

Effect of Orlistat on Weight and Body Composition in Obese Adolescents

A Randomized Controlled Trial

Jean-Pierre Chanoine, MD, PhD

Sarah Hampl, MD, FAAP

Craig Jensen, MD

Mark Boldrin, MS

Jonathan Hauptman, MD

THE PREVALENCE OF OVER-weight in adolescents is increasing worldwide. In the United States, the proportion of adolescents with a body mass index (BMI) at or above the 95th percentile for age, a widely accepted definition of obesity in adolescents,^{1,2} has increased 15.5% to 23.4% in certain ethnic minorities.³ A similar picture is seen in European countries: the prevalence of overweight in adolescents has increased 8% to 21% in northern European countries and 17% to 23% in southern European countries.⁴

Excess weight in adolescents is associated with an increased risk of disorders such as hyperlipidemia and type 2 diabetes⁵ and can result in decreased emotional and physical quality of life.^{6,7} In addition, childhood obesity results in increased risk of morbidity and mortality in adulthood.^{8,9} Long-term follow-up studies of children and adolescents indicate that overweight children have a 15-fold greater risk of becoming overweight adults compared with those children and adolescents who were not overweight.⁸ Effective weight management in children and adolescents

Context The prevalence of overweight and obesity in children and adolescents is increasing rapidly. In this population, behavioral therapy alone has had limited success in providing meaningful, sustained weight reduction, and pharmacological treatment has not been extensively studied.

Objective To determine the efficacy and safety of orlistat in weight management of adolescents.

Design, Setting, and Patients Multicenter, 54-week (August 2000–October 2002), randomized, double-blind study of 539 obese adolescents (aged 12–16 years; body mass index [BMI] ≥ 2 units above the 95th percentile) at 32 centers in the United States and Canada.

Interventions A 120-mg dose of orlistat ($n=357$) or placebo ($n=182$) 3 times daily for 1 year, plus a mildly hypocaloric diet (30% fat calories), exercise, and behavioral therapy.

Main Outcome Measures Change in BMI; secondary measures included changes in waist and hip circumference, weight loss, lipid measurements, and glucose and insulin responses to oral glucose challenge.

Results There was a decrease in BMI in both treatment groups up to week 12, thereafter stabilizing with orlistat but increasing beyond baseline with placebo. At the end of the study, BMI had decreased by 0.55 with orlistat but increased by 0.31 with placebo ($P=.001$). Compared with 15.7% of the placebo group, 26.5% of participants taking orlistat had a 5% or higher decrease in BMI ($P=.005$); 4.5% and 13.3%, respectively, had a 10% or higher decrease in BMI ($P=.002$). At study end, weight had increased 0.53 kg with orlistat and 3.14 kg with placebo ($P<.001$). Dual-energy x-ray absorptiometry showed that this difference was explained by changes in fat mass. Waist circumference decreased in the orlistat group but increased in the placebo group (-1.33 cm vs $+0.12$ cm; $P<.05$). Generally mild to moderate gastrointestinal tract adverse events occurred in 9% to 50% of the orlistat group and in 1% to 13% of the placebo group.

Conclusions In combination with diet, exercise, and behavioral modification, orlistat statistically significantly improved weight management in obese adolescents compared with placebo. The use of orlistat for 1 year in this adolescent population did not raise major safety issues although gastrointestinal adverse events were more common in the orlistat group.

JAMA. 2005;293:2873–2883

www.jama.com

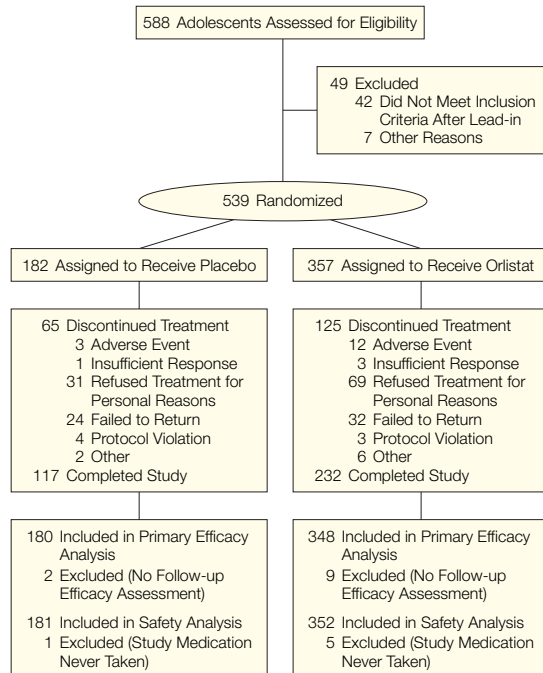
may therefore have important immediate and future societal health benefits.

Treatment of obesity in the pediatric age group, and in particular during adolescence,¹⁰ is notoriously difficult. While behavioral therapy has had some success in treating obesity in young children (aged 6–12 years), most stud-

Author Affiliations: Endocrinology and Diabetes Unit, British Columbia Children's Hospital, Vancouver (Dr Chanoine); Children's Mercy Hospitals and Clinics, Kansas City, Mo (Dr Hampl); Department of Medicine, Baylor College of Medicine, Houston, Tex (Dr Jensen); and Hoffmann-La Roche Inc, Nutley, NJ (Mr Boldrin and Dr Hauptman).

Corresponding Author: Jean-Pierre Chanoine, MD, PhD, Endocrinology and Diabetes Unit, K4-212, British Columbia Children's Hospital, 4480 Oak St, Vancouver, British Columbia V6H 3V4, Canada (jchanoine@cw.bc.ca).

For editorial comment see p 2932.

Figure 1. Study Design of Trial

ies have found that the long-term success of such therapy depends on the type of intervention used.¹¹⁻¹⁴ It is possible that pharmacotherapy could play a significant role in improving the results obtained with behavioral therapy. Pharmacological treatments have not been extensively studied in children and adolescents although sibutramine plus behavioral therapy has previously been examined in a 1-year study in obese adolescents.¹⁵ However, anorexiant that act on the central nervous system currently used in the treatment of adult obesity may not be appropriate in children and adolescents.^{15,16}

Orlistat is a gastrointestinal tract lipase inhibitor which decreases intestinal fat absorption by up to 30%. In adults, it has a good safety profile, is generally well tolerated, has minimal systemic absorption, and produces clinically meaningful and sustained decreases in weight and BMI when combined with a mildly hypocaloric diet and exercise.¹⁷⁻¹⁹ Orlistat is approved for use in weight management in overweight and obese adults in more than 120 countries and to date there have been more than 22 million pa-

tients who have received the drug. Based on these clinical and safety characteristics in adult populations, it was believed that orlistat may be a useful adjunct to diet, exercise, and behavioral counseling in the treatment of obese adolescents. In December 2003, based partly on the unpublished results of the present study, the use of orlistat in an adolescent population at the dose of 120 mg 3 times daily was added to the approved label in the United States.

The primary objective of this study was to characterize the efficacy and safety of orlistat plus diet, exercise, and behavioral therapy in treating obese adolescents. Secondary objectives were to assess the impact of orlistat treatment on obesity-related risk factors, including waist circumference, lipid levels, blood pressure, and glucose and insulin responses to an oral glucose challenge.

METHODS

Participants

Participants were recruited at institutions with established pediatric obesity treatment programs and clinical research expertise. Patients were re-

cruited through advertisements posted in clinics, through direct referrals from family physicians, or through spontaneous reply to newspaper advertising. Adolescents (aged 12-16 years) were eligible for enrollment if they (1) had a BMI (calculated as weight in kilograms divided by the square of height in meters) 2 units or higher than the US weighted mean for the 95th percentile based on age and sex¹ (2) had a parent or guardian prepared to attend study visits with them, and (3) were willing to be actively involved in behavioral modification. Because this was the first long-term study investigating the safety and efficacy of orlistat in the pediatric age group, 2 units were added to the 95th percentile of BMI at the request of the US Food and Drug Administration to ensure that only patients with the greatest potential for benefiting from study participation were included. Using these criteria, minimum BMI for inclusion ranged from 28.5 in boys and 29.5 in girls at 12 years to 31.8 and 31.9, respectively, at 16 years.

