CLINICAL REVIEW

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Reviewer Name	Patricia Beaston, M.D., Ph.D.
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Established Name	Sibutramine
Trade Name	Meridia
Therapeutic Class	Obesity
Applicant	Abbott
Priority Designation	P
Formulation	Capsule
Dosing Regimen	Daily
Indication	Obesity
(b) (4)	

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1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

Approve for labeling change. (b) (4).

1.2 Recommendation on Postmarketing Actions

(b) (4) no recommendations for postmarketing actions are made. Any pediatric studies conducted in the future will need to address theoretical psychiatric risks (i.e., depression, impaired cognitive function) of sibutramine.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

Sibutramine hydrochloride monohydrate, chemical class tertiary amine, trade name Meridia, is a serotonin and norepinephrine re-uptake inhibitor (b) (4) Sibutramine was approved for the long-term management of obesity in November 1997, for adult patients with an initial body mass index (BMI) ≥ 30 kg/m^2 or ≥ 27 kg/m^2 in the presence of other risk factors (e.g., hypertension, diabetes, dyslipidemia).

The efficacy and safety of sibutramine in pediatric patients was assessed in a single study as outlined in the Agency's 12 July 2000 Written Request. The study was a 12-month, randomized (3:1), double-blind, placebo-controlled, non-forced dose-escalation trial of 498 obese adolescents (BMI > 2 units above the 95^{th} percentile).

1.3.2 Efficacy

The primary endpoint of the study was the absolute change in body mass index, (BMI) expressed as weight in kg divided by height in m^2. Although change in weight is the typical endpoint used in the evaluation of weight-loss drugs in adults, in children, both increased adiposity and normal growth contribute to weight gain. Calculation of BMI based on measurement of height and weight is therefore the best measure of efficacy of a drug intended to induce weight loss in growing children.

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[redacted]

1.3.3 Safety

Cardiovascular:
Ambulatory Blood Pressure Monitoring (ABPM) and 'Cuff' Blood Pressure: ABPM was performed in the seventh month of exposure to study drug. Standard 'cuff' measurements were made at several time points throughout the study. A review of ABPM curves suggests an increase from baseline in DBP (about 1-3 mm Hg) and SBP (about 3-5 mm Hg) in sibutramine-treated subjects. There is a small but consistent increase in DBP outliers in sibutramine-treated subjects compared to placebo (see table below for definition of outliers). In addition, there was an increase in treatment-emergent hypertension in sibutramine-treated subjects compared to placebo (11% vs. 8%, respectively). The evidence suggests that sibutramine may increase BP in susceptible adolescents. The results of 'cuff' blood pressure monitoring did not show a statistically significant difference between sibutramine and placebo treated subjects. However, the interpretation of these data is perhaps limited in that subjects were prohibited from taking study medication the morning of the days they were scheduled to have blood pressure measurements.

Pulse measurements: The results of pulse monitoring did not show a statistically significant difference between sibutramine and placebo treated subjects. However, as with the blood pressure measurements, the interpretation of these data are potentially limited in that subjects were prohibited from taking study medication the mornings of the days they were scheduled to have pulse measurements.

Shortcomings in data gathering aside, the incidence of outliers for blood pressure and/or pulse was significantly greater in sibutramine-treated subjects (32%) compared to placebo-treated subjects (16%).

The criteria for evaluating outliers are outlined in the following table:

Variable	Single Visit		Three Consecutive Visits	
	Absolute Threshold	Change from Baseline	Absolute Threshold	Change from Baseline
SBP (mmHg)	> 150	> 20	NA	> 15 but ≤ 20
DBP (mmHg)	> 95	> 15	NA	> 10 but ≤ 15
Pulse Rate (bpm)	> 110	> 20	> 105 but ≤ 110	> 15 but ≤ 20

Echocardiography: Echocardiographic evaluations in 105 sibutramine and 34 placebo[1] patients did not reveal any abnormalities in valvular structure or function, nor did it detect evidence of sibutramine-induced left ventricular hypertrophy. However, as pointed out by the consulting reviewer from the Division of CardioRenal Drug Products, interpretation of the echocardiographic findings is limited due to missing data and the small size of the subset of patients studied.

Psychiatric:
Two suicide attempts were reported, 1 in the sibutramine-treatment group (0.3%) and 1 in the placebo-treatment group (1%). Suicidal ideation was reported in 2 sibutramine-treated subjects. These subjects were prematurely discontinued from the study. Depression or depressed state was reported in 3 sibutramine-treated subjects. Accidental injury was reported in a greater number of sibutramine treated subjects (41; 11%) compared to placebo-treated subjects (8; 6%).

The increased incidence of CNS and other psychiatric adverse events raises concerns that sibutramine, a drug initially developed as an antidepressant, may increase the risk of depression or other mood disturbances. The increased incidence of 'accidental injury' in the sibutramine group compared to placebo may also reflect outcomes due to depression or mood disturbances. The company was requested to provide full narratives of the 'accidental injuries' to further investigate the nature of these occurrences. However, Abbott responded that they were unable to provide these records because the source information had not been compiled. At the request of the Agency (letter date June 22, 2005), Abbott is performing an analysis for suicidality. All narratives related to accidental injuries will be evaluated during this assessment. Until completion of that assessment, the absence of complete narratives makes it impossible to further elucidate the contribution, if any, sibutramine may have made in the imbalance of 'accidental injuries'.

This study was not designed to assess the neuropsychiatric effects of sibutramine .

Given the recent concern that some antidepressants may increase the risk for suicidality in adolescents with psychiatric disorders together with the fact sibutramine's mechanism of action to inhibit the re-uptake of serotonin and norepinephrine is similar to some antidepressants, it would be prudent to include precautionary language, shown below, in the drug's labeling.

Pediatric Use

The efficacy of sibutramine in adolescents who are obese has not been adequately studied.

Sibutramine's mechanism of action inhibiting the reuptake of serotonin and norepinephrine is similar to the mechanism of action of some antidepressants. Pooled analyses of short-term placebo-controlled trials of antidepressants in children and adolescents with major depressive

1 This is consistent with the 3:1 randomization of the subjects.

disorder (MDD), obsessive compulsive disorder (OCD), and other psychiatric disorders have revealed a greater risk of adverse events representing suicidal behavior or thinking during the first few months of treatment in those receiving antidepressants. The average risk of such events in patients receiving antidepressants was 4%, twice the placebo risk of 2%.

No placebo-controlled trials of sibutramine have been conducted in children or adolescents with MDD, OCD, or other psychiatric disorders. In a study of adolescents with obesity in which 368 patients were treated with sibutramine and (b) (4) patients with placebo, one patient in the sibutramine group and one patient in the placebo group attempted suicide. Suicidal ideation was reported by 2 sibutramine-treated patients and none of the placebo patients. It is unknown if sibutramine increases the risk of suicidal behavior or thinking in pediatric patients.

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1.3.5 Drug-Drug Interactions

No new drug-drug interaction data were provided in this submission.

1.3.6 Special Populations

This was a pediatric study conducted in response to a Pediatric Written Request. The Written Request specified that the study population should be composed of 50-75% females. Efforts should be directed to obtain a study population comprising approximately 30% African-American. The study enrolled 322 females (64.7%) and 105 African-Americans (21.1%). The enrollment of these subjects satisfied this component of the Written Request.

With the exception of obesity, all subjects enrolled in the trial were otherwise healthy. Subjects were excluded if they had psychiatric or medical disorders.

2 INTRODUCTION AND BACKGROUND

Childhood overweight/obesity is defined as a body mass index (BMI) ≥ 95th percentile for age and gender[2]. Obese children are at increased risk for hypertension, type 2 diabetes, and dyslipidemia and are much more likely than normal-weight children to be obese when adults.

Studies involving behavioral modification, including diet and exercise, have been shown to be successful in reducing weight in obese adolescents, especially when the parents and community (e.g., the school system) are involved[3].

2.1 Product Information

Sibutramine hydrochloride monohydrate, chemical class tertiary amine, trade name Meridia, is a serotonin and norepinephrine re-uptake inhibitor (b) (4) Sibutramine was approved for the long-term management of obesity in November 1997, for adult patients with an initial body mass index (BMI) ≥ 30 kg/m^2 or ≥ 27 kg/m^2 in the presence of other risk factors (e.g., hypertension, diabetes, and dyslipidemia).

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2 CDC growth charts and parameters at www.cdc.gov

Hammer LD, Kraemer HC, Wilson DM, Ritter PL, Dornbusch SM. Standardized percentile curves of body-mass index for children and adolescents. American Journal of Disease of Child. 1991; 145:259–263.

Pietrobelli A, Faith MS, Allison DB, Gallagher D, Chiumello G, Heymsfield, SB. Body mass index as a measure of adiposity among children and adolescents: A validation study. Journal of Pediatrics. 1998; 132:204–210.

3 Epstein LH. (1993) Methodological issues and ten-year outcomes for obese children. Ann NY Acad Sci 699:237-49.

2.3 Availability of Proposed Active Ingredient in the United States

Sibutramine is marketed in the US as 5 mg, 10 mg, and 15 mg capsules under the trade name Meridia.

2.4 Important Issues With Pharmacologically Related Products

Psychiatric: Recent studies and marketing experience have raised concern for an increase in suicidality with use of some antidepressants in children. Sibutramine, as a serotonin and norepinephrine reuptake inhibitor, is pharmacodynamically related to the selective serotonin reuptake inhibitors [sertraline (Zoloft), fluoxetine (Prozac), paroxetine (Paxil), and citalopram (Celexa) and to the serotonin and norepinephrine reuptake inhibitor venfalaxine (Effexor)]. Some studies suggest an increase in psychopathology, including but not limited to depression, in obese adolescents compared to non-obese adolescents[4].

Cardiovascular: Fenfluramine and dexfenfluramine, serotonin releasing agents once marketed in the US as obesity drugs, have been associated with the development of primary pulmonary hypertension (PPH) and left-sided cardiac valve dysfunction[5]. To date, sibutramine has not been associated with PPH or cardiac valve dysfunction in adults.

2.5 Presubmission Regulatory Activity

This study was performed in response the Agency's Written Request for a pediatric study of sibutramine. The initial request was dated 01 June 1999, with amendments on 12 July 2000, and 17 December 2003.

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC

No new data were submitted.

3.2 Animal Pharmacology/Toxicology

No new data were submitted.

4 McElroy SL, Kotwal R. Malhotra S, Nelson EB, Keck PE, Nemeroff CB (2004) Are mood disorders and obesity related? A review for the mental health professional. J Clin Psychiatry. 65(5):634-51
Erermis S, Cetin N, Tamar M, Bukusoglu N, Akdeniz F, Goksen D. (2004) Is obesity a risk factor for psychopathology among adolescents? Pediatr Int. 46(3):296-301.
5 Abenhaim L, Moride Y, Brenot F. (1996) Appetite suppressant drugs and the risk of primary pulmonary hypertension. N Engl J Med 335(19):609-16.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

The primary source of the data in this review was the electronic submission of the NDA. The review was conducted using the data analyses included in the discussions by Abbott, the raw data in the electronic submission, additional data requested after submission of the NDA, and independent analyses by the biometrics reviewer, Dr. Japobrata Choudhury. A literature search was performed, using PubMed and MicroMedix databases, primarily to provide information on safety and standard of care for the management of pediatric obesity.

Consults were requested to address the two main safety issues, the effects of sibutramine on blood pressure and pulse and neuropsychiatric parameters. The analyses and comments by Dr. Shari Targum of the Division Cardiovascular and Renal Drug Products (HFD-110) and Dr. Paul Andreason of the Division of Neurological Drug Products (HFD-120) are incorporated into the discussion of safety (Section 7.1).

4.2 Tables of Clinical Studies

There was one pivotal study for this submission.

4.3 Review Strategy

All materials submitted were reviewed.

