Subgroup Analyses of Efficacy

Efficacy (change in body weight from baseline) was examined in several subgroups. These groups included age (<40, >40 but <60, >60), gender, race (Caucasian, Black, Hispanic, other), and BMI (<30, >30<35, >35).

There was no significant age or BMI effect for weight loss efficacy during Year 1. Race and gender, however, were significant. The mean placebo-subtracted weight loss in females was 3.3 kg and 2.6 kg in males. The mean placebo-subtracted weight loss was 3.4 kg in Caucasians, 2.1 kg in Blacks, and 5.1 kg in Hispanics. No significant subgroup effects were observed for Year 2.

Summary of the Changes in Comorbidities by Degree of Weight Loss

The table below summarizes the changes from baseline to Year 1 in the common obesity-related comorbidities for three categories of weight loss: <5%, ≥5% to <10%, and ≥10%.

Change in Risk Factor from Baseline to Year 1 by Degree of Weight Loss (Completers)

Risk Factor	<5%		≥5% to <10%		≥10%	
	Orlistat	Placebo	Orlistat	Placebo	Orlistat	Placebo
ΔTC	0%†††	5%	-2%†††	5%	-5%††	1%
ΔLDL	-2%†††	6%	-5%†††	6%	-7%†	-1%
ΔHDL	5%†††	10%	12%†	16%	17%†	23%
ΔTG	14%†	9%	-2%	-4%	-14%	-18%
ΔSBP (mmHg)	2	2	-3	-1	-2	-4
ΔDBP(mmHg)	1	1	-2†	0	-3	-2
ΔG_0 (mg/dl)	0.5	2	-1	-3	-4	-3
ΔIRI (pmol/L)	7	11	-12	-11	-22	-15

†p<0.05, ††p<0.01, †††p<0.001 orlistat vs placebo
G_0=fasting glucose, IRI=fasting insulin

On balance, these data indicate progressive improvements in the comorbid risk factors with increasing amounts of weight loss in the orlistat-treated patients.

EFFECT OF ORLISTAT ON BODY COMPOSITION

The effect of orlistat on body composition was assessed in a subgroup of 240 patients from studies BM14119C and BM14149. The techniques used to measure body composition included DEXA, TBK, anthropometric measurements, and bioelectrical impedance. The majority of the data are the result of anthropometric measurements derived from formulas previously calibrated against CT measurements. Changes as assessed by DEXA were the second most frequent measurements reported. And total body

potassium was determined in a small number of patients and only for the first year of treatment.

With few exceptions, there was good agreement among the various methods used to measure body composition. Weight loss associated with orlistat treatment was largely due to a reduction in fat mass. Although loss of fat-free mass occurred in both placebo and orlistat groups following weight loss, the difference between the active-treatment and placebo groups was not clinically significant. These results are in agreement with the expected changes associated with diet-induced weight loss.

Overview of Safety

Exposure

A total of 7072 patients have participated in orlistat's global development program, with 4852 receiving at least one dose of orlistat. Approximately 2847 subjects participated in the phase III studies; 2153 of these patients received at least 1 year of treatment with orlistat and 884 received at least 2 years of treatment. The orlistat dose with the greatest exposure was 120mg; approximately 2038 subjects received 120mg of orlistat for 1 year and 1068 received this dose for over 1 year. A total of 510 patients were treated with 120mg for 2 years.

Demographics

The mean age of the participants was 45 years (range 18-78 yrs), the majority (80%) were female and Caucasian (91%), and the average BMI was 35 kg/m^2 (range 26-47 kg/m^2).

Disposition of Patients

The table below lists the reasons for premature withdrawal during Year 1. Adverse events were the most common reason for premature withdrawal in the orlistat groups, while lost to follow-up was the most common reason for premature withdrawal in the placebo group. A similar pattern was observed during Year 2.

Reason for Dropout	Placebo n=1466	120mg n=1913
Adverse event	4.9%	8.8%
Treatment failure	2.6%	1.0%
Early improvement	0.1%	0.0%
Refused treatment	3.2%	1.5%
Died during study	0.0%	0.1%
Lost to follow-up	9.8%	7.7%
Did not cooperate	6.5%	3.8%
Protocol violation	2.2%	2.0%

Reason for Dropout	Placebo n=1466	120mg n=1913
Entry violation	0.2%	0.3%
Administrative	5.8%	4.0%
Total no. of withdrawal	35.3%	29.1%

Deaths

There were seven deaths in the phase III studies as shown in the table below.

