# CENTER FOR DRUG EVALUATION AND RESEARCH

**Approval Package for:**

**Application Number:** 020632

**Trade Name:** MERIDIA CAPSULES 5MG, 10 MG and 15 MG

**Generic Name:** SIBUTRAMINE HYDROCHLORIDE MONOHYDRATE

**Sponsor:** KNOLL PHARMACEUTICAL COMPANY

**Approval Date:** 11/22/97

# CENTER FOR DRUG EVALUATION AND RESEARCH

## APPLICATION: 020632

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# CENTER FOR DRUG EVALUATION AND RESEARCH

**Application Number:** 020632

# APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-632

NOV 22 1997

Knoll Pharmaceutical Company
Attention: Robert Ashworth, Ph.D.
Director, Regulatory Affairs
199 Cherry Hill Road
Parsippany, New Jersey 07054

Dear Dr. Ashworth:

Please refer to your new drug application dated August 7, 1995, received August 9, 1995, under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Meridia® (sibutramine hydrochloride monohydrate) Capsules, 5, 10, and 15 mg.

We acknowledge receipt of your submissions dated August 21 and 28, September 19, November 14, and December 1, 6, 8, 13, 19, and 20, 1995; February 9, March 1, 5, 13, 14, 20, 26, and 28, April 8, 9, and 22, May 2, 12, 13, and 15, June 4, 13, and 20, July 15, 18, and 19, August 1(2), 7, 8, 12, 21, 22, 23, 27, and 30, September 20 and 23, October 4(2), 9, 15(2), 16, 17, 22, 25, and 29, November 12, 18, 25, and 26, and December 17, 1996; and January 3, 20, 23, and 29, February 5, 10,14, 27, and 28, April 15, May 23, June 4, 5, and 17, July 2, September 4, 19(2), and 29, October 8, 20, 21, 23, 28, and 30, and November 7, 13, 19, 21(fax), and 22(fax)(4), 1997. Additionally, we also refer to our November 8, 1996, approvable letter. The user fee goal date for this resubmitted application is November 23, 1997.

This new drug application provides for the use of Meridia® Capsules in the management of obesity, including weight loss and maintenance of weight loss, and should be used in conjunction with a reduced calorie diet.

We have completed the review of this application, including the submitted draft labeling, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the draft labeling dated November 22, 1997. Accordingly, the application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the draft physician and patient (version 2) labeling submitted on November 22, 1997, and the draft bottle labels submitted on November 21, 1997. Marketing the product with FPL that is not identical to this draft labeling may render the product misbranded and an unapproved new drug.

Please submit 20 copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FINAL PRINTED LABELING" for approved NDA 20-632. Approval of this submission by FDA is not required before the labeling is used.

Should additional information relating to the safety and effectiveness of the drug become available, revision of that labeling may be required.

We remind you of your Phase 4 commitment specified in your submission dated November 22, 1997:

Protocols, data, and final reports should be submitted to your IND for this product and a copy of the cover letter sent to this NDA. In addition, we request under 21 CFR 314.81(b)(2)(vii) that you include a status summary of this commitment in your annual report to this application. The status summary should include the number of patients entered in the study, expected completion and submission dates, and any changes in plans since the last annual report. For administrative purposes, all submissions, including labeling supplements, relating to this Phase 4 commitment should be clearly designated "Phase 4 Commitment."

In addition, please submit three copies of the introductory promotional material that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to the Division of Metabolic and Endocrine Drug Products and two copies of both the promotional material and the package insert directly to:

Food and Drug Administration
Division of Drug Marketing, Advertising, and Communications, HFD-40
5600 Fishers Lane
Rockville, Maryland 20857

Our laboratories have completed methods validation of the proposed NDA methodology and find that they are suitable for regulatory purposes. However, the test method for assay, determination of degradation and related substances, and dissolution include calculations that are very difficult to understand. These calculations and the explanations of terminology used in them should be simplified and/or clarified.

Please submit one market package of the drug product when it is available.

We remind you of your obligation under the Controlled Substances Act not to market the drug product until the Drug Enforcement Administration makes a final scheduling decision on it. We note that the signature of Dr. Abraham Varghese of Knoll on the form FDA 356h submitted with your original NDA signifies your commitment not to market this product until the scheduling process is complete.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, please contact Maureen Hess, M.P.H., R.D., Project Manager, at (301) 827-6411.

Sincerely yours,

James Bilstad, M.D.
Director
Office of Drug Evaluation II
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

cc:
Original NDA 20-632
HFD-510/Div. files
HFD-510/CSO/M.Hess
HFD-510/Colman/Haber/Steigerwalt
HFD-002/ORM (with labeling)
HFD-102/Office Director (with labeling)
HFD-101/L.Carter
HFD-820/ONDC Division Director
DISTRICT OFFICE
HF-2/Medwatch (with labeling)
HFD-92/DDM-DIAB (with labeling)
HFD-40/DDMAC (with labeling)
HFD-613/OGD (with labeling)
HFD-735/DPE (with labeling) - for all NDAs and supplements for adverse reaction changes.
HFI-20/Press Office (with labeling)
HFD-021/ACS (with labeling)

Drafted by: JRhee/November 21, 1997/ a:20632.ap
Initialed by:Ripper 11-21-97/Ripper 11-22-97
final: JRhee 11-22-97 11-22-97

APPROVAL (AP) [with Phase 4 Commitment]

APPEARS THIS WAY
ON ORIGINAL

# CENTER FOR DRUG EVALUATION AND RESEARCH

**APPLICATION NUMBER:** 020632

# APPROVABLE LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-632

Knoll Pharmaceutical Company
Attention: Abraham Varghese, Ph.D.
Associate Director, Regulatory Affairs
199 Cherry Hill Road
Parsippany, New Jersey 07054

NOV - 8 1996

Dear Dr. Varghese:

Please refer to your new drug application dated August 7, 1995, received August 9, 1995, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Meridia (sibutramine hydrochloride monohydrate) Capsules, 5, 10, 15, and 20 mg.

We acknowledge receipt of your submissions dated August 21 and 28, September 19(2), November 14, and December 1, 6, 8, 13, 19, and 20, 1995, and February 9, March 1, 5, 13, 14, 19, 20, 26, and 28, April 8, 9, and 22, May 2, 10, 13, and 15, June 4, 13, and 20, July 15, 18, and 19, August 1, 7, 8, 12, 21, 22, 23, 27, and 30, September 20 and 23, and October 4(2), 9, 15, 16, 17, 22, and 25, 1996. Your May 10 submission extended the user fee due date to November 9, 1996.

Information submitted on October 9, 1996, has not been completely reviewed because it arrived late in the review cycle.

We have completed the review of this application as submitted with draft labeling, and it is approvable. Before this application may be approved, however, it will be necessary for you to submit the following information.

A. Further analyses of blood pressure data from the clinical trials of sibutramine, especially studies 852 and 1047, are necessary to provide appropriate labeling of the drug product for monitoring blood pressure. For example, such analyses should include the distribution of the mean changes in blood pressure over the entire study period for individual patients. The relationship of early blood pressure response to later blood pressure levels also should be further analyzed. Additional details of these analyses will need to be developed in collaboration with the Division of Metabolic and Endocrine Drug Products. The outcome of these analyses may result in a request for one or more phase 4 studies to define more fully the blood pressure response to sibutramine.

B. In order that we may complete our abuse liability assessment, we request that you conduct and submit the results of the following two preclinical studies in addition to the results of your ongoing preclinical (primate self-administered) and clinical (protocols BPI 883 and BPI 893) studies.

1. Comparative Pharmacology: Comparison of the discriminative stimulus effects of sibutramine and its two active metabolites to the discriminative stimulus effects elicited by the hallucinogen MDMA.

   Results from submitted preclinical studies have suggested that the pharmacologic profiles of the metabolites BTS 54 505 and BTS 54 354 resemble that of methylenedioxymethamphetamine (MDMA). Like MDMA, these metabolites mediate their effects by both serotonin and dopamine; they all result in an increased level of dopamine and serotonin in the brain. MDMA is a potent dopamine- and serotonin-reuptake inhibitor and releasing agent. Sibutramine's active metabolites are potent dopamine- and serotonin-reuptake inhibitors, and they also possess some dopamine- and serotonin-releasing properties. Both dopamine and serotonin have been associated with mediating the addictive properties of drugs; an increase in dopamine level in the limbic system mediates the addictive properties of the psychostimulants and serotonin mediates the addictive properties of hallucinogens. MDMA produces a mixture of central stimulant and hallucinogenic effects that are mediated by dopamine and serotonin. It is believed that because of this dual mechanism, MDMA possesses both hallucinogenic- and stimulant-like discriminative stimulus properties.

   Consistent with these preclinical findings, results from the clinical trial conducted by J. Cole suggested that sibutramine may possess hallucinogenic properties. Therefore, MDMA is probably a more appropriate positive control than d-amphetamine would be. Sibutramine's active metabolites have been shown to have a neurochemical profile similar to that of MDMA. As such, they may elicit MDMA-like discriminative stimulus responses. To test this hypothesis, rats trained to discriminate between MDMA and saline should be challenged with MDMA, sibutramine, BTS 54 354, and BTS 54 505.

2. Physical-dependence-producing potential of sibutramine.

   Abstinence-associated withdrawal signs, which are the consequence of physical dependence, are a frequent motivator of continued drug intake. A study should be conducted to assess the physical-dependence potential of sibutramine in primates. We suggest a 10-week, 2-dose study in 3 male and 3 female rhesus monkeys.

For specific suggestions on the design of the protocols, we suggest you contact our Division of Anesthetic, Critical Care, and Addiction Drug Products.

C. Because several individual impurities/degradants in the drug product have been identified, individual limits should be set for each identified impurity. A limit for total unidentified impurities should also be specified. These limits should be established based on actual data for qualification batches. A justification for proposed limits should be given.

Provide revised tests and specification sheets and revised stability protocols to reflect the above.

D. Also, the following additions and revisions should be made to the labeling:

1. The following additions/modifications should be made in the DESCRIPTION section of the package insert:

   a. In the first sentence, replace the word "agent" with the word "anorectic."

   b. In the second sentence, replace the word "product" with the words "active ingredient."

   c. After the second sentence, add the sentence "It is a racemic mixture of the (+) and (-) enantiomers."

   d. In the part of the structural formula denoting the cyclobutane ring, please replace the simple square of lines with a formula in which the carbon and hydrogen atoms are indicated by the letters "C" and "H" as in other parts of the formula.

2. As conveyed to you in our facsimile transmission of March 29, we are working to standardize the content and presentation of the information in the **Pharmacokinetics** subsection of the CLINICAL PHARMACOLOGY section of the labeling. The **Pharmacokinetics** subsection should present information as appropriate under the subheadings of *Absorption, Distribution, Metabolism, and Excretion*. Following this, there should be further subheading of *Special Populations* with sub-subheadings of *Geriatric, Pediatric, Gender, Race, Renal Insufficiency, Hepatic Insufficiency,* and *Drug-Drug Interactions*. Where relevant information is lacking, it should be so stated.

   This subsection should also contain a table with pharmacokinetic parameters including (as appropriate) absolute bioavailability, time to peak, clearance, volume of distribution, half-life, and renal clearance for normals and each special population (including the drug's intended target population). Mean values with the coefficients of variation and 95% confidence intervals should be provided.

3. The INDICATIONS AND USAGE section should be revised to read as follows:

> Meridia is indicated for the management of obesity and should be used in conjunction with a reduced-calorie diet and exercise. Meridia is recommended for obese patients with an initial body mass index $\geq$30 kg/m$^2$, or $\geq$27 kg/m$^2$ in the presence of other risk factors (e.g., hypertension, diabetes, and hyperlipidemia).

4. The CONTRAINDICATIONS section should be revised to read as follows:

> Meridia is contraindicated in patients
>
> - Known to be hypersensitive to sibutramine or any of its inactive ingredients.
> - Who have anorexia nervosa or bulimia nervosa
> - Taking other centrally acting appetite suppressant drugs
> - Taking monoamine oxidase inhibitors (MAOI's) (see WARNINGS)

5. The following additions/modifications should be made in the PRECAUTIONS section of the package insert:

   a. The basis for determining the multiple of the maximum human dose should be stated in the labeling. When plasma drug levels are available, human exposure should be expressed in terms of multiples of the AUC observed in preclinical studies. Until plasma levels are available, doses should be expressed in terms of multiples of mg/m$^2$. The calculations, based on a maximum human dose of 20 mg, should be provided but should not be included in the labeling.

   b. The sentence regarding benign tumors of testicular interstitial cells in the *Carcinogenicity* subsection should be revised as follows:

> In male rats, there was a higher incidence of benign tumors of the testicular interstitial cells; such tumors commonly seen in rats are hormonally mediated.

In addition, the following sentence should be added: "Relevance of these tumors to humans is not known."

c. Under the *Mutagenicity* subheading, include the names of the in vitro and in vivo studies conducted.

d. The *Impairment of Fertility* statement should be moved to the **Carcinogenesis, mutagenesis, impairment of fertility** subsection. State the highest no-effect dose and relate it to human exposure on the basis of $mg/m^2$.

e. The **Pregnancy** subsection should revised to conform to 21 CFR 201.57(f)(6)(i)(*c*). Describe the anomalies seen in rabbits and clarify whether they were seen in the absence or presence of maternal toxicity.

f. Delete the **Labor and Delivery** subsection.

g. Revise the **Nursing Mothers** subsection to conform to 21 CFR 201.57(f)(8)(iii).

h. Delete the **Usage in Elderly** subsection.

i. Retitle the **Usage in Children** subsection **Pediatric Use** and revise it to state "Safety and effectiveness of Meridia in pediatric patients have not been established."

j. After the **Pediatric Use** subsection, add a **Geriatric Use** subsection that reads:

> Clinical studies of Meridia did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently from younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

6. The table in the ADVERSE REACTIONS section should be modified as follows:

The percentage discontinuation columns should be deleted.

The adverse events under each organ system should be listed in the order of the incidence in the Meridia patients starting with the highest incidence at the top of each list.

7. In the DOSAGE AND ADMINISTRATION section, delete the sentence "If there are no clinically significant changes in heart rate and/or blood pressure (see below) Meridia may be given in doses not to exceed 30 mg daily."

8. If the 20-mg strength and the blister packaging are to be marketed immediately, they must be added to the HOW SUPPLIED section.

9. Due to the extensive failures of dissolution at elevated temperatures, a warning to protect the capsules from heat and moisture should be included in the carton and container labels and the HOW SUPPLIED section of the labeling. the recommended storage temperature statement must be revised to conform to the USP 23 definition of either "controlled room temperature" or "room temperature."

10. Draft carton labels for all sizes of bottles and blister packs must be submitted.

11. A patient package insert must be developed.

We reserve further comment on the labeling until all the requested information is received and reviewed.

E. In addition, we request you submit a commitment to perform the following two phase 4

F. Under 21 CFR 314.50(d)(5)(vi)(*b*), we request that you update this application by submitting all safety information you now have regarding this new drug. Provide updated information as listed below:

1. Retabulate all safety data including results of trials that were still ongoing at the time of NDA submission. The tabulation can take the same form as in your initial submission. Tables comparing adverse reactions at the time the NDA was submitted versus now will facilitate review.

2. Retabulate drop-outs with new drop-outs identified. Discuss, if appropriate.

3. Provide details of any significant changes or findings, if any.

4. Summarize worldwide experience on the safety of this drug.

5. Submit case report forms for each patient who died during a clinical study or who did not complete a study because of an adverse event.

Also, update this application with respect to reports of relevant safety information, including all deaths and any adverse events that led to discontinuation of the drug and any information suggesting a substantial difference in the rate of occurrence of common but less serious adverse events. The update should cover all studies and uses of the drug including (1) those involving indications not being sought in the present application, (2) other dosage forms, (3) other dose levels, etc.

In addition, please submit three copies of the introductory promotional material that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to the Division of Metabolic and Endocrine Drug Products and two copies of both the promotional material and the package insert directly to:

Food and Drug Administration
Division of Drug Marketing, Advertising, and Communications, HFD-40
5600 Fishers Lane
Rockville, Maryland 20857

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of such action, FDA may take action to withdraw the application.

The drug may not be legally marketed until you have been notified in writing that the application is approved.

Should you have any questions, please contact Maureen Hess, MPH, RD, Consumer Safety Officer, telephone (301) 443-3520.

Sincerely yours,

James Bilstad, M.D.
Director
Office of Drug Evaluation II
Center for Drug Evaluation and Research

**APPEARS THIS WAY
ON ORIGINAL**

# CENTER FOR DRUG EVALUATION AND RESEARCH

## APPLICATION NUMBER: 020632

## MEDICAL REVIEW(S)

# MEDICAL REVIEW

**NDA #:** 20-632

**SPONSOR:** Knoll Pharmaceuticals

**DRUG:** Sibutramine Hydrochloride

**SUBMISSION:** Two **preliminary** clinical reports: Studies SB 1049 and SB 2059

**DATE OF SUBMISSION:** 6/20/1996

**DATE RECEIVED, M.O.:** 6/27/1996

**DATE OF REVIEW:** 6/27/1996

## 8.15 SB 1049

*Efficacy and Tolerability of Sibutramine versus Placebo in Maintenance or Improvement of Weight Loss, in Obese Patients, Following a Very Low Calorie Diet*

### OBJECTIVE/RATIONALE

**8.15.1** The objective of this study was to evaluate the efficacy and tolerability of sibutramine in maintaining/improving long-term weight loss in obese patients following a very low calorie diet (VLCD).

### DESIGN

**8.15.2** SB 1049 was a double-blind, multicenter, parallel-group, placebo-controlled study of 160 patients conducted in France. The study comprised a 5-week run-in period, a 12-month treatment period, followed by three months follow-up. Patients were screened at week -5 and were given a four week (±1) VLCD (calorific intake was between 220 and 800 kcal/day). Those patients who achieved a weight loss of at least 6 kg were randomized into the treatment phase and received either sibutramine 10 mg once daily or matching placebo. Assessments were made at week 2, month 1 and thereafter at monthly intervals during the treatment period. Patients were followed up at months 13 and 15, i.e. for three months after cessation of therapy. Patients were stratified before starting VLCD based on BMI; one group with a BMI of > 30 and ≤ 35, and the other a BMI of > 35 kg/m$^2$.

### PROTOCOL

### POPULATION

**8.15.3.1** This study included male and female patients aged with a BMI equal to or greater than 30 kg/m$^2$. Only those patients who lost at least 6 kg of body weight after 4 weeks on a VLCD were eligible for the study. The following exclusion criteria were used:

- Diastolic blood pressure greater than 100 mmHg.
- Obesity of endocrine origin.
- DM requiring insulin treatment.
- NIDDM not well controlled: FBS greater than 7.8 mmol/l (140 mg/dl)
- Any significant medical condition.
- Patients who have followed without success a VLCD treatment in the previous 6 months.
- Patients taking antidepressants, antiserotoninergics, barbiturates, and neuroleptics.

### ENDPOINTS

**8.15.3.2** Assessments included weight, waist and hip circumferences, laboratory investigations,

vital signs and adverse events.

## STATISTICAL CONSIDERATIONS

**8.15.3.3** All patients entering the study were included in an outcome analysis on an intent-to-treat basis. The study outcome was analyzed by analysis of variance of ranked data with factors for treatment group and centre; the treatment group-by-centre interaction was tested using the Boos-Brownie[1] approach. The point estimate of the treatment effect was calculated as the Wilcoxon-Mann-Whitney estimator P (X < Y); a 95% confidence interval was calculated by the method of Boos-Brownie with each centre given a sample dependent weighting.

Differences between the treatment groups for absolute and percentage body weight following VLCD were analyzed by repeated measures analysis of variance, with factors fitted as above plus time (week 2 and each monthly follow-up) and treatment group by time interaction. This analysis was performed on three datasets:

- All available data with no account taken of missing data (observed analysis)
- As above, but with missing values replaced by carryforward (LOCF)
- Patients who completed the active phase of the study, with a few individual missing values replaced by carryforward (LOCF completers)

The proportion of patients maintaining ≥100%, ≥50% and ≥25% of weight loss after VLCD and the proportion of patients losing ≥5% or ≥10% of screening body weight at months 6 and 12 and at endpoint was compared between treatment groups by the chi-squared test. Treatment group differences were represented by the odds ratio and associated 95% CI.

## RESULTS

## POPULATIONS ENROLLED/ANALYZED

**8.15.4.1** Overall, 205 patients entered into the trial at 12 centres between 15 March and 27 December 1994; 45 withdrew prior to receiving any trial medication and were not included in any of the statistical tabulations. Eighty-two patients received sibutramine 10 mg and 78 received placebo; 108 patients completed the 12-month double-blind treatment phase, 60 (73%) and 48 (62%) in the sibutramine and placebo groups, respectively.

Of the 160 patients who entered the double-blind phase, only one did not provide a post-baseline assessment of body weight (in the sibutramine treatment group); therefore, 159 patients were included in the change to endpoint analysis. A total of 108 patients completed the study, but nine patients (six on sibutramine and three on placebo) were excluded from the analysis of completers as the month-12 assessment was performed more than six days after the last dosing date.

Baseline Demographic Characteristics

The treatment groups were comparable with respect to baseline demographic characteristics. The mean age of patients entering the study was 37.7 years , and the mean height was 165.0 cm . Of the 160 patients who entered the double-blind period, 154 were Caucasian (96%) and 127 were female (79%). At screening, mean body weight (i.e. before VLCD) was 104.2 kg and mean BMI was 38.3 kg/m$^2$

During the VLCD phase (median duration 30 days), patients lost 7.6 kg of body weight There was no difference between the two groups with respect to the amount of weight lost during the VLCD phase.

Patient Disposition

Table 8.15.4.1.1 provides the number of patients who withdrew from the study and the reason for withdrawal.

**TABLE 8.15.4.1.1**
**Summary of patient withdrawals**

| Reason for withdrawal | Treatment group | | |
|---|---|---|---|
| | Sibutramine 10 mg | Placebo | |
| Total no of patients | 82 | 78 | |
| Adverse event | 2 | 5 | |
| Lack of efficacy | 1 | 6 | |
| Other | 19 | 19 | |
| Total withdrawn | 22 (27%) | 30 (38%) | |
| Comparison of withdrawal rates | Chi-square | df | p |
| Overall | 2.68 | 1 | 0.10 |
| Adverse event/lack of efficacy | 5.62 | 1 | 0.02 |

## EFFICACY ENDPOINT OUTCOMES

### 8.15.4.2 Body Weight

There was a statistically significant change in body weight from baseline to both endpoint and month 12 for completers treated with sibutramine compared to placebo ($p<0.001$ and $p=0.004$, respectively) (Table 8.15.4.2.1).

**TABLE 8.15.4.2.1**
**Analysis of variance for the change in mean body weight from baseline to endpoint and from baseline to month 12 for completers**

| Body weight (kg) | At endpoint | | At month 12 for completers | |
|---|---|---|---|---|
| | Sibutramine 10 mg | Placebo | Sibutramine 10 mg | Placebo |
| Total no. of patients | 81 | 78 | 54 | 45 |
| Baseline | 95.7 | 97.7 | 96.4 | 100.2 |
| Follow-up | 90.6 | 98.2 | 90.3 | 100.4 |
| Change from baseline [a] | -5.2 | +0.9 | -5.5 | +0.1 |
| Diff between adjusted means [b] | -6.2 | | -5.5 | |
| 95% CI for diff | -8.2,-4.1 | | -8.5,-2.6 | |

a: adjusted for effects of centre, stratification and for the endpoint analysis treatment -by-centre interaction
b: sibutramine 10 mg minus placebo. A negative difference indicates sibutramine 10 mg favoured.

The analysis of variance of change from baseline in absolute and percentage body weight at each assessment is presented in Table 8.15.4.2.1

**TABLE 8.15.4.2.1**
**Mean changes from baseline in absolute and percentage body weight by treatment group**

| Assessment | LOCF analysis | | Completers | |
|---|---|---|---|---|
| | Sibutramine 10mg | Placebo | Sibutramine 10 mg | Placebo |
| No. of pts | 81 | 78 | 60 | 48 |
| Month 1● | -3.0 (-3.1%) | -1.5(-1.5%) | -3.1 (-3.3%) | -1.9 (-1.8%) |
| Month 3● | -5.8 (-6.1%) | -2.3 (-2.3%) | -6.3 (-6.6%) | -3.2 (-3.1%) |
| Month 6● | -6.4 (-6.6%) | -1.7 (-1.5%) | -7.1 (-7.3%) | -3.3 (-2.9%) |
| Month 9● | -5.5 (-5.7%) | -0.4 (-0.2%) | -6.1 (-6.3%) | -1.5 (-1.1%) |
| Month 12● | -5.2 (-5.3%) | +0.5 (+0.6%) | -5.6 (-5.8%) | -0.1 (+0.2%) |

●p<0.05 sibutramine vs placebo; LOCF and completers datasets

These data indicate that treatment with sibutramine was associated with statistically significantly greater weight loss throughout the study.

The proportion of patients who maintained ≥100, ≥50 or ≥25% of their weight loss following VLCD was statistically significant for all time points for the sibutramine group compared to the placebo group ($p<0.01$) with the exception of ≥25% at month 6 only.

The percentage of patients who lost ≥5% or 10% of their weight loss from screening was statistically significant for all time points for the sibutramine group compared to the placebo group ($p \leq 0.001$) (Table 8.15.4.2.2).

TABLE 8.15.4.2.2
**Proportion of patients losing ≥5% or ≥10% of body weight from screening**

| Parameter | Month 6 | | Month 12 | | Endpoint | |
|---|---|---|---|---|---|---|
| | Sib 10 mg | Placebo | Sib 10 mg | Placebo | Sib 10 mg | Placebo |
| N | 73 | 68 | 55 | 45 | 81 | 78 |
| ≥5% | 97% | 82% | 87% | 53% | 86% | 55% |
| ≥10% | 71% | 41% | 60% | 22% | 54% | 23% |

Waist to Hip Circumference

There were no significant differences between the two groups in the change in waist to hip circumference. However, there were significant reductions in waist circumference in the sibutramine-treated subjects compared to placebo-treated patients at months 6 and 12, as well as at endpoint.