Exclusion criteria were BMI of 44 or higher (to increase homogeneity of the group); body weight of 130 kg or higher or less than 55 kg; weight loss of 3 kg or higher within 3 months prior to screening; diabetes requiring antidiabetic medication; obesity associated with genetic disorders; history or presence of psychiatric disease; use of dexamphetamine or methylphenidate; active gastrointestinal tract disorders; ongoing bulimia or laxative abuse; and use of anorexiant or weight-reduction treatments during the 3 months before randomization.

Study Design

We conducted a 54-week, multicenter, placebo-controlled study from August 2000 to October 2002 at 32 centers located in the United States and Canada. Following a 2-week, single-blind, placebo lead-in period, participants entered a 52-week, double-blind treatment period in which they were randomized at a 2 to 1 ratio to receive 120 mg of orlistat or placebo 3 times daily (FIGURE 1). Placebo and orlistat capsules looked identical and, ex-

cept for the active ingredient, had exactly the same composition. General guidelines for diet, exercise, and behavioral modification were supplied to all centers involved in the study (as detailed below), but each center remained free to use its own strategy. There was no study-specific assessment of the compliance with these general guidelines.

Screening included a physical examination consisting of Tanner stage assessment; vital signs and physical measurements (weight, height, waist and hip circumference); and clinical laboratory tests (hematology, blood chemistry, vitamin levels, glucose and insulin responses to a 2-hour oral glucose challenge). Following the placebo lead-in period, vital signs were taken and weight and height were measured every 2 weeks for the first 4 months, and then every month until the end of the study (18 visits in total). Waist and hip circumferences were measured every month for the first 4 months and then every 2 months until study end. Tanner stage was graded 1 to 5 after 6 and 12 months and based on breast development in girls and genital development in boys. Clinical laboratory tests were repeated on day 1 and after 3, 6, 9, and 12 months. Sex hormone measurements (estradiol, free testosterone, and sex hormone-binding globulin) were taken on day 1 and after 6 and 12 months. Blood samples were drawn in the morning following an overnight fast and all samples were analyzed by a central laboratory. Twelve-lead electrocardiographic examinations, gallbladder and renal ultrasound examinations, and bone mineral content and body composition measurements (determined by whole body dual-energy x-ray absorptiometry for patients at centers that had such equipment) were performed at baseline among a subset of participants and at week 52. All radiology technicians followed specific guidelines to ensure that standard operating procedures were adhered to across all centers.

The study was conducted in accordance with good clinical practice, the

Declaration of Helsinki, and the laws and regulations of the countries in which the research was conducted, whichever afforded greater protection to the individual. The study was approved by the institutional review board at each participating center. Written informed consent was received from the parents or guardians and written assent was received from each patient.

Diet

Participants were maintained on a nutritionally balanced, hypocaloric diet designed to produce an initial weight loss of 0.5 to 1.0 kg per week. The caloric distribution of the diet was 30% as fat (10% saturated, 10% monounsaturated, and 10% polyunsaturated; ≤ 70 g/d maximum), 50% as carbohydrate, and 20% as protein. Maximum intakes of cholesterol and calcium were 300 mg/d and 1300 mg/d, respectively. The caloric intake prescribed in this study was calculated to provide a reduction in estimated caloric requirements of approximately 40%. Caloric requirements were determined by sex and baseline body weight, using estimates of total energy requirements based on the World Health Organization's equations for basal metabolic rate²⁰ and corrected for activity. Assigned caloric intake ranged from 1400 kcal/d (body weight < 70 kg) to 1800 kcal/d (body weight > 100 kg) in boys and from 1200 to 1600 kcal/d in girls. The daily caloric intake was adjusted during the double-blind treatment period if the participant reached a BMI of 22 or if the participant was losing weight too rapidly (> 1 kg per week). At each study visit, the dietician spoke with the patient about compliance with diet. Participants in both treatment groups received a commercially available daily multivitamin supplement (Centrum Kids Extra Calcium; Wyeth Consumer Healthcare, Madison, NJ) throughout the active period of the study.

Behavioral Modification

All study centers had behavioral modification programs in place, but used a study-specific manual as a guideline.²¹ Programs generally involved record-

ing food intake and activity; limiting high-calorie and high-fat foods in the household; restricting food intake to the dining area at meal times; eating slowly; avoiding snacking; encouraging participants to understand their cues for overeating; and substituting new behaviors for overeating. Staff at the study centers were to support and reinforce behavioral modification techniques regularly.

Exercise Counseling

Guidelines were provided to encourage regular physical activity and reduce sedentary behavior. Strength, flexibility, and aerobic activities were included as part of the exercise plan wherever possible. A behavioral psychologist spoke with patients about compliance with the exercise program at each study visit.

Efficacy Parameters

The primary efficacy parameter was the change in BMI from baseline to study end (or study exit). Secondary efficacy parameters included change in body weight, levels of total, high-density lipoprotein, and low-density lipoprotein cholesterol, ratio of low-density lipoprotein to high-density lipoprotein cholesterol, triglyceride levels, systolic and diastolic blood pressure, waist and hip circumference, glucose and insulin responses to an oral glucose challenge, and changes in body composition.

Safety Parameters

At each visit, the participant was systematically questioned by the investigator on the presence of gastrointestinal tract adverse effects, using a specially designed dictionary of standard terms for defecation patterns for reproducibility and consistency of reporting. Nongastrointestinal tract adverse events were noted by investigators at each clinic visit following general questioning. Any adverse event was discussed at each subsequent visit until resolution. For adverse events extending beyond the end of the study, the participant was contacted 4 weeks af-

ter the last visit to assess the outcome. All adverse events were considered resolved at the time of the last contact with the participant. Other safety parameters that were directly measured included physical and sexual maturation, vitamin levels, sex hormone levels, gallbladder and renal structure, cardiac function, and bone mineral content.

Statistical Analysis

We planned to enroll at least 450 individuals to provide more than 80% power to detect a difference of 1 BMI unit, as-

suming a 30% dropout rate. Patients were randomized centrally according to a computer-generated randomization schedule prepared by the study's sponsor, with stratification by body weight (<80 kg or ≥80 kg) on day 1 and by weight loss during the lead-in period (<1 kg or ≥1 kg). The allocation process was triple-blind; the allotted treatment group was obtained through an automated telephone system.

The safety population consisted of all randomized participants who received at least 1 dose of study drug and had at least 1 follow-up assessment. Ef-

ficacy was assessed in a modified intent-to-treat population, comprising all randomized participants with a baseline assessment and at least 1 postbaseline efficacy measurement. Efficacy analyses were performed using the last observation carried forward method for those who dropped out.

Primary and secondary efficacy analyses were performed using mixed-model analysis of variance. For the primary efficacy parameter, the analysis of variance model included change from baseline as the response variable, with treatment,

