U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Pharmacoepidemiology and Statistical Science
Office of Biostatistics

Statistical Review and Evaluation

CLINICAL STUDIES

NDA/Serial Number: 20-632/ (b) (4) 21

Drug Name: Meridia ® (sibutramine hydrochloride monohydrate) Oral Capsule

Indication(s): Obesity

Applicant: Abbott Laboratories

Date(s): Submitted June 21, 2004

User fee goal date: December 20, 2004

Review Priority: Priority

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Keywords: Clinical studies, NDA review, pediatric exclusivity

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1. EXECUTIVE SUMMARY

Sibutramine treatment in obese adolescents has been examined in three small independent investigator-initiated studies each of at least 6 months duration. Synopses of these studies are presented in the sNDA Section 8.7 "Other Studies and Information".

This reviewer has performed a statistical review of only the sponsor-initiated study SB238. The objectives of SB238 were to assess the efficacy and safety of Meridia ® (sibutramine hydrochloride monohydrate) 10 and 15 mg in obese adolescents ages 12 to 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 sex.

Remaining information on the EXECUTIVE SUMMARY is distributed in the following three sub-sections.

Note: Supplemental New Drug Application is abbreviated by sNDA and the Clinical Study Report in the sNDA is abbreviated by CSR. Except where specifically mentioned otherwise (in italics, as notes, reviewer's comments, conclusions, etc.) or clear from the context, all other results and statements in this document are the sponsor's. Sometimes, the sponsor's statements may be slightly changed for brevity or for clarity.

1.1 Conclusions and Recommendations

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1.2 Brief Overview of Clinical Studies

SB238 was a randomized, double blind, placebo-controlled, multicenter, parallel-arm, 12-month, dose titration study. The study consisted of a screening period and a 52-week double-blind treatment period. All subjects received instruction in lifestyle modification to include healthy eating behavior, exercise and bodyweight control.

SB238 was designed to evaluate the tolerability of up-titration from 10 mg to 15 mg in obese adolescents to conform to the Dosage and Administration labeling for adults. All subjects

randomized to sibutramine remained on 10 mg for the first 6 months. At 6 months, all subjects who had not lost > 10% of their initial BMI were "up-titrated" in a blinded fashion: subjects on sibutramine were "up-titrated" to 15 mg daily and subjects on placebo were "up-titrated" to placebo for the duration of the study. The initial dose of sibutramine was 10 mg in accordance with current prescribing recommendations for adults.

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The primary measure of efficacy was absolute change in BMI from Baseline to Endpoint.

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The secondary efficacy endpoints included changes in bodyweight, waist circumference, and lipid and glycemic parameters. Safety was assessed by evaluating clinical laboratory parameters, vital signs, and echocardiographic findings. Growth was assessed by changes in height.

The efficacy of sibutramine as a weight loss medication for obese adolescents was evaluated in this one year trial that randomized a total of 498 obese adolescents aged 11 years and 11 months to 16 years (mean 13.7 years) with a BMI 28.1 to 46.3 kg/m^2 (mean 36.1 kg/m^2). The subjects were randomized in a 3:1 ratio to treatment with sibutramine (n = 368) or placebo (n = 130). Overall 72% of subjects completed the study, 76% in the sibutramine group and 62% in the placebo group.

The study population characteristic: by sex (64.7% females and 35.3% males) and race (56.6% Caucasian, 21.1% African-American (*Written request mentioned approximately 30%*), 15.7% Hispanic/Mexican-American, 1.4% Oriental/Asian, 0.4% Indian/Pakistani and 4.8% "other").

In this population of obese adolescents, already more than half (52.3%) of the subjects had dyslipidemia at Baseline (184 [50.5%] in the sibutramine group and 74 [57.4%] in the placebo group, p = 0.183) defined as triglycerides ≥ 150 mg/dL, and/or HDL cholesterol ≤40 mg/dL, and/or LDL cholesterol > 160 mg/dL, or previous diagnosis. Patients with diabetes (type 1 or type 2) were not enrolled. Only 5 subjects had impaired fasting glucose at Baseline (3 [0.8%] in the sibutramine group and 2 [1.6%] in the placebo group, p = 0.472) defined by Baseline fasting glucose ≥ 110 but <126 mg/dL.