## SAFETY OUTCOMES

### 8.15.4.3 Adverse Experiences

The most commonly reported adverse events are summarized below in Table 8.15.4.3.1.

TABLE 8.15.4.3.1
**Adverse events reported by more than 5% of one or more of the treatment groups**

| COSTART preferred term | Number (%) of patients reporting | |
|---|---|---|
| | Sibutramine 10 mg n=82 | Placebo n=78 |
| ASTHENIA | 9 (11%) | 8 (10%) |
| FLU SYND | 9 (11%) | 8 (10%) |
| HEADACHE | 13 (16%) | 10 (13%) |
| INFECT | 5 (6%) | 3 (4%) |
| INJURY ACCID | 7 (9%) | 6 (8%) |
| PAIN | 8 (10%) | 3 (4%) |
| PAIN ABDO | 5 (6%) | 6 (8%) |
| PAIN BACK | 11 (13%) | 9 (12%) |
| REACT UNEVAL | 2 (2%) | 4 (5%) |
| MIGRAINE | 2 (2%) | 4 (5%) |
| VASC DIS PERIPH | 1 (1%) | 5 (6%) |
| CONSTIP | 15 (18%) | 4 (5%) |
| DIARRHEA | 4 (5%) | 6 (8%) |
| GASTROENTERITIS | 4 (5%) | 5 (6%) |
| NAUSEA | 9 (11%) | 3 (4%) |
| RECTAL DIS | 6 (7%) | 1 (1%) |
| TOOTH DIS | 3 (4%) | 4 (5%) |
| ARTHRALGIA | 4 (5%) | 5 (6%) |
| ANXIETY | 9 (11%) | 5 (6%) |
| DEPRESSION | 7 (9%) | 4 (5%) |
| DIZZINESS | 2 (2%) | 4 (5%) |
| DRY MOUTH | 8 (10%) | 4 (5%) |
| INSOMNIA | 9 (11%) | 7 (9%) |
| NERVOUSNESS | 4 (5%) | 1 (1%) |
| BRONCHITIS | 12 (15%) | 9 (12%) |
| PHARYNGITIS | 17 (21%) | 18 (23%) |
| RHINITIS | 7 (9%) | 5(6%) |

| | | |
|---|---|---|
| SINUSITIS | 4 (5%) | 1 (1%) |
| RASH | 2 (2%) | 4 (5%) |
| CONJUNCTIVITIS | 0 (0%) | 5 (6%) |
| INFECT URIN TRACT | 4 (5%) | 2 (3%) |

Those events that were more common in the sibutramine group included headache, infection, constipation, nausea, anxiety, depression, dry mouth, insomnia and nervousness. Notable adverse events reported by patients on sibutramine or placebo included palpitation in one placebo patient, tachycardia in three sibutramine patients, and hypertension and dyspnoea both reported in one patient in each group.

Vital Signs

Blood Pressure

In general, both systolic and diastolic blood pressures were higher in the sibutramine-treated subjects compared to the placebo-treated subjects; with most of the differences not reaching statistical significance. However, the change in supine diastolic blood pressure from baseline averaged over all time points for completers was significantly higher in the sibubtramine group compared to the placebo group (2.1 vs -1.4 mmHg, p=0.01; 95% CI 0.8, 6.1)). Similarly, at month 6, supine diastolic blood pressure increased by 1.4 mmHg in the sibutramine-treated subjects and decreased by 1.7 mmHg in the placebo treated patients (p=0.03; 95% CI 0.2, 6.1). It is interesting to note that all blood pressure measurements decreased in the sibutramine subjects following completion of the study (month-13 assessment). This finding highlights the pressor effect of sibutramine.

Pulse

Mean heart rate was increased in the sibutramine 10 mg group, with statistically significant differences to placebo in the following datasets: change from baseline averaged over all time points (sibutramine 6.0, placebo 3.1 bpm: p=0.02), change from baseline averaged over all time points for completers (sibutramine 6.3, placebo 0.8 bpm: p<0.001), change from baseline to month 6 (sibutramine 7.7, placebo 4.2 bpm: p=0.02), and change from baseline to month 12 (sibutramine 4.9, placebo -0.3 bpm: p=0.03). The change from month 12 to month 13 for completers was also statistically significant with a fall of -1.6 bpm for the sibutramine group and an increase of 2.8 bpm for the placebo group (p=0.04).

Clinical Laboratory Evaluations

There were statistically significant differences between sibutramine and placebo for some clinical laboratory variables; these are summarized in the Table 8.15.4.3.2

TABLE 8.15.4.3.2
**Summary of statistically significant differences between sibutramine and placebo for laboratory variables**

| Variable | Assessment | Median as a percentage of normal range | | p |
|---|---|---|---|---|
| | | Sibutramine 10 mg | Placebo | |
| Triglycerides | Month 1 | | | 0.0014 |
| | Month 6 | | | 0.02 |
| | Endpoint | | | 0.04 |
| VLDL triglycerides | Month 1 | | | 0.045 |
| | Month 6 | | | 0.04 |
| Cholesterol | Month 6 | | | 0.055 |
| LDL-cholesterol | Month 6 | | | 0.02 |
| HDL-cholesterol | Month 12 | | | 0.003 |
| | Endpoint | | | 0.03 |
| Total cholesterol/HDL cholesterol ratio | Month 12 | | | 0.02 |
| LDL/HDL cholesterol ratio | Month 12 | | | 0.0099 |
| | Endpoint | | | 0.04 |
| HDL+ LDL triglycerides | Month 6 | | | 0.0105 |
| | Month 12 | | | 0.003 |
| | Endpoint | | | 0.008 |
| Platelets | Month 6 | | | 0.02 |
| Apolipoprotein A1/B ratio | Month 6 | | | 0.03 |
| | Month 12 | | | 0.02 |
| Apolipoprotein B | Month 6 | | | 0.049 |
| Uric acid[a] | Month 6 | | | 0.003 |
| | Endpoint | | | 0.003 |
| Chloride[a] | Month 6 | | | 0.03 |

a: mean as a percentage of normal range

There was no clinically relevant change in haematological parameters. Other laboratory parameters including electrolytes, urea, creatinine and liver function tests remained relatively stable and similar to placebo.

There was a mean decrease in triglycerides at endpoint compared to baseline which was statistically significant from placebo (-4.4 vs +10.0 mg/dl; p=0.04). There was also a significant mean increase in HDL on sibutramine compared to placebo (+13 vs +9 mg/dl; p=0.03), and a beneficial change in the LDL : HDL ratio (-0.4 vs -0.1; p=0.04). Although not statistically significant, cholesterol and LDL showed upward trends in both treatment groups with the largest increase in the placebo group. VLDL remained unchanged in both groups.

## 8.15.5 SPONSOR'S CONCLUSIONS

"Following four weeks of a VLCD, patients treated with sibutramine 10 mg for one year had an additional weight loss that was maintained and statistically significant from placebo up to and including month 12. All indices of weight loss showed consistent significant effects and there were beneficial changes in lipid profile. Sibutramine was well tolerated; the adverse event profile and changes in blood pressure and heart rate were consistent with previous studies."

## MEDICAL OFFICER'S CONCLUSIONS

This 1-year study of 160 obese, primarily Caucasian female subjects, indicated that 10 mg of once-daily sibutramine is more effective than placebo in maintaining weight loss after successful completion of a 1-month VLCD. Seventy-three percent of the sibutramine-treated subjects completed the 12-month study compared to 51% of comparably treated subjects in the 12-month pivotal study SB 1047. Study enhancement — the inclusion of only those subjects who lost at least 6 kg of weight following a 1-month VLCD — may explain, in part, the favorable completion rate.

The sibutramine-treated subjects who completed the study had a mean weight loss of 5.5 kg (12 lbs), whereas the placebo subjects had a mean increase in weight of 0.1 kg (0.22 lbs). Despite an impressive reduction in body weight, the subjects treated with sibutramine for 12 months experienced an increase in supine diastolic blood pressure relative to the change in the placebo subjects (2.1 vs -1.4 mmHg; p=0.01). As observed in other sibutramine studies, pulse rate increased in sibutramine-treated subjects.

Sibutramine-induced weight loss was associated with improvements in some lipid parameters; most notably an increase in high-density lipoprotein lipid of 14 mg/dl vs 9.0 mg/dl in the placebo subjects. However, 12 months of active treatment did not significantly improve levels of total cholesterol, triglyceride, or low-density lipoprotein lipid.

### 8.16 SB 2059

*An Evaluation of Sibutramine Compared to Placebo in the Treatment of Obese Subjects with Specific Hyperlipidemia*

## OBJECTIVE/RATIONALE

**8.16.1** The objectives of this study were to evaluate the efficacy and tolerability of sibutramine 10 mg once daily in inducing weight loss in obese patients with hyperlipidemia and to evaluate the effect of that weight loss on the plasma lipid profile.

## DESIGN

**8.16.2** SB 2059 was a 16-week, multicenter, double-blind, parallel-group, placebo-controlled study conducted in Spain. Patients were restricted to a daily caloric intake of 1500 kcals. Fasted serum lipid levels were measured at screening and weeks 4, 8 and 16. Patients were followed up at week 20, i.e. one month after cessation of therapy.

## PROTOCOL

## POPULATION

**8.16.3.1** This study included male and female subjects aged with a BMI of . Only subjects suffering from mixed hyperlipidemia defined from the guidelines of the Spanish Society of Arteriosclerosis were included in the study. These criteria were a total cholesterol (TC) in the range and/or a triglyceride level in the range of Exclusion criteria included the following:

- Diastolic BP > 95 mmHg. (patients with stabilized BP on CCB or ACE-I were allowed to participate in the study).
- Patients taking antilipid medications within 6 months of the study.
- Patients with DM or patients with a FBS > 140 mg/dl.
- Patients with any significant medical problems.
- Patients taking antidepressants, antiserotoninergics, barbiturates, or antipsychotics.

## ENDPOINTS

**8.16.3.2** The primary endpoint assessment included serum lipid levels which were measured at baseline and at weeks 4, 8, 16, and 20. Additional assessments included plasma insulin levels, body weight, waist and hip circumference, laboratory investigations, vital signs and adverse events. Blood pressure and pulse were measured after the patient had been seated for 5 minutes.

## STATISTICAL CONSIDERATIONS

**8.16.3.3** The primary measures were the changes to endpoint (last observation carried forward, LOCF) in the serum levels of total cholesterol, LDL-cholesterol, HDL-cholesterol, triglycerides and VLDL and body weight. Comparability between the treatment groups for age, baseline body weight and baseline serum levels of total cholesterol, LDL-cholesterol, HDL-cholesterol, VLDL and the LDL/HDL ratio was tested using two-sample t-tests; the serum level of triglycerides was tested using the Wilcoxon rank-sum test. The Chi-square test was used to compare the distribution of sex.

For the variables: weight loss (both absolute and percentage), total cholesterol, HDL and LDL-cholesterol, triglycerides, VLDL and the LDL/HDL ratio, the treatment groups were compared on the change from baseline/screening using repeated measures analysis of variance with factors as above but including time (weeks 2, 4, 8, 12 and 16 for weight loss and weeks 4, 8 and 16 for serum levels).

## RESULTS

## POPULATIONS ENROLLED/ANALYZED

**8.16.4.1** Overall, 182 patients entered into the trial, 91 randomized to sibutramine 10 mg and 91 to placebo. One hundred and sixty-six patients completed the 16-week treatment period, 81 and 85 in the sibutramine and placebo groups, respectively. Of the 182 patients who entered the double-blind phase, one sibutramine-treated patient did not provide a post-baseline assessment of body weight and two sibutramine-treated and one placebo patient did not have a value for total cholesterol.

Baseline Demographics and Lipid Levels

All patients were Caucasian with a mean age of 45.5 years mean height of 160.3 cm , mean BMI of 34.6 kg/m$^2$ ; and 73 % were female. The treatment groups were comparable on age, sex, body weight, BMI, and baseline (screening) measures of lipids; none of the comparisons was statistically significant. Table 8.16.4.1.1 provides the mean baseline lipid levels for the two groups.

**Table 8.16.4.1.1**
**Baseline lipoprotein lipid levels in mg/dl**

| Lipid Parameter | Sibutramine n=89 | Placebo n=90 |
|---|---|---|
| TC | 249 | 248 |
| LDL-C | 137 | 138 |
| HDL-C | 57 | 56 |
| TG | 146 | 159 |

Patient Disposition

There were no significant differences between the two groups in withdrawal rate (Table 8.16.4.1.20).

**Table 8.16.4.1.2**
**Summary of patient withdrawals**

| Reason for withdrawal | Treatment group | | | |
|---|---|---|---|---|
| | Sibutramine 10 mg | | Placebo | |
| Total no of patients | 91 | | 91 | |
| Adverse event | 2 | | 2 | |
| Lost to follow up | 6 | | 2 | |
| Protocol violation | 2 | | 0 | |
| Other | 0 | | 2 | |
| Total withdrawn | 10 (11%) | | 6 (7%) | |
| Comparison of withdrawal rates | Chi-square | df | | p |
| Overall | 1.10 | 1 | | 0.30 |

## EFFICACY ENDPOINT OUTCOMES

### 8.16.4.2 Lipid Levels

The rank analysis of variance for the change in triglycerides and total cholesterol from baseline to endpoint and from baseline to week 16 for completers is summarized in Table 8.16.4.2.1

**Table 8.16.4.2.1**
**Rank analysis of variance for the change from baseline to endpoint and week 16 for completers**

| Variable | At endpoint | | At week 16 for completers | |
|---|---|---|---|---|
| | Sib 10 mg | Placebo | Sib 10 mg | Placebo |
| Total no. of patients | 89 | 90 | 78 | 84 |
| Triglycerides (mg/dl) | | | | |
| Baseline median | 129 | 152 | 130 | 155 |
| Follow up median | 101 | 118 | 107 | 118 |
| Median change from baseline | -23 | -13 | -22 | -14 |
| Difference in adjusted mean ranks | -5.21 | | -0.95 | |
| Cholesterol (mg/dl) | | | | |
| Baseline median | 250 | 243 | 250 | 238 |
| Follow up median | 240 | 244 | 245 | 243 |
| Median change from baseline | -9 | 1 | -10 | -2 |
| Difference in adjusted mean ranks | -9.88 | | -8.30 | |

There were trends in favor of the sibutramine 10 mg group but no statistically significant differences between the treatment groups. In the endpoint analyses, LDL-C levels decreased in both groups (-6.0 vs -3.0 mg/dl; sibutramine vs placebo, respectively, p=0.4), and HDL-C levels did not change in the sibutramine group (0.00 mg/dl) and increased 1.0 mg/dl in the placebo group (p=0.9).

Sub-group Analysis

A sub-group analysis of those patients with values of >150 mg/dl for triglycerides at baseline showed greater falls in triglyceride levels with median changes to endpoint of -70 mg/dl for patients on sibutramine (n=31) and -37 mg/dl on placebo (n=46); p=0.05.

Body Weight

The analysis of variance for the actual change in body weight from baseline to endpoint and from baseline to week 16 for completers is presented in Table 8.16.4.2.2.

**TABLE 8.16.4.2.2**

**Analysis of the actual change in body weight from baseline to endpoint and week 16 for completers**

| Body weight (kg) | At endpoint | | At week 16 for completers | |
|---|---|---|---|---|
| | Sib 10 mg | Placebo | Sib 10 mg | Placebo |
| Total no. of patients | 90 | 91 | 80 | 85 |
| Baseline | 88.3 | 89.9 | 87.5 | 90.0 |
| Follow-up | 80.9 | 84.7 | 79.6 | 84.6 |
| Change from baseline[a] | -7.8 | -5.6 | -8.1 | -5.7 |
| Difference between adjusted means | -2.2 | | -2.4 | |

a: adjusted for the effect of center

The difference between the adjusted means for both datasets was statistically significantly in favor of sibutramine; p<0.001. At endpoint and at week 16, the percentage of patients with a reduction in body weight from baseline of ≥5% was 70% and 76% for patients on sibutramine compared to 49% and 51% on placebo; p=0.003 at endpoint and p<0.001 at week 16.

Waist and Hip Circumferences

Waist and hip circumferences were reduced in both treatment groups. The analysis of change to week 16 in waist circumference was, however, significantly in favor of sibutramine with a fall of 7.2 cm compared to 4.8 cm for placebo, p=0.02. Hip circumferences were reduced by 6.0 and 4.5 cm, and waist/hip ratio by 1.6 and 0.9, respectively for the sibutramine and placebo groups; the difference between the groups was in favor of sibutramine but was not statistically significant.

## SAFETY OUTCOMES

### 8.16.4.3 Adverse Experiences

The most frequently reported adverse events (i.e. reported by more than 5% of patients) are

summarized in Table 8.16.4.3.1.

TABLE 8.16.4.3.1
**Adverse events reported by more than 5% of one or more of the treatment groups**

| COSTART preferred term | Number (%) of patients reporting | |
|---|---|---|
| | Sibutramine 10 mg n=91 | Placebo n=91 |
| FLU SYND | 11 (12%) | 11 (12%) |
| HEADACHE | 8 (9%) | 11 (12%) |
| CONSTIP | 16 (18%) | 8 (9%) |
| DIZZINESS | 6 (7%) | 4 (4%) |
| ANXIETY | 7 (8%) | 3 (3%) |
| DRY MOUTH | 14 (15%) | 4 (4%) |
| INSOMNIA | 7 (8%) | 3 (3%) |
| NERVOUSNESS | 5 (6%) | 2 (2%) |
| PHARYNGITIS | 11 (12%) | 4 (4%) |
| INFECT URIN TRACT | 2 (2%) | 5 (6%) |

Those events that were more common in the sibutramine group included constipation, dizziness, anxiety, dry mouth, insomnia, nervousness and pharyngitis.

Vital Signs

Blood Pressure

Both SBP and DBP were reduced from baseline in the sibutramine and placebo treatment groups; at week 16 for completers, the adjusted mean changes in SBP were -3.4 and -6.4 mmHg and for DBP were -1.2 and -3.6 mmHg for the sibutramine (n=80) and placebo (n=84) groups, respectively. The differences were not statistically significant.

Pulse

Heart rate (by palpation) was increased in sibutramine-treated patients compared to placebo patients at endpoint and for completers to week 16. At week 16, the adjusted mean change was +3.2 bpm on sibutramine (n=77) compared to -2.0 bpm on placebo (n=80; p=0.003).

Clinical Laboratory Evaluations

The Sponsor did not provided clinical laboratory data in this preliminary report.

### 8.16.5 SPONSOR'S CONCLUSIONS

"Obese patients with specific hyperlipidemia who received sibutramine 10 mg once daily for 16 weeks had statistically significant reductions in both absolute body weight and BMI compared to placebo. The changes in lipid parameters were in favor of sibutramine and statistical significance was almost achieved when patients with raised triglyceride levels at baseline were assessed in a sub-group analysis. Sibutramine was well tolerated with an adverse event profile similar to that seen in patients with uncomplicated obesity. Blood pressure was reduced from baseline overall but there was an increase in heart rate of approximately 3 bpm, consistent with that seen in previous studies."

### MEDICAL OFFICER'S CONCLUSIONS

This is the first study to specifically examine the effect of sibutramine-induced weight loss on lipoprotein lipid levels in dyslipidemic patients. Much like the effects of sibutramine-induced weight loss on glycemic control in patients with NIDDM, there were no significant improvements in lipoprotein lipid levels following drug-induced weight loss.

The results of studies SB 1049 and 2059 echo the observations from other clinical studies: Sibutramine is more "effective" than placebo in producing and maintaining weight loss; however, the drug has an undesirable pressor effect and has not shown the ability to produce consistent improvements in lipid levels when compared to subjects treated with placebo.

In conclusion, the data presented in these two preliminary reports appear to lend support to this Reviewer's original recommendation of non-approval for NDA 20-632.

– 6/28/96

Eric Colman, M.D.

10-11-96

cc: NDA Arch
Hedin/Drs EColman/GTroendle/SSobel

APPEARS THIS WAY
ON ORIGINAL

JUN 25 1996

# MEDICAL OFFICER'S REVIEW of the ORIGINAL SUBMISSION of NDA 20-632

**DATE SUBMITTED:** August 7, 1995
**DATE RECEIVED, CDER:** August 18, 1995
**DATE RECEIVED, MEDICAL OFFICER:** August 19, 1995
**DATE REVIEW COMPLETED:** May 10, 1996

**DRUG NAME:**
**GENERIC NAME:** Sibutramine hydrochloride monohydrate
**TRADE NAME:** Meridia
**CHEMICAL NAME:** Cyclobutanemethanamine, 1-(4-chlorophenyl)-N,N-dimthyl-α-(2-methyopropyl)-, hydrochloride, monohydrate, (±)

**SPONSOR:** Knoll Pharmaceutical Company

**PHARMACOLOGICAL CATEGORY:** Norepinephrine and 5-hydroxytryptamine reuptake inhibitor, appetite suppressant, anti-obesity

**PROPOSED INDICATION:** Treatment of obesity

**DOSAGE FORM:** Hard gelatin capsule containing a white to off-white

**RELATED DRUGS:** Effexor®, Venlafaxine (antidepressant)

## TABLE OF CONTENTS

## 3. VOLUMES REVIEWED

| | | |
|---|---|---|
| 1.2 | 1.107-1.165 | 1.330-1.437 |
| 1.3 | 1.166-1.319 | 1.438-1.444 |
| 1.320-1.329 | 1.445-1.452 | 1.453 |
| 1.47-1.84 | 1.40-1.46 | 2.1-2.6 |
| 1.84-1.88 | | |

## 4. CHEMISTRY/MANUFACTURING CONTROLS

see chemistry review

## 5. ANIMAL PHARMACOLOGY/TOXICOLOGY

Sibutramine inhibits the reuptake of norepinephrine (NE) and 5-hydroxytryptamine (5-HT) in vivo. The effects of the drug are mediated through the active metabolites: BTS 54 354 and BTS 54 505. In addition to the inhibition of reuptake of NE and 5-HT, these metabolites are weak inhibitors of dopamine (DA) reuptake. Sibutramine reduces food intake in a dose-response fashion. In animals, sibutramine increases oxygen consumption and body temperature. Studies utilizing β-blockers indicate that sibutramine indirectly stimulates $\beta_3$-receptors.

Neither sibutramine, nor its active metabolites, have any affinity for a wide range of neurotransmitter receptors. They also have no antihistaminergic, anticholinergic, or monoamine oxidase inhibitor action. Repeated doses of sibutramine down-regulate $\beta_1$, $\alpha_2$, and 5-$HT_{1a}$ receptors.

The lowest lethal oral dose of sibutramine in mice is 200 mg/kg, 100 mg/kg in rats, 40 mg/kg in dogs, and 50 mg/kg in monkeys. Sibutramine has produced no consistent effects on the hepatic or cardiovascular systems.

Sibutramine-related material binds reversibly to melanin-containing tissue in vivo. In the dog, 24 weeks of maximum tolerated doses of sibutramine produced prolonged mydriasis and inhibition of the pupillary light reflex. There were no changes detected by ophthalmoscopy or histology.

The Sponsor concludes that sibutramine is not a chemical teratogen, although studies in which the drug was administered during the end of pregnancy and during lactation indicated that there was a higher incidence of perinatal mortality associated with the drug.

Oncogenicity studies in mice at doses of 20 mg/kg showed no increase in tumor incidence. In rats, doses of sibutramine of 1, 3, and 9 mg/kg revealed a higher incidence of interstitial cell hyperplasia and adenomas in the testes; there was no increase in malignancies. The increase in adenomas of the testes was presumably related to the increased levels of LH in the treated animals. The incidence of mammary fibroadenomas was also increased in both male and

females.

Studies in mice, rats, dogs, and monkeys showed no neurotoxic effects of sibutramine. The Sponsor reports that sibutramine and its active metabolites are not mutagenic.

## 6. CLINICAL BACKGROUND

### 6.1 RELEVANT NDA - NDA 20-151 - Venlafaxine (Effexor®)

Venlafaxine was approved for the treatment of depression by the Neuropharmacology Division in 1993. Venlafaxine, like sibutramine, inhibits the reuptake of norepinephrine and 5-hydroxytryptamine.

The following adverse events were reported more commonly in venlafaxine-treated subjects compared to placebo-treated subjects:

1. Anxiety
2. Nervousness
3. Insomnia
4. Somnolence
5. Dizziness
6. Dry mouth
7. Mania/hypomania
8. Rash
9. Hypertension
10. Nausea
11. Abnormal ejaculation
12. Impotence
13. Headache
14. Asthenia
15. Sweating

There were no reported deaths associated with the use of venlafaxine at the time of the review. Limited data regarding overdose suggest that venlafaxine is not associated with respiratory depression or significant cardiovascular disturbances. Furthermore, although not systematically studied at the time of the clinical review, there was no evidence of abuse potential. A retrospective analysis of data from phase 2 and 3 studies suggest that the discontinuation of venlafaxine may be associated with a mild withdrawal syndrome.

### 6.2 HUMAN PHARMACOLOGY/PHARMACOKINETICS/PHARMACODYNAMICS

**DOSE TOLERANCE STUDIES**

**BPI 801** was a double-blind, placebo-controlled study in 24 healthy males measuring the effects of 12.5 25, 50, and 75 mg of sibutramine. Doses of 50 and 75 mg produced increases in heart rate and blood pressure, QT intervals, and pupil sizes, as well as a decrease in salivary secretions. Adverse events included weakness, tremor, drowsiness, nausea, hyperactive feelings, and lightheadedness.

**BPI 802** was a double-blind, placebo-controlled crossover study using amitriptyline, followed by four double-blind, ascending-dose randomization crossover treatment sessions in which subjects received a single dose of placebo or 5, 15, or 50 mg of sibutramine. The study included 12 healthy males. The 5 and 15 mg doses were categorized as antidepressants and the 50 mg dose was categorized as a CNS depressant.