4.4 Data Quality and Integrity

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

The primary endpoint, change in body mass index [BMI = (weight in kg)/(height in cm)^2], depends on the accuracy in measuring the weights and heights of the subjects throughout the course of the trial. Review of the raw data for height revealed inconsistencies ranging from wide fluctuations in height over time in some subjects to no variation (to the second decimal point) in height for others. These findings call into question the validity of the primary efficacy parameter, change in BMI.

4.5 Compliance with Good Clinical Practices

The collection and documentation of subjects' heights may not be considered to support 'good clinical practice' in a study in which height is a key component of the primary efficacy endpoint and a safety endpoint. Failure to provide interpretable data due to poor implementation of the study may not adhere to the 'principles of the Declaration of Helsinki' in that subjects were put at risk by exposing them to a study drug, but efficacy data are unreliable and cannot support any conclusion regarding an efficacy to risk assessment.

Protocol Deviations at Baseline: Protocol violations at baseline are found in the Appendix (Section 10). A total of 70/368 (19.0%) subjects randomized to sibutramine and 24/130 (18.5%) subjects randomized to placebo did not satisfy at least one of the Baseline protocol inclusion and exclusion criteria required by the protocol.

Comment: Fifteen subjects (14 sibutramine; 1 placebo) were found to have 'untreated hypothyroidism as defined by TSH > 4.0 mU/L at baseline. With the exception of hypothyroidism, the protocol violations were not likely to have affected the outcome of the study.

Because there is no mention of whether the subjects with elevated TSH levels received treatment with L-thyroxine, it is not possible to evaluate the impact these protocol violations might have had on the efficacy results. If all of these patients did indeed have hypothyroidism and they were treated with appropriate doses of L-thyroxine, this might bias the weight loss data in favor of sibutramine, since thyroid replacement therapy would enhance weight loss in 14 sibutramine-treated subjects vs. a single placebo-treated subject.

The finding of 15 subjects with hypothyroidism may be unusual. However, this Reviewer could not find any studies reporting the incidence or prevalence of undiagnosed hypothyroidism in adolescents evaluated for obesity. Because there was no repeat TSH or the addition of thyroxin levels, it is impossible to predict the effect this finding may have had on the study results.

Protocol Deviations During the study: Twelve sibutramine-treated and 9 placebo-treated subjects were prematurely discontinued from the study due to protocol deviations.

Pregnancy: Two pregnancies were reported during the trial; both subjects were in the sibutramine group. The first (ID 1924) had a positive pregnancy test on Study day 176, and an uncomplicated delivery 8 months after the last dose of study medication. The baby had an APCAR score of 9/9. The second subject (ID 2330) reported a positive pregnancy test on Study Day 252, the positive test was not confirmed and the subject was lost to follow-up.

Non-compliance: Eight subjects (4 sibutramine; 4 placebo) were reported to be non-compliant with study medication. Compliance with the site-specific behavioral modification programs was not documented.

Incorrect dosing: Two subjects received study medication intended for the other subject (subject 824, sibutramine; subject 803, placebo).

Comment: The listed protocol deviations would not be expected to materially affect the primary outcome of the trial.

Non-Adherence to Study Schedule: The following deviations from the study schedule were noted:

DXA Determination of Body Composition: DXA data were scheduled to be obtained at Month 6. However to incorporate follow-up DXA data that were obtained before or after Month 6, the body composition variables were analyzed to Endpoint.

Ambulatory Blood Pressure Monitoring: ABPM data were scheduled to be obtained at Month 7. However, some subjects performed the ABPM later than Month 7, and some subjects repeated the ABPM. Therefore, the ABPM data were analyzed to Endpoint rather than Month 7, to include the latest available follow-up assessment for all subjects who provided ABPM measurements.

Comment: The degree of deviation from the study schedule for these measures was not discussed in the presentation of the data and therefore the influence these deviations have on the evaluation of efficacy or safety can not be estimated. Furthermore, there was no discussion regarding the circumstances requiring repeated ABPM measurements or the number of subjects requiring repeat measurements.

4.6 Financial Disclosures

Financial disclosure information was provided by Abbott Laboratories, who certified that, save for one investigator (see below), no financial arrangements had been made with any of the clinical investigators that would influence the outcome of the study. [21 CFR54.2 (b)]

Dr. (b) (6) disclosed that he has received significant payments from Abbott Laboratories (b) (6) with a value in excess of $25,000.

Comment: (b) (6)

5 CLINICAL PHARMACOLOGY

5.1 Pharmacokinetics

Please refer to Dr. Wie Qiu's Clinical Pharmacology and Biopharmaceutics Review for complete details of the pharmacokinetics study conducted in accordance with the Written Request.

According to Dr. Qiu's review, there were no significant differences in the pharmacokinetics of sibutramine or its active metabolites between adolescents and adults.

Dr. Qiu further commented that 'Related to cardiac safety issues, it may be worth noting that the potential for QT prolongation for sibutramine has not been studied in a prospective QT prolongation study'.

6 INTEGRATED REVIEW OF EFFICACY

6.1 Indication

The indication as stated in the Written Request was:

> 'Treatment of obese adolescents who have a body mass index (BMI) at least two units above the U.S. weighted mean for the 95th percentile based on gender and age to an upper BMI limit of 44 kg/m^2.'

(b) (4)

6.1.1 Methods

As discussed in Section 2.5 of this review, a single trial was performed to support the efficacy and safety of sibutramine in the pediatric population. This study, SB238, was a 12-month, randomized, double-blind, placebo-controlled trial, with a non-forced dose titration at Month 6.

The study was designed to address the cardiovascular safety issues (i.e., blood pressure and pulse) known at the time of Written Request[6]. The study was also to include behavioral intervention (in both the active treatment and placebo groups) and measurements of 'cognitive function (i.e., learning, memory, and psychometrics) in all of the sibutramine- and all of the placebo-treated patients'; however, the company has not provided evidence that the behavioral interventions were adequately implemented by all study sites. In addition, there has been considerable inter-Agency debate regarding whether the cognitive measurements made during the trial assessed the parameters called for in the Written Request.

6.1.2 General Discussion of Endpoints

Primary – Body Mass Index

The primary endpoint of the study was the absolute change in body mass index (BMI), expressed as weight in kg divided by height in m^2. Although change in weight is the typical endpoint used in the evaluation of weight-loss drugs in adults, this measurement does not capture the influence

6 Written Request Amendment #2, December 17, 2003.

increasing height has on the change in bodyweight in children, particularly adolescents; as such, change in BMI is the standard efficacy parameter for studies of pediatric obesity.

Secondary

1) Percent change from Baseline in BMI.
2) BMI outcome score at Endpoint.
3) Proportion of subjects achieving ≥ 5% and ≥ 10% BMI reduction from Baseline.
4) Absolute and percent change from Baseline in bodyweight.
5) Proportion of subjects achieving ≥ 5% and ≥ 10% reduction in bodyweight.

Comment: **For the approval of weight-loss drugs in adults, the study must demonstrate either a 5% greater weight loss in the treated group compared to placebo, or that a statistically significantly greater proportion of subjects in the active-treated vs. placebo-treated group lose at least ≥ 5% of their baseline weight.**

6) Absolute change from Baseline in waist circumference

Comment: Abbott did not discuss a way to normalize the change in waist circumference in a growing child or to make comparisons across age groups.

7) Absolute change from Baseline in body composition variables as measured by DXA.

Comment: **DXA has been used to assess body composition and can estimate the relative percent of lean and non-lean (fat) body mass. This measurement is helpful in demonstrating that weight loss is not at the expense of lean body mass, but rather due to a decrease in body fat.**

8) Absolute and percent change from Baseline in fasting lipid variables (triglycerides, HDL cholesterol, LDL cholesterol and total cholesterol). Fasting glycemic variables (glucose, insulin, HOMA[7]).

Comment: **Fasting glycemic and lipid variables are surrogate markers for co-morbidities associated with obesity, principally cardiovascular disease. The expectation is that these risk factors would improve or normalize with weight loss.**

Additional endpoints related to safety included in the Written Request were: height, growth (including Tanner staging), blood pressure, pulse, and findings on echocardiography. The request included psychiatric/psychological assessments as well. These measures are discussed in the Safety Evaluation Section 7.1.

7 HOMA – homeostasis model assessment – An estimate of insulin sensitivity from the mathematical modeling of fasting plasma glucose and insulin concentrations according to the formula: fasting serum insulin (pmol/L) × fasting plasma glucose (mmol/L)/22.5.

6.1.3 Study Design

SB-238 was a double-blind, randomized, placebo-controlled, multi-center, parallel-arm, 12-month, non-forced dose-escalation study to evaluate the safety and efficacy of sibutramine 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 a 3:1 fashion. All subjects were to receive instruction in lifestyle modification including healthy eating behavior, exercise, and bodyweight control.

A pharmacokinetics study at doses of 10 mg and 15 mg was to be conducted in 12 to 16-year-old obese adolescents. 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.

Population: Obese male and female adolescents (age 12-16 years) with no major medical or psychiatric conditions.

Randomization was stratified by BMI: Subjects with a BMI lower limit of inclusion 2 units above the U.S. weighted mean for the 95th percentile based on age and gender, but with a BMI ≤ 37 kg/m^2 were randomized to the lowest available randomization number and subjects with a BMI > 37 but ≤ 44 kg/m^2 were randomized to the highest available randomization number in order to balance BMI across treatment groups.

Inclusion Criteria:

1. Obese adolescent males and females in good general health with a BMI lower limit of inclusion 2 units above the U.S. weighted mean for the 95th percentile based on age and gender, (see protocol Attachment 8), to an upper limit of BMI of 44 kg/m^2, aged 12-16 years at randomization.
2. Both the subject and legal guardian/parent were to communicate meaningfully with the Investigator, be legally competent and provide written informed consent/assent.
3. All subjects were to exhibit sufficient comprehension of written materials and be able to follow diet and exercise recommendations and to complete written behavioral assessments.
4. Female subjects of childbearing potential were required to have a negative pregnancy test prior to inclusion. Sexually active female subjects were required to be using adequate contraceptive precautions (i.e. oral contraceptives for ≥ 3 months prior to starting study medication, approved hormonal implant, intrauterine device, diaphragm with spermicide or condom with spermicide).
5. A negative serum pregnancy test was required of all female subjects.
6. All subjects were to have at the Screening and Baseline visits, a systolic blood pressure (SBP) ≤ 130 mmHg, a diastolic blood pressure (DBP) ≤ 85 mmHg and a pulse rate ≤ 95

beats per minute. Adequately treated hypertensive subjects were allowed in the study if the antihypertensive medication had been stable for ≥ 3 months.

Exclusion Criteria:

1. History of anorexia nervosa.
2. History of clinically significant cardiac disease, congenital heart disease, any clinically significant abnormal cardiac condition, or to be known to have a clinically significantly abnormal ECG. Specifically excluded conditions included coronary artery disease, clinically significant cardiac arrhythmias and congestive heart failure.
3. History of stroke.
4. History of asthma requiring chronic oral beta agonist treatment or chronic oral corticosteroid therapy. The subject may have had a history of asthma requiring inhaled beta agonist therapy and/or inhaled corticosteroid therapy if stable (3 months on same dose). A short-course of oral corticosteroid medication (≤ 7 days) was permitted for an acute exacerbation.
5. History of narrow angle glaucoma.
6. History of gallstones unless status post cholecystectomy.
7. History of seizures with the exception of childhood febrile seizure.
8. Evidence of possible renal dysfunction (creatinine > 1.7 mg/dL) or hepatic dysfunction [alanine transaminase (ALT) > 50 IU/L, bilirubin > 1.0 mg/dL] or evidence of active or chronic Hepatitis B or C infection.
9. Use of the following medications: monoamine oxidase inhibitors (e.g., furazolidone, phenelzine, procarbazine hydrochloride, selegiline), antidepressant agents (including the use of antidepressant agents for more than 2 weeks during the 90-day period prior to Screening), lithium, serotonin reuptake inhibitors, certain opioids (e.g., dextromethorphan, meperidine, pentazocine, fentanyl), prescribed or over-the-counter weight loss agents, centrally acting appetite suppressants, tryptophan, sympathomimetics, serotonergic migraine agents (e.g., sumatriptan succinate, dihydroergotamine) or any other medication that, in the opinion of the Investigator, may pose harm to the subject, obscure the effects of study medication or interfere with the process of drug absorption, distribution, metabolism or excretion (i.e., enzyme inducers or enzyme inhibitors).
10. Removal of antidepressant therapy for the purposes of entering this study.
11. History of alcohol or drug addiction or substance abuse by the subject or the parent/legal guardian within the previous 2 years.
12. Above the 95th percentile for gender and age for the following categories at screening, as assessed by the CBCL: "thought problems," "delinquent behavior," "aggressive behavior," or "attention problems."

