## 2.0 Synopsis

<table>
<thead>
<tr>
<th>Name of Company:</th>
<th>Abbott Laboratories</th>
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<tbody>
<tr>
<td>Name of Study Drug:</td>
<td>Meridia®</td>
</tr>
<tr>
<td>Name of Active Ingredient:</td>
<td>Sibutramine hydrochloride monohydrate</td>
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<tr>
<td>Title of Study:</td>
<td>A 12-Month Study to Assess the Safety and Efficacy of Meridia® (sibutramine hydrochloride monohydrate) 10 and 15 mg in Obese Adolescents</td>
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<td>Investigators:</td>
<td>Multicenter; the coordinating Investigator was 33 investigator sites enrolled subjects.</td>
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<td>Study Sites:</td>
<td>Multicenter (United States)</td>
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<tr>
<td>Study Period (Years):</td>
<td>Initiation Date: 19 July 2000 Completion Date: 18 February 2002</td>
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<tr>
<td>Publications:</td>
<td>None</td>
</tr>
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<td>Phase of Development:</td>
<td>3</td>
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### Objectives:

The objectives of this study were:

1. To assess the efficacy and safety of Meridia® (sibutramine hydrochloride monohydrate) 10 and 15 mg in 400 obese adolescents (300 sibutramine, 100 placebo) ages 12-16 years with a BMI lower limit of inclusion 2 units above the U.S. weighted mean for the 95th percentile based on age and gender, to a BMI upper limit of 44 kg/m².

2. To assess the steady state pharmacokinetics of sibutramine and its active metabolites in 12 to 16 year old obese adolescents.

### Methodology:

This was a double-blind, randomized, placebo-controlled, multicenter, parallel arm, 12-month, dose titration study to evaluate the safety and efficacy of sibutramine 10 and 15 mg daily when given to obese adolescents. The study consisted of a screening period and a 52-week double-blind treatment period. Four hundred subjects were to be randomized to either sibutramine or placebo in 3:1 fashion. All subjects received instruction in lifestyle modification to include healthy eating behavior, exercise, and bodyweight control.
Methodology (continued):
All subjects randomized remained on 10 mg of study drug for the first 6 months. At 6 months, all subjects who had not lost > 10% of their initial BMI were to be up-titrated to 15 mg of study drug for the duration of the study. Subjects were to be seen weekly for the first 2 weeks, then every 2 weeks for the next 10 weeks, and then monthly (except for an additional visit at Month 6.5) thereafter until study completion.

Efficacy measurements included the change from Baseline in BMI, bodyweight, waist circumference, body composition via dual x-ray absorptiometry (DXA), and fasting lipid and glycemic variables.

Steady-state pharmacokinetics included measurement of plasma trough concentrations of sibutramine and its active metabolites M1 and M2 for qualitative comparison to adult reference studies.

Safety measurements included adverse events, laboratory variables, vital signs and ambulatory blood pressure monitoring (ABPM) data, electrocardiography (ECG) parameters, echocardiography, focused cardiovascular and general physical examination, growth (assessed as height) and sexual maturation (assessed by Tanner staging)

Behavior, cognitive function (i.e., learning, memory, and psychometrics) and Quality-of-Life measurements were assessed using the following tools: Child Depression Inventory (CDI), Piers-Harris Children's Self-Concept Scale, Eating Inventory, Child Behavior CheckList (CBCL), Impact of Weight on Quality-of-Life Questionnaire (IWQOL) and IWQOL-Lite both modified for adolescents and the Pediatric Quality-of-Life Inventory (Peds QL™). The IWQOL-Lite is another way of scoring the IWQOL. It utilizes three domains: physical function, self-esteem and public distress.

Number of Subjects (Planned and Analyzed):
The planned sample size was 400 obese adolescents. Randomized: 498 (368 sibutramine, 130 placebo). Full Analysis Set: 490 (363 sibutramine, 127 placebo).

Diagnosis and Main Criteria for Inclusion:
Obese adolescents ages 12-16 years, with BMI lower limit of inclusion 2 units above the United States weighted mean for the 95th percentile based on age and gender, to an upper limit for BMI of 44 kg/m². Efforts were to be made to obtain a study population comprising 50-75% females and at least 30% African-Americans across the study.

