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 overweight 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, has increased 15.5% to 23.4% in certain ethnic minorities. 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.

Excess weight in adolescents is associated with an increased risk of disorders such as hyperlipidemia and type 2 diabetes and can result in decreased emotional and physical quality of life. In addition, childhood obesity results in increased risk of morbidity and mortality in adulthood. 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. Effective weight management in children and adolescents may therefore have important immediate and future societal health benefits.

Treatment of obesity in the pediatric age group, and in particular during adolescence, is notoriously difficult. While behavioral therapy has had some success in treating obesity in young children (aged 6-12 years), most stud-
Figure 1. Study Design of Trial

<table>
<thead>
<tr>
<th>Adolescents Assessed for Eligibility</th>
<th>588</th>
</tr>
</thead>
<tbody>
<tr>
<td>Excluded</td>
<td>49</td>
</tr>
<tr>
<td>Did Not Meet Inclusion Criteria</td>
<td></td>
</tr>
<tr>
<td>After Lead-in</td>
<td></td>
</tr>
<tr>
<td>Other Reasons</td>
<td>7</td>
</tr>
<tr>
<td>Randomized</td>
<td>539</td>
</tr>
<tr>
<td>Assigned to Receive Placebo</td>
<td>182</td>
</tr>
<tr>
<td>Discontinued Treatment</td>
<td>65</td>
</tr>
<tr>
<td>Adverse Event</td>
<td></td>
</tr>
<tr>
<td>Insufficient Response</td>
<td>1</td>
</tr>
<tr>
<td>Refused Treatment for Personal Reasons</td>
<td>31</td>
</tr>
<tr>
<td>Protocol Violation</td>
<td>4</td>
</tr>
<tr>
<td>Other</td>
<td>2</td>
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<tr>
<td>Completed Study</td>
<td>117</td>
</tr>
<tr>
<td>Assigned to Receive Orlistat</td>
<td>357</td>
</tr>
<tr>
<td>Discontinued Treatment</td>
<td>125</td>
</tr>
<tr>
<td>Adverse Event</td>
<td></td>
</tr>
<tr>
<td>Insufficient Response</td>
<td>12</td>
</tr>
<tr>
<td>Refused Treatment for Personal Reasons</td>
<td>69</td>
</tr>
<tr>
<td>Protocol Violation</td>
<td>3</td>
</tr>
<tr>
<td>Other</td>
<td>6</td>
</tr>
<tr>
<td>Completed Study</td>
<td>232</td>
</tr>
<tr>
<td>Included in Primary Efficacy Analysis</td>
<td>348</td>
</tr>
<tr>
<td>Excluded (No Follow-up Efficacy Assessment)</td>
<td>2</td>
</tr>
<tr>
<td>Included in Safety Analysis</td>
<td>181</td>
</tr>
<tr>
<td>Excluded (Study Medication Never Taken)</td>
<td>1</td>
</tr>
<tr>
<td>Excluded</td>
<td></td>
</tr>
<tr>
<td>勘察 After Lead-in</td>
<td></td>
</tr>
<tr>
<td>Other Reasons</td>
<td>6</td>
</tr>
<tr>
<td>Completed Study</td>
<td>232</td>
</tr>
</tbody>
</table>

EFFECT OF ORLISTAT ON WEIGHT AMONG ADOLESCENTS

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. 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 patients 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 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 sex (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 dextroamphetamine 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 2:1 ratio to receive 120 mg of orlistat or placebo 3 times daily (Figure 1). Placebo and orlistat capsules looked identical and, ex-

Downloaded from www.jama.com at Medical Library of the PLA, on August 22, 2007
cect for the active ingredient, had ex-
actly the same composition. General
guidelines for diet, exercise, and be-

data of Helsinki, and the laws
and regulations of the countries in
which the research was conducted,\nwherever afforded greater protection
to the individual. The study was ap-
proved by the institutional review board
at each participating center. Written in-
formed consent was received from the
parents or guardians and written as-
sent was received from each patient.