Table 1. Demographic and Baseline Data

	Placebo			Orlistat		
	All (n = 181)	Completed (n = 117)	Discontinued (n = 64)	All (n = 352)	Completed (n = 232)	Discontinued (n = 120)
	No. (%) of Participants					
Female	129 (71)	86 (74)	43 (66)	228 (65)	161 (69)	67 (54)
Race						
White	141 (78)	93 (80)	48 (75)	264 (75)	178 (77)	86 (72)
Black	25 (14)	15 (13)	10 (16)	65 (19)	40 (17)	25 (21)
Other	15 (8)	9 (7)	6 (9)	23 (6)	14 (6)	9 (7)
	Mean (SD)					
Age, y	13.5 (1.2)	13.5 (1.2)	13.8 (1.4)	13.6 (1.3)	13.7 (1.4)	13.6 (1.3)
Anthropomorphic measurements						
Weight, kg	95.1 (14.2)	94.9 (15.3)	95.5 (12.0)	97.7 (15.0)	96.8 (15.1)	99.7 (14.6)
Height, cm	163.7 (7.7)	164.0 (8.2)	162.9 (6.9)	165.2 (8.4)	164.7 (8.7)	166.1 (7.9)
BMI	35.4 (4.1)	35.1 (4.0)	36.0 (4.2)	35.7 (4.2)	35.6 (4.1)	36.1 (4.2)
Waist circumference, cm	104.5 (10.6)	103.8 (11.1)	105.9 (9.6)	106.4 (11.2)	105.8 (10.9)	107.8 (11.7)
Blood pressure, mm Hg						
Diastolic	67 (10)	67 (9)	67 (10)	68 (10)	67 (10)	70 (9)
Systolic	114 (12)	115 (11)	113 (13)	114 (12)	114 (13)	113 (11)
Lipid levels, mg/dL						
Cholesterol						
Total	163 (33)	161 (34)	164 (32)	161 (32)	159 (31)	166 (33)
HDL	42 (8)	42 (8)	42 (9)	42 (10)	43 (9)	41 (11)
LDL	97 (27)	96 (28)	99 (26)	97 (28)*	95 (28)	99 (28)
Ratio of LDL to HDL	2.4 (0.8)	2.4 (0.8)	2.5 (0.9)	2.4 (0.9)*	2.3 (0.9)	2.5 (0.9)
Triglycerides	121 (72)	126 (77)	118 (64)	116 (55)	110 (48)	126 (67)
Change in glucose level, mg/dL						
At 0 min	92 (12)†	93 (10)	89 (17)	90 (11)‡	90 (11)	92 (8)
At 120 min	108 (20)†	108 (19)	106 (30)	109 (22)§	107 (22)	111 (24)
Insulin, µU/mL						
At 0 min	22 (33)	20 (22)	32 (70)	20 (20)	17 (14)	20 (13)
At 120 min	75 (64)#	70 (53)	96 (106)	82 (86)**	71 (74)	93 (81)

Abbreviations: BMI, body mass index, calculated as weight in kilograms divided by the square of height in meters; HDL, high-density lipoprotein; LDL, low-density lipoprotein. SI conversion factors: To convert total, high-density lipoprotein, and low-density lipoprotein cholesterol to mmol/L, multiply by 0.0259; triglycerides to mmol/L, multiply by 0.0113; glucose to mmol/L, multiply by 0.0555.

*For this analysis, n = 351.

†For this analysis, n = 171.

‡For this analysis, n = 339.

§For this analysis, n = 340.

||For this analysis, n = 166.

¶For this analysis, n = 326.

#For this analysis, n = 167.

**For this analysis, n = 329.

center, treatment by center interaction and baseline stratification as terms. Between-group treatment differences with 95% confidence intervals and *P* values were calculated based on least-squares means. Body weight and BMI were corrected for age and sex by *z* score (the difference between the value and the mean, divided by the SD) based on Centers for Disease Control and Prevention charts.²² In contrast, a simplified repeated-measures analysis of variance was used to analyze secondary quantitative efficacy variables. Change from baseline was analyzed using center, treatment, and treatment by center as covariates. *P* < .05 was considered significant. All analyses were performed using SPSS statistical software 12.0.2 for Windows (SPSS Inc, Chicago, Ill).

RESULTS

Participants

A total of 539 patients were randomized (357 to orlistat and 182 to placebo; Figure 1). Similar proportions of participants in each treatment group completed the study (65% for orlistat and 64% for placebo). The baseline characteristics of those who dropped out were similar to those participants who completed the study in each treatment group (TABLE 1). A total of 190 participants did not complete the study. Reasons for noncompletion were similar for the 2 groups (Figure 1). Mean study drug compliance rates, assessed by pill counts, were 73% for orlistat and 72% for placebo. Two hundred fifteen participants in the orlistat group and 107 in the placebo group underwent dual-energy x-ray absorptiometry.

Demographic and clinical characteristics of the safety population were similar for the orlistat and placebo groups (Table 1). Overall, 25.3% of participants at randomization had the metabolic syndrome using the Adult Treatment Panel III criteria.²³ Few participants had elevated blood pressure (<3%); the proportions of participants with elevated levels of low-density lipoprotein cholesterol or triglycerides, impaired glucose toler-

Table 2. Proportion of Participants With Risk Factors at Baseline

Parameter	No. (%) of Participants	
	Placebo (n = 181)	Orlistat (n = 352)
Blood pressure		
Diastolic ≥ 90 mm Hg	1 (1)	3 (1)
Systolic ≥ 140 mm Hg	5 (3)	10 (3)
Cholesterol		
HDL < 35 mg/dL	38 (21)	66 (19)
LDL ≥ 130 mg/dL	22 (12)	42 (12)
Ratio of LDL to HDL ≥ 3.5	23 (13)	44 (13)
Triglycerides ≥ 225 mg/dL	13 (7)	14 (4)
Waist circumference		
Male ≥ 102 cm	37 (20)	97 (28)
Female ≥ 84 cm	128 (71)	228 (65)
Insulin ≥ 90 μ U/mL	121 (67)	252 (72)
At 0 min		
Normal level: < 110 mg/dL	158 (87)	315 (89)
Impaired level: ≥ 110 mg/dL or < 126 mg/dL	12 (7)	12 (3)
Diabetic level: ≥ 126 mg/dL	1 (1)	1 (<1)
At 120 min		
Normal level: < 141 mg/dL	159 (88)	315 (89)
Impaired level: ≥ 141 mg/dL or < 200 mg/dL	12 (7)	23 (7)
Diabetic level: ≥ 200 mg/dL	0	2 (1)

Abbreviations: HDL, high-density lipoprotein; LDL, low-density lipoprotein. Conversion factor: To convert insulin to pmol/L, multiply by 6.945.

ance, or type 2 diabetes were also low (TABLE 2). Most participants had an elevated waist circumference or high fasting insulin levels (Table 2).

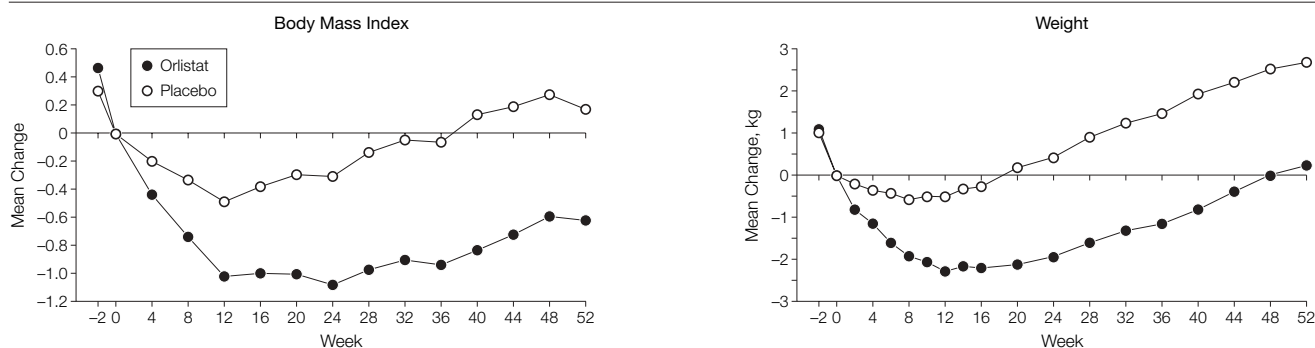
Primary Efficacy Result

During the first 12 weeks after randomization, both groups experienced a mean decrease in BMI. Subsequently, the BMI tended to stabilize in the orlistat group, but increased to beyond baseline in the placebo group (FIGURE 2). By the end of the study, the least-squares mean BMI of participants treated with orlistat had decreased from baseline by 0.55 and increased by 0.31 in the placebo group (*P* = .001; TABLE 3). There was no significant center by treatment interaction (*P* = .81), indicating that the treatment effect across centers was similar. Compared with 15.7% of the placebo group, 26.5% of orlistat-treated participants had a 5% or higher decrease in BMI and 4.5% of the placebo group and 13.3% of the orlistat group had a 10% or higher decrease in BMI (Table 3).

Secondary Efficacy Results

Compared with baseline, both groups lost weight during the first 4 weeks of the study, although participants receiving orlistat lost more weight (Figure 2). Starting at week 4, participants treated with orlistat continued to lose weight steadily to a maximum weight loss at week 12. In contrast, placebo-treated participants' weight was stable during weeks 4 through 12. Subsequently, both groups regained weight, but the effect attributable to the drug (ie, the between-group difference in body weight) after 6 months was sustained.

