CLINICAL REVIEW

Division of Metabolic and Endocrine Drug Products (HFD-510)

Application #:	NDA 20-766 / S	**Application Type:**	
Sponsor:	Hoffmann-LaRoche, Inc	**Proprietary Name:**	Orlistat
Pharmaceutical Category:	Lipase Inhibitor	**Route of Administration:**	Oral
Indication:	Obesity management of adolescent patients aged 12 to 16 years	**Dosage:**	120mg tid with meals
Reviewer:	Theresa Kehoe, MD	**Date Review Completed:**	December 5, 2003

Chemistry Reviewer: N/A
Pharmacology Reviewer: N/A
Biopharmaceutics Reviewer: Wei Qiu, Ph.D.
Statistical Reviewer: Japo Choudhury, Ph.D.

REVIEW SUMMARY: In response to the Agency's Written Request, the efficacy and safety of orlistat in pediatric patients were assessed in two studies. The first was a 52-week, randomized (2:1), double-blind, placebo-controlled study of 539 obese adolescents (BMI > 97th percentile). The second was a 22-day, randomized (1:1) double-blind, placebo-controlled mineral balance study in 32 obese adolescents. Approximately 65% of the patients in each treatment group completed the one-year study and 94% of the subjects in each treatment group completed the mineral balance study. In the one-year study, orlistat use resulted in a statistically significant decrease in BMI when compared to placebo (-0.55 kg/m^2 vs. 0.31 kg/m^2; p=0.001). Overall, 26.5% of orlistat-treated patients and 15.7% of placebo-treated patients had a 5% reduction of their baseline BMI (p=0.005), while 13.3% of orlistat-treated patients and 4.5% of placebo-treated patients had a 10% reduction of their baseline BMI (p=0.002). Body weight and height increased in both groups, as one would expect in this growing population. However, the increase in body weight in the orlistat group (0.53 kg) was significantly less than the increase in the placebo group (3.1 kg) (p<0.001). Similar to results seen with BMI, 19% of orlistat-treated patients and 11% of placebo-treated patients had a 5% reduction in body weight, while 9.5% of orlistat-treated patients and 3.3% of placebo-treated patients had a 10% reduction in body weight. In previous studies of obese adults, approximately 60% of orlistat- treated patients and 31% of placebo-treated patients had a 5% reduction of their baseline body weight, while 27% of orlistat-treated patients and 11% of placebo-treated patients had a 10% reduction in body weight at one year of therapy. There was no statistical difference in the effect of orlistat on blood pressure, lipid parameters and glucose or insulin levels in this low-risk adolescent population. In the mineral balance study, all minerals, with the exception of iron, were maintained in positive balance in both the placebo and orlistat treatment groups. Both groups had decreases in mean iron levels, with larger decreased in the orlistat-treated subjects, a trend previously noted in mineral balance studies conducted in obese adult male subjects. There were no new safety signals noted from these studies in obese adolescent subjects. Similar to the adult population, gastrointestinal adverse events including fatty/oily stools were common in the orlistat-treated group. Fat soluble vitamin levels increased during the study in all subjects with larger increases in the placebo-treated subjects, probably because of universal daily multivitamin supplementation. In the adult orlistat studies, universal multivitamin supplementation was not implemented and the use of orlistat in these studies was associated with a lowering of some fat soluble vitamin levels. These findings suggest that the effects of orlistat use on fat soluble vitamins can be successfully ameliorated with concomitant multivitamin usage (i.e., 2 hours before or after taking orlistat).

OUTSTANDING ISSUE:

RECOMMENDED REGULATORY ACTION: N drive location:

New clinical studies	_____	**Clinical Hold**	_____ **Study May Proceed**
NDA, Efficacy/Label supplement:	_____	**Approvable**	_____ **Not Approvable**
	X	**Approve**	

SIGNATURES: **Medical Reviewer:** Theresa Kehoe, M.D. **Date:** December 5, 2003 .

Medical Team Leader: Eric Colman, M.D. **Date:** _____.

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Clinical Review for NDA 20-766 / S-018

Executive Summary

I. Recommendations

A. Recommendation on Approvability
Approve

B. Recommendation on Phase 4 Studies and/or Risk Management Steps
Roche should strongly consider packaging the drug product with a multivitamin for use in the adolescent population.

II. Summary of Clinical Findings

A. Current Therapeutic Options for the Treatment of Obesity in Adolescents
The are currently no approved medical therapies for obesity management in adolescents.

B. Brief Overview of Clinical Program
Orlistat, trade name Xenical, chemical name tetrahydrolipistatin, is a pancreatic lipase inhibitor that acts by inhibiting the absorption of dietary fats. Orlistat was approved for the long-term treatment of obesity on 4/23/99, for adult patients with an initial body mass index (BMI) >30 kg/m^2 or > 27 kg/m^2 in the presence of other risk factors (e. g., hypertension, diabetes, dyslipidemia).

The efficacy and safety of orlistat in pediatric patients were assessed in two studies, as outlined in the Agency's 9 August 2000 Written Request. The first was a 52-week, randomized (2:1), double-blind, placebo-controlled study of 539 obese adolescents (BMI > 97^{th} percentile). The second was a 22-day, randomized (1:1) double-blind, placebo-controlled mineral balance study in 32 obese adolescents.

C. Efficacy
In the one-year trial, approximately 65% of the patients in each treatment group completed the study. Orlistat use in the adolescent population resulted in a statistically significant decrease in BMI (-0.55 kg/m^2) when compared to placebo (+0.31 kg/m^2) (p=0.001). Overall, 26.5% of orlistat-treated patients and 15.7% of placebo-treated patients had at least a 5% reduction of their baseline BMI (p=0.005), while 13.3% of orlistat-treated patients and 4.5% of placebo-treated patients had at least a 10% reduction of their baseline BMI (p=0.002). Body weight and height increased in both groups, as one would expect in this growing population. However, the increase in body weight in the orlistat group (0.53 kg) was significantly less than the increase in the placebo group (3.1 kg) (p=0.001). Similar to results seen with BMI, significantly more patients treated with

orlistat had at least 5% (19%) and 10% (9.5%) reductions in baseline body weight when compared with placebo-treated patients (11.7% and 3.3%, respectively ($p<0.05$ for both comparisons).).

In previously conducted studies of obese adults, approximately 60% of orlistat-treated patients and 31% of placebo-treated patients had at least a 5% reduction of their baseline body weight, while 27% of orlistat-treated patients and 11% of placebo-treated patients had at least a 10% reduction in body weight at one year of therapy.

Waist circumference decreased by an average of –2.6 cm in the orlistat group and by –0.6 cm in the placebo group ($p=0.008$). Hip circumference decreased by 1.3 cm in the orlistat-treated patients and increased by 0.1 cm in the placebo-treated subjects ($p=0.01$).

Fat mass and fat-free mass were directly measured by DEXA in a subgroup of 152 orlistat and 77 placebo subjects. At the end of treatment, the orlistat group had an average weight loss of -0.54 kg; whereas, the placebo subjects gained an average of 1.45 kg. Fat mass decreased by a mean of –2.4 kg in the orlistat group and increased by 0.38 kg in the placebo group ($p=0.03$).

There were no statistically significant differences between treatment groups in the changes in blood pressure, lipid parameters, and glucose or insulin levels in the low risk adolescent population.

In the 3-week mineral balance investigation, 94% of the subjects in each treatment group completed the study. Positive balance was maintained for calcium, magnesium, phosphorus, and zinc in both the orlistat and placebo groups, when measured on Day 22. Copper balance was –0.4 umol/24 hr in the orlistat group and 0.1 umol/24 hr in the placebo group. Both groups had decreases in mean iron balance (–32.9 μmol/24 hour in the placebo group versus –49.7 μmol/24 hour in the orlistat group). Negative iron balance was previously noted in mineral balance studies conducted in obese adult male subjects (–10.80 ± 11.10 in the placebo treated group, –18.90 ± 10.50 in the orlistat treated group). The etiology of the net loss of iron is unclear. There was no association between gender and iron balance. No significant differences were detected between treatment groups at Day 22 for either mean serum sodium (placebo, 141.7 mmol/L; orlistat, 142.4 mmol/L) or potassium (placebo, 4.1 mmol/L; orlistat, 4.1 mmol/L). There was also no significant difference detected in mean urine sodium (placebo, 108.2 mmol/L; orlistat, 113.4 mmol/L) or potassium (placebo, 60.0 mmol/L; orlistat, 43.0 mmol/L) levels.

D. Safety

In the two adolescent studies reviewed, a total of 373 subjects received at least one dose of orlistat and 198 subjects received at least one dose of placebo. Overall, 65% of orlistat-treated patients and 63% of placebo-treated patients completed the 52-week study and 94% of both orlistat and placebo treated subjects completed the 22 day inpatient study. The calculated compliance based on pill count was 73% in the orlistat treatment group and 72% in the placebo treatment group. There were no new safety signals noted from these studies in obese adolescent subjects. Similar to studies of orlistat in obese adults, gastrointestinal adverse events including fatty/oily stools were more common in the orlistat-treated group. Fat soluble vitamin levels

increased during the study in all subjects most likely because of the daily multivitamin supplementation. Vitamin levels were, however, lower in the orlistat- vs. the placebo-treated group. These differences were statistically significant for beta Carotene (3.00 μg/dl in the placebo group and 0.59 μg/dl in the orlistat group, p = 0.001) and Vitamin E (52.18 μmol/L in the placebo group and 11.92 μmol/Lin the orlistat group, p = 0.089). In the adults studies, universal multivitamin supplementation was not instituted and the use of orlistat was associated with a significant lowering of some plasma-fat soluble vitamin levels. These findings support the recommendation that all orlistat-treated patients take a daily supplement that contains all of the fat-soluble vitamins. There was no evidence that orlistat use had an impact on pulse, height, physical exam, sexual maturation, QTc interval or sex hormone levels.

E. Dosing

A single dose of orlistat was utilized in these clinical trials in obese adolescents. The dose used in these studies was the current marketed adult dose, 120mg t.i.d. The majority (88%) of subjects enrolled in these studies had a baseline body weight over 80kg, which is comparable to a normal weight adult population.

F. Special Populations

The efficacy and safety of orlistat use in the adolescent population correlates with that seen with orlistat use in the adult population. These adolescent studies enrolled subjects representing multiple races and spanned the adolescent ages from 12 – 16 years. Both male and female subjects were enrolled in these trials. Results were adequately analyzed for the effect of gender and none was found.