13. T-score of > 65 (significantly above average) for the total CDI score and the subject must not have given the following answer to Item #9 of the CDI score: "I want to kill myself."
14. Participation in rigorous, structured weight loss programs for more than 2 weeks within the past 6 months prior to screening. Continuing participation in less rigorous programs such as Weight Watchers® was allowed; however, subjects must have been participants for ≥ 6 months prior to screening to be allowed in the study.
15. Participation in any investigational drug study within 30 days prior to screening.
16. Use of a prescription or over the counter (or herbal) weight control medication for more than 2 weeks during the 180-day period immediately preceding screening. In addition, any such medication was not allowed during the trial.
17. Previous patient/subject in a sibutramine trial or other use of sibutramine.
18. Pregnant.
19. Pathophysiologic or genetic syndromes associated with obesity, for example Cushing's syndrome, Turner's syndrome, Prader-Willi syndrome, etc.
20. Diabetes mellitus or confirmed fasting blood glucose ≥ 126 mg/dL.
21. Untreated hypothyroidism [thyroid stimulating hormone TSH > 4.0 mU/L for a second generation test].
22. Malignancy.
23. Positive drug screen for recreational drugs.
24. History of coagulopathies or bleeding disorders.
25. History of gastric bypass or other surgical procedure, which had the potential to interfere with absorption of study medication, or gastric restrictive surgery.
26. Major psychiatric illness in either the subject or subject's legal guardian/parent(s) such as bi-polar disorder, attention deficit disorder, major depression, bulimia, schizophrenia, psychosis, etc.
27. Failure to maintain a minimum level of academic achievement during the previous 6 months prior to screening (subjects were excluded if receiving multiple failing grades in school).
28. History of any other severe medical or psychiatric disorder that precluded participation.

Treatment/Dose Escalation

The dose of sibutramine was increased from 10 mg to 15 mg in subjects who did not achieve a reduction in BMI of at least 10% of their baseline BMI at six months.

Subjects were instructed to take 1 capsule of study medication at about the same time each day, preferably, in the morning, with approximately 4 ounces of water. On clinic visit days for the Week 12, Month 6 and Month 12 visits (fasting blood laboratory evaluation visits), subjects were

not to take their study medication until after the blood samples were collected. Subjects who were to have a blood sample collected for pharmacokinetic assessments on the Month 8, 9 and 10 visits were not to take their study medication until after the samples were collected. (9.4.1)

Dietary/Exercise/Lifestyle Modification

Subjects were to be instructed in lifestyle modification strategies that included self-monitoring of eating habits and physical activity, stress management, stimulus control, problem solving, contingency management, cognitive restructuring and social support. Subjects were to be encouraged to exercise, and counseling was to be provided to enhance incorporation of exercise and increased physical activity into daily activities. Exercise was to be initiated slowly and the intensity increased gradually. Nutritional counseling was to be provided with a goal to have subjects develop healthful eating habits and to consume a calorie-restricted diet designed to produce a daily calorie deficit of ≥ 500 kilocalories. Each site used an individual dietary, exercise and lifestyle modification regime that was specific to that site. (9.4.9)

Comment: The original submission did not contain documentation outlining the behavioral modification programs used at the various centers. At this Reviewer's request, Abbott provided information on behavioral treatment (in the form of a summary table) for all 33 clinical sites. The programs were widely variable from frequent one-on-one interactions with staff including psychologists, nutritionist and other staff to infrequent group meetings with non-specific recommendations. Behavioral modification/instruction was not included in the flow chart of study procedures (Table 2, page 95), nor was any assessment of compliance with the program. Because of the high variability of the behavioral modification programs, the number of centers, and the relatively small number of subjects enrolled at any site, no reliable comments on the interaction between behavioral modification (placebo alone) and weight loss can be made.

Measurement of primary efficacy variable: BMI is calculated as the weight in kg/height in m^2.

Weight: Body weight was to be measured on an officially calibrated scale with the patient in underwear (or lightweight patient gown) without shoes. Weight was to be recorded in pounds to the nearest 0.25 pound, or in kilograms to the nearest 0.1 kg. The same scale was to be used for all measurements. (From section 7.9 of protocol, page 1504)

Height: Height was to be measured without shoes. Height was to be recorded in inches to the nearest 0.25 inch, or in centimeters to the nearest 0.5 cm. (From section 7.10 of protocol)

Comment: **The instruments used for measurement of weights and heights were not specified in the submission or protocol. The recording of height to the nearest 0.25 inch or 0.5 cm is too liberal in this Reviewer's opinion. The use of a stadiometer and appropriately trained personnel would provide more accurate information with an expected error < 0.3 cm[8]. To minimize error, the use of a stadiometer generally requires repeated measures (3-**

8 Rudolph's Pediatrics, 21st Edition (2002), Electronic. Chapter 24.2 Disorders of the Anterior Pituitary gland,

10) with a pre-defined plan for excluding outliers and averaging measurements. The protocol did not contain any specifications, other than as stated above, for the measurement of height.

Given that both weight and height are components of the primary efficacy variable, BMI, and that height is a safety measure (adequate growth over the course of the study), appropriate and sensitive instruments to measure height should have been employed by trained personnel. Failure to do so resulted in inconsistencies in the data as discussed in Section 4.4.

Study Schedule (For full study schedule please refer to Appendix, Section 10.1.1)

Behavioral (CBCL, CDI, Eating Inventory, Piers-Harris Children's Self-Concept) and Quality of Life (Peds QL, IWQOL) assessments were performed at screening, Month 3, Month 6, and at Month 12 or premature discontinuation visit.

Body weight, vital signs, and cardiovascular exam (as part of a focused or full physical exam) were evaluated at every visit.

Comment: **On the whole, the study schedule appears appropriate with the exception of the frequency of measuring weight and for the prohibition of taking study medication on the morning of clinical evaluations.**

a. Early and frequent measures of weight may influence both the subject and the staff. Studies with adults demonstrated that those subjects who would respond to sibutramine would do so within the first 4 weeks. Evidence of weight loss in the first month of study may have influenced the interaction, including encouragement, of the staff with the subjects.

b. Prohibition against taking study medication prior to clinical evaluation at several time-points would limit the ability to measure the effects of sibutramine on pulse and blood pressure at or near C_{max}.

6.1.4 Efficacy Findings

Population

Randomized: 498 subjects were randomized to the study. Subjects were randomized to 33 centers, the minimum number of subjects enrolled at any center was 4 and the maximum number was 29.

The baseline demographics, anthropomorphics, and vital signs for the 490 subjects contributing safety and efficacy data are summarized in the following tables:

Hypothalamus, and Growth. E.O. Reiter and A.J. D'Ercole.

Baseline Demographics and Anthropomorphics	Sibutramine N = 363 n (%)	Placebo N = 127 n (%)	p-value	Total N = 490 n (%)
Age (years)			0.551	
11	1 (0.3)	0 (0.0)		1 (0.2)
12	81 (22.3)	31 (24.4)		112 (22.9)
13	91 (25.1)	31 (24.4)		122 (24.9)
14	78 (21.5)	33 (26.0)		111 (22.7)
15	70 (19.3)	17 (13.4)		87 (17.8)
16	42 (11.6)	15 (11.8)		57 (11.6)
Mean ± SD	13.7 ± 1.3	13.6 ± 1.3		13.7± 1.3
Range	11.0 to 16.0	12.0 to 16.0		11.0 to 16.0
Gender			0.340	
Female	240 (66.1)	78 (61.4)		318 (64.9)
Male	123 (33.9)	49 (38.6)		172 (35.1)
Race			0.804	
Black/African-American	78 (21.5)	25 (19.7)		103 (21.0)
Caucasian/White	205 (56.5)	73 (57.5)		278 (56.7)
Hispanic/Mexican American	59 (16.3)	18 (14.2)		77 (15.7)
Indian/Pakistani	1 (0.3)	1 (0.8)		2 (0.4)
Oriental/Asian	4 (1.1)	3 (2.4)		7 (1.4)
Other	16 (4.4)	7 (5.5)		23 (4.7)
Height (cm)			0.343	
Mean ± SD	164.2 ± 7.6	165.0 ± 7.9		164.4 ± 7.7
Range	138.8 to 186.7	141.0 to 185.4		138.8 to 186.7
Weight (kg)			0.970	
Mean	97.8	97.8		97.8
STD	14.7	14.7		14.7
Range	57.3 to 140.8	64.8 to 140.2		57.3 to 140.8
Body Mass Index (kg/m^2)			0.441	
≤ 37 kg/m^2	223 (61.4)	82 (64.6)		305 (62.2)
> 37 kg/m^2	140 (38.6)	45 (35.4)		185 (37.8)
Mean ± SD	36.1 ± 3.8	35.8 ± 4.1		36.1 ± 3.9
Range	28.1 to 45.7	28.5 to 46.3		28.1 to 46.3

Baseline Vital Signs	Sibutramine N = 363 n (%)	Placebo N = 127 n (%)	p-value	Total N = 490 n (%)
Seated Pulse Rate (BPM)			0.047	
Mean ± SD	77.2 ± 8.7	75.4 ± 8.9		76.7 ± 8.8
Range	52.0 to 105.0	57.0 to 99.0		52.0 to 105.0
Seated Diastolic BP (mmHg)			0.649	
Mean ± SD	69.0 ± 7.6	69.4 ± 7.4		69.1 ± 7.5
Range	49.0 to 91.0	49.0 to 85.0		49.0 to 91.0
Seated Systolic BP (mmHg)			0.757	
Mean ± SD	113.3 ± 9.1	113.0 ± 9.4		113.2 ± 9.2
Range	89.0 to 135.0	90.0 to 131.0		89.0 to 135.0

COMMENT: When examined as a whole, the baseline demographics, anthropomorphics, and vital signs were generally well-balanced. There were no significant differences in the

incidences of comorbidities associated with obesity such as impaired fasting glucose, dyslipidemia, and hypertension between the treatment groups.

Disposition of subjects

Eight subjects (5 sibutramine, and 3 placebo) did not contribute data after randomization. The remaining 490 subjects contributed both safety and efficacy data and are referred to as the 'Full Analysis Set' in the submission. These subjects represent the intent-to-treat population. The dispositions of all subjects randomized are found in the following table:

Disposition of Subjects	Total Randomized N = 498	
	Sibutramine N = 368	Placebo N = 130
	n (%)	n (%)
Completed	281 (76)	80 (62)
Premature Discontinuation	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)

Comment: Abbott did not report a category of 'lack of efficacy'. Due to the 3:1 randomization of subjects, dropouts in the placebo group resulted in 9 centers having only 1 or no subjects randomized to placebo contributing 'completer' data. Because 'behavior modification' varied greatly among the centers it is impossible to comment on the influence 'behavior modification' had on the weight loss reported in the sibutramine-treated subjects at these centers.

(b) (4)

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6.1.5 Clinical Microbiology

Not Applicable

6.1.6 Efficacy Conclusions

(b) (4)

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

The initial NDA for the registration of sibutramine and studies in obese and overweight adults were reviewed for comparison to the findings in adolescents. When appropriate, similarities and differences between the two populations will be made under **Comments**.

Consults from the appropriate review divisions within CDER were obtained to address specific concerns for cardiovascular and neuropsychiatric safety.