Ref: Clinical Overview of the sNDA.

1.3 Statistical Issues and Findings

Ref: Some from Clinical Overview of the sNDA.

2. INTRODUCTION

2.1 Overview

Note: Except where specifically mentioned otherwise (in italics, as notes, reviewer's comments, conclusions, etc.) or clear from the context, all other results and statements in this document are the sponsor's. Sometimes, the sponsor's statements may be slightly changed for brevity or for clarity.

Sibutramine is a serotonin and norepinephrine re-uptake inhibitor (b) (4) Based on bodyweight loss in early clinical trials, clinical development of sibutramine was begun as a bodyweight management agent. Sibutramine received FDA approval in November 1997 for use in the management of obesity in adults.

Placebo-controlled studies in obese and overweight adults have demonstrated that sibutramine produces dose-related weight loss and commensurate improvements in metabolic parameters, including glycemic and lipid variables. Sibutramine has also been shown to be effective in maintaining long-term weight loss and weight loss-related improvements in obesity-associated comorbidities such as dyslipidemia (HDL cholesterol and triglycerides) and visceral adiposity (waist circumference) for up to 2 years.

Adverse events for sibutramine are expected based upon its known mechanism of action as a serotonin and norepinephrine reuptake inhibitor. Relative to placebo, sibutramine treatment is associated with small mean increases in both pulse rate (4-5 bpm) and blood pressure (1-3 mmHg) in adults. There is no evidence to suggest abuse potential of sibutramine from a theoretical standpoint or in clinical studies of subjects who are experienced in stimulant abuse.

Certain serotonin releasing agents (e. g., fenfluramine, dexfenfluramine) previously indicated for treatment of obesity have been associated with the development of primary pulmonary hypertension (PPH) and left-sided cardiac valve dysfunction. Sibutramine is not a serotonin-releasing agent. Drugs with a mechanism of action similar to sibutramine (e. g., selective serotonin reuptake inhibitors) have not been associated with PPH or with valvular heart disease. Clinical data from adults treated with sibutramine indicate that there is no association with PPH or cardiac valve dysfunction.

Ref: **Introduction** (to the study report)

Sibutramine treatment in obese adolescents has been examined in three small independent investigator-initiated studies each of at least 6 months duration. Synopses of these studies are presented in sNDA Section 8.7 "Other Studies and Information".

This reviewer has performed a statistical review of only the sponsor-initiated study SB238. The objectives of SB238 were to assess the efficacy and safety of Meridia ® (sibutramine hydrochloride monohydrate) 10 and 15 mg in obese adolescents ages 12 to 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 sex.

SB238 was a randomized, double blind, placebo-controlled, multicenter, parallel-arm, 12-month, dose titration study. The study consisted of a screening period and a 52- week double-blind treatment period. All subjects received instruction in lifestyle modification to include healthy eating behavior, exercise and bodyweight control.

SB238 was designed to evaluate the tolerability of up-titration from 10 mg to 15 mg in obese adolescents to conform to the Dosage and Administration labeling for adults. All subjects randomized to sibutramine remained on 10 mg for the first 6 months. At 6 months, all subjects who had not lost > 10% of their initial BMI were "up-titrated" in a blinded fashion: subjects on sibutramine were "up-titrated" to 15 mg daily and subjects on placebo were "up-titrated" to placebo for the duration of the study. This study was not designed to evaluate the dose response effects of the 10 mg and 15 mg daily doses on weight loss and related Endpoints. The initial dose of sibutramine was 10 mg in accordance with current prescribing recommendations for adults.

The primary efficacy endpoint was change in BMI and secondary efficacy endpoints included changes in bodyweight, waist circumference, and lipid and glycemic parameters. Safety was assessed by evaluating clinical laboratory parameters, vital signs, and echocardiographic

findings. Growth was assessed by changes in height and sexual maturation was assessed by changes in Tanner staging.

