ADDENDUM TO ORLISTAT (NDA 20-766) MEDICAL REVIEW

August 21, 1997

During the conduct of the seven phase 3 trials with orlistat ten cases of breast cancer in subjects randomized to drug and one case in a patient randomized to placebo were diagnosed. In a follow-up survey, the sponsor determined that breast cancer was detected in two additional subjects who were randomized to 120mg tid of orlistat and in one patient originally randomized to placebo. At the May 14, 1997 advisory committee meeting the sponsor commented that detection bias or chance were likely explanations for the excess number of breast cancer cases diagnosed during the trials.

The mean weight change from baseline (time of randomization to drug) to time of breast cancer detection in the ten orlistat cases ranged from -12.6 kg to +2.3 kg (table below). This wide range in weight loss does not support the hypothesis that the orlistat cases had significant weight loss with a subsequent change in breast architecture and a resultant facilitation of breast tumor detection[redacted]

Protocol/Dose/Pt #	Day of Detection	BWΔ from initial weight (kg)	BWΔ from baseline weight (kg)
149/60mg/006	36	-4.7	-3.0
185/120mg/436	32	-8.7	-3.5
302/120mg/68	55	-5.4	+1.4
302/120mg/40	170	-13.4	+2.3
149/120mg/007	191	-3.3	-11.2
149/120mg/065	342	-12.9	-12.6
149/120mg/010	370	-5.1	-2.6
185/120mg/924	428	-3.2	-3.1
185/120mg/1858	665	-9.9	-8.2
161/120mg/617	703	-3.4	-2.5
149/Placebo/023	443	-2.5	-2.1

Initial weight is weight prior to placebo lead-in phase; baseline weight is weight at randomization to orlistat or placebo

[redacted]

The possibility that the breast cancer finding is a chance occurrence cannot be discounted. However, the statistical analyses — those calculated by the Agency and the sponsor — indicate that a chance finding is "unlikely". In a submission dated 8/21/97, the sponsor calculated that the relative risk for the development of breast cancer in women 45 years of age and older who received 120mg tid of orlistat versus those who received placebo was 4.02 with a 95% confidence interval of 0.88 - 37.35. Although this 95% confidence interval includes one (p=0.08), the 90% confidence interval — 1.05 - 25.35 — exclude one (memo from Dr. Pian dated 8/22/97). Given the grave consequences of breast cancer, the use of a 90% confidence interval seems appropriate in this situation.

Thus, the clinical trial and follow-up data indicate that for women aged 45 years of age and older, the risk for the development of breast cancer was four times greater in patients who received 120mg tid of orlistat compared with placebo-treated patients. The significance of this relative risk is even greater considering the high absolute risk for the development of breast cancer in middle-aged and older women.

The above data call for a re-examination of the risk-benefit profile for orlistat. Given the modest weight-loss efficacy of the drug, the seriousness of breast cancer, the magnitude of the breast cancer risk observed in the orlistat clinical trials, and the relatively low probability that the finding was the result of chance, I am rescinding my original recommendation for approval and now recommend non-approval of orlistat for the treatment of obesity.

[redacted]., /S/ 9/22/97

Eric Colman, M.D.

cc: NDA file
Hess/Colman/Stadel/Pian/Troendle/Sobel

APPEARS THIS WAY ON ORIGINAL

HESS

MAY - 1 1997

MEDICAL OFFICER'S REVIEW OF NDA 20-766

DATE SUBMITTED: 11/26/96
DATE RECEIVED, CDER: 11/27/96
DATE RECEIVED, MEDICAL OFFICER: 12/2/96
DATE REVIEW COMPLETED: 4/30/97

DRUG NAME

GENERIC NAME: Orlistat
TRADE NAME: Xenical
CHEMICAL NAME: Tetrahydrolipistatin

SPONSOR: Hoffmann-La Roche Inc.

PHARMACOLOGICAL CATEGORY: Lipase inhibitor

PROPOSED INDICATION: Long-term treatment of obesity

SUMMARY

The mean percent reduction in body weight following one year of treatment with 120mg three times daily (tid) of orlistat was approximately 8.0 - 10.0%, with placebo-subtracted values of 3.0 - 4.0%. This difference between drug and placebo falls short of the 5% difference recommended in the Division's Obesity Guidance Document. However, the efficacy of orlistat was evident in the categorical analyses. Pooled data from five phase III studies indicate that nearly 60% of orlistat-treated patients and 31% of placebo-treated patients lost at least 5% of baseline body weight following one year of treatment ($p<0.01$). Moreover, 27% of drug-treated subjects lost at least 10% of baseline body weight after one year of treatment compared with only 11% of patients randomized to placebo ($p<0.01$).