Results:

Drug Exposure: *The mean exposure to study drug was 294 days in the sibutramine group and 254 days in the placebo group. The median exposure to study drug was 336 days in both treatment groups.* (b) (4)

Adverse Events: A total of 1741 adverse events were reported by 440/498 (88%) of the subjects. At least one adverse event was reported by 329/368 (89.4%) of sibutramine-treated subjects and 111/130 (85.4%) of placebo-treated subjects (from adverse event data set).

The difference between treatment groups in the total incidence of subjects reporting treatment-emergent adverse events was not statistically significant (p = 0.347). The difference between treatment groups in the specific incidence of treatment-emergent adverse events for tachycardia was statistically significant (nominal p = 0.049); treatment-emergent adverse events for tachycardia were reported for 46/368 (13%) of subjects in the sibutramine group and 8/130 (6%) of subjects in the placebo group. All treatment-emergent adverse events for tachycardia were mild or moderate in severity. No other statistically significant differences were observed.

7.1.1 Deaths

No deaths occurred during this trial.

7.1.2 Other Serious Adverse Events

Serious Adverse Events: Serious adverse events were reported for 10/368 (3%) of sibutramine-treated subjects and 1/120 (1%) of placebo-treated subjects.

SERIOUS ADVERSE EVENTS							
Sub ID	**Age (yrs)/ Gender**	**Day of Onset[a]**	**Day of Resolution[a]**	**Description**	**COSTART Term**	**Severity**	**Outcome**
Sibutramine							
106	14/F	29	Ongoing	Suicidal Ideation Significant Depression Bulimia	Depression[c] Increased Appetite[d]	Hospitalized Severe	Not resolved
208	12/F	96	97	Elective Ankle Surgery to Correct Bone Malformation	Bone Disorder	Hospitalized Moderate	Resolved
221	13/F	52	68	Granulomatosis Uviitis	Uveitis	Severe	Resolved
508	12/F	53	57	Abdominal Pain, Removal of Peritubular Cyst	Cyst	Hospitalized Severe	Resolved
604	14/M	225	227 (1)	Excessive Nausea Excessive Vomiting	Nausea[c] Vomiting[c]	Severe	Resolved
1006	15/F	104	104	Suicide Attempt	Suicide Attempt[c]	NA	Resolved
1402	13/M	358	Ongoing	Prolonged QT Interval	QT Interval Prolonged	Mild	Not resolved
2223	16/M	245	Ongoing	Suicide Idealization	Depression[c]	Moderate	Resolved with sequelae
2702	15/F	183	183	Tonsillectomy	Pharyngitis	Hospitalized Moderate	Resolved
2714	13/M	179	179	Bilateral Mastectomy	Gynecomastia	Hospitalized Severe	Resolved
Placebo							
2505	14/F	115 (30)	115 (30)	Suicide Attempt	Suicide Attempt[c]	Hospitalized Moderate	Resolved

M = Male; F = Female; NA = Not Assessed Table 14.3__2.2 and Appendix 16.2__7.1

a. Number in parentheses represents the number of days after the last dose of study drug.
b. The number of days that the subject received 15 mg dose, if the subject was up-titrated to 15 mg.
c. Subject prematurely discontinued the study due to this adverse event.

Suicide attempts/ideation and Depression: Two suicide attempts were reported, 1 in the sibutramine-treatment group (0.3%) and 1 in the placebo-treatment group (1%). Suicidal ideation was reported in 2 sibutramine-treated subjects (Subjects 106 and 2223). These subjects were prematurely discontinued from the study. Depression or depressed state was reported in 3 sibutramine-treated subjects (Subjects 3401, 3406, and 1122).

Comment: In the original NDA for registration for the treatment of obesity (adult population), 2 deaths by suicide and an attempted suicide were reported. In the pivotal trial for registration, there were 11 reports of depression (7, 9% for sibutramine treated; 4, 5% for placebo treated). Other psychiatric/CNS adverse events included anxiety (9, 11% for sibutramine treated; 5, 6% for placebo treated), nervousness, (4, 5% for sibutramine treated; 1, 1% for placebo treated), and insomnia (9, 11% for sibutramine treated; 7, 9% for placebo treated). [Taken from table 8.15.4.3.1, reporting AE reported by > 5% of one or more treatment groups, as copied in the review.] There was one reported suicide attempt (sibutramine treated). No statistically or clinically significant changes in the scores on the Hamilton Depression Scale were reported. Changes in the Modified Norris Assessment were reported as 'not statistically significant' but it was noted that the absolute changes favored sibutramine for 'mental and physical sedation, tranquilization, and other feelings'. Not all studies enrolling adults had complete assessments for depression/mood changes.

7.1.3 Dropouts and Other Significant Adverse Events

7.1.3.1 Overall profile of dropouts

Premature Discontinuation (Drop Outs)	Total Randomized N = 498	
	Sibutramine N = 368 n (%)	Placebo N = 130 n (%)
Adverse event	22 (6)	7 (5)
Withdrawal of consent	16 (4)	12 (9)
Protocol deviation	12 (3)	9 (7)
Administrative reasons	14 (4)	4 (3)
Lost to follow-up	23 (6)	18 (14)

Table 14.1_3

Comment: Review listings for subjects who prematurely discontinued treatment revealed some inconsistencies in assignment of category. Subjects who withdrew consent or left for administrative reasons were noted to have adverse events or protocol deviations. The proximity of these findings to the time of discontinuation was not evaluated. Overall, the misassignment of a few subjects is unlikely to affect the interpretation of the safety data.

7.1.3.2 Adverse events associated with dropouts

A total of 34 treatment-emergent adverse events resulted in premature discontinuation of 30 subjects; 22/368 (6.0%) of sibutramine-treated subjects and 7/130 (5%) of placebo-treated subjects. Tachycardia and hypertension were the most commonly reported treatment-emergent adverse events that resulted in premature discontinuation (Sibutramine 9 for tachycardia, 5 for hypertension; Placebo 2 for tachycardia, 0 for blood pressure).

Tachycardia: The reported incidence of treatment-emergent adverse events for tachycardia was 46/368 (13%) for sibutramine-treated subjects and 8/130 (6%) of placebo-treated subjects. Of the 46 sibutramine-treated subjects, 34 had onset of tachycardia within the 1st 6 months of treatment (10 mg); and 12 had the onset during the 2nd 6 months (3 continuing at 10 mg and 9 at titrated to 15 mg). For the placebo treated subjects, 5 had the onset of tachycardia during the 1st 6 months and 3 in the 2nd 6 months.

Hypertension: The reported incidence of treatment-emergent adverse events for hypertension was 39/368 (11%) for sibutramine-treated subjects and 11/130 (8%) of placebo-treated subjects. Of the 39 sibutramine-treated subjects, 35 had onset of hypertension within the 1st 6 months of treatment (10 mg); and 4 had the onset during the 2nd 6 months (2 continuing at 10 mg and 2 at titrated to 15 mg). For the placebo-treated subjects, 9 had the onset of hypertension during the 1st 6 months and 2 in the 2nd 6 months.

7.1.3.3 Other significant adverse events

Accidental Injury: Accidental injuries were reported for 41 (11%) of sibutramine-treated and 8 (6%) of placebo-treated children.

Comment: **In the original NDA for registration (adult population), there was no difference in the reports of adverse events for accidental injury (7/82, 9% for the sibutramine-treated and 6/78, 8% for the placebo-treated group).**

7.1.4 Other Search Strategies

Information for adverse events was obtained from the general text of the submission, the statistical summary tables, and from the raw data.

7.1.5 Common Adverse Events

7.1.5.2 Appropriateness of adverse event categorization and preferred terms

Adverse events were categorized by COSTART term. Detailed review of the adverse event data base shows that the majority of adverse events were categorized similarly by the investigators. The few exceptions are noted in the appropriate sections of this review.

7.1.5.4 Common adverse event tables

Summary of the Treatment-Emergent Adverse Events Reported by ≥ 5.0% of Subjects in Either Treatment Group by COSTART Term				
COSTART Term	**Sibutramine** N=368		**Placebo** N=130	
	n	%	n	%
ANY ADVERSE EVENT	327	89%	111	85%
Infection	167	45%	53	41%
Headache	113	31%	39	30%
Pharyngitis	49	13%	23	18%
Tachycardia	**46**	**13%**	**8**	**6%**
Accidental injury	**41**	**11%**	**8**	**6%**
Dry mouth	**41**	**11%**	**8**	**6%**
Pain	42	11%	12	9%
Hypertension	**39**	**11%**	**11**	**8%**
Rhinitis	41	11%	17	13%
Abdominal pain	37	10%	12	9%
Dysmenorrhea[a]	21	9%	13	16%
Vomiting	32	9%	7	5%
Cough increased	28	8%	12	9%
Nausea	31	8%	12	9%
Dizziness	**28**	**8%**	**5**	**4%**
Rash	25	7%	7	5%
Sinusitis	24	7%	6	5%
Constipation	24	7%	3	2%
Flu Syndrome	23	6%	7	5%
Insomnia	**23**	**6%**	**4**	**3%**
Viral infection	20	5%	2	2%
Allergic reaction	18	5%	7	5%

[a]Female-specific AE (Sib N=242; Plac N=80). Tables 41 and Table 14.3__1.6.

7.1.5.5 Identifying common and drug-related adverse events

Cardiovascular– There was an increased number of sibutramine-treated subjects with hypertension and tachycardia compared to placebo.

Comment: The increases in blood pressure and pulse are similar to the findings in the adult studies. These findings are consistent with the adrenergic properties of sibutramine.

CNS– There was an increased number of sibutramine-treated subjects with insomnia compared to placebo. In addition to insomnia (captured in the evaluation of AE occurring in ≥ 5%) the following adverse events were also reported:

Abnormal dreams- nightmares (1 sibutramine)
Apathy- apathy (1 placebo)
Confusion- confusion (1 placebo)
Emotional liability- emotional liability, mood altered (3 sibutramine)
Hyperkinesia- hyperactivity (1 placebo)
Insomnia- insomnia, sleep restlessness (23 [6%] sibutramine, 4 [3%] placebo)

Somnolence- drowsiness, lethargy (5 sibutramine)
Personality disorder- behavior abnormal (1 sibutramine), verbosity (1 placebo)

Body as a whole–
Asthenia- fatigue, tiredness, weakness generalized (12 sibutramine, 6 placebo)
Hostility- aggressive reaction (1 sibutramine)
Malaise- malaise (1 sibutramine)

Comment: **Although some of these findings may be attributable to the adrenergic properties of sibutramine, when considered in conjunction with the reports of suicide attempt, suicidal ideation, and depression, additional exploration of the events is in order. Because the majority of these adverse events were reported in subjects taking sibutramine, they raise concerns for a constellation of complaints that may represent undetected depression or dysphoria.**

7.1.7 Laboratory Findings

7.1.7.1 Overview of laboratory testing in the development program

The following table contains a summary of the screening and safety laboratory studies performed. Fasting lipid profile, serum glucose, serum insulin levels were changed from safety endpoints to efficacy endpoints and have been presented in Section 6.1.4.

Laboratory Parameters
Hematology: Complete blood count with platelet count
Serum Chemistry: Albumin, Alkaline phosphatase, ALT/SGPT, AST/SGOT, Bicarbonate, Blood urea nitrogen, Calcium, Chloride, Creatinine, Inorganic phosphorus, Lactate dehydrogenase, Potassium, Sodium, Total bilirubin, Total protein, Uric acid
Fasting Serum Lipids*: Total cholesterol, High-density lipoprotein (HDL) cholesterol, Low-density lipoprotein (LDL) cholesterol, Triglycerides; **Fasting Serum Insulin***; **Fasting Plasma Glucose***
Pregnancy Test: serum and urine (if applicable); **Serum Thyroid Stimulating Hormone (TSH)**
Urine Drug Screen (amphetamines, barbiturates, benzodiazepines, cannabis, cocaine, methadone, methaqualone, opiates, phencyclidine, propoxyphene)
Hepatitis Screen: Hepatitis B: hepatitis B surface antigen (HBsAg), hepatitis B surface antibody (anti-HBs), hepatitis B core antibody (anti-HBc); Hepatitis C: hepatitis C virus antibody (anti-HCV)

*Measures used in efficacy assessment.