Clinical Review

I. Introduction and Background

I.A. Drug Established and Proposed Trade Name, Drug Class, Sponsor's Proposed Indication(s), Dose, Regimens, Age Groups

Orlistat, trade name Xenical, chemical name tetrahydrolipistatin, is a pancreatic lipase inhibitor that acts by inhibiting the absorption of dietary fats. This supplemental marketing application is submitted in response to a written request for pediatric studies evaluating the use of the adult orlistat dose regimen (120mg three times a day) in adolescent obesity management.

I.B. State of Armamentarium for Indication(s)

Orlistat is the only lipase inhibitor that is approved for the long-term treatment of obesity. Sibutramine (Meridia) was approved for weight loss in 1997. There are no products currently approved for obesity management in adolescents.

I.C. Important Milestones in Product Development

Orlistat was approved for the long-term treatment of obesity on 4/23/99, for obese patients with an initial body mass index (BMI) >30 kg/m^2 or > 27 kg/m^2 in the presence of other risk factors (e. g., hypertension, diabetes, dyslipidemia). (b) (4) The sponsor received a written request for pediatric studies for obesity management from the FDA in a letter dated August 9, 2000.

I.D. Other Relevant Information

(b) (4)

I.E. Important Issues with Pharmacologically Related Agents

Orlistat is the only lipase inhibitor that is approved for the long-term treatment of obesity.

II. Clinically Relevant Findings From Chemistry, Animal Pharmacology and Toxicology, Microbiology, Biopharmaceutics, Statistics and/or Other Consultant Reviews

The chemistry review of orlistat was completed with the original NDA submission. There are no new chemistry issues with this submission. Orlistat is (S)-2-formylamino-4-methyl-pentanoic acid (S)-1-[[(2S, 3S)-3-hexyl-4-oxo-2-oxetanyl] methyl]-dodecyl ester. Its empirical formula is $C_{29}H_{53}NO_5$, and its molecular weight is 495.7. It is a single diastereomeric molecule that contains four chiral centers, with a negative optical rotation in ethanol at 529 nm.

The animal pharmacology and toxicology review was conducted for the original marketing application. Decreased concentrations of the fat soluble vitamins, vitamin D and vitamin E, and beta carotene have been observed in animal studies. No new pharmacology and toxicology studies were submitted with this application.

The statistical review of this supplement was completed by Dr. Choudhury. The analyses performed agreed with that of the sponsor. Please see Dr. Choudhury's review for complete details.

III. Human Pharmacokinetics and Pharmacodynamics

Pharmacokinetics and pharmacodynamic studies in adults were reviewed in the original marketing application.

III.A. Pharmacokinetics

The vast majority (> 99%) of orally ingested orlistat is excreted unchanged in the feces. The small amount that is absorbed undergoes extensive first pass metabolism. New pharmacokinetic data in this submission relate to the evaluation of orlistat and an interaction with metformin, which showed no interaction. Please see Dr. Qiu's review for further details.

III.B. Pharmacodynamics

Orlistat is a reversible inhibitor of gastrointestinal lipases: pancreatic lipase, gastric/ lingual lipase, and carboxyl ester lipase. In the gastrointestinal tract, the drug's site of action, orlistat inhibits absorption of dietary triglycerides. Sequestration of orlistat with unabsorbed triglycerides reduces cholesterol absorption. Orlistat also inhibits lipoprotein, hepatic, hormone sensitive, and diacylglycerol lipases, though its extremely low bioavailability precludes a clinically meaningful effect on these lipases. Decreased concentrations of the fat soluble vitamins, vitamin D and vitamin E, and beta carotene have been observed in prior clinical studies in overweight and obese adults.

IV. Description of Clinical Data and Sources

IV.A. Overall Data

The orlistat clinical development program for obese adolescent patients was undertaken to provide information on the safety and efficacy of orlistat in obese adolescent patients, as requested in the formal Written Request for pediatric studies dated August 9, 2000. This clinical development program was prospectively designed based on the extensive previous clinical experience in the adult population and after identifying and considering the potential differences between the two patient populations. Over 7000 subjects participated in the original global development program for orlistat. The phase 3 clinical program included 4,230 obese and overweight adult patients (body mass index (BMI) of 28 kg/m^2 to 43 kg/m^2) in seven large-scale double-blind, placebo controlled trials lasting up to two years. There have now been close to one hundred controlled clinical trials in over 30,000 patients with studies of up to four years in duration.

The clinical studies in the adult population used body weight as a primary efficacy parameter. Since adolescent subjects are likely to still be growing, body mass index (BMI), which takes into account increases in height and the concomitant increases in lean body weight, rather than body weight alone was used as study entry criteria and the primary efficacy endpoint for the adolescent studies. Based on the mechanism of action of orlistat, other potential differences between the adult and adolescent patient populations including gastrointestinal pathology, diet, mineral balance, and the absorption of fat-soluble vitamins were considered and evaluated.

IV.B. Tables Listing the Clinical Trials

Orlistat Trials in Adolescent Obesity				
		Subjects enrolled/completed	Duration	Endpoint
NM16189	total	539 (349)	54 weeks	BMI
	Orlistat120 tid	357 (232)		
	Placebo tid	182 (117)		
PP16203	total	32 (30)	22 days	Mineral balance
	Orlistat120 tid	16 (15)		
	Placebo tid	16 (15)		

IV.C. Postmarketing Experience

Orlistat has been on the market in the EU since July 1998 and in the US since April 1999. The total estimated exposure to orlistat up until January 2003 is approximately 16 million patient treatments. Information on any adverse event reported for children 17 years of age or younger was obtained from the sponsor's database, which includes events reported globally from health professionals, consumers, and literature reports. A total of eight adverse events, two of which were serious, have been reported in children less than 12 years of age. The two serious adverse events were mydriasis and accidental exposure, both of which were reported in a 3-year-old male who accidentally ingested orlistat. A total of 12 adverse events, two of which were serious, have been reported in children and adolescents between the ages of 12 and 16. The two serious adverse events included gastrointestinal disorder and drug interaction, both of which were reported by a 16-year-old female who was consuming Olestra-containing snacks while taking orlistat.

IV.D. Literature Review

A literature search for studies of orlistat in obese adolescents was conducted using the following databases: (b) (4) . Two studies conducted in obese adolescents were identified. One was a 6-month study on the efficacy of orlistat in overweight adolescents with obesity-related co-morbid conditions conducted by The Division of Nutrition Research Coordination (NIDDK) at the National Institutes of Health (NIH). The second was a 12-week study conducted in 11 obese prepubertal children. The safety profile of orlistat in both of these studies was similar to that previously observed in the sponsor conducted clinical trials and no new events of clinical concern were reported.

V. Clinical Review Methods

V.A. How the Review was Conducted

This review focuses on study NM16189, which evaluated the safety and efficacy of orlistat use for obesity management in adolescent patients aged 12 to 16 years.

V.A. Overview of Materials Consulted in Review

This review was conducted utilizing data in the electronic submission of the NDA. All trials were conducted under IND (b) (4).

V.B. Overview of Methods Used to Evaluate Data Quality and Integrity

The Division of Scientific Investigation (DSI) was not consulted for this supplemental NDA.

V.C. Were Trials Conducted in Accordance with Accepted Ethical Standards

All studies appear to have been conducted in accordance with FDA guidelines on "Good Clinical Practice" and the principles of the Declaration of Helsinki.

V.D. Evaluation of Financial Disclosure

Financial disclosure information was provided by the sponsor and reviewed by this reviewer. None of the investigators involved with trials NM16189 and PP16203 reported any financial interests.

VI. Integrated Review of Efficacy

VI.A. Brief Statement of Conclusions

Orlistat is effective for use in weight management in the adolescent population, ages 12 to 16 years. The observed weight loss effect is not as robust as what was seen in the adult population, but remains statistically significant.

VI.B. General Approach to Review of the Efficacy of the Drug

The pivotal trials requested in the pediatric written request are reviewed in depth in this review. Study NM16189 was a multicenter, randomized, double-blind, placebo-controlled, parallel-group study of obese adolescents aged 12 to 16 years. Study PP16203 was an inpatient, single-center, double-blind, randomized, placebo-controlled, parallel-group, study in obese adolescents evaluating the effect of orlistat on the balance of selected minerals.

VI.C. Detailed Review of Trials by Indication

VI.C.1. Study NM16189: This was a multicenter, randomized, double-blind, placebo-controlled, 54-week study conducted in obese adolescent patients.

Objectives: The primary objectives of this study were:

1. To characterize the efficacy of orlistat administered daily (120 mg tid with meals) as an adjunct to diet in the treatment of obese pediatric patients.
2. To characterize the safety profile of orlistat administered daily (120 mg tid with meals) in obese pediatric patients, using the following endpoints: gastrointestinal tolerability, linear growth and Tanner pubertal stage assessment, bone mineral content, body composition (DEXA), fat-soluble vitamin, beta-carotene, parathyroid hormone, and serum calcium levels, and gall bladder and renal ultrasound

The secondary objective of this study was:

1. To characterize changes in obesity-related risk factors, including total cholesterol, LDL-cholesterol, HDL-cholesterol, LDL/HDL cholesterol ratio, triglycerides, systolic and diastolic blood pressure, waist circumference, and glucose and insulin responses to an oral glucose challenge

Study Design: This was a multicenter, randomized, double-blind, placebo-controlled, 54-week study conducted in obese adolescent patients. A 2-week placebo lead in period preceded the 52-weekdouble-blind treatment period. Patients received nutritional, behavior modification, and exercise counseling beginning with the placebo lead-in period. A hypocaloric diet was to be maintained and multivitamin supplementation was to be taken to all patients during the active-treatment period. Following the completion of the treatment period, patients were followed for an additional 28 days.

Population: Obese male and female adolescents between 12 and 16 years of age at the time of screening were enrolled from 32 centers.

Inclusion Criteria

- BMI at the time of screening that was 2 units greater than the US weighted mean for the 95th percentile based on age and gender, as outlined in the table below.