No significant differences were found between the 2 groups with respect to changes in lipid or glucose levels. By the end of the study, 2-hour insulin levels for orlistat recipients were lower than at baseline, but the decrease was not significantly different from that in the placebo group (TABLE 4). In contrast, participants treated with orlistat experienced significantly greater decreases from baseline to end point in both waist circumference and hip circumference than participants receiving placebo

Figure 2. Change in Mean Body Mass Index and Weight

$P = .001$ for body mass index (orlistat vs placebo). $P < .001$ for weight change (orlistat vs placebo). Body Mass Index is calculated as weight in kilograms divided by the square of height in meters. Coefficient of variation is about 14% for each data point for body mass index and about 16% for weight.

Table 3. Changes in Weight, Height, Waist Circumference, and BMI at the End of Treatment

	Placebo (n = 181)	Orlistat (n = 352)	P Value
Change in parameter vs baseline in LSM			
Body weight, kg	+3.14	+0.53	<.001
Height, cm	+1.91	+1.82	.74
Waist circumference, cm	+0.12	-1.33	<.05
BMI	+0.31	-0.55	.001
No. (%) of Participants			
Categorical loss in BMI, %			
≥5	29 (15.7)	93 (26.5)	.005
≥10	8 (4.5)	46 (13.3)	.002
Categorical weight loss, %			
≥5	21 (11.7)	67 (19.0)	.03
≥10	6 (3.3)	34 (9.5)	.01

Abbreviations: BMI, body mass index, which is calculated as weight in kilograms divided by the square of height in meters; LSM, least squares mean.

Table 4. Secondary Efficacy End Points

	Placebo		Orlistat		P Value
	LSM Change vs Baseline	No. of Participants (n = 181)	LSM Change vs Baseline	No. of Participants (n = 352)	
Circumference, cm					
Waist	-0.89	178	-2.67	347	.01
Hip	-0.10	178	-1.52	347	.01
Blood pressure, mm Hg					
Diastolic	+1.30	180	-0.51	347	.04
Systolic	+1.31	180	+1.09	347	.84
Cholesterol, mg/dL					
Total	+3.39	163	+2.26	323	.59
HDL	-0.31	163	+0.07	323	.62
LDL	+0.88	162	-0.99	322	.29
Ratio of LDL to HDL	+0.04	162	-0.07	322	.08
Triglycerides, mg/dL	+11.68	163	+17.90	323	.30
Insulin, μ U/mL					
At 0 min	-5.4	132	-2.8	271	.41
At 120 min	-20.6	133	-25.7	276	.44
Glucose, mg/dL					
Fasting at 0 min	-5.24	136	-2.40	282	.06
At 120 min	-10.11	136	-11.20	283	.68

Abbreviations: HDL, high-density lipoprotein; LDL, low-density lipoprotein; LSM, least squares mean.

(Table 4). From baseline to study end, diastolic blood pressure decreased in participants treated with orlistat and increased in placebo recipients ($P = .04$; Table 4). There was no statistically significant change in systolic blood pressure in either treatment group.

Safety Results

In total, 97% of participants in the orlistat group and 94% in the placebo group reported at least 1 adverse event during the 1-year study. Twelve orlistat and 3 placebo participants discontinued treatment because of adverse events (Figure 1); the timing of participant withdrawals in the 2 groups was similar. The baseline characteristics of the participants who dropped out were similar to those of the participants who completed the study in each group (Table 1). The most common adverse events were gastrointestinal tract-related; these were more common in the orlistat group (TABLE 5). The majority of participants reporting gastrointestinal tract adverse events reported 1 event. Gastrointestinal tract adverse events were mostly mild to moderate in intensity and led to discontinuation in 2% of the orlistat group. The decrease in BMI was not affected by gastrointestinal tract adverse events in the orlistat group.

Overall, 3% of participants in each group had at least 1 serious adverse event. The 5 serious adverse events in the placebo group were acute demy-

Table 5. Participants With Gastrointestinal Tract Adverse Events

Gastrointestinal Tract Adverse Event	No. (%) of Participants Taking Placebo (n = 181)			No. (%) of Participants Taking Orlistat (n = 352)		
	Total With Adverse Event	1 Adverse Event	>1 Adverse Event	Total With Adverse Event	1 Adverse Event	>1 Adverse Event
Fatty/oily stool	15 (8.3)	10 (5.5)	5 (2.8)	177 (50.3)	122 (34.7)	55 (15.6)
Oily spotting	7 (3.9)	5 (2.8)	2 (1.1)	102 (29.0)	72 (20.5)	30 (8.5)
Oily evacuation	3 (1.7)	1 (0.6)	2 (1.1)	82 (23.3)	51 (14.5)	31 (8.8)
Abdominal pain	20 (11.0)	14 (7.7)	6 (3.3)	77 (21.9)	54 (15.3)	23 (6.5)
Fecal urgency	20 (11.0)	11 (6.1)	9 (5.0)	73 (20.7)	48 (13.6)	25 (7.1)
Flatus with discharge	5 (2.8)	4 (2.2)	1 (0.6)	70 (19.9)	48 (13.6)	22 (6.3)
Soft stool	19 (10.5)	17 (9.4)	2 (1.1)	53 (15.1)	47 (13.4)	6 (1.7)
Nausea	23 (12.7)	20 (11.0)	3 (1.7)	52 (14.8)	48 (13.6)	4 (1.1)
Increased defecation	16 (8.8)	16 (8.8)	0	48 (13.6)	42 (11.9)	6 (1.7)
Flatulence	8 (4.4)	4 (2.2)	4 (2.2)	32 (9.1)	29 (8.2)	3 (0.8)
Fecal incontinence	1 (0.6)	1 (0.6)	0	31 (8.8)	24 (6.8)	7 (2.0)

elinating encephalomyelitis, facial palsy, pneumonia, worsening of asthma, and pain in the right side (TABLE 6). The 11 serious adverse events in the orlistat group were pilonidal abscess, depression (n=2), asthma attack, seizure, admission for repair of deviated nasal septum, appendicitis, cholelithiasis, gallbladder disorder followed by cholecystectomy, adenoidal hypertrophy, and aseptic meningitis. Only the symptomatic cholelithiasis that led to cholecystectomy in a 15-year-old girl treated with orlistat was considered possibly related to study medication by the investigators; the patient had lost 15.8 kg by the time of the adverse event. Ultrasound revealed multiple tiny gallbladder calculi but no gallbladder thickening, pericholecystic fluid, or dilated biliary tree. No patient developed acute cholecystitis during the study. One placebo and 10 orlistat recipients developed abnormalities during the study that were detected on electrocardiograms. None of these were believed to be related to the medication based on review by an independent cardiologist. Pulse (76/min) and QT segment length (410 ms) were similar in both groups and were not affected by the intervention.

In general, levels of vitamins A, D, E and beta carotene were within the normal range and increased in both groups during treatment (TABLE 7). The levels of estradiol among girls de-

creased from baseline in the orlistat group compared with a slight increase in the placebo group (-7.5 pg/mL vs $+0.7$ pg/mL; $P=.05$) at study end. There was no significant difference in height gain between groups (Table 3). Participants in both groups experienced normal sexual maturation, as shown by changes in Tanner stage over the 52 weeks of the study (TABLE 8).

In the orlistat group, 14 participants had a baseline abnormality revealed by gallbladder ultrasound, including 8 participants with fatty liver infiltration or hepatomegaly and 3 participants with gallstones. Of these, 2 patients still had gallstones at the end of the study; the third patient did not have a follow-up examination. At the end of the study, 6 participants in the orlistat group were found to have asymptomatic gallstones not seen at baseline; 5 of these patients had lost large amounts of weight (8.2-29.4 kg) and 2 were siblings. Another patient had multiple gallstones on ultrasound at day 167 after a 15.8-kg weight loss and had a subsequent cholecystectomy.