7.1.7.3 Standard analyses and explorations of laboratory data

Abbott reported that the mean changes from Baseline to Endpoint in chemistry and hematology variables (summarized in the following tables) were '*small in each treatment group and not considered clinically significant*'. The statistically significant differences between treatment groups in mean change from Baseline to Endpoint were observed for monocytes, RBC count, and uric acid.

CHEMISTRY	Baseline		Endpoint		Change from Baseline			Between Group Comparisons Compared to Placebo		
Lab (unit) Treatment	Mean	Median	Mean	Median	Mean	SD	Median	Mean	SE	p-value
Sodium (meq/l)										
Sibutramine	140.1	140.0	140.7	141.0	0.6	2.93	0.0	0.02	0.32	0.959
Placebo	139.9	140.0	140.4	140.0	0.6	2.36	0.0			
Potassium (meq/l)										
Sibutramine	4.3	4.3	4.3	4.2	0.0	0.38	0.0	0.04	0.04	0.367
Placebo	4.3	4.3	4.3	4.2	0.0	0.33	-0.1			
Chloride (meq/l)										
Sibutramine	102.9	103.0	104.2	104.0	1.3	3.67	1.0	0.44	0.42	0.298
Placebo	103.3	103.0	104.2	104.0	0.9	3.57	1.0			
Bicarbonate (meq/l)										
Sibutramine	23.9	24.0	24.6	25.0	0.7	2.46	1.0	0.52	0.28	0.065
Placebo	23.8	23.0	23.9	24.0	0.2	2.44	1.0			
Blood urea nitrogen (mg/dl)										
Sibutramine	11.5	11.0	11.7	11.0	0.3	2.97	0.0	0.09	0.34	0.780
Placebo	11.5	11.0	11.6	11.5	0.2	2.80	0.0			
Creatinine (mg/dl)										
Sibutramine	0.8	0.8	0.7	0.7	-0.1	0.13	-0.1	0.01	0.02	0.359
Placebo	0.8	0.8	0.7	0.7	-0.1	0.13	-0.1			
Calcium (mg/dl)										
Sibutramine	9.6	9.6	9.5	9.6	-0.1	0.39	-0.1	-0.03	0.04	0.437
Placebo	9.6	9.6	9.6	9.6	-0.1	0.34	-0.1			
Albumin (g/dl)										
Sibutramine	4.3	4.3	4.2	4.2	-0.1	0.25	-0.1	0.04	0.03	0.219
Placebo	4.3	4.3	4.2	4.2	-0.2	0.24	-0.2			
Total Protein (g/dl)										
Sibutramine	7.5	7.5	7.3	7.3	-0.1	0.38	-0.1	-0.01	0.04	0.762
Placebo	7.5	7.5	7.4	7.4	-0.1	0.37	-0.2			
Alkaline phosphatase (u/l)										
Sibutramine	202.5	173.5	157.9	122.5	-44.6	47.82	-34.0	-7.17	5.49	0.192
Placebo	205.3	193.5	167.9	136.0	-37.4	46.46	-26.5			
Inorganic phosphorus (mg/dl)										
Sibutramine	4.4	4.3	4.4	4.4	0.1	0.58	0.1	0.03	0.07	0.657
Placebo	4.5	4.4	4.5	4.4	0.1	0.59	0.0			
Lactate dehydrogenase (u/l)										
Sibutramine	197.0	192.5	183.0	174.5	-14.0	40.03	-18.5	4.45	4.60	0.334
Placebo	203.8	196.0	185.4	182.0	-18.4	38.95	-17.5			
SGOT/AST (U/l)										
Sibutramine	20.5	20.0	19.9	18.5	-0.5	6.21	0.0	0.98	0.73	0.182
Placebo	22.1	20.5	20.6	19.0	-1.5	6.71	-1.0			
SGPT/ALT (U/l)										
Sibutramine	21.8	18.0	18.7	16.0	-3.1	9.16	-2.5	-0.84	1.06	0.425
Placebo	23.	20.0	21.5	18.0	-2.2	9.09	-2.0			
Total Bilirubin (mg/dl)										
Sibutramine	0.4	0.4	0.4	0.4	0.0	0.17	0.1	0.02	0.02	0.245
Placebo	0.4	0.4	0.4	0.3	0.0	0.19	0.0			
Uric Acid (mg/dl)										
Sibutramine	5.8	5.7	5.5	5.3	-0.2	0.89	-0.3	-0.32	0.10	0.002
Placebo	5.8	5.7	5.9	5.8	0.1	0.81	0.1			

Sibutramine N = 318; Placebo N = 98 *Sibutramine N = 3 Table 1.43_4.6

HEMATOLOGY	Baseline		Endpoint		Change from Baseline			Between Group Comparisons Compared to Placebo		
Lab (unit) Treatment	Mean	Median	Mean	Median	Mean	SD	Median	Mean	SE	p-value
WBC (k/mm^3)										
Sibutramine	7.3	7.0	7.3	7.1	0.0	1.90	0.1	-0.08	0.22	0.701
Placebo	7.5	7.3	7.5	7.5	0.1	1.59	0.1			
Hemoglobin (g/dl)										
Sibutramine	13.5	13.5	13.4	13.4	-0.1	0.74	-0.1	-0.09	0.09	0.291
Placebo	13.4	13.5	13.4	13.3	0.0	0.76	0.0			
Hematocrit (%)										
Sibutramine	43.2	42.9	42.1	42.0	-1.1	2.65	-1.2	-0.30	0.31	0.340
Placebo	42.9	43.0	42.1	41.9	-0.8	2.68	-1.1			
RBC (m/mm^3)										
Sibutramine	4.9	4.9	4.7	4.7	-0.2	0.27	-0.2	-0.08	0.03	0.013
Placebo	4.9	4.9	4.8	4.8	-0.1	0.28	-0.1			
Platelets (k/mm^3)										
Sibutramine	326.8	320.0	306.2	304.0	-20.6	46.25	-20.0	4.98	5.25	0.343
Placebo	326.6	319.0	301.0	292.0	-25.6	38.23	-24.5			
Basophils (%)										
Sibutramine	0.6	0.5	0.7	0.7	0.1	0.40	0.1	0.03	0.05	0.476
Placebo	0.6	0.6	0.7	0.6	0.1	0.46	0.1			
Eosinophils (%)										
Sibutramine	2.2	1.9	1.9	1.5	-0.3	1.20	-0.3	-0.01	0.15	0.929
Placebo	2.4	1.8	2.1	1.5	-0.3	1.45	-0.3			
Lymphocytes (%)										
Sibutramine	33.0	32.4	32.4	31.0	-0.6	8.33	-1.2	0.06	0.94	0.953
Placebo	32.7	31.9	32.1	32.0	-0.6	6.65	-0.2			
Monocytes (%)										
Sibutramine	5.5	5.2	5.3	5.2	-0.2	1.89	-0.1	-0.44	0.22	0.047
Placebo	5.6	5.2	5.8	5.5	0.2	1.84	0.1			
Neutrophils (%)										
Sibutramine	56.8	57.3	57.7	58.7	0.9	8.85	2.2	0.50	1.02	0.624
Placebo	56.9	56.4	57.3	58.0	0.4	7.95	-0.2			
Large unstained cells (%)										
Sibutramine	1.9	1.8	2.0	2.0	0.0	0.87	0.1	-0.12	0.10	0.252
Placebo	1.9	1.9	2.1	2.1	0.2	0.92	0.2			

Sibutramine N = 305; Placebo N = 94 Table 14.3_4.7

Comment: The laboratory findings did not show any clinically significant differences. These findings are similar to those reported in the adult studies. Shift tables and evaluations for outliers did not reveal any trends for laboratory abnormalities associated with the use of sibutramine in adolescents.

Abbott has proposed that the decrease in uric acid is associated with an improvement in cardiovascular risk. In a recent review, Kanellis and Kang[9] discuss the potential benefits and risks associated with uric acid in that it has been described as both an anti-oxidant and a pro-oxidant. They note that despite decades of debate the issue has not been settled. Therefore, in the absence of outcome data, no conclusions can be drawn from the finding.

9 Kanellis, J an dKang, D-H. (2005) Uric Acid as a Mediator of Endothelial Dysfunction, Inflammation, and Vascular Disease. Sem Nephrol, 25:39-42.

7.1.8 Vital Signs

7.1.8.1 Overview of vital signs testing in the development program

Heart rate (pulse) and blood pressure were assessed according to the study schedule (See Appendix 10.1.1.3). Additional evaluations included 24-hour ambulatory blood pressure monitoring. The protocols and withdrawal criteria for these evaluations were as follows:

Vital signs:

1. Pulse and blood pressure (BP) were recorded in the seated position and taken around the same time of day (± 2 hours). The final measurement was an average of 3 separate readings taken 2 minutes apart. The same BP cuff and the same arm were used throughout the study.

   BP/Pulse Withdrawals:

   a. Any subject who developed on a single visit a mean diastolic blood pressure (DBP) > 95 mm Hg or an increase in DBP > an 15 mm Hg from baseline, or a mean systolic blood pressure (SBP) > 150 mm Hg or increase in SBP > 20 mm Hg from baseline could be brought back within 72 hours or was considered a BP "outlier," withdrawn from the study and followed biweekly for one month, or until BP returned to acceptable values.

   b. Any subject who developed a 10-15 mm Hg mean increase from baseline in DBP or a 15-20 mm Hg mean increase from baseline in SBP would be brought back within 7 days for repeat measurement. Subjects with the above increases on three consecutive visits were considered BP "outliers", withdrawn from the study and followed for at least one month, or until BP returned to an acceptable value.

   c. Any subject who developed on any single visit during double-blind treatment a mean pulse rate > 100 bpm or an increase from baseline in pulse rate > 20 bpm, could be brought back within 72 hours at the discretion of the investigator or immediately considered a pulse rate "outlier"; the subject would be withdrawn from the study and followed biweekly for one month, or until the pulse rate returned to an acceptable value.

   d. Any subject with a mean pulse rate of 106-110 bpm or a mean increase from baseline > 15 bpm was brought back within 7 days for a repeat measurement. Subjects with these increases on three consecutive visits during the treatment period were considered a pulse rate "outlier", withdrawn from the study and followed for at least one month, or until pulse rate returned to acceptable values.

2. ABPM (ambulatory blood pressure monitoring) procedure (protocol Attachment 4): At selected sites, ABPM was planned at baseline and at Month 7. The accuracy and precision of the monitors were confirmed by simultaneous measurements with a mercury sphygmomanometer at the beginning of the test period; if differences exceeded 10 mm Hg (SBP or DBP), the subject was excluded from the ABPM portion of the study. The monitors were programmed to measure BP every 20 minutes from 7 am to 9 pm, and every 30 minutes from 9 pm to 7 am. A minimum of 30 recordings were planned during the 24-hour study

period. A diary was given to subjects for recording activity levels. Daytime was defined as 9 am- 6 pm; nighttime was defined as 12 – 6 am while sleeping. ABPM tapes were downloaded immediately after device removal; subjects with unacceptable ABPM recordings could undergo a repeat study once within 2 weeks.

The sample size for ABPM was based on a 30% drop-out rate by Month 7 and, given a 3:1 randomization ratio, would result in about 40 subjects on sibutramine and 15 on placebo having ABPM at Month 7 if 80 subjects had ABPM at baseline.

Comment: According to the Cardio/Renal Consultant the methodology of ABPM acquisition and measurements appear to be appropriate.