Treatment	Sex	Age at Death	Day of Death	Cause of Death
Diet lead-in	F	40	-107	MVA
Lead-in	F	48	-8	MVA
Placebo	F	36	637	MVA
120mg/Placebo	F	40	748	MVA
60mg	M	61	449	MI
120mg	M	60	707	Cardiac Arrest
120mg	M	55	317	MI

A review of the summaries of the above deaths does not raise suspicion that orlistat was a causative agent. Four of the subjects were not receiving drug at the time of death and two of the three patients who died from acute myocardial infarction had significant histories of cardiac disease.

Serious Adverse Events (SAEs)

Serious adverse events were defined as those which clearly presented or could be expected to present a threat to the well being of the patient. Specifically, this included any event which was fatal or life threatening, permanently disabling, required in-patient hospitalization, or prolongation of hospitalization, caused a congenital anomaly, caused a cancer, or was an overdose.

Approximately 6% of the patients in the placebo and orlistat 30mg, 60mg, and 120mg groups, respectively, reported serious adverse events during Year 1. For patients who received 2 full years of treatment with placebo or orlistat, 60mg or 120mg, the incidence of SAEs was 12%, 15%, and 10%, respectively. During both time periods the most commonly reported SAEs were from the following body systems: reproductive system-female, body as a whole, and gastrointestinal.

Reproductive disorders, female: The overall incidence of SAEs in this category was similar among the placebo and orlistat groups. Approximately 3% of patients in the placebo and orlistat 120mg groups reported one or more SAEs during 2 full years of treatment.

Body as a whole: Approximately 0.8% to 3.0% of patients reported SAEs in this category. The incidences were not markedly different among the placebo and active-treatment groups. Furthermore, there did not appear to a dose-related effect in the orlistat groups. The majority of the reported cases within this body system were surgical procedures. The most common procedures were hysterectomy (six orlistat and two placebo) and knee surgery (three orlistat and four placebo).

Gastrointestinal: There were relatively few SAEs reported in this category and the incidences were similar for the placebo and orlistat groups: 0.5% to 1.3% during Year 1 and 1.5% to 3.0% during 2 years of treatment. One case of a GI neoplasm was reported in the placebo group and in the orlistat 60mg group. Importantly, less than 1% of patients reported SAEs in the liver of biliary systems and the incidences were not significantly different between the placebo and orlistat groups.

Adverse Drug Reactions (ADRs)

The table below summarizes the body system disorders in which at least one treatment group reported an ADR with an incidence of greater than 5%. The most commonly reported ADRs occurred in the GI system in which the incidence was higher for the orlistat groups compared to the placebo group.

Body System Disorder	One Year of Treatment		Two Years of Treatment	
	Placebo n=1466	120mg n=1913	Placebo n=524	120mg n=613
GI system	57%	80%	68%	82%
Respiratory system	40%	46%	61%	60%
Resistance Mech	39%	42%	55%	56%
Musc-Skel System	39%	39%	60%	52%
Nervous System	34%	36%	49%	44%
Body as a Whole	21%	23%	33%	30%
Skin	18%	19%	31%	28%
Female-Reproduct	14%	17%	26%	25%
Urinary System	9%	10%	15%	16%
Psychiatric	7%	9%	13%	14%
Met and Nutr	7%	6%	4%	2%
Hearing	5%	5%	8%	10%
CV	6%	5%	11%	9%
Vision	4%	4%	6%	5%

The Sponsor defined an adverse event as potentially treatment related if the difference in incidence between placebo and drug was at least 3%. Using this definition and excluding GI ADRs, upper respiratory tract infection, influenza syndrome, and headache were reported in active-treated patients with an incidence of approximately 3-4% higher than placebo. There did not appear to be a dose-related increase in the incidences of these events.

The increased frequency of reported GI ADRs warrants a more detailed review of these events. Seven GI ADRs were identified as being almost exclusively related to orlistat treatment, and occurred with an incidence rate 5% higher and in more than twice as many patients in the 120mg group than in the placebo group (see table below). These ADRs include: oily spotting, flatus with discharge, fecal urgency, fatty/oily stool, oily evacuation, increased defecation, and fecal incontinence.