**BPI 803** was a double-blind, placebo-controlled study to determine the maximum tolerated sequential repeated dose of sibutramine (5, 10, 20, or 30 mg) in 32 healthy males. The 30 mg dose was not well tolerated and two subjects dropped from the study: one because of emotional sensitivity and one because of premature atrial contractions (PACs). All subjects in the 30 mg group reported complaints in the first week; these included insomnia, constipation, blurred vision, hot flashes, dizziness, anorexia, decreased libido, headache, fatigue and urinary difficulty. Inconsistent findings were noted with regard to effects on pulse and blood pressure. Mean standing pulse rate appeared to increase in the active drug groups. Some changes in ST and T wave morphology were noted at higher doses. Plasma catecholamines, notably dopamine, were elevated following 30 mg dosing.

**BPI 809** was a double-blind, placebo-controlled 6-week study that examined the safety and tolerability of ascending, repeated doses of sibutramine (2.5 to 5 mg and 5 to 10 mg once daily over a six-week period, two weeks at the lower dose followed by four weeks at the higher dose) in two successive groups of normal healthy males. The study included 41 subjects. Adverse events appeared to be dose related and included tiredness, headache, and insomnia. In the 2.5-5 mg group there were chronic slight reductions in supine blood pressure (-5.8 mmHg) and increased standing systolic blood pressure (6 mmHg) at day 7. There was a dose-dependent weight loss of up to 2.9 kg.

**BPI 813** was a double-blind, placebo-controlled parallel group study that assessed the safety and tolerability of ascending doses in healthy males. The subjects received 15 mg of drug daily for two weeks followed by 30 mg daily for four weeks. Change in mean supine pulse rate was 5.9 bpm at day 14 of 15 mg once daily (QD); 16.1 bpm at day 28 (two further weeks at 30 mg) and 17.2 bpm at day 42. Headache was reported by 73% of subjects, anorexia by 47%, dry mouth by 80%, and insomnia by 33%. Changes in supine and standing blood pressures were variable. Body weight decreased by 5.7% in the sibutramine-treated completers compared to a 0.9% increase in the placebo group.

**MS 86004** was a double-blind, randomized, placebo-controlled, parallel-group study in 24 healthy males to evaluate the chronic effects of sibutramine on the cardiovascular system and

neurohumoral parameters. Fifteen mg twice/day for up to five days led to inhibition of uptake of noradrenaline and 5-hydroxytryptamine. The active metabolites of sibutramine (1 and 2) appeared rapidly in the plasma and reached steady state concentrations by 48 and 72 hours, respectively. The elimination half-lives were approximately 20 and 16 hours for metabolites 1 and 2, respectively. The results suggested that there is a direct relationship between metabolite concentration and inhibition of monoamine uptake. The study was terminated early because of the adverse event profile (activation of the autonomic nervous system).

## PHARMACOKINETICS

Sibutramine undergoes a large first-pass metabolism which yields the active metabolites 1 and 2. Further hydroxylation of metabolite 2 and conjugation with glucuronic acid yields metabolites 5 and 6. Metabolites are excreted preferentially in urine where the major metabolites 5 and 6 are accompanied by numerous minor polar metabolites.
Based on the results of one study, the $T_{max}$ of sibutramine is 1.2 hours, the $t_{1/2}$ is 1.1 hours and the drug has a very high oral clearance value (1750 L/Hr).

In studies of healthy volunteers, the $T_{max}$ of the active metabolites 1 and 2 is approximately 3 hours and the elimination half-life is about 14 and 16 hours, respectively. Linear kinetics have been shown over the dose range of 10 to 30 mg with no dose-related change in elimination half-lives and a dose proportionate increase in plasma concentrations. Concentrations of metabolite 2 are twice that of metabolite 1. Steady-state concentrations of metabolites 1 and 2 are achieved within four days. The pharmacokinetics of sibutramine are the same in obese individuals as non-obese subjects.

Food delays the rate of appearance of metabolites 1 and 2 but has no effect on the extent of formation of these active metabolites. There is no evidence that gender has any effect on the pharmacokinetics of the drug. The drug metabolism is not altered in the elderly and no reduction in dose would be required according to the sponsor. Studies in patients with moderate hepatic dysfunction did not indicate any significant changes in metabolism.

The major cytochrome P450 isoenzyme responsible for sibutramine metabolism is CYP3A4. Ketoconazole does appear to inhibit metabolism of sibutramine at therapeutic concentrations.

## PHARMACODYNAMICS

**BPI 810** was a double-blind, placebo-controlled, parallel-group study to evaluate the cardiovascular effects of 5 and 20 mg of sibutramine in 24 males. There was a dose-related trend in overall mean heart rate increase that reached statistical significance on day 7 for the 20 mg group; the 20 mg group had a +7.6 bpm change in mean heart rate from 24-hour holter recordings during the 7-day study. The change from baseline in the total number of ventricular premature beats was 99.9 in the 20 mg group and 3.3 and -10.7 in the placebo and 5 mg groups, respectively.

**PBI 822** was a placebo-controlled, fixed-dose, double-blind, crossover study that examined the cardiovascular effects of 20 mg of sibutramine in 12 healthy male subjects. The sibutramine group had significantly higher pulse rates compared to the placebo group (8.0 bpm vs -1.0 bpm).

**SB 3814** was a double-blind, placebo-controlled, crossover study that examined the cardiovascular and neurohumoral effects of a single dose of 60 mg of sibutramine in the presence or absence of atenolol 50 mg vs placebo in 6 healthy males. Sibutramine alone increased blood pressure (6 mmHg relative to placebo) and heart rate (10 bpm relative to placebo. The addition of atenolol eliminated the changes on blood pressure and pulse. There were no differences between groups with respect to plasma catecholamine levels.

**MS 85004** was a double-blind, 3-way crossover, placebo-controlled study that compared the cardiovascular effects of 60 mg of sibutramine with 50 mg of amitriptyline and placebo. Compared to placebo, sibutramine increased supine systolic and diastolic blood pressures, mean arterial blood pressure, and heart rate. Sibutramine had no effect on stroke volume, cardiac output, or systolic time intervals.

**BPI 802** was a double-blind, single-dose, placebo-controlled crossover study with a single-blind adaptation session using amitriptyline, followed by four double-blind, ascending-dose randomized crossover treatment sessions in which subjects received placebo or 5, 15, or 50 mg QD of sibutramine in 12 healthy males. The 5 and 15 mg doses was categorized as an antidepressant and the 50 mg dose was categorized as a CNS depressant.

**BPI 862** was a double-blind, placebo-controlled, parallel-group, fixed-dose study to evaluate the effects of 20 mg of daily sibutramine on the endocrine axes in 30 healthy males. The triple stimulation test with insulin, gonadorelin, and TRH diminished prolactin response on stimulation in the sibutramine group.

## 6.3 DIRECTIONS FOR USE

The Sponsor states that sibutramine is indicated for the long-term treatment of obesity (BMI $\geq$ 27.0 kg/m$^2$) and should be used in conjunction with diet and exercise. The recommended starting dose is 5 mg per day with or without food. If weight loss is inadequate **(not defined)** the dose may be titrated up every two weeks in increments of 5 mg to a total of 20 mg per day. In the absence of significant changes in heart rate and/or blood pressure **(not defined)** the drug may be given in doses not to exceed 30 mg per day.

## 7. DESCRIPTION OF CLINICAL DATA SOURCES

### 7.1.1 STUDY TYPE AND DESIGN/PATIENT ENUMERATION

Table 7.1.1.1 provides the enumeration of patients by study type and treatment group.

| TABLE 7.1.1.1 | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| **Study population** | **Placebo-controlled** | | | **Active-controlled** | | **Uncontrolled** | **All studies** | | |
| | Sib | Pl | Comp | Sib | Comp | Sib | Sib | Pl | Comp |
| Uncomplicated obesity | 1635 | 480 | 25 | 112 | 114 | 572 | 2319 | 480 | 139 |
| Obese — hypertensive | 72 | 75 | 0 | 0 | 0 | 103 | 126 | 75 | 0 |
| Obese Diabetic | 59 | 50 | 0 | 0 | 0 | 74 | 96 | 50 | 0 |
| All obese | 1766 | 605 | 25 | 112 | 114 | 749 | 2541 | 605 | 139 |
| Depressed | 895 | 349 | 259 | 0 | 0 | 313 | 1208 | 349 | 259 |
| Volunteers | 238 | 178 | 43 | 0 | 0 | 219 | 457 | 178 | 43 |
| All subjects | 2899 | 1132 | 327 | 112 | 114 | 1281 | 4206* | 1132 | 441 |

Sib=sibutramine Pl=placebo Comp=comparator

* represents some subjects who participated in more than one study and some subjects who had prolonged periods off therapy between a double-blind study and its open extension phase and were counted as two exposures.

## 7.1.2 PATIENT DEMOGRAPHICS

Eighty percent of the obese participants treated with sibutramine were female. Eighty-seven percent of these subjects were between the ages The vast majority (86%) were Caucasian. The mean BMI was 33.7 kg/m$^2$.

Fifty-three percent of the obese patients had at least one coexisting disease at baseline. These conditions and their prevalence are shown in table 7.1.2.1

| Table 7.1.2.1 | |
|---|---|
| **Condition** | **Prevalence ((%)** |
| Hypertension | 9 |
| Osteoarthritis | 7 |
| Headache | 4 |
| Diabetes Mellitus | 4 |



## 7.1.3 EXTENT OF EXPOSURE

As of September 30, 1994 four-hundred twenty-three subjects received sibutramine for over 52

weeks. The sponsor estimates that there were 1245 patient-years exposure to sibutramine of doses of ≥ 5 mg per day.

## 7.2 POST-MARKETING EXPERIENCE

Sibutramine is not marketed in the United States or elsewhere.

## 7.3 RELEVANT LITERATURE

The limited published literature on sibutramine does not provide any additional information to the data in the NDA.

# 8. CLINICAL STUDIES

## *PIVOTAL STUDIES*

### 8.1 BPI 852

### OBJECTIVE/RATIONALE

**8.1.1** The objective of this study was to define the dose-range and efficacy of sibutramine and to assess its safety profile in patients with uncomplicated obesity.

### DESIGN

**8.1.2** A 24-week multicenter, double-blind, repeated-dose, placebo-controlled, parallel-group, dose-ranging weight loss study in 1047 obese patients. The following doses were evaluated relative to placebo: 1, 5, 10, 15, 20, and 30 mg per day. The primary outcome measures were the changes in body weight, vital signs and waist and hip circumferences. Consummatory behavior and safety data were also assessed. A reduction in drug dose was allowed if a subject had an intolerable adverse event.

### PROTOCOL

### POPULATION

**8.1.3.1** This study included male and female patients aged _____ with a BMI of _____. Patients were instructed to adhere to modest caloric restriction and lifestyle and activity changes. Subjects were provided with written information on behavioral modification techniques and were instructed by a dietician to engage in a daily walking program of 20-30 minutes per day. Subjects currently treated for hypertension or diabetes mellitus (type I and II) were excluded. A scale to measure the possible withdrawal effects of sibutramine was to be included in this study; however, due to logistical difficulties it was not implemented. Subjects

with two supine or standing mean heart rates greater than 90 bpm; resting supine or standing blood pressure greater than 160 mmHg (systolic) or 95 mmHg (diastolic) were excluded. Subjects participating in a formal weight loss program within three months of the study were also excluded.

## ENDPOINTS

**8.1.3.2** The primary endpoints are clearly delineated and were measured in a reasonable manner. Consummatory behavior assessments were made using a hunger, satiety, appetite, craving for food type, and carbohydrate snacking scales. A three-day food intake diary was completed during the placebo run-in phase and was used by the dietitian to create a caloric restriction plan. The mean of three measurements was calculated for the vital signs. Serum levels of the drug were obtained at baseline, 12, and 24 weeks. The Hamilton depression scale was administered at baseline and at study termination at sites 03 and 06.

## STATISTICAL CONSIDERATIONS

**8.1.3.3** A number of efficacy variables were analyzed, some at every visit and others at weeks 12 and 24. Efficacy evaluations were conducted for continuous variables by using an ANOVA model containing factors for site, treatment, and site by treatment interaction. Comparisons of active treatments versus placebo were conducted using the Dunnett's test for continuous data and the pairwise Fisher's Exact test for categorical data. The last observation carried forward (LOCF) and observed analyses for both evaluable patients (defined as patients having at least one dose of randomized medication and at least one double-blind study visit evaluation) and completers were performed. For dose-response data only data recorded prior to a dose reduction was analyzed. For weight loss efficacy, data prior to and after a dose reduction were analyzed.

## RESULTS

## POPULATIONS ENROLLED/ANALYZED

**8.1.4.1** A total of 1463 patients were screened. Of these, 1047 patients at seven sites were enrolled and randomized. Of these 1047 patients, 824 patients (79%) completed 12 weeks and 684 (65%) completed 24 weeks of the study. Twenty-three patients were excluded from the efficacy analyses primarily because of lack of post-baseline data. Of the population randomized, 80% were female, 78% Caucasians, 15% Black, and 7% Mexican-Americans. The mean age was 43.6 years with a range The baseline distribution of demographic variables was similar for treatment groups. The levels of compliance were comparable among the groups, and in general, were higher during the run-in and wash-out phases. There appeared to be no differences among the groups with respect to concomitant drug use initiated during the study.

Table 8.1.4.1.1 summarizes the number of patients enrolled and the numbers and reasons for discontinuation or withdrawal from the study.

| TABLE 8.1.4.1.1 | | | | | | | |
|---|---|---|---|---|---|---|---|
| 1463 patients screened | | | | | | | |
| 1047 patients enrolled and randomized | | | | | | | |
| 1024 - 23 patients without post-baseline data not included in efficacy analyses | | | | | | | |
| **Tx group** | **Pl** | **1 mg** | **5 mg** | **10 mg** | **15 mg** | **20 mg** | **30 mg** |
| n | 148 | 149 | 151 | 150 | 152 | 146 | 151 |
| Adverse event | 12 | 17 | 8 | 13 | 17 | 19 | 27 |
| Lack of efficacy | 11 | 11 | 8 | 2 | 3 | 4 | 2 |
| Lost to foll-up | 2 | 2 | 2 | 4 | 5 | 4 | 3 |
| Prot violation | 26 | 17 | 20 | 27 | 22 | 20 | 14 |
| Other | 10 | 7 | 6 | 5 | 7 | 3 | 4 |
| **Total withdrew** | **61** | **54** | **44** | **51** | **54** | **50** | **50** |
| **Completed** | **87** | **95** | **107** | **99** | **98** | **96** | **101** |

At week 24 there were 55% placebo; 65% 1 mg; 70% 5 mg; 63% 10 mg; 60% 15 mg; 58% 20 mg and 55% of the 30 mg subjects remaining in the study.

## EFFICACY ENDPOINT OUTCOMES

### 8.1.4.2 Body weight

Figure 8.1.4.1.1 illustrates the mean weight loss (kg) for all dose groups combined, by month, for completers vs drop-outs. It is readily apparent that those subjects who dropped out of the study lost less weight at the time of discontinuation when compared to those subjects who completed.

Figure 8.1.4.1.1

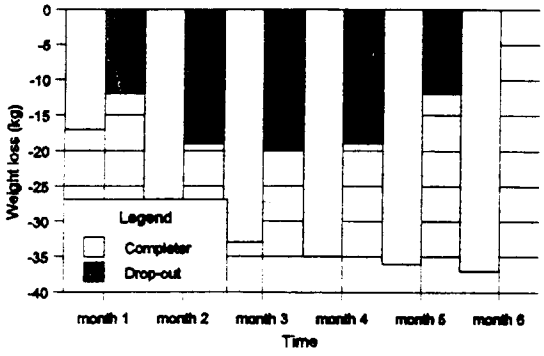


Table 8.1.4.2.1 provides the absolute change in bodyweight from baseline to week 24 for completed patients - dose reduction data retained.

| TABLE 8.1.4.2.1 | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **Tx** | **N** | **Wt loss** | **1 mg** | **5 mg** | **10 mg** | **15 mg** | **20 mg** | **30 mg** |
| **Placebo** | 83 | -1.3 kg | NS | * | * | * | * | * |
| **1 mg** | 89 | -2.4 kg | | NS | * | * | * | * |
| **5 mg** | 100 | -3.7 kg | | | NS | * | * | * |
| **10 mg** | 93 | -5.7 kg | | | | NS | * | * |
| **15 mg** | 94 | -7.0 kg | | | | | NS | NS |
| **20 mg** | 89 | -8.2 kg | | | | | | NS |
| **30 mg** | 94 | -9.0 kg | | | | | | |

*P < 0.05 Statistical comparisons made using Tukey's HSD test.

These data indicate that there were no statistically significant differences in weight loss between the 30 mg and 20 and 15 mg groups; or between the 20 mg group and the 15 mg group, etc.

Figure 8.1.4.2.1 illustrates the percent change from baseline weight for the completers dataset - dose reduction data retained. At week 24 the percent change in body weight was statistically significantly greater for 5, 10, 15, 20, and 30 mg compared to placebo. However, only doses of 10-30 mg produced a percent weight loss that was at least 5% greater than the loss with placebo.

**Figure 8.1.4.2.1**

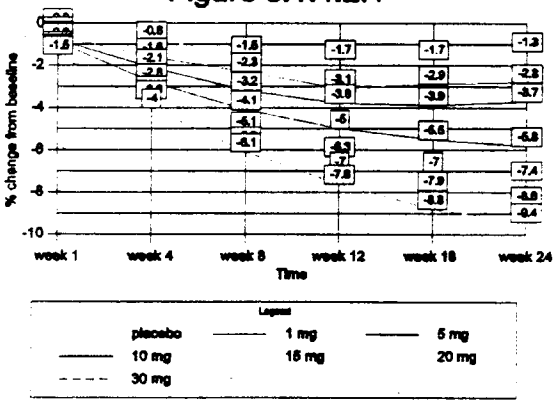





Figure 8.1.4.2.2 illustrates the percent weight loss from baseline for the intent-to-treat dataset. Although doses of 5-30 mg produced statistically significantly greater weight loss when

compared to placebo, only the 20 and 30 mg doses produced weight loss that was at least 5% greater than placebo.

Figure 8.1.4.2.2

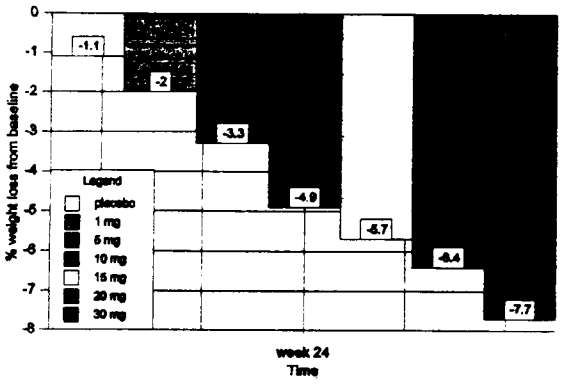





Table 8.1.4.2.2 provides the percentage of patients losing 5% of baseline body weight for the completed patients dataset.

**TABLE 8.1.4.2.2**

| Dose-reduction data retained | | | | Completed patients, n=683 | | | |
|---|---|---|---|---|---|---|---|
| **Wk** | **Placebo** | **1 mg** | **5 mg** | **10 mg** | **15 mg** | **20 mg** | **30 mg** |
| 12 | 18% | 25% | 40%* | 52%* | 64%* | 69%* | 76%* |
| 24 | 20% | 25% | 37%* | 60%* | 67%* | 72%* | 77%* |

*P<0.001 compared to placebo

Table 8.1.4.2.3 provides the percentage of patients losing 5% of baseline body weight for the strict intent-to-treat dataset (all subjects randomized are included).

**TABLE 8.1.4.2.3**

| Dose-reduction data retained | | | | Intent-to-Treat Analysis n=1047 | | | |
|---|---|---|---|---|---|---|---|
| **Wk** | **Placebo** | **1 mg** | **5 mg** | **10 mg** | **15 mg** | **20 mg** | **30 mg** |
| 12 | 11% | 16% | 33%* | 37%* | 45%* | 49%* | 57%* |
| 24 | 11% | 15% | 27%* | 38%* | 41%* | 45%* | 48%* |

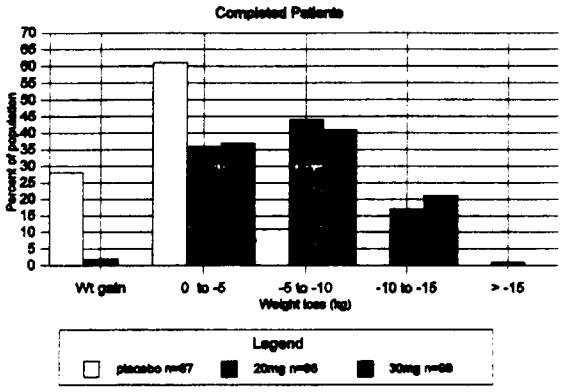
*P < 0.001 compared to placebo

Although far fewer subjects achieved 5% or greater weight loss in the intent-to-treat analysis, the results are similar, statistically, between the intent-to-treat and the completers analyses.

However, there were no statistically significant differences in the proportion of subjects losing at least 5% of initial body weight between 30 mg and 20 mg, 20 mg and 15 mg, 15 mg and 10 mg, etc.

Figure 8.1.4.2.3 illustrates the frequency distribution of weight loss in kg for the placebo, 20 mg, and 30 mg groups at week 24.

**Figure 8.1.4.2.3**




These data suggest that the 20 and 30 mg doses are essentially equivalent.



Dose-response data

Regression analyses from the various datasets indicate that the slope of the line relating weight loss to log-drug dose is steepest between 5-20 mg. Again, these data support the contention that efficacy is not appreciably increased with doses above 20 mg per day.

Correlation between drug dose and plasma concentration of active metabolites

There were statistically significant correlations between drug dose and plasma concentrations of the active metabolites ($r=0.59$, $p=0.0001$ and $r=0.76$, $p=0.0001$ for metabolite 1 at week 12 and 24, respectively; and $r=0.57$, $p=0.0001$ and $r=0.69$, $p=0.0001$ for metabolite 2 at week 12 and 24, respectively). These data are from 470 patients at week 12 and 398 subjects at week 24.

There were statistically significant correlations between the change in body weight at week 12 and 24 with the plasma concentrations of metabolites 1 and 2 as shown in table 8.1.4.2.4.

| TABLE 8.1.4.2.4 | | | | |
|---|---|---|---|---|
| | **Correlation with metabolite 1** | | **Correlation with metabolite 2** | |
| | Week 12 | Week 24 | Week 12 | Week 24 |

| TABLE 8.1.4.2.4 | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Correlation with met: bolite 1 | | | | Correlation with metabolite 2 | | | |
| | r | p | r | p | r | p | r | p |
| Δ Wt loss | -0.19 | 0.0001 | -0.23 | 0.0001 | -0.34 | 0.0001 | -0.39 | 0.0001 |

Waist and Hip Circumferences

Statistically significant decreases in waist circumference were observed with doses of 10-30 mg QD at week 24. The changes in hip circumferences were similar to those of the waist circumferences and thus there were no changes in the waist to hip ratios. Waist circumference represents a crude index of visceral fat and the correlation between changes in waist circumference and visceral fat is modest and varies by gender and age. Thus, valid conclusions regarding changes in visceral fat content cannot, in general, be made based on changes in waist circumference. These relationships are weakened further because of the multicenter design and interobserver variations in waist circumference measurements. CT scanning represents the most accurate method of measuring changes in visceral fat content. The Sponsor should be encouraged to conduct such studies.

Consummatory Behavior Measurements

Changes in the overall appetite and carbohydrate craving scales followed a pattern in which there was a dose-dependent decrease in the variable up to weeks 4-6. Thereafter, appetite and carbohydrate craving increased slightly, but still remained below baseline values at week 24.

## SAFETY OUTCOMES

### 8.1.4.3 Adverse experiences

For treatment-emergent events, two datasets were used: (1) the randomized dataset comprised those data collected at the randomized dose. If a patient had a dose reduction, adverse event data reported at the lower dose were not included in this dataset; (2) The actual dataset included those data collected at the randomized dose and after a dose reduction. Therefore, in this dataset, all adverse event information is summarized. In preparing this dataset, two conventions were used: for incidence tables an event occurring at two dose levels was assigned to the lower dose and for both incidence and occurrence tables the treatment group numbers reflect the number of patients randomized to that dose plus the number of patients who fell back to that dose.

It should be noted that there were some events reported in the "actual dataset" that were statistically significantly different between active treatment and placebo (increased appetite, hyperkinesia, nervousness, ejaculatory abnormality, and epididymitis) that were not statistically

significantly different among the groups in the "randomized dataset". Similarly, there were two events (asthenia and ecchymosis) that did not occur at a statistically significantly different rate in the "actual dataset" but did in the "randomized dataset."

The number and percent of patients exposed by duration of double-blind therapy is presented in table 8.1.4.3.1.

**TABLE 8.1.4.3.1**

| Tx group | Duration of double-blind therapy (weeks) | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | ≤1 | >1≤4 | >4≤8 | >8≤12 | >12≤16 | >16≤24 | >24≤28 | >28≤32 | >32≤36 |
| Placebo n=148 | 99% | 80.4% | 78.4% | 71.6% | 65.5% | 61.5% | 60.1% | 31.8% | 2.0% |
| 1 mg n=149 | 100% | 86.6% | 85.2% | 79.2% | 76.5% | 72.5% | 67.8% | 32.2% | 2.7% |
| 5 mg n=151 | 100% | 84.8% | 82.8% | 80.8% | 76.8% | 74.8% | 41.1% | 2.0% | 0.0% |
| 10 mg n=150 | 99% | 81.3% | 80.7% | 77.3% | 74.0% | 70.7% | 69.3% | 39.3% | 2.0% |
| 15 mg n=152 | 100% | 85.5% | 84.2% | 78.3% | 74.3% | 69.1% | 68.4% | 35.5% | 3.3% |
| 20 mg n=146 | 100% | 84.9% | 84.2% | 78.1% | 74.7% | 74.0% | 71.9% | 35.6% | 2.1% |
| 30 mg n=151 | 100% | 92.1% | 89.4% | 84.1% | 80.1% | 76.2% | 70.9% | 37.1% | 0.0% |
| total n=1047 | 100% | 85.1% | 83.6% | 78.5% | 74.6% | 71.3% | 64.2% | 30.5% | 1.7% |

The duration of exposure appeared to be equal in the various dosage groups.

