The sponsor was requested to provide analyses that include site 12327, and therefore all sites are presented in the adjusted mean analyses for pooled studies in this document. In general, the conclusions are similar to those in which the site is excluded.

6.1.4.4 Primary Efficacy Studies

6.1.4.4.1 Body Weight

6.1.4.4.1.1 Responder Analyses

Table 6.1.4.4.1.1.A describes the categorical weight loss in the pooled studies (obese population) using the ITT LOCF population. A statistical analysis was only performed on the ≥ 5% category. As seen below, a similar proportion of subjects randomized to the orlistat 60 and 120 mg doses reached the ≥ 5% benchmark after six months (42% and 45%, respectively). This was highly statistically significant for both groups versus placebo (23%). Results were similar in the ITT observed population (≥ 5% weight loss in 26%, 47%, and 49% of placebo, orlistat 60 mg, and orlistat 120 mg treatment groups, respectively; $p < 0.001$ orlistat *vs.* placebo) and the six-month completers population (29%, 49%, and 52%, respectively; $p < 0.001$ orlistat *vs.* placebo).

In all analysis populations it appears that both orlistat 60 and 120 mg also had a higher rate of individuals losing at least 10% of body weight than placebo at six months, although statistical testing was not done.

Table 6.1.4.4.1.1.A. Percent Body Weight Change from Baseline to 6 Months – LOCF ITT Population

Studies: BM14149, NM14161

Weight Change from Baseline	Placebo (N=448)		Orlistat 60 mg TID (N=452)		Orlistat 120 mg TID (N=451)	
	n	(%)	n	(%)	n	(%)
Gained ≥ 5%	13	(2.9)	6	(1.3)	6	(1.3)
Gained ≥ 0 - < 5%	138	(30.8)	76	(16.8)	59	(13.1)
Lost > 0 - < 5%	194	(43.3)	179	(39.6)	185	(41.0)
Lost ≥ 5 - <10%	78	(17.4)	125	(27.7)	124	(27.5)
Lost ≥ 10%	25	(5.6)	66	(14.6)	77	(17.1)
Total	448	(100.0)	452	(100.0)	451	(100.0)
Lost ≥ 5%	**103**	**(23.0)**	**191**	**(42.3)**	**201**	**(44.6)**
P-value vs. Placebo (Fisher's exact test)			**<0.001**		**<0.001**	

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Although not provided with the nonprescription NDA, this reviewer is including the categorical weight loss results from studies BM14149 and NM14161 at the one-year time point, which was reported in the original review of prescription orlistat.[28] These results are being provided in the event that nonprescription orlistat is ultimately approved for use beyond six months (i.e., chronic

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use, as would be suggested for the medical treatment of any chronic condition). It should be noted that these results are based on completers data.

BM14149 – one year
The percentage of subjects who lost > 5% of baseline body weight was 33%, 52%, and 60% in the placebo-, orlistat 60 mg-, and orlistat 120 mg-treated groups, respectively ($p < 0.01$, orlistat *vs.* placebo). The percentage of subjects who lost > 10% of baseline body weight was 16%, 26%, and 31% in the placebo-, orlistat 60 mg-, and orlistat 120 mg-treated groups, respectively ($p = 0.04$, orlistat 60 mg *vs.* placebo; $p = 0.003$, orlistat 120 mg *vs.* placebo).

NM14161 – one year
The percentage of subjects who lost > 5% of baseline body weight was 25%, 36%, and 47% in the placebo-, orlistat 60 mg-, and orlistat 120 mg-treated groups, respectively ($p < 0.05$, orlistat *vs.* placebo). The percentage of subjects who lost > 10% of baseline body weight was 7%, 17%, and 25% in the placebo-, orlistat 60 mg-, and orlistat 120 mg-treated groups, respectively ($p < 0.01$, orlistat *vs.* placebo).

In study NM17247, the difference in the percent of subjects achieving a 5% weight loss in the orlistat versus placebo-treated subjects did *not* reach statistical significance (Table 6.1.4.4.1.1.B). The percent of subjects achieving a 3% weight loss was significantly greater for the orlistat-compared to the placebo-treated subjects, however (Table 6.1.4.4.1.1.C). A 3% weight loss is not a recognized efficacy benchmark by the Division of Metabolism and Endocrinology Products. Results were similar for the completers population (≥ 5%: 35% *vs.* 45%, placebo *vs.* orlistat, respectively, $p = 0.142$; ≥ 3%: 51% *vs.* 67%, $p = 0.004$).

Table 6.1.4.4.1.1.B. Subjects who Lost ≥ 5% of Baseline Body Weight by 4 months – Study NM17247

	Placebo		Orlistat 60 mg TID		P-value[a]
Observed Data	36.2%	(50/138)	43.5%	(67/154)	0.206
LOCF	28.3%	(52/184)	36.1%	(70/194)	0.104

[a] from Fisher's exact test

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Table 6.1.4.4.1.1.C. Subjects who Lost ≥ 3% of Baseline Body Weight by 4 Months – Study NM17247

	Placebo		Orlistat 60 mg TID		P-value[a]
Observed Data	51.4%	(71/138)	66.9%	(103/154)	0.007
LOCF	41.8%	(77/184)	56.7%	(110/194)	0.004

[a] from Fisher's exact test

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It is of some interest to note that while the proportion of 5% responders at four months in the orlistat 60 mg group (36%) was slightly less than the 60 mg group in the six-month pooled studies (42%), the proportion of responders in the placebo group from study NM17247 was somewhat higher than that of the placebo group in the pooled studies (28% *vs.* 23%, respectively). It is difficult to attribute all of this placebo effect to differences in dietary counseling between the studies (NM17247 appeared to have similar, or possibly slightly greater counseling to study NM14161); therefore, one consideration is whether subjects in this lower

BMI group are more successful with dietary treatment than those in the higher BMI groups, resulting in a smaller drug effect. Additionally, study NM17247 did not utilize a lead-in period, so in some sense, there was a greater opportunity for study subjects to achieve the 5% benchmark. It is unknown whether the absence of a lead-in period would explain the lack of statistical significance seen between the two treatment groups; in any event, the study design of NM17247 better mimics use of drug in a nonprescription setting, given that there is no lead-in period in this setting. The issue of the placebo effect in the different studies will be addressed further in Section 6.1.4.4.1.3, in the discussion of the placebo-subtracted adjusted mean body weight change.

Finally, although one might not necessarily expect a significantly greater number of orlistat- versus placebo-treated subjects to achieve 5% weight loss as early as four months, it is notable that in the pooled studies BM14149 and NM14161, which included patients with higher baseline BMIs than those in study NM17247, a statistically significantly greater number of orlistat 60 mg-treated subjects compared with placebo-treated subjects reached this benchmark at four months (33.6% *vs.* 17.4%; $p < 0.001$). These findings further support the possibility that orlistat may be less effective in overweight compared with obese individuals.

6.1.4.4.1.2 Body Weight Change over Time

In the pooled studies, NM14161 and BM14149, all treatment groups lost similar amounts of weight during the four-week placebo lead-in period. Weight loss was seen as early as 15 days after randomization. At four weeks, a separation of the weight loss effect was apparent from baseline values, with reduction of 1.01%, 1.69%, and 1.81% for placebo, 60 mg, and 120 mg, respectively (Table 6.1.4.4.1.2.A).

The mean percent reduction from baseline weight at the end of 24 weeks was 2.55%, 4.95%, and 5.65% for placebo, orlistat 60 mg, and orlistat 120 mg treatment groups, respectively; equivalent to an unadjusted placebo-subtracted percent weight loss at 24 weeks of 2.4% for orlistat 60 mg and 3.1% for orlistat 120 mg. Although not the time point of interest in the current application, the 52-week results are relevant, and are presented in the table and figures. Observed weight loss is graphically represented in Figure 6.1.4.4.1.2.A, and corroborates the claim that weight loss in the orlistat 60 and 120 mg groups is similar early on in the studies (up to 24 weeks).

Table 6.1.4.4.1.2.A. Body Weight over Time; ITT Population, Pooled Studies										
Treatment Group	**Study Day**	**Value (kg) at Scheduled Visit**			**Change from Baseline Value**			**% Change from Baseline Value**		
		N	**Mean**	**SD**	**N**	**Mean**	**SD**	**N**	**Mean**	**SD**
Placebo	Week -4	446	99.64	14.750	446	2.49	2.035	446	2.63	2.120
	Day 1	448	97.16	14.704	448	0.00	0.000	448	0.00	0.000
	Week 4	439	96.09	14.502	439	-0.96	1.450	439	-1.01	1.509
	Week 12	422	95.16	15.127	422	-1.94	3.420	422	-2.05	3.497
	Week 24	387	94.47	15.424	387	-2.41	4.561	387	-2.55	4.711
	Week 52	304	93.81	16.015	304	-2.40	5.963	304	-2.60	6.200
60 mg TID	Week -4	450	99.69	14.475	450	2.53	2.089	450	2.66	2.186
	Day 1	452	97.26	14.392	452	0.00	0.000	452	0.00	0.000
	Week 4	449	95.67	14.352	449	-1.62	1.556	449	-1.69	1.574
	Week 12	445	93.70	14.778	445	-3.59	3.521	445	-3.75	3.619
	Week 24	407	92.71	15.390	407	-4.73	5.014	407	-4.95	5.088
	Week 52	349	92.16	15.923	349	-5.00	6.217	349	-5.24	6.294
120 mg TID	Week -4	450	98.51	14.126	450	2.52	2.213	450	2.67	2.303
	Day 1	451	95.97	13.791	451	0.00	0.000	451	0.00	0.000
	Week 4	446	94.27	13.677	446	-1.73	1.430	446	-1.81	1.503
	Week 12	441	92.13	13.926	441	-3.89	3.600	441	-4.09	3.734
	Week 24	408	90.48	14.312	408	-5.36	4.920	408	-5.65	5.129
	Week 52	352	89.97	14.737	352	-5.68	6.122	352	-5.97	6.307

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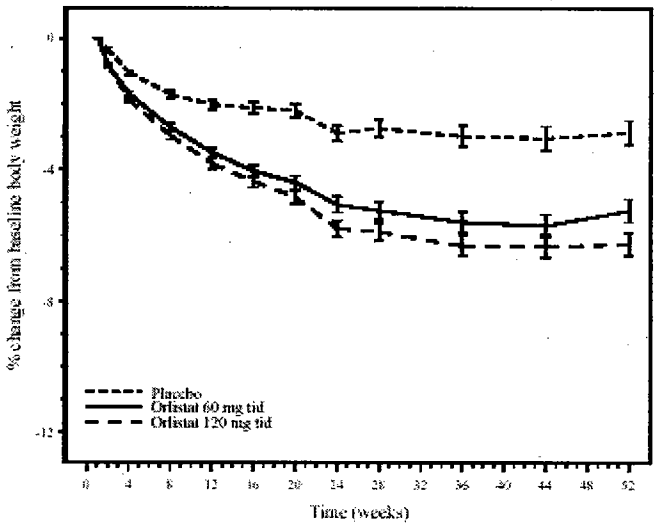
Figure 6.1.4.4.1.2.A.

Mean percent change (±SEM) from baseline weight over time - BM14149 and NM14161



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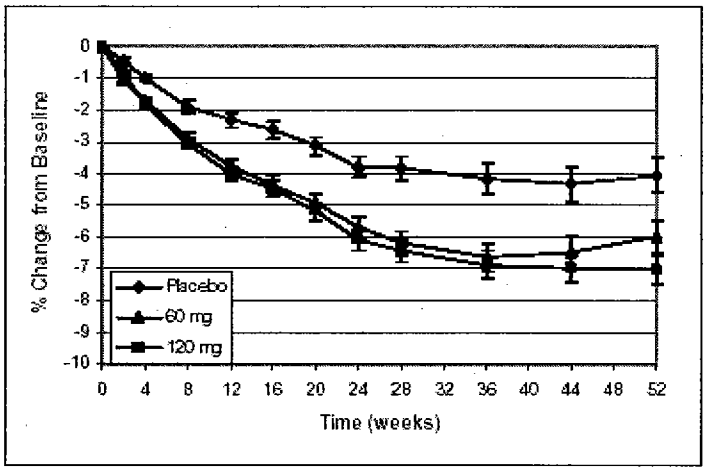
The graphical representation of percent weight loss over time is particularly interesting when assessing the two phase 3 studies separately (Figures 6.1.4.4.1.2.B and 6.1.4.4.1.2.C). BM14149, the study with intensive dietary intervention, demonstrates a robust placebo response, whereas study NM14161, the study with less dietary intervention, demonstrates a minimal placebo response and less weight loss in all groups over time.

Figure 6.1.4.4.1.2.B.

Mean percent change (±SEM) from baseline weight over time - study BM14149



ITT population, observed data

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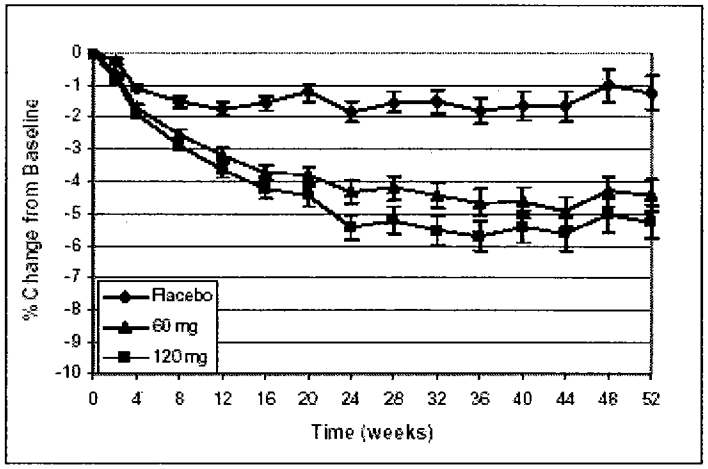
Figure 6.1.4.4.1.2.C.

Mean percent change (±SEM) from baseline weight over time - study NM14161



ITT population, observed data

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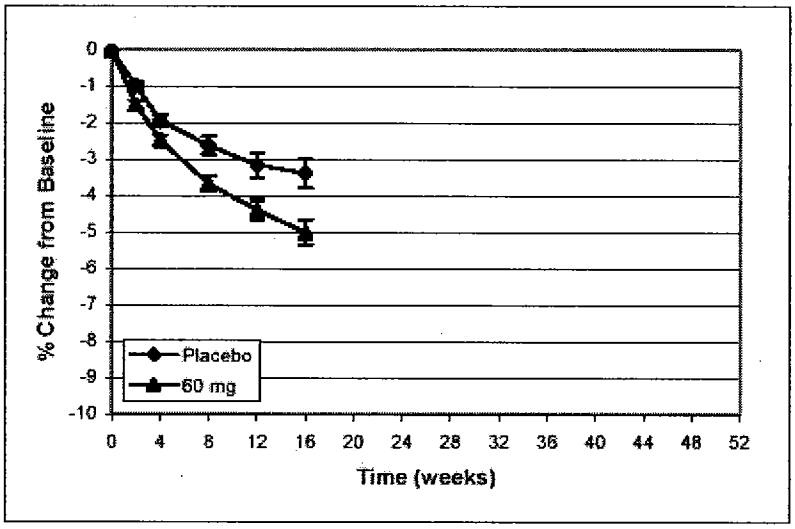
In study NM17247, after 15 days of treatment after randomization, weight loss from baseline was 0.73 kg (1.00%) and 1.10 kg (1.51%) for placebo and orlistat 60 mg, respectively. As

illustrated in Figure 6.1.4.4.1.2.D, after 16 weeks of treatment the mean percent weight reduction from baseline was 2.45 kg (3.38%) and 3.65 kg (5.00%) for subjects randomized to placebo and orlistat 60 mg, respectively; equivalent to a 1.6% placebo-subtracted weight loss (similar to the placebo-subtracted percent weight loss at week 12 in the pooled studies; see Table 6.1.4.4.1.2.A, above). Results were similar for the completers population and somewhat lower in each treatment group in the LOCF ITT population (2.70% *vs.* 4.25%, respectively).

Figure 6.1.4.4.1.2.D.

Mean percent change (±SEM) from baseline weight over time - study NM17247



ITT population, observed data

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6.1.4.4.1.3 Differences in Mean Weight Change (4 - 6 Months)

Table 6.1.4.4.1.3.A demonstrates that there was a statistically significant difference in weight loss between placebo and both the 60 mg and 120 mg orlistat treatment groups in all clinical studies at the time point of interest (six months, pooled studies; four months, NM17247). The least mean square analyses for the ITT observed and completers populations were similar.

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Table 6.1.4.4.1.3.A. Least Squares Mean Differences from Placebo at 6 Months (Weight in kg); LOCF ITT, All Study Sites					
			Difference from Placebo		
Study	Treatment Group	Adjusted Mean Change from BL +/- SE	Adjusted Mean +/- SE	95% Confidence Interval	P-Value
BM14149	Placebo	-2.88 ± 0.318			
	Orlistat 60 mg	-4.89 ± 0.311	-2.02 ± 0.433	(-2.87, -1.17)	<0.001
	Orlistat 120 mg	-5.19 ± 0.314	-2.32 ± 0.430	(-3.16, -1.47)	<0.001
NM14161	Placebo	-0.85 ± 0.310			
	Orlistat 60 mg	-3.37 ± 0.306	-2.52 ± 0.430	(-3.36, -1.67)	<0.001
	Orlistat 120 mg	-4.21 ± 0.307	-3.36 ± 0.434	(-4.21, -2.50)	<0.001
Pooled Studies	Placebo	-1.88 ± 0.223			
	Orlistat 60 mg	-4.14 ± 0.218	-2.29 ± 0.308	(-2.89, -1.68)	<0.001
	Orlistat 120 mg	-4.71 ± 0.221	-2.88 ± 0.309	(-3.49, -2.28)	<0.001
NM17247*	Placebo	-1.90			
	Orlistat 60 mg	-3.05	-1.15 ± 0.31	(-1.76, -0.54)	<0.001

*Applies to least square mean differences at the end of 4 months of therapy.
Studies BM14149, NM14161: means adjusted for site, lead-in weight loss category, baseline weight, baseline weight by site interaction, and interaction between treatment and site.
Pooled studies: means adjusted for study, site nested in study, lead-in weight loss category, baseline weight, baseline weight by site interaction, and interaction between treatment and site nested in study.
Study NM17247: means adjusted for site and baseline value.

The phase 3 study with intensive dietary intervention (NM14149) demonstrated greater weight loss in all groups, including placebo; however, the placebo-subtracted weight loss was numerically lower in this study than in the phase 3 study with less dietary intervention (NM14161). Adjusted mean weight loss in the placebo group in study NM14161 was much lower than that seen in other studies, including the study in subjects with a lower BMI (NM17247). The orlistat 60 mg adjusted mean difference from placebo is numerically less in study NM17247 than in the other studies, probably due to a combination of the lower baseline body weight and the shorter study duration.

It is important to highlight the absolute degree of placebo-corrected weight loss seen in the above studies. For example, in study NM17247 (a lower baseline BMI population to which the nonprescription product is being targeted), one might question the clinical relevance of a 1.2 kg weight loss. Furthermore, in this population, the amount of weight loss conceivably attributable to the diet (1.9 kg, weight loss in the placebo-treated group) is greater than that attributable to the drug (1.2 kg, placebo-subtracted weight loss). (This reviewer also notes that in the best-case scenario, that is, the orlistat 120 mg dose group in the study with intensive dietary intervention, BM14149, the *absolute* mean weight loss over six months was less than a half pound per week.)

Because of the mechanism of action of orlistat, weight loss is likely to be undermined by compensating for the decrease in fat intake/absorption by an increase in carbohydrate or protein intake, and by excessive snacking. Ostensibly, those who lose weight on orlistat without making the necessary lifestyle adjustments will regain weight as soon as the drug is withdrawn. Therefore, compliance with a hypocaloric diet, with fat intake distributed among three meals per day, is critical for successful use of the drug. However, given the degree of interaction with the health care provider, the above studies do not address how well individuals, without interaction

with a healthcare provider, will comply with and benefit from the written educational materials on lifestyle changes that accompany nonprescription orlistat.

