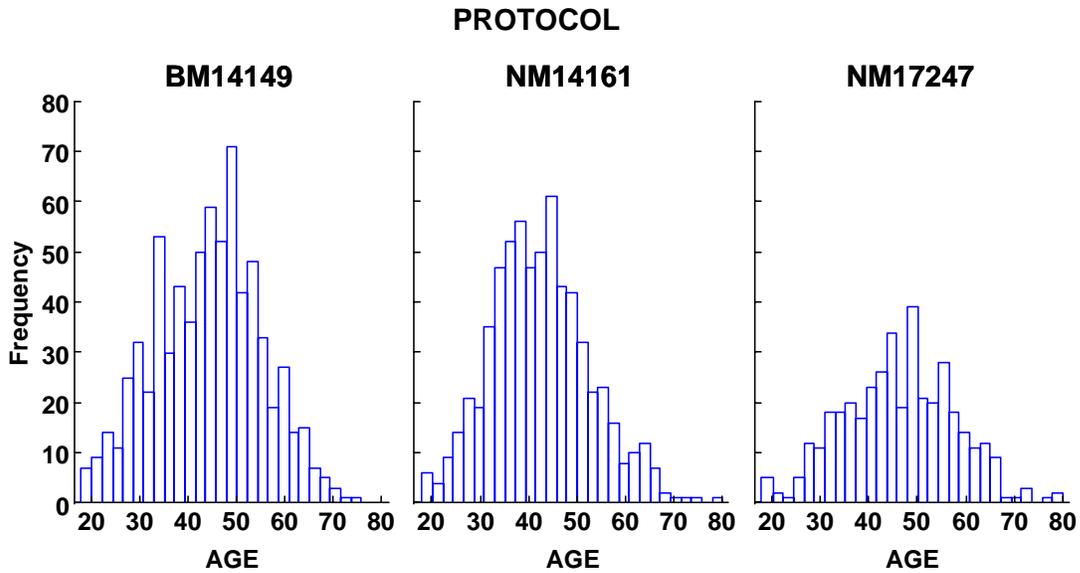
The majority of the patients taking orlistat experience at least one GI ADE ; about 70% with one year of treatment and 57% in Study NM17247 (33% in the placebo group) after 4 months of treatment. GI adverse events generally show up early so this reviewer would recommend that if orlistat is approved for OTC use that there be a trial package of 10-15 capsules available to give the patient an opportunity to see if he/she is willing to tolerate the GI side effects.

This reviewer concludes that though a statistically significant weight loss for orlistat 60 mg compared to placebo is seen, there is no evidence presented that a modest, transient weight loss due to orlistat will afford any long-term clinical benefit through either a change in behavior or a reduced risk of serious clinical diseases manifested by being overweight.