In the placebo group, 8 participants had a baseline abnormality, including 4 who had a fatty liver, 1 who had previously had a cholecystectomy, and 2 with gallstones that were still evident at the final visit. At the end of the study, 1 participant in the placebo group was found to have gallstones not seen at baseline. Ultra-

Table 6. Participants With Nongastrointestinal Tract Adverse Events

Nongastrointestinal Tract Adverse Event	No. (%) of Participants	
	Placebo (n = 181)	Orlistat (n = 352)
Headache	56 (30.9)	134 (38.1)
Upper respiratory tract infection	48 (26.5)	114 (32.4)
Nasopharyngitis	46 (25.4)	99 (28.1)
Sore throat	29 (16.0)	59 (16.8)
Sinusitis	19 (10.5)	40 (11.4)
Joint sprain	17 (9.4)	35 (9.9)
Nasal congestion	11 (6.1)	31 (8.8)
Back pain	11 (6.1)	28 (8.0)
Gastroenteritis	8 (4.4)	23 (6.5)
Seasonal rhinitis	9 (5.0)	21 (6.0)
Limb injury	5 (2.8)	18 (5.1)

sound also identified 2 additional new renal abnormalities in the orlistat group (mild left hydronephrosis and 6-mm echogenic focus without evidence of renal calculus).

In the subgroup of participants undergoing dual-energy x-ray absorptiometry evaluation, bone mineral content (+182 g in the orlistat group and +177 g in the placebo group) and bone mineral density ($+0.04$ g/cm² in both groups) increased similarly in the 2 treatment groups independently of sex. Participants in the orlistat group (+2312 g) gained a similar amount of fat-free body mass as those in the placebo group (+2116 g). However, participants in the orlistat group lost significantly more fat mass than those in the placebo group (-2401 g in the or-

Table 7. Vitamin Levels Before and After Treatment for 1 Year

	Placebo (n = 150)	Orlistat (n = 307)	Difference	P Value
Beta carotene, µg/dL				
Mean level at baseline	8.8	7.8	-2.4	
LSM change	3.0	0.6		<.001
Vitamin A, µg/dL				
Mean level at baseline	48.5	49.5	1.51	
LSM change	1.8	3.3		.13
25-Hydroxyvitamin D, ng/mL*				
Mean level at baseline	18.1	17.7	-0.39	
LSM change	1.8	1.4		.57
Vitamin E, µg/dL				
Mean level at baseline	810	797	-40	
LSM change	52	12		.09

Abbreviation: LSM, least squares mean.

*For this analysis, n = 313 for orlistat.

Table 8. Tanner Stage at Baseline and End of Treatment

Tanner Stage	No. (%) of Participants			
	Placebo (n = 144)		Orlistat (n = 305)	
	Baseline	End of Treatment	Baseline	End of Treatment
1	2 (1.4)	1 (0.7)	9 (3.0)	3 (1.0)
2	26 (18.1)	8 (5.6)	37 (12.1)	11 (3.6)
3	26 (18.1)	17 (11.8)	60 (19.7)	33 (10.8)
4	39 (27.1)	37 (25.7)	80 (26.2)	82 (26.9)
5	51 (35.4)	81 (56.3)	119 (39.0)	176 (57.7)

listat group vs -380 g in the placebo group; $P = .03$).

COMMENT

This study evaluates the use of orlistat, a lipase inhibitor, in the treatment of obese adolescents. In conjunction with a reduced-calorie diet, exercise, and behavioral modification, treatment with 120 mg of orlistat 3 times daily for 52 weeks statistically significantly decreased BMI, waist circumference, and body fat compared with placebo. This effect is probably due to the decrease in the absorption of fat and its associated calories.²⁴ Gastrointestinal tract adverse effects were observed more frequently with orlistat. In these 352 adolescents studied over a 1-year period, no major safety issues were raised.

Orlistat has been shown to cause meaningful and sustained weight loss in overweight or obese adults when given at a dose of 120 mg 3 times daily and combined with a mildly reduced-calorie diet for up to 4

years.^{17-19,25} Because of the nonsystemic mechanism of action of orlistat, it was considered a logical choice for study in the obese pediatric population. In the current study, the same dosage of orlistat was associated with a statistically significant decrease in BMI over the course of 1 year in contrast to a BMI increase in the placebo group. This result must be interpreted considering the characteristics of an adolescent rather than an adult population. Because adolescents' bodies are growing and acquiring muscle, bone, and skin, accurately quantifying the effects of weight management therapy in adolescents requires the use of age- and sex-corrected growth curves and BMI values.²² Second, adolescents represent a notoriously difficult-to-treat population. In the absence of intervention, overweight and obese adolescents can continue to gain weight rapidly well into adulthood. For instance, while only 10% of 10- to 15-year-old children and adolescents with a BMI

below the 85th percentile will become obese adults, the vast majority (83%) of those with a BMI greater than the 95th percentile will become obese adults.²⁶ Finally, the prevalence of metabolic syndrome among obese children and adolescents has been shown to increase faster with more rapid weight gain, and the onset of cardiovascular complications may also be more rapid when type 2 diabetes develops in adolescence rather than in adulthood.⁵ In obese adolescents, slower weight gain has been associated with delayed development of complications such as type 2 diabetes over a 2-year period,²⁷ suggesting that a therapeutic approach that contributes to decreased weight gain is important.

Body mass index decreased with orlistat but increased with placebo. The relationship between the changes in BMI and body composition is explained through the dual-energy x-ray absorptiometry results obtained from a subset of our study population. The increase in fat-free mass and bone mineral content was similar in both groups, reflecting normal growth. In contrast, change in fat mass was markedly different between groups. In the subset with dual-energy x-ray absorptiometry measurements, the placebo group experienced an increase in body weight (+1.68 kg) with a decrease of 0.6 kg in fat mass while the orlistat group experienced a decrease in body weight (-0.35 kg) and a decrease of 2.53 kg in fat mass. Thus, the difference in absolute weight experienced by participants receiving orlistat was mostly due to a loss in fat mass, suggesting a favorable change in body composition.

Orlistat treatment resulted in decreases in weight of 2.61 kg and in BMI of 0.86. Although the latter is lower than the power goal of the study, it is within the 95% confidence interval of the difference (0.37-1.34). This improvement in BMI was similar to that observed after 1 year in 5 major placebo-controlled studies in adults (between-group BMI

difference of -0.74 to -1.32 in favor of orlistat [data on file]). Compared with 15.7% of the placebo group, 26.5% of the orlistat group had a 5% or higher decrease in BMI; and 4.5% and 13.3%, respectively had a 10% or higher decrease in BMI. These values are similar to those reported in studies of obese adults without severe comorbidities in which orlistat-treated participants were up to 2.0 times more likely to experience a 5% or higher decrease in weight than placebo recipients and up to 2.5 times more likely to experience a 10% or higher decrease in weight than placebo recipients.²⁸

We attempted to clarify the baseline characteristics of those patients achieving these decreases. While the study was not powered to address this question, these descriptive data may enhance the design of future studies attempting to predict which participants will benefit most from pharmacotherapy. Within the orlistat group, 35% of participants were male, as were 32% of participants achieving a less than 5% decrease in BMI; males accounted for 41% of the participants achieving a 5% or higher decrease in BMI and 44% of those achieving a 10% or higher decrease in BMI. Blacks represented 19% of patients assigned to orlistat at baseline and 21% of those in the orlistat group who had a less than 5% decrease in BMI; blacks accounted for 18% of those achieving a 5% or higher decrease in BMI and 7% of those achieving a 10% or higher decrease in BMI. Thus, from this study, orlistat appears to have similar efficacy in males and females and there is no evidence of any influence of ethnic origin. Baseline age and BMI were not predictive of a greater decrease in BMI over the duration of the study. In contrast, a weight loss of greater than 5% after 12 weeks of orlistat treatment was associated with a decrease of 7.6 kg or a decrease in BMI of 3.7.

Secondary efficacy parameters, including lipid and glucose levels and diastolic and systolic blood pressure, were mostly normal at baseline. This contrasts with an earlier, pilot study of weight loss with orlistat in 20 adolescent participants, in which obesity was extremely severe (mean BMI, 44), and

obesity-related metabolic risk factors (hypertension, sleep apnea, abnormalities in lipid levels, and glycemic control) were more frequent.²⁹ As such, orlistat generally demonstrated minimal effects on these metabolic risk factors, although it did significantly reduce waist circumference and diastolic blood pressure compared with placebo.