Minimum BMI for Study Eligibility		
Age	BMI	
(years)	Male	Female
12	28.5	29.5
13	29.1	30.6
14	29.8	31.3
15	30.7	31.6
16	31.8	31.9

- Age: 12 to 16 years at screening;
- Gender: male or female patients of all racial and ethnic groups. Females of childbearing potential had to have a negative serum pregnancy test at screening and randomization, and had to use an acceptable method of contraception during the study if sexually active;
- Patients without any chronic medical condition or with mild chronic medical

conditions (i.e., hypertension, asthma, arthritis, etc.) who do not require treatment or are medically stable on treatment;
- Availability of a parent or guardian to attend study visits with the patients and to be actively involved in the behavior modification plan.
- Give written informed consent before any study specific screening procedures with the understanding that the patient has the right to withdraw from the study at any time.

Exclusion Criteria: Patients meeting any of the following criteria were excluded from the study:
- BMI $\geq$ 44 kg/m^2 and/or body weight $\geq$ 130 kg
- Body weight < 55 kg
- Weight loss of $\geq$ 3 kg within three months prior to screening
- Pregnancy or lactation
- Diagnoses of diabetes requiring anti-diabetic medication
- Obesity associated with genetic disorders such as Prader-Willi, Bardet-Biedl, and Cohen syndromes
- History or presence of significant medical (e.g. renal cancer, hepatic cancer, or endocrine disorders) or psychiatric conditions or diseases which could impact on the results of the study, without prior approval of the sponsor
- Current use of dexamphetamine or methylphenidate (Ritalin) including in patients diagnosed with Attention Deficit Hyperactivity Disorder (ADHD)
- Hypothyroidism not controlled with a stable dose of thyroxine replacement therapy for at least.
- Abnormal laboratory test results of clinical significance
- Presence of chronic diarrhea or cholestasis
- Presence of active gastrointestinal disorders such as malabsorption syndrome
- Ongoing bulimia or laxative abuse
- Use of approved or experimental weight reduction medications or treatments currently or within 3 months of randomization
- Dependence on any substance of abuse, including alcoholism
- Unwilling or unable to comply with the protocol requirements or considered by the investigator to be an inappropriate candidate for the study
- A known hypersensitivity to orlistat or any of its components
- Failure to discontinue the use of all vitamin preparations one month prior to randomization
- Inability to swallow hard shell #2 capsules
- Participation in a clinical trial within 30 days of screening
- Use of any of the following prohibited medications within 3 months prior to randomization:
  - Anorexic medications, prescription and/or over the counter
  - Antidepressants, prescription and/or over the counter
  - Anticonvulsants
  - Antiarrythmic medications

- Systemic steroids other than oral contraceptives

Study Medication: Oral dosing with 120mg orlistat (marketed formulation) or placebo capsules three times per day with meals.

Efficacy Measures

Primary: The primary efficacy parameter for this study was the change in BMI from baseline to the end of the study or at study exit. Body weight was measured to the nearest one-tenth of a kilogram. Two consecutive measurements within 0.5 kg of each other were averaged and recorded. Height was measured to the nearest one-tenth of a centimeter using a wall mounted stadiometer. Two consecutive measurements within 0.5cm of each other were averaged and recorded.

Secondary: The secondary efficacy parameters included change in body weight, total cholesterol, LDL cholesterol, HDL cholesterol, LDL/HDL ratio, triglycerides, diastolic and systolic blood pressure, waist circumference, and glucose and insulin responses to an oral glucose challenge. In addition, hip circumference and categorical changes in BMI and body weight were analyzed.

Safety Measures: Discussed in detail in the Integrated Summary of Safety. Safety parameters included adverse events, laboratory tests, pulse rate, 12-lead ECG, physical examinations, linear growth, Tanner stage assessment, bone mineral content, body composition, fat soluble vitamin and beta-carotene levels, and gallbladder and renal ultrasound findings.

Study Methods: During the 2-week placebo lead-in period, patient's vital signs, weight, height, and waist and hip measurements were recorded. Patients received nutritional, behavior modification, and exercise counseling and began the recommended hypocaloric diet and exercise regimen.

Diet: Patients were maintained on a nutritionally balanced, hypocaloric diet designed to produce an initial weight loss of 0.5 to 1.0 kg/week. The caloric distribution of the diet was 30% as fat, 50% as carbohydrate, and 20% as protein, with a maximum of 300 mg/day cholesterol and 1300 mg calcium intake per day. The maximum amount of fat in the diet was not to exceed 70 g per day. Dietary caloric intake was assigned to patients according to their body weight on study day -14 (see table below). The daily caloric intake assignment was adjusted if the subject reached a BMI of 22 kg/m^2 or less or if the patient was losing weight too rapidly.

Caloric Intake Assignment		
Body Weight (Kg)	**Total Calorie Intake: Male** (Kcal/day)	**Total Calorie Intake: Female** (Kcal/day)
< 70	1400	1200
70 to < 80	1500	1300
80 to < 90	1600	1400
90 to <100	1700	1500
> 100	1800	1600

Behavior modification: All centers had behavior modification programs in place. The programs utilized unifying principles including self monitoring of diet and activity, stimulus control, behavioral substitution, speed of food intake and information and motivational support.

Exercise: Exercise guidelines were provided to help the patients establish patterns of regular physical activity and encourage the gradual development of physical conditioning.

Vital signs were recorded at each study visit. Body weight was recorded at each visit with the patient wearing street clothing and no shoes, outerwear, or accessories. Weight was measured in kilograms (kg) and recorded to the nearest one-tenth of a kg. The patient was weighed at least twice until two consecutive measurements were within 0.5 kg of each other. Height, without shoes, was measured at every visit. Height was measured in centimeter (cm) and recorded to the nearest one-tenth of a cm. The standing height was measured at least twice until two consecutive measurements were within 0.5cm of each other. Waist and hip circumference measurements were obtained monthly. Other outcome measures included: total cholesterol, LDL cholesterol, HDL cholesterol, LDL/HDL ratio, triglycerides at baseline (Day1), Weeks 13, 25, and 52 or at study exit; glucose and insulin responses to an oral glucose challenge at baseline (Day1), Week 25 and Week 52 or study end; Tanner staging at baseline (Screening), Week 25 and Week 52 or study end; serum levels of sex-hormone binding globulin, estradiol (females), and free testosterone (males) levels at baseline (Day1), Week 25 and Week 52 or study end; and electrocardiogram at baseline (Day 1) and Week 52 or study exit. A subgroup of 18 study centers performed DEXA to assess of changes in body composition at baseline and Week 52 or study exit. A total of 229 subjects had DEXA assessments (77 in the placebo group and 152 in the orlistat group).

Withdrawal criteria: Subjects could withdraw from the study at any time. Investigators could withdraw patients in the event of intercurrent illness, adverse events, treatment failure after a prescribed procedure, protocol violations, cure, administrative reasons, or other reasons.
The investigator was required to report all pregnancies to the sponsor within 24 hours and all pregnancies were to be followed to their conclusion. Patients who were withdrawn from the study were not replaced.

Statistical Analyses: A total of 539 patients from 32 study centers were randomized (182 to the placebo group and 357 to the orlistat group). A total of 349 patients completed the study [117 (64%) in the placebo group and 232 (65%) in the orlistat group]. The standard deviation of change from baseline BMI is not larger than the estimated 2.6 and therefore, the power is more than 80%. Efficacy was analyzed for all patients who had baseline efficacy assessments and at least one post-baseline efficacy measurement (ITT population). Primary and secondary efficacy endpoints were also analyzed for all patients who completed a final visit at week 52 (Completers population). All efficacy endpoints were derived using the last-observation-carried-forward (LOCF) data set. Change from baseline to week 52 in BMI was analyzed using an analysis of covariance model (ANCOVA) that included change from baseline value as the response, and treatment, center, and treatment-by-center, and baseline stratification terms.

Protocol Amendments: There were no amendments to this protocol.

Results

Patient Disposition: A total of 539 patients from 32 centers were randomized. Of these 539 patients, 182 were randomized to the placebo group and 357 were randomized to the orlistat group. A similar percentage of patients in each treatment group (placebo, 64%; orlistat 65%) completed the study. The calculated compliance based on pill count was 73% in the orlistat treatment group and 72% in the placebo treatment group. Eleven subjects were excluded from the ITT analysis because they did not have a follow-up efficacy assessment

Study NM16189: Patient Disposition		
	Placebo	Orlistat
Enrolled	182	357
Included in ITT	180	348
Withdrew - Safety	3 (2)	12 (3)
Withdrew - Nonsafety	61 (34)	108 (31)
Deaths	0	0
Completed	117 (64)	232 (65)

Protocol Violations:

Five subjects (3 in the placebo group, 2 in the orlistat group) were withdrawn from the study due to protocol violations. Administration of the following medications was not permitted at the time of enrollment or during the study:

- Anorexic medications, including but not limited to fluoxetine, sertraline, paroxetine
- Antiarrhythmic medication
- Antidepressants
- Anticonvulsants
- Anxiolytics if taken regularly (i.e. benzodiazepines)
- Cyclosporine
- Dexamphetamine or methylphenidate (Ritalin)
- Fat soluble vitamins (unless given as part of the study) or fish oil supplements
- Olestra containing foods such as (b) (4)
- Insulin and/or oral hypoglycemic agents
- Systemic steroids other than oral contraceptives (i.e., glucocorticoids, anabolic steroids)

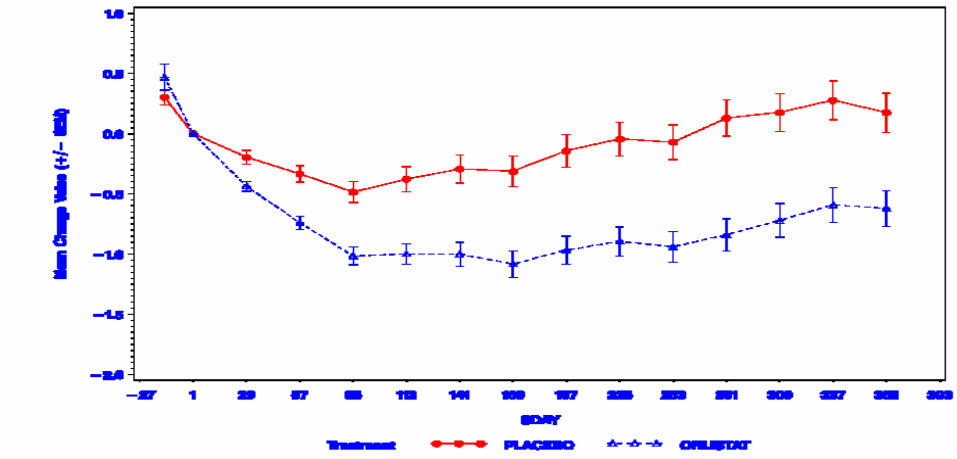
Eight subjects received incorrect study medication in the early stages of the study. Two subjects assigned to receive orlistat received placebo (one for 3 days and one for 87 days). Six subjects assigned to receive placebo received orlistat, all for less than 42 days.