GI System Disorder	One Year of Treatment		Two Years of Treatment	
	Placebo n=1466	120mg n=1913	Placebo n=524	120mg n=613
Oily Spotting	1%	27%	1%	22%
Flatus with Discharge	1%	24%	1%	17%
Fecal Urgency	7%	22%	7%	22%
Abdominal Pain	16%	21%	245	23%
Fatty/Oily Stool	3%	20%	55	26%
Flatulence	13%	16%	12%	15%
Liquid Stool	11%	16%	18%	19%
Oily Evacuation	1%	12%	1%	10%
Increased Defecation	4%	115	5%	13%
Soft Stools	7%	9%	10%	13%
Nausea	7%	8%	9%	11%
Fecal Incontinence	1%	8%	1%	7%

A larger percentage of patients who received 120mg orlistat compared with placebo experienced two episodes of the GI adverse events listed in the table above. It appeared that the incidence of GI ADRs decreased during the second year of the study suggesting that the intestinal tract may, over time, adjust to effects of orlistat. However, the possibility of bias due to drop outs — those subjects who experienced GI adverse events during the first year dropped out of the study — cannot be dismissed. Although the incidence was only 1.3%, it should be recognized that treatment with the 120mg dose of orlistat was associated with an increased incidence of discolored feces compared with placebo.

As shown in the table below many of the patients reporting GI ADRs that were thought to be related to, or increased with, orlistat treatment had their first occurrence within the first 12 weeks of treatment. Of

note, however, was the increased occurrence of abdominal pain and liquid stools over time.

TIME TO EVENT

Adverse Event	120mg Orlistat			
	≤ 1 Wk	≤ 12 Wk	≤ 48 Wk	≥ 96 Wk
Oily Spotting	11%	20%	25%	26%
Flatus with Discharge	11%	19%	23%	23%
Fecal Urgency	9%	17%	21%	22%
Oily Stool	7%	15%	19%	22%
Oily Evacuation	5%	9%	12%	13%
Increased Defecation	4%	8%	11%	12%
Fecal Incontinence	2%	5%	8%	9%
Abdominal Pain	4%	13%	19%	24%
Liquid Stools	3%	9%	15%	19%

In most cases, a majority of the GI ADRs events in the orlistat treatment group lasted for less than 1 week (see table below). Although some of the events (flatus with discharge, fecal urgency) lasted beyond 24 weeks.

DURATION OF EVENTS

Adverse Event	120mg Orlistat n=1913			
	≤ 1 Wk	>1≤ 4 Wk	> 4 ≤ 24 Wk	> 24 ≤ 96 Wk
Oily Spotting	50%	15%	19%	13%
Flatus with Discharge	38%	15%	24%	18%
Fecal Urgency	33%	18%	26%	18%
Oily Stool	45%	15%	21%	14%
Oily Evacuation	46%	19%	20%	13%
Increased Defecation	39%	24%	21%	12%
Fecal Incontinence	70%	14%	12%	4%
Abdominal Pain	56%	17%	17%	6%
Liquid Stools	74%	14%	9%	25

Subgroup Analysis of GI Adverse Events

The incidence of GI adverse events during Year 1 was examined in several subgroups. These groups included age (<40, >40<60, >60), gender, race (Caucasian and Black), and BMI (<30, >30<35, >35). Because the number of statistical comparisons among groups was so large only those comparisons with a p value of 0.01 or less will be considered here. Several adverse events were reported more frequently by Blacks compared with Caucasians. These include fecal urgency, flatus with discharge, and oily spotting. Other subgroup comparisons were not significant.

Laboratory Parameters

Because orlistat has a very low bioavailability one would not anticipate that use of the drug would be associated with clinically significant laboratory or urine abnormalities. Indeed, this was the case. Evaluable laboratory tests were obtained on approximately 1800 patients who received 120mg tid of orlistat for one year and approximately 600 patients who received this treatment for two years. Although the changes in some laboratory and urine parameters led to statistically significantly differences between the orlistat 120mg and placebo groups, none of the changes were large and they were not of clinical significance. Additionally, the percentage of patients with shifts to abnormal values was similar for the placebo and drug-treated patients.

In preclinical studies, high doses of orlistat were associated with increased levels of serum triglycerides; this action is presumably the result of orlistat's inhibition of lipoprotein lipase. Appropriately so, the Sponsor analyzed the triglyceride levels of 25 patients with serum levels of orlistat greater than 3ng/ml. There was no evidence that the triglyceride levels were significantly increased — when measured at the time of pharmacokinetic sampling for plasma orlistat levels.

Fat-Soluble Vitamin and β-carotene Levels

Review of the individual phase III studies indicated that, compared with placebo, the mean levels of vitamin E and β-carotene were reduced in patients receiving 120mg of orlistat. Some, but not all studies, reported lower levels of vitamin D following treatment with orlistat 120mg. The mean levels of vitamin A were not significantly affected by treatment with orlistat when compared with the changes seen in the placebo groups. And prothrombin times — the surrogate used for vitamin K assessment— were not significantly different between orlistat and placebo patients.