On balance, treatment with orlistat was associated with small, relative improvements in the levels of total and LDL cholesterol and systolic and diastolic blood pressure. In addition, there were modest improvements in the concentrations of fasting and post-load glucose and insulin following one year of drug treatment. When considered in isolation, the magnitude of these improvements was of questionable clinical significance. Yet, taken together, the data argue in favor of a clinically meaningful improvement in the overall risk factor profile. Moreover, the data are compatible with the notion that the comorbidities continue to improve as orlistat-associated weight loss increases.

Since negligible amounts of orlistat and its metabolites reach the systemic circulation, the central safety issues relate to the drug's effect in the GI tract. Based on the pharmacodynamic action of orlistat, one might expect the drug to inhibit the absorption of fat-soluble vitamins and β-carotene. And indeed, the totality of the phase III data indicate that the use of orlistat is associated with a lowering of plasma levels of vitamins E, D, and β-carotene. While it is true that the magnitude of the reduction in the plasma levels of these nutrients was small, the magnitude of the vitamin depleting effect of long-term orlistat use was undoubtedly underestimated because significantly more drug than placebo-treated patients required (per protocol) vitamin supplementation for low plasma levels. Moreover, up to 22% of drug-treated patients had a plasma vitamin levels below the "normal limit" on two or more consecutive occasions —reductions consistent with a deficiency state.

There is evidence that fat malabsorption is associated with vitamin K deficiency[1]. It is interesting, therefore, that the Sponsor states that orlistat does not reduce the absorption of vitamin K. The Sponsor's use of prothrombin time — an insensitive indicator of vitamin K status — to assess the effect of orlistat on vitamin K precludes one from making definitive statements about the effect of this drug on vitamin K homeostasis[2,3]. Serum levels of undercarboxylated osteocalcin, plasma levels of phylloquinone, and urinary levels of γ-carboxyglutamic acid are more sensitive measures of vitamin K status[4,2] and the Sponsor should be encouraged to use one of these surrogates to further investigate the interaction between orlistat and vitamin K.

Regarding vitamin A, the mean levels of plasma retinol did not significantly differ between orlistat and placebo patients following one or two years of treatment. Still, plasma levels of this vitamin are tightly regulated and one cannot discount the possibility that a marginal deficiency of vitamin A — one reflected by reduced hepatic but not plasma levels — may develop after extended use of orlistat[5].

Thus, taken together, the data in this NDA suggest that orlistat reduces the absorption of vitamins D, E and β-carotene and leave open the question of its effect on vitamins A and K. Undoubtedly, the benefit-to-risk profile of orlistat would be maximized if the vitamin depleting effect of the drug were minimized. To this end, thought should be given to universal vitamin supplementation. Although the qualitative and quantitative composition of the most appropriate supplement is open to debate, this alternative may prove salutary and should be discussed with the Sponsor.

To summarize, from the perspective of efficacy, the long-term use of 120mg tid of orlistat is more effective than placebo in producing a 5% reduction in body weight. Furthermore, orlistat-associated weight loss is accompanied by an improvement — albeit modest —in comorbidities. From the perspective of safety, a central issue is orlistat's inhibition of the absorption of fat-soluble nutrients including some vitamins and β-carotene. The provision of a

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Correspondence with Sponsor

I. During a January 7, 1997 teleconference with the Sponsor I requested the following information:

1. A statistical comparison of the following baseline variables for each treatment group for the intent-to-treat dataset:

age, BMI, %female, race, systolic and diastolic blood pressure, lipid fractions, fasting glucose and insulin, fat-soluble vitamins and beta-carotene, OGTT parameters, % of patients with hypertension and NIDDM, % of patients receiving antihypertensive and lipid lowering medication, average dose of oral hypoglycemic medication, and HbA1c.

2. A statistical comparison of the following baseline variables for each treatment group within the appropriate predefined risk-factor subgroup (i.e., HDL<0.905 mmol./L):

fasting insulin, LDL, HDL, TG, systolic and diastolic blood pressure, and waist circumference.