In this 1-year trial, orlistat did not raise any safety issues, and the adverse event profiles—except for gastrointestinal tract adverse events—were similar between the orlistat and placebo groups. However, the efficacy and tolerability of orlistat for more than 1 year of treatment has only been confirmed in adults.^{17-19,30-32} Additional longer-term studies in a larger number of adolescents will be needed to confirm the safety of orlistat in this population. Gastrointestinal tract adverse events were reported by a higher proportion of orlistat-treated participants than placebo recipients, although the majority of the participants did experience a specific adverse event only once; these adverse events were generally mild to moderate in intensity and may relate to the mechanism of action of orlistat.^{33,34} However, they did not affect outcome as shown by similar BMI decreases in orlistat-treated participants with or without gastrointestinal tract adverse events. Gastrointestinal tract adverse events also occurred in a small percentage of placebo recipients, which has been previously reported in adult studies. This is consistent with the specific questioning for named gastrointestinal tract adverse events and also the known occurrence of gastrointestinal tract adverse events in obese patients not receiving any pharmacotherapy.³⁵

There were no clinically relevant differences in any of the laboratory tests between the 2 groups. Fat-soluble vitamins A, D, E, and beta-carotene increased in both groups at the end of the study as expected with daily multivitamin supplementation.

Levels of the sex hormones, estradiol, free testosterone, and sex hormone-binding globulin were also assessed. The only notable difference

between treatment groups was the greater decrease in estradiol levels in girls treated with orlistat rather than placebo. This is consistent with the known effect of weight loss on estradiol levels in adolescent girls.³⁶ In our study, girls treated with orlistat had greater decreases in BMI and lost more weight than those receiving placebo.

It is well established that there is an increased incidence of gallstones in obese adults and adolescents.³⁷ In adults, gallstones are more frequent in females than males and this is mirrored in adolescents.³⁸ In adults, both excess weight and rapid weight loss are associated with gallstone development. In our study, placebo recipients, who generally did not have significant weight reductions from baseline, did not develop gallstones. In contrast, a greater proportion of orlistat-treated participants achieved significantly greater weight loss from baseline and would therefore be at higher risk of developing gallstones. At study end, 6 of the orlistat-treated participants, all girls aged 13 to 15 years with a mean weight loss of 17.6 kg, had asymptomatic cholelithiasis identified on ultrasound. Five of these participants developed gallstones during the study and 1 additional participant already had a cholecystectomy prior to study entry. However, the absence of gallstone formation in orlistat-treated participants who had BMI decreases without large weight reductions suggests that gallstone development was related to weight loss and not to the intrinsic effect of orlistat. Indeed, previous studies have shown no increase in the lithogenic index of bile and no evidence of microcrystal formation in the gallbladder with orlistat treatment.³³ There were no cases of acute cholecystitis, although 1 patient who lost approximately 15 kg and was taking oral contraceptives had symptomatic cholelithiasis and a subsequent cholecystectomy.

Certain limitations of this study should be considered. First, diet, exercise, and behavioral modification were not standardized. However, the ab-

sence of a significant center by treatment interaction suggests that the treatment effect across centers was similar. Second, the study was performed in a predominantly white population and as is common in such studies,³⁹ most participants were female. The average participant was at the 98th percentile for BMI, a significant degree of obesity, so it is not known if less obese adolescents would achieve similar results. The present study excluded participants with certain characteristics more likely to be associated with metabolic syndrome, although one quarter of the participants did have the metabolic syndrome at randomization. How these characteristics affect the generalizability of our results is not clear. However, recent results in obese adults attending community weight clinics⁴⁰ or in general practice⁴¹ were similar to those from double-blind, randomized trials.^{17,18} Third, the number of participants and the study duration do not allow adequate assessment of safety beyond 1 year. Fourth, quality of life was not investigated in this study, making an objective assessment of tolerability difficult. It should be noted that, although similar between groups, the dropout rate was 35% to 36%. This rate is well within that usually seen in obesity trials, particularly those of more than 1-year duration, in which dropout rates range from 10% to 80%. Trials of obesity therapies face the added problem of patients stopping treatment when weight loss plateaus in addition to the common issue of patient perseverance seen in most long-term trials. It would be useful in the future to study other adolescent populations for longer periods.

Study withdrawals were handled by the last observation carried forward method, which assumes that individual data at the time of drop out are representative of data at the end of the study if the participant had completed it. Therefore, the results of the study may be affected if participants with lower success drop out more often, or if the characteristics or timing of drop out differs between the 2 groups. How-

ever, we have verified that this was not the case: the timing of drop out was similar in the 2 groups ($P = .90$; Mann-Whitney test), and similar primary efficacy results were obtained for completers (BMI difference between the orlistat and placebo groups at 12 months: 0.70, 95% confidence interval, 0.19-1.21; $P = .007$). In addition, baseline characteristics among participants who dropped out were similar to those of completers within each study group (Table 1), and the timing of withdrawals was similar between the 2 groups. Taken together, these analyses show that last observation carried forward analysis did not affect the interpretation of our results.

We conclude that treatment with 120 mg of orlistat 3 times daily for 52 weeks, in conjunction with a reduced-calorie diet, exercise, and behavioral modification, statistically significantly improves weight management in obese adolescent participants. Body composition analysis showed that orlistat did not affect the normal increase in lean body mass physiologically observed in adolescents. In contrast, the weight difference between the placebo and orlistat groups was due to a difference in fat mass. In these 352 adolescents studied over a 1-year period, orlistat did not raise major safety issues and the adverse event profiles revealed that gastrointestinal tract adverse events were more common in the orlistat group.

Author Contributions: Dr Chanoine had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Boldrin, Hauptman.

Acquisition of data: Chanoine, Hampl, Jensen, Boldrin.

Analysis and interpretation of data: Chanoine, Hampl, Jensen, Boldrin, Hauptman.

Drafting of the manuscript: Boldrin, Hauptman.

Critical revision of the manuscript for important intellectual content: Chanoine, Hampl, Jensen, Hauptman.

Statistical analysis: Boldrin.

Administrative, technical, or material support: Jensen, Hauptman.

Study supervision: Chanoine, Jensen, Hauptman.

Financial Disclosures: Dr Chanoine has received honoraria from Hoffmann-La Roche for speakers presentations. No other authors reported financial disclosures.

Funding/Support: This study was funded by F. Hoffmann-La Roche Ltd.

Independent Statistical Review: All study data were transferred from Hoffman-La Roche to the Depart-

ment of Statistics at the British Columbia Children's Hospital for independent reanalysis. Statistical reanalyses of the raw data were performed by Ruth Milner and Victor M. Espinosa, MSc. There were only minor discrepancies between the reanalysis and the original interpretation of the results and conclusions. When there was a discrepancy Dr Chanoine included the results from the reanalyses performed at the British Columbia Children's Hospital.

Role of the Sponsor: Hoffmann-La Roche was involved in the study design and conduct and in the analysis and interpretation of the data. All data were independently reanalyzed by an academic statistician. The sponsor was permitted to review the manuscript, but the final decision on content was with the corresponding author in conjunction with the other authors.

Participating Investigators: J. Anderson (University of Kentucky, Lexington); T. Bravender (Duke Children's Primary Care, Durham, NC); L. Cheskin (John Hopkins Bayview Medical Center, Baltimore, Md); E. Cummings (IWK Grace Health Centre for Children, Women and Families, Halifax, Nova Scotia); W. Dahms (University Hospitals of Cleveland, Cleveland, Ohio); H. Dean (Children's Hospital, Winnipeg, Manitoba); M. A. Dreihobl (Scripps Clinic, San Diego, Calif); K. Ellis (Memorial Family Practice Center, Savannah, Ga); F. Franklin (Children's Hospital, Birmingham, Ala); K. Fujioaka (Scripps Clinic, San Diego, Calif); K. Hasan (Phoenix Children's Hospital, Phoenix, Ariz); R. Heptulla (Bay State Medical Center, Springfield, Mass); T. Higgins (Boulder Medical Center, Boulder, Colo); A. G. Hudnut (Sutter Medical Group Family Practice, Elk Grove, Calif); C. Huot (Hospital St Justine, Montreal, Quebec); M. S. Jacobson (Schneider Children's Hospital, New Hyde Park, NY); G. Kletter (Children's Hospital and Regional Medical Center, Seattle, Wash); L. Legault (Montreal Children's Hospital, Montreal, Quebec); P. O'Neill (Medical University of South Carolina, Charleston); D. Pacaud (Alberta Children's Hospital, Calgary); T. Poling (Heartland Research Associates, Wichita, Kan); R. Portman (University of Texas—Houston Health Science Center, Houston); J. Sanchez (Riley Hospital for Children, Indianapolis, Ind); L. Schnell (Aurora, Ill); D. Smith (CSRA Partners in Health, Augusta, Ga); J. Spitzer (Kalamazoo, Mich); R. S. Strauss (UMDMU-Robert Wood Johnson Medical School, New Brunswick, NJ); S. Travers (Denver, Colo); I. Vargas (New York, NY).