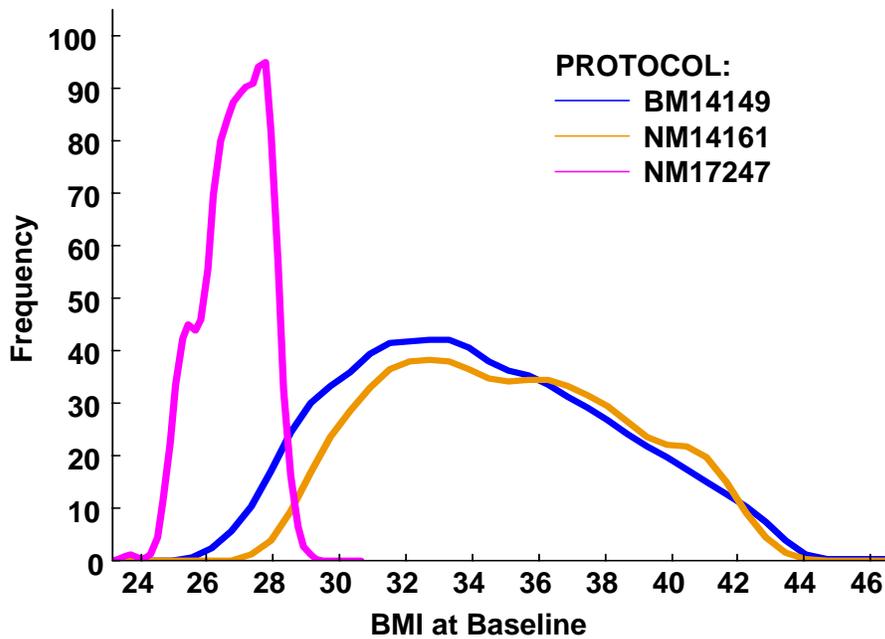


Appendices

Appendix 6.1 Age distribution by study

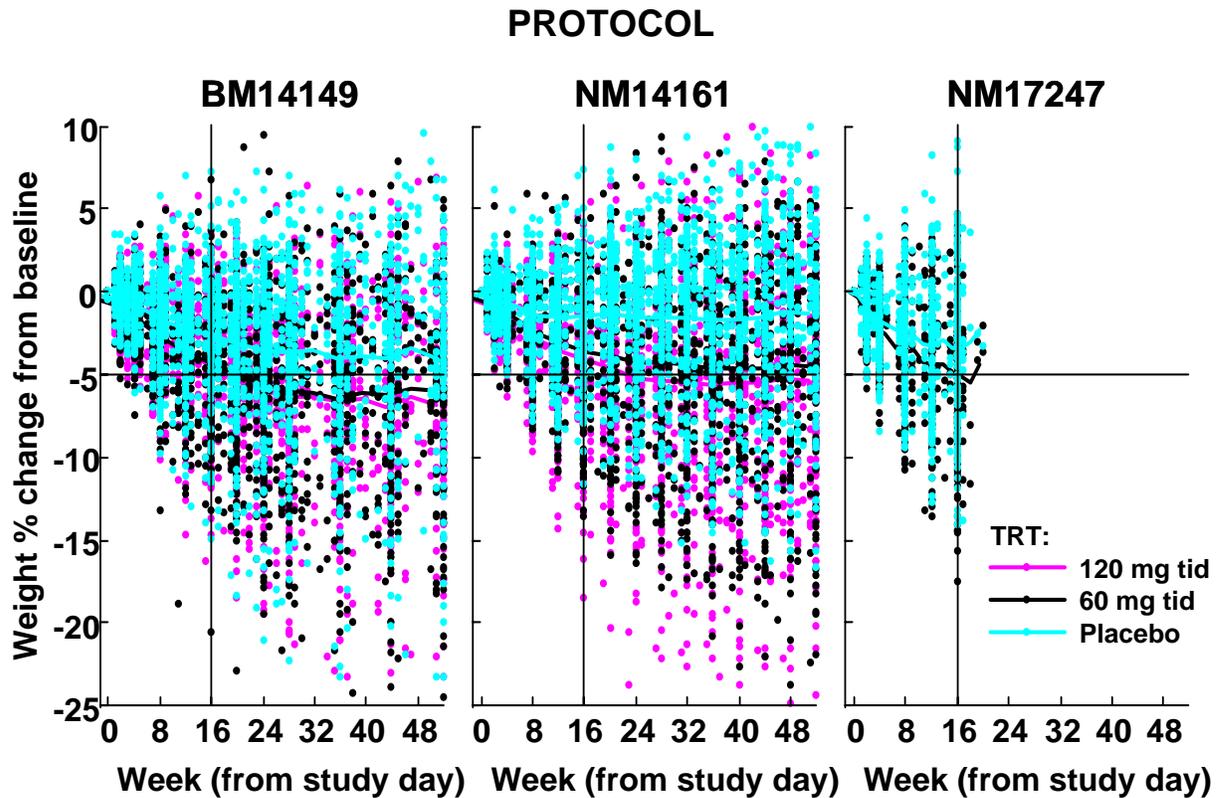


Appendix 6.2 Kernel density curves for baseline BMI by study

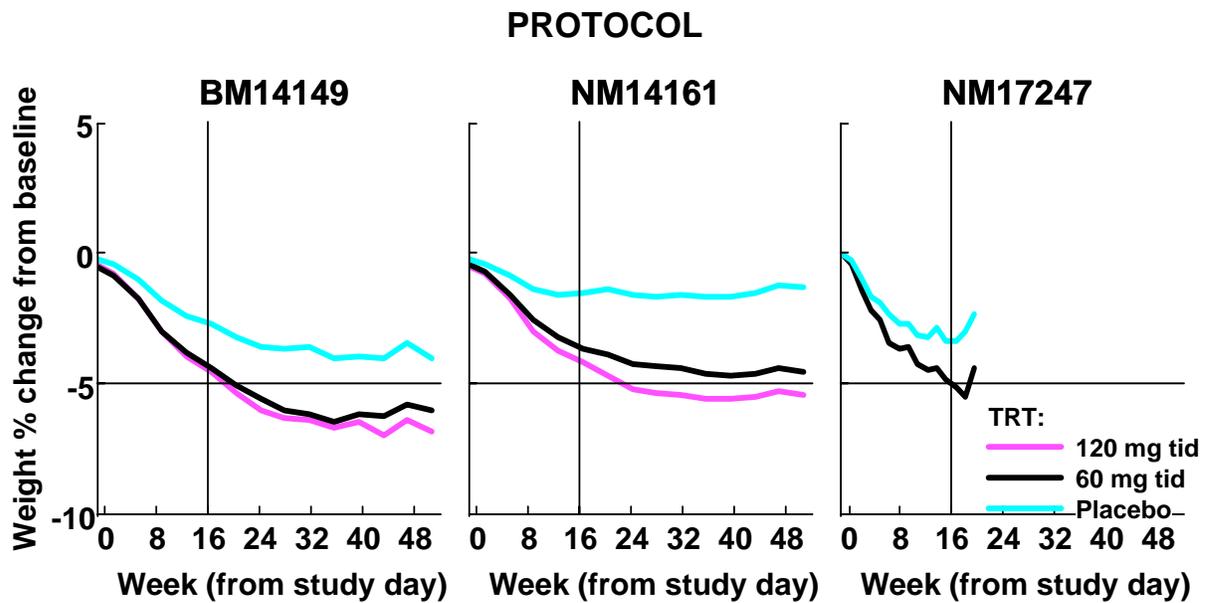


Appendix 6.3 Weight Loss overtime for observed cases