The response to the information requested above was submitted by the Sponsor on January 28, 1997.

II. On January 1997 I requested the following information:

VITAMINS AND β-CAROTENE

- Was any patient withdrawn from a study because of the inability to normalize a plasma vitamin level after supplementation?
- Of the subjects that required supplementation, at what time of the day were they instructed to take the supplement?
- Of the subjects that had a reduction in a vitamin or beta-carotene value to below normal on two consecutive visits, how many had a reduction in more than one parameter. Please compare the percentages statistically; placebo vs Orlistat.
- We are not aware of published "normal" values for plasma beta-carotene. How were the normal ranges for this nutrient derived?
- Was there a particular pattern in the time to first occurrence of two consecutive low vitamin levels?
- In the integrated summary of safety data set please provide a statistical comparison of the percentages of patients in the orlistat vs the placebo groups with at least two consecutive low vitamin or beta- carotene values. Please also provide for the patients with low vitamin levels on two consecutive occasions, the mean vitamin and beta-carotene values prior to supplementation.
- In study NM14302, what were the exact levels of vitamin A, D, E, and beta-carotene in the Centrum supplement?

BM14119C

- Please provide the baseline demographic characteristics of the placebo and orlistat 120mg groups with statistical comparisons. Were any of the women on ERT? Please also provide a statistical comparison of the BMDs and biochemical bone markers in the two groups.

- Please provide the data on weight loss for the two groups.
- Please provide the DEXA data on those patients with outlier values for urinary excretion of calcium and hydroxyproline. Please also provide the change in plasma vitamin D levels in these subjects.

BM14149

- Please provide the baseline demographic characteristics of the placebo and orlistat groups with statistical comparisons. Please also provide a statistical comparison of the BMDs at baseline and after one and two years of treatment. Were any of the women on ERT?

- Please provide the data on weight loss for the two groups

INTEGRATED SUMMARIES OF EFFICACY AND SAFETY

- Please provide the results of subgroup analyses (age, gender, race, BMI) for efficacy and safety (adverse events and vitamin levels)

- Please provide additional information on the 11 cases of breast cancer that were detected during the trials. The following information would be particularly helpful.

dose of orlistat
duration of treatment prior to diagnosis
age at diagnosis
vitamin A, D, and E and beta-carotene levels during the trial
if available, the plasma levels of orlistat, menopausal status, hormonal replacement status

The Sponsor began to submit answers to the above questions on February 5, 1997.

III. On February 5, 1997 I requested the five and 10% responder analyses for the intent-to-treat and completers populations. The Sponsor replied on February 7, 1997.

IV. On February 12, 1997 I requested the following information from the Sponsor:

- Please provide the extent of exposure (in weeks) for the patients on drug and placebo in the studies in which a case of breast cancer was identified.

- Please verify that a mineral balance study will be conducted to address the issue of orlistat's effect on calcium, magnesium, zinc, etc. homeostasis.

- For study NM14336, please provide the five and 10% responder analyses for the ITT and completers datasets. In addition, please provide a statistical comparison between drug and placebo for the incidence of low vitamin levels of two consecutive occasions.

The Sponsor responded the above requests on February 13, 1997.

V. On February 19, 1997 I spoke with Dr. Anthony Rhymer of Roche. I suggested that the Company contact an expert in the field of breast cancer epidemiology to help them analyze the cases that occurred during the clinical trials. Dr. Rhymer stated that they would contact an expert and asked if I could provide him with the names of some appropriate people. I told him that I would speak to Dr. Stadel and provide him with the names of a few experts. On February 20, 1997 I left a message on Dr. Rhymer's voice mail that gave him the following epidemiologists:

1. Noel Weiss, MD, DrPH
2. James Schlesselman, PhD
3. Dimitrios Trichopolous, MD, PhD

VI. On February 21, 1997 I requested that the comorbidity data from the one-year pooled data be submitted for patients that lost 0-<5%, 5-<10%, and ≥10% of body weight. Dr. John Mathieson was very agreeable and stated that I should receive this information the following week. The Sponsor submitted these analyses on February 24, 1997.