A number of patients had their dose reduced during the study. Table 8.1.4.3.2 illustrates the percent of patients whose dose was reduced during the double-blind phase presented by reason and initial dose.

**TABLE 8.1.4.3.2**

| Reason | Placebo | 1 mg | 5 mg | 10 mg | 15 mg | 20 mg | 30 mg | Total |
|---|---|---|---|---|---|---|---|---|
| Did not reduce dose | 94% | 93% | 91% | 88% | 87% | 77% | 71% | 86% |
| Reduced dose | 6% | 7% | 9% | 12% | 13% | 23% | 29% | 14% |
| Adverse event | 2% | 5% | 3% | 7% | 4% | 10% | 15% | 6% |
| Blood pressure○ | 3% | 1% | 1% | 3% | 4% | 3% | 9% | 3% |

| TABLE 8.1.4.3.2 | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **Reason** | **Placebo** | **1 mg** | **5 mg** | **10 mg** | **15 mg** | **20 mg** | **30 mg** | **Total** |
| Pulse rate● | 1% | 1% | 1% | 0% | 3% | 8% | 3% | 2% |
| Other | 0% | 1% | 4% | 2% | 3% | 1% | 2% | 2% |
| Unknown | 0% | 0% | 1% | 1% | 0% | 1% | 1% | 0% |

○ dose was reduced for patients whose mean systolic blood pressure was > 160 mmHg or whose mean diastolic blood pressure was > 95 mmHg.

● dose was reduced for patients whose mean pulse rate was > 100 bpm.

These data suggest that the 20 and 30 mg doses were not as well tolerated compared to the lower doses. In particular, the 30 mg dose group had a larger percentage of subjects who had their dose reduced because of an increase in blood pressure.

Based on the criteria of an incidence of greater than 1% in a sibutramine group and an incidence greater than placebo, the following adverse events were associated with permanent dose reductions due to sibutramine treatment: asthenia, headache, chest pain, hypertension, palpitations, tachycardia, anorexia, nausea, agitation, anxiety, dizziness, dry mouth, hyperkinesia, insomnia, nervousness, tremor, rash, and dyspnea. Events that occurred with a statistically significantly (or near statistically significantly) greater incidence in the sibutramine group included anorexia ($p=0.005$), agitation ($p=0.066$), dry mouth ($p<0.001$), insomnia ($p<0.001$), tremor ($p=0.068$), rash ($p=0.07$), and dyspnea ($p=0.061$).

The percentages of patients with at least one **treatment-emergent severe adverse** event were as follows: placebo (8%), 1 mg (13%), 5 mg (14%), 10 mg (14%), 15 mg (15%), 20 mg (13%), and 30 mg (15%).

When the adverse event rates for all the drug treatment groups were combined and compared to the rate in the placebo group the following adverse events were statistically more common in the active treatment groups compared to the placebo group:

1. Vasodilatation (2.8 vs 0.0%, $p=0.038$)
2. Anorexia (25 vs 13%, $p<0.001$)
3. Constipation (11 vs 4%, $p=0.009$)
4. Dry mouth (22 vs 6%, $p<0.001$)
5. Insomnia (13 vs 7%, $p=0.039$)

Table 8.1.4.3.3 illustrates the percentage of patients, by dosage, reporting at least one adverse event that was statistically significant compared to placebo.

| TABLE 8.1.4.3.3 | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | **Placebo** | **1mg** | **5mg** | **10mg** | **15mg** | **20mg** | **30mg** | **P Value** |
| Hypotesnion | 0 | 0 | 0 | 0 | 0 | 2 | 0 | 0.017 |

| TABLE 8.1.4.3.3 | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Placebo | 1mg | 5mg | 10mg | 15mg | 20mg | 30mg | P Value |
| Palpitation | 1 | 2 | | 5 | 3 | 4 | 6 | 0.004 |
| Tachycardia | 1 | 1 | 2 | 4 | 8 | 7 | 3 | 0.001 |
| Vasodilitat | 0 | 1 | 2 | 2 | 2 | 5 | 5 | 0.015 |
| Anorexia | 12 | 20 | 19 | 19 | 21 | 32 | 32 | 0.001 |
| Inc appetite | 8 | 11 | 17 | 17 | 14 | 12 | 21 | 0.017 |
| Constipation | 4 | 7 | 13 | 11 | 12 | 12 | 8 | 0.031 |
| Diarrhea | 5 | 10 | 6 | 4 | 2 | 3 | 3 | 0.011 |
| Dyspepsia | 7 | 4 | 4 | 4 | 8 | 5 | 13 | 0.017 |
| Nausea | 4 | 3 | 4 | 3 | 5 | 8 | 13 | 0.002 |
| Dry mouth | 6 | 6 | 12 | 17 | 26 | 32 | 32 | 0.001 |
| Hyperkinesia | 0 | 0 | 1 | 0 | 0 | 3 | 1 | 0.030 |
| Insomnia | 6 | 12 | 8 | 9 | 10 | 10 | 25 | 0.001 |
| Nervousness | 6 | 5 | 5 | 6 | 8 | 12 | 11 | 0.044 |
| Dyspepsia | 0 | 1 | 1 | 1 | 1 | 1 | 5 | 0.024 |
| Sweating | 0 | 0 | 1 | 1 | 3 | 4 | 3 | 0.026 |

p value is from a Cochran-Mantel-Haenszel Chi-square test
The majority (85%) of adverse events were considered mild in severity.

Ordered from highest to lowest difference between placebo and active treatment, these adverse events were: dry mouth, anorexia, appetite increase, nausea, tachycardia, nervousness, dyspepsia, palpitations, vasodilatation, dyspnea, and sweating.

Based on the criteria of an incidence greater than 1% in two treatment groups and an incidence greater than placebo, the events listed in table 8.1.4.3.4 appeared to be associated with **treatment-related discontinuation.**

| TABLE 8.1.4.3.4 | | | | | | | |
|---|---|---|---|---|---|---|---|
| Event | **placebo** n=148 | **1 mg** n=149 | **5 mg** n=151 | **10 mg** n=150 | **15 mg** n=152 | **20 mg** n=146 | **30 mg** n=151 |
| Hypertension | 1 | 0 | 1 | 0 | 2 | 3 | 7 |
| Palpitations | 0 | 0 | 0 | 2 | 0 | 0 | 2 |
| Tachycardia | 1 | 0 | 0 | 0 | 2 | 4 | 1 |
| Insomnia | 1 | 1 | 0 | 1 | 0 | 3 | 2 |
| Dyspnea | 0 | 2 | 0 | 1 | 2 | 0 | 1 |

Discontinuations from the study due to hypertension were more numerous for sibutramine doses 15-30 mg relative to placebo.

Table 8.1.4.3.5 provides the details of the **serious adverse events** reported during the study.

TABLE 8.1.4.3.5

| number | sex | age | dose | drug duration | event | comment |
|---|---|---|---|---|---|---|
| 2010 | M | 38 | 1mg | 8wk | near syncope | withdrew at 10wk, no f/u |
| 5053 | F | 38 | 1mg | 8wk | gastric distress | withdrew 12 wks, cholecystectomy |
| 1122 | F | 45 | 5mg | 17wk | hemorrhage L eye | completed study |
| 4023 | M | 20 | 5mg | 2-days post | severe depression | recovered after 6-days |
| 2153 | M | 59 | 10mg | 8wk | syncope | recovered, completed |
| 2069 | F | 38 | 15mg-10mg | 7wk | cva after 2wk of 10mg | sxs resolved 1 day. No f/u |
| 6145 | F | 36 | 15mg | 5days | anxiety | patient withdrew |
| 1048 | F | 48 | 20mg | 3wk | L eye flashes | completed at 10 mg |
| 1139 | F | 39 | 20mg-10mg | 13days | seizure-like activity | patient withdrawn at 13 days |
| 1141 | F | 46 | 20mg | 1 day | moderate depression | patient withdrew and recovered |
| 2006 | F | 60 | 20mg-10mg | 2wk | moderate tachycardia | patient withdrawn |
| 1107 | M | 61 | 30mg | 4 days | anxiety | patient withdrew, anxiety resolved |
| 2169 | F | 25 | 30mg-15mg | 7wk | anxiety,tachycardia,suicide attempt | patient withdrawn for counseling |
| 5118 | F | 44 | 30mg | 9days | breast lump and toxic thyroid | lump resolved after thyroidectomy |
| 7019 | F | 53 | 30mg | 24wk | thyroid nodule | lobectomy |
| 1016 | M | 53 | 15mg | 2wk | hypertension | started on vasotec and completed study. Had a hx of untreated hypertension. |

It is of interest to note that no serious adverse events were reported for subjects receiving placebo.

Dysmenorrhea was reported by 3% of women in the 10 mg group (p=0.032 vs placebo) during the placebo washout period. There were three serious post-treatment adverse events reported. One subject in the placebo group was diagnosed with squamous cell carcinoma of the throat; another patient who received 20-10 mg of sibutramine developed nervousness and tachycardia after 8 wk of therapy and was withdrawn from the study at 18 weeks because of hypertension (150/102), he then developed chest pain at 6 weeks post-study, he ruled out for a myocardial infarction; the third patient was randomized to 30 mg of drug treatment which was reduced to 15

mg for constipation and she completed the study. During the post-treatment period she was diagnosed with vaginal dysplasia.

Correlation between the change in bodyweight with the number of unique adverse events

It is interesting to note that there were statistically significant correlations between the change in body weight with the number of unique adverse events in the 10, 15, 20 ,and 30 mg groups, but not in the 5 mg, 1 mg, or placebo groups.

Clinical laboratory evaluations

There was a dose-related increase in the mean platelet count for the doses 10-30 mg; however, there were no clinically significant changes. There were isolated abnormalities in serum chemistry values, but none were clinically significant (i.e. $\geq$ 3 times upper limit of normal for AST). One female developed an elevated ALT value that had not resolved by her last evaluation and two subjects developed hyperglycemia that was present at their last evaluation. There were no significant patterns of change in the thyroid function tests during the study.

Lipoprotein lipids

Although the lipid levels tended to change in a favorable directions with sibutramine, there were no obvious dose-response relationships and no consistent, statistically significant changes between the active-treated groups compared to the placebo group. The Sponsor indicated that compliance with fasting prior to the sampling was variable.

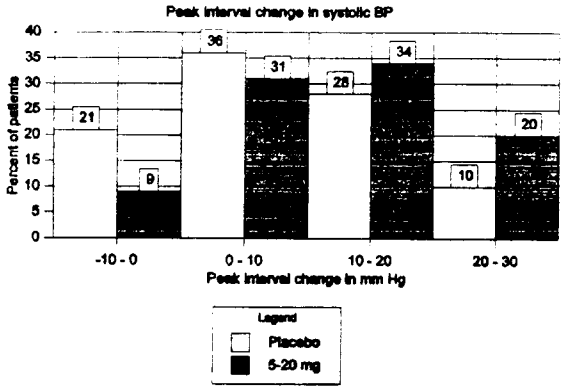
Vital signs

Systolic BP

Mean increases in supine systolic blood pressure were observed at all time points for sibutramine patients relative to placebo. However, a dose-response relationship was not obvious. For all sibutramine doses, changes in systolic pressure tended to rise and plateau at week 8. Mean ranges during the double-blind treatment period for the placebo group were -1.3 to 1.7 mmHg, and for the sibutramine groups were -0.1 to 7.5 mmHg. Statistically significant overall treatment effects were noted at weeks 6, 8, 10, 12, 15, 18, and 21.

Figure 8.1.4.3.1 illustrates the peak interval change in 5 minute supine systolic blood pressure for doses of 5-20 mg combined vs placebo.

Figure 8.1.4.3.1




These data illustrate that a greater percentage of placebo patients had a peak interval change of -10-0 mmHg compared to sibutramine-treated patients and a greater percentage of sibutramine subjects had a peak interval change of 20-30 mmHg relative to placebo subjects.

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Diastolic BP

Changes in supine diastolic blood pressure tended to mimic those of supine systolic blood pressure. Increases in diastolic pressure for sibutramine doses relative to placebo were noted, although an obvious dose-response relationship was not apparent. Similar to changes in systolic blood pressure, diastolic blood pressures tended to rise and plateau at week 8. There was no evidence that the pressures declined over the course of the 24-week study. Changes for placebo ranged from -1.3 to 1.3 mmHg, and for sibutramine doses the range was -0.7 to 5.0 mmHg. Statistically significant overall treatment effects were noted at weeks 4, 6, 8, 10, 12, 15, 18 and 21, as well at weeks 27 and 30 (3 and 6-weeks post-treatment). The only consistent, statistically significant findings relative to placebo were for the 20 mg dose group at weeks 6, 8, 10, 12, 15, 18, and 24. Three patients had significant increases from baseline for supine diastolic blood pressure: (1) patient #3006, taking 20 mg daily had an increase from 82 to 118 mmHg, (2) patient #3027, taking 30 mg daily had an increase from 86 to 110 mmHg and, (3) patient #7059, also taking 30 mg daily had an increase from 82 to 108 mmHg.

Figure 8.1.4.3.2

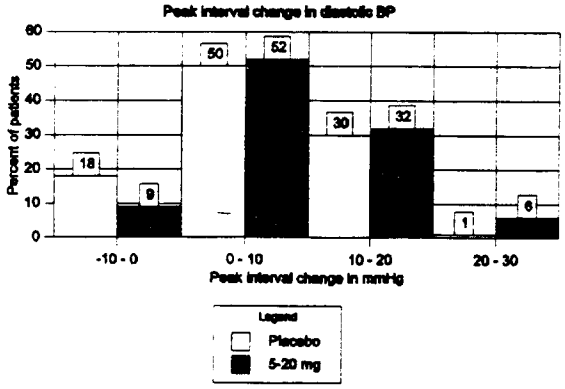


Figure 8.1.4.3.2 illustrates the peak interval change in 5 minute supine diastolic blood pressure for doses of 5-20 mg combined vs placebo.

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Similar to the peak interval changes in systolic blood pressure, a greater percentage of placebo patients had a peak interval change in diastolic blood pressure of -10-0 mmHg compared to sibutramine patients, whereas, a greater percentage of sibutramine patients had a peak interval change of 20-30 mmHg compared to placebo subjects.

Regarding changes in standing diastolic pressure, one placebo patient and 12 sibutramine-treated patients had clinically significant increases from baseline in standing diastolic pressure. The values in mmHg are noted below.

| Treatment | Baseline value | Abnormal value |
|---|---|---|
| Placebo | 92 | 108 |
| 5 mg | 82 | 110 |
| | 74 | 110 |
| | 78 | 110 |
| 10 mg | 82 | 108 |
| | 78 | 107 |
| | 94 | 110 |
| 20 mg | 74 | 106 |
| 30 mg. | 70 | 110 |
| | 90 | 110 |
| | 80 | 110 |
| | 80 | 108 |
| | 60 | 108 |

APPEARS THIS WAY
ON ORIGINAL

Pulse

Consistent increases in mean supine pulse rate relative to placebo were observed for the 5-30 mg doses. Increases tended to be dose-related. The changes reached a maximum by week 8 and plateaued thereafter. Changes for placebo through week 24 ranged from -0.6 to 2.8 bpm, and for sibutramine from 0.0 to 8.8 bpm.

Table 8.1.4.3.6 summarizes the mean changes (±SD) in vital signs from baseline to weeks 12 and 24.

| TABLE 8.1.4.3.6 | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **Parameter** | **Week** | **Placebo** | **1 mg** | **5 mg** | **10 mg** | **15 mg** | **20 mg** | **30 mg** |
| | 12 (n) | 99 | 114 | 125 | 115 | 108 | 111 | 117 |
| | 24 (n) | 84 | 92 | 103 | 95 | 94 | 89 | 96 |

| TABLE 8.1.4.3.6 | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **Parameter** | **Week** | **Placebo** | **1 mg** | **5 mg** | **10 mg** | **15 mg** | **20 mg** | **30 mg** |
| Supine❶ SBP | 12 | 0.6 (12) | 2.0 (10) | 3.3 (11) | 5.1 (10)• | 3.7 (11) | 5.2 (12)• | 3.5 (13) |
| | 24 | 1.7 (12) | 1.2 (11) | 2.5 (11) | 4.2 (11) | 3.4 (12) | 5.0 (12) | 4.1 (12) |
| Standing SBP | 12 | -0.7 (11) | 1.0 (10) | 1.9 (12) | 4.0 (12)• | 2.8 (13) | 4.2 (12)• | 1.6 (14) |
| | 24 | 0.5 (13) | 0.8 (12) | 0.8 (12) | 4.1 (12) | 4.5 (12) | 3.5 (13) | 3.3 (14) |
| Supine DBP | 12 | 0.7 (8) | 0.3 (7) | 2.4 (9) | 2.9 (8) | 2.8 (8) | 4.9 (10)• | 2.1 (8) |
| | 24 | 0.8 (8) | 0.3 (7) | 2.1 (8) | 2.8 (8) | 2.7 (8) | 4.0 (9)• | 3.3 (8) |
| Standing DBP | 12 | 0.6 (8) | -1.1 (7) | 1.4 (8) | 2.0 (9) | 4.1 (8)• | 3.3 (10) | 1.6 (9) |
| | 24 | 0.5 (9) | -1.6 (9) | 0.2 (10) | 2.4 (9) | 4.1 (8)• | 2.6 (8) | 2.3 (9) |
| Supine❶ pulse | 12 | 0.6 (7) | 0.3 (7) | 3.6 (7)• | 4.4 (7)• | 6.3 (9)• | 7.0 (8)• | 6.6 (9)• |
| | 24 | 0.6 (6) | 0.3 (8) | 3.3 (8) | 6.0 (8)• | 6.1 (8)• | 7.0 (9)• | 5.3 (8)• |
| Standing pulse | 12 | 0.2 (8) | 0.8 (8) | 3.6 (8)• | 4.0 (9)• | 6.6 (9)• | 7.9 (9)• | 7.3 (10)• |
| | 24 | -0.3 (7) | -0.6 (8) | 2.8 (9) | 4.4 (8)• | 5.8 (8)• | 7.8 (10)• | 5.3 (9)• |

❶Blood pressure in mm Hg; pulse in bpm.
• $p<0.05$ active treatment vs placebo

Interestingly, there were statistically significant correlations between the plasma concentrations of metabolites 1 and 2 with the changes in pulse rate at week 12, but not with the changes in blood pressure.

Electrocardiograms

There were dose-related increases in heart rate. The changes in heart rate reached a maximum by week 2 and remained constant thereafter. The changes in heart rate at week 24 were as follows: placebo, 1bpm; 1 mg, 3 bpm; 5 mg, 5 bpm; 10 mg, 5 bpm; 15 mg, 5 bpm; 20 mg, 6 bpm; 30 mg, 10 bpm. At each visit, (except week 24, 10 mg) the sibutramine 10, 15, 20, and 30 mg groups had statistically significant increases in heart rate compared to placebo. Significance for the sibutramine 5 mg group was only occasional. At week 6 and thereafter, the PR intervals for the sibutramine groups were shortened when compared to the changes in the placebo group. These differences were not clinically significant. There were no clinically meaningful changes in the QRS or QT intervals in the sibutramine groups relative to the changes in the placebo group. There were several patients who had an increase in the number of premature atrial contractions (PACs) during the study; however, all but one of these subjects had a reduced number of PACs by week 24. There were a number of patients who had an increase in the number of premature ventricular contractions (PVCs) from baseline during the study. Five sibutramine subjects went from 0 PVCs/2min at baseline to greater than 5 PVCs/2min during the study. Three placebo

patients developed PVCs during the study. Most of the patients had persistent PVCs at the final evaluation. The clinical significance of a potential increase in the rate of PVCs in unknown, but does raise some concern if the drug is used by patients with known or occult coronary heart disease.

Neuropsychiatric evaluations

There were no statistically or clinically significant changes in the scores on the Hamilton Depression Scale for sibutramine or placebo subjects. Changes in the Modified Norris Assessment were, in general, not statistically significant. The absolute changes favored the sibutramine group for the categories of mental and physical sedation, tranquilization, and other feelings. No data were obtained regarding withdrawal effects.

### 8.1.5 SPONSOR'S CONCLUSIONS

"The results of this study indicate that in the healthy, obese patients treated in this study sibutramine, in doses of 5-30 mg, was both safe and effective."

### 8.1.6. MEDICAL OFFICER'S SUMMARY AND CONCLUSIONS

This Reviewer agrees with the Sponsor's conclusion that doses of 5-30 mg were "effective." The 5% responder analysis in both the completers and intent-to-treat datasets verified that doses of 5-30 mg were more effective in achieving a 5% weight loss when compared to placebo.

The adverse events that appeared to be drug related were, in general, not serious and reflected the pharmacological actions of the drug: increased serotonergic and adrenergic activity. Of concern, however, was the dose-related increase in pulse rate and a trend for an increase in blood pressure in the patients treated with doses greater than 5 mg QD. Nearly 30% of the subjects randomized to 30 mg had their dose reduced; fifteen percent because of an adverse event and 9% because of increase in blood pressure (SBP > 160 mmHg or DBP > 95 mmHg). Seven subjects in the 30 mg group were withdrawn from the study because of a hypertensive response compared to one subject in the placebo group. The inverse association between sibutramine-induced weight loss and blood pressure is a critical, negative feature of the drug, and will play a major role in the risk — benefit analysis.

Given the increased incidence of adverse events and hypertension in the 30 mg group, coupled with the dose-response curve plateauing at 20 mg and the lack of statistically significant differences in weight loss between the 20 and 30 mg doses, this Reviewer believes that the elimination of the 30 mg dose would increase safety without reducing overall efficacy.

## 8.2 BPI 852X

### OBJECTIVE/RATIONALE

**8.2.1** The objective of this study is to assess the long-term safety, tolerability and efficacy of sibutramine for up to 24 months.

**DESIGN**

**8.2.2** A multicenter, open-label, flexible-dose study to evaluate the long-term effects of sibutramine administered for up to 24 additional months to relatively healthy obese patients who have previously participated in BPI 852.

**PROTOCOL**

**POPULATION**

**8.2.3.1** Male and female patients between the ages of _____ years with a BMI of _____ The following patients were not eligible for this study: patients who discontinued from BPI 852 prior to week 24, or who discontinued at week 24 due to an adverse event, and those who were noncompliant with dosing in BPI 852.

**ENDPOINTS**

**8.2.3.2** The primary endpoints are the assessment of long-term safety and tolerability of sibutramine. Secondary endpoints included the assessment of optimal doses of sibutramine in inducing and maintaining weight loss for up to 24 months, and assessing withdrawal potential during a 6-month follow-up period.

**RESULTS**

**POPULATIONS ENROLLED/ANALYZED**

**8.2.4.1** Six-hundred eighty-three patients completed 24 weeks of study BPI 852. Five-hundred ninety-one of these patients were screened for BPI 852X, and five-hundred seventy-two patients received active treatment. Two-hundred thirty-five patients had withdrawn from the study as of September 30, 1994; 72 due to adverse events, 24 due to lack of efficacy, 24 were lost to follow-up, 82 discontinued due to protocol violations, and 33 discontinued for other reasons.

**SAFETY OUTCOMES**

**8.2.4.2** There have been no deaths reported in this study. Of the 72 patients who were withdrawn from the study because of an adverse event a large percentage were due to hypertension, depression or mood alterations, and headaches. Refer to the overview of safety section for details on safety data submitted 12/19/95.

**8.3 SB 1047 UK**

## OBJECTIVE/RATIONALE

**8.3.1** The aim of this study was to evaluate the long-term (1 year) efficacy, tolerability, and safety of sibutramine in patients with uncomplicated obesity.

## DESIGN

**8.3.2** This was a 12-month, multicenter, double-blind, placebo-controlled, parallel-group study of 10 and 15 mg QD of sibutramine in 485 patients. There was a 1-month follow-up period after the 12-month active treatment phase. The principle outcome variable was the change in body weight. Additional parameters that were measured include vital signs, waist and hip circumferences, and patient self assessments of hunger, satiety, and appetite.

## PROTOCOL

## POPULATION

**8.3.3.1** The patient population consisted of 485 subjects of which 20% were men and 80% women. The mean age was 42 years with a range of_____ years. The vast majority (> 98%) were Caucasian. The average BMI was 32.7 kg/m$^2$ with a range of Patients treated for hypertension were allowed to participate in the study if their condition had been stabilized by medication(s) for six months or more.

## ENDPOINTS

**8.3.3.2** The primary efficacy endpoint was change in body weight. This parameter was measured during the 2 week placebo run-in period and monthly thereafter. All participating study centers were provided with the same scale to measure body weight. Compliance, adverse events, and concomitant medication use were evaluated at each monthly visit. Laboratory investigations and ECGs were conducted at baseline, and months 6 and 12. Total cholesterol, triglyceride, and glucose levels were measured in the **non**fasting state. Blood pressure and pulse measurements were conducted with the subjects in the seated position.

## STATISTICAL CONSIDERATIONS

**8.3.3.3** All statistical tests were 2-tailed with $p<0.05$ considered significant. All analyses were performed on an intent-to-treat basis. Patients who completed the study were assigned to one of 10 categories based on the percentage of weight loss over the course of the study: withdrawal because of treatment success; loss of >20% of initial bodyweight; 15.1%-20.0% lost; 10.1%-15.0% lost; 5.1%-10.0% lost; 0.1%-5.0% lost; no change; weight gain; withdrawal because of adverse event; and withdrawal because of lack of efficacy. This analysis was repeated on the dataset formed after patients who withdrew for reasons unconnected with the safety and efficacy of the drug were excluded. The differences between the treatment groups in weight loss were

analyzed using repeated measures analysis of variance. The repeated measures analyses were performed on four datasets: 1) all available data with no account taken of missing values; 2) all available data but with missing values estimated by LOCF; 3) patients who completed the 12-month double-blind phase of the study; and 4) all available data with the addition that, for the within-group tests, the missing values were replaced by predicted values calculated from the model fitted to the data. Patients who did not have an assessment of body weight following the 1-month assessment were not included in the analyses for datasets 1 and 4.