6.1.4.4.1.4 Differences in Mean Weight Change (One Year)

The following data, derived from the original study reports from studies BM14149 and NM14161, are provided to demonstrate that although weight loss remains durable over one year, the absolute amount of placebo-subtracted weight loss is still modest; particularly in study BM14149, the phase 3 study with intensive dietary intervention. It is also notable that there is loss of statistical significance in the orlistat 60 mg group at one year in the completers population in this study. This may be a reflection of the benefit that intensive dietary counseling provided the placebo group, particularly in those who completed the study. In study NM14161, under a setting of less dietary intervention, weight loss is minimal in the placebo group after one year, and there is a relatively greater drug effect. Overall, weight loss at the end of one year was modest in this study.

Table 6.1.4.4.1.4.A. Least Square Mean (LSM) Change in Body Weight (kg) from the Start of Double-Blind Treatment to End of 52 Weeks of Treatment; Study BM14149

Analysis Population	Treatment Group	N	LSM Change from Randomization	Difference from Placebo		
				LSM +/- SE	95% CI	p-value
ITT	Placebo	234	-2.53			
	Orlistat 60	237	-4.57	-2.04 +/- 0.55	-3.11, -0.96	0.000
	Orlistat 120	240	-4.91	-2.38 +/- 0.55	-3.45, -1.31	0.000
Completers	Placebo	131	-3.71			
	Orlistat 60	155	-5.15	-1.44 +/- 0.84	-3.08, 0.20	0.085
	Orlistat 120	156	-6.24	-2.53 +/- 0.82	-4.15, -0.92	0.002

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Table 6.1.4.4.1.4.B. Least Square Mean (LSM) Change in Body Weight (kg) from the Start of Double-Blind Treatment to End of 52 Weeks of Treatment; Study NM14161 (all sites)

Analysis Population	Treatment Group	N	LSM Change from Randomization	Difference from Placebo		
				LSM +/- SE	95% CI	p-value
ITT	Placebo	212	-0.33			
	Orlistat 60	237	-3.48	-3.15 +/- 0.52	-4.17, -2.12	0.000
	Orlistat 120	240	-4.12	-3.78 +/- 0.56	-4.81, -2.75	0.000
Completers	Placebo	120	-1.20			
	Orlistat 60	152	-4.42	-3.22 +/- 0.79	-4.77, -1.67	0.001
	Orlistat 120	149	-5.26	-4.05 +/- 0.79	-5.61, -2.50	0.000

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6.1.4.4.1.5 Weight Regain

The issue of weight regain has been addressed both in subjects who remain on orlistat for up to two years, and perhaps more relevant for this nonprescription proposal, in individuals who are on the drug and then discontinue it.

In all the studies out to two years, subjects were on a hypocaloric, or weight loss diet, for the first year, and then were switched over to a eucaloric, or weight maintenance diet, for the second year.

The two-year data from studies BM14149 and NM14161 are demonstrated in Figure 6.1.4.4.1.5.A.[29] The continuation of orlistat for two years clearly demonstrates drug efficacy over placebo in both studies, although all groups, including the orlistat groups, experience mean weight regain. Furthermore, the study with less dietary counseling, NM14161, experiences more weight regain in all groups as compared to the study with more intensive dietary counseling, BM14149.

Figure 6.1.4.4.1.5.A. Weight Change Over Two Years – Completers

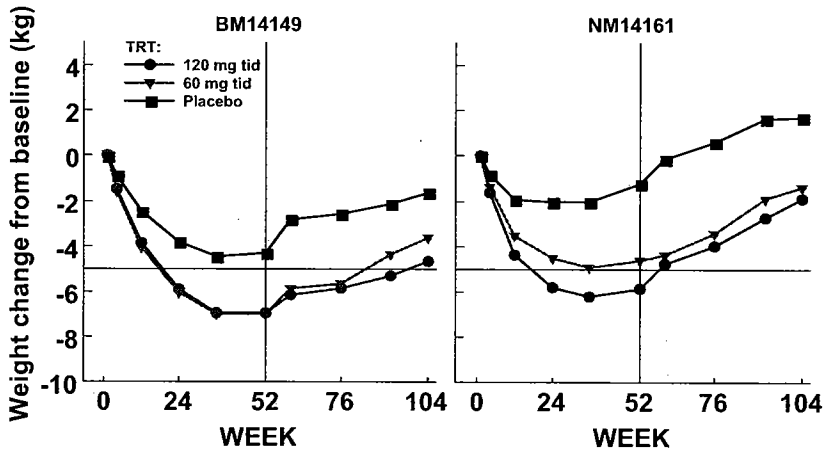

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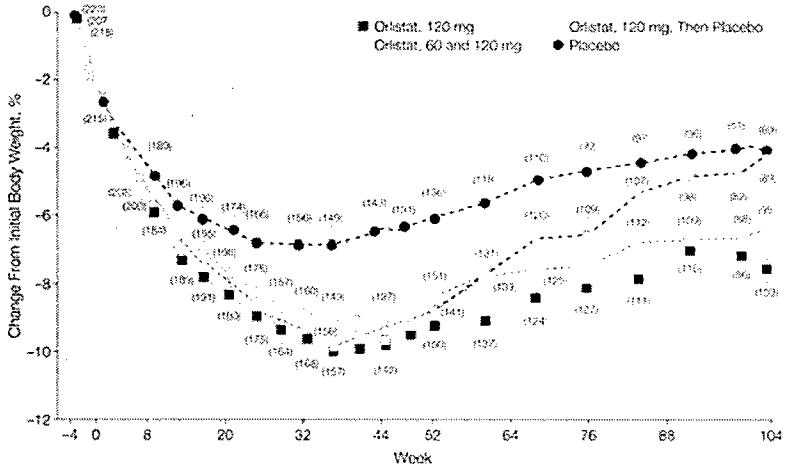
Figure 6.1.4.4.1.5.B illustrates the findings from a two-year study published in JAMA in 1999.[5] This paper was based on a study conducted by Roche in support of the prescription NDA. The study design included a four-week placebo lead-in period, after which time subjects were randomized to placebo or orlistat 120 mg for one year, then the orlistat groups were either given orlistat 120 mg, 60 mg, or placebo for the second year. Dietary instruction was undertaken with the use of dieticians, food records, and behavior modification sessions.

29 Mele, J. Statistical Review of NDA 21-887

Figure 6.1.4.4.1.5.B. Mean Body Weight Change ({+/-}SEM) During 2 Years of Double-Blind Treatment



Davidson, M. H. et al. JAMA 1999;281:235-242.

In those subjects who were originally on orlistat 120 mg and then switched to placebo after one year, subjects gradually regained their weight such that weight change at the end of two years was similar to the weight change as those subjects who were randomized to placebo for the entire two years. This was in the best-case scenario, in which dieticians and behavioral modification were likely a major factor in maintaining some amount of weight loss over this time period, and in addition, these are completers data so the figure does not include the weight change of subjects who dropped out early.

Overweight and obesity are chronic conditions. Similar to drug treatment of other chronic conditions such as hypertension or dyslipidemia, once the drug is stopped, the benefits of the drug are lost. In the case of weight loss drugs, this means lost weight is regained and improvements in co-morbidities reversed.

6.1.4.4.1.6 Subgroup Analysis

In general, the weight loss results from subgroup analyses were similar to the overall results. Lack of statistical significance for certain subgroups [non-white, $\geq$ 65 years, BMI $\geq$ 28 - 30 kg/m^2 (bolded) in pooled studies; male, $\geq$ 65 years, BMI $\geq$ 28 - 30 kg/m^2 in study NM17247] was likely due to small sample sizes and reduced statistical power. It is noteworthy that a population of interest in this application, the BMI group 28 - 30 kg/m^2 has only a marginal placebo-subtracted effect in the pooled studies. Although this finding may reflect low sample size, it speaks to the fact that the database has a limited number of subjects in this BMI range.

It is noted that the subjects treated with orlistat 60 mg in the highest BMI group ($\geq$ 35 kg/m^2) actually had less absolute and placebo-adjusted weight loss than those in the moderately obese group (BMI 30 - 35 kg/m^2). This pattern was not observed for the 120 mg dose.

Table 6.1.4.4.1.6.A. Body Weight Change at 6 Months by Subgroup – BM14149 and NM14161					
	Adjusted Mean Change from Baseline			Adjusted Mean Difference	
Subgroup	**Placebo**	**Orlistat 60 mg TID**	**Orlistat 120 mg TID**	**60 mg vs Placebo**	**120 mg vs Placebo**
	-1.85 ± 0.718	-4.24 ± 0.599	-4.93 ± 0.689	-2.40 ± 0.856	-3.08 ± 0.915
Male	n=67	n=96	n=75	(p=0.006)	(p<0.001)
	-2.02 ± 0.264	-4.32 ± 0.261	-5.02 ± 0.253	-2.30 ± 0.357	-3.00 ± 0.348
Female	N=320	n=311	n=333	(p<0.001)	(p<0.001)
	-2.19 ± 0.251	-4.49 ± 0.239	-5.10 ± 0.241	-2.30 ± 0.334	-2.91 ± 0.335
White	N=368	n=393	n=387	(p<0.001)	(p<0.001)
	-2.67 ± 1.717	-2.38 ± 1.590	-6.59 ± 1.781	0.29 ± 1.886	-3.92 ± 1.532
Non-white	n=19	n=14	n=21	(p=0.879)	(p=0.015)
	-2.16 ± 0.247	-4.41 ± 0.235	-5.12 ± 0.238	-2.25 ± 0.332	-2.96 ± 0.331
< 65 years	N=377	n=398	n=397	(p<0.001)	(p<0.001)
	-0.79 ± 1.295	-5.50 ± 1.304	-3.55 ± 1.247	-4.71 ± 2.019	-2.76 ± 1.807
≥ 65 years	n=10	n=9	n=11	(p=0.045)	(p=0.161)
	-2.13 ± 0.660	**-4.10 ± 0.777**	**-3.76 ± 0.705**	**-1.96 ± 0.958**	**-1.63 ± 0.895**
≥ 28-30 kg/m^2	**n=45**	**n=38**	**n=48**	**(p=0.043)**	**(p=0.072)**
	-2.08 ± 0.336	-4.65 ± 0.307	-4.95 ± 0.307	-2.57 ± 0.448	-2.87 ± 0.445
≥ 30-35 kg/m^2	N=153	n=186	n=180	(p<0.001)	(p<0.001)
	-2.14 ± 0.397	-4.18 ± 0.404	-5.33 ± 0.405	-2.03 ± 0.558	-3.18 ± 0.556
≥ 35 kg/m^2	N=182	n=178	n=177	(p<0.001)	(p<0.001)

Adjusted mean change from baseline was adjusted for study, site nested in study, baseline weight, and lead-in period weight loss category. An interaction term for site by baseline weight was also included for the female, white, and < 65 years subgroups.
There were too few observations to fit a model for the BMI <28 kg/m^2 subgroup.

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Table 6.1.4.4.1.6.B. Body Weight Change at 4 Months by Subgroup – Study NM17247			
	Adjusted Mean Change from Baseline		Adjusted Mean Difference
Subgroup	Placebo	Orlistat 60 mg TID	
Male	-6.62 +/- 1.228	-2.56 +/- 1.237	4.06 +/- 2.275
	n=8	n=9	(p=0.149)
Female	-2.31 +/- 0.292	-3.51 +/- 0.273	-1.20 +/- 0.384
	N=130	n=145	(p=0.002)
White	-2.34 +/- 0.305	-3.56 +/- 0.278	-1.23 +/- 0.399
	N=122	n=138	(p=0.002)
Non-white	-2.07 +/- 0.493	-3.70 +/- 0.548	-1.63 +/- 0.746
	n=16	n=16	(p=0.046)
<65 years	-2.29 +/- 0.291	-3.46 +/- 0.267	-1.17 +/- 0.380
	N=131	n=145	(p=0.002)
≥ 65 years	-3.31 +/- 2.165	-4.48 +/- 2.056	-1.17 +/- 3.468
	n=7	n=9	(p=0.759)
≥ 25-28 kg/m^2	-2.47 +/- 0.308	-3.51 +/- 0.291	-1.04 +/- 0.412
	N=119	n=129	(p=0.012)
≥ 28-30 kg/m^2	-2.31 +/- 0.803	-3.85 +/- 0.590	-1.54 +/- 0.954
	n=16	n=20	(p=0.122)
Adjusted mean change from baseline is adjusted for site and baseline weight. There were too few observations to fit a model for the BMI <25 kg/m^2 subgroup.			

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6.1.4.4.2 Body Mass Index

The following tables demonstrate the change in BMI in both obese and high overweight (Table 6.1.4.4.2.A) and low overweight (Table 6.1.4.4.2.B) subjects. Differences in mean BMI change in the orlistat groups were statistically significant from placebo, and reflect mean weight changes. It is noted that although subjects from the pooled studies were starting with a higher mean baseline BMI (~35 kg/m^2), the mean change from baseline in the placebo group was similar, or even slightly lower than the BMI change in the subjects in the placebo group in four-month study with a lower mean baseline BMI (~27 kg/m^2).

Table 6.1.4.4.2.A. Pooled Studies: BMI Change at 6 Months – LOCF Data, ITT Population								
	Within Treatment			Difference from Placebo				
Treatment	N	Mean Baseline Value	LS Mean Change From Baseline	LS Mean	SE	95% CI Lower	95% CI Upper	P-value
Placebo	448	34.82	-0.66					
Orlistat 60	452	34.59	-1.46	-0.81	0.11	-1.02	-0.60	<0.001
Orlistat 120	451	34.42	-1.66	-1.02	0.11	-1.23	-0.81	<0.001
Analysis was conducted for the pooled studies (BM14149, NM14161) using the ITT population and LOCF data, all sites. Adjusted means are adjusted for study, site nested in study, lead-in period weight loss (≤ 2 kg, >2 kg), baseline BMI, and treatment by site interaction. Baseline was at the end of the lead-in period, at the start of study medication.								

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Table 6.1.4.4.2.B. Study NM17247: BMI Change at 4 Months - LOCF Data, ITT Population								
	Within Treatment			Difference from Placebo				
Treatment	N	Mean Baseline Value	LS Mean Change From Baseline	LS Mean	SE	95% CI Lower	95% CI Upper	P-value
Placebo	184	26.84	-0.71					
Orlistat 60 mg	194	26.82	-1.12	-0.42	0.11	-0.64	-0.20	0.000

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6.1.4.4.3 Anthropometry

The following tables demonstrate the change in waist and hip circumference in both obese (Table 6.1.4.4.3.A) and overweight (Table 6.1.4.4.3.B) subjects.

Table 6.1.4.4.3.A. Change in Anthropometric Measurements at 6 Months – Pooled Studies, LOCF ITT								
Treatment	N	Within Treatment		Difference From Placebo				
		Mean Baseline Value	LS Mean Change From Baseline	LS Mean	SE	95% CI Lower	95% CI Upper	P-Value
Waist Circumference (cm)								
Placebo	361	103.49	-3.45					
Orlistat 60	391	103.76	-4.50	-1.08	0.40	-1.86	-0.30	0.007
Orlistat 120	398	102.60	-4.79	-1.41	0.40	-2.19	-0.64	<0.001
Hip Circumference (cm)								
Placebo	360	118.32	-2.27					
Orlistat 60	391	117.42	-3.72	-1.45	0.31	-2.06	-0.83	<0.001
Orlistat 120	398	117.23	-4.24	-1.97	0.31	-2.58	-1.36	<0.001
Analysis was conducted for the pooled studies (NM14149, BM14161) using the ITT population and observed data. Adjusted means for waist circumference are adjusted for study, site nested in study, lead-in period weight loss (<2 kg, ≥2 kg), baseline waist circumference, baseline waist circumference by site nested in study interaction, and treatment by site nested in study interaction. Adjusted means for hip circumference are adjusted for study, site nested in study, lead-in weight loss, and baseline hip circumference.								

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Table 6.1.4.4.3.B. Change in Anthropometric Measurements at 4 Months – NM17247, LOCF ITT								
Treatment	N	Within Treatment		Difference From Placebo				
		Mean Baseline Value	LS Mean Change From Baseline	LS Mean	SE	95% CI Lower	95% CI Upper	P-Value
Waist Circumference (cm)								
Placebo	184	85.61	-2.73					
Orlistat 60	194	84.90	-3.70	-0.97	0.43	-1.82	-0.11	0.026
Hip Circumference (cm)								
Placebo	184	104.33	-2.64					
Orlistat 60	194	103.89	-3.44	-0.80	0.39	-1.57	-0.04	0.040
Waist/Hip Ratio								
Placebo	184	0.82	-0.01					
Orlistat 60	194	0.82	-0.01	-0.00	0.00	-0.01	0.00	0.403

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Since both the waist and hip circumferences decreased to a similar extent, there was no statistically significant change in waist-to-hip ratio in pooled studies (analysis not provided) or study NM17247 (Table 6.1.4.4.3.B). The sponsor comments:

Waist circumference was used as a measure of upper body obesity and hip circumference as a measure of lower body obesity. Changes in each of these measurements are better indicators of change in overweight and obese status than change in the waist:hip ratio. The reason is that when the change in waist circumference and hip circumference are similar in magnitude and direction, the ratio of waist:hip circumference will not be sensitive to these changes.

This is true; however, if one was interested in whether there were metabolic changes attributed to the weight loss, the mean change in waist-to-hip ratio might be important as an indicator of preferential loss of central adiposity. It is well-established that weight loss causes a loss in "inches", so a decrease in waist and hip circumference would be expected to be proportional to the amount of weight lost (i.e., one would expect that subjects in the orlistat group had a greater decrease in waist and hip circumference as more weight was lost in this group).

6.1.4.4.4 Quality of Life

Quality of life measures for studies BM14149 and NM14161 were performed at baseline (the beginning of the lead-in period) and after 52 weeks of treatment (or at the time of premature withdrawal). The primary measures were changes in Satisfaction with Treatment, Overweight Distress, and Depression. The self-administered questionnaire was developed and validated specifically for Hoffman-La Roche.

Quality of life scores actually decreased (i.e., became less favorable) from baseline for both orlistat- and placebo-treated groups for the majority of questions. In study BM14149 (intensive dietary counseling), the only statistically significant change in quality of life measures for the orlistat treatment groups compared to placebo was satisfaction with medication for weight loss. In study NM14161, all quality of life measures in the orlistat-treated subjects were statistically significantly different (less negative) than those in the placebo-treated group ($p < 0.01$). In the subjects randomized to placebo, these measures appear to decrease less in the study with intensive dietary counseling (BM14149) than in the study without such counseling (NM14161).

Although technically, overweight distress and depression could be considered safety measures, they are briefly mentioned here with the rest of the quality of life measures for studies BM14149 and NM14161. There was no significant difference in the orlistat-treatment groups from placebo in the overweight distress and depression scores in these two studies. Overweight distress decreases in all treatment groups in both studies. However, it is noted that the depression scores actually *increased* from baseline in all treatment groups (after an initial decrease in the placebo lead-in) for both studies.

The three-question treatment satisfaction questionnaire that was administered in study NM17247 appears to have been the same questionnaire used in studies BM14149 and NM14161. Most treatment satisfaction assessments were similar in the placebo and orlistat treatment groups; however, a higher percentage of placebo-treated patients reported being either 'somewhat

dissatisfied' or 'very dissatisfied' with both study medication and the progress of weight loss than orlistat-treated patients. Statistical testing was not performed.

6.1.4.5 Supportive Studies

6.1.4.5.1 Study BM14150

Study BM14150 was a phase 2 dose-ranging protocol comparing 24 weeks of treatment with orlistat 30, 60, 120, 240 mg, and placebo, in a multi-center, double-blind, randomized, double-dummy, placebo-controlled, parallel design. Subjects included men and non-pregnant women ≥ 18 years of age with a BMI 28 - 43 kg/m^2. Subjects entered the randomized treatment phase after a four-week placebo lead-in period. Subjects received dietary counseling throughout the study.