The efficacy of sibutramine as a weight loss medication for obese adolescents was evaluated in this one year trial that randomized a total of 498 obese adolescents aged 11 years and 11 months to 16 years (mean 13.7 years) with a BMI 28.1 to 46.3 kg/m^2 (mean 36.1 kg/m^2). The subjects were randomized in a 3:1 ratio to treatment with sibutramine (n = 368) or placebo (n = 130). Overall 72% of subjects completed the study, 76% in the sibutramine group and 62% in the placebo group.

The study population was diversified by sex (64.7% females and 35.3% males) and race (56.6% Caucasian, 21.1% African-American, 15.7% Hispanic/Mexican-American, 1.4% Oriental/Asian, 0.4% Indian/Pakistani and 4.8% "other").

In this population of obese adolescents, already more than half (52.3%) of the subjects had dyslipidemia at Baseline (184 [50.5%] in the sibutramine group and 74 [57.4%] in the placebo group, p = 0.183) defined as triglycerides ≥ 150 mg/dL, and/or HDL cholesterol 40 mg/dL, and/or LDL cholesterol > 160 mg/dL, or previous diagnosis. Patients with diabetes (type 1 or type 2) were not enrolled. Only 5 subjects had impaired fasting glucose at Baseline (3 [0.8%] in the sibutramine group and 2 [1.6%] in the placebo group, p = 0.472) defined by Baseline fasting glucose ≥ 110 but <126 mg/dL.

2.2 Data Sources

Location of the NDA in EDR (electronic documents room):

\\CDSESUB1\20-632\(b) (4)21\2004-06-21

Related data provided are in the electronic document room: \\CDSESUB1\20-632\(b) (4)21\2004-06-21\crt

Statistical Amendments:

\\CDSESUB1\20-632\(b) (4)21\2004-09-13

\\CDSESUB1\20-632\(b) (4)21\2004-10-14 and

\\CDSESUB1\20-632\(b) (4)21\2004-11-29

3. STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

The subsections in this Section are: **Study Design and Endpoints; Patient Disposition, Demographic and Baseline Characteristics; Statistical Methodologies; Results and Conclusions.**

A list of abbreviation and definition of terms has been provided in the sNDA and is reproduced in this document as Appendix I.

Study Design and Endpoints

This was a double-blind, randomized, placebo-controlled, multi-center, 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 12-16 years of age. 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 ratio. All subjects received instruction in lifestyle modification to include healthy eating behavior, exercise and bodyweight control.

All subjects randomized to sibutramine remained on 10 mg for the first 6 months. At 6 months, all subjects who had not lost > 10% of their initial BMI were to be up-titrated in a blinded fashion: subjects on sibutramine were to be up-titrated to 15 mg daily and subjects on placebo were to be "up-titrated" to placebo for the duration of the study.

Subjects were 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.

Important changes to the statistical analysis plan in the study protocol (including clarification or expansion of the safety and efficacy variables) were made prior to database lock. These changes were reviewed and accepted by the FDA (*stated by the sponsor*) prior to blind-break, and are documented in the statistical analysis plan (Appendix 16.1__ 9.1). Based on these changes, the following variables were to be analyzed.

Evaluation of efficacy was to include the change from Baseline in BMI, bodyweight, waist circumference, body composition via dual x-ray absorptiometry (DXA), and fasting lipid and glycemic variables.