Test Product, Dose/Strength/Concentration, Mode of Administration and Lot Number:
Sibutramine HCl 10 mg capsule administered once daily orally, batch number W011087 and W011088; Sibutramine HCl 15 mg capsule administered once daily orally, batch number W013643.

Duration of Treatment:
12 months

Reference Therapy, Dose and Mode of Administration, Lot Number:
Placebo capsule administered once daily orally, batch number 216-K150-P5-0399.
Criteria for Evaluation:

Efficacy:
The primary outcome measure for efficacy assessment was the absolute change in BMI from Baseline to Endpoint. The secondary efficacy variables for this study were the percent change from Baseline in BMI; BMI outcome score at Endpoint, the proportions of subjects achieving ≥ 5% and ≥ 10% BMI reduction from Baseline, the proportions of subjects achieving ≥ 5% and ≥ 10% reduction in bodyweight, the absolute and percent change from Baseline in bodyweight; the absolute change from Baseline in waist circumference, the absolute change from Baseline in body composition variables as measured by DXA, and the absolute and percent change from Baseline in fasting lipid variables (triglycerides, HDL cholesterol, LDL cholesterol and total cholesterol) and fasting glycemic variables (glucose, insulin, HOMA).

An outcome score was assessed for percent change in BMI using the following categories: ≥ 20% decrease of Baseline BMI; ≥ 15% to < 20% decrease; ≥ 10% to < 15% decrease; ≥ 5% to < 10% decrease; > 0% to < 5% decrease; no change; or increase. Two further categories, for subjects who withdrew from the study, were defined such that subjects who withdrew for lack of efficacy or adverse event, and subjects who died, were assigned to the worst category, and all other withdrawals were assigned to the second worst category.

Pharmacokinetics:
Trough plasma concentrations of sibutramine and its main metabolites in an adolescent population were qualitatively compared to those in adults from previous studies.

Safety:
The following safety parameters were summarized and analyzed for significance between treatment differences as appropriate: adverse events, routine laboratory parameters, vital signs and ABPM data, ECG parameters, echocardiography, focused cardiovascular and general physical examination, growth (assessed as height), sexual maturation (assessed by Tanner staging) and current and concurrent medications.

Behavior, cognitive function (i.e., learning, memory, and psychometrics) and Quality-of-Life were to be assessed by using the following validated, written instruments: CDI, Piers-Harris Children's Self-Concept Scale, Eating Inventory, CBCL, IWQOL and IWQOL-Lite both modified for adolescents and the Peds QL™. These tools were to be self-administered by the subjects except for the CBCL, which was to be completed by the guardian/parent at the time of the office visit.

Statistical Methods:

Efficacy:
The primary measure of efficacy was the absolute change from Baseline to Endpoint in BMI for the full analysis set. The null hypothesis of no difference between sibutramine and placebo was tested using an ANCOVA model with factors for treatment group, center, age and gender, and with Baseline BMI as a covariate. The adjusted means and standard errors derived from the main effects model for each treatment group, as well as an estimate and 95% confidence interval for the difference between treatments, were reported. A separate test for the treatment group-by-center interaction was performed and significance determined by reference to the 10% level. If the interaction was statistically significant, further investigation was to be carried out to assess the impact of the interaction on the estimate of treatment effect.
Statistical Methods (continued):

The ANOVA model specified in the protocol, for the absolute change from Baseline to Endpoint in BMI with factors for treatment group and center, was also presented for information and to assess the robustness of the primary efficacy analysis using ANCOVA. Any differences in interpretation of the results between the 2 methods were to be investigated. If warranted by differences observed, this method may have been used to repeat each of the appropriate secondary analyses described below.

The ANCOVA model with factors for treatment group, center, age and gender and with the Baseline value of the variable being analyzed as a covariate was also formed to test for differences between sibutramine and placebo for:

- Percent change from Baseline to Endpoint in BMI;
- Absolute and percent change from Baseline to Endpoint in bodyweight;
- Absolute change from Baseline to Endpoint in waist circumference;
- Absolute change to Month 6/Endpoint in DXA body composition variables;
- Absolute and percent change from Baseline to Endpoint in serum lipids; and
- Absolute and percent change from Baseline to Endpoint in glycemic parameters.

Each of these analyses performed on the change from Baseline to Endpoint for the full analysis set was repeated for the change from Baseline to Month 12 for the completers set.