Table 6.1.4.5.1.A. Number of Subjects

	Randomized	Efficacy (ITT)
Placebo	125	123
30 mg TID	122	122
60 mg TID	124	123
120 mg TID	122	120
240 mg TID	120	117

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Table 6.1.4.5.1.B demonstrates that subjects in the orlistat 60 mg TID, 120 mg TID, and 240 mg TID groups had a statistically significantly greater decrease in body weight than the placebo treatment group at Week 24. Although it appears that a greater proportion of orlistat-treated patients lost more than 10% of initial body weight than did placebo-treated patients in a dose-related manner, statistical testing on these categorical data was not provided. Similarly, a modestly greater proportion of orlistat-treated subjects lost > 5% of body weight than placebo (51.2% placebo *vs.* 61.8% orlistat 60 mg); although, again, statistical testing was not provided.

Table 6.1.4.5.1.B. Change in Body Weight, ITT Population

Parameter	Placebo	30 mg tid	60 mg tid	120 mg tid	240 mg tid
	Change in Body Weight (ITT Population)				
Difference from placebo of least squares mean change in body weight from start of double-blind treatment to Week 24 (p-value)	-	-0.95 (0.106)	-1.86 (0.002)	-2.55 (0.000)	-2.81 (0.000)
Mean % change (SD) from initial body weight at Week 24	-6.45 (5.84)	-8.49 (6.09)	-8.79 (5.99)	-9.76 (5.40)	-9.29 (5.82)
No. (%) patients losing >10% of initial body weight at Week 24	23 (18.7)	34 (27.9)	34 (27.6)	44 (36.7)	44 (37.6)

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6.1.4.5.2 Uncontrolled Studies

In support of the nonprescription indication for orlistat, the sponsor conducted two uncontrolled studies to evaluate actual use (NM17285) and use in a naturalistic setting (RCH-ORL-002):

Table 6.1.4.5.2.A. Level of Dietary Intervention in Uncontrolled Studies

Study	Dose (mg)	Study Duration	Study Design	Dietary Instruction and Intervention	Behavioral Modification	Exercise
RCH-ORL-002 N = 162	60	1 month	Open-label, uncontrolled, multi-center, mall intercept	No clinical visits during study duration	Self-instructional materials	Self-instructional
NM17285 N = 237	60-120	3 months	Open-label, uncontrolled, pharmacy-based sites	No clinical visits during study duration Self-instructional materials	Self-instructional materials	Self-instructional

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These studies will be discussed in more detail in Section 7 in order to address the safety issues surrounding this product in a nonprescription setting, and by FDA reviewers from the Division of Nonprescription Drug Evaluation. Although weight findings are briefly summarized below, these studies are in *no* way considered to be informative regarding how effective this drug is in the nonprescription setting, given the lack of a comparator treatment group.

6.1.4.5.2.1 Study NM17285

In this three-month actual use study, 'efficacy' was assessed based on self-reported weight loss, measured weight loss, satisfaction with the study drug, and perceived efficacy. Although reported weight loss appears to be similar to measured weight loss (Tables 6.1.4.5.2.1.A and 6.1.4.5.2.1.B, respectively); recall bias is highly likely for the former and loss to follow-up bias is highly likely for the latter.

Note: the amount of weight lost was asked *only* of subjects who indicated that they had lost weight (this is shown in the first row of Table 6.1.4.5.2.1.A).

Table 6.1.4.5.2.1.A. Self-Reported Weight Loss (Users Group N=237)								
	Day 14 Interview		Day 30 Interview		Day 60 Interview		Day 90 Interview	
Self-Reported Weight Loss[a]	(N=217)		(N=219)		(N=197)		(N=148)	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects who lost weight since starting orlistat	98	(45.2)	161	(73.5)	164	(83.2)	134	(90.5)
1 - 5 pounds	71	(72.4)	81	(50.3)	47	(28.7)	24	(17.9)
6 - 10 pounds	17	(17.3)	54	(33.5)	64	(39.0)	51	(38.1)
11 - 15 pounds	3	(3.1)	9	(5.6)	27	(16.5)	29	(21.6)
16 - 20 pounds	0		2	(1.2)	11	(6.7)	11	(8.2)
21 - 25 pounds	0		0		1	(0.6)	10	(7.5)
>25 pounds	0		1	(0.6)	4	(2.4)	6	(4.5)
Missing	7	(7.1)	14	(8.7)	10	(6.1)	3	(2.2)
Mean ± SD	4.2 +/- 3.02		5.9 +/- 3.87		9.3 +/- 6.15		11.7 +/- 7.39	
Median	3		5		8		10	
Range	1 - 15		1 - 30		2 - 45		2 - 45	
N	91		147		154		131	

[a] amount of weight lost was asked only of subjects who indicated that they had lost weight

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Table 6.1.4.5.2.1.B. Measured Weight Loss (Users Group N=237)								
	Time of Measurement[a]							
	1 - 30 Days		31-60 Days		>60 Days		Final Return Visit[b]	
Measured Weight Loss	(N=37)		(N=77)		(N=60)		(N=106)	
	N	(%)	n	(%)	n	(%)	n	(%)
Gained weight	3	(8.1)	12	(15.6)	7	(11.7)	15	(14.2)
Lost no weight	0		2	(2.6)	2	(3.3)	4	(3.8)
≤ 5 pounds	18	(48.6)	29	(37.7)	12	(20.0)	33	(31.1)
6 - 10 pounds	8	(21.6)	21	(27.3)	10	(16.7)	28	(26.4)
11 - 15 pounds	1	(2.7)	8	(10.4)	9	(15.0)	11	(10.4)
16 - 20 pounds	2	(5.4)	3	(3.9)	5	(8.3)	5	(4.7)
21 - 25 pounds	1	(2.7)	1	(1.3)	5	(8.3)	6	(5.7)
> 25 pounds	0		0		4	(6.7)	4	(3.8)
Missing	4	(10.8)	1	(1.3)	6	(10.0)	0	
Mean +/- SD	5.5 +/- 5.70		5.1 +/- 5.72		10.1+/- 11.84		7.2 +/- 9.64	
Median	4		5		8		6	
Range	-6 - 21		-7 - 24		-8 - 52		-8 - 52	
N	33		76		54		106	

[a] days from enrollment to pharmacy visit; the last measurement in each interval was tabulated
[b] measurement taken at subject's final pharmacy visit, regardless of time from enrollment

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There was a mean weight loss in those subjects who returned for a weight measurement of 7.2 lbs +/- 9.6 lbs at the final visit. Interestingly, 12-15% of subjects who returned for weight measures actually gained weight after the first month. Without a placebo group, however, it is impossible to evaluate the clinical significance of these findings. Again, as stated above, follow-up bias (i.e., subjects who lost weight are more likely to follow up than those who did not) may have materially influenced the weight loss results in this uncontrolled study.

In terms of satisfaction with orlistat, approximately 80% of subjects indicated they were satisfied or very satisfied; most subjects reporting 'weight loss' and 'the drug was working' as reasons. The degree of satisfaction increased with the amount of weight lost. Ten (10) – 15% of subjects were not satisfied and the main reason provided (60%) was lack of weight loss. Negative side effects were the reason provided by about 25%.

Table 6.1.4.5.2.1.C. Satisfaction with Orlistat (Users Group N=237)								
	Day 14 Interview (N=217)		Day 30 Interview (N=219)		Day 60 Interview (N=197)		Day 90 Interview (N=148)	
Satisfaction	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
Very satisfied	65	(30.0)	70	(32.0)	61	(31.0)	56	(37.8)
Satisfied	109	(50.2)	112	(51.1)	98	(49.7)	64	(43.2)
Unsatisfied	11	(5.1)	20	(9.1)	23	(11.7)	15	(10.1)
Not at all satisfied	6	(2.8)	9	(4.1)	9	(4.6)	8	(5.4)
No answer	25	(11.5)	6	(2.7)	4	(2.0)	2	(1.4)
Missing	1	(0.5)	2	(0.9)	2	(1.0)	3	(2.0)

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6.1.4.5.2.2 Study RCH-ORL-002

In this one-month consumer use study, efficacy assessments were based on body weight data before and after treatment with orlistat in 141 subjects whose self-reported weight information was available. The mean decrease in body weight was statistically significant (mean change: -8 lbs, $p < 0.001$, two-sided paired t-test); although, again, it is impossible to derive any conclusions from these findings without a placebo group and considering likely reporting bias.

Table 6.1.4.5.2.2.A. Summary of Body Weight before and after Study Drug Usage	
VARIABLE	TOTAL
Number of Subjects	141
Beginning Weight (lbs)	
Mean	214.85
SD	41.17
Range	153.0-391.0
Ending Weight (lbs)	
Mean	206.38
SD	40.64
Range	141.0-380.0
Change[a] (lbs)	
Mean	-8.29
SD	6.39
Range	-34.0-2.0
[a] Change calculated as ending weight minus beginning weight.	

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6.1.5 Clinical Microbiology

Not applicable (orlistat is not an antimicrobial).

6.1.6 Efficacy Conclusions

Given the sponsor's proposal to market nonprescription orlistat for short-term use, the six-month time point was chosen as the efficacy endpoint of interest from the two prescription NDA clinical studies (BMI 28 - 43 kg/m^2). In these studies, which were pooled due to similar study designs and patient populations, 42% of subjects treated with orlistat 60 mg, 45% of subjects treated with orlistat 120 mg, and 23% of those treated with placebo achieved a weight loss of $\geq$ 5% at six months ($p < 0.001$, orlistat *vs.* placebo). Placebo-subtracted mean weight loss in the two prescription NDA clinical studies at six months was 2.3 kg (~2.4%) in subjects on the 60 mg dose and 2.9 kg (~3.1%) in those on the 120 mg dose.

By contrast, in the nonprescription NDA clinical study (BMI 25 - 28 kg/m^2), 36% of orlistat 60 mg-treated subjects *vs.* 28% of placebo-treated subjects lost at least 5% of their baseline body weight at four months (between-group difference non-significant, $p = 0.104$). In the nonprescription NDA clinical study, after four months of treatment with orlistat 60 mg, the placebo-subtracted mean weight loss was 1.2 kg (~1.6%).

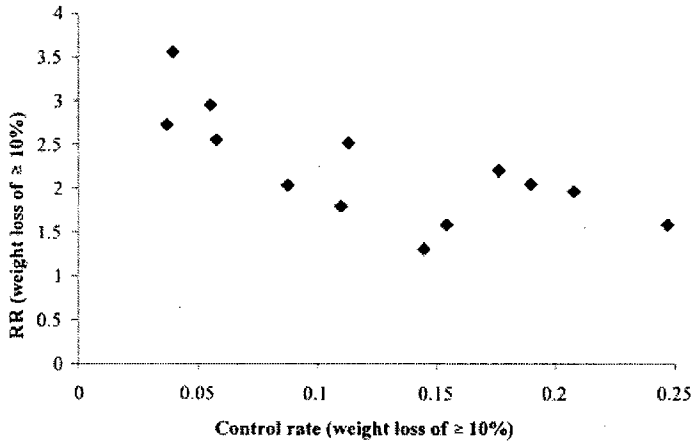
These findings raise the possibility that orlistat may be less effective in mildly overweight individuals (i.e., BMI*s* 25 - 28 kg/m^2) than in obese subjects. However, because the sponsor has not studied the effects of six months of orlistat therapy in mildly overweight subjects, we can only make assumptions about the six-month efficacy in this group.

Because the two prescription studies in subjects with BMI 28 - 43 kg/m^2 had differing degrees of lifestyle intervention (one study utilized dieticians and regular collection of food records were used to provide feedback, and the other occurred in the primary care physicians' offices where subjects were provided general encouragement, but no specialized counseling), the differential findings help inform efficacy issues related to dietary compliance. For example, there was less of a treatment and dose effect in the study with intensive lifestyle modification, although overall, weight loss was greater in this study. This finding is supported by a recent meta-analysis, in which the "relative risk" of $\geq$ 10% weight loss in the orlistat studies as compared to the rate in the control group in one-year studies was calculated (similar results were found at $\geq$ 5% weight loss, not shown).[30] Figure 6.1.6.A from the referenced paper demonstrates declining beneficial effect of orlistat noted with increased rates of success in the control group. The authors concluded that this finding "emphasizes the degree to which following a hypocaloric diet (and perhaps increasing physical activity) can influence weight loss." This finding supports the contention that the better the adjunctive lifestyle program, the less of a benefit one may derive from orlistat.

Given the importance of these lifestyle measures for weight loss, weight maintenance, and overall health, this reviewer believes that the approval of nonprescription orlistat (a setting in which lifestyle changes are not being monitored, drug compliance is not being monitored, and a risk-benefit analysis is not being done) would be sending the wrong public health message.

30 Hutton B, et al. Am J Clin Nutr. 2004 Dec;80(6):1461-8.

Figure 6.1.6.A. Relative risk of clinically important weight loss versus the rate in the control group in 1-y studies.



Hutton B, et al. Am J Clin Nutr. 2004 Dec;80(6):1461-8.

In conclusion, GlaxoSmithKline (or previously, Roche) has shown in randomized, placebo-controlled clinical trials that: 1) subjects with BMIs $\geq$ 28 kg/m^2 lose a clinically significantly[2] greater amount of weight loss on orlistat as compared to those on placebo when receiving lifestyle intervention under the supervision of a health care provider; 2) subjects with BMIs $\geq$ 25 kg/m^2 lose a statistically, but not necessarily a clinically, significantly greater amount of weight with orlistat than placebo when receiving lifestyle intervention under the supervision of a health care provider; 3) changes in co-morbidities are what one would expect with the observed changes in body weight; and 4) under health care provider supervision, when orlistat is discontinued, weight is regained, irrespective of the concomitant lifestyle intervention received.

In this reviewer's opinion, deficiencies in the efficacy database, such as the fact that GSK has not demonstrated that consumers are able to lose more weight than placebo under "actual use" conditions, necessitates a long-term (e.g., one year) placebo-controlled actual use study.

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

7.1.1 Deaths

There were four deaths reported in the studies supporting this NDA; all were in studies from the original prescription NDA. Two deaths occurred during the lead-in period: one death in a woman in study NM14302 after she was struck by an automobile, and one death in a woman in study BM14150 who had a respiratory arrest (asthma). The other two deaths were due to myocardial infarctions in subjects randomized to orlistat; one experienced by a man in study

BM14149 (60 mg TID) and another man in study NM14161 (120 mg TID). This reviewer cannot reasonably attribute either of these deaths to the drug. Narratives of these deaths are listed in the Appendix (Section 10.1). There were no deaths in studies NM17247, RCH-ORL-002, or NM17285.

Four additional deaths were noted in the phase 3 studies from the original prescription NDA that were not reviewed for his NDA: one subject from the lead-in period (MVA), one subject in the placebo-treated group (MVA), one subject in the orlistat 120 mg-treated group (cardiac arrest), and one subject in the orlistat 120 mg/placebo-treated group, during the placebo-treated period (MVA). No suspicion was raised that orlistat was a causative agent.

A total of 58 crude reports of death were found in AERS with orlistat as suspect or secondary drug. Most of the deaths were cardiovascular in nature. There was no obvious pattern or reason to suspect that orlistat contributes to cardiovascular mortality.

7.1.2 Other Serious Adverse Events

7.1.2.1 Pooled studies

Table 7.1.2.1.A demonstrates that the incidence of serious adverse events (SAE*s*) in the pooled studies during the first six months of treatment was similar across the treatment groups (3.5% placebo, 3.4% orlistat 60 mg, and 3.5% orlistat 120 mg).

The incidence of gastrointestinal (GI) SAE*s* was similar between treatment groups; even though, as described in Section 7.1.4.1, the incidence of GI adverse events overall was greater in the orlistat-treated groups. During the first six months of treatment, there was one SAE of lower abdominal pain in the orlistat 120 mg group, and one SAE of abdominal pain in the orlistat 60 mg group. The lower abdominal pain occurred on the first day of treatment in a 34-year-old female receiving orlistat 120 mg. The pain was moderate in intensity, the duration was 264 days, and the subject recovered. The case of abdominal pain occurred in a 38-year-old female on Day 72 of treatment with orlistat 60 mg. The pain was severe in intensity, the duration was nine days, and the subject recovered. Neither of these subjects was discontinued due to these adverse events.

One case of colon adenocarcinoma in a polyp was reported in a 49-year-old female subject in the orlistat 60 mg group who had a family history of colon carcinoma. She complained of rectal bleeding on Day 89. On Day 198, a colonoscopy revealed a polyp with well-differentiated adenocarcinoma. It was successfully treated by a polypectomy. One subject (62-year-old female) in the orlistat 120 mg dose group experienced GI bleeding due to a peptic ulcer. The subject was also taking naproxen to treat rheumatoid arthritis. Neither of these subjects was discontinued due to these adverse events.

Table 7.1.2.1.A. Serious Adverse Events in First 6 Months of Treatment, Safety Population						
Body System	**Placebo**		**60 mg TID**		**120 mg TID**	
	N = 634		**N = 623**		**N = 632**	
Preferred Term	**n (%)**	**NAE**	**n (%)**	**NAE**	**n (%)**	**NAE**
# Subjects with at Least One SAE	22 (3.5)	23	21 (3.4)	24	22 (3.5)	24
Reproductive Disorders, Female	3 (0.5)	3	2 (0.3)	3	5 (0.8)	5
Neoplasm Breast Female	0	0	1 (0.2)	1	2 (0.3)	2
Tumor Breast	0	0	0	0	1 (0.2)	1
Uterovaginal prolapse	0	0	0	0	1 (0.2)	1
Vaginal prolapse	0	0	0	0	1 (0.2)	1
Carcinoma cervix	0	0	1 (0.2)	1	0	0
Cervial dysplasia	0	0	1 (0.2)	1	0	0
Urinary System Disorders	0	0	0	0	3 (0.5)	4
Urinary Incontinence	0	0	0	0	2 (0.3)	2
Bladder prolapse	0	0	0	0	1 (0.2)	1
Ureteral calculus	0	0	0	0	1 (0.2)	1
Gastro-Intestinal System Disorders	3 (0.5)	3	5 (0.8)	5	2 (0.3)	2
Abdominal pain lower	0	0	0	0	1 (0.2)	1
GI hemorrhage	0	0	0	0	1 (0.2)	1
Hernia Inguinal	0	0	2 (0.3)	2	0	0
Abdominal pain	0	0	1 (0.2)	1	0	0
Colon carcinoma	0	0	1 (0.2)	1	0	0
Diverticulitis	0	0	1 (0.2)	1	0	0
Liver And Biliary System Disorders	4 (0.6)	4	3 (0.5)	3	2 (0.3)	2
Cholecystitis	3 (0.5)	3	2 (0.3)	2	1 (0.2)	1
Cholelithiasis	0	0	1 (0.2)	1	1 (0.2)	1
Biliary colic	1 (0.2)	1	0	0	0	0
Musculo-Skeletal System Disorders	4 (0.6)	4	2 (0.3)	2	2 (0.3)	2
Pain Knee	0	0	0	0	1 (0.2)	1
Sprains and strains	0	0	0	0	1 (0.2)	1
Intervertebral Disc Disorder	1 (0.2)	1	1 (0.2)	1	0	0
Pain nape	0	0	1 (0.2)	1	0	0
Myo-, Endo-, Pericardial & Valve Disord.	1 (0.2)	1	0	0	2 (0.3)	2
Angina Pectoris	1 (0.2)	1	0	0	1 (0.2)	1
Malf. Of prostheses and hemographs	0	0	0	0	1 (0.2)	1
Psychiatric Disorders	1 (0.2)	1	0	0	2 (0.3)	2
Depression	1 (0.2)	1	0	0	1 (0.2)	1
Suicide attempt	0	0	0	0	1 (0.2)	1
Respiratory System Disorder	0	0	2 (0.3)	2	1 (0.2)	1
Chronic obstructive lung disease	0	0	0	0	1 (0.2)	1
Dyspnea	0	0	1 (0.2)	1	0	0
Sinusitis	0	0	1 (0.2)	1	0	0
Central & Periph. Nervous Syst. Disord.	1 (0.2)	1	1 (0.2)	1	1 (0.2)	1
Headache	0	0	0	0	1 (0.2)	1
Neuralgia sciatic	0	0	1 (0.2)	1	0	0
Heart Rate And Rhythm	0	0	1 (0.2)	1	1 (0.2)	1
Fibrillation atrial	0	0	0	0	1 (0.2)	1
Paroxysmal superventricular tachycardia	0	0	1 (0.2)	1	0	0
Endocrine Disorders	0	0	0	0	1 (0.2)	1
Tumor thyroid	0	0	0	0	1 (0.2)	1
Vascular (Extracardiac) Disorders	0	0	0	0	1 (0.2)	1
Varicose veins	0	0	0	0	1 (0.2)	1

Table 7.1.2.1.A. Serious Adverse Events in First 6 Months of Treatment, Safety Population						
Body System	**Placebo N = 634**		**60 mg TID N = 623**		**120 mg TID N = 632**	
Preferred Term	**n (%)**	**NAE**	**n (%)**	**NAE**	**n (%)**	**NAE**
Body As A Whole - General Disorders	5 (0.8)	5	3 (0.5)	3	0	0
Surgical Procedure	4 (0.6)	4	3 (0.5)	3	0	0
Autonomic Nervous System Disorder	0	0	1 (0.2)	1	0	0
Syncope	0	0	1 (0.2)	1	0	0
Cardiovascular Disorders	0	0	1 (0.2)	1	0	0
Cardiac failure	0	0	1 (0.2)	1	0	0
Skin And Appendages Disorders	0	0	1 (0.2)	1	0	0
Pruritus	0	0	1 (0.2)	1	0	0
Urticaria	0	0	1 (0.2)	1	0	0
Resistance Mechanism Disorders	1 (0.2)	1	0	0	0	0
n (%) is the number (percentage) of subjects who experienced the event; NAE is the number of occurrences of the event. Preferred Terms with 0 AEs in either orlistat group were omitted from the table.						