For the overview of safety, vitamin data were pooled and analyzed from two US studies (NM14185 and NM14161) and two non-US studies (BM14119 and BM14149). Analyzing the US and non-US studies separately seems appropriate because of the different methodologies and laboratories used in the US and the non-US studies. The following data represent two years of therapy with orlistat or placebo.

Vitamin A

At the end of Year 2 the mean values for the change in vitamin A levels did not differ significantly between the 120mg and placebo groups. Seven subjects in the placebo and 120mg groups received vitamin supplementation because of low vitamin A levels on two consecutive measurements; these patients had vitamin A levels within the normal range at the completion of the study. The results from

the non-US studies were similar to the US findings.

Vitamin D

The mean levels of vitamin D decreased gradually during the first 72 weeks of the studies, after which time the levels increased slightly up to Week 104. At the completion of the studies, the values of vitamin D were lower in both groups compared with their respective baseline values. Still, the orlistat-treated patients had a mean plasma level of vitamin D that was 6.9 mmol/L lower than the respective value in the placebo group ($p<0.001$). Similar results were obtained in the non-US studies

Approximately 13% of placebo patients and 18% of 120mg subjects with normal baseline vitamin D levels had two consecutive low values during the two years of treatment.

The incidence of vitamin supplementation was 15% for the 120mg group compared with 9% for the placebo group. Approximately 70% of the subjects who received vitamin supplementation in the 120mg group had a value that was within normal limits at the last determination.

An analysis of post-menopausal women not taking estrogen replacement was conducted to evaluate whether this population — which is at higher risk for osteoporosis — had lower vitamin D levels following treatment with orlistat. In this group of patients ($n>100$ per group) there did not appear to be a significantly greater reduction in mean vitamin D levels after two years of treatment when compared with placebo patients, or to the overall study population. Moreover, the percentage of post-menopausal patients in the 120mg group with two consecutive low values was lower than the percentage in the placebo group. Of interest, the reported dietary intake of vitamin D was approximately 135-145 IU, considerably lower than the RDA of 200 to 400 IU per day. The results of the non-US studies were similar to the US data.

Vitamin E

In the US studies, the reduction in plasma vitamin E levels in the orlistat 120mg group compared with the change in the placebo group was significant (-1.6 umol/L, $p=0.008$). However, when the vitamin E status was expressed as the ratio of vitamin E to LDL cholesterol — an appropriate adjustment given that lipid levels have a marked effect on vitamin E concentrations — there were no significant differences between the 120mg and placebo groups following two years of double-blind treatment. Of the subjects with normal baseline values for vitamin E, 1% of placebo and 4% of orlistat subjects had two or more consecutive low vitamin E levels during two years of treatment. Approximately 4% of 120mg subjects and 1% of placebo subjects were supplemented. One hundred percent of placebo patients and 73% of the 120mg subjects who required and received supplementation had normal vitamin E levels at the completion of the study. The results from the non-US studies were similar to the US results.

β-carotene

It should be pointed out that a "normal range" for β-carotene is not defined or widely accepted. For the purposes of these clinical studies the Sponsor derived project specific "normal" ranges for the 2 US and the two non-US studies. These project specific ranges were calculated using 2.5-97.5 percentiles for the baseline (pretreatment) values for all patients. Thus, the "normal" range for subjects in the non-US studies was 0.09-1.06 umol/L and 0.056-1.289 umol/L in the US studies.

In the US studies, the change in β-carotene level in the 120mg group following two years of treatment was 0.08 umol/L lower than the change in the placebo group, this difference was statistically significant ($p<0.001$). Approximately 3% of placebo patients and 8% of 120mg subjects had two or more consecutive low serum values during the study, and as a result, more orlistat patients received supplementation compared with placebo patients. Of the supplemented patients, nearly 90% had β-carotene values within the normal range at the final laboratory determination. The results from the non-US studies did not differ substantially from the US data.

Vitamin K

Assessment of vitamin K status was conducted by measurement of prothrombin time (PT). In both the US and non-US studies, the mean values of PT decreased slightly in the placebo and 120mg groups from baseline to Week 104. The use of PT to assess marked hypovitaminosis K is reasonable. However, when assessing subtle deficiencies in vitamin K, one has to question the validity of using PT, as some data indicate that PT remains normal with mild to moderate deficiencies of vitamin K.