**Diet**

Participants were maintained on a nu-
tritionally balanced, hypocaloric diet de-
gined to produce an initial weight loss
of 0.5 to 1.0 kg per week. The caloric dis-
tribution of the diet was 30% as fat (10%
saturated, 10% monounsaturated, and
10% polyunsaturated; ≤70 g/d maxi-
mum), 50% as carbohydrate, and 20%
as protein. Maximum intakes of choles-
terol and calcium were 300 mg/d and
1300 mg/d, respectively. The caloric in-
take prescribed in this study was calcu-
lated to provide a reduction in estimated
caloric requirements of approximately
40%. Caloric requirements were deter-
mined by sex and baseline body weight,
using estimates of total energy require-
ments based on the World Health Or-
ganization’s equations for basal metabolic
rate 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 par-
ticipant reached a BMI of 22 or if the par-
ticipant 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
either treatment groups received a com-
mercially available daily multivitamin
supplement (Centrum Kids Extra Cal-
cium; Wyeth Consumer Healthcare,
Madison, NJ) throughout the active pe-
riod of the study.

**Behavioral Modification**

All study centers had behavioral modi-
fication programs in place, but used a
study-specific manual as a guideline.\n
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 par-
ticipants to understand their cues for
overeating; and substituting new be-
aviors for overeating. Staff at the study
centers were to support and reinforce
behavioral modification techniques
regularly.

**Exercise Counseling**

Guidelines were provided to encour-
age regular physical activity and re-

duce sedentary behavior. Strength, flex-
bility, and aerobic activities were

**Safety Parameters**

At each visit, the participant was sys-
tematically questioned by the investi-
gator on the presence of gastrointestinal
tract adverse effects, using a specially
designed dictionary of standard
terms for defecation patterns for
reproducibility and consistency of re-
porting. Nongastrointestinal tract ad-
verse events were noted by investiga-
tors at each clinic visit following general
questioning. Any adverse event was dis-
cussed at each subsequent visit until
resolution. For adverse events extend-
ing beyond the end of the study, the
participant was contacted 4 weeks af-

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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, assuming 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. Efficacy 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, gender, and weight loss during the lead-in period as factors.

### Table 1. Demographic and Baseline Data

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Orlistat</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All</td>
<td>Completed</td>
</tr>
<tr>
<td></td>
<td>(n = 181)</td>
<td>(n = 117)</td>
</tr>
<tr>
<td>No. (%) of Participants</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>129 (71)</td>
<td>86 (74)</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>141 (78)</td>
<td>93 (80)</td>
</tr>
<tr>
<td>Black</td>
<td>25 (14)</td>
<td>15 (13)</td>
</tr>
<tr>
<td>Other</td>
<td>15 (8)</td>
<td>9 (7)</td>
</tr>
<tr>
<td>Age, y</td>
<td>13.5 (1.2)</td>
<td>13.5 (1.2)</td>
</tr>
<tr>
<td>Anthropomorphic measurements</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight, kg</td>
<td>95.1 (14.2)</td>
<td>94.9 (15.3)</td>
</tr>
<tr>
<td>Height, cm</td>
<td>163.7 (7.7)</td>
<td>164.0 (8.2)</td>
</tr>
<tr>
<td>BMI</td>
<td>35.4 (4.1)</td>
<td>35.1 (4.0)</td>
</tr>
<tr>
<td>Waist circumference, cm</td>
<td>104.5 (10.6)</td>
<td>103.8 (11.1)</td>
</tr>
<tr>
<td>Blood pressure, mm Hg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diastolic</td>
<td>67 (10)</td>
<td>67 (9)</td>
</tr>
<tr>
<td>Systolic</td>
<td>114 (12)</td>
<td>115 (11)</td>
</tr>
<tr>
<td>Lipid levels, mg/dL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cholesterol</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>163 (33)</td>
<td>161 (34)</td>
</tr>
<tr>
<td>HDL</td>
<td>42 (8)</td>
<td>42 (8)</td>
</tr>
<tr>
<td>LDL</td>
<td>97 (27)</td>
<td>96 (28)</td>
</tr>
<tr>
<td>Ratio of LDL to HDL</td>
<td>2.4 (0.8)</td>
<td>2.4 (0.8)</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>121 (72)</td>
<td>126 (77)</td>
</tr>
<tr>
<td>Change in glucose level, mg/dL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>At 0 min</td>
<td>92 (12)†</td>
<td>93 (10)</td>
</tr>
<tr>
<td>At 120 min</td>
<td>108 (20)†</td>
<td>108 (19)</td>
</tr>
<tr>
<td>Insulin, µIU/mL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>At 0 min</td>
<td>22 (33)</td>
<td>20 (22)</td>
</tr>
<tr>
<td>At 120 min</td>
<td>75 (64)</td>
<td>70 (53)</td>
</tr>
</tbody>
</table>