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In the evaluation of SAE*s* in the first year of treatment, as with the first six months, the incidence of SAE*s* overall was similar between groups (5.8% placebo, 5.9% orlistat 60 mg, and 5.4% orlistat 120 mg). There was a slight numerical imbalance of GI SAE*s* in the orlistat groups as compared to placebo (4/634, 0.6% placebo; 7/623, 1.1% orlistat 60 mg; 5/632, 0.8% orlistat 120 mg); however, there was no dose-response. Please see the Appendix (Section 10.3.1) for a full listing of the SAE*s* from the first year of the pooled studies.

Although there has been some concern that orlistat may be lithogenic and a potential contributor to gallbladder disease (see Section 7.1.12.2.2.1), the incidence of adverse events of cholelithiasis and cholecystitis combined is similar between orlistat and placebo up to the first six months of treatment. There were three additional subjects who developed SAE*s* of cholecystitis in the second six months of treatment; however, two of the three subjects were in the placebo group. There were three more subjects with SAE*s* of cholelithiasis in the one-year data compared to the six-month data. One of the subjects was randomized to placebo and two were randomized to orlistat 120 mg. It should be noted that one subject with an SAE of cholelithiasis randomized to orlistat 60 mg developed gallstone pancreatitis (see Section 7.1.12.2.2.2).

7.1.2.2 Study NM17247

In study NM17247, there were two SAE*s* in the orlistat 60 mg group (2/196, 1.0%) and none in the placebo group (0/195): a 47-year-old White female had an umbilical hernia repair on study day 35, and a 41-year-old White female was hospitalized for a herniated disk reinjury on study day 79. Neither event appears to have been related to the drug. Please see the Appendix (Section 10.2) for narratives of these events.

7.1.2.3 Study BM14150

In the 24-week study BM14150, the number (%) of subjects who reported at least one SAE is as follows: placebo, 2 (1.6%); orlistat 30 mg, 6 (4.9%); orlistat 60 mg, 2 (1.6%); orlistat 120 mg, 1 (0.8%); and orlistat 240 mg, 3 (2.6%).

There were four reports of SAE*s* of abdominal pain; three events were not specified (one each in subjects randomized to orlistat 30, 60, and 240 mg) and one was attributed to diverticulitis (orlistat 30 mg). All but one of these subjects (orlistat 240 mg) prematurely discontinued from the study. The subject randomized to orlistat 60 mg TID who reported severe abdominal pain was a 28-year-old White female. The event started on study day 97 and the subject was discontinued from the study on day 108. Her symptomatology continued and she was hospitalized five days later. She underwent an extensive workup including upper and lower endoscopies and abdominal CT; however, no diagnosis could be established and she was discharged five days later. Her symptoms subsided 17 days after her last dose of orlistat.

7.1.2.4 Study NM17285

In the three-month actual use study, five subjects (1.8%) experienced six SAE*s* (Table 7.1.2.4.A). One subject, a 46-year-old Black female with a history of iron-deficiency anemia, developed an SAE of abdominal pain one month after starting on orlistat 60 mg TID associated with severe nausea and vomiting. She was hospitalized but the cause of her abdominal pain was not established. Diagnostic tests included CT and ultrasound of the abdomen. All tests were negative except for a low blood count, for which the physician recommended a transfusion. She was discharged one day later and her abdominal pain resolved four days after discharge.

A 48-year-old White female developed severe, crushing chest and jaw pain (preferred term = chest pain) five weeks after starting treatment with orlistat. An emergency room cardiac work-up was negative, and she was discharged with a diagnosis of esophageal spasm.

Table 7.1.2.4.A. Summary of Serious Adverse Events, Safety Population		
	Orlistat 60 mg N = 284	
System Organ Class Preferred Term	**n (%)**	**NAE**
Subjects With At Least One Serious Adverse Event	5 (1.8)	6
Infections And Infestations	2 (0.7)	2
Kidney Infection NOS	1 (0.4)	1
Methicillin-Resistant Staphylococcal Aureus Infection	1 (0.4)	1
Gastrointestinal Disorders	1 (0.4)	1
Abdominal Pain NOS	1 (0.4)	1
General Disorders And Administration Site Conditions	1 (0.4)	1
Chest Pain NEC	1 (0.4)	1
Pregnancy, Puerperium And Perinatal Conditions	1 (0.4)	1
Abortion Spontaneous NOS	1 (0.4)	1
Vascular Disorders	1 (0.4)	1
Transient Ischaemic Attack	1 (0.4)	1

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7.1.2.5 Study RCH-ORL-002

There were no SAE*s* reported in this four-week consumer use study.

7.1.3 Dropouts and Other Significant Adverse Events

7.1.3.1 Overall profile of dropouts

Tables 7.1.3.1.A and 7.1.3.1.B detail the causes of premature discontinuation in the pooled studies and study NM17247, respectively. The first year of the pooled studies was tabulated by the sponsor, and the first 24 weeks (second half of Table 7.1.3.1.A) was compiled by this reviewer and therefore should be considered exploratory. Both tables demonstrate that placebo-treated subjects were more likely to discontinue than orlistat-treated subjects, although orlistat-treated subjects were more likely to discontinue due to an adverse event (see Section 7.1.3.2, below), with about twice as many subjects treated with orlistat 60 mg discontinuing as those treated with placebo. Subjects treated with orlistat 120 mg had slightly more discontinuations due to adverse events than those treated with 60 mg. Rates of discontinuation are slightly higher in the four-month study (NM17247, low overweight population) than in the first 24 weeks (six months) of the pooled studies (high overweight and obese population) for both placebo and orlistat groups.

This reviewer considers that reasons for discontinuation such as, 'refused treatment', 'lost to follow-up', or 'did not cooperate', may be related to subjects not losing weight. This may describe the imbalances between placebo and orlistat due to these reasons.

Table 7.1.3.1.A. Reasons for Premature Withdrawal during the First Year of Treatment; Pooled Phase III Studies						
	Placebo		Orlistat 60 mg TID		Orlistat 120 mg TID	
Reason for Withdrawal	(N=634) n (%)		(N=623) n (%)		(N=632) n (%)	
First Year						
Total subjects withdrawn	220	(34.7)	156	(25.0)	175	(27.7)
Adverse event	21	(3.3)	42	(6.7)	56	(8.9)
Treatment failure	14	(2.2)	10	(1.6)	8	(1.3)
Refused treatment	28	(4.4)	17	(2.7)	21	(3.3)
Died during study	0	(0.0)	0	(0.0)	1	(0.2)
Lost to follow-up	61	(9.6)	36	(5.8)	42	(6.6)
Did not cooperate	38	(6.0)	20	(3.2)	22	(3.5)
Protocol violation	14	(2.2)	10	(1.6)	11	(1.7)
Entry violation	2	(0.3)	0	(0.0)	0	(0.0)
Administrative	42	(6.6)	21	(3.4)	14	(2.2)
24 Weeks*						
Total subjects withdrawn	133	(21.0)	93	(14.9)	110	(17.4)
Adverse event	14	(2.2)	31	(5.0)	45	(7.1)
Lost to follow-up	47	(7.4)	23	(3.7)	30	(4.7)
Did not cooperate	17	(2.7)	10	(1.6)	10	(1.6)
Refused treatment	12	(1.9)	6	(1.0)	9	(1.4)
Administrative	23	(3.6)	14	(2.2)	7	(1.1)
Protocol violation	10	(1.6)	4	(0.6)	6	(0.9)
Treatment failure	8	(1.3)	5	(0.8)	3	(0.5)
Entry violation	2	(0.3)	0	(0.0)	0	(0.0)

Studies BM14149, NM14161, NM14302
*As calculated by the reviewer: up to study day 210 (end of the week 24 window); total discontinuations due to adverse events at 24 weeks is slightly different that that calculated by the sponsor (Table 4.4.2.1.A, likely due to different counting rules).

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Table 7.1.3.1.B. Reasons for Premature Withdrawal; 4-Month Phase III Study				
	Placebo		Orlistat 60 mg TID	
Reason for Withdrawal	(N=195) n (%)		(N=196) n (%)	
Total subjects withdrawn	55	(28.2)	44	(22.4)
Adverse event[a]	6	(3.1)	14	(7.1)
Failure to return	16	(8.2)	12	(6.1)
Refused treatment[b]	30	(15.4)	11	(5.6)
Entry violation	0		2	(1.0)
Other protocol violation	2	(1.0)	2	(1.0)
Other	1	(0.5)	3	(1.5)

a includes intercurrent illness
b includes 'did not cooperate', 'withdrew consent'

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The incidence of discontinuations overall and due to adverse events was comparable in the supportive six-month study BM14150 to the six months of treatment in the pooled studies, and was not clearly dose-related (Table 7.1.3.1.C). A significantly higher proportion of subjects treated with orlistat 60 mg discontinued due to an adverse event in the three-month actual use

trial NM17285 (15%). In the four-week consumer use study, 3.7% prematurely discontinued due to an adverse event.

Table 7.1.3.1.C. Study BM14150: Summary of Reasons for Premature Withdrawal during the Double-Blind Treatment Period; All Randomized Patients

	Placebo (N = 125)		Orlistat 30 mg tid (N = 122)		Orlistat 60 mg tid (N = 124)		Orlistat 120 mg tid (N = 122)		Orlistat 240 mg tid (N = 120)	
Reasons for Withdrawal[a]	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Refused Treatment	10	(8.0)	9	(7.4)	8	(6.5)	3	(2.5)	6	(5.0)
Adverse Event	3	(2.4)	7	(5.7)	6	(4.8)	2	(1.6)	3	(2.5)
Lost to follow-up	9	(7.2)	7	(5.7)	7	(5.6)	9	(7.4)	6	(5.0)
Did not cooperate	1	(0.8)	3	(2.5)	3	(2.4)	3	(2.5)	5	(4.2)
Administrative	3	(2.4)	2	(1.6)	4	(3.2)	4	(3.3)	0	(0)
Protocol violation	1	(0.8)	1	(0.8)	1	(0.8)	1	(0.8)	0	(0)
Entry violation	0	(0)	0	(0)	0	(0)	1	(0.8)	0	(0)
Total Patients Withdrawn	27	(21.6)	29	(23.8)	29	(23.4)	23	(18.9)	20	(16.7)

[a] Only the primary reason is counted for each patient

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7.1.3.2 Adverse events associated with dropouts

7.1.3.2.1 Pooled studies

In the first six months of treatment, there was a dose-related incidence of discontinuation due to adverse events in the pooled studies, mostly due to gastrointestinal events. Please see the Appendix (Section 10.3.2) for a full listing of adverse events that led to discontinuation in the first year of the pooled studies, including that of the orlistat 30 mg dose (not included in Table 7.1.3.2.1.A).

Table 7.1.3.2.1.A. Adverse Events Leading to Discontinuation in the First 6 Months of Treatment, Pooled Phase III Studies						
WHO-ART Body System Preferred Term	Placebo N = 634 n (%)		60 mg TID N = 623 n (%)		120 mg TID N = 632 n (%)	
Subjects with ≥ 1 AE leading to discontinuation	13	(2.1)	30	(4.8)	46	(7.3)
Gastrointestinal system disorders	5	(0.8)	20	(3.2)	34	(5.4)
Fecal incontinence	0		7	(1.1)	10	(1.6)
Oily spotting	0		1	(0.2)	7	(1.1)
Liquid stools	0		2	(0.3)	4	(0.6)
Flatus with discharge	0		1	(0.2)	4	(0.6)
Fecal urgency	1	(0.2)	4	(0.6)	3	(0.5)
Abdominal pain	0		3	(0.5)	2	(0.3)
Feces bloodstained	0		0		1	(0.2)
Stomach ulcer	0		0		1	(0.2)
Oily evacuation	0		1	(0.2)	0	
Flatulence	2	(0.3)	0		0	
Central & peripheral nervous system disorders	0		3	(0.5)	2	(0.3)
Confusion	0		0		1	(0.2)
Dizziness	0		0		1	(0.2)
Vertigo	0		2	(0.3)	0	
Reproductive disorders, female	0		2	(0.3)	2	(0.3)
Neoplasm breast female	0		1	(0.2)	2	(0.3)
Carcinoma cervix	0		1	(0.2)	0	
Myo- Endo-, Pericardial, & Valve Disorders	0		0		2	(0.3)
Angina pectoris	0		0		1	(0.2)
Malf. of prostheses and hemographs	0		0		1	(0.2)
Psychiatric Disorders	0		2	(0.3)	1	(0.2)
Suicide attempt	0		0		1	(0.2)
Anxiety	0		1	(0.2)	0	
Depression	0		1	(0.2)	0	
Respiratory System Disorders	0		1	(0.2)	1	(0.2)
Chronic obstructive lung disease	0		0		1	(0.2)
Dyspnea	0		1	(0.2)	0	
Body as a Whole – General Disorders	2	(0.3)	0		1	(0.2)
Liver and Biliary System Disorders	0		0		1	(0.2)
Cholecystitis	0		0		1	(0.2)
Endocrine Disorders	1	(0.2)	0		1	(0.2)
Thyroiditis	0		0		1	(0.2)
Hyperthyroidism	1	(0.2)	0		0	
Urinary System Disorders	0		0		1	(0.2)
Cystitis hemorrhagic	0		0		1	(0.2)
Skin and Appendages Disorders	3	(0.5)	1	(0.2)	0	
Resistance Mechanism Disorders	0		1	(0.2)	0	
Infection viral	0		1	(0.2)	0	

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7.1.3.2.2 Study NM17247

As with the pooled studies, orlistat-treated subjects in study NM17247 had a higher incidence of discontinuation due to adverse events compared to placebo (Table 7.1.3.2.2.A), mostly

attributable to gastrointestinal events. The incidence of discontinuations in the orlistat 60 mg-treated group (when adjusting for incidence rates in the placebo group) due to adverse events overall, as well as due to gastrointestinal adverse events, is slightly higher in the four-month study in the lower-overweight population (study NM17247) as compared to the six-month study in the upper overweight and obese population (pooled studies).

Table 7.1.3.2.2.A. Adverse Events Leading to Discontinuation in 4 Months of Treatment; 4-Month Phase III Study

MedDRA Body System **Preferred Term**	Placebo N = 195 n (%)		Orlistat 60 mg TID N = 196 n (%)	
Subjects with ≥ 1 AE leading to discontinuation	6	(3.1)	13	(6.6)
Gastrointestinal system disorders	2	(1.0)	10	(5.1)
Oily spotting	0		2	(1.0)
Abdominal pain lower	0		2	(1.0)
Abdominal pain upper	0		2	(1.0)
Abdominal distention	0		1	(0.5)
Abdominal pain NOS	1	(0.5)	0	
Decreased defecation	1	(0.5)	0	
Faeces hard	0		1	(0.5)
Fecal incontinence	0		1	(0.5)
Increased defecation	0		1	(0.5)
Nervous system disorders	2	(1.0)	0	
Dizziness (exc vertigo)	2	(1.0)	0	
Infections and Infestations	1	(0.5)	0	
Viral infection NOS	1	(0.5)	0	
Musculoskeletal, Connective Tissue, and Bone Disorders	0		1	(0.5)
Intervertebral disk prolapse	0		1	(0.5)
Neoplasms Benign and Malignant	0		1	(0.5)
Cyst NOS	0		1	(0.5)
Renal and Urinary Disorders	1	(0.5)	0	
Fluid retention	1	(0.5)	0	
Vascular Disorders	0		1	(0.5)
Hypertension NOS	0		1	(0.5)

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7.1.3.2.3 Study BM14150

Most adverse events leading to discontinuation in study BM14150 occurred in only one subject each. Total adverse events leading to discontinuation were not dose-related (of note, seven subjects in the 30 mg group and three subjects in the 240 mg group discontinued due to an AE).

Table 7.1.3.2.3.A. Patients Prematurely Withdrawn from the Study Because of Adverse Events

Body System **Adverse Event**	**Placebo** **N = 125**	**60 mg TID** **N = 124**	**120 mg TID** **N = 122**
Total	3 (2.4)	6 (4.8)	2 (1.6)
Gastrointestinal	1 (0.8)	2 (1.6)	2 (1.6)
Abdominal pain	1 (0.8)	1 (0.8)	0
Liquid stools	0	0	1 (0.8)
Musculoskeletal	0	0	0
Psychiatric	0	1 (0.8)	0
Depression	0	1 (0.8)	0
Reproductive, male	0	1 (0.8)	0
Skin and appendages	1 (0.8)	0	0
Liver and biliary system disorders	0	1 (0.8)	0
Laboratory abnormality	1 (0.8)	0	0
Body as a whole	0	1 (0.8)	0

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7.1.3.2.4 Uncontrolled studies

The majority of the AEs leading to discontinuation in studies NM17285 (Table 7.1.3.2.4.A) and RCH-ORL-002 (Table 7.1.3.2.4.B) were gastrointestinal in nature.

Table 7.1.3.2.4.A. Adverse Events Leading to Discontinuation in ≥ 2 Subjects; 3-Month Phase IV Study

MedDRA Body System **Preferred Term**	**Orlistat 60 mg TID** **(N = 284)** **n (%)**
Subjects with ≥ 1 AE leading to discontinuation	43 (15.1)
Gastrointestinal disorders	
Flatulence	8 (2.8)
Fecal incontinence	5 (1.8)
Fecal urgency	5 (1.8)
Liquid stools	5 (1.8)
Abdominal pain NOS	4 (1.4)
Decreased defecation	3 (1.1)
Flatus with discharge	3 (1.1)
Oily evacuation	3 (1.1)
Oily spotting	3 (1.1)
Soft stools	3 (1.1)
Abdominal pain other	2 (0.7)
Increased defecation	2 (0.7)
Vomiting NOS	2 (0.7)
Infections and infestations	
Gastrointestinal viral NOS	2 (0.7)

Table 7.1.3.2.4.A. Adverse Events Leading to Discontinuation in ≥ 2 Subjects; 3-Month Phase IV Study	
MedDRA Body System Preferred Term	**Orlistat 60 mg TID (N = 284) n (%)**
Vascular disorders	
Hypertension NOS	2 (0.7)

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Table 7.1.3.2.4.B. Listing of Subjects Prematurely Withdrawn from Treatment for Adverse Events, Safety Population; 4-Week Phase IV Study	
Subject	**Adverse Event**
5-40001	Abdominal pain
7-24002	Pain
	Diarrhea
	Fecal incontinence
	Flatulence
8-14007	Abdominal pain
	Abnormal stools
	Headache
	Vasodilatation
	Nausea
	Oily spotting
10-14003	Abdominal pain
	Diarrhea
	Abnormal stools
	Gastrointestinal disorder
	Dysmenorrhea
11-25003	Pain
	Diarrhea
	Dizziness
	Fever
	Nausea
	Vomiting
	Asthenia
12-3005	Diarrhea
	Abnormal stools

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7.1.3.3 Other significant adverse events

Given the fact that orlistat is not significantly systemically absorbed, the majority of drug-related adverse events are local (i.e., gastrointestinal) in nature. As described in other sections of this review, rare, theoretical, or potential adverse events that may or may not be related to orlistat, have been considered and are discussed in other sections of this review. No adverse events identified from the clinical trials can be classified as "other significant adverse events" as defined by the International Conference on Harmonisation (ICH).