## RESULTS

## POPULATION ENROLLED/ANALYZED

**8.3.4.1** Five-hundred and ten patients were enrolled in the study. Twenty-five withdrew during the washout period, thus 485 patients entered the double-blind phase. A total of 256 completed the 12-month study. Eighty of 163 completed the study in the placebo group, 82 of 161 completed in the 10 mg group, and 94 of 161 completed in the 15 mg group.

The groups were comparable at baseline with respect to mean age and mean BMI. However, the male subjects in the 10 mg group weighed less than the male subjects in the other two groups. The mean BMI values were similar for the male patients in all groups.

Ten subjects in the placebo group, 7 in the 10 mg group, and 5 in the 15 mg group started antidepressive, tranquillizers, or psychomimetics during the study. Eleven subjects in the placebo group, 7 in the 10 mg group, and 8 in the 15 mg group started antihistamine/anti-allergic medications during the study. Fifteen subjects in the placebo group, 10 in the 10 mg group, and 14 in the 15 mg group started corticosteroid therapy during the study. Thirty-eight placebo subjects: 55 in the 10 mg group and 59 in the 15 mg group started antibiotic or other antibacterial therapy during the study

Table 8.3.4.1.1 summarizes the enrollment and withdrawals from the study

| **TABLE 8.3.4.1.1** | | | |
|---|---|---|---|
| 510 ENROLLED | | | |
| 25 | | | Withdrew during washout period |
| 485 | | | Randomized |
| Placebo n=163 | 10 mg n=161 | 15 mg n=161 | Treatment groups |
| 48 | 56 | 44 | Withdrew-other reasons |
| 34 | 23 | 22 | Withdrew-lack of efficacy and/or adverse event |

| Placebo n=163 | 10 mg n=161 | 15 mg n=161 | Treatment groups |
|---|---|---|---|
| 81 | 82 | 95 | completed 12-months |
| 4 | 2 | 1 | excluded from completers analysis |

Fifty percent, 51%, and 59% of the placebo, 10 mg, and 15 mg subjects, respectively completed the study.

## EFFICACY ENDPOINT OUTCOMES

Body weight

Table 8.3.4.2.1 illustrates the results of the categorical analysis of weight loss for all patients.

**TABLE 8.3.4.2.1**

| Outcome category | Frequency | | |
|---|---|---|---|
| | **Placebo n=163** | **10 mg n=161** | **15 mg n=161** |
| **Treatment successes** | 1 | 0 | 1 |
| **> 20% weight loss** | 1 | 3 | 6 |
| **15.1%-20.0% weight loss** | 1 | 11 | 8 |
| **10.1%-15.0% weight loss** | 4 | 11 | 23 |
| **5.1%-10.0% weight loss** | 16 | 21 | 24 |
| **0.1%-5.0% weight loss** | 29 | 21 | 18 |
| **No change** | 1 | 0 | 2 |
| **Weight gain** | 28 | 15 | 13 |
| **Withdrew-other reasons** | 48 | 56 | 44 |
| **Withdrew-lack of efficacy and/or adverse event** | 34 | 23 | 22 |

The sibutramine 10 and 15 mg groups had more favorable outcomes compared to the placebo group ($p<0.05$ and $p<0.001$, respectively). The two drug treatment groups did not differ statistically from one another.

Table 8.3.4.2.2 illustrates the adjusted (*) mean weight loss (kg) for each of the 12 months of the study for completers.

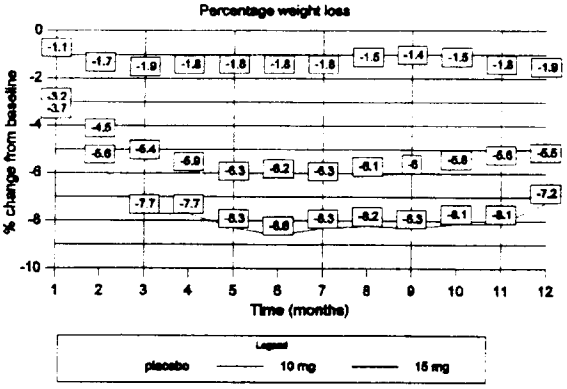
| TABLE 8.3.4.2.2 | | | |
|---|---|---|---|
| **Month of study** | **Placebo** n=76/163 | **10 mg** n=80/161 | **15 mg** n=93/161 |
| 1 | -1.0[a] | -2.8[b] | -3.2[b] |
| 2 | -1.5[a] | -4.0[b] | -4.8[c] |
| 3 | -1.8[a] | -4.7[b] | -6.0[c] |
| 4 | -1.6[a] | -5.1[b] | -6.6[c] |
| 5 | -2.0[a] | -5.5[b] | -7.2[c] |
| 6 | -1.7[a] | -5.4[b] | -7.4[c] |
| 7 | -1.6[a] | -5.5[b] | -7.1[b] |
| 8 | -1.4[a] | -5.4[b] | -7.0[b] |
| 9 | -1.4[a] | -5.2[b] | -7.2[c] |
| 10 | -1.4[a] | -5.1[b] | -7.0[c] |
| 11 | -1.7[a] | -4.9[b] | -6.5[b] |
| 12 | -1.8[a] | -4.8[b] | -6.1[b] |

* Mean weight loss was adjusted for center and interaction effects.
Values with different superscripts are significant at $p<0.05$.

The unbalanced analysis produced results that were similar to the completers analysis; in general, the p values were lower for the comparisons between the 10 and 15 mg groups. The balanced and carryforward approaches differed from the completers analysis in that the absolute values for weight loss were lower for each group at each month and the values were statistically significantly different for the 10 vs 15 mg groups at all 12 months. At 12 months, the 10 mg group lost approximately 3.0 kg more weight compared to the placebo group and the 15 mg group lost approximately 4.3 kg more weight compared to the placebo group. Peak weight loss occurred at approximately the 6$^{th}$ and 7$^{th}$ months and then declined toward the 12$^{th}$ month.

Figure 8.3.4.2.1 illustrates the adjusted mean percentage weight loss from baseline at each month during the study for the completers.

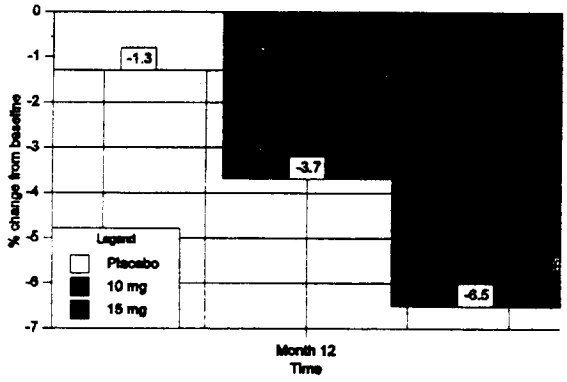
Figure 8.3.4.2.1




Compared to the placebo group, the 10 and 15 mg sibutramine groups lost significantly more weight at each time point ($p<0.001$). Compared to the 10 mg group, the 15 mg group lost significantly more weight during months 2-10 ($p<0.05$). The 10 and 15 mg groups did not differ significantly at months 11 and 12. At month 12, only the 15 mg dose produced a mean percentage weight loss that was at least 5% greater than placebo.

Figure 8.3.4.2.2 illustrates the adjusted mean percentage weight loss from baseline at month 12 for the intent-to-treat - LOCF dataset.

Figure 8.3.4.2.2




At month 12, both the 10 mg and 15 mg groups had a statistically significantly greater percentage weight loss compared to placebo ($p<0.001$). In addition, the 15 mg dose was statistically different from the 10 mg dose ($p<0.001$). It is noteworthy that only the 15 mg dose produced a weight loss that was at least 5% greater than placebo by the end of the trial.

Table 8.3.4.2.3 provides the percentage of patients who lost > 5% of baseline body weight at months 6 and 12 for the completers.

**TABLE 8.3.4.2.3**

| Treatment | Month 6 | | | Month 12 | | |
|---|---|---|---|---|---|---|
| | n | % | odds ratio | n | % | odds ratio |
| Placebo | 106 | 26 | | 76 | 29 | |
| 10 mg | 116 | 57●● | 3.59 | 80 | 56● | 2.54 |

| TABLE 8.3.4.2.3 | | | | | | |
|---|---|---|---|---|---|---|
| **Treatment** | **Month 6** | | | **Month 12** | | |
| | n | % | odds ratio | n | % | odds ratio |
| 15 mg | 124 | 69●● | 6.77 | 93 | 65●● | 5.40 |

Odds ratio of success/failure relative to placebo
●p<0.01, ●● p<0.001 compared to placebo

In the intent-to-treat analysis, 20% of placebo subjects, 37% of 10 mg subjects, and 54% of 15 mg patients achieved a weight loss of at least 5% of initial body weight (10 and 15 mg vs placebo, p<0.01).

In an analysis that included weight change from baseline to month 12 including patients who withdrew but returned for the month-12 assessment, the adjusted mean weight losses for the placebo, 10 mg, and 15 mg groups were 1.9 kg (n=98), 4.0 kg (n=99), and 4.9 kg (n=108), respectively. The differences between all pairs of treatment groups were significant at p<0.05.

Waist circumference

The adjusted mean reductions in waist circumference from baseline to endpoint were -3.12 cm, -7.12 cm, and -8.40 cm for the placebo, 10mg, and 15mg groups, respectively. The reductions in waist circumference in the 10 and 15 mg groups were statistically significantly greater compared to placebo (p<0.01).

Consummatory behavior

Subjects who received 10 mg of sibutramine reported reduced hunger and cravings for sweet foods and increased satiety compared to placebo subjects. Subjects who received 15 mg of sibutramine had reduced hunger, appetite, craving for sweet and carbohydrate foods and greater dietary compliance compared to placebo subjects. These findings support the notion that sibutramine works by reducing appetite and cravings for simple and complex carbohydrates.

Patients in the 15 mg group had statistically significantly reduced appetite (p<0.001) and greater dietary compliance (p<0.05) compared to those in the sibutramine 10 mg group.

## SAFETY OUTCOMES

### 8.3.4.3 Adverse events

Table 8.3.4.3.1 provides the number of subjects who withdrew from the study and the reasons for withdrawal.

| TABLE 8.3.4.3.1 | | | |
|---|---|---|---|
| **REASON FOR WITHDRAWAL** | **TREATMENT GROUP** | | |
| | **N=163** | **N=161** | **N=161** |
| | Placebo | 10 mg | 15 mg |
| Adverse event | 24 | 18 | 20 |
| Lack of efficacy | 10 | 5 | 2 |
| Did not attend | 31 | 40 | 27 |
| Lost to follow-up | - | 1 | 2 |
| Recovered | 1 | - | 1 |
| Protocol violation | 6 | 7 | 8 |
| Withdrew consent | 9 | 4 | 2 |
| Domestic situation | 1 | 1 | 1 |
| Moved from area | - | 3 | 3 |
| Trying pregnancy | 1 | - | 1 |

There were no statistically significant differences between the groups for overall withdrawal rates. Six subjects in the placebo group, 7 in the 10 mg group, and 8 in the 15 mg group did not provide a post-baseline assessment of body weight. These 21 subjects are not included in the endpoint analyses.

A total of 256 subjects completed the 12 month study. A total of 249 patients were included in the analyses of completers because 7 patients had their 12-month assessments 14 days after the final dose.

Table 8.3.4.3.2 provides the percentages of patients reporting adverse events by COSTART body system.

| TABLE 8.3.4.3.2 | | | |
|---|---|---|---|
| **BODY SYSTEM** | **PLACEBO** | **10 MG** | **15 MG** |
| | N=163 | N=161 | N=161 |
| Overall | 67%[a] | 76%[ab] | 82%[b] |
| Body as a whole | 40% | 43% | 47 |
| Cardiovascular | 4% | 6% | 10% |
| Digestive | 17%[a] | 26%[ab] | 30%[b] |

| TABLE 8.3.4.3.2 | | | |
|---|---|---|---|
| **BODY SYSTEM** | **PLACEBO** | **10 MG** | **15 MG** |
| Heme and lymphatic | 0%[a] | 1%[ab] | 3%[b] |
| Metabolic | 4% | 2% | 4% |
| Musculo-skeletal | 9% | 12% | 14% |
| Nervous system | 15%[a] | 24%[ab] | 35%[b] |
| Respiratory | 22% | 24% | 22% |
| Skin | 12% | 12% | 19% |
| Special senses | 1%[a] | 12%[b] | 11%[b] |
| Urogenital | 10% | 16% | 19% |

Values with different superscripts are significant at $p<0.001$ except haemic and lymphatic which is significant at $p<0.05$.

Adverse events which appear to have occurred more frequently in the active treatment groups were: pain: back pain, abdominal pain; constipation, nausea, tenosynovitis, dizziness, dry mouth, and pharyngitis.

Table 8.3.4.3.3 provides the adverse events reported by more than 5% of patients.

| Table 8.3.4.3.3 | | | |
|---|---|---|---|
| **COSTART term** | **Placebo** | **10 mg** | **15 mg** |
| Headache | 13 | 17 | 11 |
| Infection | 18 | 19 | 23 |
| Inury/accident | 10 | 9 | 13 |
| Pain/back | 7 | 10 | 11 |
| Constipation | 5 | 12 | 14 |
| Arthralgia | 9 | 7 | 10 |
| Dry mouth | 2 | 19● | 21● |
| Pharyngitis | 13 | 22 | 26 |
| Rhinitis | 13 | 5 | 7 |

● $p<0.001$ compared to placebo

The Sponsor states that during the one-month follow-up period 30 adverse events were reported by the placebo group, 24 events were reported by the 10 mg group, and 40 events were reported by subjects in the 15 mg group. In addition, five subjects reported depression during the month

of follow-up; two in the placebo group and three in the 15 mg group. There was no evidence of withdrawal according to the Sponsor. However, the depression and anxiety inventories were administered one week following the 12-month endpoint. This may not be an optimal time to administer these inventories as potential withdrawal symptoms may manifest later than one week following the discontinuation of drug therapy.

Table 8.3.4.3.5 provides the details of the adverse events reported as **serious** in the active drug treatment groups.

**TABLE 8.3.4.3.4**

| number | sex | age (yrs) | dose (mg) | duration (days) | event | comment |
|---|---|---|---|---|---|---|
| 11 | F | 49 | 10 | 126 | 4 drop attacks | Hx of epilepsy withdrew |
| 109 | F | 62 | 10 | 22 | perforated diverticulum | withdrew |
| 121 | F | 32 | 15 | 246 | PVCs | amiodarone prescribed withdrew |
| 424 | F | 22 | 15 | 203 | pregnancy | no complications withdrew |
| 3 | M | 20 | 10 | 35 | amputation of finger | withdrew |
| 32 | F | 43 | 10 | 130 | hysterectomy | reason not provided |
| 34 | F | 50 | 10 | 53 | abdominal pain | patient recovered without dx |
| 75 | F | 53 | 10 | 76 | vaginal bleed | normal findings at surgery |
| 119 | M | 61 | 10 | 312 | urinary fequency | prostatectomy finding unknown |
| 343 | F | 62 | 10 | 85 | arthralgia | steriod injection |
| 438 | F | 47 | 10 | 100 | abdominal pain | adhesions removed persistant pain withdrew |
| 453 | F | 48 | 10 | 188 | urethroplasty | withdrew because of nausea |
| 502 | F | 37 | 10 | 307 | colpo-suspension | no reason or findings provided |
| 35 | F | 48 | 15 | 18 | irritable bowel syndrome | |
| 53 | F | 38 | 15 | 9 | neck pain following an accident | |
| 79 | M | 61 | 15 | 239 | chalazia of eyelid | removed surgically |
| 95 | F | 34 | 15 | 222 | elective lumpectomy | finding not reported |
| 202 | F | 34 | 15 | 187 | surgery for adhesions | recovered |
| 219 | F | 43 | 15 | 258 | work-up for arthritis | no definitive dx |

| TABLE 8.3.4.3.4 | | | | | | |
|---|---|---|---|---|---|---|
| **number** | **sex** | **age (yrs)** | **dose (mg)** | **duration (days)** | **event** | **comment** |
| 298 | M | 60 | 15 | 129 | atrial fibrillation | condition may have predated sibutramine tx ? |
| 369 | F | 38 | 15 | 78 | reversal of tubal ligation | |
| 434 | M | 63 | 15 | 364 | developed distal neuropathy | |
| 459 | F | 44 | 15 | 247 | syncope possible SAH | persistent neurological sxs |
| 464 | F | 32 | 15 | 365 | pregnancy | neonatal seizures |

Table 8.3.4.3.6 shows the **10 mg** sibutramine subjects who **withdrew** from the study for "non-serious" adverse events.

| TABLE 8.3.4.3.5 | | | | | |
|---|---|---|---|---|---|
| **number** | **sex** | **age (yrs)** | **duration (days)** | **event** | **comment** |
| 75 | F | 53 | 245 | constipation | resolved |
| 91 | F | 41 | 93 | carpal tunnel syndrome | outcome unknown |
| 126 | M | 37 | 194 | chest pains and hypertension | outcome unknown |
| 180 | F | 52 | 24 | nausea | resolved |
| 182 | F | 42 | 180 | fluid retention | resolved |
| 206 | F | 25 | 47 | emotional lability | resolved |
| 257 | F | 30 | 62 | dizziness | recovered |
| 332 | F | 37 | 54 | headaches | recovered |
| 335 | F | 44 | 4 | dizziness | recovered |
| 363 | F | 64 | 187 | insomnia | recovered |
| 378 | F | 43 | 96 | migraines | recovered |
| 406 | F | 34 | 188 | ankle pain | recovered |
| 445 | M | 58 | 33 | constipation | recovered |
| 453 | F | 48 | ? | nausea | recovered |

| TABLE 8.3.4.3.5 | | | | | |
|---|---|---|---|---|---|
| **number** | **sex** | **age (yrs)** | **duration (days)** | **event** | **comment** |
| 471 | F | 40 | 220 | sinusitis | recovered |
| 520 | F | 48 | 226 | paraesthesia in legs | continued after withdrawal |

Table 8.3.4.3.7 shows the **15 mg** sibutramine subjects who **withdrew** from the study because of a non-serious adverse event.

| TABLE 8.3.4.3.6 | | | | | |
|---|---|---|---|---|---|
| **number** | **sex** | **age (yrs)** | **duration (days)** | **event** | **comment** |
| 40 | F | 30 | 51 | irritability | recovered |
| 45 | F | 58 | 207 | abnormal LFTs | recovered after 10 weeks |
| 112 | F | 55 | 53 | emotional lability | recovered |
| 181 | F | 38 | 59 | panic attacks | recovered |
| 191 | F | 37 | 278 | palpitations | recovered |
| 205 | F | 31 | 22 | depressed | recovered |
| 216 | M | 47 | 1 | nausea, tremor | recovered |
| 218 | F | 63 | 264 | dry mouth | recovered |
| 231 | F | 35 | 14 | headaches | recovered |
| 300 | F | 60 | 244 | cervical spondylosis | recovered |
| 326 | F | 26 | 65 | sweating | recovered |
| 331 | F | 34 | 26 | nausea | recovered |
| 344 | F | 39 | 19 | insomnia | recovered |
| 351 | F | 49 | 25 | constipation | recovered |
| 478 | F | 37 | 248 | dizziness | ongoing ? |
| 485 | F | 36 | 109 | constipation | ongoing at 1-month post-study |
| 499 | F | 36 | 8 | light headedness | recovered |
| 387 | F | 21 | 129 | chest pain | ongoing 1-month post-study |

Laboratory values

Table 8.3.4.3.4 provides the laboratory values that changed during the trial.

| TABLE 8.3.4.3.7 | | | | | |
|---|---|---|---|---|---|
| **Variable** | **Tx group** | **6 months** | **12 months** | **Endpoint** | **Final** |
| **Platelets (×10⁹/l)** | placebo | - | -12.2a n=66 | -6.9a n=111 | -6.5a n=135 |
| | 10 mg | - | 8.4b n=74 | 9.2b n=118 | 5.9b n=130 |
| | 15 mg | - | 3.7b n=83 | 2.3a n=122 | 3.3b n=134 |
| **Triglyceride (mmol/l)** | placebo | -0.07a | - | - | - |
| | 10 mg | -0.37b | - | - | - |
| | 15 mg | -0.41b | - | - | - |
| **Eosinophils (×10⁹/l)** | placebo | - | - | - | -0.006a n=135 |
| | 10 mg | - | - | - | 0.024b n=130 |
| | 15 mg | - | - | - | 0.005a n=134 |
| **Creatinine (umol/l)** | placebo | - | -3.5ab n=68 | -4.0ab n=114 | -4.0ab n=137 |
| | 10 mg | - | -2.8b n=75 | -2.8b n=122 | -2.6b n=135 |
| | 15 mg | - | -5.9a n=84 | -6.2a n=123 | -5.9a n=134 |
| **Uric acid (umol/l)** | placebo | -6.9a n=113 | - | -9.1a n=114 | -8.7a n=137 |
| | 10 mg | -20.2b n=122 | - | -21.0ab n=122 | -16.9a n=135 |
| | 15 mg | -21.6b n=122 | - | -26.5b n=123 | -28.6b n=134 |

Values with different superscripts are statistically significantly different at least $p<0.05$

The changes in clinical chemistries were not clinically significant. It should be noted that thyroid function test were evaluated in only one subject at 6 months, one subject at endpoint, and two subjects at the final assessment.

Lipoprotein lipids

At month 6, triglyceride levels were reduced by 3% in the placebo group, 18% in the sibutramine 10 mg group, and 19% in the sibutramine 15 mg group. The reductions in the active treatment groups were statistically significantly different compared to response in the placebo subjects. However, there were no statistically significant differences in triglyceride levels among the three groups at 12 months or endpoint. Total cholesterol levels did not change significantly in the drug or placebo-treated subjects.

Vital signs

There was a small, but statistically significant increase in diastolic blood pressure in the 10 mg group (1.6 mm Hg) compared to the placebo group (-0.9 mm Hg, $p<0.01$) when averaged over all time points. There was also a significant increase in pulse rate in the 15 mg group (3.5 bpm) compared to the placebc group (0.1 bpm, $p=0.007$).

Table 8.3.4.3.8 provides the percentage of patients in each group that had at least one systolic blood pressure reading > 160 mmHg and at least one diastolic blood pressure reading > 90 mmHg during the trial.

| TABLE 8.3.4.3.8 | | | |
|---|---|---|---|
| | **Placebo** | **10 mg** | **15 mg** |
| % of patients with at least one SBP > 140 | 43% | 51% | 46% |
| % of patients with at least one DPB > 90 | 27% | 34% | 35% |
| % of patients with at least one SBP > 140 or DBP > 90 | 45% | 55% | 50% |

SBP = systolic blood pressure and DBP = diastolic blood pressure in mm Hg

Table 8.3.4.3.9 illustrates the Pearson correlation coefficients for the change from baseline in body weight vs the change from baseline in both systolic and diastolic blood pressures in the placebo and sibutramine-treated groups.

| TABLE 8.3.4.3.9 | | | | |
|---|---|---|---|---|
| | **Sibutramine** | | **Placebo** | |
| **Month** | **Δ in SBP** | **Δ in DBP** | **Δ in SBP** | **Δ DBP** |

| TABLE 8.3.4.3.9 | | | | |
|---|---|---|---|---|
| | Sibutramine | | Placebo | |
| 12 | 0.07 | 0.12 | 0.25● | 0.13 |
| Endpoint | 0.06 | 0.09 | 0.26● | 0.14 |

●$p<0.05$

These data illustrate that there were no significant correlations between the change in body weight and the change in systolic or diastolic blood pressure in the sibutramine-treated subjects, whereas there was a significant correlation between the reduction in body weight and a reduction in systolic blood pressure in the placebo group.

Electrocardiograms

The adjusted mean change in heart rate from baseline to endpoint recorded from ECGs increased in the 15 mg group compared to the placebo group (4.9 vs -0.5 bpm, $p<0.01$). Moreover, the adjusted mean change in ECG heart rate from baseline to month 6 increased by 4.5 bpm and 5.8 bpm in the 10 and 15 mg groups, respectively, whereas the mean pulse rate decreased by 1.3 bpm in the placebo group (these changes were statistically significant at $p<0.01$) The adjusted mean change in PR interval from baseline to 6 months was decreased significantly in the 15 mg group compared to placebo (-5.3 vs 4.3 msec, $p<0.01$) as well as compared to the 10 mg group (-5.3 vs 3.0 msec, $p<0.01$). The adjusted mean change in the QT interval from baseline to 6 months was decreased in the 10 and 15 mg groups compared to the placebo group (-7.3 vs 9.1 msec, $p<0.01$ and -12.5 vs 9.1 msec, $p<0.001$, respectively). At endpoint the only significant difference was between the 15 mg group vs placebo (-7.7 vs 6.9 msec, $p<0.05$). These changes do not appear to be clinically significant.

Psychiatric evaluation

The protocol specified that 100 patients would complete the Beck depression and State anxiety inventories. Only 63 and 67 subjects completed these inventories, respectively. There were no significant differences between the groups for these two inventories when compared from the end of the double-blind treatment period to one week after treatment ended. Importantly, these inventories were not administered at baseline, so conclusions regarding any changes in mood from baseline to study completion cannot be made.

## 8.3.5. SPONSOR'S CONCLUSIONS

"This study demonstrated that sibutramine was efficacious over a 12-month treatment period with statistically significant reductions in weight compared to placebo, up to and including month 12, in mild to moderately obese patients.

The adverse event profile was generally good and sibutramine was well tolerated. Heart rate increased with sibutramine from baseline to month 6; however, it decreased again from month 6 to month 12."

### 8.3.6 MEDICAL OFFICER'S SUMMARY AND CONCLUSIONS

The results of the 5% responder analysis (completers and intent-to-treat datasets), support the Sponsor's claim that sibutramine was efficacious when compared to placebo over a 12-month treatment period.