ANOVA models with factors for treatment group and gender were performed for the absolute change from Baseline to Endpoint for the full analysis set for each efficacy variable, and for the percentage change for BMI and bodyweight.

An analysis of outcome was performed on percent change in BMI using the following categories: 

- ≥ 20% decrease of Baseline BMI; 
- ≥ 15% to < 20% decrease; 
- ≥ 10% to < 15% decrease; 
- ≥ 5% to < 10% decrease; 
- > 0% to < 5% decrease; 
- no change; 
- increase in BMI; 
- withdrew for non-treatment related reasons; and 
- withdrew for treatment-related reasons. Additionally, the proportions of subjects who achieved ≥ 5% and ≥ 10% reduction in BMI from Baseline (5% and 10% BMI responders, respectively), and ≥ 5% and ≥ 10% reduction in bodyweight from Baseline (5% and 10% bodyweight responders, respectively) were summarized.

Subgroup presentations, shift tables for lipid and glycemic variables and additional presentations by final dose received were provided.

Pharmacokinetics:

Pre-dose (trough) plasma concentrations of sibutramine, and its active metabolites (M1 and M2) collected from a subset of subjects at Months 8, 9 and 10 were summarized descriptively by month, as well as by subject and dose. This descriptive summary included means, medians, standard deviations, coefficients of variation, range, and 95% confidence intervals for the central values (for M1 and M2 only).

Trough samples of M1 and M2 were analyzed using a linear mixed effect model. The model included fixed effects for dose, month, gender, race, Tanner stage of male/female puberty, and a random effect for subject. Body mass index and age were included in the model as covariates. The adolescent concentration data were also compared to the data collected from a trial in obese adults, Study BPI852, using a mixed effect model.
Statistical Methods (continued):

Safety:

Treatment-emergent adverse events, defined as those reported to have started on or after the day of first dose of study medication, were tabulated in the main report. All serious adverse events reported as started prior to the day of first dose were also summarized; all non-serious pre-study events were listed in an appendix to the study report only.

Adverse events were analyzed by presenting frequency and percentage of subjects with adverse events. For specific adverse event COSTART V preferred terms, each preferred term was counted only once per subject, and if different categories (e.g., for severity or relationship to trial drug) occurred, the worst one was taken. Fisher's Exact Test was used to test for differences in incidence of reporting each preferred term between treatment groups.

Summary tables were prepared for adverse events which presented the number and percentage of subjects (for the safety analysis set) by treatment group with the following types of treatment-emergent adverse events:

- Summary of any adverse event, any adverse event leading to death, any serious adverse event, any adverse event resulting in withdrawal, any adverse event resulting in a dose reduction or interruption, any severe adverse event, and any adverse event with possible, probable or definite relation to study drug;
- Adverse events by preferred term. In addition, subject identifiers were given to each preferred term;
- Common adverse events, defined as those with a relative frequency of at least 5% in at least one of the treatment groups;
- Adverse events by severity; and
- Adverse events by relationship to trial drug.

For each of the hematology and serum chemistry variables (except for glycemic and lipid variables), the treatment groups were compared for the change from Baseline to Endpoint for all subjects, using a one-way ANOVA model. Both mean and median changes were presented.

Shift tables detailing changes in normality/abnormality status from Baseline to Endpoint, according to the Very High/Very Low criteria (modified FDA guidelines), were generated for each laboratory variable (including glycemic and lipid variables).

For all subjects with at least one potentially clinically significant value for a laboratory variable, defined according to the Very High/Very Low criteria (modified FDA guidelines), all values recorded for that laboratory variable for that subject during the study were listed.

Vital signs were described by summary statistics (n, mean, standard deviation, minimum, median, maximum) by visit, and for the changes from Baseline to each time point for the full analysis set, the observed analysis set, and study completers. Changes to the minimum and maximum values recorded for each subject were also summarized.

The change from Baseline to Endpoint for the full analysis set, and to Month 12 for the completers set, in vital sign variables was analyzed using ANCOVA with a factor for treatment group, and the Baseline value included as a covariate. Adjusted means for the treatment groups were presented, with 95% confidence intervals for the difference. These analyses were repeated for subjects achieving < 5%, at least 5%, and also at least 10% reduction in BMI at Endpoint.
### Statistical Methods (continued):

#### Safety (continued):

For all subjects in the safety set with at least one potentially clinically significant value for a vital signs variable, defined according to the Very High/Very Low criteria (modified FDA guidelines), all values recorded for that vital signs variable for that subject during the study were listed.