7.1.4 Other Search Strategies

Gastrointestinal adverse events related to the mechanism of action of the drug were reviewed separately and are presented below. Searches in the published literature and in AERS that were conducted to evaluate the association between orlistat and adverse events of interest, such as orlistat and vitamin deficiencies with potential sequelae (e.g., bone turnover and warfarin), orlistat and lipophilic drugs (e.g., cyclosporine and amiodarone), orlistat and lithogenicity (e.g., kidney and gallstones), orlistat and liver toxicity, and orlistat and pancreatitis are presented in other relevant sections of this review.

7.1.4.1 Gastrointestinal Events

Because gastrointestinal (GI) events in subjects treated with orlistat are the most common adverse events, events most likely to lead to termination of therapy, as well as events related to the pharmacological action of orlistat, Roche (the sponsor of the original prescription NDA) devised a dictionary of descriptive preferred terms to more accurately capture potentially drug-related GI events. This dictionary (Table 7.1.4.1.A) was used in the phase 2 and 3 studies from the original prescription NDA, as well as the studies supporting the nonprescription NDA.

Table 7.1.4.1.A. Dictionary of Standard Terms for Changes in Defecation Pattern

Term	Definition
*fecal incontinence	uncontrolled, spontaneous defecation
*oily spotting	uncontrolled seepage of oil without stool
*flatus with discharge	flatus with small amounts of oil or stool
*fecal urgency	urgent, but controlled, need to produce stools
*oily evacuation	controlled discharge of oil without stool
fatty/oily stool	stools mixed with fat or with a separate oily layer
liquid stools	stools almost all liquid with very few solid parts
increased defecation	increased frequency of bowel movements
soft stools	stools mushy and deliquescent (i.e., stools not formed but of rather fluid consistency)
decreased defecation	decreased frequency of bowel movements
pellets	stools hard and in the shape of small pellets

* Events that are attributable to the pharmacological action of orlistat and were always to be considered AEs. These items appear in the list in decreasing order of clinical significance.

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7.1.4.1.1 Pooled Studies

The incidence of gastrointestinal AE*s* was moderately higher in the orlistat treatment groups than in the placebo group, with more subjects experiencing AE*s* in the 120 mg dose group than those in the 60 mg group. The biggest discrepancy between placebo and orlistat groups was for the AE*s* of fecal urgency, oily spotting, flatus with discharge, fatty/oily stool, oily evacuation, and fecal incontinence.

Table 7.1.4.1.1.A. GI Adverse Events with Incidence ≥ 1% during 6 Months of Treatment; Pooled Phase 3 Studies						
WHO-ART Preferred Term	**Placebo (N=634)**		**Orlistat 60 mg TID (N=623)**		**Orlistat 120 mg TID (N=632)**	
	n	**(%)**	**n**	**(%)**	**n**	**(%)**
Subjects with ≥1 GI AE	326	(51.4)	428	(68.7)	472	(74.7)
Abdominal pain	83	(13.1)	125	(20.1)	132	(20.9)
*Fecal urgency	50	(7.9)	117	(18.8)	148	(23.4)
Flatulence	114	(18.0)	116	(18.6)	114	(18.0)
*Oily spotting	7	(1.1)	110	(17.7)	137	(21.7)
*Flatus with discharge	12	(1.9)	108	(17.3)	126	(19.9)
*Fatty/oily stool	17	(2.7)	107	(17.2)	137	(21.7)
Liquid stools	47	(7.4)	74	(11.9)	90	(14.2)
*Oily evacuation	4	(0.6)	72	(11.6)	85	(13.4)
Stools soft	37	(5.8)	63	(10.1)	49	(7.8)
*Increased defecation	17	(2.7)	44	(7.1)	52	(8.2)
*Fecal incontinence	5	(0.8)	29	(4.7)	49	(7.8)
Nausea	41	(6.5)	29	(4.7)	47	(7.4)
Decreased defecation	53	(8.4)	27	(4.3)	23	(3.6)
Enteritis	23	(3.6)	18	(2.9)	24	(3.8)
Toothache	12	(1.9)	14	(2.2)	15	(2.4)
Hemorrhoids	11	(1.7)	7	(1.1)	15	(2.4)
Fullness abdominal	5	(0.8)	6	(1.0)	3	(0.5)
Periodontal breakdown	4	(0.6)	5	(0.8)	9	(1.4)
Table includes events with incidence in either orlistat group ≥1% and greater than that in the placebo group. *Orlistat incidence ≥ 5% and at least twice the placebo incidence						

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Studies conducted up to four years have suggested that gastrointestinal AEs diminish over time with use of orlistat.[31] However, the extent to which this is a true "tolerance" of the effect or a function of the either the premature discontinuation of subjects who are intolerant to the GI effects or do not adhere to the reduction in dietary fat intake is somewhat unclear. This reviewer's exploratory analysis suggests that in the six-month completers, the majority of the events were in the first few weeks. Furthermore, the sponsor notes that the first GI event in the majority of subjects occurred within the first 12 weeks, with very few subjects experiencing their first episode after six months.

The evaluation of the number of episodes experienced by the subjects during treatment, demonstrates that, as expected, the orlistat-treated subjects have a higher incidence of multiple episodes than placebo-treated subjects, although the orlistat 60 mg and 120 mg dose groups are fairly similar in rates of multiple GI episodes (Table 7.1.4.1.1.B).

31 Torgerson JS, et al. Diabetes Care; 27:155-161, 2004.

Table 7.1.4.1.1.B. Number of Gastrointestinal Adverse Events per Subject in First 6 Months of Treatment; Pooled Phase III Studies			
Number of GI AEs	**Placebo (N=634) n (%)**	**Orlistat 60 mg TID (N=623) n (%)**	**Orlistat 120 mg TID (N=632) n (%)**
0	308 (48.6)	195 (31.3)	160 (25.3)
1	142 (22.4)	100 (16.1)	107 (16.9)
2	74 (11.7)	94 (15.1)	95 (15.0)
3	46 (7.3)	71 (11.4)	82 (13.0)
4	25 (3.9)	54 (8.7)	61 (9.7)
5	14 (2.2)	34 (5.5)	22 (3.5)
6	3 (0.5)	23 (3.7)	32 (5.1)
7	7 (1.1)	10 (1.6)	32 (5.1)
8	4 (0.6)	12 (1.9)	15 (2.4)
9	5 (0.8)	8 (1.3)	8 (1.3)
10-18	6 (1.0)	22 (3.5)	18 (2.8)

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7.1.4.1.2 Study NM17247

In four months of treatment, the orlistat group experienced about twice as many gastrointestinal AE*s* as the placebo group; the majority of these attributable to fatty/oily stool, fecal urgency, oily spotting, flatus with discharge, and increased defecation.

Table 7.1.4.1.2.A. Gastrointestinal Adverse Events with Incidence ≥ 2% in 4 Months of Treatment; 4-Month Phase III Study				
MedDRA Preferred Term	**Placebo (N=195)**		**Orlistat 60 mg TID (N=196)**	
	n	**(%)**	**n**	**(%)**
Subjects with ≥1 GI AE	64	(32.8)	112	(57.1)
*Fatty/oily stool	5	(2.6)	44	(22.4)
*Fecal urgency	11	(5.6)	33	(16.8)
*Oily spotting	0		22	(11.2)
*Flatus with discharge	3	(1.5)	18	(9.2)
*Increased defecation	7	(3.6)	17	(8.7)
Stools soft	7	(3.6)	11	(5.6)
Abdominal pain NOS	6	(3.1)	8	(4.1)
Dyspepsia	0		6	(3.1)
Fecal incontinence	0		6	(3.1)
Oily evacuation	0		6	(3.1)
Table includes events with incidence in the orlistat group ≥ 2% and greater than that in the placebo group. *Orlistat incidence ≥ 5% and at least twice the placebo incidence.				

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Interestingly, the incidence of gastrointestinal events in the orlistat-treated group does not appear to be related to amount of weight lost in this patient population (Table 7.1.4.1.2.B), supporting the notion that orlistat can maintain efficacy in the absence of gastrointestinal side effects. Conversely, considering that the proportion of gastrointestinal AE*s* in subjects who did not lose weight, or even gained weight, is similar to those who lost weight, indicates that an individual

should not assume the drug "is working" (i.e., promoting weight loss) in the absence of dietary adherence if he or she experiences drug-related effects such as oily stool or spotting.

Table 7.1.4.1.2.B. Gastrointestinal Adverse Events by Amount of Weight Lost; Safety Population								
Preferred Term	**0% loss or gain**		**> 0% to 5% loss**		**> 5% to 10% loss**		**> 10% loss**	
	Orlistat N = 27 n (%)	Placebo N = 52 n (%)	Orlistat N = 98 n (%)	Placebo N = 81 n (%)	Orlistat N = 50 n (%)	Placebo N = 42 n (%)	Orlistat N = 19 n (%)	Placebo N = 9 n (%)
Fatty/Oily Stool	5 (18.5)	1 (1.9)	25 (25.5)	1 (1.2)	11 (22.0)	3 (7.1)	3 (15.8)	0 (0.0)
Fecal Urgency	6 (22.2)	3 (5.8)	16 (16.3)	4 (4.9)	7 (14.0)	4 (9.5)	4 (21.1)	0 (0.0)
Oily Spotting	5 (18.5)	0 (0.0)	8 (8.2)	0 (0.0)	6 (12.0)	0 (0.0)	3 (15.8)	0 (0.0)
Flatus With Discharge	1 (3.7)	0 (0.0)	12 (12.2)	2 (2.5)	4 (8.0)	1 (2.4)	1 (5.3)	0 (0.0)
Increased Defecation	4 (14.8)	1 (1.9)	6 (6.1)	5 (6.2)	7 (14.0)	0 (0.0)	0 (0.0)	1 (11.1)
Stools Soft	2 (7.4)	2 (3.8)	7 (7.1)	4 (4.9)	1 (2.0)	0 (0.0)	1 (5.3)	1 (11.1)
Abdominal Pain NOS	1 (3.7)	2 (3.8)	4 (4.1)	1 (1.2)	3 (6.0)	2 (4.8)	0 (0.0)	1 (11.1)
Dyspepsia	0 (0.0)	0 (0.0)	4 (4.1)	0 (0.0)	1 (2.0)	0 (0.0)	1 (5.3)	0 (0.0)
Fecal Incontinence	3 (11.1)	0 (0.0)	3 (3.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Oily Evacuation	0 (0.0)	0 (0.0)	4 (4.1)	0 (0.0)	0 (0.0)	0 (0.0)	2 (10.5)	1 (11.1)

Adapted from GSK Response to FDA Information Request of November 29, 2005

7.1.4.1.3 Study BM14150

Most gastrointestinal AE*s* in this six-month dose-ranging study were dose-related (Table 7.1.4.1.3.A).

Table 7.1.4.1.3.A. N (%) Gastrointestinal Adverse Events in Study BM14150					
Adverse Event	**Placebo N = 124**	**30 mg TID N = 122**	**60 mg TID N = 123**	**120 mg TID N = 120**	**240 mg TID N = 117**
Total	57 (46.0)	74 (60.7)	93 (75.6)	85 (70.8)	97 (82.9)
Fatty/Oily Stool	2 (2.4)	25 (20.5)	39 (31.7)	45 (37.5)	43 (36.8)
Oily Spotting	0	10 (8.2)	18 (14.6)	15 (12.5)	26 (22.2)
Stools Soft	10 (8.1)	14 (11.5)	23 (18.7)	16 (13.3)	24 (20.5)
Abdominal Pain	17 (13.7)	18 (14.8)	20 (16.3)	20 (16.7)	22 (18.8)
Increased Defecation	7 (5.6)	23 (18.9)	23 (18.7)	23 (19.2)	21 (17.9)
Fecal Urgency	2 (1.6)	7 (5.7)	10 (8.1)	8 (6.7)	16 (13.7)
Liquid Stools	15 (12.1)	14 (11.5)	24 (19.5)	20 (16.7)	15 (12.8)
Oily Evacuation	0	8 (6.6)	7 (5.7)	10 (8.3)	13 (11.1)
Flatus with Discharge	0	3 (2.5)	8 (6.5)	9 (7.5)	11 (9.4)
Fecal Incontinence	0	2 (1.6)	4 (3.3)	6 (5.0)	9 (7.7)
Flatulence	4 (3.2)	12 (9.8)	12 (9.8)	8 (6.7)	9 (7.7)
Decreased Defecation	16 (12.9)	9 (7.4)	13 (10.6)	9 (7.5)	7 (6.0)
Enteritis	6 (4.8)	4 (3.3)	4 (2.4)	3 (2.5)	5 (4.3)
Nausea	7 (5.6)	8 (6.6)	9 (7.3)	9 (7.5)	4 (3.4)
Stools Solid	3 (2.4)	4 (3.3)	3 (2.4)	3 (2.5)	4 (3.4)
Hemorrhage Rectum	0	0	0	4 (3.3)	1 (0.9)
Vomiting	4 (3.2)	1 (0.8)	3 (2.4)	3 (2.5)	3 (2.6)

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7.1.4.1.4 Study NM17285

Although this study is difficult to analyze given the lack of a placebo, the wide range of BMIs, and the possibility of dose-titration, the incidence of gastrointestinal AEs (59.2%) in this three-month actual use study was comparable with the incidence of gastrointestinal AEs in the four-month placebo-controlled trial (NM17247). Table 7.1.4.1.4.A presents those AEs defined as defecation pattern change. Thirty-five percent (35%) of subjects with a defecation pattern change event had the drug interrupted or discontinued as a result of the AE.

Table 7.1.4.1.4.A. GI Adverse Events: Defecation Pattern Change Events by Action Taken

	Safety Popn.			Action Taken[a]					
	(N=284)			None		Interrupted		Discontinued	
	n	(%)	NAE	n	(%)	n	(%)	n	(%)
Any defecation pattern change AE	136	(47.9)	322	89	(65.4)	23	(16.9)	24	(17.7)
Oily spotting	38	(13.4)	52	31	(81.6)	4	(10.5)	3	(7.9)
Fecal urgency	36	(12.7)	51	26	(72.2)	5	(13.9)	5	(13.9)
Liquid stools	31	(10.9)	44	17	(54.8)	9	(29.0)	5	(16.1)
Flatus with discharge	30	(10.6)	39	22	(73.3)	5	(16.7)	3	(10.0)
Fecal incontinence	23	(8.1)	33	15	(65.2)	3	(13.0)	5	(21.7)
Fatty/oily stool	20	(7.0)	26	18	(90.0)	2	(10.0)	0	
Oily evacuation	20	(7.0)	27	14	(70.0)	3	(15.0)	3	(15.0)
Increased defecation	15	(5.3)	19	10	(66.7)	3	(20.0)	2	(13.3)
Decreased defecation	14	(4.9)	17	10	(71.4)	1	(7.1)	3	(21.4)
Soft stools	12	(4.2)	14	9	(75.0)	0		3	(25.0)

n (%) are number (percent) of subjects; NAE is the number of adverse events
[a] the most extreme outcome is tabulated for each subject (discontinuation, interruption, no action, in that order)

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7.1.4.1.5 RCH-ORL-002

In one month of treatment in this consumer use study, 101 subjects (62%) experienced at least one digestive system AE. Table 7.1.4.1.5.A does not include abdominal pain, which occurred in 11 (7%) of subjects.

Table 7.1.4.1.5.A. Digestive System Adverse Events: Study RCH-ORL-002	
Adverse Event	**Orlistat 60 mg N = 162 n (%)**
Digestive System	101 (62%)
Abnormal stools	46 (28%)
Colitis	1 (1%)
Diarrhea	37 (23%)
Dry mouth	1 (1%)
Dyspepsia	6 (4%)
Fecal incontinence	9 (6%)
Flatulence	36 (22%)
Gastroenteritis	1 (1%)
Gastrointestinal disorder	62 (38%)
Loss of appetite	1 (1%)
Nausea	3 (2%)
Oily spotting	18 (11%)
Rectal disorder	1 (1%)
Thirst	1 (1%)
Vomiting	1 (1%)

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7.1.5 Common Adverse Events

7.1.5.1 Eliciting adverse events data in the development program

Because the individual studies may have elicited adverse events differently, the methods used will be described for each study individually.

7.1.5.1.1 Studies BM14149, NM14161, NM14302, and BM14150

Adverse events were recorded in the case report form (CRF), based on information volunteered by or elicited from the patient, or from observations made by the investigator or staff. In addition, investigators were given the dictionary of standard terms (see Table 7.1.4.1.A) for recording defecation patterns, since gastrointestinal adverse events were expected to be high, and were to use the rules described in Section 7.1.5.2 when recording defecation patterns that occurred as a complex (i.e., more than one event occurring at the same time).

7.1.5.1.2 Study NM17247

Adverse events were recorded in the case report form (CRF), based on information volunteered by or elicited from the patient, or from observations made by the investigator or staff. In addition, the investigator was instructed to use the dictionary of standard terms for changes in defecation pattern (Table 7.1.4.1.A) when entering an adverse event relating to defecation pattern.

In order to accurately identify the adverse experience that the patient reported, the investigator was instructed to ask the following questions:

- Was the event controlled or uncontrolled?
- Was it oil alone, stool alone, or oil mixed with stool?
- Was the discharge of oil or stool with or without flatus?
- When did the symptoms start and stop?
- Was it inconvenient?

Similar rules to those listed for the studies in Section 7.1.5.1.1 regarding multiple concurrent events also applied for study NM17247.

7.1.5.1.3 Study NM17285

Adverse events were recorded in the case report form (CRF), based on information volunteered by or elicited from the subject, or from observations made by the investigator or staff.

7.1.5.1.4 Study RCH-ORL-002

Subjects were instructed to record in a diary all voluntarily reported adverse events that occur during the course of the study including a description, date, time, and severity of the event. Subjects were instructed to call West Pharmaceutical Services, Consumer Healthcare Research (WPS) to report adverse events; a toll free number was listed on the informed consent form. All adverse event information was then transferred to a CRF by WPS.

7.1.5.2 Appropriateness of adverse event categorization and preferred terms

The use of a dedicated dictionary for GI terms was appropriate for capturing the nature of adverse events associated with orlistat. However, a few issues regarding the appropriateness of preferred terms in capturing the verbatim adverse event text in the AE dataset warrant comment. First, at least one preferred term from the pooled studies (WHO-ART dictionary) was inappropriately coded: an AE of bulimia nervosa was coded as *appetite exaggerated.* This reviewer did not find any other AE*s* of bulimia under this verbatim term. Second, this reviewer noted several instances of multiple verbatim AE*s* listed under a single preferred term. The sponsor clarified this issue as follows:

To ensure consistency across studies, the following rules were used by investigators in all orlistat controlled clinical studies when recording defecation patterns which occurred as a complex (i.e., more than one defecation pattern occurring at the same time):

1. The most descriptive term (i.e., that event which the patient described as the most bothersome) for the complex was to be recorded as the adverse event. For the US studies, if the most descriptive term was not a starred term, and any starred (*) term(s) occurred as part of that complex, the most descriptive term was to be recorded as a separate AE. All of the starred [and any remaining unstarred term(s)] were to be listed on a single AE entry line.

2. If no single event could be selected as most bothersome, the investigator was to list all of the events on a single GI entry line. The term which appeared highest on the list in the Table of Dictionary of Standard Terms for Changes in Defecation Pattern (see Table 7.1.4.1.A, above) was later chosen as the preferred term by the sponsor.

For both situations 1 and 2 (above), if AE*s* of differing durations were reported, each of these events was to be reported as a separate AE. Whenever a single AE term was selected to represent a complex of defecation patterns, the severity rating of the most severe event was assigned.