VII. On April 1, 1997 I requested the statistical analyses on urinary oxalate data. I also requested the oxalate data from the subjects that developed kidney stones in study 14161, as well as a grand total of the number of patients on 120mg tid of orlistat and placebo that developed kidney stones. I received all but the statistical analysis of the urinary oxalate data on 4/9/97, and the statistical information on 4/11/97.

VIII. I requested a shift table of the abnormally high PTH values for the placebo and 120mg patients in study NM14161 on 4/9/97. I received this information on 4/11/97.

IX. I spoke with Peggy Jack on 4/10/97 to let her know that I considered the urinary oxalate and renal ultrasound data suggestive of an orlistat effect. I also wanted to verify that the patients with stones visualized by ultrasound did not have symptoms suggestive of neprholitiasis. I also expressed my belief that I thought it would be useful to know the size of the stones that were visualized by ultrasound.

3. VOLUMES REVIEWED

20 95 96 97 121 153 465 153 278 314 394 417
445 363 457 461 465

4. CHEMISTRY/MANUFACTURING CONTROLS

see chemistry review

5. PRECLINICAL PHARMACOLOGY/TOXICOLOGY

see pharmacology review in addition to information below

Pharmacology

Orlistat is a reversible inhibitor of gastrointestinal lipases: pancreatic lipase, gastric/lingual lipase, and carboxylester lipase. The drug also inhibits lipoprotein, hepatic, hormone-sensitive, and diacylglycerol lipases; however, the extremely low bioavailability precludes a clinically meaningful effect on these lipases. At its site of action, the gastrointestinal tract, orlistat inhibits the absorption of dietary triglycerides. In addition, cholesterol absorption is reduced because of its sequestration with unabsorbed triglycerides.

Acute Toxicity

Single-dose toxicity studies at maximal oral doses of 5000mg/kg in rats and mice, and 1000mg/kg in dogs did not reveal any drug-associated mortality or adverse clinical events.

Chronic Toxicity

In studies of up to one-year duration, drug-related adverse effects were observed at doses ≥ 100-150mg/kg. Of interest, animals tended to compensate for the reduced caloric absorption through increased consumption of protein and carbohydrate. At doses > 450mg/kg/day, hypertriglyceridemia, hyperbilirubinemia, and hypocholesterolemia were noted. In rats decreased plasma α-amylase activity and increased BUN were observed. A reduction in fat-soluble vitamins was also observed. Some of the Sponsor's conclusions about the drug include:

1. Plasma levels of orlistat are rarely detectable at oral doses below 100-150 mg/kg/day
2. Systemic exposure to the drug after oral administration is highly variable across species of animal.
3. Systemic exposure increases with dose.
4. In most studies, plasma levels of the drug tend to be higher in females.
5. Some accumulation of unchanged drug occurs during studies longer than 13 weeks in duration.

A potential adverse effect of orlistat is the stimulation of colonic mucosa by bile acids and fatty acids. In rats, the short-term administration of orlistat at doses of 8.5 and 116mg/kg/day results in an increase in colonic mucosal proliferation. However, the longer-term treatment (three weeks) with orlistat was not associated with a proliferative effect. A nine-month study in rats is ongoing and will add to the database regarding orlistat's effect on colonic mucosa.

In a one-year dog study, the ingestion of 10, 100, or 1000mg/kg/day of orlistat did not reveal any macroscopic or microscopic adverse effects in the colon. Of note, however, increased levels of plasma urea, decreased levels of cholesterol and vitamins D and E, and postprandial hypertriglyceridemia (at the two higher doses) were observed. In addition, hepatic levels of vitamins A and E were decreased.

The vast majority (>99%) of orally ingested orlistat is excreted unchanged in the feces. The small amount absorbed undergoes extensive first-pass metabolism.

6. CLINICAL BACKGROUND

6.1 RELEVANT BACKGROUND INFORMATION

The Sponsor was granted a waiver via a telephone conversation with Dr. David Orloff on 8/1/1996 for the submission of Section 11 of this NDA in paper format due to the size of the patient data base.

6.2 FOREIGN EXPERIENCE

Orlistat is not marketed in any foreign country.

6.3 RELEVANT NDAs

Orlistat is a novel agent and there are no relevant NDAs.

6.4 POST-MARKETING EXPERIENCE

Orlistat is not approved for marketing in any Country

6.5 RELEVANT LITERATURE

A MEDLINE search inclusive of years 1991-1996 revealed 33 published papers on orlistat. A large portion of the data from these papers are included in the NDA. The publications not included in the NDA do not add materially to the review.