Subjects in the safety set identified as "outliers" with respect to their vital sign data, as defined in the study protocol, were summarized categorically and analyzed using logistic regression.

Additional presentations for vital signs data described the whole study population, and identified "outliers" in detail.

Summary statistics for the change from Baseline to Month 7/Endpoint were provided for each ABPM variable. Plots illustrated mean SBP and DBP by 3-hour intervals at Baseline and Endpoint by treatment group. Rank ANCOVA models were used to analyze one change from Baseline to Endpoint in each behavior, cognitive function and Quality-of-Life Variable.

Summary statistics and analyses of the change from Baseline to Endpoint in ECG heart rate, and ECG PR, QRS, QT and QTc intervals, were presented and performed similarly to the vital sign variables for the safety set.

For all subjects with at least one potentially clinically significant value for an ECG variable, defined according to the Very High/Very Low criteria (modified FDA guidelines), all values recorded for that ECG variable for that subject during the study were listed.

For the subset of subjects for whom echocardiography was performed, the number and frequency of subjects with aortic insufficiency (AI), mitral regurgitation (MR), AI and/or MR, left-sided valvular heart disease, pulmonary insufficiency (PI), tricuspid regurgitation (TR), PI and/or TR was presented at Baseline and at Month 12 or premature termination. For the subjects without each condition listed above at Baseline, logistic regression with factors for treatment group, center, age and gender, was used to compare the new occurrence at Month 12 or premature termination of each condition separately between treatment groups. The odds ratio of a new recording of each condition in the sibutramine treatment group compared to the placebo treatment group was presented with the associated 90% confidence interval.

### Summary/Conclusions:

#### Efficacy Results:

A total of 72% of the enrolled subjects completed the study. The proportion of subjects who completed the study was greater in the sibutramine treatment group (76%) compared to the placebo treatment group (62%).

The primary efficacy variable for this study was the mean absolute change in BMI from Baseline to Endpoint. In the full analysis set, the difference between the sibutramine and placebo groups in mean absolute change in BMI from Baseline to Endpoint (-2.6 kg/m²) was statistically significant (p < 0.001).

Greater reductions in mean absolute BMI were observed in the sibutramine treatment group compared to the placebo treatment group at all study visits after Baseline. Greater reductions from Baseline to Endpoint in mean absolute BMI were observed in the sibutramine treatment group regardless of gender, age, race, (Caucasian versus non-Caucasian) and maturation.
Summary/Conclusions (continued):

Efficacy Results (continued):

When data from the full analysis set were summarized by final dose received, mean change in absolute BMI from Baseline to Endpoint were greater in subjects whose final dose was sibutramine 10 mg (-3.9 kg/m²) compared to subjects whose final dose was sibutramine 15 mg (-1.8 kg/m²), or placebo (-0.3 kg/m²). Exploratory analysis using the current adult recommendations for the adolescent data demonstrated that approximately 68.4% of adolescent subjects who lost at least 4 pounds during the first 4 weeks of sibutramine therapy lost ≥ 5% (placebo-subtracted) of their initial BMI at Endpoint, and that approximately 68.2% of adolescent subjects who did not lose at least 4 lbs. during the first 4 weeks of sibutramine therapy did not lose ≥ 5% (placebo-subtracted) of their initial BMI at Endpoint.

Sibutramine treatment compared to placebo was associated with significant improvements in the secondary efficacy variables that were measured. Placebo-subtracted improvements from Baseline to Endpoint were observed in percent BMI (-7.4%; p < 0.001), absolute (-7.0 kg; p < 0.001) and percent (-8.3%; p < 0.001) bodyweight, and waist circumference (-5.0 cm; p < 0.001). In the full analysis set, the proportion of subjects achieving ≥ 5% BMI reduction from Baseline to Endpoint was 62.3% and 18.1%, in the sibutramine and placebo groups, respectively. The proportions of subjects achieving ≥ 10% BMI reduction from Baseline to Endpoint were 38.8% and 5.5%, in the sibutramine and placebo groups, respectively. The odds ratio for achieving ≥ 5% and ≥ 10% BMI reductions with sibutramine treatment compared to placebo were 10.1 and 14.2, respectively (p < 0.001 for both ratios).