Acknowledgment: We are grateful to Victor M. Espinosa, MSc, for his statistical expertise and assistance.

REFERENCES

1. Rosner B, Prineas R, Loggie J, Daniels SR. Percentile for body mass index in US children 5 to 17 years of age. *J Pediatr*. 1998;132:211-222.
2. Barlow SE, Dietz WH; Maternal and Child Health Resources and Services Administration and Department of Health and Human Services. Obesity evaluation and treatment: expert committee recommendations. *Pediatrics*. 1998;102:E29.
3. Ogden CL, Flegal KM, Carroll MD, Johnson CL. Prevalence and trends in overweight among US children and adolescents, 1999-2000. *JAMA*. 2002;288:1728-1732.
4. Lobstein T, Baur L, Uauy R; IASO International Obesity TaskForce. Obesity in children and young people: a crisis in public health. *Obes Rev*. 2004;5(suppl 1):4-85.
5. Goran MI, Ball GD, Cruz ML. Obesity and risk of type 2 diabetes and cardiovascular disease in children and adolescents. *J Clin Endocrinol Metab*. 2003;88:1417-1427.
6. Schwimmer JB, Burwinkle TM, Varni JW. Health-related quality of life of severely obese children and adolescents. *JAMA*. 2003;289:1813-1819.
7. Williams J, Wake M, Hesketh K, Maher E, Waters

- E. Health-related quality of life of overweight and obese children. *JAMA*. 2005;293:70-76.
8. Must A, Jacques PF, Dallal GE, Bajema CJ, Dietz WH. Long-term morbidity and mortality of overweight adolescents: a follow-up of the Harvard Growth Study of 1922 to 1935. *N Engl J Med*. 1992;327:1350-1355.
9. Must A. Morbidity and mortality associated with elevated body weight in children and adolescents. *Am J Clin Nutr*. 1996;63(suppl 3):S445-S447.
10. Thomas-Doberson DA, Butler-Simon N, Flesher M. Evaluation of a weight management intervention program in adolescents with insulin-dependent diabetes mellitus. *J Am Diet Assoc*. 1993;93:535-540.
11. Epstein LH, Valoski A, Wing RR, McCurley J. Ten-year follow-up of behavioral, family-based treatment for obese children. *JAMA*. 1990;264:2519-2523.
12. Epstein LH, Valoski A, Wing RR, McCurley J. Ten-year outcomes of behavioral family-based treatment for childhood obesity. *Health Psychol*. 1994;13:373-383.
13. Sumerbell CD, Ashton V, Campbell KJ, Edmunds L, Kelly S, Waters E. Interventions for treating obesity in children. *Cochrane Database Syst Rev*. 2003;CD001872.
14. Epstein LH, Roemmich JN, Raynor HA. Behavioral therapy in the treatment of pediatric obesity. *Pediatr Clin North Am*. 2001;48:981-993.
15. Berkowitz RI, Wadden TA, Tershakovec AM, Cronquist JL. Behavior therapy and sibutramine for the treatment of adolescent obesity: a randomized controlled trial. *JAMA*. 2003;289:1805-1812.
16. McCann UD, Seiden LS, Rubin LJ, Ricaurte GA. Brain serotonin neurotoxicity and primary pulmonary hypertension from fenfluramine and dexfenfluramine: a systematic review of the evidence. *JAMA*. 1997;278:666-672.
17. Sjöström L, Rissanen A, Andersen T, et al; European Multicenter Orlistat Study Group. Randomised placebo-controlled trial of orlistat for weight loss and prevention of weight regain in obese subjects. *Lancet*. 1998;352:167-172.
18. Davidson MH, Hauptman J, DiGirolamo M, et al. Weight control and risk factor reduction in obese subjects treated for 2 years with orlistat: a randomized controlled trial. *JAMA*. 1999;281:235-242.
19. Torgerson J, Hauptman J, Boldrin MN, Sjöström L. Xenical in the Prevention of Diabetes in Obese Subjects (XENDOS) study: a randomized study of orlistat as an adjunct to lifestyle changes for the prevention of type 2 diabetes in obese patients. *Diabetes Care*. 2004;27:155-161.
20. World Health Organization. Energy and protein requirements. In: Report of a Joint FAO/WHO/UNU Expert Consultation. Geneva, Switzerland: World Health Organization; 1985.
21. Wadden TA, Berkowitz RI. Weight reduction and pride program: special medication issue July 2000. University of Pennsylvania: Philadelphia; 2000.
22. Growth charts. Centers for Disease Control. Available at: <http://www.cdc.gov/growthcharts>. Accessed February 10, 2005.
23. Goodman E, Daniels SR, Morrison JA, Huang B, Dolan L. Contrasting prevalence of demographic disparities in the World Health Organization and National Cholesterol Education Program Adult Treatment Panel III definitions of metabolic syndrome among adolescents. *J Pediatr*. 2004;145:445-451.
24. Zhi J, Mulligan TE, Hauptman JB. Long-term systemic exposure of orlistat, a lipase inhibitor, and its metabolites in obese patients. *J Clin Pharmacol*. 1999;39:41-46.
25. Krempf M, Louvet JP, Allanic H, Miloradovich T, Joubert JM, Attali JR. Weight reduction and long-term maintenance after 18 months treatment with orlistat for obesity. *Int J Obes Relat Metab Disord*. 2003;27:591-597.
26. Whitaker RC, Wright JA, Pepe MS, Seidel KD, Dietz WH. Predicting obesity in young adulthood from childhood and parental obesity. *N Engl J Med*. 1997;337:869-873.
27. Weiss R, Dziura J, Burgert TS, et al. Obesity and the metabolic syndrome in children and adolescents. *N Engl J Med*. 2004;350:2362-2374.
28. Curran MP, Scott LJ. Orlistat: a review of its use in the management of patients with obesity. *Drugs*. 2004;64:2845-2864.
29. McDuffie JR, Calis KA, Uwaifo GI, et al. Three-month tolerability of orlistat in adolescents with obesity-related comorbid conditions. *Obes Res*. 2002;10:642-650.
30. Hollander PA, Elbein SC, Hirsch IB, et al. Role of orlistat in the treatment of obese subjects with type 2 diabetes: a 1-year randomized double-blind study. *Diabetes Care*. 1998;21:1288-1294.
31. Muls E, Kolanowski J, Scheen A, Van Gaal L. Obel-Hyx Study Group. The effects of orlistat on weight and on serum lipids in obese subjects with hypercholesterolemia: a randomized, double-blind, placebo-controlled, multicenter study. *Int J Obes Relat Metab Disord*. 2001;25:1713-1721.
32. Broom I, Wilding J, Stott P, Myers N; UK Multimorbidity Study Group. Randomised trial of the effect of orlistat on body weight and cardiovascular disease risk profile in obese patients: UK Multimorbidity Study. *Int J Clin Pract*. 2002;56:494-499.
33. Guercioli R. Mode of action of orlistat. *Int J Obes Relat Metab Disord*. 1997;21(suppl 3):S12-S23.
34. Zhi J, Melia AT, Eggers H, Joly R, Patel IH. Review of limited systemic absorption of orlistat, a lipase inhibitor, in healthy human volunteers. *J Clin Pharmacol*. 1995;35:1103-1108.
35. Talley NJ, Howell S, Poulton R. Obesity and chronic gastrointestinal tract symptoms in young adults: a birth cohort study. *Am J Gastroenterol*. 2004;99:1807-1814.
36. Wabitsch M, Hauner H, Heinze E, et al. Body fat distribution and steroid hormone concentrations in obese adolescent girls before and after weight reduction. *J Clin Endocrinol Metab*. 1995;80:3469-3475.
37. Waldhausen JHT, Benjamin DR. Cholecystectomy is becoming an increasingly common operation in children. *Am J Surg*. 1999;177:364-367.
38. Wesdorp I, Bosman D, de Graaff A, Aronson D, van der Blij F, Taminiau J. Clinical presentations and predisposing factors of cholelithiasis and sludge in children. *J Pediatr Gastroenterol Nutr*. 2000;31:411-417.
39. Jeffrey RW, McGuire MT, Brelje KL, et al. Recruitment to mail and telephone interventions for obesity in a managed care environment: the Weight-To-Be Project. *Am J Manag Care*. 2004;10:378-382.
40. Porter JA, Raebel MA, Conner DA, et al. The Long-term Outcomes of Sibutramine Effectiveness on Weight (LOSE Weight) study: evaluating the role of drug therapy within a weight management program in a group-model health maintenance organization. *Am J Manag Care*. 2004;10:369-376.
41. Wirth A. Reduction of body weight and comorbidities by orlistat: the XXL Primary Health Care Trial. *Diabetes Obes Metab*. 2005;7:21-27.