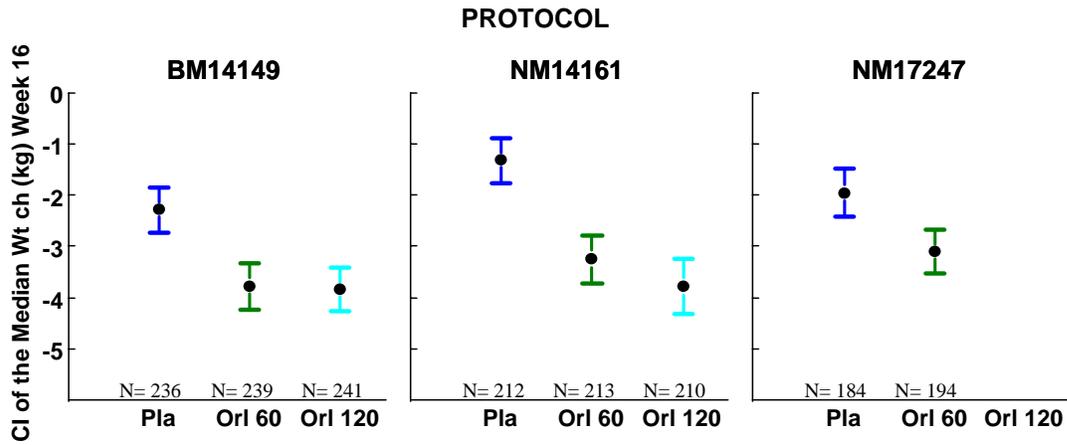
(no locf data depicted). Time is based on actual study day of the weight measurement. Dots represent observations and lines are smoothed curves.



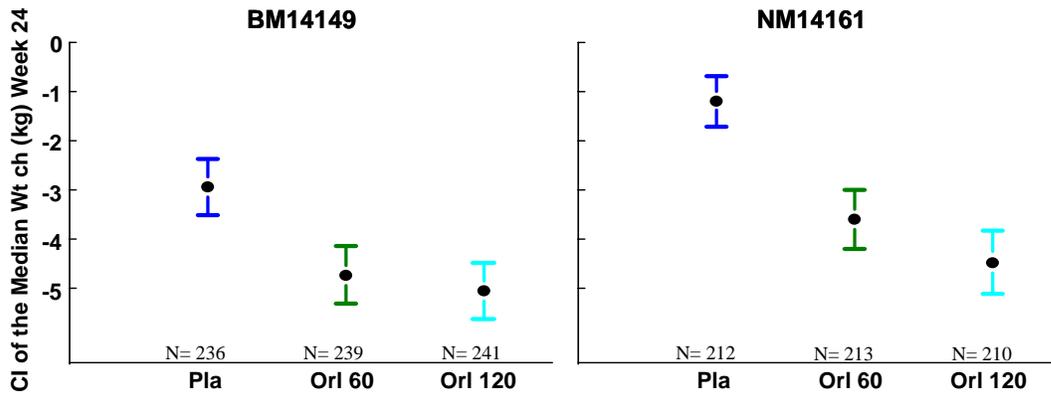
Same graph without the datapoints and with the scale magnified.