In general, this Reviewer agrees with the Sponsor's comment that the adverse event profile was generally good. The Sponsor's comment that pulse rate increased from baseline to month 6 and decreased from month 6 to month 12 is true, but may reflect the drop-out of subjects with elevated pulse rates from month 6 to month 12. Diastolic blood pressure was also increased in the 10 mg group compared to the placebo group (1.6 vs -0.9 mmHg, $p<0.01$). It is worth emphasizing that, in contrast to the significant correlation between the change in weight with the change in systolic blood pressure observed in the placebo group, sibutramine-induced weight loss was not associated with a reduction in blood pressure. In fact, overall, sibutramine-induced weight loss was associated with an increase in diastolic blood pressure.

*NON-PIVOTAL STUDIES*

### 8.4 SB 1042 UK

**OBJECTIVE/RATIONALE**

**8.4.1** The objectives of this study were to assess the weight-reducing effects of 1, 10, and 20 mg once-daily doses of sibutramine and placebo and to evaluate the safety and tolerability of sibutramine in an obese population.

**DESIGN**

**8.4.2** A 12-week multicenter (3 centers with 2 Principal Investigators), double-blind, parallel-group, dose-ranging study. This study employed a one-week washout period prior to the start of the study and a 12-week follow-up period.

**PROTOCOL**

**POPULATION**

**8.4.3.1** Inclusion criteria:
1. Male or female
2. Age____

3. Obese: BMI

Exclusion criteria:
1. Pregnant or lactating women
2. Seated heart rate over 100 bpm
3. Seated diastolic blood pressure greater than 95 mmHg
4. Patients treated for hypertension
5. Presence of significant medical illness
6. Patients taking any medication that may alter body weight
7. Patients who lost more than 3 kg in the previous 3 months

Subjects were provided with written information on appropriate food selections. In addition, subjects had the option of returning to the center at additional times for dietary counseling.

**ENDPOINTS**

**8.4.3.2** The primary endpoint was the change in body weight. Other assessments included blood pressure, heart rate, dietary compliance, and concomitant therapy changes. These endpoints were measured at weeks -1, baseline, weeks 2, 4, 8, and 12. Optional visits (dietary compliance and counseling) occurred at weeks 1, 3, 5, 7, 9, 10, and 11. Follow-up visits was conducted at weeks 16, 20, and 24. Waist and hip circumferences were measured at weeks 0, 12, and 24. Laboratory assessments were conducted at weeks -1, baseline, weeks 4, 12, and 24. An ECG was obtained at baseline and week 12.

**STATISTICAL CONSIDERATIONS**

**8.4.3.3** The change in absolute body weight was the primary endpoint and was analyzed by repeated measures ANOVA with factors for treatment group, investigator, the investigator-by-treatment group interactions, time, and the time-by-treatment group interaction. These analyses were performed on four datasets:
1. Unbalanced-all available data with no account taken for missing values.
2. Balanced-all available data with the missing data replaced. Predicted values were calculated from a model fitted to all available data.
3. LOCF-this approach violated the 70% rule and was therefore only performed for completers.
4. Completers-patients who completed the 12-week, double-blind treatment phase of the study.
Baseline body weights were not equal in the randomized groups. An analysis using ANCOVA was therefore performed to adjust for the unequal baseline values.

**RESULTS**

**POPULATIONS ENROLLED/ANALYZED**

**8.4.4.1** Two-hundred twenty-five patients entered the study. Nineteen subjects withdrew during

the washout leaving 206 who entered the double-blind phase. One-hundred patients completed the 12-week double-blind treatment phase.

Table 8.4.4.1.1 illustrates the reasons for withdrawal and the numbers of subjects who withdrew from the different groups.

| TABLE 8.4.4.1.1 | | | | |
|---|---|---|---|---|
| **Reason for withdrawal** | **Placebo** | **1mg** | **10mg** | **20mg** |
| | n=51 | n=50 | n=56 | n=49 |
| Adverse event | 5 | 3 | 7 | 5 |
| Lack of efficacy | 6 | 14 | 7 | 3 |
| Lost to follow-up | 6 | 1 | 2 | 3 |
| Protocol violation | 0 | 2 | 6 | 0 |
| Other+ | 10 | 11 | 7 | 8 |
| Total withdrawn | 27 (53%) | 31 (62%) | 29 (52%) | 19 (39%) |

+ includes patients who lost interest in the study, domestic stress, lack of transport, went on holiday, trial incompatible with work.

There were no statistically significant differences between groups with respect to reason for withdrawal.

| TABLE 8.4.4.1.2 | | | | | | |
|---|---|---|---|---|---|---|
| **VARIABLE** | | **TREATMENT GROUP** | | | | **OVERALL** |
| | | **Placebo** | **1mg** | **10mg** | **20mg** | |
| | | n=51 | n=50 | n=56 | n=49 | n=206 |
| **Age (yrs)** | mean | 38.8 | 39.4 | 38.8 | 38.3 | 38.8 |
| | range | | | | | |
| **Sex** | male | 4 | 6 | 7 | 5 | 22 |
| | female | 47 | 44 | 49 | 44 | 184 |
| **Race** | Cauc | 51 | 50 | 55 | 49 | 205 |
| | Af-Amer | 0 | 0 | 1 | 0 | 1 |
| **BMI ($kg/m^2$)** | mean | 32.2 | 32.7 | 32.8 | 32.3 | 32.5 |
| | range | | | | | |

As shown in table 8.4.4.1.2, the groups were balanced with respect to important baseline demographic characteristics. However, the subjects in the 1 mg group in center 2 and the 20 mg subjects in center 3 were older compared to the other groups. There did not appear to be any significant differences between the groups with respect to concomitant drug usage at baseline or during the study.

Table 8.4.4.1.3 provides the protocol violations by treatment group.

**TABLE 8.4.4.1.3**

| Protocol Violation | Placebo | 1mg | 10mg | 20mg | Overall |
|---|---|---|---|---|---|
| | n=51 | n=50 | n=56 | n=49 | n=206 |
| Visits >3 days earlier than scheduled | 2 | 1 | 4 | 3 | 10 |
| Visit > number of days for which drug was dispensed | 15 | 10 | 14 | 14 | 53 |
| BMI < 27 kg/m$^2$ | 4 | 0 | 1 | 2 | 7 |
| BMI > 40 kg/m$^2$ | 2 | 2 | 1 | 1 | 6 |
| Lost > 3 kg during washout | 2 | 5 | 4 | 6 | 17 |
| ECG abnormality at baseline | 0 | 2 | 5 | 0 | 7 |
| Mildly depressed | 0 | 0 | 1 | 0 | 1 |
| Taking anti-depressant | 0 | 0 | 1 | 1 | 2 |
| On holiday during trial | 9 | 10 | 8 | 17 | 44 |
| Compliance < 70% | 7 | 8 | 6 | 3 | 24 |
| Compliance > 130% | 7 | 7 | 8 | 4 | 25 |

Five patients (2 in the 10 mg group, 2 in the 20 mg group, and 1 in the placebo group) started taking laxatives during the study. These subjects remained in the study. It does not appear that there were any imbalances in the distribution of protocol violations and thus they most likely did not affect the study results.

## EFFICACY ENDPOINT OUTCOMES

Body weight

**8.4.4.2** A comparison of the absolute weight loss (kg) in each group from the balanced analysis is shown in the following table 8.4.4.2.1

| TABLE 8.4.4.2.1 | | | | |
|---|---|---|---|---|
| BALANCED ANALYSIS | | | | |
| **Week of study** | **Placebo** n=41 | **1mg** n=37 | **10mg** n=45 | **20mg** n=41 |
| 2 | -1.0 | -1.3 | -1.8 | -2.4 |
| vs placebo | | p=ns | p=0.01 | p=0.01 |
| vs 1mg | | | ns | p=0.001 |
| vs 10mg | | | | ns |
| 4 | -1.6 | -1.6 | -3.1 | -3.8 |
| vs placebo | | p=ns | p=0.01 | p=0.01 |
| vs 1mg | | | p=0.001 | p=0.001 |
| vs 10mg | | | | p=0.05 |
| 8 | -3.0 | -2.7 | -4.6 | -5.8 |
| vs placebo | | p=ns | p=0.01 | p=0.01 |
| vs 1mg | | | p=0.001 | p=0.001 |
| vs 10mg | | | | p=0.05 |
| 12 | -3.4 | -3.4 | -5.9 | -7.3 |
| vs placebo | | p=ns | p=0.01 | p=0.01 |
| vs 1mg | | | p=0.001 | p=0.001 |
| vs 10mg | | | | p=0.05 |

Table 8.4.4.2.2 illustrates the similar results seen in the completers analysis as with those in the other datasets.

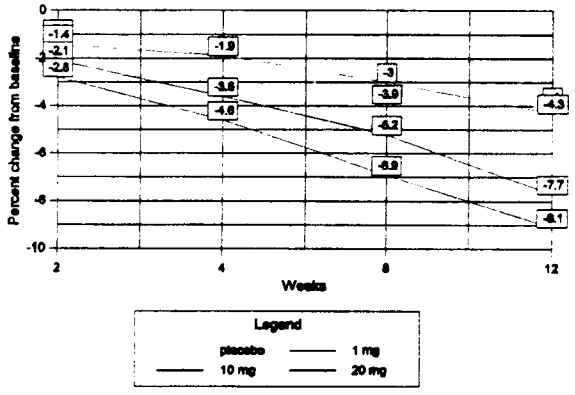
| TABLE 8.4.4.2.2 | | | | |
|---|---|---|---|---|
| COMPLETERS ANALYSIS | | | | |
| **Week of study** | **placebo** n=24 | **1mg** n=18 | **10mg** n=27 | **20mg** n=30 |
| 2 | -0.9 | -1.5 | -2.1 | -2.3 |
| vs placebo | | p=ns | p=0.01 | p=0.01 |
| vs 1mg | | | p=ns | p=ns |
| vs 10mg | | | | p=ns |
| 4 | -1.7 | -2.1 | -3.7 | -4.0 |

| TABLE 8.4.4.2.1 | | | | |
|---|---|---|---|---|
| COMPLETERS ANALYSIS | | | | |
| **Week of study** | **placebo** n=24 | **1mg** n=18 | **10mg** n=27 | **20mg** n=30 |
| vs placebo | | p=ns | p=0.01 | p=0.01 |
| vs 1mg | | | p=0.01 | p=0.001 |
| vs 10mg | | | | p=ns |
| 8 | -3.1 | -3.5 | -5.8 | -6.0 |
| vs placebo | | p=ns | p=0.01 | p=0.01 |
| vs 1mg | | | p=0.01 | p=0.01 |
| vs 10MG | | | | p=ns |
| 12 | -3.5 | -4.1 | -6.9 | -7.6 |
| vs placebo | | p=ns | p=0.01 | p=0.01 |
| vs 1mg | | | p=0.05 | p=0.01 |
| vs 10mg | | | | p=ns |

The results of the analysis of the unbalanced dataset were similar to those of the completers analysis: Ten and 20 mg were statistically superior to placebo and 1 mg at 12 weeks, whereas 10 and 20 mg were not significantly different from one another at week 12.

Figure 8.4.4.2.1 illustrates the percent change from baseline in body weight for the unbalanced dataset.

**Figure 8.4.4.2.1**




At 12 weeks the placebo, 1 mg, 10 mg, and 20 mg groups had a percentage weight loss of -4.0, -4.3, -7.7, and -9.1%, respectively.

Table 8.4.4.2.3 provides the level of statistical significance for the various differences between

the groups illustrated in figure 8.4.4.2.1.

| TABLE 8.4.4.2.3 | | | | | |
|---|---|---|---|---|---|
| **Week** | **Group** | **N** | **vs placebo** | **vs 10 mg** | **vs 20 mg** |
| 2 | placebo | 41 | | | |
| | 1 mg | 37 | ns | ns | 0.001 |
| | 10 mg | 45 | 0.05 | | ns |
| | 20 mg | 41 | 0.01 | | |
| 4 | placebo | 38 | | | |
| | 1 mg | 32 | ns | 0.001 | 0.001 |
| | 10 mg | 44 | 0.01 | | 0.05 |
| | 20 mg | 38 | 0.01 | | |
| 8 | placebo | 26 | | | |
| | 1 mg | 23 | ns | 0.05 | 0.001 |
| | 10 mg | 30 | ns | | ns |
| | 20 mg | 34 | 0.01 | | |
| 12 | placebo | 24 | | | |
| | 1 mg | 18 | ns | 0.05 | 0.001 |
| | 10 mg | 27 | 0.01 | | ns |
| | 20 mg | 30 | 0.01 | | |

The results of the balanced and completers datasets were similar to the unbalanced dataset. One exception was the statistically significant difference between the 10 and 20 mg groups at 12 weeks in the balanced dataset.

The results of the analysis of the proportion of subjects losing greater than 5% of baseline weight at week 12 for the completers is shown in table 8.4.4.2.4

| TABLE 8.4.4.2.4 | | | |
|---|---|---|---|
| **Treatment group** | **n** | **Proportion losing > 5%** | **p-value vs placebo** |
| Placebo | 24 | 42% | |
| 1 mg | 18 | 44% | 0.86 |
| 10 mg | 27 | 74% | 0.02 |

| TABLE 8.4.4.2.4 | | | |
|---|---|---|---|
| **Treatment group** | **n** | **Proportion losing > 5%** | **p-value vs placebo** |
| 20 mg | 30 | 83% | 0.002 |

Waist circumference

There were no significant differences between the groups with respect to the reduction in waist circumference following weight loss.

## SAFETY OUTCOMES

**8.4.4.3** A limited number of subjects received extensive exposure to the various drug dosages. Only 16/51, 12/50, 17/56, and 14/49 of the subjects in the placebo, 1mg, 10mg, and 20mg groups, respectively received more than 84 days of exposure.

Adverse events

Seventy-one percent of the subjects in the 20 mg group reported adverse events compared to 43% of the subjects in the placebo group ($p<0.001$) and 44% of the subjects in the 1 mg group ($p=0.01$).

Adverse events reported by more than 5 subjects are summarized in Table 8.4.4.3.1.

| TABLE 8.4.4.3.1 | | | | |
|---|---|---|---|---|
| **EVENT** | **NUMBER OF PATIENTS REPORTING** | | | |
| | **Placebo** | **1 mg** | **10 mg** | **20 mg** |
| Asthenia | 3 | 1 | 3 | 1 |
| Headache | 2 | 2 | 6 | 7 |
| React uneval | 2 | 1 | 2 | 2 |
| Constip | 1 | - | 5 | 4 |
| Diarrhea | 2 | 1 | 2 | 1 |
| Nausea | 1 | 1 | 1 | 4 |
| Thirst | - | - | 2 | 4 |
| Depression | 2 | 1 | 1 | 2 |
| Dizziness | - | 1 | 1 | 6 |

| TABLE 8.4.4.3.1 | | | | |
|---|---|---|---|---|
| EVENT | NUMBER OF PATIENTS REPORTING | | | |
| | **Placebo** | **1 mg** | **10 mg** | **20 mg** |
| Dry mouth | - | 2 | 2 | 11 |
| Insomnia | 1 | 1 | 1 | 6 |
| Taste perv | - | - | - | 7 |

Details of the adverse events that led to patient withdrawal are summarized in Table 8.4.4.3.2

| TABLE 8.4.4.3.2 | | | | | | |
|---|---|---|---|---|---|---|
| **Number** | **Sex** | **Age** | **Dose** | **Duration** | **Event** | **Comment** |
| 114 | F | 44 | Pl | 47 | Breast Ca | recovered |
| 162 | M | 33 | 20 | 49 | Convulsions | Brain tumor, removed and recovered |
| 199 | F | 38 | 20 | 49 | severe constipation | Hemorrhoidectomy |
| 6 | F | 25 | Pl | 14 | nausea, vomiting | possibly viral |
| 15 | F | 20 | Pl | 70 | pregnant | terminated |
| 59 | F | 64 | Pl | 23 | diarrhea | recovered |
| 159 | F | 38 | Pl | 21 | severe headache | ? |
| 78 | F | 26 | 1 | 14 | abdominal cramps, diarrhea | ? |
| 156 | M | 33 | 1 | 70 | hypertension | ? |
| 171 | F | 46 | 1 | 7 | hypertension | recovered |
| 47 | M | 37 | 10 | 42 | renal colic | recovered |
| 154 | M | 28 | 10 | 28 | influenza | recovered |
| 160 | F | 39 | 10 | 30 | anxious about adverse events | ? |
| 172 | F | 42 | 10 | 63 | backache | recovered |
| 214 | F | 29 | 10 | 7 | hypertension | recovered |
| 217 | F | 30 | 10 | 7 | URI sxs | recovered |
| 265 | M | 46 | 10 | 14 | abnormal chemistries | normal at 1-month follow-up |

| TABLE 8.4.4.2 | | | | | | |
|---|---|---|---|---|---|---|
| **Number** | **Sex** | **Age** | **Dose** | **Duration** | **Event** | **Comment** |
| 74 | F | 27 | 20 | 30 | depression, ?hypertension | recovered |
| 97 | F | 55 | 20 | 21 | headache, nausea | ? |
| 192 | F | 21 | 20 | 63 | pregnancy | terminated |

Clinical Chemistries

Although there were statistically significant changes in packed cell volume, potassium, and albumin these changes were not clinically significant. In addition, there were no obvious dose-related changes. Urinalysis results did not show any significant changes with drug treatment. There were small and nonsignificant reductions in triglyceride and total cholesterol levels in the 10 and 20 mg groups.

Vital signs

The systolic and diastolic blood pressures decreased slightly at the endpoint assessment. These changes were not statistically significant. Although heart rate measured manually did not change significantly, heart rate measured from ECG did increase significantly in the 10 mg (5.9 bpm) and 20 mg (6.1 bpm) groups ($p<0.01$; 10 and 20 mg vs placebo). The QRS interval decreased in the 10 mg group (-0.9 ms) and in the 20 mg group (-0.2 ms) ($p<0.01$ 10 mg vs placebo and 1 mg; $p<0.05$ 10 mg vs 20 mg)

## 8.4.5 CONCLUSIONS

Three features of this study merit comment. First, compared to other studies using similar doses, subjects in the placebo group achieved a greater amount of weight loss. Second, this is the only study were the pulse rate (measured manually) was reduced with drug treatment. And third, unlike other studies, blood pressure was reduced with active treatment. However, conclusions regarding the efficacy and safety of sibutramine cannot be accurately made because of the relatively small percentage of subjects who completed the study.

## 8.5 BP 850

## OBJECTIVE/RATIONALE

**8.5.1** The primary objective of this 8-week study was to evaluate the weight-reducing effects of 5 and 20 mg QD of sibutramine vs placebo when taken in conjunction with modest caloric restriction, exercise, and behavior modification.

## DESIGN

**8.5.2** This was a single-center, block-randomized, double-blind, placebo-controlled, parallel-group, 8-week study. The study consisted of a screening visit at week -3, two run-in visits at weeks -2 and -1 and a baseline evaluation at which time qualified subjects were assigned, using a stratified randomization format, to one of two dose regimens of sibutramine (5 or 20 mg) or to placebo. Subjects then entered an 8-week active treatment phase, with evaluations at weeks 2, 4, 6, and 8. A follow-up visit was conducted at week 9. All subjects received an individualized caloric restriction program, an exercise program, and behavior modification. Randomization was performed according to a prospective stratification procedure based upon factors that influence the likelihood of successful weight loss. The likelihood of successful weight loss was computed from points assigned to the following variables: gender, annual family income, habitual nighttime snacking, age of onset of obesity, physician rating of motivation, and weight loss between week -2 and baseline. Four strata were defined. For every six subjects enrolled in each stratum, two were randomly assigned to each treatment group.

## PROTOCOL

## POPULATION

**8.5.3.1** The entry criteria for this study included male or surgically sterilized or postmenopausal women between the ages of _____ . Their body weight had to be between _____ of ideal body weight. Pulse rate and diastolic blood pressure had to be _____ respectively.

## ENDPOINTS

**8.5.3.2** Standard endpoints included the change from baseline in body weight, blood pressure, pulse, ECG parameters, and laboratory parameters including lipid and thyroid panels.

## STATISTICAL CONSIDERATIONS

**8.5.3.3** A cursory explanation of the statistical approach was provided in the protocol dated 7/26/89. A detailed description of the statistical techniques was provided in the report section of volume 1.119. The principle efficacy parameter, change in body weight was analyzed in four ways.

1). The observed change in weight from baseline was analyzed using a one-way ANOVA procedure with treatment as the only factor. This was done for each week (2, 4, 6, and 8) separately.

2). An analysis as conducted in 1, except that only those completing the treatment period were included.

3). A repeated measured ANOVA was performed. An incomplete three-way ANOVA with the following factors treatment, subject within treatment, week, and treatment by week.

4). LOCF.
5). Observed change from baseline for weight was analyzed using a two-way ANOVA procedure with treatment, stratum, and the treatment by stratum interaction as factors. This procedure was done for each week separately.
6). The same analysis as that in 5, except that an endpoint analysis was done.
7). A repeated measures ANOVA for overall change in weight was performed; it considered stratification as well as treatment effects. The analyses were performed using an incomplete four-way ANOVA with the following factors: treatment, subject within treatment, stratum, week, and all of the interactions of treatment, stratum, and week.

Categorical assessments of yes or no were made for subject compliance, exercise, and behavior modification. Fisher's exact tests were performed for both the observed and endpoint approaches.

## RESULTS

## POPULATIONS ENROLLED/ANALYZED

**8.5.4.1** A total of 331 potential subjects were screened by telephone. Of this number, 126 met the inclusion criteria. One-hundred nine subjects attended the informational meeting, 39 were subsequently excluded. Three subjects decided not to attend the additional screening visits and an additional 7 subjects were excluded during this time. Sixty subjects were thus enrolled in the study: 19 to 5 mg, 21 to 20 mg, and 20 to placebo. Table 8.5.4.1.1 illustrates the mean (range) baseline characteristics of the subjects by treatment group.

**TABLE 8.5.4.1.1**

| | **5 mg n=19** | **20 mg n=21** | **Placebo n=20** |
|---|---|---|---|
| Age (years) | 49.6 | 46.5 | 46.5 |
| Sex (% female) | 74 | 66 | 70 |
| Race (% Caucasian) | 94 | 90 | 96 |
| Weight (kg) | 97.3 | 101.2 | 96.0 |
| Height (cm) | 168.1 | 170.0 | 167.0 |

There were no statistically significant differences between the groups.

## EFFICACY ENDPOINT OUTCOMES

Body weight

**8.5.4.2** Table 8.5.4.2.1 provides the percent weight change from baseline for subjects completing the study.

| TABLE 8.5.4.2.1 | | | | | |
|---|---|---|---|---|---|
| **Visit** | **p value** | **Treatment** | **n** | **Mean %** | **Comparison** |
| Week 2 | 0.0001 | Placebo | 19 | -0.85 | A |
| | | 5 mg | 18 | -1.36 | A |
| | | 20 mg | 18 | -2.44 | B |
| Week 4 | 0.0001 | Placebo | 19 | -1.13 | A |
| | | 5 mg | 18 | -2.20 | B |
| | | 20 mg | 18 | -4.04 | C |
| Week 6 | 0.0002 | Placebo | 19 | -1.10 | A |
| | | 5 mg | 18 | -2.31 | A |
| | | 20 mg | 18 | -4.14 | C |
| Week 8 | 0.0001 | Placebo | 19 | -1.31 | A |
| | | 5 mg | 18 | -2.97 | B |
| | | 20 mg | 18 | -5.07 | C |

Values with different letters are significant at $p < 0.05$.

The results of the other analyses were essentially the same. There were no stratum or treatment by stratum interactions that were significant. In general, the 20 mg dose was statistically and clinically superior to the 5 mg dose as well as to the placebo group at all time points. While the 5 mg group was significantly different from the placebo group at certain time points in some of the analyses, the clinical significance of the differences was minimal.

At week 8 the percent difference in body weights from baseline were -1.27%, -2.78%, and -4.98% for the placebo, 5 mg, and 20 mg groups, respectively.

## SAFETY OUTCOMES

Adverse Events

**8.5.4.3** There were no serious, unexpected or life-threatening adverse events during the study.

Five subjects withdrew from the study because of an adverse event. One subject in the placebo group experienced a rash. One subject in the 5 mg group complained of headache, dizziness, nausea, cramps, and feeling faint. Three subjects in the 20 mg group withdrew because of adverse events: one because of headache, feeling depressed, fatigued, and early awakening; one because panic attacks, puritis, depression, fatigue, dry mouth, and chills and fever; and one because of stomach pain, heartburn, and decreased appetite.

Symptoms related to the nervous system were reported most frequently. Dry mouth was reported by 32% of subjects in the 5 mg group, 29% of 20 mg subjects, and 20% of placebo subjects. Insomnia was reported by 5% of 5 mg subjects, 33% of 20 mg subjects, and by none of the placebo subjects. Nervousness was reported by 0% of the 5 mg group, 24% of the 20 mg group, and 5% of the placebo group.

Clinical Chemistries

There were no significant changes in serum chemistry values during the study. Similarly, there were no significant changes in thyroid function test values or in urinalysis values.

Lipoprotein Lipids

There were no beneficial changes in serum lipid levels during the study in any of the treatment groups.

Vital Signs

The change in diastolic blood pressure at week 2 was statistically significantly different between the sibutramine and placebo groups (5.26, 4.48, and 0.0 mmHg for the 5 mg, 20 mg, and placebo subjects, respectively, p=0.03). There were no other statistically significant changes in any of the vital sign parameters.

**CONCLUSIONS**

**8.5.5** In this 8-week study of obese patients, 20 mg QD of sibutramine led to statistically significantly greater weight loss compared to 5 mg QD of sibutramine or to placebo. The absolute decrease in body weight in the 20 mg group was approximately 4-5 kg. In general, the drug was well tolerated and there were few drop-outs related to adverse events. There were no significant changes in serum chemistry values, and other than a small increase in diastolic blood pressure in the sibutramine groups, vital signs did not change significantly.