7.1.8.3 Standard analyses and explorations of vital signs data

Findings for systolic and diastolic blood pressures are summarized in the following table:

Treatment Group	Full Analysis Set				Completers Set			
	Month 6				Month 6			
Systolic Blood Pressure (mmHg)	**N**	**BL Mean mmHg (SD)**	**Mean Change mmHg (SD)**	**Max. Change mmHg**	**N**	**BL Mean mmHg (SD)**	**Mean Change mmHg (SD)**	**Max. Change mmHg**
Sibutramine	363	113.3 (9.1)	-1.3 (8.4)	24	205	113 (9.0)	-1.2 (8.2)	22
Placebo	127	113.0 (9.4)	-2.0 (7.8)	18	65	112.0 (9.5)	-2.0 (7.7)	10
	Endpoint				Month 12			
	N	**BL Mean mmHg (SE)**	**Mean Change mmHg (SE)**	**Max. Change mmHg**	**N**	**BL Mean mmHg (SE)**	**Mean Change mmHg (SE)**	**Max. Change mmHg**
Sibutramine	363	113.3 (0.5)	-2.1 (0.4)	20	281	113.5 (0.5)	-2.3 (0.4)	18
Placebo	127	113.0 (0.8)	-2.0	18	79	113.0 (1.0)	-2.5 (0.7)	12
Mean Tr. Diff. (SE)	0.0 (0.7)				0.2 (0.8)			
95% CI	-1.3, 1.4				-1.4, 1.9			
p-value	0.988				0.772			
	Month 6				Month 6			
Diastolic Blood Pressure (mmHg)	**N**	**BL Mean mmHg (SD)**	**Mean Change mmHg (SD)**	**Max. Change mmHg**	**N**	**BL Mean mmHg (SD)**	**Mean Change mmHg (SD)**	**Max. Change mmHg**
Sibutramine	363	69.0 (7.6)	0.4 (7.7)	20	205	68.8 (7.2)	0.6 (7.1)	19
Placebo	127	69.4 (7.4)	-1.3 (7.9)	20	65	69.7 (6.5)	-0.7 (6.7)	18
	Endpoint				Month 12			
	N	**BL Mean mmHg (SE)**	**Mean Change mmHg (SE)**	**Max. Change mmHg**	**N**	**BL Mean mmHg (SE)**	**Mean Change mmHg (SE)**	**Max. Change mmHg**
Sibutramine	363	69.0 (0.4)	-0.1 (0.4)	24	281	68.9 (0.4)	-0.5 (0.4)	24
Placebo	127	69.4 (0.7)	-1.1 (0.6)	19	79	69.3 (0.8)	-0.9 (0.7)	25
Mean Tr. Diff. (SE)	1.0 (0.7)				0.4 (0.8)			
95% CI	-0.3, 2.4				-1.2, 2.0			
p-value	0.136				0.646			

Table 49

Comment: **Mean changes in blood pressure appear consistent for the full analysis and completers populations. According to the Cardio/Renal consultant, there were no statistically or clinically significant differences between groups.**

Findings for pulse are summarized in the following table:

Treatment Group	Full Analysis Set				Completers Set			
	Month 6				Month 6			
Pulse Rate (bpm)	N	BL Mean bpm (SD)	Mean Change bpm (SD)	Max. Change bpm	N	BL Mean bpm (SD)	Mean Change bpm (SD)	Max. Change bpm
Sibutramine	363	77.2 (8.7)	0.8 (9.1)	48	205	77.5 (8.5)	0.0 (8.5)	19
Placebo	127	75.4 (8.9)	-0.7 (8.9)	34	65	75.0 (8.9)	-2.3 (8.2)	17
	Endpoint				Month 12			
	N	BL Mean bpm (SE)	Mean Change bpm (SE)	Max. Change bpm	N	BL Mean bpm (SE)	Mean Change bpm (SE)	Max. Change bpm
Sibutramine	363	77.2 (0.5)	-0.2 (0.4)	32	281	77.6 (0.5)	-0.7 (0.4)	32
Placebo	127	75.4 (0.8)	-1.8 (0.7)	34	79	75.7 (1.0)	-2.3 (0.8)	26
Mean Tr. Diff. (SE)	1.6 (0.8)				1.7 (1.0)			
95% CI	0.0, 3.1				-0.2, 3.5			
p-value	0.055				0.083			

Table 49

Comment: Mean changes in pulse appear consistent between the full analysis and completers populations. According to the Cardio/Renal Consultant, there were no statistically or clinically significant differences between groups.

The representative value of the findings for blood pressure and pulse at the 6-month and 12-month endpoints is in question. According to the protocol, all subjects were to refrain from taking the study medications prior to the Week 12, Month 6, and Month 12 visits, and those subjects in the pharmacokinetic substudy were to also refrain from taking the study medication prior to the Month 8, Month 9, and Month 10 visits. Therefore, for several of the time points measured, including the safety measures reported in the above tables, subject did not take the study medication on the day of the evaluation. Therefore, changes in blood pressure and pulse as a result of exposure to study medication at C_{max} may have been less apparent.

7.1.8.3.2 Analyses focused on outliers or shifts from normal to abnormal

The criteria for evaluating outliers are outlined in the following table:

Variable	Single Visit		Three Consecutive Visits	
	Absolute Threshold	Change from Baseline	Absolute Threshold	Change from Baseline
SBP (mmHg)	> 150	> 20	NA	> 15 but ≤ 20
DBP (mmHg)	> 95	> 15	NA	> 10 but ≤ 15
Pulse Rate (bpm)	> 110	> 20	> 105 but ≤ 110	> 15 but ≤ 20

Table 52

According to the analyses provided by Abbott, 'the incidence of vital sign outliers was 117/363 (32%) of subjects in the sibutramine group and 21/130 (16%) of subjects in the placebo group; the difference in the incidence of outliers between treatment groups was statistically significant (p = 0.001, logistic regression)'.

7.1.8.3.3 Marked outliers and dropouts for vital sign abnormalities

Marked outliers for vital sign abnormalities are summarized in the following table:

Vital Sign	Elevation Category	Sibutramine 10 mg (N=194) n (%)	Sibutramine 15 mg (N=174) n (%)	Sibutramine Overall (N=368) n (%)	Placebo (N=130) n (%)
SBP	> 150 mmHg	0 (0%)	0 (0%)	0 (0%)	0 (0%)
	> 20 mmHg greater than BL	7 (4%)	11 (6%)	18 (5%)	5 (4%)
	> 150 mmHg and > 20 mmHg greater than BL	0 (0%)	0 (0%)	0 (0%)	0 (0%)
	> 15 but ≤ 20 mmHg greater than BL on 3 consecutive visits	1 (1%)	0 (0%)	1 (0%)	0 (0%)
DBP	> 95 mmHg	2 (1%)	1 (1%)	3 (1%)	0 (0%)
	> 15 mmHg greater than BL	21 (11%)	17 (10%)	38 (10%)	10 (8%)
	> 95 mmHg and > 15 mmHg greater than BL	1 (1%)	1 (1%)	2 (1%)	0 (0%)
	> 10 but ≤ 15 mmHg greater than BL on 3 consecutive visits	5 (3%)	3 (2%)	8 (2%)	0 (0%)
Pulse Rate	> 110 bpm	5 (3%)	5 (3%)	10 (3%)	0 (0%)
	> 20 bpm greater than BL	37 (19%)	35 (20%)	72 (20%)	8 (6%)
	> 110 bpm and > 20 bpm greater than BL	5 (3%)	4 (2%)	9 (2%)	0 (0%)
	> 105 but ≤ 110 or > 15 but ≤ 20 bpm greater than BL on 3 consecutive visits	4 (2%)	2 (1%)	6 (2%)	1 (1%)

From Table 54

Comment: The Cardio/Renal Consultant noted that 'There is an increase in percentage heart rate outliers in sibutramine-treated patients compared to placebo; this is most evident in the group that experienced > 20 bpm increase from baseline. In addition, there may be an increase in DBP outliers taking sibutramine compared to placebo.'

She further commented that 'It may be argued that there was a baseline imbalance in heart rate between the two treatment groups that may have confounded the finding of increased mean heart rate in sibutramine-treated subjects at endpoint (Table 3). However, since these vital signs were not necessarily performed at peak drug concentrations, these results do not exclude heart rate increases at Tmax. Furthermore, there is an increased rate of

"pulse rate outliers" in sibutramine-treated subjects compared to placebo (20% vs. 6%, respectively). There is, in addition, a statistically significant increase in treatment emergent tachycardia in sibutramine-treated subjects compared to placebo (13% vs. 6%, respectively). This reviewer feels that there is enough evidence that sibutramine may increase heart rate in susceptible adolescents.'

7.1.8.4 Additional analyses and explorations

ABPM was performed in a subset of patients at 6 sites. A total of 78 subjects (56 sibutramine, 22 placebo) underwent baseline 24-hour APBM. The demographics for the subset were balanced between treatment groups. The subjects were between 12 and 16 years of age (mean 14.0 years); 70.5% female; and about 61.5% Caucasian (14.1% Hispanic/Mexican-American and 15.4% Black/African-American).

Results- A total of A total of 47/56 (84%) sibutramine and 16/22 (73%) placebo subjects provided baseline and endpoint ABPM results. Of the 47 sibutramine-treated subjects 16 subjects were taking the 10 mg dose and 31 subjects had been titrated to the 15 mg dose.

Mean Change from Baseline to Endpoint in Systolic and Diastolic Blood Pressure Measured by Ambulatory Blood Pressure Monitoring – Safety Set

Treatment Group	N	Systolic Blood Pressure		Diastolic Blood Pressure	
		Baseline Mean mmHg (SD)	Mean Change mmHg (SD)	Baseline Mean mmHg (SD)	Mean Change mmHg (SD)
Mean 24-Hour					
Sibutramine	47	117.3 (7.0)	-0.3 (6.1)	66.9 (6.0)	1.6 (5.2)
Sibutramine Final Dose					
Sibutramine 10 mg	16	115.0 (7.7)	-0.5 (5.5)	66.8 (5.9)	2.4 (4.7)
Sibutramine 15 mg	31	118.5 (6.4)	-0.2 (6.5)	67.0 (6.1)	1.2 (5.5)
Placebo	16	120.9 (8.9)	-0.3 (6.5)	70.0 (5.8)	-2.1 (4.7)
Mean Daytime					
Sibutramine	47	120.4 (8.1)	-1.6 (7.1)	71.1 (7.1)	0.4 (6.2)
Sibutramine Final Dose					
Sibutramine 10 mg	16	119.2 (8.1)	-2.8 (6.9)	72.3 (7.5)	0.1 (6.2)
Sibutramine 15 mg	31	121.0 (8.1)	-0.9 (7.2)	70.4 (6.9)	0.6 (6.3)
Placebo	16	123.9 (9.2)	0.4 (7.4)	73. 0(6.1)	-1.5 (5.7)
Mean Nighttime					
Sibutramine	47	108.6 (8.2)	1.5 (8.5)	57.1 (6.8)	2.5 (6.9)
Sibutramine Final Dose					
Sibutramine 10 mg	16	105.8 (8.1)	-0.4 (6.6)	57.0 (5.9)	1.3 (4.8)
Sibutramine 15 mg	31	109.9 (8.0)	2.5 (9.2)	57.2 (7.4)	3.2 (7.8)
Placebo	16	113.2 (9.5)	-1.7 (10.3)	60.3 (7.0)	-2.9 (8.5)
Mean Daytime - Mean Nighttime					
Sibutramine	47	11.9 (9.1)	-3.1 (7.9)	14.0 (7.7)	-2.1 (8.7)
Sibutramine Final Dose					
Sibutramine 10 mg	16	13.4 (6.2)	-2.3 (6.2)	15.4 (8.5)	-1.2 (7.0)
Sibutramine 15 mg	31	11.1 (10.3)	-3.5 (8.8)	13.3 (7.4)	-2.6 (9.5)
Placebo	16	10.7 (7.8)	2.1 (11.9)	12.7 (7.5)	1.4 (10.5)

Comment: According to the Cardio/Renal Consultant, 'a review of ABPM curves suggests an increase from baseline in DBP (about 1-3 mm Hg) and SBP (about 3-5 mm Hg) in sibutramine-treated subjects. There is a slight but consistent increase in DBP outliers in sibutramine-treated subjects compared to placebo. In addition, there was an increase in treatment-emergent hypertension in sibutramine-treated subjects compared to placebo (11% vs. 8%, respectively). The evidence suggests that sibutramine may increase BP in susceptible adolescents.'