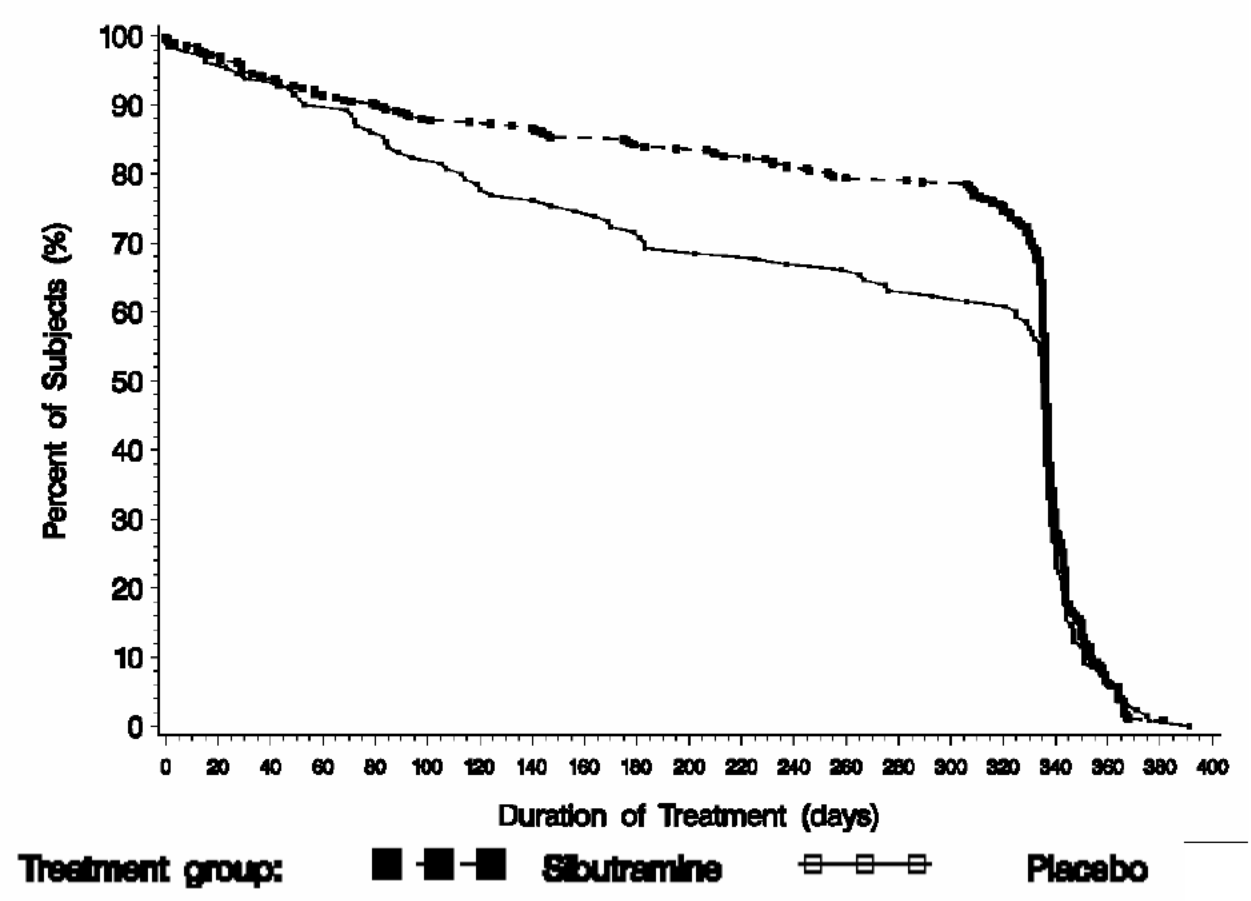
Evaluation of steady-state pharmacokinetics was to be done by measurement of plasma trough concentrations of sibutramine and its active metabolites M1 and M2 for qualitative comparison to adult reference studies.

Evaluation of safety was to include 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).

Evaluation of behavior, cognitive function (i.e., learning, memory, and psychometrics) and Quality-of-Life were to be 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.

Patient Disposition, Demographic and Baseline Characteristics

Percent of Subjects in Study over Time



A total of 498 subjects were randomized in a 3:1 ratio to treatment with sibutramine (n= 368) or placebo (n= 130). The total number of subjects who completed the study was 361/498 (72%): the proportion of subjects who completed the study was greater in the sibutramine group 281/368 (76%) compared to the placebo group 80/130 (62%). The number of subjects and reasons for premature discontinuation are presented in the Figure below. There was no significant difference between the proportions of subjects who prematurely discontinued due to an adverse event in the sibutramine (23/368; 6%) and placebo (7/130; 5%) treatment groups (p =0.832); Table 14.3__ 1.1 of the sNDA study report.