**8.6 BPI 851**

**OBJECTIVE/RATIONALE**

**8.6.1** To evaluate the weight reducing effectiveness and safety of sibutramine 10 mg QD compared to placebo over a 12 week period in obese subjects. Additional objectives included examining the effects of sibutramine on appetite, food intake, percent body fat, resting metabolic rate, thyroid function, and serum lipid levels.

**DESIGN**

**8.6.2** This was a 12-week, single-center, double-blind, block-randomized, placebo-controlled, pilot efficacy and safety study in 30 obese subjects. There was a 2 week screening period and a post-dosing assessment at 2 to 4 weeks after the completion of the double-blind phase. All patients received counseling by a dietitian and were instructed to consume a diet of 1500 Kcal/day for men or 1200 Kcal/day for women.

## PROTOCOL

## POPULATION

**8.6.3.1** The study population was comprised of male and female subjects aged _____ with a BMI

## ENDPOINTS

**8.6.3.2** Baseline assessment included body weight, BMI, vital signs, percent body fat, food intake, and resting metabolic rate (RMR). Efficacy (body weight) and safety measurements were performed at weeks 2, 6, 9, and 12. At weeks 2, 6, and 12, an ECG, hemogram, serum chemistry and Modified Norris Assessment evaluations were obtained. Resting metabolic rate was measured at weeks 2 and 12. Percent body fat was assessed at week 12. At weeks 6 and 12 urinalysis, serum lipid, thyroid panel, appetite scale, and food intake determinations were made. Assessment of body composition was done by skinfold thickness, hydrodensitomitry, and total body electrical conductivity. Changes in mental sedation, physical sedation, tranquilization, and other attitudes were assessed using the modified Norris assessment.

## STATISTICAL CONSIDERATIONS

**8.6.3.3** A two-factor analysis of variance model was conducted to evaluate treatment differences in weight change at weeks 6 and 12. Factors in the model included sex, treatment, and a sex by treatment interaction. Both endpoint (LOCF) and observed analyses were carried out for all efficacy parameters except for the percent of subjects compliant with their diet and changes in percent body fat, where only observed analyses were performed. Endpoint and observed changes from baseline for body weight and BMI were examined using a one-way (by treatment) ANOVA. A repeated measures ANOVA was performed for overall changes in observed body weight and BMI data using an incomplete three-way (by treatment, by subject within treatment, by week, and by treatment by week) ANOVA.

## RESULTS

## POPULATIONS ENROLLED/ANALYZED

**8.6.4.1** Thirty-three subjects were screened and randomized to receive placebo (16) or sibutramine (17). Eleven placebo and 16 sibutramine subjects completed the 12 week study.

Table 8.6.4.1.1 provides the baseline demographic characteristics of the study subjects.

| TABLE 8.6.4.1.1 | | |
|---|---|---|
| **Baseline characteristic** | **Sibutramine n=17** | **Placebo n=16** |
| Age (yrs) | 55.8 | 55 |
| Gender (% female) | 82% | 94% |
| Race (% Caucasians) | 76% | 82% |
| Weight (kg) | 91.9 | 91.3 |
| BMI (kg/m$^2$) | 34.2 | 34.3 |
| Skinfold thickness (% bodyfat) | 46.8 | 46.8 |
| Hydrodensitometry (% bodyfat) | 49 | 47.3 |
| Electromagnetic Scan (% bodyfat) | 42.4 | 43.8 |
| Total food intake (g/meal) | 470 | 432 |
| Meal duration (min) | 7.9 | 5.9 |
| Initial rate of intake (g/min) | 63.8 | 75.7 |
| Deceleration of intake (g/min) | 2.3 | 3.0 |

Values in parentheses are ranges

Four placebo subjects and one sibutramine subject discontinued the study for personal reasons. One additional placebo subject was lost to follow-up.There were a number of protocol violation regarding inclusion and exclusion criteria in both groups. It is unlikely that these violations significantly affected the study results.

## EFFICACY ENDPOINT OUTCOMES

**8.6.4.2** Table 8.6.4.2.1 provides the mean weight change (kg) from baseline in the observed dataset.

| TABLE 8.6.4.2.1 | | | | |
|---|---|---|---|---|
| **Visit** | **Treatment** | **N** | **Mean** | **P value** |
| | | | | |
| Week-2 | Placebo | 14 | -1.1 | |
| | Sib | 17 | -2.1 | 0.08 |
| Week-6 | Placebo | 11 | -2.4 | |

| TABLE 8.6.4.2.1 | | | | |
|---|---|---|---|---|
| **Visit** | **Treatment** | **N** | **Mean** | **P value** |
| | Sib | 15 | -4.0 | 0.2 |
| Week-9 | Placebo | 11 | -2.4 | |
| | Sib | 16 | -4.4 | 0.2 |
| Week-12 | Placebo | 11 | -3.2 | |
| | Sib | 16 | -5.6 | 0.2 |
| Week-14 | Placebo | 11 | -3.0 | |
| | Sib | 14 | -4.7 | 0.4 |

The results of the analyses of the endpoint dataset and the repeated measures ANOVA provided similar results; there were no statistically significant differences between the two groups.

Body composition

Changes in body composition were not statistically significantly different between groups. The percent body fat was reduced to a greater extent in the placebo group compared to the sibutramine group when measured by hydrodensitometry (-3.4 vs -2.4%) and electromagnetic scan (-1.3 vs -0.9%). However, these data must be interpreted cautiously as there were different numbers of subjects who had final assessments by the various methods.

Food intake

There were statistically significant reductions in the appetite scale in the sibutramine group compared to the placebo group at week 12 (p=0.001). There were no statistically significant differences between the two groups with respect to the measures of food intake at week 12.

## SAFETY OUTCOMES

Adverse events

**8.6.4.3** There were no serious adverse events or deaths reported during the study. There were no major differences between the two groups in reported adverse events. Table 8.6.4.3.1 provides the list of treatment-emergent adverse events that occurred in two or more subjects.

| TABLE 8.6.4.3.1 | | | | |
|---|---|---|---|---|
| **Adverse event** | **Placebo** | | **Sibutramine** | |
| | N | # of occurrences | N | # of occurrences |
| Headache | 4 | 4 | 5 | 7 |
| Dry mouth | 3 | 3 | 2 | 2 |
| Asthenia | 3 | 6 | 0 | 0 |
| Back pain | 1 | 1 | 2 | 2 |
| Chest pain | 0 | 0 | 3 | 3 |
| Constipation | 0 | 0 | 3 | 4 |
| Dizziness | 1 | 1 | 2 | 2 |
| Abdominal pain | 0 | 0 | 2 | 4 |
| Pain | 1 | 1 | 1 | 1 |
| Depression | 1 | 1 | 1 | 1 |
| Insomnia | 0 | 0 | 2 | 2 |

Clinical chemistries

There were no significant changes in serum chemistry, thyroid function, or urinalysis values during the study.

Lipoprotein lipids

Total cholesterol decreased by 10.2 mg/dl in the placebo group and by 19.7 mg/dl in the sibutramine group. Triglyceride levels decreased by 60 mg/dl in the placebo group and by 8 mg/dl in the sibutramine group. Similarly, HDL-C levels decreased by 7.0 mg/dl and 4.6 mg/dl in the placebo and sibutramine subjects, respectively. The Sponsor did not provide the results of the statistical analyses for the lipid data.

Vital signs and Electrocardiograms

In general, there were no significant changes in blood pressure during the study in either group. At week 12, the sibutramine group had a statistically significantly higher supine pulse rate (1.3 bpm) compared to the placebo group (-7.5 bpm, p=0.04) When measured by ECG, the heart rate in the sibutramine group was increased by 4.8 bpm at week 12 and reduced by 2.8 bpm in the placebo group (p=0.06). The PR intervals decreased in the sibutramine group and increased in the placebo group, these differences did not reach statistical significance. No other ECG parameters were significantly different between the two groups.

Resting metabolic rate

In the endpoint analysis (LOCF), the resting metabolic rate decreased in the sibutramine group (-106 Kcal/day) and the placebo group (-56 Kcal/day) (p=0.60). In the observed analysis, the RMR decreased by 132 Kcal/day in the placebo group and by 94 Kcal/day in the sibutramine group. These differences are due to the different number of subjects analyzed in the two datasets. The endpoint dataset had 12 placebo subjects and 17 sibutramine subjects, whereas the observed dataset was comprised of 9 placebo subjects and 16 sibutramine subjects.

Mood and affect

In general, the sibutramine group had more favorable changes in the Modified Norris Assessment than the placebo group.

**8.6.5 CONCLUSIONS**

In this study of obese subjects taking 10 mg QD of sibutramine for 12 weeks, the active drug did not produce significantly more weight loss than placebo (-5.6 vs -3.2 kg, p=0.2). There were no significant changes in percent body fat as assessed by several methods and their were no significant changes in RMR. In general, the drug was well tolerated and did not produce any serious adverse events. Aside from a minor increase in supine pulse rate and heart rate measured by ECG, there were no significant changes in vital signs or ECG parameters.

**8.7 SB 1043**

**OBJECTIVE/RATIONALE**

**8.7.1** The primary objective of this study was to compare the weight-reducing effects of 5, 10, and 15 mg QD of sibutramine vs placebo in an obese population. An additional objective was to assess the safety and tolerability of various doses of sibutramine.

**DESIGN**

**8.7.2** This study was a multicenter (20), double-blind, placebo-controlled, dose-ranging study. There was a 1-week washout phase followed by a 12-week active-treatment phase and a 4-week post-treatment follow-up period.

**PROTOCOL**

**POPULATION**

**8.7.3.1** Two-hundred patients were recruited (50 in each group) for this study. Inclusion criteria included:

1. Male or female patients
2. Age
3. BMI

Exclusion criteria included:
1. A seated heart rate of over 100 bpm or a seated diastolic blood pressure greater than 95 mmHg on repeated measurements, or patients being treated for hypertension
2. Patients who lost more than 3 kg in the previous 3 months

## ENDPOINTS

**8.7.3.2** The primary endpoint in this study was the change in body weight which was measured at screening, baseline, weeks 2, 4, 8, 12, and week 16. Other endpoints included the CGI depression scale, alcohol and tobacco usage, patient assessment of hunger, satiety, and appetite, dietary compliance, waist and hip circumferences, ECG and vital signs, serum chemistries, and adverse event reporting.

## STATISTICAL CONSIDERATIONS

**8.7.3.3** For the primary efficacy variable: change in body weight, the differences between groups were tested using repeated measures ANOVA with factors for treatment group, center, center-by-treatment group interaction, time, and time-by-treatment group interaction. Williams test was used to make the significance of comparisons among sibutramine groups with placebo and Fisher's LSD method was used to compare mean weight loss between sibutramine groups. Three datasets were analyzed:
1. Unbalanced - all available data with no account taken of missing values.
2. Balanced - missing values will be interpolated
3. All available data using the LOCF.
4. Completers - values from individuals who completed the study.

An intent-to-treat analysis (endpoint) was conducted in which data from individuals who did not have a weight measurement after week 2 were included. The time factor was not included in this ANOVA. The study was powered with 50 subjects in each group to detect a 3.0 kg difference in body weight between the groups.

## RESULTS

## POPULATIONS ENROLLED/ANALYZED

**8.7.4.1** Overall, 252 patients were screened for entry into the study between May 13, 1992 and December 7, 1992 at 18 hospital centers. Of these, 16 patients withdrew during the washout, therefore 236 patients entered the double-blind phase of the study. A total of 205 patients completed the 12 week double-blind treatment phase. Two-hundred and twenty-seven subjects

provided an assessment of body weight after week 2 and were included in the primary analysis of weight loss.

There were no statistically significant differences between the treatment groups with respect to drop-out rate. Table 8.7.4.1.1 illustrates the protocol violations for the 4 groups.

| TABLE 8.7.4.1.1 | | | | |
|---|---|---|---|---|
| **PROTOCOL VIOLATION** | **Placebo** | **5mg** | **10mg** | **15mg** |
| Total number of patients | 59 | 56 | 59 | 62 |
| Visit >3 days earlier than scheduled | 8 | 3 | 7 | 14 |
| Visit >number of days for which drug dispensed | 27 | 21 | 28 | 23 |
| BMI < 27 kg/m2 | 1 | 1 | 0 | 1 |
| BMI > 40 kg/m2 | 0 | 1 | 1 | 1 |
| Lost > 3kg during washout | 0 | 1 | 1 | 1 |
| Taking prohibited medication | 3 | 8 | 5 | 2 |
| Compliance < 70% | 7 | 5 | 9 | |

Table 8.7.4.1.2 provides the baseline demographic and physical characteristics of the patients.

| TABLE 8.7.4.1.2 | | | | |
|---|---|---|---|---|
| **Variable** | **Placebo n=59** | **5mg n=56** | **10mg n=59** | **15mg n=62** |
| Age (yrs) | 39.6 | 39.7 | 34.8 | 35.4 |
| # Female | 52 | 52 | 50 | 52 |
| # Caucasian | 56 | 54 | 57 | 61 |
| Weight (kg)+ | 84 | 83.3 | 85 | 88.3 |
| BMI ($kg/m^2$) | 32.1 | 32.4 | 31.9 | 33.2 |

+ median values

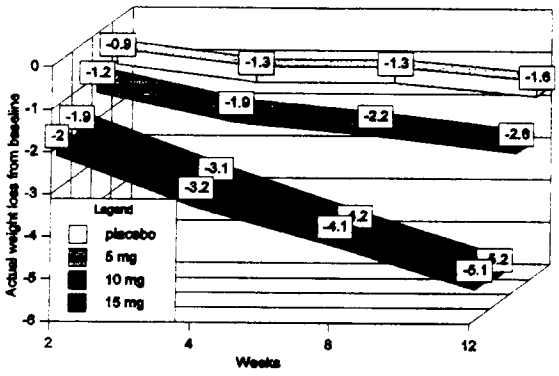
As noted in the above table, the subjects in the 15 mg group tended to be heavier; however, baseline BMIs were comparable across groups. Forty-three patients (18%) had borderline depression, with no treatment group differences. During the study, new concomitant medications were started by 47% of the patients. These included some medications that were prohibited by the protocol: 15 patients took antidepressants/tranquillizers and 5 took laxatives.

## EFFICACY ENDPOINT OUTCOMES

Body weight

**8.7.4.2** There were significant center effects in all of the datasets analyzed; however, there were no significant center-by-treatment group interactions. The results of the analyses of all the datasets were similar. Figure 8.7.4.2.1 illustrates the adjusted mean change in weight (kg) for the unbalanced dataset.

**Figure 8.7.4.2.1**




Weight loss in the 5 mg group did not differ from the placebo group. Both the 10 and 15 mg groups lost significantly more weight than the placebo and 5 mg groups ($p=0.01$). There were no statistically significant differences in weight loss between the 10 and 15 mg groups.



The results of the analyses of percentage weight loss were similar to the results of the absolute weigh loss in kilograms. At week 12 the placebo and 5 mg groups lost an average of -1.7% and -3.1% of initial body weight, respectively; the 10 and 15 mg groups lost -6.1% and -5.8% of initial body weight, respectively. Again, the placebo and 5 mg groups did not differ. The 10 and 15 mg groups lost a significantly greater percentage of body weight than the placebo or 5 mg groups. There were no differences between the 10 and 15 mg groups.

Fifty-three percent of the 10 mg group and 58% of the 15 mg group lost > 5% of baseline body weight compared to 19% and 23% in the placebo and 5 mg group, respectively ($p<0.001$).

Waist circumference

Although there were no significant changes in the waist to hip ratio for any of the treatment groups, the waist circumferences were reduced by 3.0, 1.8, 5.9, and 5.2 cm in the placebo, 5 mg, 10 mg, and 15 mg groups, respectively. The reductions of 3.0 and 1.8 cm in the placebo and 5 mg groups, respectively, do not agree with the overall reductions in body weight. It would not be expected to loss a greater proportion of waist circumference with a lower degree of weight loss. The accuracy of the waist circumference is therefore questionable.

**SAFETY OUTCOMES**

Adverse events

**8.7.4.2** The 15 mg group had an increased incidence of adverse events reported for the Digestive and Nervous Systems compared to the placebo and 5 mg groups. However, there were no statistically significant differences in the proportions of patients in each treatment group reporting an adverse event. Table 8.7.4.2.1 illustrates the percentage of patients in each group reporting an adverse event by COSTART body system.

| TABLE 8.7.4.2.1 | | | | |
|---|---|---|---|---|
| **COSTART** | **Placebo** | **5 mg** | **10 mg** | **15 mg** |
| Body as a whole | 36 | 34 | 34 | 37 |
| Cardiovascular | 17 | 9 | 8 | 18 |
| Digestive | 19 | 27 | 27 | 35 |
| Heme and lymph | - | - | - | 2 |
| Metabolic | 5 | 9 | 3 | 6 |
| Musculo-skeletal | 3 | 2 | 7 | 5 |
| Nervous | 29 | 30 | 37 | 47 |
| Respiratory | 17 | 14 | 5 | 21 |
| Skin | 2 | 4 | 5 | 5 |
| Special senses | - | 2 | 7 | 3 |
| Urogenital | 12 | 4 | 8 | 10 |
| Overall | 71 | 66 | 71 | 76 |

There were no statistically significant differences between the groups with respect to the number of patients reporting the adverse events as mild, moderate, severe, or unknown.

Table 8.7.4.2.2 illustrates the number of subjects in each group reporting the common adverse events.

| TABLE 8.7.4.2.2 | | | | |
|---|---|---|---|---|
| **COSTART term** | **Placebo** | **5 mg** | **10 mg** | **15 mg** |
| Asthenia | 3 | 3 | 3 | 5 |
| Flu syndrome | 2 | 3 | 1 | 6 |
| Headache | 9 | 5 | 6 | 7 |
| Abd pain | 1 | 2 | 3 | 5 |
| Constipation | 4 | 7 | 10 | 12 |

| TABLE 8.7.4.2.2 | | | | |
|---|---|---|---|---|
| **COSTART term** | **Placebo** | **5 mg** | **10 mg** | **15 mg** |
| Nausea | 1 | 3 | 3 | 5 |
| Dry mouth | 5 | 6 | 6 | 11 |
| Insomnia | 5 | 6 | 7 | 17 |
| Nervousness | 4 | 2 | 4 | 4 |
| Pharyngitis | 6 | 4 | 2 | 5 |

Table 8.7.4.2.3 provides the reasons for withdrawal from the study.

| TABLE 8.7.4.2.3 | | | | | | |
|---|---|---|---|---|---|---|
| **Number** | **Sex** | **Age** | **Duration (days)** | **Dose mg** | **Event** | **Comment** |
| 86 | F | 30 | 42 | 10 | severe pyelonephritis | Hospitalized and recovered |
| 14 | F | 30 | 84 | 15 | sudden deafness in right ear | Cochleo-vestibular syndrome |
| 16 | F | 23 | 42 | Pl | headaches | recovered |
| 116 | F | 39 | 56 | Pl | hypertension | unknown follow-up |
| 131 | F | 48 | 4 | Pl | headache | prescribed dihydroergotamine |
| 149 | F | 30 | 35 | Pl | dysuria | recovered |
| 22 | F | 56 | 63 | 5 | moderate irratiblity | ? |
| 151 | F | 48 | 70 | 5 | recurrent drowsiness | recovered |
| 205 | F | 39 | 56 | 5 | moderate depression | recovered after drug withdrawn |
| 119 | F | 50 | 63 | 10 | severe depression | ? |
| 127 | F | 32 | 35 | 10 | moderate depression | recovered 2-weeks after drug stopped |
| 171 | M | 25 | 84 | 10 | insomnia and agitation | recovered after drug stopped |
| 232 | F | 44 | 14 | 10 | vertigo | recovered after drug stopped |
| 84 | M | 30 | 28 | 15 | epigastralgia | recovered after drug stopped |
| 147 | F | 51 | 73 | 15 | hypertension and palpitations | recovered after drug stopped |
| 173 | F | 41 | 84 | 15 | migraine | recovered after drug stopped |

| TABLE 8.7.4.2.3 | | | | | | |
|---|---|---|---|---|---|---|
| **Number** | **Sex** | **Age** | **Duration (days)** | **Dose mg** | **Event** | **Comment** |
| 221 | F | 57 | 70 | 15 | nausea, sweating | recovered 8 days after medication stopped |

One subject in the 5 mg group experienced depressive symptoms during the follow-up phase. The patient was hospitalized and the episode resolved by the week 16.

Clinical chemistries

The neutrophil count in the 10 and 15 mg groups declined by -0.2 and -0.3 $\times 10^9$/l, respectively compared to an increase of 0.4 $\times 10^9$/l in the placebo group ($p<0.01$). This difference is not clinically significant. One subject in the 10 mg group had an elevated creatine value at week 12 (242 umol/l).

Lipoprotein lipids

There were no statistically significant differences in the reductions in cholesterol levels among the groups.

Vital signs and electrocardiograms

There were no significant changes in blood pressure to endpoint in the 4 groups. Heart rate increased by 4.2 and 3.8 bpm in the 15 and 10 mg groups, respectively compared to a mean decrease of 2.0 bpm in the placebo group and a 1.2 bpm increase in the 5 mg group. The changes in the 10 and 15 mg groups were statistically significant compared to the placebo group ($p=0.001$). The clinical significance of these minor increases in pulse rate is unknown. The increase in pulse rate in the 10 and 15 mg groups (8.2 and 5.2 bpm, respectively) were higher when measured by ECG than by manual measurement. These changes were also statistically significantly different compared to the change in pulse rate in the placebo group (-3.0 bpm, $p<0.001$). The only statistically significant change noted on ECG was an increase in the QT interval in the placebo group (25.2 ms) relative to the change noted in the sibutramine groups (-8.9, 3.0, and 2.0 ms, for the 5, 10, and 15 mg groups, respectively). The changes in the QT interval are not clinically meaningful.

## 8.7.5 CONCLUSIONS

This study demonstrated that once-daily doses of 10 and 15 mg of sibutramine produce statistically significantly greater weight loss compared to 5 mg QD of sibutramine and placebo. The absolute amount of weight loss in the 10 and 15 mg groups (approx 5-6 kg at week 12) was similar to the amount of weight lost in the pivotal study BPI 852 as well as other studies using

similar doses. There were however, a number of protocol violations and this increases the potential for bias and reduces the vigor with which one can make conclusions about the study results. As with the other clinical studies involving 10 and 15 mg of sibutramine the consistent finding of increases in pulse and blood pressure are expected pharmacodynamic effects of an inhibitor of norepinephrine reuptake.

*CO-MORBIDITY STUDIES*

*NON-INSULIN DEPENDENT DIABETES*

**8.8 BPI 853**

**OBJECTIVE/RATIONALE**

**8.8.1** The primary objective of this study was to evaluate the effects of four days of 30 mg QD of sibutramine on fasting glucose levels, glucose tolerance during an oral glucose tolerance test, and C-peptide production in a population of obese patients with non-insulin dependent diabetes mellitus (NIDDM). The secondary objective was to evaluate the effects of 12 weeks of treatment with 20 mg QD of sibutramine on body weight, parameters of glucose control, as well as safety and tolerability.

**DESIGN**

**8.8.2** This study was a single-site, placebo-controlled, double-blind, parallel-group study. Eighteen subjects were enrolled in the study. The study included a 3-4 day placebo run-in period and a 5-day placebo-controlled, double-blind inpatient phase. During the inpatient period 12 subjects were randomized to 30 mg of sibutramine QD and 6 subjects were given placebo. An outpatient phase of 12 weeks followed the inpatient phase during which time subjects initially treated with 30 mg QD of sibutramine were treated with 20 mg QD and those subjects initially randomized to placebo remained on placebo during the 12-week period. Patients were allowed to reduce the dose to 10 mg if they suffered an adverse event. The study concluded with a 7-day single-blind placebo washout period.

**PROTOCOL**

**POPULATION**

**8.8.3.1** The population of this study included patients with a history of NIDDM (duration of at least 3 months prior to the start of the study), obese and age ____, years. Subjects with hypertension who were controlled on a singe antihypertensive agent were also allowed to participate in the study. Oral hypoglycemic agents were permissible. Subjects on insulin were excluded. There is no mention of dietary or exercise education or prescription.

## ENDPOINTS

**8.8.3.2** The principle endpoints are appropriate and clearly defined in the protocol and included the change in metabolic control, vital signs, and clinical chemistries.

## STATISTICAL CONSIDERATIONS

**8.8.3.3** The original protocol dated 2/15/91 does not provide the details of the planned statistical analyses. The report dated 9/18/93 from the NDA submission does detail the statistical approaches. It is stated that the changes in fasting glucose levels and body weight were analyzed by a one-way ANOVA and paired t-tests for between and within treatment comparisons. If a subject had missing data for a specific time period that individual was excluded form the analysis of interest. The procedure for handling fall-back doses is not discussed.

## RESULTS

## POPULATIONS ENROLLED/ANALYZED

**8.8.4.1** Of the 18 subjects enrolled in the study 6/6 subjects randomized to placebo completed the study and 9/12 randomized to drug completed the study.

Table 8.8.4.1.1 illustrates the baseline demographics for the study participants.

**TABLE 8.8.4.1.1**

| | **Placebo n=6** | **Sibutramine 30-20 mg n=12** |
|---|---|---|
| Male | 33% | 17% |
| Female | 67% | 83% |
| Black | 33% | 25% |
| Caucasian | 67% | 75% |
| Weight (kg) | 95.2 | 96.4 |
| Age (yrs) | 51.4 | 52.4 |
| Plasma glucose (mg/dl) | 190 | 201 |
| C-peptide (ng/ml) | 40 | 24 |
| $HbA1_c$ (%) | 9.0 | 8.5 |

• $p<0.05$

The baseline C-peptide levels were significantly lower in the sibutramine group compared to the placebo group. In addition, there was a greater percentage of males in the placebo group

compared to the active-drug group at baseline.

In the 30-20 mg group, at baseline, one patient was taking captopril and two subjects in this group were taking verapamil. Ten subjects were taking oral hypoglycemics; eight at screening and two at week 13. In the placebo group one subject was taking lisinopril, one subject was taking nifedipine, and one subject was taking lovastatin. Four subjects were on oral hypoglycemics; three at screening and one at week 13.