Demographics: The two groups were well matched for baseline demographic characteristics (Table below). The mean age of the participants was 13.5 years, approximately 75% of the subjects were Caucasian, and the average BMI was 35.

NM16189: Patient Demographics		
	Placebo	**Orlistat**
N	181	352
Age (yrs.)	13.50 ± 1.24	13.61 ± 1.35
Sex		
Male	52 (28.7%)	124 (35.2%)
Female	129 (71.3%)	228 (64.8%)
Body Weight (kg)	95.11 ± 14.18	97.71 ±14.96
Body Height (cm)	163.65 ± 7.74	165.16 ± 8.43
BMI (kg/m2)	35.43 ± 4.07	35.72 ± 4.17
Race		
Caucasian	141 (77.9%)	264 (75.0%)
Black	25 (13.8%)	66 (18.8%)
Other	15 (8.3%)	22 (6.3%)
Lead-In BW loss		
< 1%	95 (52.5%)	166 (47.2%)
≥ 1%	86 (47.5%)	186 (52.8%)
Baseline BW		
< 80 kg	22 (12.2%)	36 (10.2%)
≥ 80kg	159 (87.8%)	316 (89.8%)

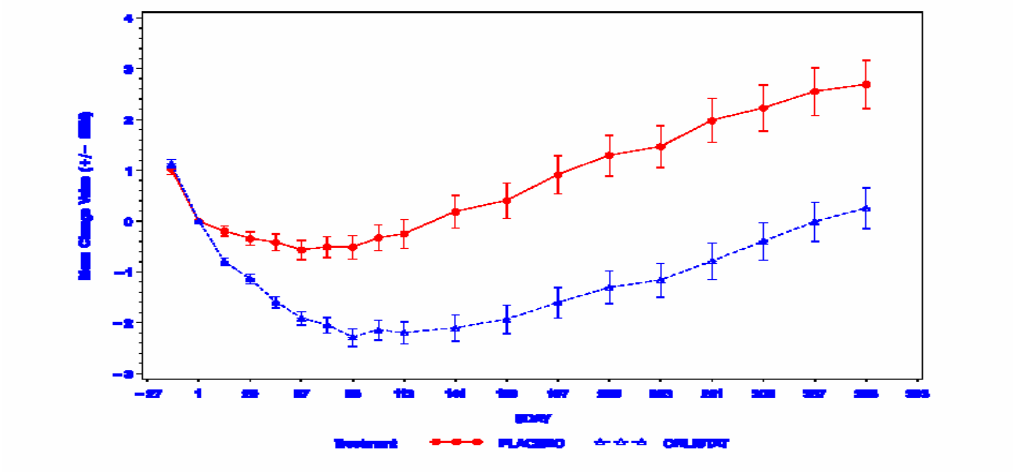
Primary Efficacy Outcomes

Body Mass Index: The primary efficacy parameter for this study was change in BMI from baseline to week 52 or study exit. During the first 12 weeks of treatment, subjects in both groups had a decrease in BMI (see figure below). In the ITT population, the least squares mean (LSM) change from baseline to study end was -0.55 kg/m^2 in the orlistat group and +0.31 kg/m^2 in the placebo-treated patients. This difference between the two treatment groups was statistically significant (p = 0.001). Similar results were seen for the Completers population. Overall, 26.5% of orlistat-treated patients and 15.7% of placebo-treated patients had at least a 5% reduction of their baseline BMI, while 13.3% of orlistat-treated patients and 4.5% of placebo-treated patients had at least a 10% reduction of their baseline BMI.



Secondary Efficacy Outcomes

Body Weight: All subjects initially lost weight during the first four weeks of the study then began to gain weight for the remainder of the study period. (see figure below) At study end, the LSM change from baseline in body weight was 0.53 kg for orlistat-treated patients and 3.14 kg for placebo-treated patients. This difference was statistically significant (p = 0.000). Similar to results seen with BMI, significantly more patients treated with orlistat had at lease 5% (19%) and a 10% (9.5%) reductions in baseline body weight than patients treated with placebo (11.7% of patients had at a least a 5% weight loss and 3.3% of patients had at lease a 10% weight loss; (p<0.05). .



Lipid Parameters: Very few of the patients in this study had abnormalities in serum lipids at baseline. As shown in the following table, there were no statistically or clinically significant improvements by the end of the study and no significant differences between orlistat treated subjects and placebo-treated subjects.

NM16189: Lipid Parameters					
Treatment	**N**	**Baseline**	**LSM Change**	**Difference from Placebo**	
			%	LSM	p
Total cholesterol					
Placebo	163	4.20	3.10		
Orlistat	323	4.18	2.29	-0.81	0.558
LDL cholesterol					
Placebo	163	2.50	2.99		
Orlistat	322	2.49	1.26	- 1.73	0.352
HDL cholesterol					
Placebo	163	1.08	0.65		
Orlistat	323	1.10	2.29	1.8963	0.389
Triglycerides					
Placebo	163	1.39	16.81		
Orlistat	323	1.30	22.47	5.66	0.281

Glucose and Insulin levels: The majority of patients (> 92%) in both treatment groups had normal glucose tolerance at baseline. Mean 0 minute and 120 minute glucose values were similar at baseline in the placebo and orlistat treatment groups and patients in both treatment groups had a similar decrease in these values by the end of the study. Patients in both treatment groups had a large decrease in baseline insulin levels at the end of the study. Patients treated with orlistat had a larger decrease in insulin at both the 0 minute (orlistat, -28.1; placebo -20.33) and 120 minute (orlistat, - 171.8; placebo 133.7) time points. This differences were not statistically significant however.

Anthropometric Measurements: Waist Circumference: Mean waist circumference was similar in both treatment groups at baseline (104.61 cm in the placebo group vs. 106.34 cm in the orlistat group). The LSM change from baseline to the end of the study was -2.55 cm in the orlistat treatment group and -0.62 cm in the placebo treatment group. This difference was statistically significant (p = 0.008). Hip Circumference: Mean hip circumference was similar in both treatment groups at baseline (116.03 cm in the placebo group vs. 116.57 cm in the orlistat group). The LSM change from baseline to the end of the study was -1.33 cm in the orlistat treatment group and +0.12 cm in the placebo treatment group. This difference was statistically significant (p = 0.013).

Blood Pressure: Baseline blood pressure values were similar for the two groups. The LSM change from baseline to the end of treatment for systolic blood pressure was 0.71 mmHg for orlistat-treated patients and 1.31 mmHg for placebo treated patients. This difference was not statistically significant. The LSM change from baseline to the end of treatment for diastolic blood pressure was -0.40 mmHg for the orlistat-treated patients and 1.06 mmHg for the placebo-treated patients and this difference was statistically significant (p = 0.047).

DEXA: In the one-year study , 18 sites were qualified to do DEXA measurements. The results indicate that changes in body weight are accounted for mostly by decreases in body fat and increases in fat free mass (soft tissue) (see table below).

DEXA Results for Adolescents (Study NM16189)					
	Mean Change from BL		**ANCOVA Results**		
Parameter	Orlistat (N=152)	Placebo (N=77)	LSM Difference from Placebo	Confidence Interval	p-value
BMC (kg)	0.196	0.182	0.005	-0.051to 0.061	0.857
BMD (g/cm^2)	0.04	0.04	0.00	-0.01 to 0.01	0.666
Fat free mass soft tissue (kg)	2.116	2.312	-.0.53	-1.220 to 1.114	0.929
Fat mass (kg)	-2.401	-0.382	-1.981	-3.806 to -0.157	0.033
Note: BMC = bone mineral content; BMD = bone mineral density; BL = baseline					

Subgroup and Additional Analyses: Weight management was analyzed separately in subgroups based on sex, race, age and pubertal status. These analyses were post-hoc and sample sizes were small, therefore their value is limited. Gender: The LSM change from baseline to end of treatment was –0.38 kg/m2 for female patients treated with orlistat and 0.19 kg/m2 for female patients treated with placebo and this difference was statistically significant (p = 0.048). The LSM change from baseline to the end of treatment was -1.08 kg/m2 for male patients treated with orlistat and 0.15 kg/m2 for male patients treated with placebo (p = 0.004). The gender by

treatment interaction was not significant (p = 0.1965). Race: The LSM change from baseline to study end for BMI was 0.10 kg/m2 for black patients treated with orlistat and 0.74 kg/m2 for black patients treated with placebo. For white patients the corresponding LSM change from baseline to the end of treatment for BMI was -0.72 kg/m2 for patients treated with orlistat and 0.06 kg/m2 for patients treated with placebo. The race by treatment interaction was not significant (p = 0.4089). Age: For patients aged ≤14 years, the LSM change from baseline to the end of the study for BMI was -0. 59 kg/m2 for patients treated with orlistat and 0.24 kg/m2 for patients treated with placebo (p = 0.001). For patients aged >14 years, the corresponding LSM change from baseline to the end of the study for BMI was -0.70 kg/m2 for patients treated with orlistat and -0.03 kg/m2 for patients treated with placebo (p= .211). The age by treatment interaction was not significant (p = 0.7912). Pubertal Status: For subjects who were prepubertal (Tanner stage 1 through 4) at screening, the LSM change from baseline to the end of the study for BMI was -0.76 kg/m2 for patients treated with orlistat and 0.18 kg/m2 for patients treated with placebo (p = 0.001). For Tanner stage 5 subjects, the corresponding LSM change from baseline to the end of the study for BMI was -0.65 kg/m2 for patients treated with orlistat and 1.35 kg/m2 for patients treated with placebo (p=.173). The tanner stage by treatment interaction was not significant (p = 0.4686).