	Treatment Group n (%)	
	Sibutramine	**Placebo**
Number of Subjects Planned	300	100

Number of Randomized Subjects	368		130
Completed Study	281	(76%)	80 (62%)
Prematurely Terminated	87 (24%)		50 (38%)
Lost to follow-up	23	(6%)	18 (14%)
Adverse event	22	(6%)	7 (5%)
Withdrawal of consent	16	(4%)	12 (9%)
Administrative reasons	14	(4%)	4 (3%)
Protocol deviation	12	(3%)	9 (7%)

The following plot displays the proportion of subjects in the study by the number of days since first dose. Subjects are counted in the proportion until the day of termination for those who prematurely discontinued the study or until the day of their last dose of study drug for those who completed the study. The log-rank test for the time to withdrawal was statistically significant.

Demographic and baseline characteristics:

Demographic Characteristics - Safety Set

			Treatment Group n (%)			
Variable	**Sibutramine (N=368)**		**Placebo (N=130)**		**Total (N=498)**	
Gender						
Female	242	(65.8%)	80	(61.5%)	322	(64.7%)
Male	126	(34.2%)	50	(38.5%)	176	(35.3%)
Race						
Caucasian	206	(56.0%)	76	(58.5%)	282	(56.6%)
Black/African-American	80	(21.7%)	25	(19.2%)	105	(21.1%)
Hispanic/Mexican-American	60	(16.3%)	18	(13.8%)	78	(15.7%)
Oriental/Asian	4	(1.1%)	3	(2.3%)	7	(1.4%)
Indian/Pakistani	1	(0.3%)	1	(0.8%)	2	(0.4%)
Other	17	(4.6%)	7	(5.4%)	24	(4.8%)
Age (years)						
11	1	(0.3%)	0	(0%)	1	(0.2%)
12	81	(22.0%)	32	(24.6%)	113	(22.7%)
13	93	(25.3%)	32	(24.6%)	125	(25.1%)
14	79	(21.5%)	33	(25.4%)	112	(22.5%)
15	71	(19.3%)	17	(13.1%)	88	(17.7%)
16	43	(11.7%)	16	(12.3%)	59	(11.8%)
Mean (SD)	13.7 (1.3)		13.6 (1.3)		13.7 (1.3)	
Minimum - Maximum	11.0 - 16.0		12.0 - 16.0		11.0 - 16.0	
BMI (kg/m^2)						
≤ 37	228	(62.0%)	83	(63.8%)	311	(62.4%)
> 37	140	(38.0%)	47	(36.2%)	187	(37.6%)
Mean (SD)	36.1 (3.8)		35.9 (4.1)		36.1 (3.9)	
Minimum - Maximum	28.1 - 45.7		28.5 - 46.3		28.1 - 46.3	

SD = Standard Deviation

The safety set (n = 498) was diversified by gender [322 (64.7%) females and 176 (35.3%) males] and race [282 (56.6%) Caucasian, 105 (21.1%) African-American (*written request recommended 30%*), 78 (15.7%) Hispanic/Mexican-American, 7 (1.4%) Oriental/ Asian, 2 (0.4%) Indian/

Pakistani and 24 (4.8%) "other"]. All subjects were between 12 and 16 years of age except one sibutramine subject (703), who was 11 years 11 months of age at time of randomization.

Table 14.1__ 1.3, Appendix 16.2__ 4.1 of the Study Report in the sNDA also contains the p-values for baseline differences. No statistically significant baseline differences were observed between the treatment groups with respect to gender, race, age, height, bodyweight or BMI. The mean age across treatment groups was 13.7 years. The mean BMI across treatment groups was 36.1 kg/ m^2, ranging from 28.1 to 46.3 kg/m^2. Randomization was stratified by BMI; eligible subjects whose screening BMI was ≤ 37 kg/m2 (62.4% of all subjects) were randomized to the lowest available randomization number and subjects whose screening BMI was > 37 kg/m^2 (37.6% of all subjects) were randomized to the highest available randomization number.