The Written Request specified that the study include a 'report of 24-hour ambulatory blood pressure and pulse data during at least a one-week period at a dose of 15 mg per day.' Inclusion of these subjects was to represent the effects of the maximum dose studied. However, given that those patients who had dose increases were 'non-responders' (did not lose ≥ 10% of baseline BMI by 6-months), and by examination of the weight loss data, continued to be 'non-responders' throughout the trial (Refer to Section 6.1.4), they may respond to sibutramine differently and may not be representative of the effects of the 15-mg dose of sibutramine on pulse and blood pressure in patients who lost ≥ 10% of baseline BMI by Month 6.

7.1.9 Electrocardiograms (ECGs)

7.1.9.1 Overview of ECG testing in the development program, including brief review of preclinical results.

There was no mention of the need for additional ECG testing or QT studies in the Written Request. According to the protocol: 'A standard, 12-lead ECG was to be recorded at Screening, any Unscheduled Visit if clinically significant and the Month 12/Premature Discontinuation Visit. The PR, QRS and QT intervals were to be calculated from Lead II at the study site. Heart rate was to be determined from the RR intervals by the study site, but was requested on the eCRF as ventricular heart rate, defined by the number of QRS complexes per minute. The calculated PR, QRS and QT intervals and pulse rate were to be recorded on the eCRF by site personnel. QTc intervals were calculated from database QT values by Abbott Laboratories using Bazett's correction formula: QT interval/(60/ECG pulse rate).'

7.1.9.3 Standard analyses and explorations of ECG data

ECG Variable	N	Baseline Mean (SE)	Endpoint Mean (SE)	Mean Change (SE)
PR Interval (msec)				
Sibutramine	317	147.3 (1.0)	147.4 (1.2)	-0.1 (0.9)
Placebo	98	148.4 (1.8)	152.3 (2.1)	4.1 (1.7)
QRS Interval (msec)				
Sibutramine	317	83.9 (0.7)	83.3 (0.7)	-0.6 (0.6)
Placebo	98	83.7 (1.2)	84.2 (1.2)	0.4 (1.1)
QT Interval (msec)				
Sibutramine	316	373.8 (1.7)	365.5 (1.8)	-8.7 (1.6)
Placebo	98	376.6 (3.0)	378.8 (3.2)	3.4 (2.9)
QTc Interval (msec)[a]				
Sibutramine	316	411.6 (1.4)	412.0 (1.6)	0.6 (1.5)
Placebo	98	409.4 (2.5)	405.7 (2.9)	-4.7 (2.7)
Ventricular Heart Rate (bpm)				
Sibutramine	317	73.9 (0.7)	77.4 (0.7)	3.7 (0.6)
Placebo	99	72.1 (1.2)	69.7 (1.2)	-3.1 (1.0)

Table 61

7.1.9.3.2 Analyses focused on outliers or shifts from normal to abnormal

Subjects with Very High/Very Low Post-Baseline ECG Sign Values	Treatment Group n (%) Sibutramine	Placebo
ECG Very High/Very Low Criteria (units)	**(N=368)**	**(N=130)**
PR: < 120 msec	18 (4.9%)	2 (1.5%)
PR: > 200 msec	2 (0.5%)	0
QRS: < 60 msec	3 (0.8%)	1 (0.8%)
QRS: > 100 msec	16 (4.3%)	3 (2.3%)
QTc: > 480 msec[a]	3 (0.8%)	0
Ventricular Heart Rate: ≤ 50 bpm	1 (0.3%)	3 (2.3%)
Ventricular Heart Rate: decrease ≥ 15 bpm from Baseline	22 (6.0%)	10 (7.7%)
Ventricular Heart Rate: increase ≥ 15 bpm from Baseline	60 (16.3%)	8 (6.2%)

Table 62

7.1.9.3.3 Marked outliers and dropouts for ECG abnormalities

Subject Number	Study Day	Post Dosing Yes/No/Day	Ventricular Heart Rate (bpm)	QT (msec)	QTc Bazett (msec)	QTc Fridericia (msec)
1402	Baseline	No	76	388	436.7	419.8
	358	No	70	428	462.3[a]	450.6
	364	Yes/6 days	83	387	455.2	431.2
	388	Yes/30 days	77	447	506.4	485.8
2221	Baseline	No	86	424	507.6	478.1
	177	Yes/8 days	95	400	503.3	466.2
	191	Yes/22 days	91	408	502.5	468.8
2801	Baseline	No	78	320	364.9	349.2
	335	No	90	396	485.0	453.3

Table 63

Comments: According to the Cardio/Renal Consultant, 'While this Division was not specifically asked to comment about QT effects, the presence of a serious adverse event related to prolonged QT led this reviewer to review the QTc results. Since the timing of ECGs were not specified, the reviewer will assume that these ECGs were not performed at the time of peak active drug concentrations. In addition, since sibutramine may have heart rate effects, Bazett's correction may not be the ideal method for calculating QTc.'

The design of this study does not allow conclusions to be made regarding sibutramine and QT prolongation. Because the Regulatory Recommendation is non-approval a request for a formal QT study in pediatric patients is not warranted at this time.

7.1.10 Immunogenicity

Not Applicable

7.1.11 Human Carcinogenicity

No data on the carcinogenetic potential of sibutramine were included in this submission, nor have any data regarding this topic come to this Reviewer's attention.

7.1.12 Special Safety Studies

7.1.12.1 – Echocardiography

Echocardiography (protocol Attachment 5): At selected sites, echocardiographic assessments were planned at baseline and at Month 12 or at premature termination after Month 6. It was pre-specified that all subjects should undergo 2-dimensional and color Doppler imaging, using all standard echocardiographic views. Potential valve insufficiency should be interrogated; if insufficiency was present, continuous wave Doppler would be recorded. A separate tape was used to record the echocardiogram for each subject; a copy was stored at the source echocardiography lab and the original recordings were batched and shipped weekly to a core laboratory (b) (4) A single evaluator evaluated all echocardiograms for left ventricular measurements and quantification of valvular regurgitation. All echocardiograms were reviewed (b) (4) for confirmation of valvular pathology; in addition, every echocardiogram was reanalyzed (b) (4) for purposes of chamber measurements, description of anatomic abnormalities and determination of valvular insufficiency. One-third of the studies were to be completely and independently reviewed (b) (4) providing a 'secondary read'. Significant discrepancies would be noted and sent to the sponsor. No specific mention of 'blinding' the reader(s) was made in the submission or protocol.

Comment: **According to the Cardio/Renal Consultant, the methodology of echocardiography acquisition and measurements appear to be appropriate.**

Results: A summary of the results are presented in the following table:

Sub-Sample Echocardiogram Changes from Baseline to Endpoint (Safety Set)			
Intraventricular Septal Thickness in Diastole (mm)			
	N	**Baseline Mean**	**Mean Change**
Sibutramine	87	9.1	-0.4
Placebo	21	9.7	-0.6
Mean Tr. Diff. (SE)		0.1 (0.3)	
90% Confidence Interval		-0.3, 0.5	
p-value		0.660	
Left Ventricular Mass (g)			
	N	**Baseline Mean**	**Mean Change**
Sibutramine	86	166.4	-11.9
Placebo	21	174.0	-14.1
Mean Tr. Diff. (SE)		2.2 (7.5)	
90% Confidence Interval		-10.2, 14.6	
p-value		0.771	
Left Ventricular Posterior Wall Thickness in Diastole (mm)			
	N	**Baseline Mean**	**Mean Change**
Sibutramine	87	9.0	-0.4
Placebo	21	9.4	-0.4
Mean Tr. Diff. (SE)		-0.1 (0.2)	
90% Confidence Interval		-0.5, 0.3	
p-value		0.734	

Table 66

Comment: According to the Cardio/Renal Consultant 'the available echocardiography results did not reveal a safety signal. However, interpretation of the findings is limited by missing data and the sample size.'

7.1.12.2 – Behavioral Assessment

The Written Request included a 'report of effects of sibutramine on cognitive function (i.e. learning, memory, and psychometrics) in all of sibutramine- and all of placebo-treated patients'.

Behavioral, Cognition, and Quality-of-Life Assessments: In the full analysis set, behavior, cognitive function (*i.e.,* learning, memory, and psychometrics) and Quality-of-Life were assessed using a comprehensive battery of behavioral and quality-of-life measures. Specific instruments were selected to comprehensively assess broad behavioral, cognitive and quality-of-life outcomes. These instruments were appropriate for assessing patient-reported outcomes in adolescents, and possessed acceptable evidence supporting psychometric characteristics (*i.e.,* reliability, validity). A comprehensive battery of well-validated instruments, including the CDI, the Piers-Harris Self-Concept Scale, the Three-Factor Eating Questionnaire, the CBCL, the IWQOL, and the Peds QL were to be assessed at Baseline, Month 3, Month 6 and the Month 12 or discontinuation visit.

Results: No clear or consistent differences were observed on these psychological rating scale parameters.

Comment: According to the Neurology/Psychiatry Consultant, the assessments listed above are not sufficient to measure cognitive function (learning, memory). However, the consultant noted that these measures were sufficient and appropriate to make comments regarding the potential for depression in this population of obese adolescents.

The increased incidence of CNS and other psychiatric adverse events raised concerns that sibutramine, a drug initially developed as an antidepressant, may increase the risk of depression or other mood disturbances. The increased incidence of 'accidental injury' in the sibutramine group compared to placebo may also reflect outcomes due to depression or mood disturbances. On the other hand they may be related to non-psychiatric effects including but not limited to CNS or cardiovascular mediated effects of the drug.

The company was requested to provide full narratives of the 'accidental injuries' to further investigate the nature of these occurrences. However, Abbott responded that they were unable to provide these records the narratives were not compiled. All narratives related to accidental injuries will be evaluated during the assessment for suicidality. Until completion of that assessment, the absence of complete narratives makes it impossible to further elucidate the contribution, if any, sibutramine may have made in the imbalance of 'accidental injuries'.

This study was not designed to address neuropsychiatric effects of the drug.

Given the recent concern that some antidepressants may increase the risk for suicidality in adolescents with psychiatric disorders together with the fact sibutramine's mechanism of action to inhibit the re-uptake of serotonin and norepinephrine is similar to some antidepressants, it would be prudent to include precautionary language, shown below, in the drug's labeling.

Pediatric Use

The efficacy of sibutramine in adolescents who are obese has not been adequately studied.

Sibutramine's mechanism of action inhibiting the reuptake of serotonin and norepinephrine is similar to the mechanism of action of some antidepressants. Pooled analyses of short-term placebo-controlled trials of antidepressants in children and adolescents with major depressive disorder (MDD), obsessive compulsive disorder (OCD), and other psychiatric disorders have revealed a greater risk of adverse events representing suicidal behavior or thinking during the first few months of treatment in those receiving antidepressants. The average risk of such events in patients receiving antidepressants was 4%, twice the placebo risk of 2%.

No placebo-controlled trials of sibutramine have been conducted in children or adolescents with MDD, OCD, or other psychiatric disorders. In a study of adolescents with obesity in

which 368 patients were treated with sibutramine and (b) (4) patients with placebo, one patient in the sibutramine group and one patient in the placebo group attempted suicide. Suicidal ideation was reported by 2 sibutramine-treated patients and none of the placebo patients. It is unknown if sibutramine increases the risk of suicidal behavior or thinking in pediatric patients.

(b) (4)

7.1.15 Assessment of Effect on Growth

The majority of adolescents were not reported to have an appreciable increase in height over the 1-year course of the study. Because of the limitations in the collection of the data, however, this finding reflects inaccurate measurement of height rather than a growth-inhibiting effect of sibutramine.

7.2 Adequacy of Patient Exposure and Safety Assessments

7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

7.2.1.1 Study type and design/patient enumeration

SB-238 was a double-blind, randomized, placebo-controlled, multi-center, parallel arm, 12-month, non-forced dose-escalation study to evaluate the safety and efficacy of sibutramine when given to obese adolescents. The study consisted of a screening period and a 52-week double-blind treatment period.