The Incidence of Low Vitamin Levels During 2 Years of Treatment

As shown in the table below, over the course of the 2-year studies M14119, M14149, M14161, and M14185, when compared with placebo, a statistically significantly larger percentage of patients receiving 120mg of orlistat had low levels of vitamins D, E, and β-carotene on two or more consecutive occasions.

Incidence of Low Vitamin Values on Two or More Consecutive Visits (Patients with normal baseline values - first and second year)

	Placebo	120mg	P
Vitamin A	1.0%	2.2%	0.1
Vitamin D	6.6%	12.0%	0.002
Vitamin E	1.0%	5.8%	<0.0001
β-carotene	1.7%	6.1%	0.0002

Given the tendency of orlistat to impair absorption of the fat-soluble vitamins and β-carotene it is not surprising that in the two US studies, 17% of the 120mg patients and 5% of the placebo patients ($p=0.07$) had at least two different vitamin values that were low on two or more consecutive occasions. It is also not surprising that the individuals who developed two or more consecutive low vitamin levels had low normal baseline values for these fat-soluble nutrients.

Time to First Occurrence of Two Consecutive Low Vitamin Levels

Examination of curves depicting the cumulative incidence of two consecutive low vitamin levels indicates that for vitamins D, E, and β-carotene there is a constant rate of accumulation of individuals with low values. This being the case, screening for low vitamin levels would not be practical.

Other Vitamin Data

Data from three studies that are not included in the above discussion are briefly summarized below

Study BM14119B was a non-US trial comparing 120mg of orlistat to placebo for one year. Following 52 weeks of treatment the mean change from baseline in β-carotene was -0.11 umol/L in the orlistat group and 0.0 umol/L in the placebo group ($p<0.001$). No significant differences between the two groups in the mean change from baseline in vitamins A and D or in the ratio of vitamin E/total cholesterol. A greater percentage of orlistat patients had two or more consecutive low vitamin A, D, and E values compared with the placebo subjects.

Study NM14336 was a one-year trial comparing 120mg of orlistat to placebo in patients with NIDDM. Following 52 weeks of treatment, the mean change from baseline in β-carotene was -0.12 umol/L in the orlistat group and -0.03 umol/L in the placebo group ($p<0.001$). There were no significant differences between the two groups in the mean change from baseline in vitamins A and D or in the ratio of vitamin E/total cholesterol. However, more active-treatment subjects had two or more consecutive low vitamin D and E and β-carotene values during the trial (see table below).

Incidence of Low Vitamin Values on Two or More Consecutive Visits in Patients with Normal Baseline Values

	Placebo	120mg	P
Vitamin D	9%	22%	0.002
Vitamin E	1%	3%	0.3
β-carotene	1%	12%	0.0002

Similarly, more orlistat patients required a vitamin supplement because of low values (see table below). In most cases, the supplement appeared to increase the vitamin or β-carotene values to within normal limits at the time of the last determination.

Outcome of Vitamin Supplementation

	Placebo	120mg
Vitamin D		
Received Supplement	7%	17%
Last Value Low	9%	0%
Vitamin E		
Received Supplement	0.6%	1.3%
Last Value Low	0%	0%
β-carotene		
Received Supplement	0%	9%
Last Value Low	0%	7%

Study NM14302 was an 18-month trial in which obese patients were instructed to maintain a hypocaloric diet for six months, after which time subjects were randomized to one of four groups: placebo, orlistat 30mgtid, orlistat 60mg tid, or orlistat 120mg tid for an additional 12 months. All patients were instructed to take a once-a-day multivitamin (Centrum) with breakfast throughout the 18-month study. At the completion of the 52-week active-treatment phase the levels of vitamins D, E, and β-carotene were significantly fower in the active-treatment groups compared with the placebo group. In addition, the value of vitamin E/total cholesterol was significantly lower in the three active-treatment groups compared with the placebo group. The percentage of patients with two or more consecutive low vitamin D, E or β-carotene values was higher in the 120mg group than the placebo group. Since all of the orlistat-treated patients received a multivitamin during the trial it is not possible to accurately assess the efficacy of the supplementation.

Subgroup Analyses of the Incidence of Low Vitamin Levels

The incidence of two consecutive low vitamin levels in patients with normal baseline values was examined in several subgroups. These groups included age (<40, >40<60, >60), gender, race (Caucasian, Black, Hispanic, and other), and BMI (<30, >30<35, >35). The US and non-US studies were pooled separately. To simplify matters only those subgroups that are significant in both the US and non-US studies will be reported. Significant placebo vs drug differences in the incidence of two consecutive low vitamin A levels during Year 1 were observed for age. This was because none of the subjects over the age of 60 years had two consecutive low vitamin A levels. For vitamins D, E, and β-carotene none of the subgroup analyses were significant in both the US and non-US studies.