Medical Officer's Conclusions: This study shows that, similar to the adult population, orlistat use in the adolescent population resulted in a small, but statistically significant change in the primary efficacy variable, BMI (-0.55 kg/m^2 in the orlistat group and +0.31 kg/m^2 in the placebo group, p=0.001). Overall, 26.5% of orlistat-treated patients and 15.7% of placebo-treated patients had a 5% reduction of their baseline BMI (p=0.005) while 13. 3% of orlistat-treated patients and 4.5% of placebo-treated patients had a 10% reduction of their baseline BMI (p=0.002). Body weight and height increased in both groups, as one would expect in this growing population. The difference in change of body weight between the groups (0.53 kg for the orlistat group vs. 3.14 kg for placebo group) was statistically significant (p = 0.001). Similar to results seen with BMI, significantly more patients treated with orlistat had 5% (19%) and a 10% (9.5%) reduction in baseline body weight than patients treated with placebo (11.7% of patients had a 5% weight loss and 3.3% of patients had a 10% weight loss; p-value for difference from orlistat-treated patients is 0.032 and 0.011, respectively). Body composition was analyzed by DEXA and showed significant decrease in fat mass (p = 0.033). Anthropometric measurements were statistically different between the orlistat and placebo groups for both waist (-2.55 cm in the orlistat group and -0.62 cm in the placebo group, p = 0.008) and hip circumference (-1.33 cm in the orlistat group and +0.12 cm in the placebo group, p = 0.013). There was no statistical difference in the effect of orlistat on blood pressure, lipid parameters, glucose or insulin levels in this low risk adolescent population.

VI.C.2. Study PP16203: This was an inpatient, single-center, double-blind, randomized, placebo-controlled, study evaluating the effect of orlistat on the mineral balance.

Objectives: The primary objective of the study was to assess the effect of orlistat on the balance (dietary intake minus urinary and fecal excretion) of selected minerals in obese subjects, 12-16 years old.

The secondary objectives of the study were:

1. To assess the effect of orlistat treatment on plasma and urine sodium and potassium and urine creatinine.
2. To evaluate the extent of fecal fat excretion induced by orlistat in this population.
3. To evaluate plasma levels of orlistat and its M1 and M3 metabolites.

Study Design: This was a single-center, double-blind, randomized, placebo-controlled, parallel-group, in-patient study in obese adolescents. Obesity was defined as a BMI of ≥ 85th percentile adjusted for age and sex at the time of screening. The study consisted of a screening period (days -21 to -1), a dosing period (days 1 to 21), and a follow-up period (day 22). Subjects were randomized to either a placebo or orlistat treatment group in a 1:1 ratio. Every attempt was made to have an equal number of male and female subjects in each treatment group. Since one of the minerals assessed, iron, could be affected by menstruation, every attempt was also made to include females of child bearing potential, who were not menstruating or expected to menstruate during the days critical for the mineral balance segment of the study (days 15 to 22 inclusive).

Population: Obese adolescent subjects between 12 and 16 years of age at the time of screening were enrolled. A total of 32 subjects (n = 32) were enrolled in the study and randomized in a 1:1 ratio to either the placebo or orlistat treatment group.

Inclusion Criteria

- BMI ≥ the 85th percentile, adjusted for age and sex (see table below).

PP16203: BMI 85th Percentile		
Age	**BMI**	
(years)	**Male**	**Female**
12	22.6	23.6
13	23.2	24.4
14	23.7	24.9
15	24.5	25.2
16	25.1	25.5

- Age range: 12-16 years
- Gender: male or female
- Negative serum pregnancy test at screening and randomization (females of childbearing potential only). Use of an acceptable method of contraception if sexually active
- Willingness to give written informed consent and to participate and comply with the study
- Non-smoker

Exclusion Criteria

- Treatment with prescription medications within 14 days, or over the-counter medications, including vitamin supplements, within 3 days of the study, or anticipated their need during the study with the exception of drugs which had been approved by the Sponsor including paracetamol and acetaminophen

- History of clinically relevant respiratory, cardiovascular, endocrine, hematological, gastrointestinal, renal, hepatic or neurological disorders
- History or presence of any conditions that cause malabsorption of fat (e.g., celiac disease, tropical sprue, regional enteritis, pancreatitis) or history of lactose intolerance.
- Diarrhea (> 2 liquid stools/day) during 1 week prior to the study, or constipation (ε 3 days duration) within the last 2 weeks prior to the study
- Known allergy or sensitivity to orlistat or to a component of the radio-opaque pellets including barium sulphate (minimum of 33%), calcium, zinc, or gelatin
- Donated or lost blood greater than 200 mL within 3 months prior to the start of the study
- Subjects who were on a special diet (e.g. vegetarian, kosher, lactose intolerant) or who could not fulfill the dietary requirements
- Use of, or dependence on, any substances of abuse including a history of alcohol intake;
- Unable or unwilling to comply with the protocol requirements or considered by the investigator to be unfit for the study; or
- Participated in a clinical trial within 3 months prior to entry.

Study Medication: Oral dosing with 120mg orlistat (marketed formulation) or placebo capsules three times per day with meals. Patients also received one capsule containing 10 radio-opaque markers three times a day with meals. For both treatment groups, all drugs were administered mid-meal (i.e., 5 minutes after the start of breakfast, lunch and dinner) at the study unit.

Efficacy Measures: Pharmacodynamic assessments included the balance of calcium, copper, iron, magnesium, phosphorous, and zinc. Mineral balance was defined as minerals ingested minus minerals excreted. Because variation in gut transit time could affect mineral balance, the method used to assess mineral balance needed to make no assumptions about day-to-day variations in bowel habit, was easy to perform, and practical and accurate. A method of continuous administration of radio-opaque pellets described by Cummings, et. al.[1] was used in this study to correct mineral fecal excretion by fecal recovery. Additional pharmacodynamic assessments included serum and urine levels of sodium, potassium, and urine creatinine, and fecal fat content.

Safety Measures: Safety assessments included adverse events, clinical laboratory parameters, vital signs, and 12-lead electrocardiograms (ECGs).

Study Methods: Subjects were admitted to the study center on the evening of study day –1 and were not discharged until completion of follow-up assessments on study day 22. While on the inpatient unit, subjects were maintained on a standardized meal plan of 1800kcal with 30% of calories derived from fat. The total volume of urine voided was collected in 24-hour intervals (7 am to 7 am of the following day) starting in the morning of day 10 through day 22. Fecal collection commenced on the morning of day 10 and continued through to the morning of day 22. Each sample produced was collected individually into separate labeled bags over a 24-hour period (7 am to 7 am the following day). At the end of the 24-hour period all samples collected

[1] Cummings JH, Jenkins DJA, Wiggins HS. Measurement of the mean transit time of dietary residue through the human gut. GUT 1979:17:210-218.

within that time were placed into an additional bag and given a sample number for that particular day. All samples collected were X-rayed at the study site for the number of radio-opaque markers. Samples collected on days 15 to 22 were analyzed for mineral output and for fecal fat content.

Withdrawal criteria: Subjects had the right to withdraw from the study at any time for any reason. The investigator also had the right to withdraw subjects from the study if it was in the best interest of the subject. Subjects who were discontinued prematurely from the study were not to be replaced unless the number of dropouts per treatment group was greater than 3.

Statistical Analyses: A total of 32 subjects were planned to be enrolled in two equal size groups of 16 subjects per group, with the expectation of obtaining 13 evaluable subjects per group. Assuming a standard deviation of 1.75, 80% power, ⟨= 0.05 (two-sided test), a difference of 2 mmol/24 hrs in calcium mineral balance could be detected between the two treatment groups. The standard deviation of 1.75 was observed in (b) (4), an adult mineral balance study.

Protocol Amendments: There were no amendments to this protocol.

Results

Patient Disposition: Thirty-two subjects, 16 subjects in the placebo treatment group and 16 subjects in the orlistat treatment group, were enrolled in the study. Two subjects, one from each treatment group, were discontinued for refusing treatment. These subjects were not replaced. Thirty subjects completed the study.

Protocol Violations: It was necessary to redefine the analysis population used for analyses of mineral balance and fecal fat since 3 subjects did not have fecal samples (fecal marker recovery) during the day 15 to day 22 collection period. The new analysis population included subjects who completed the study and had at least one recovered fecal maker during the day 15 to day 22 collection period. Mean fecal marker recovery was 70% for the placebo treatment group and 69% for the orlistat treatment group. The population analyzed includes 14 orlistat-treated subjects and 13 placebo-treated subjects.

Demographics: The two treatment groups were balanced with respect to demographic characteristics. Mean BMI was 34.1 kg/m^2 in the placebo treatment group and 34.2 kg/m^2 in the orlistat treatment group. Overall, 44% of subjects in the placebo treatment group and 63% of subjects in the orlistat treatment group were non-Caucasian. Seven subjects in the placebo treatment group and 3 subjects in the orlistat treatment group had a BMI < 30 kg/m^2.

PP16203: Patient Demographics		
	Placebo	**Orlistat**
N	16	16
Age (yrs.)	14.0 ± 1.26	14.2 ± 1.28
Sex		
Male	6 (38%)	7 (44%)
Female	10 (63%)	9 (56%)

PP16203: Patient Demographics		
	Placebo	**Orlistat**
Body Weight (kg)	98.9 ± 30.62	102.0 ± 23.28
Body Height (cm)	168.9 ± 10.85	172.5 ± 9.32
BMI (kg/m^2)	34.1 ± 7.75	34.2 ± 6.37
Race		
Caucasian	9 (56%)	6 (38%)
Black	3 (19%)	4 (25%)
Other	4 (25%)	6 (38%)

Primary Efficacy Outcomes

Mineral Balance (Calcium, Copper, Iron, Magnesium, Phosphorus, and Zinc):
Mineral balances were calculated by subtracting fecal and urinary mineral content from dietary mineral intake. For all minerals, other than iron, slightly more mineral was ingested than excreted during the 24-hour period in both the placebo and orlistat treatment groups within the population with at least one fecal marker recovered. Radio opaque marker recovery was 0.69 in the orlistat group and 0.70 in the placebo group. Mean net fractional mineral absorption (percent intake) for the placebo and orlistat treatment groups are illustrated in the table below.