6.6 HUMAN PHARMACOLOGY/PHARMACOKINETICS/PHARMACODYNAMICS

Absorption

Following the oral administration of 360mg of radio labeled orlistat plasma levels of intact drug were nonmeasurable (<5ng/ml). Less than 2% was excreted in the urine, and approximately 97% was excreted in the feces. Data from phase I, II, and III trials (up to two years in duration) indicate that at doses of 120mg-240mg tid, 80% of patients had plasma levels of orlistat that were undetectable (<0.2ng/ml). The remaining 20% of patients had concentrations ranging from 0.2 to 5ng/ml.

Distribution

In vitro, orlistat is 99% bound to plasma proteins (lipoproteins and albumin).

Metabolism

There are two primary metabolites of the small quantity of orlistat absorbed systemically: M1 and M3. The half-life of M1 is approximately three hours, whereas the secondary metabolite M3 is approximately 13.5 hours. These metabolites have weak lipase inhibitory properties (1000 and 2500 fold less than orlistat, respectively).

Elimination

Fecal excretion is the major route of elimination. The mean renal elimination is approx. 1.5% of the 360mg dose. The time to reach complete excretion is 3-5 days. The disposition of orlistat seems similar between normal weight and obese subjects. It should be noted that orlistat and the metabolites M1 and M3 are subject to biliary excretion.

Dose-Response Data

To gain an understanding of the optimal dose of orlistat for the treatment of obesity the Sponsor analyzed data from 19 phase I studies. The daily mean fecal fat content was used as an indicator of the inhibition of dietary fat absorption and was plotted against the dose of orlistat. The results indicate that the dose-response curve is steepest up to approx. 400mg per day and then plateaus. At this nadir, approximately 30-35% of dietary fat absorption is inhibited. Therefore, the total daily dose of 360 mg seems appropriate. These phase I findings were confirmed in phase II studies. In a six-month study, obese patients were dosed with either 30mg, 60mg, 120mg, or 240mg tid. The results indicated that the 30mg dose was no more effective than placebo; the 60mg dose was more effective than placebo but less effective than the 120mg and 240mg doses; and the 240mg dose was no more effective than the 120mg dose and was associated with a greater incidence of gastrointestinal (GI) events.

Food Effect

The pharmacological effect of the drug is not affected when it is taken within two hours of a meal. In addition, for a given dose of orlistat, there is an increased incidence of GI adverse events as the dietary fat content is increased. One factor that dramatically increases fecal fat excretion is directly mixing orlistat with dietary fat.

Other Effects of Orlistat

There is some evidence that orlistat shortens the gastric transit times for both fat and protein; though the data are not consistent. Similarly, some data, but not all, suggest that orlistat may lower the post-prandial gastric pH. There is no evidence from two trials that orlistat significantly alters gallbladder motility, or the potential to form gallstones as measured by the cholesterol saturation index. One finding of interest is that orlistat appears to lower post-prandial (180 minute AUC) plasma CCK levels. This effect may depend on formulation of the meal (solid, liquid, etc.). Orlistat does not appear to significantly effect the post-prandial levels of plasma gastrin or secretin. Fecal fat and fecal and fecal water free fatty acids are increased, while fecal coprostanol and total neutral fat decrease following one month of treatment with 120mg tid of orlistat. There is some evidence that the levels of biliary acids in the feces are reduced following treatment with orlistat. Limited data do not indicate that orlistat causes a significant increase in fecal calcium content.

There is no evidence that orlistat, at clinically intended doses, appreciably effects the activities of the two systemic lipases: lipoprotein lipase (LPL) or hepatic lipase (HL). Moreover, there are no data to suggest that orlistat increases post-prandial triglyceride (TG) levels.

The concomitant administration of orlistat (120mg tid) with β-carotene and vitamin E acetate is associated with an approximately 60 % reduction in the absorption of these compounds The results of these short-term studies raise concern about the effects of the long-term treatment with orlistat on fat-soluble vitamins. Particular attention will be given to the evaluation of plasma levels of fat-soluble vitamins in the review of the primary studies and in the Integrated Summary of Safety (ISS).