7.2.1.2 Demographics

Refer to Section 6.1.4.

7.2.1.3 Extent of exposure (dose/duration)

Drug Exposure: *The mean exposure to study drug was 294 days in the sibutramine group and 254 days in the placebo group. The median exposure to study drug was 336 days in both treatment groups.* (b) (4)

Drug Exposure	Randomized Treatment Group		Sibutramine by Dose Level		Placebo by Dose Level	
	Sibutramine N = 368	Placebo N = 130	10 mg N = 368	15 mg N = 174	10 mg N = 130	15 mg N = 85
Days of Exposure	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
1 - 28	20 (5.4)	9 (6.9)	20 (5.4)	4 (2.3)	9 (6.9)	4 (4.7)
29 - 56	12 (3.3)	5 (3.8)	12 (3.3)	6 (3.4)	5 (3.8)	1 (1.2)
57 - 84	10 (2.7)	9 (6.9)	10 (2.7)	5 (2.9)	9 (6.9)	3 (3.5)
85 - 112	8 (2.2)	6 (4.6)	8 (2.2)	2 (1.1)	6 (4.6)	2 (2.4)
113 - 140	3 (0.8)	3 (2.3)	4 (1.1)	8 (4.6)	4 (3.1)	1 (1.2)
141 - 168	3 (0.8)	4 (3.1)	60 (16.3)	84 (48.3)	34 (26.2)	36 (42.4)
169 - 196	7 (1.9)	6 (4.6)	116 (31.5)	60 (34.5)	54 (41.5)	36 (42.4)
197 - 224	6 (1.6)	1 (0.8)	1 (0.3)	1 (0.6)	1 (0.8)	1 (1.2)
225 - 252	6 (1.6)	3 (2.3)	0 (0.0)	1 (0.6)	1 (0.8)	1 (1.2)
253 - 280	2 (0.5)	2 (1.5)	1 (0.3)	1 (0.6)	0 (0.0)	0 (0.0)
281 - 308	7 (1.9)	3 (2.3)	3 (0.8)	0 (0.0)	2 (1.5)	0 (0.0)
309 - 336	112 (30.4)	28 (21.5)	58 (15.8)	0 (0.0)	1 (0.8)	0 (0.0)
337 - 364	148 (40.2)	45 (34.6)	61 (16.6)	0 (0.0)	3 (2.3)	0 (0.0)
>= 365	24 (6.5)	6 (4.6)	14 (3.8)	2 (1.1)	1 (0.8)	0 (0.0)
N	368	130	368	174	130	85
Mean	294.5	253.7	220.0	159.4	151.6	156.2
STD	117.2	125.7	116.5	49.6	71.4	43.5
Median	336	336	175	168	168	168
Sum	108362	32981	80972	27728	19713	13281
Range	1 to 788	1 to 453	1 to 788	1 to 426	1 to 453	1 to 225

Table 14.1_2.1

7.2.8 Assessment of Quality and Completeness of Data

Height, a key component of the primary efficacy endpoint, was found to be unreliably measured and this in turn limits ones ability to interpret of the BMI data.

7.4.1 Pooling Data Across Studies to Estimate and Compare Incidence

There was only one pivotal study.

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

All subjects were started on 10 mg of sibutramine (or equivalent placebo). After 6 months of treatment subjects who did not achieve a ≥ 10% decrease in BMI from baseline had the dose increased to 15 mg of sibutramine (or equivalent placebo).

The timing of dose (i.e. in the morning, before meals or with meals) was not specified in the protocol with the exception of certain study days that doses were not to be taken:

Subjects were instructed to take 1 capsule of study medication at about the same time each day, preferably, in the morning, with approximately 4 ounces of water. On clinic visit days for the Week 12, Month 6 and Month 12 visits (fasting blood laboratory evaluation visits), subjects were not to take their study medication until after the blood samples were collected. Subjects who were to have a blood sample collected for pharmacokinetic assessments on the Month 8, 9 and 10 visits were not to take their study medication until after the samples were collected. (9.4.1)

Comment: **As noted in the discussions for safety, because study medications were held prior to the clinic visit, evaluations of heart rate and blood pressure at some of the time points would have measured the drug's effects at trough rather than peak serum levels. This may underestimate sibutramine's effect on blood pressure and pulse.**

8.2 Drug-Drug Interactions

No drug-drug interaction data were included in this submission.

8.3 Special Populations

This is a pediatric study conducted in response to a Pediatric Written Request. The Written Request specified that 'The study population should be comprised of 50-75% females. Efforts should be directed to obtain a study population comprising approximately 30% African-Americans. The study enrolled 322 females (64.7%) and 105 African Americans (21.1%). The enrollment of these subjects satisfied this component of the Written Request.

With the exception of obesity, all subjects enrolled in the trial were otherwise healthy. Subjects were excluded if they had psychiatric or medical disorders.

8.4 Pediatrics

This is a pediatric study of adolescents 12 to 16 years of age.

8.5 Advisory Committee Meeting

An Advisory Committee Meeting was not convened for this pediatric supplement.

8.6 Literature Review

Literature review included articles on weight loss paradigms and the effects of antidepressants in adolescents.

8.7 Postmarketing Risk Management Plan

None.

9 OVERALL ASSESSMENT

9.1 Conclusions

(b) (4)

The varied use of 'behavioral modification' across 33 centers enrolling relatively small numbers of subjects further limits interpretation of the effects of sibutramine over 'behavioral modification'.

Despite an extensive cardiovascular safety program, including echocardiography and ambulatory blood pressure monitoring, the timing of measuring pulse and blood pressure and the duration of exposure to sibutramine do not suggest that evaluations were made at adequate exposures.

Safety concerns regarding the psychiatric findings have not been adequately addressed in this study.

(b) (4)

Whether the safety data are sufficient to require that labeling be added to make this a 'contraindicated' treatment group is being evaluated by way of ongoing suicidality analyses. Abbott has told the Division that these analyses should be completed in November 2005.

9.2 Recommendation on Regulatory Action

Approve for labeling change. (b) (4)

9.3 Recommendation on Postmarketing Actions

None indicated.

9.4 Labeling Review

Based on the limitations of the data as outlined in the review, no new indication will be granted. However, due to the safety concerns raised by the psychiatric/CNS adverse events, the following addition to the pediatric section is recommended:

Pediatric Use

The efficacy of sibutramine in adolescents who are obese has not been adequately studied.

Sibutramine's mechanism of action inhibiting the reuptake of serotonin and norepinephrine is similar to the mechanism of action of some antidepressants. Pooled analyses of short-term placebo-controlled trials of antidepressants in children and adolescents with major depressive

disorder (MDD), obsessive compulsive disorder (OCD), and other psychiatric disorders have revealed a greater risk of adverse events representing suicidal behavior or thinking during the first few months of treatment in those receiving antidepressants. The average risk of such events in patients receiving antidepressants was 4%, twice the placebo risk of 2%.

No placebo-controlled trials of sibutramine have been conducted in children or adolescents with MDD, OCD, or other psychiatric disorders. In a study of adolescents with obesity in which 368 patients were treated with sibutramine and (b) (4) patients with placebo, one patient in the sibutramine group and one patient in the placebo group attempted suicide. Suicidal ideation was reported by 2 sibutramine-treated patients and none of the placebo patients. It is unknown if sibutramine increases the risk of suicidal behavior or thinking in pediatric patients.

(b) (4)

9.5 Comments to Applicant

We await your response to the letter dated June 22, 2005 requesting an evaluation of suicidality in accordance to the 'Guidance for exploring placebo-controlled clinical trials databases for suicidality and preparing data sets for analysis by FDA'.

10 APPENDICES

10.1 Review of Individual Study Reports

10.1.1 Study SB238

10.1.1.1 Protocol Deviations at Baseline

PROTOCOL DEVIATIONS at BASELINE			
Subjects that Did Not Meet Inclusion Criteria, but Entered Study			
	Description of Deviation	**Sibutramine**	**Placebo**
Inclusion Criteria	Good general health	2120	
	BMI above the lower limit of inclusion (2 units above the U.S. weighted mean for the 95th percentile based on age and gender)	108, 302, 307, 509, 2207, 2301, 2605, 2808, 3401	1301, 1703, 2813, 3005, 3108
	BMI below the upper limit of inclusion (44 kg/m^2)	121, 914, 923, 1121, 1122, 2811, 3123, 3715, 3718	122, 3023, 3404
	Screening mean blood pressure ≤ 130 and ≤ 85 mmHg	529, 705, 808, 823, 915, 920, 923, 1053, 1803, 3124, 3411, 3412	403, 423, 1823, 2720, 3707
	Screening/Baseline mean pulse rate ≤ 95 bpm	503, 920, 1512, 1519, 2918, 3622, 3701	403, 3721
	12 to 16 years of age at randomization	703[a]	
Subjects that Met Exclusion Criteria, but Entered Study			
	Description of Deviation	**Sibutramine**	**Placebo**
Exclusion Criteria	CDI t > 65	224	
	Total bilirubin ≤ 1 mg/dL	2225	528
	Screening fasting blood glucose > 126 mg/dL	2923	
	Untreated hypothyroidism as defined by TSH > 4.0 mU/L	305, 606, 709, 917, 1519, 2112, 2322, 2402, 2602, 2906, 3024, 3118, 3703, 3718	3023
	Parent had a major psychiatric illness	2219	
	Subject had attention deficit disorder	3403	1509
	Failed to maintain a minimum level of academic achievement during the previous 6 months prior to screening		810
	Positive drug screen for recreational drugs		1724
	Evidence of possible hepatic dysfunction as defined by ALT ≥ 50 IU/L	308, 722, 904, 1058, 2906, 3505, 3507, 3706, 3723	1013, 1123, 1509, 3702
	History of alcohol or drug addiction or substance abuse within the previous 2 years		3702
	Contraindicated concomitant medications[b]	405, 1012, 1524, 3524, 3718	2407
	Abnormal echocardiogram at Screening	3102, 3124	
Data Recorded Prior to Informed Consent			
		Sibutramine	**Placebo**
		402, 720, 3004	501, 531

10.1.1.2 Study Flow Chart

Evaluation	Study Visit: Weeks SCR	(W 0)	1	2	4	6	8	10	12	Months 4	5	6	6.5	7	8	9	10	11	Unscheduled Visit	Mont 12/ Premature Discontinuation Visit
Informed consent	X																			
Behavioral assessment[a]	X								X			X								X
Quality-of-Life assessment[b]	X								X			X								X
Tanner staging	X								X			X								X
Background information	X																			
Inclusion/exclusion criteria	X	X																		
Medical history	X																			
Physical exam (complete)[c]	X								X			X							X	X
Cardiovascular exam			X	X	X	X	X	X		X	X		X	X	X	X	X	X		
Height, waist	X	X					X		X	X	X	X		X	X	X	X	X	X	X
circumference, BMI				X																
Bodyweight	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Echocardiogram[d]		X																		X
ECG	X																		X	X
DXA[d]		X										X								
ABPM[d]		X												X						
Pregnancy test[e]	X	X							X			X				X				X
Lab evaluation	X								X			X							X	X
Pharmacokinetic samples[a]															X	X	X			
Drug and hepatitis screen	X																			
Drug administration record		X					X		X	X	X	X		X	X	X	X	X		X
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse events		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

[a] CBCL, CDI, Eating Inventory, Piers-Harris Children's Self-Concept; (Excerpted from Table 2, pages 95/96)
[b] Peds QL , IWQOL
[c] Complete Physical Examination includes a Cardiovascular Examination.
[d] Echocardiogram, DXA, ABPM and measurement of trough plasma concentration of sibutramine and its active metabolites were to be performed in a subset of Subjects with Baseline echocardiogram who withdrew after Month 6 were to have repeat echocardiogram at premature discontinuation visit.
[e] Serum pregnancy test at screening, urine pregnancy test thereafter, with confirmation of positive tests by serum test.

10.2 Line-by-Line Labeling Review

Not appropriate for this review. Please refer to Section 9.4.

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/s/

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10/31/2005 03:52:38 PM
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