PP16203: Summary of Mean Mineral Balance Per 24 hours								
Mineral	**Orlistat (n=14)**				**Placebo (n =13)**			
(per 24 hrs)	**Mean**	**SE**	**Median**	**CI**	**Mean**	**SE**	**Median**	**CI**
Calcium (mmol)	2.3	1.2	2.0	-0.4, 5.1	1.9	1.5	1.4	-1.0, 4.7
Copper (µmol)	0.6	0.7	-0.4	-0.7, 2.0	0.1	0.7	0.1	-1.4, 1.5
Iron (µmol)	-64.7	20.4	-49.7	-98.0, -31.4	-40.4	10.1	-32.9	-75.0, -5.9
Magnesium (mmol)	3.0	0.2	2.7	2.5, 3.5	2.7	0.2	2.3	2.2, 3.2
Phosphorus (mmol)	6.4	1.3	6.8	3.8, 9.1	5.8	1.3	4.1	3.1, 8.6
Zinc (µmol)	7.6	8.9	10.2	-7.5, 22.7	5.0	5.3	12.8	-10.6, 20.7

Copper balance was –0.4 umol/24 hr in the orlistat group and 0.1 umol/24 hr in the placebo group. Both treatment groups had decreases in mean iron balance (-32.9 µmol/24 hour in the placebo group versus -49.7 µmol/24 hour in the orlistat group). An *ad hoc* analysis of variance for the association of menstrual cycles and iron was performed for iron balance in male *versus* female. There was no association between gender and iron balance.

Secondary Efficacy Outcomes

Electrolytes (Sodium and Potassium)
Mean serum and urine sodium and potassium levels were similar between the placebo and orlistat treatment groups at baseline. No significant differences were detected between treatment groups at Day 22 for either mean serum sodium (placebo, 141.7 mmol/L; orlistat, 142.4 mmol/L) or potassium (placebo, 4.1 mmol/L; orlistat, 4.1 mmol/L). There was also no significant difference detected in mean urine sodium (placebo, 108.2 mmol/L; orlistat, 113.4 mmol/L) or potassium (placebo, 60.0 mmol/L; orlistat, 43.0 mmol/L) levels.

Urine Volume, Creatinine Concentration, and Creatinine Excretion
No significant differences between treatment groups were seen for either mean daily urine volume (placebo, 995 ml; orlistat, 959 ml), mean urine creatinine concentration (placebo, 147 mg/dL; orlistat, 170 mg/dL) during days 15 to 22, or mean urine creatinine excretion (placebo, 1378 mg/24 hour; orlistat, 1480 mg/24 hour).

Fecal Fat
Mean fat intake was similar in both groups. Orlistat-treated subjects excreted more fat daily (mean of 15.9 g/24 hour or 27% of dietary intake) than did placebo-treated (mean of 4.1 g/24 hour or 7% of dietary intake) subjects.

Pharmacokinetic Results for Orlistat, M1, and M3: Please see Dr. Qiu's review and discussion of the pharmacokinetic results.

Sponsor's Conclusions: In obese adolescents, orlistat has low systemic exposure, significantly inhibits dietary fat absorption, has no significant effects on either mineral absorption or mineral balance, and is well tolerated. These results are consistent with those seen in orlistat-treated obese adults.

Medical Officer's Conclusions: This study has demonstrated that, with the exception of iron, there is no significant alteration in mineral balance with orlistat use, at least over a 3-week period. Copper balance was –0.4 umol/24 hr in the orlistat group and 0.1 umol/24 hr in the placebo group. Both treatment groups had decreases in mean iron balance (-32.9 μmol/24 hour in the placebo group versus -49.7 μmol/24 hour in the orlistat group). These decreases are consistent with trends seen in a previous orlistat mineral balance study conducted in male adult subjects (-10.80 ± 11.10 in the placebo treated group, -18.90 ± 10.50 in the orlistat treated group). No significant differences were detected between treatment groups at Day 22 for either mean serum sodium (placebo, 141.7 mmol/L; orlistat, 142.4 mmol/L) or potassium (placebo, 4.1 mmol/L; orlistat, 4.1 mmol/L). There was also no significant difference detected in mean urine sodium (placebo, 108.2 mmol/L; orlistat, 113.4 mmol/L) or potassium (placebo, 60.0 mmol/L; orlistat, 43.0 mmol/L) levels. Orlistat-treated subjects excreted more fat daily (mean of 15.9 g/24 hour or 27% of dietary intake) than did placebo-treated (mean of 4.1 g/24 hour or 7% of dietary intake) subjects.

VI.D. Efficacy Conclusions
Orlistat use in the adolescent population resulted in a statistically significant decrease in BMI (-0.55 kg/m^2) when compared to placebo (+0.31 kg/m^2) (p=0.001). Overall, 26.5% of orlistat-treated patients and 15.7% of placebo-treated patients had a 5% reduction of their baseline BMI (p=0.005) while 13. 3% of orlistat-treated patients and 4.5% of placebo-treated patients had a 10% reduction of their baseline BMI (p=0.002). Body weight and height increased in both groups, as one would expect in this growing population. The difference in change of body weight between the groups (0.53 kg for the orlistat group vs. 3.14 kg for placebo group) was statistically significant (p = 0.001). Similar to results seen with BMI, significantly more patients treated with orlistat had 5% (19%) and a 10% (9.5%) reduction in baseline body weight than patients treated with placebo (11.7% of patients had a 5% weight loss and 3.3% of patients had a

10% weight loss; p-value for difference from orlistat-treated patients is 0.032 and 0.011, respectively). In the adult population, approximately 60% of orlistat treated patients and 31% of placebo-treated patients had a 5% reduction of their baseline body weight while 27% of orlistat-treated patients and 11% of placebo-treated patients had a 10% reduction in body weight at one year of therapy. Body composition, analyzed by DEXA, showed significant decrease in fat mass ($p = 0.033$) with no decrease in fat free mass in adolescents evaluated. In the adult population, decreases in both fat mass and fat free mass were seen. Anthropometric measurements were statistically different between the orlistat and placebo groups for both waist (-2.55 cm in the orlistat group and -0.62 cm in the placebo group, $p = 0.008$) and hip circumference (-1.33 cm in the orlistat group and +0.12 cm in the placebo group, $p = 0.013$). There was no statistical difference in the effect of orlistat on blood pressure, lipid parameters and glucose or insulin levels in the low risk adolescent population. For most minerals, a positive balance was achieved on day 22 in both the placebo and orlistat treatment groups. Copper balance was –0.4 umol/24 hr in the orlistat group and 0.1 umol/24 hr in the placebo group. Both groups had decreases in mean iron balance (-32.9 μmol/24 hour in the placebo group versus -49.7 μmol/24 hour in the orlistat group). Negative iron balance was previously noted in mineral balance studies conducted in obese adult male subjects (-10.80 ± 11.10 in the placebo treated group, -18.90 ± 10.50 in the orlistat treated group). The etiology of the net loss of iron is unclear, though may be a consequence of the high conservation of the mineral in this age group. There was no association between gender and iron balance. No significant differences were detected between treatment groups at Day 22 for either mean serum sodium (placebo, 141.7 mmol/L; orlistat, 142.4 mmol/L) or potassium (placebo, 4.1 mmol/L; orlistat, 4.1 mmol/L). There was also no significant difference detected in mean urine sodium (placebo, 108.2 mmol/L; orlistat, 113.4 mmol/L) or potassium (placebo, 60.0 mmol/L; orlistat, 43.0 mmol/L) levels.

VII. Integrated Review of Safety

VII.A. Brief Statement of Conclusions

There were no new safety signals noted from these studies in obese adolescent subjects. Similar to the adult population, gastrointestinal adverse events including fatty/oily stools were common in the orlistat-treated group. Fat soluble vitamin levels increased during the study in all subjects, most likely because of the daily multivitamin supplementation. In the adults studies multivitamin usage was not a planned part of the protocols and the use of orlistat was associated with a lowering of plasma fat soluble vitamin levels. There is no evidence that orlistat use had an impact on pulse, height, physical exam, sexual maturation, QTc interval or sex hormone levels.

VII.B. Description of Patient Exposure

Overall, 65% of orlistat-treated patients and 63% of placebo-treated patients completed the 52 week study. The calculated compliance based on pill count was 73% in the orlistat treatment group and 72% in the placebo treatment group. The mean cumulative dose of orlistat received was 161751.5 mg of drug. Eight subjects received incorrect study medication in the early stages of the study. Two subjects assigned to receive orlistat received placebo (one for 3 days and one for 87 days). Six subjects assigned to receive placebo received orlistat, all for less than 42 days.

In the 22 day inpatient study, fourteen subjects completed the study and received a cumulative dose of 7.56 g of orlistat. One subject withdrew after 7 days of treatment (2.52 g orlistat), and another withdrew after 17 days of treatment (6.12 g orlistat).

VII.C. Methods and Specific Findings of Safety Review
Both studies were reviewed in depth for safety. The mineral balance of study PP16203 has been reviewed in the efficacy review section. Adverse events for that study are reviewed here.

VII.C.1. Study NM16189: This was a multicenter, randomized, double-blind, placebo-controlled, 54-week study conducted in obese adolescent patients.

Demographics: Six patients were excluded from the safety population because they did not have a follow-up safety assessment.

Exposure: Overall, 65% of orlistat-treated patients and 63% of placebo-treated patients completed the 52 week study (see table below). The calculated compliance based on pill count was 73% in the orlistat treatment group and 72% in the placebo treatment group. The mean cumulative dose of orlistat received was 161751.5 mg of drug.

Study NM16189: Drug Exposure		
	Placebo	Orlistat
	N = 181	N = 352
	No. (%)	No. (%)
Orlistat Group		
Treatment Duration (days)		
1 - 42	1 (<1)	18 (5)
43 - 70	-	15 (4)
71 - 98	1 (<1)	12 (3)
99 - 140	-	18 (5)
141 - 196	-	26 (7)
197 - 252	-	16 (5)
253 - 316	-	19 (5)
317 - 420	-	228 (65)
Total Cumulative Dose (MG)		
Mean	16200.0	161751.5
SD	21382.91	79961.91
SEM	15120.00	4261.98
Median	16200.0	144720.0
Min	1080	1440
Max	31320	294480
n	2	352
Placebo Group		
Treatment Duration (days)		
1 - 42	7 (4)	6 (2)
43 - 70	15 (8)	-
71 - 98	8 (4)	-
99 - 140	4 (2)	-
141 - 196	15 (8)	-
197 - 252	8 (4)	-
253 - 316	10 (6)	-
317 - 420	114 (63)	-

Of note, eight subjects received incorrect study medication in the early stages of the study. Two subjects assigned to receive orlistat received placebo (one for 3 days and one for 87 days). Six subjects assigned to receive placebo received orlistat, all for less than 42 days.