No statistically significant differences were observed between the treatment groups with respect to DBP and SBP at Baseline. The difference in mean seated pulse rate at Baseline between the sibutramine (77.2 bpm) and placebo (75.2 bpm) groups was statistically nominally significant (p = 0.030; Table 14.1__ 1.3). However, with a multiple comparison adjustment for so many comparisons, it is really not statistically significant.

No statistically significant differences were observed between the treatment groups in the subgroups with impaired fasting glucose (baseline value ≥110 but < 126 mg/dL), dyslipidemia (triglycerides ≥150 mg/dL, LDL cholesterol > 160 mg/dL, HDL cholesterol ≤ 40 mg/dL or previous diagnosis) or hypertension (SBP > 130 mmHg, DBP > 85 mmHg or previous diagnosis) at Baseline.

The majority of subjects did not have impaired fasting glucose (484/489, 99.0%) or hypertension (490/ 498, 98.4%) at Baseline. The proportion of subjects with impaired fasting glucose was 3/362 (0.8%) and 2/127 (1.6%) in the sibutramine and placebo groups, respectively; the difference between groups was not statistically significant (p = 0.472). The proportion of subjects with hypertension was 5/368 (1.4%) and 3/130 (2.3%) in the sibutramine and placebo groups, respectively; the difference between groups was not statistically significant (p = 0.459). Dyslipidemia was present in 258/493 (52.3%) subjects at Baseline. The difference between the proportion of subjects with dyslipidemia in the sibutramine group (184/364, 50.5%) and the placebo group (74/129, 57.4%) was not statistically significant (p = 0.183; Table 14.1__ 1.3).

In the full analysis set and the completers set no statistically significant differences were observed between the treatment groups with respect to baseline characteristics with the exception of mean seated pulse rate.

In the full analysis set, the difference in mean seated pulse rate at Baseline between the sibutramine (77.2 bpm) and placebo (75.4 bpm) groups was statistically significant (p = 0.047) (Table 14.1__ 1.1.1.1). In males, the difference in the mean seated pulse rate between the treatment groups was not statistically significant. In females, the difference in mean seated pulse rate at Baseline between the sibutramine (77.3 bpm) and placebo (74.0 bpm) groups was statistically significant (p = 0.005) (Table 14.1__ 1.1.1.2).

In the completers set, the difference in mean seated pulse rate at Baseline between the sibutramine (77.6 bpm) and placebo (75.5 bpm) groups was not statistically significant (p = 0.057) (Table 14.1__ 1.2.1). In males, the difference in the mean seated pulse rate between the treatment groups was not statistically significant. In females, the difference in mean seated pulse rate at Baseline between the sibutramine (77.7 bpm) and placebo (73.9 bpm) groups was statistically significant (p = 0.008) (Table 14.1__ 1.2.2).

Overall, there seems to be a trend that, in females, the difference in mean seated pulse rate at Baseline between the sibutramine and placebo groups was statistically significant.

Due to the small number of subjects enrolled at each center, meaningful conclusions could not be made regarding the analysis of demographic data by center.

Statistical Methodologies

In addition to using different analysis models, the sponsor performed what the Written Request asked for. The Written Request (#2 with DFS date 12-17-03) mentioned, "The evaluation of primary and secondary parameters using a two-factor ANOVA, with explanatory variables of treatment and gender. The primary analysis population is the set of all randomized subjects."

The sponsor stated, "According to the intention-to-treat principle, the full analysis set included all randomized subjects who provided any data post-randomization. All presentations and analyses of data for the full analysis set were LOCF data, in that for visits after the first post-baseline visit at Week 1, missing data were replaced by the latest available value. Eight subjects (5 sibutramine and 3 placebo) did not record any post-baseline data and were excluded from the full analysis set." This does not seem to be a gross violation of the Written Request because we, generally, agree with the exclusion of patients who have no post-baseline data.