Body composition, evaluated by DXA at Baseline and Endpoint in a subgroup of the full analysis set, was favourably changed with sibutramine treatment compared to placebo in fat mass (p < 0.001), fat mass as a % of total tissue mass (p = 0.005), and total tissue mass (p < 0.001). The reduction is total tissue mass observed in the sibutramine group (-6.6 kg) was mostly due to a reduction in fat mass (-6.1 kg) and not a reduction in lean mass (-0.5 kg). The difference between treatment groups in bone mineral content was not significantly different (p = 0.352).

Mean fasting serum lipid and glycemic variables improved more from Baseline to Endpoint with sibutramine treatment compared to placebo. In the full analysis set, the differences between the sibutramine and placebo treatment groups at Endpoint were statistically significant for the changes in mean absolute and percent triglycerides (-19.3 mg/dL and -14.7%, respectively; p = 0.001 for both comparisons) and mean absolute and percent HDL cholesterol (3.1 mg/dL and 7.3%, respectively; p < 0.001 for both comparisons). In the full analysis set, the differences between the sibutramine and placebo treatment groups at Endpoint were statistically significant for the changes in mean absolute insulin (-7.0 µU/mL; p < 0.001) and mean absolute HOMA (-12.8; p < 0.001); non-significant differences were observed for mean absolute glucose (-0.8 mg/dL; p = 0.522). Greater improvements were observed from Baseline to Endpoint in fasting lipid and glycemic variables in both sibutramine- and placebo-treated subjects who achieved ≥ 5% BMI decrease compared to subjects with < 5% BMI decrease. Interestingly, HDL cholesterol was significantly improved among sibutramine- but not placebo-treated subjects with < 5% BMI decrease from Baseline to Endpoint, suggesting that sibutramine may increase HDL cholesterol by a mechanism that is independent of BMI and bodyweight reduction.
**Pharmacokinetic Results:**

In adolescents, doses of 10 and 15 mg per day of sibutramine produced concentrations of M1 and M2 that were similar to those in a previous adult clinical study. With regard to M2, a trend towards increasing trough concentrations with increasing dose was observed in adolescents. In adolescents, no significant differences in steady-state concentrations with respect to month, age, Tanner score or BMI were noted. As previously observed in adults, females tended to have higher concentrations compared to males. Some differences in race were noted, although these observations are limited by the smaller number of subjects in each group other than Caucasian. Since the weight-loss effect and change in vital signs variables from Baseline to Endpoint were similar across different genders and different races, the small differences in pharmacokinetics across these sub-populations are not clinically significant.

**Summary/Conclusions:**

**Safety Results:**

Sibutramine treatment was well tolerated in obese adolescents. The mean exposure to study drug was 294 days in the sibutramine group and 254 days in the placebo group. In those subjects who were titrated to sibutramine 15 mg at Month 6 the mean exposure to sibutramine 15 mg was 159 days.

At least one treatment-emergent adverse event was reported during the study for 89% of subjects in the sibutramine group and 85% of subjects in the placebo group.

Treatment-emergent adverse events for tachycardia were reported in 13% of subjects in the sibutramine group compared to 6% of subjects in the placebo group (p = 0.049).

The reported incidences of other treatment-emergent adverse events of clinical concern (i.e., depression, syncope, chest pain, arrhythmia and extrasystoles) each occurred in ≤ 1.5% of subjects (≤ 5/368 in the sibutramine group and ≤ 2/130 in the placebo group). There were no treatment-emergent adverse events for myocardial infarction, transient ischemic attack, stroke or major psychiatric disorder other than depression.

There was no evidence of dose titration effect on new onset of treatment-emergent adverse events.

No subject died during the study. Serious adverse events were reported for 3% of subjects in the sibutramine group and 1% of subjects in the placebo group (p = 0.303).

The reported incidence of serious treatment-emergent adverse events with descriptions of suicide attempt, suicide ideation and suicide idealization was 3/368 (1%) of subjects in the sibutramine group and 1/130 (1%) of subjects in the placebo group. Suicide attempt (COSTART term: suicide attempt) was reported for one sibutramine (Subject 1006) and one placebo (Subject 2505) subject. Suicidal ideation (COSTART term: depression) was reported for one sibutramine subject (Subject 106); this subject also had a history of depression. Suicide idealization (COSTART term: depression) was reported for one sibutramine subject (Subject 2223). All four events were reported to be unlikely related or unrelated to study drug. All of these subjects were prematurely withdrawn from the study.