6.7 DIRECTIONS FOR USE

The recommended dose of orlistat is one 120 mg capsule three times daily with each main meal (during or up to one hour after the meal). If a meal is missed or contains no fat, the dose of orlistat may be omitted. The patient should be on a nutritionally balanced, mildly hypocaloric diet that contains

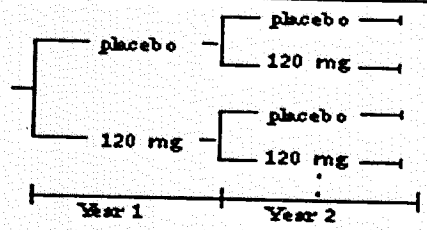
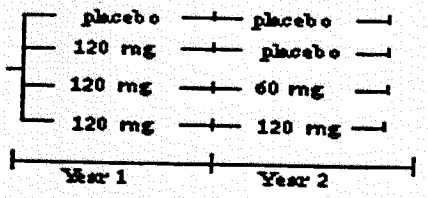
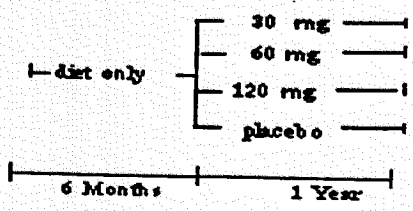
approximately 30% of calories from fat. The daily intake of fat, carbohydrate and protein should be distributed over three main meals.

7.0 DESCRIPTION OF CLINICAL DATA SOURCES

7.1 STUDY TYPE AND DESIGN OF PHASE III STUDIES

The Sponsor conducted seven primary studies: six in obese patients without a history of NIDDM and one in obese patients with NIDDM. Study BM14119C was a 2-year, placebo-controlled study of weight loss and maintenance (year 1) and prevention of weight regain (year 2). Active treatment consisted of 120mg tid of orlistat. Study NM14185 was a 2-year, placebo-controlled study of weight loss and maintenance (year 1) and prevention of weight regain (year 2). Active treatment consisted of 60 or 120mg tid. Studies BM14149 and NM14161 were 2-year, placebo-controlled studies employing 60 or 120mg tid of orlistat. Study BM1419B was a 1-year, placebo-controlled trial comparing placebo to 120mg tid of orlistat along with regular diet counseling. Study NM14302 was a 18-month, placebo-controlled trial in which all subjects received six months of diet therapy followed by one year of either placebo or 30mg, 60mg, or 120mg of orlistat tid. And finally, study NM14336 was a placebo-controlled, one-year study of placebo vs 120mg tid of orlistat in obese patients with NIDDM. A summary of the phase III study designs is shown in the table below.

ORLISTAT PRIMARY STUDIES

Study No.	Type of Study	Duration	Dosage (tid)/Regimen
BM14119C (Non-US)	Weight Loss and Maintenance (Year 1) and Prevention of Weight Regain (Year 2)	2 Yrs	
NM14185 (US)	Weight Loss and Maintenance (Year 1) and Prevention of Weight Regain (Year 2)	2 Yrs	
BM14149 (Non-US)	Long-Term Weight Control with Regular Diet Counseling	2 Yrs	Placebo, 60 mg or 120 mg for Both Years
NM14161 (US)	Long-Term Weight Control Using Primary Care Providers	2 Yrs	Placebo, 60 mg or 120 mg for Both Years
BM14119B (Non-US)	Weight Loss with Regular Diet Counseling	1 Yr	Placebo or 120 mg
NM14302 (US)	Weight Maintenance and Prevention of Weight Regain After 6 Months Diet	18 mos (12 months of drug treatment)	

7.2 PATIENT DEMOGRAPHICS

Approximately 80% of the study participants were women. Roughly 75% of the patients were between the ages of 40 to 65 years. Eighty-eight to 99% of the subjects were Caucasian, with few African-Americans or Asians. The average BMI was approximately 33 kg/m^2.

7.3 EXTENT OF EXPOSURE

Approximately 2847 patients received at least one dose of orlistat in phase III studies. Nearly 75% of these patients received at least one year of active treatment. A total of 1068 patients received 120mg tid of orlistat for over 1 year. Eight hundred eighty-four patients received more than two years of orlistat treatment. A total of 510 patients were treated for two years with 120mg tid of orlistat and over 100 patients were treated with 60mg tid of orlistat for two years.