Thus, to summarize, orlistat does appear to interfere with the absorption of vitamins D, E, and β-carotene. The long-term treatment with orlistat does not appear to cause frank vitamin K deficiency. Yet, the use of PT as an indicator of vitamin K status precludes one from commenting about subclinical deficiencies of this vitamin. In this Reviewer's opinion, the vitamin data argue in favor of universal vitamin supplementation.

Gallbladder Ultrasounds

Eight hundred and fifty-six patients treated with placebo and 1164 patients treated with 120mg had gallbladder ultrasounds at baseline and at the end of one year of double-blind treatment. Of patients with normal baseline ultrasounds, 22 (3.6%) placebo and 29 (3.6%) orlistat-treated patients developed stones; and one (0.2%) placebo and 4 (0.5%) orlistat-treated patients developed sludge (p=0.89 for group comparison of stones + sludge). Four hundred and two patients treated with placebo and 471 subjects treated with 120mg had ultrasounds at baseline and at the end of two full years of treatment. Of the patients with normal baseline ultrasounds, eight (2.8%) of the placebo subjects and 14 (3.9%) of the 120mg subjects developed stones; and three (1.0%) placebo and none of the 120mg subjects developed sludge (p=1.00). Of some interest, in patients with a baseline ultrasound abnormality classified as "other" abnormality (i.e., fatty liver, polyps, cysts), 5 (3.3%) placebo patients and 14 (6.0%) orlistat patients developed stones after one year of treatment; and none of the placebo and 2 (0.9%) of the orlistat-treated subjects developed sludge (p=0.17).

Renal Ultrasounds

Six hundred and seventeen patients treated with placebo and 939 patients treated with 120mg had renal ultrasounds at baseline and at the end of one year of double-blind treatment. In patients with normal baseline ultrasounds, one (0.2%) placebo patient and seven (0.8%) subjects in the 120mg group had stones visualized at the end of one year of treatment (p=0.12) Four hundred and thirteen patients treated with placebo and 476 subjects treated with 120mg had ultrasounds at baseline and at the end of two full years of treatment. In patients with normal baseline tests, one (0.3%) placebo and five (1.1%) orlistat-treated patients had stones at the completion of the study (p=0.15) (two of the patients in the orlistat group are included in both the one and two year computations).

Summary of Gallbladder and Kidney Stone Data

Advancing age, female gender, obesity, and rapid weight loss all increase the risk for the development of cholesterol gallstones. It would not be unexpected, therefore, for some patients to develop cholelithiasis following orlistat-induced weight loss. Following two years of treatment, in patients with normal baseline ultrasounds, approximately 3% of placebo and 4% of 120mg-treated patients developed gallstones, which were presumably asymptomatic. In patients with a baseline abnormality (fatty liver, polyps, cycts, etc.) as determined by ultrasound, there was an increase in the incidence of stone + sludge formation in the group receiving orlistat compared with the incidence in the placebo group. However, the heterogeneity of the baseline gallbladder abnormalities makes it difficult to assess the clinical significance of this finding. What is of clinical relevance is the low and similar incidence (0.4%) of symptomatic gallstone disease in the both the placebo and 120mg groups. Hence, it appears safe to say that in patients with normal ultrasonic examinations of the gallbladder, the use of orlistat for up to two years was not associated with a marked increase in the incidence of gallstones.

With respect to kidney stones, the ultrasound data are compatible (though not incontrovertible) with the interpretation that orlistat is associated with an increased risk for the development of ultrasound-detected renal stones. Data from study NM14161 indicate that more patients on orlistat compared with placebo had markedly elevated levels of 24-hour urinary oxalate. These data provide biological plausibility with which to link the use of orlistat with the development of nephrolithiasis. These cases of kidney stones were presumably asymptomatic; adverse event data indicate that 0.4% of placebo patients and 0.2% of

orlistat 120mg patients were coded as developing renal calculi, and 0.2% of placebo and 0.1% of orlistat 120mg subjects were coded as developing renal colic during the studies. The discrepancy between the number of stones visualized by ultrasound with the number of reported cases of renal calculi and colic is not surprising given that not all stones are symptomatic. If one accepts the assumption that orlistat — when used for at least one year — increases the risk of developing asymptomatic kidney stones, the crucial question remains: does orlistat increase the risk of symptomatic nephrolithiasis? The size of the current database does not allow one to accurately answer to this question. This Reviewer acknowledges that the current weight of evidence may not support a warning in the labeling about the risk for developing kidney stones following treatment with orlistat. Yet, without question, the Sponsor should commit to a systematic post-approval assessment of orlistat's lithogenic potential..