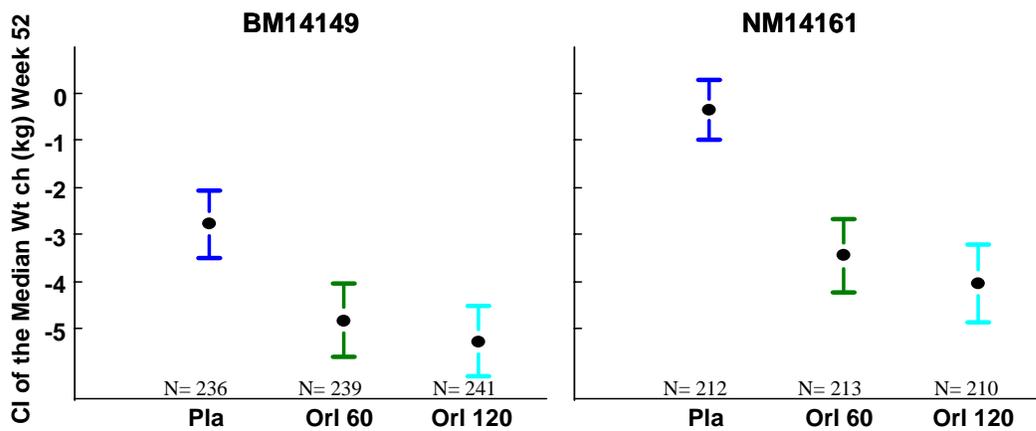
Appendix 6.4 Medians and 95%CI of weight change from baseline
Median Weight change from baseline (kg) at Week 16 LOCF



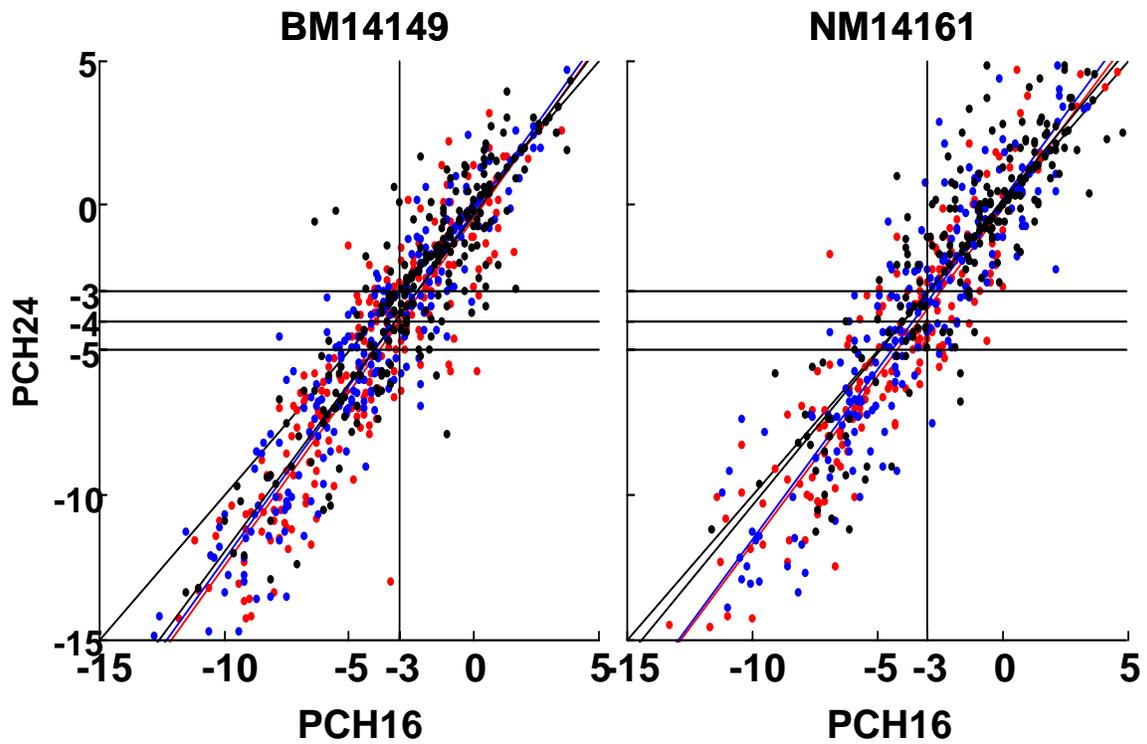
Median Weight change from baseline (kg) at Week 24 LOCF
PROTOCOL