A total of 34 treatment-emergent adverse events resulting in premature discontinuation of study drug were reported in 30 subjects (6% of subjects in the sibutramine group and 5% of subjects in the placebo group) (p = 0.832).
Safety Results (continued):

Tachycardia and hypertension were the treatment-emergent adverse events most commonly resulting in premature discontinuation of study drug.

The mean changes from Baseline to Endpoint in hematology and chemistry variables other than those considered efficacy in each treatment group were small and not considered clinically significant.

In the full analysis set, the mean absolute changes in vital signs from Baseline to Endpoint were -2.1 mmHg in both the sibutramine and placebo treatment groups for SBP; -0.1 and -1.1 mmHg, respectively for DBP; and -0.2 and -1.8 bpm, respectively for pulse rate. The differences between treatment groups for the changes in SBP, DBP and pulse rate were not statistically significant (p = 0.988, p = 0.136 and p = 0.055, respectively). Similar vital sign changes were observed from Baseline to Month 12 for the completers set.

The mean absolute changes in vital signs from Baseline to each study visit were similar between treatment groups and were not clinically significant. The mean absolute changes in vital signs during the latter half of the study increase with continued drug exposure in either the sibutramine or placebo treatment group. Dose titration from 10 mg to 15 mg did not affect the mean absolute changes in vital sign measurement, within the group of subjects that received dose up-titration.

The incidence of protocol-defined vital sign outliers was 32% of subjects in the sibutramine group and 16% of subjects in the placebo group (p = 0.001). The incidence of SBP outliers was 5% for the sibutramine group and 4% for the placebo group (p = 0.548). The incidence of DBP outliers was 12% for the sibutramine group and 8% for the placebo group (p = 0.208). The incidence of pulse rate outliers was 20% for the sibutramine group and 6% for the placebo group (p < 0.001).

The occurrences of outlier events were not affected by final dose of sibutramine.

The mean changes in ABPM variables (mean daytime, mean nighttime, mean 24-hour and mean daytime-mean nighttime) were similar between treatment groups. Normal diurnal variation was maintained during sibutramine therapy.

The mean changes from Baseline to Endpoint in ECG intervals (PR, QRS, QT, QTc and ventricular heart rate) were not clinically significant. ECG evaluations demonstrated no evidence of clinically significant QTc prolongation.

Echocardiogram evaluations showed that there were no cases of left-sided valvular heart disease in either treatment group.

Echocardiogram evaluations of the mean changes in interventricular septal thickness in diastole, left ventricular mass and left ventricular posterior wall thickness in diastole showed similar improvements between treatment groups.
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<th>Summary/Conclusions (continued):</th>
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<tr>
<td><strong>Safety Results (continued):</strong></td>
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<tr>
<td>Growth, assessed as percentile height for age and gender, and sexual maturation, assessed by Tanner staging were not affected by sibutramine therapy.</td>
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<td>Behavior, cognitive function (i.e., learning, memory, and psychometrics) and Quality-of-Life were assessed using a comprehensive battery of well validated instruments. Few statistically significant differences between the sibutramine and placebo treatment groups were noted. When statistically significant differences between treatment groups were observed, generally the differences favored the sibutramine group.</td>
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<td>Sibutramine therapy had little impact on psychological and emotional well-being of adolescents and no effect on measures of physical health, social functioning, and measures of delinquency or aggressive behavior. Sibutramine therapy was not associated with depressive symptoms or new onset depression. Sibutramine therapy had a positive effect on attention and school functioning, and the ability to modify eating behavior.</td>
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| **Conclusions:** |
| These study results indicate that sibutramine promotes safe and effective reductions in body size and metabolic risk factors in obese adolescents who are at high risk for obesity-related morbidity. The study population was diverse in age, sex, and ethnic background, making these results relevant to obese adolescents in a variety of clinical settings. Similar to sibutramine treatment in obese adults, close monitoring of vital signs during therapy is warranted. |

Date of Report: June 3, 2004