Special Studies

Effect of Orlistat on Mineral Balance, Serum and Urinary Electrolytes, Osteocalcin, Hydroxyproline, and Fecal Fat and Biliary Acids - ND14458

Background: The use of orlistat results in fat malabsorption; steatorrhea may increase the excretion of calcium and magnesium. Orlistat also increases the concentration of free fatty acids in the intestine. When dietary calcium binds to free fatty acids, oxalate is left unbound and can be absorbed and eventually excreted in increased amounts by the kidney.

Some epidemiological data suggest that a high-fat diet increases the risk for cancer of the prostate, colon, and breast. One purported mechanism that may account for the association between dietary fat and colon cancer is an increased delivery of secondary bile acids and free fatty acids to the colonic mucosa. In animal models, some bile acids and fatty acids increase colonic mucosal cell proliferation.

Objective: The primary objectives of this study were to evaluate the effects of four weeks of treatment with orlistat 120mg tid on:

- Mineral balance (calcium, phosphate, magnesium, iron, copper, and zinc) and electrolyte concentrations (sodium, potassium, magnesium, calcium, phosphate, oxalate, uric acid, bicarbonate) in the urine and serum.
- Markers of bone formation (osteocalcin and hydroxyproline)
- Composition of fecal fat and fecal biliary acids (cholic and chenodeoxycholic, deoxycholic, lithocholic, and urosdeoxycholic)

Methods: This was a 4-week, single-center, randomized, placebo-controlled study of 11 female and 11 male, obese patients. Subjects were instructed to consume a 1500 kcal/day diet, containing approximately 30% of calories as fat, 50% as carbohydrate, 20% protein, and a maximum of 300mg cholesterol per day. The diet was designed to cause a 0.25 to 0.50 kg per week weight loss. Baseline assessments were conducted during days -5 to -1 and post-treatment assessments were conducted during days 24 to 28. Mineral balance was to be calculated as
Dietary mineral intake - (urinary mineral excretion + fecal mineral excretion).

Results: Six female and five male patients were randomized to the orlistat group. One patient withdrew prematurely. The placebo group contained five female and six male patients. One patient withdrew prematurely. The groups were well matched for baseline demographic characteristics, except race; there

were eight and four Black patients in the placebo and orlistat groups, respectively. The ages of the patients ranged from 20 to 42 years and the average BMI was 34 kg/m^2. The mean weight loss in the orlistat group was 6.1 kg and 6.6 kg in the placebo group. For unexplained reasons the data obtained from the use of sitostanol as a fecal marker was highly variable and considered unreliable by the Sponsor. As a result, only group means for dietary intake, fecal excretion, and urinary excretion are provided.

Total Fat, Free Fatty Acids, and Total Bile Acids in Fecal Material: The concentrations of total fat and free fatty acids in the stool increased significantly in the orlistat group when compared with baseline values and to the changes in the placebo group. Contrarily, the levels of total bile acids decreased significantly in the orlistat group relative to baseline and placebo values. The decrease in the concentration of the individual bile acids was greater in the orlistat compared with the placebo group; the reduction in lithocholic acid was statistically significant. The concentration of neutral fecal fats decreased significantly in the orlistat group when compared with baseline and to the change in the placebo group.

Minerals and Electrolytes: In the orlistat group there were statistically significant reductions from baseline in the following minerals: fecal copper, urinary magnesium, and fecal and urinary phosphorus. Reductions of a magnitude observed in the orlistat group were seen in the placebo group for urinary magnesium and urinary phosphorus. There were no statistically significant differences between the two groups in the changes in any of the other mineral concentrations. In addition, there were no clinically significant changes in the serum electrolytes in the orlistat or placebo groups. Urinary levels of oxalate increased in the orlistat group but the change was not statistically significant. Other changes in urinary electrolyte concentrations did not appear to be of clinical relevance.

Serum Osteocalcin and 24-Hour Urine Hydroxyproline: There were no statistically significant changes noted in the levels of serum osteocalcin or urinary hydroxyproline in the orlistat group.