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 = 361.
†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. 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 tolerance, 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.
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 4). The decrease in BMI was not affected by gastrointestinal tract–related 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 demyelination.
EFFECT OF ORLISTAT ON WEIGHT AMONG ADOLESCENTS

Table 5. Participants With Gastrointestinal Tract Adverse Events

<table>
<thead>
<tr>
<th>Gastrointestinal Tract Adverse Event</th>
<th>Total With Adverse Event</th>
<th>1 Adverse Event</th>
<th>&gt;1 Adverse Event</th>
<th>Total With Adverse Event</th>
<th>1 Adverse Event</th>
<th>&gt;1 Adverse Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatty/oily stool</td>
<td>15 (8.3)</td>
<td>10 (5.5)</td>
<td>5 (2.8)</td>
<td>177 (50.3)</td>
<td>122 (34.7)</td>
<td>55 (15.6)</td>
</tr>
<tr>
<td>Oily spotting</td>
<td>7 (9.9)</td>
<td>5 (2.8)</td>
<td>2 (1.1)</td>
<td>102 (25.9)</td>
<td>72 (20.5)</td>
<td>30 (8.5)</td>
</tr>
<tr>
<td>Oily evacuation</td>
<td>3 (1.7)</td>
<td>1 (0.6)</td>
<td>2 (1.1)</td>
<td>82 (23.3)</td>
<td>51 (14.5)</td>
<td>31 (8.8)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>20 (11.0)</td>
<td>14 (7.7)</td>
<td>6 (3.3)</td>
<td>77 (21.9)</td>
<td>54 (15.5)</td>
<td>23 (6.5)</td>
</tr>
<tr>
<td>Fecal urgency</td>
<td>20 (11.0)</td>
<td>11 (6.1)</td>
<td>9 (5.0)</td>
<td>73 (20.7)</td>
<td>48 (13.6)</td>
<td>25 (7.1)</td>
</tr>
<tr>
<td>Flatus with discharge</td>
<td>5 (2.8)</td>
<td>4 (2.2)</td>
<td>1 (0.6)</td>
<td>70 (19.9)</td>
<td>48 (13.6)</td>
<td>22 (6.3)</td>
</tr>
<tr>
<td>Soft stool</td>
<td>19 (10.5)</td>
<td>17 (9.4)</td>
<td>2 (1.1)</td>
<td>53 (15.1)</td>
<td>47 (13.4)</td>
<td>6 (1.7)</td>
</tr>
<tr>
<td>Nausea</td>
<td>23 (12.7)</td>
<td>20 (11.0)</td>
<td>3 (1.7)</td>
<td>52 (14.8)</td>
<td>48 (13.6)</td>
<td>4 (1.1)</td>
</tr>
<tr>
<td>Increased defecation</td>
<td>16 (8.8)</td>
<td>16 (8.8)</td>
<td>0</td>
<td>48 (13.6)</td>
<td>42 (11.9)</td>
<td>6 (1.7)</td>
</tr>
<tr>
<td>Flatulence</td>
<td>8 (4.4)</td>
<td>4 (2.2)</td>
<td>4 (2.2)</td>
<td>32 (9.1)</td>
<td>29 (8.2)</td>
<td>3 (0.8)</td>
</tr>
<tr>
<td>Fecal incontinence</td>
<td>1 (0.6)</td>
<td>1 (0.6)</td>
<td>0</td>
<td>31 (8.8)</td>
<td>24 (6.8)</td>
<td>7 (2.0)</td>
</tr>
</tbody>
</table>