The blind was broken for the study on 12 August 2003. The date written on the Statistical Analysis Plan was 07 August 2003. The Statistical Analysis Plan stated:

> "In all efficacy analyses, the primary population of interest will be the full analysis set. All statistical tests performed will be two-tailed with significance determined by reference to 5% level, unless otherwise stated. Generally, comparisons between the treatment groups will be reported with 95% confidence intervals for the difference unless otherwise specified (90% confidence intervals, referred to once in the protocol, are

planned to be presented only for the echocardiogram data safety assessment). All analyses will be performed using a SAS type II sums of squares approach, i.e., main effects will be estimated from the model excluding any interaction terms. The interactions will, however, be tested separately at the 10% level, and if statistically significant, will be investigated further.

All efficacy and safety tables will present data grouped by treatment: placebo versus sibutramine. The sibutramine treatment group will also be separated by final dose received for selected tables. In contrast to the study protocol, formal statistical comparisons will not be performed between each sibutramine dose group and placebo, but summary statistics for the difference will be presented for information.

Analysis of covariance[4] will be used for the efficacy analyses of actual and percentage changes from baseline, in preference to the analysis of variance model[5] specified in the protocol, so that baseline values for the variable being analyzed are incorporated into the model. This is particularly relevant for the primary measure of efficacy as the randomization procedure stratified subjects by baseline BMI. Factors for age and gender are also planned to be included in each analysis of covariance model formed, with the single 11-year-old subject included with the 12-year-old subjects. Similarly, the more powerful logistic regression model[6], including factors for center, gender and age, will be used instead of a Cochran-Maentel-Haenzel test[7] stratified by center for ordinal and binary categorical data, unless otherwise specified. Age and gender are planned to be included in all appropriate analysis models, since they are anticipated to be of significant importance in this study. If unanticipated concerns such as insufficient cell sizes occur, results from analyses unadjusted for these baseline factors will also be presented.

The two centers that recruited fewer than 4 subjects, center numbers 16 and 19, will be pooled in all analyses including a factor for center. The remaining 31 centers each enrolled between 9 and 30 subjects, for a total of 498 subjects enrolled into the study.

The primary efficacy variable has not been explicitly defined in the study protocol. The efficacy objective, as described in Section 4.0 (Objectives) of the protocol, includes assessment of changes in BMI and waist circumference, while Section 14.4 (Data analysis – Efficacy) of the Statistical Methodology Section of the protocol infers change and percent change from baseline in BMI are the primary efficacy variables. The Sponsor has therefore determined the primary measure of efficacy will be the absolute change from baseline to endpoint in body mass index (BMI) for the full analysis set.

The null hypothesis of no difference between sibutramine and placebo will be tested using an analysis of covariance model with factors for treatment group, center, age and gender, and with baseline BMI as 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, will be reported. A separate test for the treatment group-by-center interaction will be performed and significance determined by reference to the 10% level. 1f the interaction is statistically significant, further investigation will be carried out to assess the impact of the interaction on the estimate of treatment effect.

The analyses of change in waist circumference and percent change in RMI are addressed in Section 5.2.2."

Note: Type II sums of squares approach puts equal weights to each patient instead of to each center.

All subjects completing the study to Month 12 were included in the presentations and analyses for the completers set. Data for visits missed during the study were not carried forward. A total of 137 subjects (87 sibutramine and 50 placebo) withdrew from the study and were excluded from the completers set. All presentations and analyses of data for the observed set were as for the full analysis set with no carry forward for missing data.

The Table below summarizes the number of subjects included in the full analysis, safety observed, and completers sets. All 498 (368 sibutramine and 130 placebo) randomized subjects were included in the safety set.

Number of Subjects Included in Each of the Analysis Sets

Number of Subjects	Sibutramine	Placebo
Randomized/Safety Set	368	130
Full Analysis Set	363	127
Observed Set	363	127
Completers Set	281	80

Cross Reference: Table 14.1__1.1.1.1, Table 14.1__1.2.1 and Table 14.1__1.3.

All presentations and analyses of data for the observed set were to be as for the full analysis set, with no carry forward for missing data.

Results and Conclusions.