8.0 CLINICAL STUDIES

There were seven primary studies conducted with orlistat. The Sponsor has not designated any of these studies as pivotal and this Reviewer will therefore not refer to "pivotal studies" when discussing the phase III trials. In general, the efficacy results (including comorbidity data) were similar for the ITT and the completer analyses. Therefore, for ease of presentation, most of the weight loss data presented in this review will be from the completers' datasets. In some cases, reference will be made to both the ITT and completers' datasets when discussing the comorbidity data, however. The safety review of the individual primary studies will include a discussion of the GI-related adverse events and the fat-soluble vitamin data. Other safety data will be discussed in the ISS.

It should be kept in mind that reference to Initial values refers to the first day of the four-week diet lead-in period and mention of Baseline refers to the first day of double-blind treatment following the four-week diet lead-in phase.

STUDY BM14119C

OBJECTIVES

8.1.1 The primary objective of this study was to determine the weight loss effect of 120mg tid of orlistat compared to placebo over a 1 year period when prescribed with a hypocaloric diet. Additional objectives included the assessment of the ability of orlistat to maintain weight loss during a second year of treatment when compared to placebo and to assess the tolerability of 120mg tid of orlistat when taken for either 52 or 104 weeks.

PROTOCOL DESIGN

8.1.2 This was a multi-center (15), double-blind, placebo-controlled, randomized, parallel-group study with a 4-week placebo-lead in period followed by 104 weeks of active treatment in 743 obese patients. During the first year 50% of the patients received placebo and 50% received 120mg tid of orlistat along with a mildly hypocaloric diet (-600kcal/day). During the second year, 50% of the placebo patients continued on placebo (pla/pla) and 50% started orlistat 120mg tid (pla/120); 50% of the orlistat subjects remained on orlistat (120/120) at 120mg tid and 50% were placed on placebo (120/pla). During the

second year patients were maintained on a eucaloric diet. Following the 4-week lead-in period patients were stratified into two weight loss categories based on the weight loss during this lead-in period: ≤2.0 kg or >2.0 kg. The Sponsor's rationale for the stratification was that the drug and placebo groups would be matched in terms of probable success at weight loss with diet alone.

During the first year of the study subjects were instructed to consume a diet consisting of 30% fat, 50% carbohydrate, 20% protein, and a maximum of 300mg/day of cholesterol. The energy content was calculated to maintain a 600kcal/day deficit. The minimum prescribed calorie level was 1200kcal/day.

STUDY POPULATION

8.1.3 Eligible patients included men and women aged 18 years and older with a BMI between 30-43 kg/m^2. The major exclusion criteria included:

- Hx or presence of significant cardiac, renal, hepatic, GI, or endocrine disorders
- MI, CABG, or PTCA within six months prior to screening
- SBP ≥ 165 mmHg or DBP ≥ 105 mmHg on two consecutive visits
- Episode of nephrolithiasis within 1 year of screening
- Active GI disease
- History of pancreatitis
- Drug-treated diabetes
- Abnormal laboratory tests

Patients were excluded if they were taking or had taken within four weeks of screening the following medications:

- appetite suppressants
- fish oil supplements
- retinoids
- tricyclics, neuroleptics, or any other medication taken for psychiatric disorders
- anticoagulants
- digoxin, anti-arrhythmics
- lipid-soluble vitamin supplements
- oral hypoglycemics
- insulin

ENDPOINTS

8.1.4 Body weight was measured at frequent intervals and the average of two measurements was recorded in the CRF. Other efficacy parameters included the waist to hip ratio, serum lipids, fasting serum glucose and insulin, and blood pressure (considered efficacy and safety). A quality of life questionnaire was also administered. Fecal fat content was measured at baseline and twice during the first year.

In addition to the standard hematology and chemistry parameters, the levels of plasma retinol, vitamin D, alpha-tocopherol, beta-carotene, TSH, and prothrombin time were measured throughout the study. Gallbladder and renal ultrasounds were also obtained at baseline and after one and two years of

treatment.

Blood samples were also collected for pharmacokinetic evaluation.