Deaths: No deaths occurred in the study population.

Serious Adverse Events: A total of 17 serious adverse events were reported in 16 subjects (6 events in the placebo group and 11 events in the orlistat group. See Appendix XI.A. for complete details. Three serious adverse events involved the gastrointestinal system: a 12-year-old male, randomized to orlistat, was hospitalized on day 19 with appendicitis; a 15-year-old female, randomized to orlistat, was hospitalized on day 168 for cholelithiasis and underwent cholecystectomy; and a 14-year-old female, randomized to orlistat, experienced right upper quadrant pain initially on day 67, was hospitalized on day 321 for laparoscopic cholecystectomy.

Adverse Events Leading to Withdrawal: The percentage of subjects who withdrew from the study because of adverse events was similar in both treatment groups (2% in the placebo group and 3% in the orlistat group). The most common types of events leading to treatment discontinuation were gastrointestinal disorders, especially in the orlistat treatment group. Two of the adverse events leading to discontinuation were serious and discussed above (a demyelinating disorder in a patient from the placebo group and depression in a patient from the orlistat group).

Adverse Events: Overall, 94% of placebo-treated and 97% of orlistat-treated patients reported at least one adverse event during the study (see table below). Gastrointestinal disorders were the most frequently reported adverse events, occurring in 71% of the placebo-treated patients and 88% of the orlistat-treated patients. A slightly higher percentage of patients treated with orlistat reported upper respiratory infections (32% versus 27%) and headache (38% versus 31%) than patients treated with placebo.

NM16189: Adverse Events, by Body System		
	Placebo	Orlistat
Subjects Receiving Dose	181	352
Subjects with At Least 1 AE	170 (94%)	342 (97%)
Events:		
Gastrointestinal	139	311
Hepato-biliary	2	6
Cardiovascular	2	2
Body as a whole	28	50
Musculoskeletal	51	94
Nervous	70	161
Infections	124	257
Respiratory	70	113
Skin and Appendages	31	70
Special Senses	25	27
Reproductive and Breast	22	33
Injury and Poisoning	49	106
Psychiatric	8	18
Immune	3	15
Blood and Lymphatic	3	3
Surgical/Medical Procedure	5	8

NM16189: Adverse Events, by Body System, continued		
	Placebo	Orlistat
Endocrine/Metabolic	4	15
Urogenital	2	8
Vascular	2	2
Benign Neoplasm	1	2

Gastrointestinal Adverse Events: Based on orlistat's mechanism of action, the frequency of gastrointestinal adverse events were much higher in the active-treatment group, as expected (see table below).

NM16189: Gastrointestinal Adverse Events		
	Placebo	Orlistat
	(N=181)	(N=352)
Fatty / Oily Stool	15 (8.3)	177 (50.3)
Oily Spotting	7 (3.9)	102 (29.0)
Oily Evacuation	3 (1.7)	82 (23.3)
Flatus with Discharge	5 (2.8)	70 (19.9)
Flatulence	8 (4.4)	32 (9.1)
Fecal Incontinence	1 (0.6)	31 (8.8)

Renal and Gallbladder Ultrasound:
Renal Ultrasound: Ten placebo subjects had abnormal renal ultrasounds at baseline including one patient with a renal calculus. Two orlistat patients had abnormal renal ultrasounds at baseline including one patient with a renal calculus. At the end of treatment, there were no new findings in the placebo group. In the orlistat group, one patient was found to have mild left hydronephrosis and one patient had a 6 mm echogenic focus seen. Repeat ultrasound did not show any evidence of a renal calculus. Gall Bladder Ultrasound: Of the 343 orlistat patients who had a baseline gall bladder ultrasound, 14 had a baseline abnormality including 3 patients with gallstones and 8 patients with fatty liver infiltration or hepatomegaly. At the end of the study, six (2%) orlistat patients were found to have asymptomatic cholelithiases. All were female and experienced weight loss ranging from 3.6 kg to 32.9 kg during the study. A seventh patient was found to have multiple gall bladder calculi on ultrasound after complaining of flank pain at day 167 after a 15.8 kg weight loss. The patient had a subsequent cholecystectomy. Of the 177 placebo patients who had a baseline gall bladder ultrasound, 8 had a baseline abnormality including 2 patients with gallstones; one patient was post cholecystectomy and 4 patients with fatty liver. One (0.05%) placebo patient was found to have gallstones on ultrasound at the end of the study. These findings are similar to what has been observed in the adult population. Risk factors for gallstone formation include female gender, obesity and rapid weight loss. Therefore, the incidence in gallstone formation was not unexpected.

Laboratory: No significant changes from baseline were seen in either treatment group for any laboratory parameter. The percentage of patients with a marked laboratory abnormality was similar between treatment groups. The most common marked laboratory abnormality was hematuria and high red blood cells in urine (54 subjects in the orlistat group (17%) and 26 subjects (16%) in the placebo group). All but one of the subjects was female and abnormalities were associated with menses and normalized on repeat testing. Elevated TSH levels were

detected in 6 subjects in the orlistat group and no subjects in the placebo group during the study. None of the patients were receiving thyroid hormone replacement at the start of the study. Three of the patients had elevated TSH levels at baseline and three of the patients had a single, non-replicated elevated TSH. Eleven patients receiving orlistat had elevated liver transaminase levels during the study. Most of these were single events and were normal on repeat testing. Two subjects had abnormal liver function tests at baseline and levels that were intermittently elevated during the study. Fifteen patients receiving orlistat and in five patients receiving placebo had elevated potassium levels. The majority returned to the normal range upon repeat testing. Seven patients receiving orlistat had elevated sodium levels. Most of these were single occurrences and normalized on repeat testing. One patient in the placebo treated group had a low ionized calcium level that normalized on repeat testing. Four subjects in the orlistat group and two subjects in the placebo group had elevated parathyroid PTH hormone levels during the study. Thirty-one patients receiving orlistat and twenty-three patients receiving placebo had markedly elevated prothrombin times. Abnormalities in prothrombin time could be an indication of Vitamin K deficiency. However, these abnormalities spanned both orlistat and placebo treated groups and were found to cluster at one or two investigative sites. Thus, the abnormalities were felt to be related to improper specimen handling and storage. The majority returned to normal upon repeat testing.

Laboratories of Special Interest

Sex steroids: Levels of free testosterone and sex hormone binding globulin were not significantly different from baseline to the end of the study among girls in the study population. There was no difference between treatment groups either. There was a decrease in estradiol levels among girls in both treatment groups. This decrease was greater for girls in the orlistat group than girls in the placebo group. The LSM change from baseline to the end of the study for estradiol was -7.5 pg/mL for the orlistat group and 0.7 pg/mL for the placebo group ($P = 0.045$). This most likely represents decreased peripheral conversion of androgen to estrogen due to the reduced fat mass. Levels of estradiol and sex hormone binding globulin decreased slightly during treatment among boys in both groups. Levels of free testosterone increased slightly in both groups. The changes were similar between treatment groups.

Fat Soluble Vitamins: All subjects in the trial were maintained on a multivitamin preparation during the course of the trial. In general, the levels of vitamins A, D, E, and beta-carotene increased during treatment for patients in both treatment groups (see table below). At baseline, 16 subjects in the placebo group and 27 subjects in the orlistat group had low Vitamin D levels while 2 subjects in the placebo group and 17 subjects in the orlistat group had low Vitamin A levels. Levels of vitamins D and A increased slightly in both the placebo and orlistat treatment groups and there was no significant difference between the two groups. Five subjects had low Vitamin D levels at study end (2 in the orlistat group and three in the placebo group). All had baseline values of Vitamin D that were low (see second table below). One subject in the orlistat group had a low Vitamin A level at study end. At baseline, one subject in the placebo group and one subject in the orlistat group had low Vitamin E levels. The levels of vitamin E increased to a greater extent in the placebo group when compared to the orlistat group, but the difference was not statistically significant. No subjects had low Vitamin E levels at study end. At baseline, 18 subjects in the placebo group and 43 subjects in the orlistat group had low beta-carotene levels.

The increase in beta-carotene levels for patients in the placebo group was significantly greater than the increases for patients in the orlistat group. The clinical significance of low antioxidant levels, such as beta-carotene, remains unclear.

NM16189: Summary of Vitamin Levels – Baseline and Study Completion, ANCOVA Results								
					Difference from Placebo			
Parameter (normal values)	Grp	N	Baseline Mean	LSM Change from BL	LSM	SE	Confidence Interval	p-value
Vitamin A	Pl	150	48.53	1.82				
(30-90 µg/dl)	Orl	307	49.53	3.33	1.51	1.00	-0.47 to 3.48	0.134
Beta Carotene	Pl	150	8.81	3.00				
(3-85 µg/dl)	Orl	307	7.84	0.59	- 2.40	0.64	- 3.66 to – 1.15	0.000
25OH Vitamin D	Pl	150	18.07	1.79				
(22.4-116.6 nmol/L)	Orl	313	17.69	1.40	- 0.39	0.69	-1.74 to 0.96	.571
Vitamin E	Pl	150	810.01	52.18				
(696 – 3369 µmol/L)	Orl	307	797.38	11.92	- 40.26	23.65	-86.75 to 6.23	0.089
Pl- placebo group; Orl – Orlistat group								

NM16189: Low Baseline Vitamin Values			
		Placebo N = 150 (%)	Orlistat N = 307[a] (%)
Vitamin A (normal range = 30 - 90 ug/dL)			
Baseline value - low		2 (1.3)	7 (2.3)
Low follow-up value[b]			
Two or more consecutive[c]			1 (14.3)
Last Value	Low		1
25 Hydroxy Vitamin D (normal range = 8.9 - 46.7 ng/mL)			
Baseline value - low		16 (10.7)	27 (8.6)
Low follow-up value[b]			
Two or more consecutive[c]		6 (37.5)	9 (33.3)
Last Value	Low	2	3
	Normal	2	5
	Missing	2	1
Vitamin E (normal range = 300 - 1580 ug/dL)			
Baseline value - low		1 (0.7)	1 (0.3)
Beta Carotene (normal range = 3 - 85 ug/dL)			
Baseline value - low		18 (12.0)	43 (14.0)
Low follow-up value[b]			
Two or more consecutive[c]		2 (11.1)	10 (23.3)
Last Value	Low	2	2
	Normal		7
	Missing		1

[a]There were 313 evaluable patients for the measurement of vitamin D.
[b] % calculated based on number of patients with normal baseline values Possibly including baseline.
[c] Based on study specific required vitamin supplementation.