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Results:

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(b) (4)

3.2 Evaluation of Safety

This reviewer did not perform any formal safety evaluation but was available to the clinical reviewer for statistical consultation.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race, and Age

Note: On the one hand, the study is not powered for subgroup results or interactions. On the other hand, adjustments for so many subgroups cannot be properly done, without pre-specifying which subgroup results will be confirmatory.

Results of these demographic characteristics (at baseline) and other prognostic factors were presented before. There were no statistically significant baseline imbalances.

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5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

(b) (4)

General Discussion: (b) (4) A thorough statistical review was made only with respect to BMI.

(b) (4)

5.2 Conclusions and Recommendations

6. APPENDICES

Appendix I: List of Abbreviations and Definitions of Terms

Abbreviations

Abbott	Abbott Laboratories
ABPM	ambulatory blood pressure monitoring
AEGIS	Adverse Event Global Information System
AI	aortic insufficiency
ALT	alanine transaminase
ANCOVA	analysis of covariance
ANOVA	analysis of variance
$^{anti\text{-}HB}c$	hepatitis B core antibody
$^{anti\text{-}HB}s$	hepatitis B surface antibody
anti-HCV	hepatitis C virus antibody
APGAR	appearance, pulse, grimace, activity and respiration
AST	aspartate transaminase
BL	baseline
BMC	bone mineral content
BMI	body mass index
bpm	beats per minute
CBCL	Child Behavior CheckList
CDI	Children's Depression Inventory
CI	confidence interval
cm	centimeters
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
DBP	diastolic blood pressure
dL	deciliter
DXA	dual x-ray absorptiometry
eCRF	electronic case report form
ECG	electrocardiogram
EDTA	ethylenediaminetetraacetic acid
EF	ejection fraction
F	Fahrenheit
FDA	Food and Drug Administration
g	gravity or grams
GCP	Good Clinical Practice
HBsAg	hepatitis B surface antigen
HDL	high-density lipoprotein
HOMA	homeostasis model assessment
HRQL	health related quality of life
ICD-9CM	International Classification of Diseases-9th Revision

	Modification
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IRB	Institutional Review Board
ITT	intent-to-treat
IU	international units
IVS	interventricular septal thickness in diastole
IWQOL	Impact of Weight on Quality-of-Life Questionnaire
kg	kilogram(s)
Knoll	Knoll Pharmaceutical Company
L	liter
lb	pound
LDH	lactate dehydrogenase
LDL	low-density lipoprotein
LOCF	last observation carried forward
LOQ	lower limit of quantitation
LV	left ventricular
LVH	left ventricular hypertrophy
m	meter
mg	milligram
mmHg	millimeters mercury
mL	milliliter
mmol	millimole
MOS	Medical Outcomes Study
MR	mitral regurgitation
NaF	sodium fluoride
NEC	not elsewhere classified
NCHS	National Center for Health Statistics
ng	nanogram
NHANES	National Health and Nutrition Examination Surveys
NIH	National Institute of Health
NOS	not otherwise specified
NPV	negative predictive value
NSVD	normal spontaneous vaginal delivery
Paragon	Paragon BioMedical Research
Peds QL™	Pediatric Quality-of-Life Inventory
PI	pulmonary insufficiency
pmole	picamole
PPH	primary pulmonary hypertension
PPV	positive predictive value
PW	left ventricular posterior wall thickness in diastole
QD	once daily
QOL	quality-of-life
rpm	rotations per minute
SBP	systolic blood pressure

SD	standard deviation
SE	standard error
sec	seconds
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
TR	tricuspid regurgitation
TSH	thyroid stimulating hormone
TSL Dose	time since last dose (same as "time postdose")
U.S.	United States
VH/VL	very high/very low
WIRB	Western Institutional Review Board
WHO DRUG	World Health Organization Drug Dictionary
μmol	micromole

Definition of Terms

Pretreatment	Occurring prior to the administration of study drug
Endpoint	Last observation after first dose of study drug
Study Day 1	First day subject took study drug
5% BMI responders	Subjects who achieved ≥ 5% BMI reduction from Baseline
10% BMI responders	Subjects who achieved ≥ 10% BMI reduction from Baseline

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