Any symptom not listed on Table 7.1.4.1.A that occurred simultaneously with a defecation pattern symptom or symptoms was to be recorded as a separate AE.

7.1.5.3 Incidence of common adverse events

Slightly more subjects on treatment (~90%) than placebo (~85%) experienced at least one adverse event in the pooled studies. This difference between groups was greater in the four-month pivotal study (70% *vs.* 55%, respectively). Most adverse events in both the pooled and four-month studies were gastrointestinal in nature, and these events generally accounted for the difference between treatment groups. However, it is noted that there was a moderately increased incidence of upper respiratory infections, sinusitis, and bronchitis in the orlistat-treated group in the four-month study NM17247 (Table 7.1.5.4.2.A). This was not noted in the pooled studies, even in this reviewer's exploratory analysis of the first four months. Although there have been no previous concerns raised about respiratory infections in studies supporting and subsequent to approval of the original NDA, one cannot be certain that subjects with a lower BMI would not be more susceptible, although this seems unlikely. In addition, these incidence rates are based on small numbers of subjects. Finally, there was no clinically significant difference in mean change in WBC count, neutrophils, or lymphocytes between treatment groups in study NM17247.

7.1.5.4 Common adverse event tables

7.1.5.4.1 Pooled Studies

Table 7.1.5.4.1.A describes adverse events with an incidence ≥ 3% in the first six months of the pooled safety studies. Please see the Appendix for a full listing of adverse events in the first six months (Section 10.3.3) and one year of treatment (Section 10.3.4), respectively, in the pooled studies.

Table 7.1.5.4.1.A. Adverse Events with Incidence ≥ 3% during First 6 Months of Treatment; Pooled Phase III Studies						
	Placebo (N=634)		Orlistat 60 mg TID (N=623)		Orlistat 120 mg TID (N=632)	
WHO-ART Preferred Term	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
Subjects with ≥ 1 AE	536	(84.5)	555	(89.1)	581	(91.9)
Gastrointestinal system disorders						
Abdominal pain	83	(13.1)	125	(20.1)	132	(20.9)
Fecal urgency	50	(7.9)	117	(18.8)	148	(23.4)
Flatulence	114	(18.0)	116	(18.6)	114	(18.0)
Oily spotting	7	(1.1)	110	(17.7)	137	(21.7)
Flatus with discharge	12	(1.9)	108	(17.3)	126	(19.9)
Fatty/oily stool	17	(2.7)	107	(17.2)	137	(21.7)
Liquid stools	47	(7.4)	74	(11.9)	90	(14.2)
Oily evacuation	4	(0.6)	72	(11.6)	85	(13.4)
Stools soft	37	(5.8)	63	(10.1)	49	(7.8)
Increased defecation	17	(2.7)	44	(7.1)	52	(8.2)
Fecal incontinence	5	(0.8)	29	(4.7)	49	(7.8)
Nausea	41	(6.5)	29	(4.7)	47	(7.4)
Enteritis	23	(3.6)	18	(2.9)	24	(3.8)
Respiratory system disorders						
Sinusitis	54	(8.5)	66	(10.6)	63	(10.0)
Upper respiratory tract infection	57	(9.0)	61	(9.8)	56	(8.9)
Rhinitis allergic atopic	25	(3.9)	27	(4.3)	29	(4.6)
Bronchitis	26	(4.1)	24	(3.9)	37	(5.9)
Pharyngitis	32	(5.0)	23	(3.7)	44	(7.0)
Resistance mechanism disorders						
Influenza syndrome	185	(29.2)	168	(27.0)	188	(29.7)
Central & peripheral nervous system disorders						
Headache	119	(18.8)	116	(18.6)	146	(23.1)
Musculoskeletal system disorders						
Back pain	37	(5.8)	45	(7.2)	51	(8.1)
Body as a whole - general disorders						
Surgical procedure	17	(2.7)	19	(3.0)	17	(2.7)
Asthenia	16	(2.5)	19	(3.0)	16	(2.5)
Reproductive disorders, female						
Dysmenorrhea	22	(3.5)	23	(3.7)	25	(4.0)
Psychiatric disorders						
Anxiety	7	(1.1)	16	(2.6)	19	(3.0)
Table includes events with incidence in either orlistat group ≥ 3% and greater than that in the placebo group.						

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7.1.5.4.2 Study NM17247

Table 7.1.5.4.2.A describes adverse events with an incidence ≥ 2% in study NM17247. Please see the Appendix (Section 10.3.5) for a full listing of adverse events in this study.

Table 7.1.5.4.2.A. Adverse Events with Incidence ≥ 2% in 4 Months of Treatment; 4-Month Phase III Study				
	Placebo (N=195)		Orlistat 60 mg TID (N=196)	
MedDRA Preferred Term	**n**	**(%)**	**n**	**(%)**
Subjects with ≥ 1 AE	106	(54.4)	137	(69.9)
Gastrointestinal system				
Fatty/oily stool	5	(2.6)	44	(22.4)
Fecal urgency	11	(5.6)	33	(16.8)
Oily spotting	0		22	(11.2)
Flatus with discharge	3	(1.5)	18	(9.2)
Increased defecation	7	(3.6)	17	(8.7)
Stools soft	7	(3.6)	11	(5.6)
Abdominal pain NOS	6	(3.1)	8	(4.1)
Dyspepsia	0		6	(3.1)
Fecal incontinence	0		6	(3.1)
Oily evacuation	0		6	(3.1)
Infections and infestations				
Upper respiratory tract infection NOS	5	(2.6)	11	(5.6)
Nasopharyngitis	5	(2.6)	6	(3.1)
Sinusitis NOS	3	(1.5)	8	(4.1)
Bronchitis NOS	1	(0.5)	5	(2.6)
Nervous system disorders				
Headache NOS	5	(2.6)	9	(4.6)
Dizziness (excl vertigo)	2	(1.0)	4	(2.0)
Musculoskeletal, connective tissue and bone disorders				
Myalgia	3	(1.5)	5	(2.6)
Table includes events with incidence in the orlistat group ≥ 2% and greater than that in the placebo group.				

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7.1.5.5 Identifying common and drug-related adverse events

The safety profile of the orlistat 120 mg dose is well-described in the obese population, and common, drug-related events are related to the pharmacological action of the drug; namely, intestinal fat malabsorption. These gastrointestinal adverse events are discussed in detail in Section 7.1.4.1.

7.1.5.6 Additional analyses and explorations

This reviewer requested the sponsor to provide a table of gastrointestinal events up to four months for the three phase 3 pooled safety studies and study NM17247 combined, by BMI at randomization. For the majority of adverse events, the incidence was similar in the BMI groups up to 35 kg/m^2, with several placebo-subtracted adverse events slightly lower in the highest BMI category, such as fatty/oily stool, fecal urgency, oily spotting/evacuation, and fecal incontinence (Table 7.1.5.6.A). From these results, it does not appear that overweight patients are likely to experience more or fewer gastrointestinal AE*s* than obese patients.

Table 7.1.5.6.A. Adverse Events in First 4 Months of Treatment by BMI at Randomization; Safety Population

Preferred Term	BMI < 30 kg/m^2			BMI 30 - < 35 kg/m^2			BMI ≥ 35 kg/m^2		
	Orlistat 60 N = 348 n (%)	Placebo N = 372 n (%)	Diff	Orlistat 60 N = 273 n (%)	Placebo N = 341 n (%)	Diff	Orlistat 60 N = 198 n (%)	Placebo N = 216 n (%)	Diff
Fatty/Oily Stool	65 (18.7)	9 (2.4)	16.3	53 (19.4)	3 (1.2)	18.2	27 (13.6)	6 (2.8)	10.8
Fecal Urgency	63 (18.1)	27 (7.3)	10.8	52 (19.0)	17 (7.1)	11.9	27 (13.6)	14 (6.5)	7.1
Oily Spotting	53 (15.2)	4 (1.1)	14.1	44 (16.1)	2 (0.8)	15.3	24 (12.1)	1 (0.5)	11.6
Flatus With Discharge	50 (14.4)	7 (1.9)	12.5	39 (14.3)	3 (1.2)	13.1	31 (15.7)	2 (0.9)	14.8
Oily Evacuation	32 (9.2)	4 (1.1)	8.1	29 (10.6)	0 (0.0)	10.6	12 (6.1)	0 (0.0)	6.1
Stools Soft	23 (6.6)	15 (4.0)	2.6	24 (8.8)	9 (3.7)	5.1	25 (12.6)	16 (7.4)	5.2
Increased Defecation	27 (7.8)	15 (4.0)	3.8	17 (6.2)	1 (0.4)	5.8	14 (7.1)	7 (3.2)	3.9
Liquid Stools	20 (5.7)	19 (5.1)	0.6	21 (7.7)	13 (5.4)	2.3	16 (8.1)	10 (4.6)	3.5
Decreased Defecation	19 (5.5)	28 (7.5)	-2.0	11 (4.0)	12 (5.0)	-1.0	3 (1.5)	19 (8.8)	-7.3
Fecal Incontinence	10 (2.9)	0 (0.0)	2.9	16 (5.9)	2 (0.8)	5.1	4 (2.0)	2 (0.9)	1.1
Pellets	0 (0.0)	3 (0.8)	-0.8	3 (1.1)	3 (1.2)	-0.1	0 (0.0)	2 (0.9)	-0.9

Diff = Orlistat 60 mg percentage - Placebo percentage

Adapted from GSK Response to FDA Information Request of November 29, 2005

7.1.6 Less Common Adverse Events

Placebo-controlled clinical trials of orlistat up to four years in duration have not provided strong signals for rare, serious adverse events. However, case reports in the literature and post-marketing databases have suggested an imbalance in pancreatitis reports as compared to the other, long-term FDA-approved medication for treatment of obesity, sibutramine (discussed in Section 7.1.12.2.2.2), and very rarely have reported hepatotoxicity in association with orlistat use (discussed in Section 7.1.12.2.2.3). In neither of these conditions has a causal association been made between the adverse event and orlistat use. Literature findings and post-marketing adverse events related to fat-soluble vitamin and drug interactions are discussed in Sections 7.1.7.3.1.2.1 and 8.2, respectively.

7.1.7 Laboratory Findings

7.1.7.1 Overview of laboratory testing in the development program

The following laboratory tests were common to all four studies in the sponsor's Integrated Summary of Safety (ISS), and were summarized using descriptive statistics:

- Hematology – hemoglobin, hematocrit, platelet count, RBC count, WBC count, basophils, eosinophils, lymphocytes, monocytes, and neutrophils.
- Serum chemistry – total protein, albumin, creatinine, BUN, total bilirubin, calcium, sodium, potassium, chloride, phosphorus, glucose, total cholesterol (TC), HDL, LDL, LDL:HDL ratio, TG, alkaline phosphatase, creatine phosphokinase, GGT, AST, ALT,TSH, amylase, uric acid, and free thyroxine.

Orlistat's effects on fat-soluble vitamins and carbohydrate metabolism and insulin function were examined in detail in the original NDA. The conclusions of these analyses were incorporated by reference in the ISS for NDA 21-887.

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

Laboratory data are presented for the three pooled phase 3 studies (BM14149, NM14161, and NM14302; 12, 24, and 52 weeks), the pivotal study NM17247 (4 months), and the supportive study BM14150 (24 weeks), where indicated. Additionally, some laboratory data, particularly related to fat-soluble vitamins, minerals, and other nutritional issues are derived from information in the original study reports and the published literature.

7.1.7.3 Standard analyses and explorations of laboratory data

7.1.7.3.1 Fat-soluble vitamins and related nutritional issues

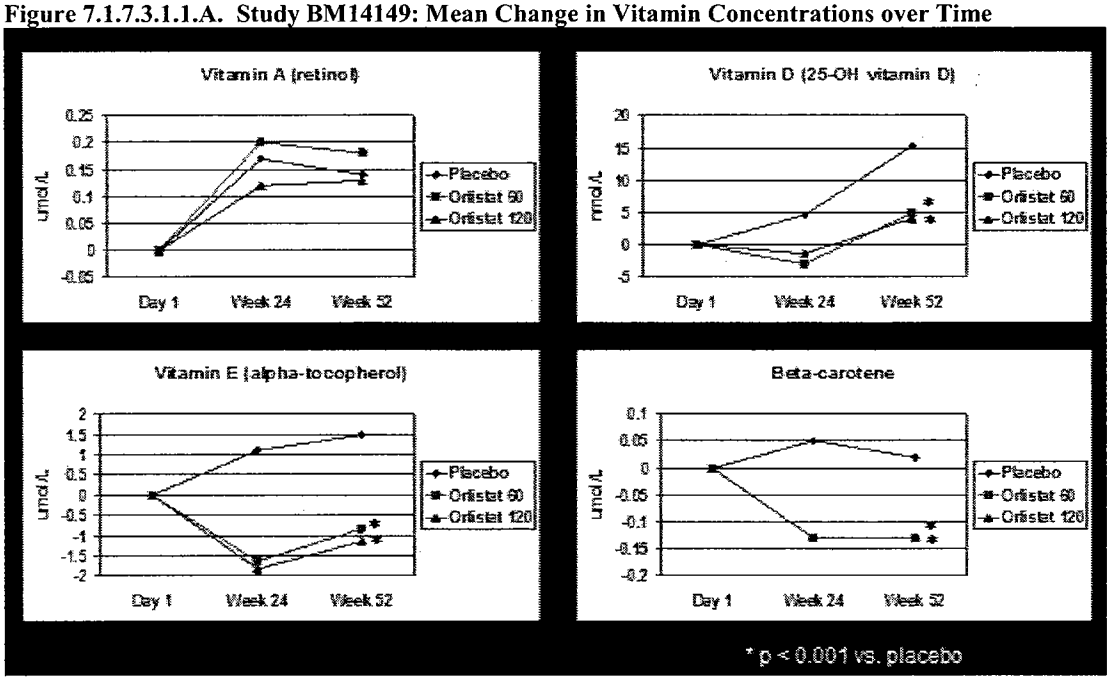
7.1.7.3.1.1 NDA Clinical Trials: Fat-Soluble Vitamins

The absorption of fat-soluble vitamins (A, D, E, and K) and beta-carotene depend on efficient absorption of dietary fat in the small intestine. As orlistat interferes with the absorption of fat, the potential for fat-soluble vitamin deficiency is a concern. In the phase 3 studies conducted under the original prescription NDA, plasma levels of vitamin A (retinol), 25-OH vitamin D, vitamin E, and beta-carotene were measured. Vitamin K activity was assessed indirectly by measuring prothrombin time (PT). Study NM14302 differed from the other phase 3 studies (prescription NDA) in that subjects were supplemented with a multivitamin daily. However, the efficacy of this supplementation during the drug treatment period is questionable as the multivitamin was given at breakfast, concomitantly with orlistat.

Figures 7.1.7.3.1.1.A, 7.1.7.3.1.1.B, and 7.1.7.3.1.1.C are graphical representations of measured vitamin changes over time in studies BM14149, NM14161, and NM14302, respectively. These graphs show change in vitamin concentrations at 24 and 52 weeks; significance testing is shown at week 52 only. Across all the studies, the mean values for fat-soluble vitamin concentrations were within the normal range. That being said, the 'normal range' for 25-OH vitamin D is somewhat of a moving target. Current recommendations suggest that serum vitamin D concentrations should be higher than the reported normal range in the original studies, and it is noted that deficiency of this nutrient is common in the United States, particularly among females, the elderly, and minorities.[9]

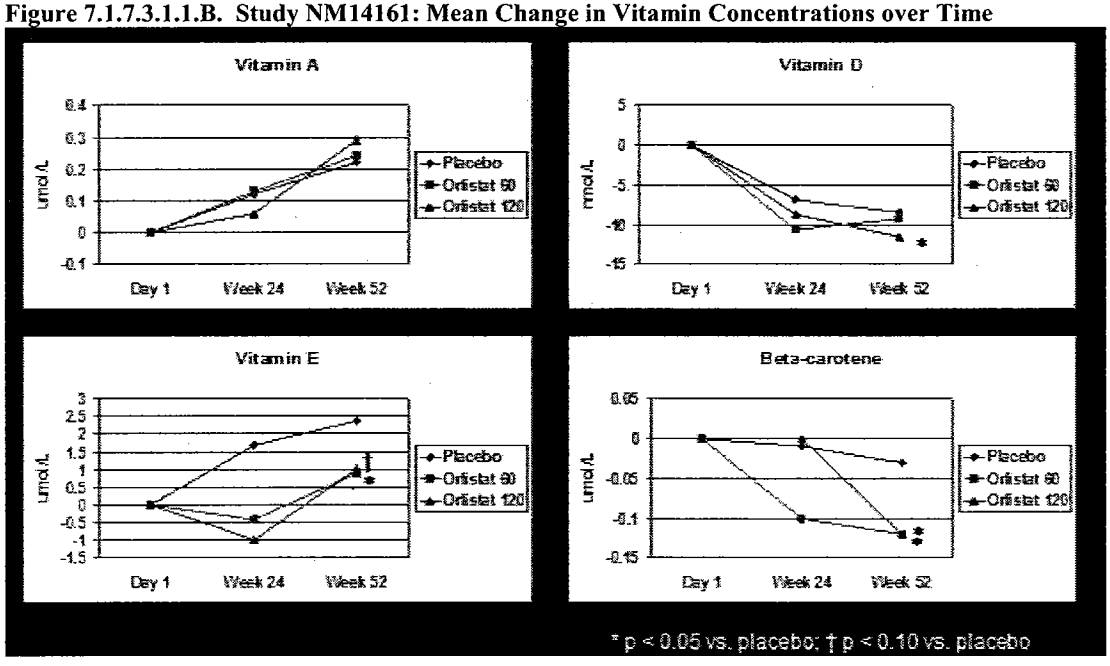
In study BM14149, mean change was significantly lower in vitamins D, E, and beta-carotene in the orlistat groups as compared to the placebo groups.

Figure 7.1.7.3.1.1.A. Study BM14149: Mean Change in Vitamin Concentrations over Time



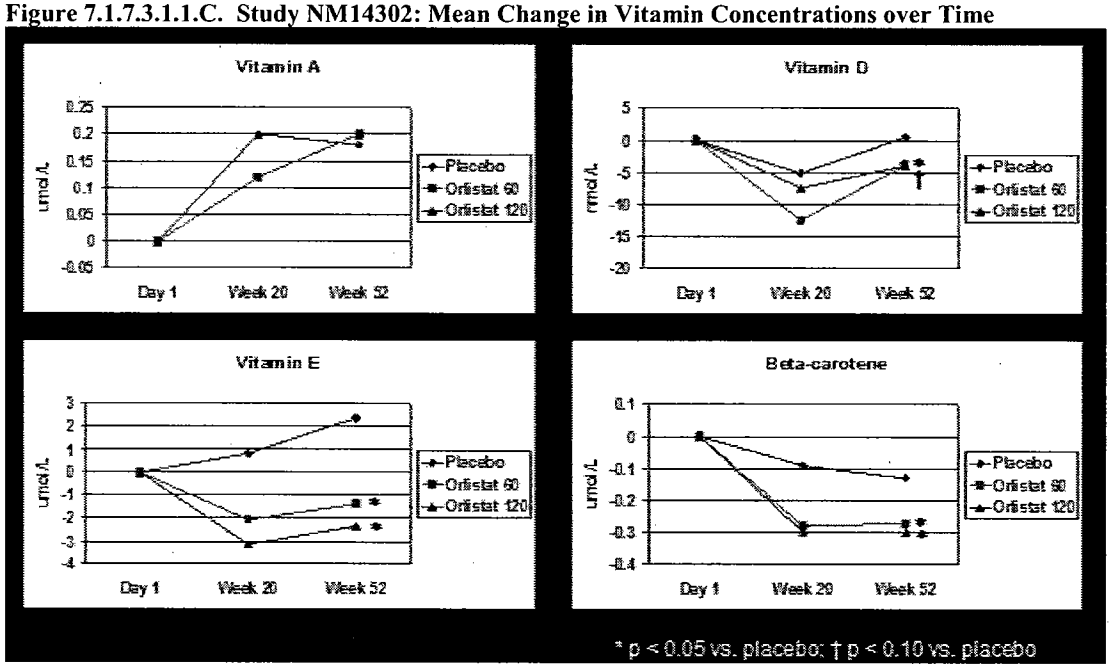
The findings in study NM14161 were similar to BM14149; it is noted that all groups in this study had a negative change in vitamin D, as compared to the previous study.