Table. Comparison of the Inhibitory Activities of 3 Antimalarial Drugs and the Drugs Predicted to Have the Highest Binding Affinity*

Drug	Targeted Protein	Calculated K_i (Rank)	Experimental Inhibitory Activity		Drug Predicted to Have Highest Affinity	
			Activity, mol/L	Source	Drug	Calculated K_i
Pyrimethamine	Dihydrofolate reductase	2.80×10^{-8} (102)	$K_i = 2.00 \times 10^{-10}$	Yuvaniyama et al ⁷	Nitro bt	7.16×10^{-12}
WR99210	Dihydrofolate reductase	1.10×10^{-8} (48)	$K_i = 1.10 \times 10^{-11}$	Yuvaniyama et al ⁷	Nitro bt	7.16×10^{-12}
EH58	Plasmeprin II	1.58×10^{-9} (7)	$K_i = 1.00 \times 10^{-7}$	Asojo et al ⁸	Remiszewski_013	1.01×10^{-10}

Abbreviation: K_i , inhibitory constant.*The calculated K_i values for these known drugs correlate with the experimentally determined inhibitory activities and usually rank within the top 5th percentile compared with the entire set of drugs.

drug binding affinity in terms of the inhibitory constant (K_i) was calculated every time the drug molecule was moved. After repeating this procedure for all of the drugs for each protein, the 20 drugs with the lowest K_i values were considered high-affinity drug candidates. Further details of the molecular dynamics simulation and docking protocols are available elsewhere.⁵

Results. We predicted 20 multitarget drugs that showed high affinity across 2 or more proteins (FIGURE). Four are drugs approved by the US Food and Drug Administration for treatment of diseases other than malaria: KN62 (targeting 3 proteins), protoporphyrin IX, phthalylsulfathiazole, and sulfaphenazole (targeting 2 proteins each). The other 16 are experimental, each targeting up to 6 proteins. The best drugs in terms of multitarget functionality were STI-571 (targeting 6 proteins), bisindolylmaleimide x, GW8510, and Piper (targeting 5 proteins each). The best combination of 2 drugs was bisindolylmaleimide x and GW8510, which together target 10 *Plasmodium* proteins. An analysis of 3 known single-target antimalarial drugs against these proteins showed that our calculated K_i s for these drugs compared well with experimentally determined values (when available) and that the inhibitory activity usually ranked within the top 5th percentile compared with our entire set of drugs (TABLE).

Conclusions. Promising vaccines targeting multiple *Plasmodium* proteins have been evaluated.^{9,10} In a similar fashion, we propose designing new antimalarial drugs that simultaneously target multiple *Plasmodium* proteins. Our computational drug screening protocol provides evidence for 20 approved or experimental drugs that bind strongly to 13 *Plasmodium* proteins. We recommend that these drug candidates be experimentally tested for inhibition of *Plasmodium* growth and used as a starting point for further design of a high-efficacy multitarget antimalarial drug.

Ekachai Jenwitheesuk, DVM, PhD
 Ram Samudrala, PhD
 ram@compbio.washington.edu
 Department of Microbiology
 University of Washington School of Medicine
 Seattle

Author Contributions: Dr Jenwitheesuk had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design; analysis and interpretation of data: Jenwitheesuk, Samudrala.

Drafting of the manuscript: Jenwitheesuk.

Critical revision of the manuscript for important intellectual content; obtained funding; study supervision: Samudrala.

Financial Disclosures: None reported.

Funding/Support: This work was supported in part by a NSF CAREER award, NSF grant DBI 0217241, NIH grant GM068152, a Searle Scholar Award, and the Puget Sound Partners in Global Health.

Role of the Sponsor: The grant sponsors had no role in the design and conduct of the study; the collection, analysis, and interpretation of the data; or the preparation, review, or approval of the manuscript.

1. Baird JK. Effectiveness of antimalarial drugs. *N Engl J Med*. 2005;352:1565-1577.
 2. Fungladda W, Honrado ER, Thimasarn K, et al. Compliance with artesunate and quinine + tetracycline treatment of uncomplicated falciparum malaria in Thailand. *Bull World Health Organ*. 1998;76(suppl 1):59-66.

3. Cserehely P, Agoston V, Pongor S. The efficiency of multi-target drugs: the network approach might help drug design. *Trends Pharmacol Sci*. 2005;26:178-182.

4. Ravi Chandra B, Gowthaman R, Raj Akhouri R, Gupta D, Sharma A. Distribution of proline-rich (PxxP) motifs in distinct proteomes: functional and therapeutic implications for malaria and tuberculosis. *Protein Eng Des Sel*. 2004;17:175-182.

5. Jenwitheesuk E, Samudrala R. Prediction of HIV-1 protease inhibitor resistance using a protein-inhibitor flexible docking approach. *Antivir Ther*. 2005;10:157-166.
 6. ChemBank. Ligand Information Subset. Available at: http://ligand.info/ligand_info_subset_1.sdf.zip. Accessed May 1, 2005.

7. Yuvaniyama J, Chitnumsub P, Kamchonwongpaisan S, et al. Insights into antifolate resistance from malarial DHFR-TS structures. *Nat Struct Biol*. 2003;10:357-365.

8. Asojo OA, Gulnik SV, Afonina E, et al. Novel uncomplexed and complexed structures of plasmeprin II, an aspartic protease from *Plasmodium falciparum*. *J Mol Biol*. 2003;327:173-181.

9. Nussenzweig RS, Long CA. Malaria vaccines: multiple targets. *Science*. 1994;265:1381-1383.

10. Heppner DG Jr, Kester K, Ockenhouse CF, et al. Towards an RTS,S-based, multi-stage, multi-antigen vaccine against falciparum malaria: progress at the Walter Reed Army Institute of Research. *Vaccine*. 2005;23:2243-2250.

CORRECTIONS

Omitted Author: In the Letter to the Editor entitled "BRCA Mutations and Ductal Carcinoma In Situ" published in the August 3, 2005, issue of *JAMA* (2005;294:553-554), there was an author omitted from the author affiliations. On page 553, after "Kathleen Klein Oros, BSc" and before "Department of Human Genetics," it should have read "Patricia N. Tonin, PhD."

Numbers Transposed: In the Original Contribution entitled "Effect of Orlistat on Weight and Body Composition in Obese Adolescents: A Randomized Controlled Trial" published in the June 15, 2005, issue of *JAMA* (2005;293:2873-2883), 2 numbers were transposed. On page 2879, the second to the last sentence in column 3 should be "Participants in the orlistat group (+2116 g) gained a similar amount of fat-free body mass as those in the placebo group (+2312 g)." Also, on page 2873, the author affiliation for Dr Jensen should be "Department of Pediatrics, Baylor College of Medicine, Houston, Tex."