Conclusions: In this small study of 22 obese patients, treatment with orlistat 120mg tid resulted in significant increases in fecal content of total fat and free fatty acids. In addition, the level of fecal bile acids was significantly reduced following treatment with orlistat for 28 days. Valid conclusion about the effect of orlistat on mineral balance cannot be made because of methodological limitations associated with the fecal marker sitostanol. The Sponsor is conducting an additional mineral balance study and the results of this study should be submitted in late April or early May 1997.

Effect of Orlistat 120mg tid on Colonic Mucosa Cell Turnover - NP15138 (See consult from Dr. Gallo Torres, Medical Officer from the Division of Gastrointestinal and Coagulation Drug Products)

Background: High levels of dietary fat have been associated with an increased risk for colon cancer in some observational studies. A potential mechanism that may explain this association invokes the proliferative effects of free fatty acids on colonic mucosa cells. Some investigators believe that risk for malignant transformation of colonic mucosa cells can be assessed by measuring biomarkers of cell proliferation such as bromodeoxyuridine (BrdU), proliferating cell nuclear antigen labeling index (PCNA), and whole crypt mitotic count value (WCMC). One pharmacodynamic effect of orlistat is to increase fecal fatty acid content. Thus, this study investigated the changes in biomarkers of cell proliferation following six weeks of treatment with orlistat 120mg tid.

Objectives: The primary objectives of this study were to evaluate the effects of six weeks of treatment with orlistat 120mg tid on:

- total fat, free fatty acid, and bile acid content in fecal material and fecal water
- colonic mucosal cell turnover from biopsy samples

Methods: This was a single-center, randomized, placebo-controlled, double-blind study conducted in 24 obese male and female patients. Subjects were instructed to consume a standardized diet consisting of 30% of calories as fat, 50% as carbohydrate, 20% as protein, and a maximum of 300 mg of cholesterol per day. The percentage of calories as fat, carbohydrate, and protein was measured by chemical analysis. Stool samples for total fat, free fatty acid and bile acid, and pH were collected at daily intervals from day -7 to day -1 and from day 36 to 42. Colonic biopsies were obtained from the rectum approximately 8-10 cm from the anus on day -7 and day 43. Analysis of samples for BrdU and PCNA were conducted at MD Anderson Cancer Center and WCMC was conducted at the Denver Veterans Affairs Medical Center.

Results: Twelve patients (6 M and 6 F) were randomized to placebo and 12 patients were randomized to orlistat (6 M and 6 F). Ten orlistat and 12 placebo patients were avaluable for pharmacodynamics. The groups were well matched for baseline demographic variables. The mean age was 41 years, the average BMI was 33 kg/m^2, and approximately 90% of the subjects were Caucasian.

Total Fat, Free Fatty Acids, Total Bile Acids, Calcium, Fecal Weight, and pH: The fecal levels of total fat and free fatty acids increased significantly in the orlistat group relative to baseline and to the change in the placebo group. The levels of total bile acid decreased significantly more in the orlistat group compared with the placebo group. The concentrations of deoxycholic and lithocholic acid accounted for most of the reduction in total bile acid in the orlistat group. The levels of calcium did not change in either group.

Biomarkers of Cell Proliferation: The baseline values for biomarkers were not significantly different in the two groups. WCMC increased by 0.6 in the placebo group and decreased by 0.04 in the orlistat group (p=ns); BrdU decreased by 0.5 and 4.0 in the placebo and orlistat groups, respectively (p=ns); and PCNA increased by 3.4 and 2.3 in the placebo and orlistat groups, respectively (p=ns). The correlation coefficients between the changes in fecal fat and FFA content with the changes in PCNA and BrdU ranged from 0.4 to 0.6 in the orlistat group and -0.2 to 0.1 in the placebo group (all ns).

Conclusions: Although none of the correlations between fecal fat and FFA content with the changes in markers of proliferation were statistically significant, the absolute values in the orlistat group are suggestive of a meaningful relationship. Statistical significance would be difficult to achieve in a sample of only 10 subjects. These data do suggest that there is a direct correlation between increased levels of fecal total fat and FFA with increased activity of the biomarkers for proliferation in the orlistat group, but not in the placebo group. However, as pointed out in Dr. Hugo Gallo Torres's consult, there is good reason to question the predictive value of colonic cell proliferation in models of carcinogenesis. Above all else, the data from this study are not worrisome enough to prevent marketing of the drug. An appropriate post-marketing surveillance study (details of which are discussed in Dr. Gallo Torres's consult) should be conducted to gain a more meaningful assessment of orlistat's effect on colonic cell physiology.