Other Safety Tests
Physical Examination: There were no clinically meaningful differences in physical examination findings between groups. Tanner Stage: Patients in both the orlistat treatment group and the placebo treatment group experienced normal sexual maturation during the study and there were no notable differences between treatment groups. Height: Patients in both treatment groups grew during the study and were taller at the end of treatment than at baseline. The change in height from baseline to the end of the study was similar in both treatment groups (1.91 cm in the placebo group versus 1.82 cm in the orlistat group). ECG and Pulse: There were no significant changes from baseline in pulse or QTc interval in either the treatment or placebo group. Twenty-three patients (9 in the placebo group and 14 in the orlistat group) had an abnormal ECG at baseline including left axis deviation; left ventricular hypertrophy; intraventricular conduction defects; right bundle branch block; 1st degree AV block; sinus bradycardia; sinus tachycardia; ST-T wave changes; and Wolff Parkinson White (WPW) syndrome. At the end of treatment few patients had new abnormalities, which were either not considered as being clinically significant or were related to underlying conditions.

Medical Officer Conclusions: There are no new safety signals noted from this study in obese adolescent subjects. Gastrointestinal adverse events were common in the orlistat treated group (50.3% with fatty/oily stools). There were also two serious adverse events of gallbladder disease that required surgical intervention. These findings are similar to what has been observed in the adult population. There is no evidence that orlistat use had an impact on growth, sex hormone levels or sexual maturation. There were no significant changes from baseline in pulse or QTc interval in either the treatment or placebo group. Fat soluble vitamin levels increased during the study in all subjects due to the daily multivitamin supplement. Vitamin levels were lower in the orlistat treated group compared to placebo. These differences were statistically significant for beta Carotene (3.00 μg/dl in the placebo group and 0.59 μg/dl in the orlistat group, $p = 0.001$) and Vitamin E (52.18 μmol/L in the placebo group and 11.92 μmol/Lin the orlistat group, $p = 0.089$). These results are similar to what was observed in the adult population.

VII.C.2. Study PP16203: This is an inpatient, single-center, double-blind, randomized, placebo-controlled, parallel-group, in-patient study in obese adolescents evaluating the effect of orlistat on the balance of selected minerals.

Demographics: Sixteen subjects were enrolled in the study; all are included in the safety population.

Exposure: Fourteen subjects completed the study and received a cumulative dose of 7.56 g of orlistat. One subject withdrew after 7 days of treatment (2.52 g orlistat), and another withdrew after 17 days of treatment (6.12 g orlistat).

Deaths: No deaths occurred in the study population.

Serious Adverse Events: No serious adverse events were reported during this study.

Adverse Events Leading to Withdrawal: No withdrawals attributed to adverse events were reported during this study.

Adverse Events: Adverse events were reported by 15 orlistat-treated subjects and 13 placebo-treated subjects. Consistent with other studies, the incidence of GI adverse events, specifically fatty/oily stool, was higher in the orlistat treated group (orlistat, 44%; placebo, no subjects).

PP16203: Adverse Events, by Body System		
	Orlistat	Placebo
Subjects Receiving Dose	16	16
Subjects with At Least 1 AE	15 (94%)	13 (81%)
Events:		
Gastrointestinal	13 (81)	9 (56)
Musculoskeletal	6 (38)	6 (38)
Injury and Poisoning	5 (31)	2 (13)
Body as a whole	2 (13)	5 (31)
Endocrine/Metabolic	4 (25)	3 (19)
Nervous	3 (19)	5 (31)
Infections	3 (19)	5 (31)

Laboratory: Three marked laboratory abnormalities were reported in 3 different female patients. A 15-year old Caucasian female in the placebo treatment group, had glycosuria on day 22. Microscopic evaluation showed the presence of white blood cells and epithelial cells. The laboratory assessment was not repeated. A 14-year-old Caucasian female in the orlistat treatment group, had hematuria on day 22 (+4) which returned to normal (0) on day 32. A 13-year-old Black female in the orlistat treatment group had an ALT of 23 U/L at baseline that increased to 79 U/L on day 22. This was the last value reported and not followed up. AST and GGT levels also increased from 15 U/L at baseline to 33 U/L on day 22 and 52 U/L at baseline to 76 U/L on day 22, respectively.

Other Safety Tests
No clinically significant changes in vital signs, physical examinations, or ECGs were noted during this study. No pregnancies were reported during the study.

Medical Officer Conclusions: There were no unexpected safety signals seen in this small, short-term trial. The most common adverse events were gastrointestinal (81% in the orlistat group vs. 56% in the placebo group).

VII.D. Adequacy of Safety Testing
The safety testing conducted in these two trials was adequate to evaluate known safety concerns and to detect new safety signals if they exist.

VII.E. Summary of Critical Safety Findings and Limitations of Data
There were no new safety signals noted from these studies in obese adolescent subjects. Gastrointestinal adverse events were common with the orlistat treated group (50.3% with fatty/oily stools). There were also two serious adverse events of gallbladder disease (one cholelithiasis and one cholecystitis) that were required surgical intervention. Ultrasound studies

showed 6 subjects in the orlistat group and 2 subjects in the placebo group developed gallbladder abnormalities during the year of the study. These findings are similar to what has been observed in the adult population and is a known potential complication of weight loss. Fat soluble vitamin levels increased during the study in all subjects due to the daily multivitamin supplement. Vitamin levels were lower in the orlistat treated group compared to placebo. These differences were statistically significant for beta Carotene (3.00 µg/dl in the placebo group and 0.59 µg/dl in the orlistat group, p = 0.001) and Vitamin E (52.18 µmol/L in the placebo group and 11.92 µmol/Lin the orlistat group, p = 0.089). These results re similar to those observed in the adult population. There were no significant changes from baseline in pulse or QTc interval in either the treatment or placebo group. There is no evidence that orlistat use had an impact on growth, sex hormone levels or sexual maturation.

VIII. Dosing, Regimen, and Administration Issues

A single dose of orlistat was utilized in these clinical trials in obese adolescents. The dose used in these studies was the current marketed adult dose, 120mg t.i.d. The majority (88%) of subjects enrolled in these studies had a baseline body weight over 80kg which is comparable to a normal weight adult population.

IX. Use in Special Populations

IX.A. Evaluation of Sponsor's Gender Effects Analyses and Adequacy of Investigation

These studies of orlistat use in the obese adolescent population enrolled both male and females subjects. Results were adequately analyzed for the effect of gender and none was found.

IX.B. Evaluation of Evidence for Age, Race, or Ethnicity Effects on Safety or Efficacy

The efficacy and safety of orlistat use in the adolescent population correlates with that seen with orlistat use in the adult population. Although these adolescent studies enrolled subjects representing multiple races and spanned the adolescent ages from 12 – 16 years, the sample size for races other than white are probably too small to make definitive statements about efficacy or safety and the age range is too narrow to dissect by age.

IX.C. Evaluation of Pediatric Program

The pediatric program and the results submitted in this application has addressed all critical issues noted in the Pediatric Written Request.

IX.D. Comments on Data Available or Needed in Other Populations

Orlistat use in the geriatric population should be analyzed.

X. Conclusions and Recommendations

X.A. Conclusions

The currently marketed dose of orlistat that has been shown to be safe and effective for weight management in the adult population is also safe and effective for use in weight management in

the adolescent population, ages 12 to 16 years. The observed weight loss effect is not as robust as what was seen in the adult population, but remains statistically and perhaps clinically significant.

X.B. Recommendations

Approve

XI. Appendix

XI.A. Study NM16189: Serious Adverse Events

1) A 17 year old female, randomized to placebo, was hospitalized on day 280 with acute demyelinating encephalomyelitis. She had received the meningococcal vaccine on study day 97 as part of a regional vaccination program. The last dose of study medication was approximately study day 275.

2) A 16-year-old female, randomized to placebo, was seen in the emergency room on day 77 with Bell's palsy.

3) A 15-year-old female, randomized to placebo, was hospitalized on day 213 with pneumonia. Study medication was interrupted from study day 212 to study day 215.

4) A 13-year-old female, randomized to placebo, was hospitalized on study day 33 with asthma exacerbation. She had a history of reactive airway disease and sinusitis. Symptoms resolved and she was discharged on study day 41, and she resumed study drug on day 43. She was readmitted with another acute on study day 251 which also resolved after 4 days of treatment.

5) A 14-year-old female, randomized to placebo, was hospitalized on day 361 with intermittent right side pain. Study drug administration was not interrupted.

6) A 14-year-old female, randomized to orlistat, was hospitalized on day 364 for excision and drainage of a pilonidal cyst.

7) A 14-year-old female, randomized to orlistat, was hospitalized on day 74 for suicidal ideation.
8) A 14-year-old female, randomized to orlistat, was hospitalized on day 83 for an asthma exacerbation. The symptoms resolved and the patient was discharged on day 86.

9) A 12-year-old male, randomized to orlistat, was hospitalized on day 93 with seizures. The patient had a history of arachnoid brain surgery and nighttime seizures. The study medication was held on study day 92 and resumed on study day 98.

10) A 15-year-old male, randomized to orlistat, was hospitalized on day 178 for deviated septum after a traumatic incident.

11) A 12-year-old male, randomized to orlistat, was hospitalized on day 19 with appendicitis. Study medication was held from study day 19 to study day 22.

12) A 15-year-old female, randomized to orlistat, was hospitalized on day 168 for cholelithiasis and underwent cholecystectomy.

13) A 14-year-old female, randomized to orlistat, experienced right upper quadrant pain initially on day 67. She underwent evaluation and was hospitalized on day 321 for laparoscopic cholecystectomy.

14) A 16-year-old male, randomized to orlistat, was hospitalized on day 108 for adenoidectomy. Study medication was interrupted between study day 108 and study day 111.

15) A 13-year-old female, randomized to orlistat, was hospitalized on day 334 for aseptic meningitis. Study medication was interrupted between study day 333 and study day 337.

16) A 15-year-old male, randomized to orlistat, was hospitalized on day 247 for depression.

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/s/

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MEDICAL OFFICER

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