Median Weight change from baseline (kg) at Week 52 LOCF
PROTOCOL



Appendix 6.5 Regression of % change at Month 4 on % change at Month 6
PROTOCOL

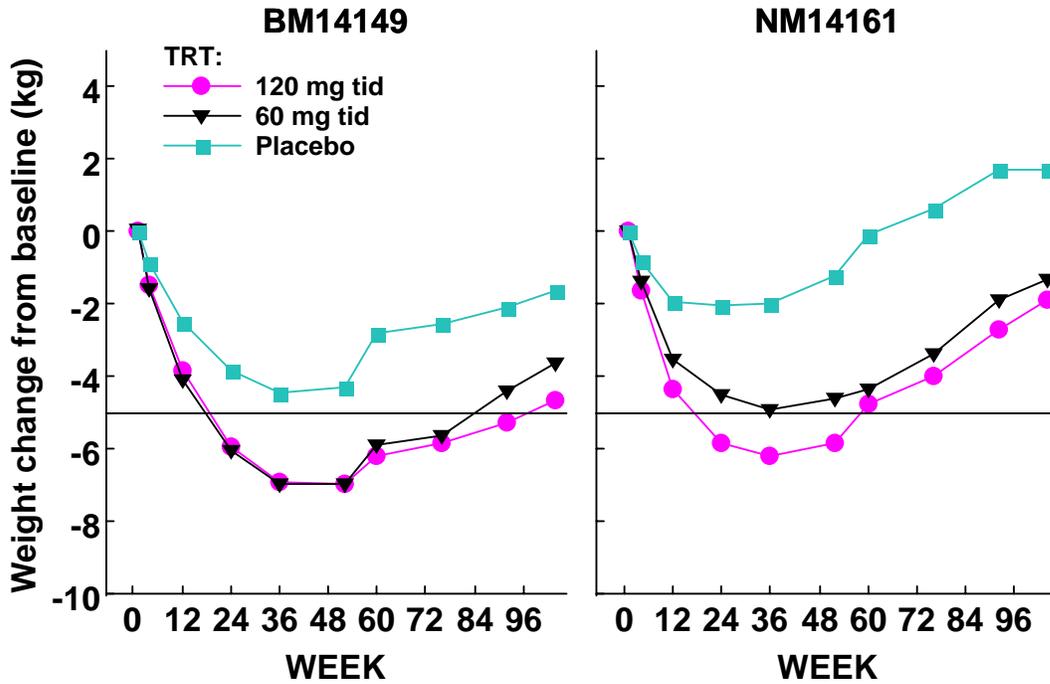


TRT:
—●— 120 mg tid
—●— 60 mg tid
—●— Placebo

Appendix 6.6 Mean weight loss in kg for 2 year period (observed data for completers)

After 52 weeks of treatment plus hypocaloric diet, patients were placed on a eucaloric diet and continued taking treatment as randomized.

PROTOCOL



Appendix 6.7 Results for the orlistat 60 mg dose in the context of the FDA guidance

Does the mean orlistat 60 mg weight loss significantly exceed the placebo weight loss by at least 5%? No, not in any of the studies at any timepoint.

LSM placebo-subtracted difference in % change from baseline and 95% CI

	NM17247	BM14149	NM14161
Month 4	-1.5% (-2.4, -0.7) **	-1.6% (-2.2, -1.0) **	-1.9% (-2.6, -1.3) **
Month 6	NA	-1.9% (-2.7, -1.1) **	-2.4% (-3.2, -1.6) **
Month 12	NA	-2.2% (-3.3, -1.1) **	-3.1% (-4.2, -2.0) **

** = statistically significant

bolded = meets criterion of 5% or more treatment difference from placebo

Is the % of subjects on orlistat 60 mg, achieving a weight loss of at least 5%, significantly greater in the orlistat 60 mg dose than the placebo group? No, in overweight patients only. Yes, in a predominantly obese population.