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 decreased 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. Ultrasound 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 6. Participants With Nongastrointestinal Tract Adverse Events

<table>
<thead>
<tr>
<th>Nongastrointestinal Tract Adverse Event</th>
<th>Placebo (n = 181)</th>
<th>Orlistat (n = 352)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>56 (30.9)</td>
<td>134 (38.1)</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>48 (26.5)</td>
<td>114 (32.4)</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>46 (25.4)</td>
<td>99 (28.1)</td>
</tr>
<tr>
<td>Sore throat</td>
<td>29 (16.0)</td>
<td>59 (16.8)</td>
</tr>
<tr>
<td>Sinusitis</td>
<td>19 (10.5)</td>
<td>40 (11.4)</td>
</tr>
<tr>
<td>Joint sprain</td>
<td>17 (9.4)</td>
<td>35 (9.9)</td>
</tr>
<tr>
<td>Nasal congestion</td>
<td>11 (6.1)</td>
<td>31 (8.8)</td>
</tr>
<tr>
<td>Back pain</td>
<td>11 (6.1)</td>
<td>28 (8.0)</td>
</tr>
<tr>
<td>Gastroenteritis</td>
<td>8 (4.4)</td>
<td>22 (6.5)</td>
</tr>
<tr>
<td>Seasonal rhinitis</td>
<td>9 (5.0)</td>
<td>21 (6.0)</td>
</tr>
<tr>
<td>Limb injury</td>
<td>5 (2.8)</td>
<td>18 (5.1)</td>
</tr>
</tbody>
</table>
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. 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. 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. 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. 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. In obese adolescents, slower weight gain has been associated with delayed development of complications such as type 2 diabetes over a 2-year period, 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 participants 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, 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 clinics or in general practice were similar to those from double-blind, randomized trials. 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. However, we have verified that this was not the case: the timing of drop out was similar in the 2 groups (P = 0.90; 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, Hamp, Jensen, Boldrin. Analysis and interpretation of data: Chanoine, Hamp, Jensen, Boldrin, Hauptman. Drafting of the manuscript: Boldrin, Hauptman. Critical revision of the manuscript for important intellectual content: Chanoine, Hamp, 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.

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Independent Statistical Review: All study data were transferred from Hoffmann-La Roche to the Department 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 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. Cumnings (IWK 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. Ca. Drehobl (Scripps Clinic, San Diego, Calif); K. Ellis (Memorial Family Practice Center, Savannah, Ga); F. Franklin (Children’s Hospital, Birmingham, Ala); K. Fujioka (Scripps Clinic, San Diego, Calif); K. Hasan (Phoenix Children’s Hospital, Phoenix, Ariz); R. Hino (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. Paca (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 (Kalamaizoo, Mich); R. S. Strauss (UMDM-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.

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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.

### 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-16 (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. 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 multtarget antimalarial drug.

### 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.  

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### Role of the Sponsor

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### Abbreviations

- DHFR-TS: dihydrofolate reductase–thymidylate synthase
- DHFR: dihydrofolate reductase
- malarial DHFR-TS: *P. falciparum* DHFR-TS
- DHFR-TS: *T. cruzi* DHFR-TS
- DHFR: *T. cruzi* DHFR
- DHFR: *T. brucei* DHFR
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