STATISTICAL CONSIDERATIONS

8.1.5 The Sponsor has defined a number of patients populations to be examined for the efficacy parameters. I will comment on the most relevant populations: intent-to-treat (ITT) and completers. During Year 1 the ITT population was defined as those subjects that received at least one dose of medication and had a subsequent efficacy assessment (this is essentially a LOCF analysis); $completers_{year1}$ were defined as those subjects who completed at least 50 weeks of treatment. During Year 2 the ITT_{52wk} population was defined as those subjects who received at least one dose during the second year and had a subsequent efficacy assessment; $completers_{year2}$ were defined as those patients who completed at least 50 weeks of treatment during the second year. For the subjects randomized to drug or placebo for two entire years ITT and completers populations were also analyzed. The Sponsor did not preform statistical analyses on the data from subjects who received placebo or active drug for two consecutive years. Two-year efficacy data will be formally addressed in other primary studies.

For the change in body weight from baseline to Week 52 and Week 104, hypothesis testing was conducted using ANOVA with terms for center, stratum, center by stratum, treatment, center by treatment, and stratum by treatment. In the event that some strata contained no patients an ANCOVA was conduced with weight change during the lead-in phase included as a covariate. Categorical analyses were also conduced using the Chi-square test statistic. Five weight change categories were defined: lost more than 10% from start of double-blind treatment, lost more than 5% but less than or equal to 10%, lost more than 0% but less than or equal to 5%, gained more than or equal than 0% but less than or equal to 5%, and gained more than 5%. The baseline values (Day 1 following the 4-week lead-in phase) for the secondary efficacy variables (lipids, blood pressure, glucose, and insulin) and vitamin levels were covariates in the ANCOVA models used to assess change from baseline. This technique would take into consideration any significant baseline differences among groups.

Input from the Agency's statistician will be required to determine whether these analyses were appropriate regarding the assumptions of the ANOVA and ANCOVA models: normality of the residual error, homogeneity of variance, statistical independence of the residual errors, and linearity of the model.

RESULTS

POPULATION ENROLLED/ANALYZED

8.1.6 Patient Disposition

Seven hundred forty-three subjects were enrolled into the study. Fifty-five withdrew during the lead-in phase and thus 688 patients were randomized to placebo (n=343) or orlistat (n=345). Seventy-six percent of the placebo patients and 82% of the orlistat subjects completed the first year of treatment. Two hundred fifty-three subjects from the Year 1 placebo group were randomized into the second year of the study (126 to placebo/placebo and 127 to orlistat/placebo). Eighty-one percent of the placebo/placebo subjects and 80% of the placebo/orlistat subjects completed the second year of the study. Two hundred

seventy-three subjects from the Year 1 orlistat group were randomized into the second year of the study (138 to orlistat/placebo and 135 to orlisat/orlistat). Eighty-five percent of patients in each group completed Year 2. Of the 345 patients randomized to orlistat for 1 year, 23 withdrew because of adverse events; of the 135 patients randomized to a second year of treatment with orlistat, three withdrew because of adverse events.

Baseline Demographics

The baseline demographic characteristics of the orlistat and placebo groups were essentially the same. The population was 83% female, the mean age was 45 years, 99% of the subjects were Caucasian, and the mean BMI was 35 kg/m^2.

Concomitant Medication

At baseline the percentage of patients taking medication was similar for the two groups. The most common medications were ACE-inhibitors (8.5%), beta-blockers (6%), and thiazides (6%).

Baseline Risk Factors

The two groups had similar baseline risk factor profiles (table below). The number of patients with hypertension (baseline DBP≥90mmHg or receiving antihypertensive medication) was similar in the two groups (35 vs 37%; orlistat vs placebo, p=0.2). Approximately 18% of these subjects were being treated with antihypertensive medications at baseline. There were 3.5% of placebo patients and 1.7% of orlistat subjects with a history of diet controlled NIDDM at baseline; the difference between groups was not statistically significant. Fewer than 2% of the subjects in both groups were taking lipid lowering medication at baseline.

BASELINE RISK FACTORS (means)

	Orlistat n=343	Placebo n=340	P value
SBP (mmHg)	129	127	0.2
DBP (mmHg)	82	82	0.5
TC (mmol/L)	5.4	5.3	0.3
LDL (mmol/L)	3.6	3.5	0.3
HDL (mmol/l)	1.16	1.15	0.8
TG (mmol/L)	1.58	1.56	0.9

Patient Daily Diet

Review of the patients' diet diaries indicated that the two groups consumed similar amounts of calories and percentages of macronutrients (approx. 30% of calories from fat).