% of patients with a 5% or more decrease in weight

	Placebo	60 mg	Difference	p-value
Month 4				
Study NM17247	29%	37%	8%	0.10
Study NM14161	14%	31%	17%	0.0004
Study BM14149	20%	36%	16%	0.003
Month 6				
Study NM14161	16%	35%	19%	0.001
Study BM14149	28%	46%	18%	<0.0001
Month 12				
Study NM14161	16%	31%	15%	0.01
Study BM14149	26%	46%	20%	<0.0001

bolded = meets criterion of statistically significant difference

EU criteria: % of patients with a 10% or more decrease in weight

	Placebo	60 mg	Difference	p-value
Month 4				
Study NM17247	5%	10%	5%	0.37
Study NM14161	0.5%	6%	5.5%	0.02
Study BM14149	4%	7%	3%	0.34
Month 6				
Study NM14161	3%	10%	7%	0.04
Study BM14149	8%	17%	9%	0.008
Month 12				
Study NM14161	4%	13%	9%	0.02
Study BM14149	12%	20%	8%	0.0008
10% within group mean decrease at month 12?				
Mth 12 within group effects	120mg		60mg	
Study NM14161	-4.0% (-4.8, -3.3) **		-3.5% (-4.2, -2.7) **	
Study BM14149	-5.1% (-5.9, -4.4) **		-4.7% (-5.5, -4.0) **	

bolded = meets criterion of statistically significant difference or 10% mean response

Appendix 6.8 Statistical review of Actual Use Study NM17285

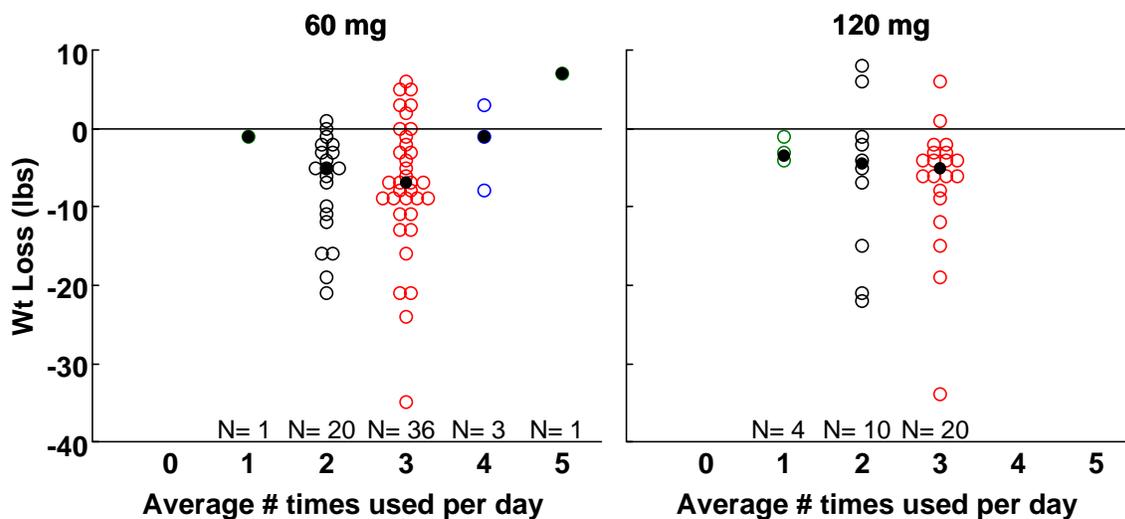
Study NM17285 was an actual use study reviewed in detail by FDA's OTC division (see Dr. Feibus' review). Although the study is open-label and unblinded and is designed to specifically look at self-selection and use of the product in the context of the labeling, the results on weight loss and dosing offer some insight as to the effect of orlistat in a setting more akin to the OTC setting than the setting of a controlled clinical trial with monthly monitoring. This reviewer describes (without formal statistical analyses) only the dosing and weight loss data.