Figure 7.1.7.3.1.1.B. Study NM14161: Mean Change in Vitamin Concentrations over Time



Similar results in mean vitamin concentration change were found in study NM14302, although these subjects were instructed to take a multivitamin.

Figure 7.1.7.3.1.1.C. Study NM14302: Mean Change in Vitamin Concentrations over Time



The sponsor provided the following table of serum concentration decreases in vitamins A, D, E, and beta-carotene from the seven original studies conducted under the prescription NDA (Table 7.1.7.3.1.1.A). During the double-blind treatment period in these studies, if the fat-soluble vitamin or beta-carotene concentrations were measured below the reference range on two consecutive measurements, the investigator provided appropriate supplementation to the subject and the concentrations continued to be monitored. This would tend to underestimate the risk of vitamin deficiency with long-term orlistat use in individuals who are not supplemented.

Table 7.1.7.3.1.1.A. Frequency of Two Consecutive Plasma Levels of Vitamins Below the Lower Limit of the Reference Range in 1 Year of Treatment (Integrated Database for 7 Phase III Trials, Prescription NDA)

Vitamin	Placebo		Orlistat 60 mg TID		Orlistat 120 mg TID	
Vitamin A	3/555	(0.5%)	2/203	(1.0%)	17/962	(1.8%)
Vitamin D	20/558	(3.6%)	8/209	(3.8%)*	73/954	(7.7%)
Vitamin E	3/565	(0.5%)	8/196	(4.1%)	37/944	(3.9%)
Beta-carotene	3/576	(0.5%)	4/207	(1.9%)*	53/977	(5.4%)

*p<0.05, 2-sided Fisher's exact test; significant difference in results for 60 mg vs. 120 mg orlistat. Statistical testing of orlistat versus placebo was not provided.

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The lower incidence of vitamin deficiency in the orlistat 60 mg *vs.* 120 mg groups as shown in Table 7.1.7.3.1.1.A, is not reassuring given that the proposed label will allow patients to take up to 120 mg TID. Furthermore, these data suggest that the incidence of vitamin deficiency is

greater for the orlistat groups than placebo in all cases (statistical testing not provided). Supportive of the above findings, the mean plasma concentrations of vitamins D and E and beta-carotene were significantly lower after one and two years of treatment with either orlistat 60 or 120 mg compared to placebo ($p < 0.05$) in studies done under the original prescription NDA.

There were a greater number of subjects who were supplemented with beta-carotene during the study in the orlistat 60 and 120 mg groups than placebo in studies NM14161 and NM14302. Supplementation was not reported for study NM14149 because the lab failed to identify low results for beta-carotene and subsequently inform the investigator of abnormal beta-carotene results.

Vitamin K data were not presented in the above table because vitamin K status in the prescription NDA was assessed by measurement of PT rather than serum vitamin concentration. Although the mean change in PT was not significantly different from placebo in the phase 3 studies, PT is a relatively insensitive measure for vitamin K deficiency. An individual may be considerably deficient in vitamin K before PT becomes abnormally prolonged.

Diet record analyses, including those of fat-soluble vitamins, were provided from study NM14161. All three treatment groups (placebo, orlistat 60, and orlistat 120 mg) generally showed a decrease in intake of fat-soluble vitamins, beta-carotene, and calcium from baseline in the first year of treatment, which then progressed during the second year. It is unknown whether these dietary components were statistically different between treatment groups. This reviewer acknowledges that underreporting is very common in dietary assessment; however, these findings further emphasize the importance of multivitamin use with orlistat.

The actual use study provides some insight into how multivitamins may be used in the nonprescription setting. The 14-day interview from this study found that 74% of orlistat users took a multivitamin regularly; however only 54% of these subjects timed the multivitamin administration correctly as instructed by the label (40% of total orlistat users).[16] Information regarding multivitamin use behavior beyond this 14-day interview was not provided.

In study NM17247, all subjects were provided with a multivitamin, and serum vitamin concentrations were not measured. No orlistat-treated subjects in this study were provided a vitamin, mineral, or electrolyte supplementation as a result of an AE. One placebo subject received potassium as part of treatment for a viral infection. One placebo subject received magnesium as treatment for muscle cramps.

Little is known about the long-term effect of orlistat on fat-soluble vitamin status in a lower-weight population. Although the sponsor is proposing that nonprescription orlistat will be labeled for six-month use only (thereby minimizing the effect of orlistat on vitamin status), this reviewer considers it possible that some individuals will prolong use of this drug, potentially without appropriate vitamin supplementation.

7.1.7.3.1.2 Literature

In addition to data provided by the sponsor in the NDA submission, this reviewer searched the literature for relevant papers on orlistat and fat-soluble vitamins, as well as orlistat and other related topics, such as minerals, bone, and osteocalcin. The effect of orlistat on vitamin K and how this relates to its interaction with warfarin is discussed in Section 8.2.2.

7.1.7.3.1.2.1 Fat-soluble vitamins

The published studies reviewed that examined serum fat-soluble vitamin concentrations demonstrated a significant decrease from baseline or as compared to control in at least one vitamin measured, with duration of study from nine days to four years;[31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41] this finding was notably consistent for serum 25-OH vitamin D. Little is known about orlistat use and certain populations at risk for vitamin D deficiency, such as Blacks, and older men and women.

7.1.7.3.1.2.2 Minerals

The potential for mineral binding in the intestine to unabsorbed dietary fat was evaluated in two 21-day mineral balance studies.[42, 43] Neither study demonstrated statistically significant alterations in the balance of micro- or macrominerals in obese adolescents or obese men as compared to placebo, nor were concentrations of serum or urine electrolytes affected. However, a negative iron balance was observed in both treatment groups in both the adolescent and adult study (Table 7.1.7.3.1.2.2.A). In the adolescent study, 16 females were enrolled (as compared to the adult study, which was comprised of men only), and four of the females were menstruating.

Table 7.1.7.3.1.2.2.A. Iron Balance in Two 21-Day Studies; Mean Value over Days 15-21

	Orlistat 120 mg Mean +/- SEM	Placebo Mean +/- SEM
Adolescents[42]	N = 14	N = 13
Iron balance (µmol/24 hrs)	-64.7 +/- 20.4	-40.4 +/- 10.1
Adults[43]	N = 14	N = 14
Iron balance (µmol/24 hrs)	-18.9 +/- 10.5	-10.8 +/- 11.1
Balance = (dietary content – fecal content) – urinary content		

7.1.7.3.1.2.3 Bone

Data on the long-term effects of orlistat on bone are somewhat limited. One study[39] suggests that one year treatment with orlistat increases bone turnover in favor of resorption with similar

32 Ozcelik O, et al. Tohoku J Exp Med. 2005 Aug;206(4):313-8.
33 Czerwienska B, et al. Pol Arch Med Wewn. 2004 Dec;112(6):1415-23.
34 Derosa G, et al. Diabetes Obes Metab. 2005 Jan;7(1):47-55.
35 McDuffie JR, et al. Obes Res. 2002 Jul;10(7):642-50.
36 Hollander PA, et al. Diabetes Care. 1998 Aug;21(8):1288-94.
37 Hauptman J, et al. Arch Fam Med. 2000;9:160-167.
38 James WP, et al. Int J Obes Relat Metab Disord. 1997 Jun;21 Suppl 3:S24-30.
39 Gotfredson A, et al. Int J Obes Relat Metab Disord. 2001 Aug;25(8):1154-60.
40 Tonstad S, et al. Eur J Clin Pharmacol. 1994;46(5):405-10.
41 Melia AT, et al. J Clin Pharmacol. 1996 Jul;36(7):647-53.
42 Zhi J, et al. J Am Coll Nutr. 2003 Oct;22(5):357-62.
43 Pace DG, et al. J Nutr. 2001 Jun;131(6):1694-9.

decreases in bone density to placebo. However, in this trial, weight loss in the orlistat-treated group was not significantly different from placebo, potentially minimizing some of the effects. In the above-mentioned 21-day mineral balance study in obese men,[43] markers of bone turnover did not differ between the orlistat- and placebo-treated groups. Furthermore, although the bone marker osteocalcin is carboxylated by vitamin K, its serum concentration appears to be unaltered by orlistat treatment in short-term studies[43, 44] as well as in a year-long study.[39]

7.1.7.3.2 Safety laboratory values

Mean changes in hematology and chemistry safety parameters in the pooled safety studies and study NM17247 were for the most part similar between treatment groups. In particular, there were no clinically significant mean differences over time or between treatment groups in serum values of sodium, potassium, or phosphorus, or in hemoglobin values.

It is noted that mean alkaline phosphatase values were higher in the orlistat groups as compared with placebo in the pooled studies at six months of treatment (Table 7.1.7.3.2.A), and the mean difference in alkaline phosphatase between treatment groups was statistically significant in the four-month pivotal study (mean difference in change: 1.41, 95% CI: 0.06, 2.76; orlistat versus placebo). Although alkaline phosphatase is unfractionated, making it difficult to conclusively determine its source, this finding is consistent with a study[39] evaluating the effect of orlistat on other markers of bone turnover (see Section 7.1.7.3.1.2.3), and has been reported elsewhere.[45] Although the clinical significance is debatable, such increases may reflect an indolent vitamin D insufficiency.

Table 7.1.7.3.2.A. Serum Alkaline Phosphatase; Pooled Studies Safety Population (normal range: 40-150 U/L)

	N	Mean Value at Visit +/- SD	Mean Change from Baseline +/- SD
Placebo			
Day 1	632	88.5 +/- 26.14	
Week 12	584	89.9 +/- 24.81	1.1 +/- 11.62
Week 24	537	90.5 +/- 25.94	1.5 +/- 12.32
Week 52	398	91.2 +/- 27.28	1.5 +/- 16.82
Orlistat 60 mg			
Day 1	622	87.1 +/- 25.09	
Week 12	602	91.6 +/- 26.62	4.7 +/- 11.81
Week 24	549	91.8 +/- 26.85	4.5 +/- 12.54
Week 52	431	91.1 +/- 25.34	3.1 +/- 13.74
Orlistat 120 mg			
Day 1	629	87.0 +/- 24.69	
Week 12	597	91.8 +/- 25.12	4.8 +/- 12.03
Week 24	551	91.2 +/- 25.18	4.7 +/- 13.25
Week 52	425	89.1 +/- 25.96	2.5 +/- 16.00

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44 Zhi J. et al. J Clin Pharmacol. 1996 Jul;36(7):659-66.
45 Sabuncu T, et al. Rom J Gastroenterol. 2003 Sep;12(3):189-92.

The sponsor summarized the incidence of marked laboratory abnormalities in the pooled studies as well as study NM17247 (Tables 7.1.7.3.2.B and 7.1.7.3.2.C, respectively). Please see the Appendix (Section 10.4) for a table of cut-offs for marked laboratory abnormalities. The incidence of marked laboratory abnormalities in one year of treatment in the pooled studies was generally similar between treatment groups. Although there was a greater percentage of subjects in the orlistat 60 mg group in study NM17247 (Table 7.1.7.3.2.C) with overall marked abnormalities than the placebo group, the incidence of individual laboratory tests with these abnormalities was generally similar between groups, with the exception of markedly low serum phosphorus (0.5% placebo, 2.6%, orlistat). This finding was not noted in the pooled studies.

Table 7.1.7.3.2.B. Frequency of Marked Laboratory Abnormalities in Year 1 of Treatment; Safety Population; Pooled Studies

	Placebo N = 634		**60 mg TID N = 623**		**120 mg TID N = 632**	
	n	**(%)**	**n**	**(%)**	**n**	**(%)**
Subjects with 1 or more marked abnormalities	37	(5.8)	33	(5.3)	42	(6.6)
Marked High Abnormalities						
Creatine Phosphokinase	14	(2.2)	15	(2.4)	13	(2.1)
GGT	3	(0.5)	1	(0.2)	5	(0.8)
Potassium	4	(0.6)	3	(0.5)	3	(0.5)
Phosphorus	0		1	(0.2)	3	(0.5)
ALT (SGPT)	2	(0.3)	0		3	(0.5)
Hematocrit	1	(0.2)	0		2	(0.3)
Hemoglobin	0		0		2	(0.3)
Thyroid Stimulating Hormone	2	(0.3)	1	(0.2)	1	(0.2)
Neutrophils	0		0		1	(0.2)
Platelet Count	1	(0.2)	0		1	(0.2)
AST (SGOT)	1	(0.2)	1	(0.2)	0	
Total Bilirubin	1	(0.2)	1	(0.2)	0	
Eosinophils	1	(0.2)	1	(0.2)	0	
Basophils	0		1	(0.2)	0	
Alkaline Phosphatase	1	(0.2)	0		0	
Sodium	1	(0.2)	0		0	
Marked Low Abnormalities						
WBC	2	(0.3)	5	(0.8)	6	(0.9)
Neutrophils	3	(0.5)	4	(0.6)	3	(0.5)
Platelet Count	4	(0.6)	4	(0.6)	2	(0.3)
Lymphocytes	0		0		2	(0.3)
Sodium	0		0		1	(0.2)
Hematocrit	2	(0.3)	1	(0.2)	0	
RBC	1	(0.2)	1	(0.2)	0	
Hemoglobin	2	(0.3)	0		0	

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Table 7.1.7.3.2.C. Frequency of Marked Laboratory Abnormalities in Four Months of Treatment; Safety Population; Study NM17247				
	Placebo N = 195		60 mg TID N = 196	
	n	(%)	n	(%)
Subjects with 1 or more marked abnormalities	15	(7.7)	22	(11.2)
Marked High Abnormalities				
ALT (SGPT)	5	(2.6)	4	(2.0)
AST (SGOT)	4	(2.1)	3	(1.5)
GGT	2	(1.0)	3	(1.5)
Potassium	1	(0.5)	1	(0.5)
Phosphorus	0		1	(0.5)
Total Bilirubin	0		1	(0.5)
Marked Low Abnormalities				
Phosphorus	1	(0.5)	5	(2.6)
Neutrophils	2	(1.0)	4	(2.0)
Lymphocytes	2	(1.0)	2	(1.0)
WBC	2	(1.0)	2	(1.0)
Platelet Count	1	(0.5)	1	(0.5)
Monocytes	0		1	(0.5)
Chloride	1	(0.5)	0	

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7.1.7.3.3 Glucose and insulin

Table 7.1.7.3.3.A illustrates changes in fasting glucose over one year in the pooled safety studies BM14149, NM14161, and NM14302, combined. Pooling of the three safety studies was probably not the most appropriate way to analyze the glucose data, as this pooling included study NM14302, in which subjects were randomized to drug treatment only after six months of a reduced diet lead-in period, and the goal of the study was to prevent regain. Data for changes in insulin were not pooled similarly to other safety measures in the Integrated Summary of Safety in the nonprescription NDA.

Despite the above limitations, it is clear that orlistat-related weight loss is associated with predictable improvements in measures of glucose homeostasis and insulin sensitivity. It is noted that subjects receiving orlistat 120 mg in studies from the original prescription NDA (not pooled) had statistically significant decreases in glucose, insulin, and insulin resistance (assessed by HOMA) compared to subjects receiving placebo over a one- and two-year period.

Moreover, the four-year XENDOS study demonstrated that 120 mg of orlistat TID plus lifestyle intervention reduced the incidence of the development of type 2 diabetes in obese patients with impaired glucose tolerance compared to those receiving placebo plus lifestyle intervention.[31]

Overweight subjects treated with orlistat 60 mg TID in study NM17247 achieved modest improvements in serum glucose over placebo, but the difference between groups was statistically significant in the ITT LOCF analysis population only (Table 7.1.7.3.3.B).

Table 7.1.7.3.3.A. Fasting Glucose (mmol/L): Safety Population; Pooled Studies BM14149, NM14161, NM14302						
Study Day	**Value at Scheduled Visit**			**Change from Start of Study Medication**		
	N	**Mean**	**SD**	**N**	**Mean**	**SD**
Placebo						
Day 1	632	5.58	0.763	632	0.00	0.000
Week 12	580	5.59	0.736	578	0.00	0.556
Week 24	537	5.61	0.794	537	0.02	0.593
Week 52	398	5.69	0.715	398	0.13	0.508
Orlistat 60 mg TID						
Day 1	622	5.58	0.720	622	0.00	0.000
Week 12	600	5.54	0.657	599	-0.05	0.442
Week 24	547	5.54	0.650	546	-0.05	0.447
Week 52	429	5.62	0.689	428	0.02	0.531
Orlistat 120 mg TID						
Day 1	629	5.55	0.584	629	0.00	0.000
Week 12	594	5.51	0.609	591	-0.05	0.462
Week 24	552	5.51	0.655	549	-0.06	0.481
Week 52	424	5.60	0.801	422	0.03	0.585

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Table 7.1.7.3.3.B. Change in Fasting Glucose (mmol/L) Measurements at 4 Months – Study NM17247								
Treatment	N	Within Treatment		Difference From Placebo				
		Mean Baseline Value	LS Mean Change From Baseline	LS Mean	SE	95% CI Lower	95% CI Upper	P-Value
ITT LOCF								
Placebo	175	4.90	0.04					
Orlistat 60	188	4.93	-0.07	-0.11	0.05	-0.21	-0.02	0.023
Completer								
Placebo	140	4.88	0.05					
Orlistat 60	152	4.92	-0.02	-0.07	0.06	-0.18	0.04	0.207
ITT Observed								
Placebo	138	4.87	0.06					
Orlistat 60	154	4.92	-0.03	-0.09	0.06	-0.19	0.02	0.126

Adapted from GSK Clinical Update

An additional consideration in the discussion of glucose and insulin changes, particularly as it relates to the nonprescription use of orlistat, is the safety of orlistat in patients with diabetes on antihyperglycemic therapy. Certainly, improvements in hemoglobin A1c (HbA1c) and decreases in antihyperglycemic medication dose are significant benefits of weight loss in patients with diabetes. In support of this concept, Roche submitted an efficacy supplement to NDA 20-766 in March 2001 seeking an indication for use in patients with type 2 diabetes who have a BMI ≥ 27 kg/m^2 in combination with background antihyperglycemic therapy; nevertheless, this indication was not approved.[46] Dr. Joanna Zawadzki's review of the four multi-center, placebo-controlled trials submitted with this supplement concluded that the data did not consistently support a diabetes indication. She noted that the lowering of HgbA1c treatment effect was modest (at the

46 Zawadzki, J. Medical Officer Review of NDA 20-766 S-008.

low end of the range of HgbA1c treatment effects for drugs currently approved for combination therapy in type 2 diabetes mellitus) in three of the four studies (two sulfonylurea studies and an insulin study) and not significant in the fourth study in which metformin was the background medication. This was of particular concern, as metformin is a widely-used medication for diabetes.

Dr. Zawadzki's review also found that in these studies, in which subjects had relatively mild diabetes and relatively non-intensive diabetes treatment, 9% of placebo-treated and 13% of orlistat-treated patients had an episode of hypoglycemia. In the insulin study, 3 orlistat- and 1 placebo-treated patient required intervention for hypoglycemia.

The risk of hypoglycemia may be greater in individuals who have more tightly-controlled diabetes, have type 1 diabetes, or are on multiple antihyperglycemic medications. Furthermore, a recent meta-analysis of placebo-controlled controlled trials with orlistat found that subjects with medication-treated diabetes who were randomized to orlistat were more likely to discontinue or reduce the dosage of an antidiabetic medication (sulfonylureas, insulin, or metformin) than those randomized to placebo.[30] Therefore, this reviewer believes that a weight loss program including orlistat would be used most safely by patients with diabetes in the prescription drug setting, in order for the appropriate management of their disease and concomitant medications.

This concern is amplified by the results provided in Table 7.1.7.3.3.C, below. Although the label as written for the actual use study included the exclusion 'taking medicine for diabetes', only 35% of such subjects in study NM17285 made an appropriate initial selection decision.