Study NM17245 was a 3-month study conducted at 18 pharmacies in the US. A total of 237 subjects (out of 703 screened) purchased and used orlistat. See Table 3.1.1.1 on page 8 for the baseline demographics of the patients who decided to purchase; demographics for the user population was nearly identical.

Weight was measured at pharmacy visits (scheduled visits at baseline and end of study plus unscheduled visits at anytime) and self-reported in telephone interviews on Days 10, 30, 60 and 90. Subjects were instructed to take 1-2 60-mg capsules with each meal containing fat up to three times a day. The average number of capsules per day, the number of times per day, and the typical number of capsules taken per time was estimated by the subject in response to questions posed in a telephone interview. For this reviewer's description of the data, the first and last weight measured in the pharmacy and the self-reported dosing data were used.

Less than half the subjects had both weight loss data and dosing data so the graph below represents only a subgroup of the subjects who actually used orlistat (95 out of 237). Most subjects lose weight with a median loss of about 5 lbs (2.3 kg); in the clinical trials the median weight loss was about 3-4 kg at Month 3. Looking at all subjects with weight loss data (n=104), the median weight change is -5.5 lbs (mean of -7.18 lbs, skewed by 4 outliers ranging from -52 to -34). Note from the graph that more frequent dosing appears to have a greater effect on weight loss than increasing the dose from 60 mg to 120 mg.

Figure 6.8.1 Weight loss (lbs) measured in the pharmacy at the last visit (maximum of 3 months) by self-reported dose averaged over the duration of the trial



A total of 233 purchasers who took orlistat had dosing data in the database provided by the

sponsor (Table 6.8.1); 148 patients were completers with dosing data at the 4th interview (Table 6.8.2). The header row in the tables below shows the doses subjects reported at the first telephone interview. Numbers in color on the diagonal represent the subjects who stayed on their initial dose numbers below the diagonal are subjects who increased their dose; numbers above the diagonal are subjects who decreased their dose.

About half the patients initially took 1 capsule with a meal, 3 times a day (60 mg TID); an additional 20% took 60 mg twice a day. Looking at all patients, about 54% of subjects stayed on the same dosing regimen for the 3 months (diagonal of Table 6.8.1); among the completers, the percentage is 50% (diagonal of Table 6.8.2). About half the subjects who started on 120 mg tid and about ¼ of the subjects on 60 mg tid decreased their dose; this suggests higher tolerability of the 60 mg dose.

Table 6.8.1 Crosstab of initial reported dose and final reported dose for all patients with dosing data (n=233)

DOSE First⇒ Last↓	60qd (n=16)	60bid (n=49)	120qd (n=5)	60tid (n=103)	120bid (n=22)	120tid (n=38)
60qd	12 (5%)	8 (3%)	1 (<1%)	8 (3%)	1 (<1%)	3 (1%)
60bid	1 (<1%)	23 (10%)	0	16 (7%)	2 (1%)	4 (2%)
120qd	1 (<1%)	3 (1%)	2 (1%)	2 (1%)	2 (1%)	1 (<1%)
60tid	1 (<1%)	4 (2%)	0	57 (24%)	0	7 (3%)
120bid	1 (<1%)	6 (3%)	2 (1%)	7 (3%)	15 (6%)	5 (2%)
120tid	0	5 (2%)	0	13 (6%)	2 (1%)	18 (8%)

Among the completers, only 24 subjects were on the highest dose of 120 mg TID at the end of the 3 months suggesting that either this dose was not well tolerated or that subjects were satisfied with their weight loss at the lower dose. It is clear that overall most subjects do not increase their dose (~73%).

Table 6.8.2 Crosstab of initial reported dose and final reported dose for all patients who completed the 4th interview (n=148)

DOSE First⇒ Last↓	60qd (n=7)	60bid (n=29)	120qd (n=3)	60tid (n=66)	120bid (n=16)	120tid (n=27)
60qd	4 (3%)	4 (3%)	1 (1%)	4 (3%)	0	1 (1%)
60bid	0	13 (9%)	0	10 (7%)	2 (1%)	4 (3%)
120qd	1 (1%)	1 (1%)	0	2 (1%)	2 (1%)	1 (1%)
60tid	1 (1%)	3 (2%)	0	36 (24%)	0	6 (4%)
120bid	1 (1%)	4 (3%)	2 (1%)	6 (4%)	10 (7%)	5 (3%)
120tid	0	4 (3%)	0	8 (5%)	2 (1%)	10 (7%)