Table 7.1.7.3.3.C. Subjects with Unconditional Labeled Exclusions: Appropriate Initial Selection Decision; Eligible Subjects, Study NM17285

	N	Initially said appropriate?	n (%)	Appropriate initial selection decision	
				Total	n (%)
Taking medicine for diabetes	46	Yes	24 (52.2)	0	16 (34.8)
		No	16 (34.8)	16	
		Don't know	6 (13.0)	0	

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7.1.7.3.4 Lipids

Orlistat has been touted as having a beneficial impact on lipid parameters. Short-term studies demonstrate that orlistat treatment is associated with reduced delivery of dietary lipid and fatty acids to the liver;[47] and long-term evidence of lowered total and LDL-cholesterol may be a byproduct of weight loss[48] or adherence to a low-fat diet.[49]

47 Reitsma JB, et al. Metabolism. 1994 Mar;43(3):293-8.
48 Dattilo AM, et al. Am J Clin Nutr. 1992 Aug;56(2):320-8.
49 Schaefer EJ, et al. Am J Clin Nutr. 2002 Feb;75(2):191-212.

As discussed with glucose, pooling of the three safety studies was probably not the most appropriate way to analyze the lipid data, as this pooling included study NM14302, in which subjects were randomized to drug treatment only after six months of a reduced diet lead-in period. In these pooled studies, the orlistat 60 mg and 120 mg treatment groups exhibited approximate decreases in total cholesterol of 3.1% and 4.9%, respectively, as compared to an increase of 2.1% in the placebo group at six months. At one year, the total cholesterol in the placebo group increased to 2.3% of baseline, whereas the improvements (decreases) in the orlistat 60 and 120 mg were attenuated somewhat, to 1.2% and 3.1%, respectively. The orlistat 60 mg and 120 mg treatment groups showed decreases in LDL cholesterol of about 5.2% and 6.4%, respectively as compared to an increase of 2.7% in the placebo group at six months. An increase in HDL cholesterol was seen in all treatment groups at six months, with the highest increase seen in the placebo group (6.6%) versus orlistat 60 mg (3.3%) and 120 mg (0.8%).

As is detailed in the review of the original prescription NDA,[28] changes after one year in total cholesterol in study BM14149 were +0.06%, -3.0%, and -7.0% in the placebo, orlistat 60 mg, and orlistat 120 mg groups, respectively ($p = 0.1$, placebo *vs.* 60 mg; $p < 0.001$, placebo *vs.* 120 mg). LDL-C changes were: -1.0%, -7.0%, and -11.0%, respectively ($p = 0.04$, placebo *vs.* 60 mg; $p < 0.001$, placebo *vs.* 120 mg). In study NM14161, changes in total cholesterol were +3.7%, +0.3%, and -1.0% in the placebo, orlistat 60 mg, and orlistat 120 mg groups, respectively ($p = 0.05$, placebo *vs.* 60 mg; $p = 0.007$, placebo *vs.* 120 mg). LDL-C changes were: +7.0%, +0.5%, and -2.5%, respectively ($p = 0.02$, placebo *vs.* 60 mg; $p = 0.001$, placebo *vs.* 120 mg). The medical reviewer, Dr. Eric Colman, also notes in his review that NM14161, the study with the least dietary intervention and the greatest weight regain in the second year, found no significant differences between the orlistat- *vs.* placebo-treated subjects in any of the lipid parameters at the end of the second year. In all three groups, most of the lipid parameters had actually increased from baseline to week 104. In study BM14149, which used intensive dietary intervention, the orlistat groups had significantly lower total and LDL-cholesterol concentrations than the placebo group at the end of the second year; however, even in this study, mean percent changes of these lipid concentrations increased for all groups.

Table 7.1.7.3.4.A illustrates the lipid changes observed in the four-month nonprescription trial in overweight subjects. Total and LDL cholesterol decreased in both groups, with a significantly greater decrease in the orlistat group. As for HDL cholesterol, whereas the placebo group had a mean increase, the orlistat group had a mean decrease; the difference between groups was not statistically significant, however. Both groups had a decrease in LDL/HDL ratio, with the orlistat group demonstrating a slightly greater decrease; the difference between groups was not statistically significant. Both groups had an approximately 15% increase in triglycerides, possibly as a result of a greater contribution of carbohydrate to the diet.

Table 7.1.7.3.4.A. Percent Change of Least Square Means in Lipids — LOCF Data, ITT Population; Study NM17247								
Treatment	**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**
Total Cholesterol								
Placebo	175	5.35	-0.09					
Orlistat 60mg	188	5.27	-3.77	-3.69	1.32	-6.28	-1.09	0.006
LDL Cholesterol								
Placebo	175	3.24	-0.48					
Orlistat 60mg	187	3.12	-5.93	-5.44	2.10	-9.57	-1.32	0.010
HDL Cholesterol								
Placebo	175	1.49	0.42					
Orlistat 60mg	188	1.51	-1.90	-2.32	1.46	-5.20	0.55	0.113
LDL/HDL Ratio*								
Placebo	175	2.32	-0.05					
Orlistat 60mg	187	2.19	-0.12	-0.07	0.05	-0.17	0.02	0.122
Triglycerides								
Placebo	175	1.37	15.06					
Orlistat 60mg	188	1.41	14.80	-0.26	5.92	-11.90	11.39	0.966
* Not a percentage change.								

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A meta-analysis of six-month and one-year studies of obese subjects comparing orlistat and placebo in five lipid measures of interest: total cholesterol, LDL cholesterol, HDL cholesterol, LDL/HDL, and triglycerides, found that orlistat significantly reduced all of these measures as compared with placebo, regardless of whether additional co-morbidities were present.[30] Although HDL is decreased, the overall atherogenic profile is considered improved based on the other cholesterol measures, including the LDL/HDL ratio. Nevertheless, none of the findings from clinical trials with orlistat would support its use as a treatment for dyslipidemia.

7.1.7.4 Additional analyses and explorations

No further laboratory analyses were performed.

7.1.7.5 Special assessments

All special laboratory assessments were described in the above sections.

7.1.8 Vital Signs

7.1.8.1 Overview of vital signs testing in the development program

Vital signs were measured in the pivotal phase 3 studies (BM14149, NM14161, NM14302, and NM17247) and the supportive phase 2 study (BM14150). Vital sign measurements were not

collected for the actual use and consumer use studies (NM17285 and RCH-ORL-002, respectively).

The subject's pulse and blood pressure were measured at each visit of each study. These measurements were taken with the subject in the sitting position after sitting quietly for five minutes. During each of the blood pressure evaluations, two readings were taken, separated by at least one minute, and the average of the two readings were recorded on the case report form.

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

Mean blood pressure results are presented for studies BM14149, NM14161, and NM14302 pooled; study NM17247; and study BM14150.

7.1.8.3 Standard analyses and explorations of vital signs data

7.1.8.3.1 Blood pressure

In the pooled studies BM14149, NM14161, and NM14302, the mean change in systolic blood pressure was small for all treatment groups. At six months, both the 60 mg and 120 mg orlistat treatment groups showed a mean change in systolic blood pressure of -0.7 mmHg compared to no change from baseline in the placebo group. At one year, the mean change in systolic blood pressure for both the 60 mg and 120 mg orlistat groups was 0.5 mmHg compared to a mean change of 1.0 mmHg for the placebo group. Mean changes in diastolic blood pressure were small as well. At six months, the orlistat 60 mg group demonstrated a mean change of -0.3 mmHg, the orlistat 120 mg group had a mean change of -0.6 mmHg, and placebo showed a mean change of 0.4 mmHg.

In the LOCF ITT population in study NM17247, the least squares mean change from baseline to the end of treatment at four months for systolic blood pressure was -4.51 mmHg for orlistat-treated subjects and -2.34 mmHg for placebo-treated subjects (adjusted for center and baseline value); this difference was statistically significant ($p = 0.035$). The least squares mean change from baseline to the end of treatment at four months for diastolic blood pressure was -2.77 mmHg for the orlistat-treated subjects and -0.30 mmHg for the placebo-treated patients; this difference was also statistically significant ($p = 0.001$). It is notable that these measurements were not adjusted for amount of weight lost; therefore, this reviewer assumes that the significant differences are due to acute weight loss rather than an independent drug effect. Furthermore, as demonstrated by the pooled studies discussed above, any effect in blood pressure is likely transient because differences between orlistat groups and placebo appear to decrease with time.

In study NM14150 (phase 2 dose-ranging), decreases in systolic and diastolic blood pressure after six months in the orlistat treatment groups (60 mg: -0.97 and -0.54 mmHg, respectively; 120 mg: -3.51 and -2.01 mmHg, respectively) were not statistically different as compared to the placebo group (-1.23 and -2.08 mmHg, respectively).

A case series published in the British Medical Journal in 2001[50] regarding post-marketing reports of orlistat and hypertension (Table 7.1.8.3.1.A), in addition to a consult by the Division requesting a comparison with sibutramine, prompted the FDA Office of Drug Safety to review whether there was a safety signal with orlistat and hypertension in the AERS database (Table 7.1.8.3.1.B).[51] It is difficult to know what to make of these post-marketing findings, particularly without a plausible biological mechanism. Nevertheless, cases in which there is a clear temporal relationship to drug, particularly where there is a documented rechallenge provide a compelling argument for drug causality. Systemic absorption of this drug is very low, and in most cases, orlistat-related weight loss improves blood pressure, even in individuals with baseline hypertension.[34] However, as discussed further in Section 7.1.12.2.2.3, in the consideration of potential liver toxicity or Section 7.1.12.2.2.2, that of pancreatitis, one cannot discount the possibility of a rare idiosyncratic reaction with orlistat use.

Table 7.1.8.3.1.A. Spontaneous reports of hypertension associated with orlistat treatment in Sweden

Case No	Sex	Age (years)	Length of treatment with orlistat	Blood pressure with orlistat treatment (mm Hg)			Adverse reactions
				Before	During	After	
1	F	41	Weeks, intermittently	Healthy	190/100	140/90	Hypertension, headache, oedema
2	F	70	9 months	165/90 (Healthy, BMI=36)	190/90	160/85	Hypertension
3	F	73	7 weeks intermittently	Orthostatic hypotension	185/100	Antihypertensive treatment	Hypertension
4	F	50	17 months	140/85 (Healthy, BMI $\geq$ 30)	180-200/100	140-130/85	Hypertension, headache
5	F	70	6 weeks	180/90, (Levothyroxine treated hypothyroidism)	245/145	180/90	Blood pressure increased

Adapted from Persson M, et al. BMJ 2001 Jan;322:111

50 Persson M, et al. BMJ 2001 Jan;322:111
51 Chang J. ODS Safety Reviewer Consult: Orlistat (Xenical®) and Fatal Outcomes; NDA 20-766.

Table 7.1.8.3.1.B. Orlistat and Hypertension in the FDA AERS Post-Marketing Database: April 23, 1999 to March 18, 2002	
Selected Characteristics	Orlistat, n=87
Baseline blood pressure (mm Hg)	n=30
Median	132/80
Mean	134/82
Blood pressure on orlistat (mm Hg)	n=58
Median	180/104
Mean	186/108
Prior history of hypertension	n=60
Yes	44
No	16
Rechallenge	
Positive	5
Negative	1
Therapy modification	
Start anti-hypertensive	18
Increase dose	1

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Given these findings, this reviewer analyzed the safety database of the current NDA for cases of hypertension or worsening blood pressure.

In studies NM14161 and BM14149, pooled, the percentage of subjects with an increased change in blood pressure from baseline at least once during the year is shown in Table 7.1.8.3.1.C (reviewer analysis; the population includes subjects who had at least one post-baseline blood pressure value).

Table 7.1.8.3.1.C. Increased Change in SBP and DBP During the First Year of Treatment; Studies NM14161 and BM14149			
	Placebo N = 273 n (%)	**Orlistat 60 mg N = 280 n (%)**	**Orlistat 120 mg N = 279 n (%)**
ΔSBP ≥ 20 mmHg	55 (20.1)	58 (20.7)	69 (24.7)
ΔDBP ≥ 10 mmHg	100 (36.6)	101 (36.1)	94 (33.7)

Incidence of adverse events of 'hypertension' in the first year of the pooled safety studies (BM14149, NM14161, and NM14302) were similar, with the exception of the orlistat 60 mg dose: 7 (1.1%), 2 (1.1%), 17 (2.7%), and 6 (0.9%), in the placebo, orlistat 30 mg, orlistat 60 mg, and orlistat 120 mg groups, respectively.

In study NM17247 (reviewer's analysis), 4 (2.3%) orlistat-treated subjects and 7 (4.3%) placebo-treated subjects had at least one episode of change from baseline in SBP ≥ 20 mmHg at some point during the four-month study. Nine (5.3%) orlistat-treated subjects and 19 (11.7%) placebo-treated subjects had at least one episode of change from baseline in DBP ≥ 10 mmHg at some point during the study. One subject treated with orlistat 60 mg was withdrawn due to worsening

hypertension. This was a 44-year-old White male who weighed 94.2 kg at baseline. He withdrew from the study on study day 61 because of elevated blood pressure. The patient had secondary diagnoses of occasional headaches, high blood pressure, occasional heartburn, arthritis of entire body, lower back pain and intermittent left knee locking (due to cartilage injury). At the time of the event, he weighed 98.0 kg and was taking propranolol, verapamil, and a multivitamin. On study day 62, the patient developed elevated blood pressure, which was moderate in intensity. He was treated with accupril. The study drug was discontinued on study day 61 and the patient withdrew from the study. At baseline, his blood pressure was 130/80, however on study day 62 it was 160/102. At the termination visit, day 71, his blood pressure was still elevated at 160/110. On study day 85, the date of last contact, the event was still ongoing.

Finally, it is noted that the four-year XENDOS study demonstrated a similar incidence between placebo and orlistat for adverse events of 'hypertension NOS' (4% and 3%, respectively) and 'hypertension aggravated' (2% in each group), as described in the medical officer review of this study.[52] Dr. Colman further notes in his review that 19 (1.2%) of the orlistat subjects and 35 (2.3%) of the placebo patients developed a SBP > 160 mmHg on two or more consecutive visits. Twenty-five (1.6%) of orlistat subjects and 35 (2.3%) of the placebo patients developed a DBP > 100 mmHg on two or more consecutive visits. Therefore, there was no signal seen for orlistat-related hypertension in this four-year controlled trial.

7.1.8.3.2 Pulse

Mean heart rate changes were small and similar between orlistat and placebo treatment groups in all studies (Table 7.1.8.3.2.A).

Table 7.1.8.3.2.A. Pulse in Pooled Safety Studies; BM14149, NM14161, and NM14302

Treatment Group	Study Day	Pulse (bpm) at scheduled visit				Change in pulse from baseline			
		N	Mean	SD	Range	N	Mean	SD	Range
Placebo	Day 1	634	71.6	8.79	46 - 100	634	0.0	0.00	0 - 0
	Week 12	600	71.8	9.65	46 - 112	600	0.3	10.01	-44 - 46
	Week 24	555	72.0	9.30	46 - 108	555	0.6	10.29	-36 - 34
	Week 52	443	71.2	9.33	48 - 101	443	0.1	9.45	-32 - 31
Orlistat 60 mg	Day 1	621	70.7	9.17	40 - 116	621	0.0	0.00	0 - 0
	Week 12	608	70.4	8.61	48 - 102	608	-0.2	9.50	-52 - 38
	Week 24	564	70.7	8.97	42 - 112	564	0.2	10.11	-48 - 34
	Week 52	487	70.5	9.03	41 - 104	487	-0.0	10.15	-46 - 40
Oristat 120 mg	Day 1	632	71.4	9.21	44 - 120	632	0.0	0.00	0 - 0
	Week 12	610	71.6	8.89	44 - 108	610	0.2	9.89	-34 - 40
	Week 24	561	71.7	9.34	48 - 108	561	0.6	10.80	-39 - 40
	Week 52	477	71.0	8.96	44 - 101	477	-0.2	9.98	-35 - 32

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There were no adverse events for palpitations or tachycardia in study NM17247. There was possibly a slight imbalance in the pooled safety studies for AEs of heart rate and rhythm, although these findings were not dose-dependent (Table 7.1.8.3.2.B). One adverse event of atrial

52 Colman E. Medical Officer Review of NDA 20-766, SE8

fibrillation (orlistat 120 mg) and one event of paroxysmal atrial tachycardia (orlistat 60 mg) were defined as serious adverse events, but no subject withdrew from the study during the first year due to these events. There is no reason to suspect that orlistat contributes to heart rate or rhythm disturbances (see Section 7.1.9, Electrocardiograms, below).

Table 7.1.8.3.2.B. Percentage of Adverse Events of Heart Rate and Rhythm Body System in the First Year; Pooled Safety Studies

	Placebo	Orlistat 30 mg	Orlistat 60 mg	Orlistat 120 mg
Heart Rate and Rhythm	1.3%	2.7%	1.6%	2.1%
Palpitation	0.8%	2.7%	1.1%	1.7%
Arrhythmia	0	0	0.3%	0.2%
Fibrillation atrial	0	0	0.2%	0.2%
Tachycardia	0.5%	0	0	0.2%
Paroxysmal superventricular tachycardia	0	0	0.2%	0

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7.1.8.4 Additional analyses and explorations

No further analyses were performed on vital signs.

7.1.9 Electrocardiograms (ECG*s*)

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

Twelve-lead ECG*s* were performed at screening, baseline, and after each year of treatment in the pooled safety studies, and at screening only in study NM17247.

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

The sponsor referred to the Integrated Summary of Safety from the original prescription NDA (20-766) for reporting ECG findings. Raw ECG data were not provided in the current submission.

7.1.9.3 Standard analyses and explorations of ECG data

According to the sponsor, the most common ECG abnormalities during treatment with orlistat were sinus bradycardia, non-specific ST or T wave changes, left axis deviation, and sinus arrhythmia. No obvious differences in ECG values could be discerned between the placebo and the orlistat treatment groups.

7.1.9.4 Additional analyses and explorations

No further analyses or explorations were done.

7.1.10 Immunogenicity

Not applicable (orlistat is not a therapeutic protein).

7.1.11 Human Carcinogenicity

There are two aspects of human carcinogenicity worth noting. First, in the original NDA for orlistat 120 mg TID, an imbalance in the number of breast cancer was observed in the orlistat-treated subjects as compared to the placebo-treated subjects. Subsequent analyses from phase 3b studies and the four-year XENDOS trial did not support this finding, and breast cancer has not surfaced as a post-marketing concern.

Second, in the original NDA, the Division of Gastrointestinal and Coagulation Drug Products was consulted regarding the study, "Effect of oral administration of orlistat (XENICAL™) on fecal fat, fecal biliary acids and colonic mucosa cell turnover in obese subjects."[53] In this six-week study, fecal matter was analyzed for total weight, total fat, FFAs, total and individual bile acid concentration, and calcium and phosphorus. Fecal water was analyzed for FFAs, total and individual bile acid concentration, and pH. Rectal biopsies were performed before and after treatment and processed for crypt compartment analysis of the biomarkers bromodeoxyuridine labeling index, proliferating cell nuclear antigen labeling, and whole crypt mitotic count value. According to the FDA consultant, analysis of the data from both the solid and liquid phase of the stool did not reveal findings of concern following orlistat treatment, and orlistat did not induce colonic epithelial cell proliferation under the experimental conditions. However, he noted that because this was only a six-week study, the long-term effects of orlistat on colonic architecture was not answered by this study. Although post-marketing surveillance in people in whom the compound may be "most dangerous" in the long term, such as those with risk factors, predisposing conditions, and premalignant lesions, was recommended by the consultant, a phase 4 commitment was not required of the sponsor. Clinical trials, including the four-year XENDOS trial, did not uncover any imbalance in colon cancer.

7.1.12 Special Safety Studies

Four special studies were reviewed with the original prescription NDA,[28] and the relevant findings from the review will be summarized in Section 7.1.12.1, below. Other special studies from the original prescription NDA included two mineral balance studies, completed after the original NDA was approved. These findings were discussed in Section 7.1.7.3.1.

Section 7.1.12.2 will discuss specific safety issues post-marketing databases as well as from clinical trials supporting the orlistat prescription and nonprescription NDA and relevant literature that inform the safety profile in the post-marketing environment.

53 Gallo-Torres HE. Medical Officer's Consult Review of Protocol NP15138, NDA 20-766.