Three subjects in the sibutramine group withdrew from the study: one because of a hospitalization for foot ulcers, one for personal reasons, and one because of a death in the family.

## EFFICACY ENDPOINT OUTCOMES

Body weight

**8.8.4.2** The changes in body weight (kg) from baseline for the placebo and sibutramine groups are shown in table 8.8.4.2.1

**TABLE 8.8.4.2.1**

| Visit | Placebo | Within group p | Sibutramine | Within group p | Between group p |
|---|---|---|---|---|---|
| Day 4 | -0.7 | ns | -0.9 | <0.05 | ns |
| Week 2 | 0.0 | ns | -1.1 | <0.05 | p<0.05 |
| Week 4 | -0.4 | ns | -1.8 | <0.05 | p<0.05 |
| Week 6 | 0.5 | ns | -2.1 | <0.05 | p<0.05 |
| Week 8 | 0.1 | ns | -2.2 | <0.05 | p<0.05 |
| Week 12 | -0.5 | ns | -2.7 | <0.05 | ns |
| Endpoint* | -0.5 | ns | -2.6 | <0.05 | ns |
| Week 13 | -0.5 | ns | -2.6 | <0.05 | ns |

*Endpoint includes LOCF n=12

Metabolic control

Table 8.8.4.2.2 provides the changes from baseline in fasting glucose concentrations (mg/dl) in the sibutramine and placebo groups.

| TABLE 8.8.4.2.2 | | | | | |
|---|---|---|---|---|---|
| **Visit** | **Placebo** | **Within group p** | **Sibutramine** | **Within group p** | **Between group p** |
| Day 4 | -15.2 | ns | -23.5 | p<0.05 | ns |
| Week 2 | -3.2 | ns | -18.5 | ns | ns |
| Week 4 | 1.7 | ns | 8.6 | ns | ns |
| Week 8 | 23.0 | ns | 5.9 | ns | ns |
| Week 12 | 22.0 | ns | 6.8 | ns | ns |
| Endpoint | 22.2 | ns | 9.3 | ns | ns |

Table 8.8.4.2.3 illustrates the changes from baseline in glucose concentrations during an oral glucose tolerance test in the sibutramine and placebo groups.

| TABLE 8.8.4.2.3 | | | | | | |
|---|---|---|---|---|---|---|
| **Visit** | **Minute** | **Placebo** | **Within group p** | **Sib** | **Within group p** | **Between group p** |
| Day 4 | 0 | -15.8 | p<0.05 | -20.6 | p<0.05 | ns |
| | 30 | -5.2 | ns | -36.0 | p<0.05 | p>0.05 |
| | 60 | -8.2 | ns | -39.7 | p<0.05 | ns |
| | 90 | -1.7 | ns | -59.3 | p<0.05 | p<0.05 |
| | 120 | -13.8 | ns | -52.8 | p<0.05 | p<0.05 |
| | 180 | -17.5 | p>0.05 | -26.0 | p<0.05 | ns |
| | 240 | -27.8 | p>0.05 | 0.6 | ns | p>0.05 |
| Week 12 | 0 | 10.0 | ns | 8.2 | ns | ns |
| | 30 | 19.2 | ns | 8.4 | ns | ns |
| | 60 | 25.0 | p>0.05 | 8.0 | ns | ns |
| | 90 | 19.5 | ns | -3.2 | ns | ns |
| | 120 | 17.2 | ns | -12.1 | ns | ns |
| | 180 | 24.7 | p>0.05 | -7.8 | ns | ns |
| | 240 | 12.0 | ns | 5.8 | ns | ns |
| Endpoint | 0 | 10.0 | ns | 7.8 | ns | ns |
| | 30 | 19.2 | ns | 2.2 | ns | ns |

| TABLE 8.8.4.2.3 | | | | | | |
|---|---|---|---|---|---|---|
| **Visit** | **Minute** | **Placebo** | **Within group p** | **Sib** | **Within group p** | **Between group p** |
| | 60 | 25.0 | p>0.05 | 7.8 | ns | ns |
| | 90 | 19.5 | ns | -22.3 | ns | ns |
| | 120 | 17.2 | ns | -27.4 | ns | ns |
| | 180 | 24.7 | p<0.05 | -15.8 | ns | ns |
| | 240 | 12.0 | ns | 6.8 | ns | ns |

As the Sponsor offers, the reductions in glucose concentrations during the day 4 oral glucose tolerance tests most likely reflect the inpatient status of the subjects and their adherence to a "control" diet.

Although the short-term, inpatient treatment with 30 mg QD of sibutramine improved glucose concentrations, treatment with 20 mg QD of sibutramine for 12 weeks did not improve fasting or post-load glucose concentrations

There were no significant changes in the 24-hour excretion of C-peptide in the placebo or sibutramine subjects. Similarly, there were no significant changes in $HbA1_c$ levels by the end of the study in either group.

One subject had his dose reduced from 20 mg QD to 10 mg QD after 2 weeks of treatment because of complaints of constipation, decreased blood pressure, increased pulse, and decreased erectile function.

## SAFETY OUTCOMES

Adverse events

**8.8.4.4** There were no deaths in this study and no subject withdrew from the trial because of an adverse event. All the patients in the sibutramine group and 83% of the placebo subjects reported at least one adverse event during the trial.

The common adverse events (%) reported during the study are shown in table 8.8.4.4.1

| TABLE 8.8.4.4.1 | | |
|---|---|---|
| **Event** | **Placebo** | **Sibutramine** |
| Headache | 33% | 50% |

| TABLE 8.8.4.4.1 | | |
|---|---|---|
| **Event** | **Placebo** | **Sibutramine** |
| Nausea | 17% | 33% |
| Pharyngitis | 33% | 25% |
| Rhinitis | 33% | 0% |
| Pain | 17% | 25% |
| Constipation | 0% | 25% |

Vital signs

There were no consistent changes in the supine or standing systolic and diastolic blood pressures in either group. However, one subject (#2, sibutramine) had a transient fall in pre-dose standing systolic blood pressure

In general, there was a minor increase in pulse rate in the sibutramine group compared to the placebo group. Only one subject (#16 sibutramine) had a treatment emergent abnormal pulse value. On day 3 at 7 pm this subjects standing pulse rate was 120 bpm. The change in heart rates calculated from ECGs were similar to those recorded from the radial pulse.

Electrocardiograms

There were no clinically significant changes noted on the ECGs.

Clinical chemistries

The mean platelet count increased by 42 x $10^6$/ml in the sibutramine group and decreased by 17 x $10^6$/ml in the placebo group. There were no significant changes in serum chemistries with the exception of glucose levels which were described in the efficacy section. There were no significant changes in thyroid profiles.

Lipoprotein lipids

The levels of total cholesterol, LDL-C, and HDL-C decreased from baseline in the placebo group while triglyceride levels increased modestly in this group. In the sibutramine group, levels of total cholesterol, LDL-C, triglyceride, and HDL-C all increased modestly.

## 8.8.5 CONCLUSIONS

This small study of obese subjects with NIDDM controlled with diet or oral hypoglycemic

agents indicated that the short-term (4-days) administration of 30 mg QD of sibutramine did not adversely affect glucose control and was not associated with significant adverse events. Additionally, 12 weeks of 20 mg QD of sibutramine was generally well tolerated. Glucose control did not change in the sibutramine group despite an average weight loss of 2.7 kg.

In comparison to the studies of patients with uncomplicated obesity, the diabetic subjects in this study lost significantly less weight. There are a number of possible explanations for this finding. First, there were no dietary instructions given to the subjects in this study. The lack of compliance with a reduced calorie diet may reduce the efficacy of the drug. Second, there was a greater percentage of African-Americans in this study; ethnicity may affect the efficacy of the drug. Third, compliance with the study drug may have been low. And finally, it is possible that sibutramine is less effective in patients with type II diabetes mellitus. Further study in a larger population of NIDDM patients is clearly warranted.

**8.9 SB 3051**

**OBJECTIVE/RATIONALE**

**8.9.1** The objective of this study was to evaluate the effects of 15 mg QD of sibutramine on body weight and glucose control in obese patients with NIDDM.

**DESIGN**

**8.9.2** This was a 2 center, randomized, double-blind, placebo-controlled 12-week study.

**PROTOCOL**

**POPULATION**

**8.9.3.1** Eligible patients included subjects of either sex, aged ___ years, obese with a BMI greater than ___ and diagnosed with NIDDM of at least six months duration. All patients had a fasting glucose level from three previous visits of ___. Patients with diastolic blood pressures greater than 100 mmHg were excluded; however, patients on stabilized hypertensive therapy were allowed to participate in the study. Stable therapy with sulfonlyureas, metformin, and insulin were acceptable. As part of the study, all patients were seen by a dietitian and provided with a weight-reducing diet.

**ENDPOINTS**

**8.9.3.2** The primary endpoint of this study was the change in body weight from baseline. Secondary endpoints included changes in fasting blood glucose, insulin, and $HbA1_c$ levels; changes in dosage of antidiabetic medications; changes in the area under the curve (AUC) for

glucose and insulin concentrations following a test meal; and the changes in waist and hip circumferences. The change from baseline to endpoint in soft-tissue mass, lean-tissue mass, and fat mass were also calculated. Safety parameters: vital signs, serum chemistries, and reported adverse events were analyzed at several time points during the trial. Several dietary intake and compliance scales were also administered.

## STATISTICAL CONSIDERATIONS

**8.9.3.3** Differences between the treatment groups in absolute weight loss were analyzed using repeated measures ANOVA, with factors for treatment group, center, the treatment group-by-center interaction, time, and the treatment group-by-time interaction. Four datasets were analyzed:

1. Unbalanced - all available data with no account taken of missing values.
2. Balanced - all available data, but for the within group tests, the missing values were replaced by predicted values calculated from the model fitted to the data. The between group tests including that for treatment were not affected.
3. LOCF - all available data, but with missing values replaced by LOCF for both between and within group tests.
4. Completers - patients who completed the double-blind phase of the study. Missing values were interpolated to ensure complete patient profiles.

Correlation plots of changes in body weight against changes in laboratory variables were also produced. The proportions of patients losing greater than 5% of baseline body weight was calculated with the 95% confidence intervals. The proportion of patients who recorded a change in dosage of diabetic control medication was calculated and the difference between the two groups tested by the Chi-square test statistic.

## RESULTS

## POPULATION ENROLLED/ANALYZED

**8.9.4.1** One-hundred subjects were entered into the study. Nine patients withdrew before the baseline visit, thus 91 patients entered the double-blind phase. Of these, 83 completed the double-blind phase. Seventy-four of these patients continued into the open-labelled study of which the results are published elsewhere (SB 3068). Forty-four patients were randomized to placebo and 47 were randomized to sibutramine. The majority of the patients were enrolled in center 1. Table 8.9.4.1.1 illustrates the baseline characteristics of the two groups.

**TABLE 8.9.4.1.1**

| | **Sibutramine n=47** | **Placebo n=44** |
|---|---|---|
| Age (yrs) | 53.7 | 54.1 |

| | Sibutramine n=47 | Placebo n=44 |
|---|---|---|
| Gender | 51% female | 55% female |
| Race | 83% Caucasian | 75% Caucasian |
| Weight(kg)* | 84.6 | 82.5 |
| BMI ($kg/m^2$) | 30.6 | 31.0 |
| Fasting glucose (mmol/l) | 10.6 | 9.8 |
| Fasting insulin (mU/l) | 19.9 | 24.6 |
| $HbA1_c$ | 9.5 | 9.4 |

* median value; values in parentheses represent ranges

The baseline characteristics of the two groups were similar.

Nine subjects in the sibutramine group were controlled with diet alone, while 4 subjects in the placebo group were diet-controlled diabetics. Thirteen subjects in the sibutramine group were taking metformin and 16 in the placebo group were taking metformin. Similarly, 12 subjects in both groups were taking at least one form of insulin therapy. Eleven subjects in the sibutramine group and 1 subject in the placebo group took an antibiotic or other antibacterial agent during the double-blind study period. Seven subjects in the sibutramine group started on a laxative during the study, whereas 1 subject in the placebo group started taking a laxative during this time period.

A summary of the protocol violations are shown in table 8.9.4.1.

**TABLE 8.9.4.1.2**

| Protocol violation | Sibutramine n=47 | Placebo n=44 |
|---|---|---|
| < 11 days between visits | 2 | 2 |
| > 17 days between visits | 16 | 7 |
| BMI < 26.0 kg/m2 | 1 | 0 |
| BMI > 35.0 kg/m2 | 3 | 3 |
| Fasting glucose < 7 mmol/L | 4 | 4 |
| Fasting glucose > 12.0 mmol/L | 13 | 17 |
| Prohibited med at entry | 4 | 7 |
| Started prohibited med● | 9 | 1 |
| Compliance < 70% | 1 | 1 |

| TABLE 8.9.4.1.2 | | |
|---|---|---|
| **Protocol violation** | **Sibutramine n=47** | **Placebo n=44** |
| Compliance > 130% | 1 | 0 |

✪ Two subjects in the sibutramine group started diuretics, and 7 patients in the sibutramine group and 1 in the placebo group started laxatives.

Two subjects in the placebo group withdrew from the study because of adverse events and 3 withdrew for this reason in the sibutramine group. One subject in each group withdrew consent, and 1 placebo subject was lost to follow-up. The overall withdrawal rate was 9% for both groups.

## EFFICACY ENDPOINT OUTCOMES

Body weight

**8.9.4.2** Eighty-three subjects completed the study and were included in the completers analysis.

The analyses preformed on all four datasets for the actual weight change from baseline provided similar results. Table 8.9.4.2.1 provides the actual weight change (kg) from baseline for the unbalanced dataset.

| TABLE 8.9.4.2.1 | | | | | | |
|---|---|---|---|---|---|---|
| **Assessment** | **Treatment** | **N** | **Baseline mean** | **Adj mean change●** | **95% CI** | **P value✪** |
| Week 2 | Sib | 39 | 84.9 | -0.6 | -0.9,-0.3 | 0.002 |
| | Pl | 35 | 85.8 | 0.1 | -0.2,0.3 | |
| Week 4 | Sib | 44 | 86.0 | -1.3 | -1.7,-0.9 | <0.001 |
| | Pl | 41 | 85.6 | -0.1 | -0.4,0.3 | |
| Week 6 | Sib | 36 | 85.9 | -1.1 | -1.7,-0.7 | <0.001 |
| | Pl | 32 | 85.7 | 0.2 | -0.3,0.6 | |
| Week 8 | Sib | 41 | 86.0 | -1.9 | -2.5,-1.3 | <0.001 |
| | Pl | 36 | 83.8 | 0.3 | -0.2,0.7 | |
| Week 10 | Sib | 32 | 87.2 | -1.5 | -2.3,-0.8 | <0.001 |
| | Pl | 33 | 86.7 | 0.5 | -0.1,1.0 | |
| Week 12 | Sib | 46 | 84.9 | -2.3 | -3.0,-1.7 | <0.001 |

| TABLE 8.9.4.2.1 | | | | | | |
|---|---|---|---|---|---|---|
| **Assessment** | **Treatment** | **N** | **Baseline mean** | **Adj mean change*** | **95% CI** | **P value◇** |
| | Pl | 40 | 85.3 | -0.2 | -0.7,0.3 | |

* Adjusted for center and interaction effects and back-transformed from log-transformed data

◇ p-value from the analysis of variance for the difference between the treatment groups in the change from baseline

Using the balanced dataset, the mean percentage change in body weight from baseline to week 12 was -2.8% and -0.3% for the sibutramine and placebo groups, respectively.

Nineteen percent of the sibutramine patients lost > 5% of baseline weight at endpoint and week 12. None of the placebo patients achieved this level of weight loss. The difference between the two groups was not statistically significant.

Body composition

There were no significant changes from baseline to week 12 in the wasit to hip ratios in either group. The mean waist circumference decreased by 1.87 cm in the sibutramine group and by 1.33 cm in the placebo group.

Results of the analysis of change in body composition measured by DEXA are presented in table 8.9.4.2.3

| TABLE 8.9.4.2.3 | | | | |
|---|---|---|---|---|
| **Assessment** | **Placebo** | | **Sibutramine 15mg** | |
| | Baseline mean | Mean change | Baseline mean | Mean change |
| Whole body | n=38 | | n=39 | |
| Soft tissue mass (kg) | 80.5 | -0.5 | 81.8 | -2.6✠ |
| Fat mass (kg) | 32.1 | -0.2 | 32.2 | -1.8✠ |
| Lean mass (kg) | 48.4 | -0.3 | 49.7 | -0.8 |
| Percentage fat mass (%) | 39.8 | -0.1 | 39.4 | -1.0✧ |
| Bone mineral content (g) | 2600 | -1.5 | 2755 | -13.1 |

✧ p<0.05 compared to placebo

✠ p<0.001 compared to placebo

Percent fat mass was significantly reduced in the sibutramine group.

Body compositional changes were analyzed for the android and gynoid regions and the changes

were similar to those of the whole body. However, there was a small, but statistically significant reduction in lean mass in the sibutramine group for the gynoid region.
It is of interest to note that the bone mineral content was reduced in the sibutramine group, however, this reduction was not statistically significant.

Metabolic control

There were no significant ($p<0.05$) differences between the two groups with respect to the change from baseline to week 12 in fasting glucose concentrations. The overall changes from baseline in fasting glucose levels were -0.3 mmol/L and 0.9 mmol/L for the sibutramine and placebo groups, respectively.

Similarly, there were no significant differences between the two groups with respect to the change from baseline to week 12 in fasting insulin levels. The overall changes from baseline in fasting insulin levels were 1.7 mmol/L and 1.0 mmol/L in the sibutramine and placebo groups, respectively.

Similarly, there were no significant differences between the two groups with respect to the change from baseline to week 12 or endpoint in $HbA1_c$ levels. Baseline values were approximately 9.4% for both groups and the overall changes from baseline to week 12 were -0.3% and 0.1% for the sibutramine and placebo groups, respectively. The Sponsor reports that there was a subgroup of 15 sibutramine-treated subjects who had a reduction in $HbA1_c$ levels of > 1.0% at endpoint. These 15 subjects also tended to lose more weight than the other active-treated subjects. While the changes in $HbA1_c$ concentrations reported for these 15 patients were favorable, they represent a post hoc-defined subgroup and therefore, reliable conclusions cannot be made regarding their response. Nevertheless, these subjects and their metabolic profiles are discussed further in the results section of SB 3068, the open-label extension phase of this study.

The changes from baseline to endpoint in glucose levels during the test meal are shown in table 8.9.4.2.4

**TABLE 8.9.4.2.4**

| Treatment group | n | Change in kinetics from baseline to endpoint of glucose for patients with complete test meal data | | |
|---|---|---|---|---|
| | | $C_{max}$ (mmol/l) | AUC (mmol.min/l) | $T_{max}$ (min) |
| Placebo | 39 | 0.5 | 21.0 | 0.0 |
| Sibutramine | 41 | -1.1* | -39.0 | 0.0 |

* p=0.04 compared to placebo

$C_{max}$=maximal concentration; AUC=area under the curve; $T_{max}$=time to maximal concentration

There were no significant differences between the two groups in the changes in AUC or $T_{max}$

following treatment.

There were no significant differences in the changes in the insulin parameters ($C_{max}$, AUC, and $T_{max}$) measured during the test meal in the sibutramine group compared to the placebo group.

Change in antidiabetic medication

Table 8.9.4.2.2 illustrates the changes in antidiabetic medications during the study. There were no statistically significant differences between treatment groups in the proportion of patients who changed their anti-diabetic therapy during the study.

**TABLE 8.9.4.2.2**

| Therapy | Reduction in dose | | Increase in dose○ | | No change in dose● | |
|---|---|---|---|---|---|---|
| | Sib | Pl | Sib | Pl | Sib | Pl |
| Insulin | 2 | 3 | 1 | 2 | 7 | 7 |
| Sulfonyl | 0 | 2 | 2 | 1 | 24 | 21 |
| Metformin | 0 | 0 | 0 | 0 | 13 | 16 |
| Total | 2 | 5 | 3 | 3 | 42 | 36 |

○ One subject started glibencamide (moved from dietary control only)

● Includes five sibutramine patients and two placebo patients who had changes in dose during the study but reverted to original dose by end of the study

Consummatory behavior

There were no significant differences between groups with respect to macronutrient intake, or visual analogue scales for hunger, satiety, or appetite.

## SAFETY OUTCOMES

Adverse events

**8.9.4.3** The percent of patients in each group reporting an adverse event are provided in table 8.9.4.3.1

**TABLE 8.9.4.3.1**

| COSTART body system | Sibutramine | Placebo |
|---|---|---|
| Body as a whole | 66 | 70 |
| Cardiovascular | 17 | 9 |

| TABLE 8.9.4.3.1 | | |
|---|---|---|
| **COSTART body system** | **Sibutramine** | **Placebo** |
| Digestive | 49 | 59 |
| Heme and lymphatic | 2 | 7 |
| Metabolic and nutritional | 23 | 16 |
| Musculoskeletal | 15 | 18 |
| Nervous | 45 | 34 |
| Respiratory | 21 | 16 |
| Skin and appendages | 19 | 16 |
| Special senses | 9 | 7 |
| Urogenital | 26 | 18 |
| Overall | 96 | 95 |

Test of proportions of patients reporting: $\chi^2=0.01$, $p=0.95$

The most common adverse events; reported by more than 5% of patients are summarized in table 8.9.4.3.2

| **Table 8.9.4.3.2** | | |
|---|---|---|
| **COSTART term** | **Placebo** | **Sibutramine** |
| Asthenia | 5 | 2 |
| Flu syndrome | 5 | 1 |
| Headache | 19 | 14 |
| Infection | 1 | 8 |
| Abdominal pain | 3 | 5 |
| Back pain | 4 | 5 |
| Chest pain | 4 | 3 |
| Constipation | 13 | 13 |
| Diarrhea | 6 | 4 |
| Dyspepsia | 2 | 5 |
| Flatulence | 6 | 3 |
| Hyperglycemia | 3 | 5 |

| Table 8.9.4.3.2 | | |
|---|---|---|
| **COSTART term** | **Placebo** | **Sibutramine** |
| Hypoglycemia | 5 | 1 |
| Arthralgia | 4 | 4 |
| Dizziness | 6 | 6 |
| Dry mouth | 5 | 10 |
| Paresthesia | 3 | 2 |
| Pharyngitis | 4 | 8 |
| Sweatiness | 2 | 4 |
| Albuminuria | 3 | 3 |

The increased number of infections reported in the sibutramine group represent upper respiratory tract infections and may be related to the drug-induced xerostomia.

Four patients experienced serious or potentially serious adverse events (one in placebo and 3 in sibutramine). A 49 year old female in the placebo group entered the hospital for endoscopy after 36 days into the study. A 52 year old female in the sibutramine group was hospitalized for arthroscopy of the knee after 83 days of treatment. A 65 year old female in the sibutramine group was hospitalized for varicose vein surgery after 50 days of treatment. And a 60 year old black female experienced deterioration in renal function after 46 days of sibutramine treatment this was felt to be possibly due to the initiation of diuretic therapy during the study.

Five patients (two in the placebo group and 3 in the sibutramine group) withdrew from the study because of an adverse event. One of the placebo patients withdrew because of moderate giddiness and vomiting and the other subject withdrew because of a severe headache. The sibutramine subjects withdrew because of moderate dizziness, moderate insomnia, and moderate diarrhea, respectively.

Clinical chemistries

The difference between the two groups for the change from baseline to endpoint was statistically significant for packed cell volume, mean cell volume, and platelets. However, none of these changes appeared to be clinically significant.

Lipoprotein lipids

In the sibutramine group there were small, non-significant mean reductions in triglyceride, total cholesterol, and VLDL levels compared with small increases in the placebo group. In addition,

there was a small mean increase in HDL-C levels in the sibutramine group compared with no change in the placebo group. The levels of LDL-C increased slightly in both groups.

Vital signs

The changes in vital signs from baseline to week 12 for completers are provided in table 8.9.4.3.2

| TABLE 8.9.4.3.2 | | |
|---|---|---|
| | **Sibutramine n=43** | **Placebo n=40** |
| Systolic blood pressure | -0.2 | -0.2 |
| Diastolic blood pressure | 3.0 | 2.5 |
| Pulse | 7.5* | 0.2 |

*p=0.005 compared to placebo; blood pressure in mmHg and pulse in beats per minute

Electrocardiograms

The mean change from baseline to endpoint in heart rate from ECG was 9.1 and -4.8 ($p<0.001$) in the sibutramine and placebo groups, respectively The only other ECG parameter that was statistically different between the two groups was the QT interval. There was a mean increase of 2.8 ms in the placebo groups and a mean decrease of 14.8 ms in the sibutramine group ($p=0.002$).

## CONCLUSIONS

**8.9.5** In this 12-week study of obese NIDDM patients, 15 mg QD of sibutramine resulted in a small, but statistically significant reduction in body weight and percent body fat when compared to placebo. However, despite a mean reduction in body weight of 2.3 kg, $HbA1_c$ levels did not change significantly in the sibutramine-treated patients. Whereas systolic blood pressure did not change in either group, diastolic blood pressure increased slightly in each group and there was a statistically significant increase in the pulse rate in the sibutramine group. The clinical significance of this moderate increase in pulse, if sustained with long-term use of sibutramine, is unknown. There were small, favorable, but non-statistically significant changes in lipid profiles in the sibutramine group.

## 8.10 SB 3068

## OBJECTIVE/RATIONALE

**8.10.1** The objective of this study was to evaluate the efficacy and tolerability of 15 mg QD of sibutramine in obese type II diabetic patients who completed the 12-week core study SB 3051.

This open-label extension study was conducted for 12 weeks.

## DESIGN

**8.10.2** This was a 2-center, open, non-comparative extension trial to examine the long-term efficacy and tolerability of sibutramine 15 mg QD in the treatment of obese patients with type II diabetes who completed the core study SB 3051. Subjects who received placebo during the core study received 15 mg QD of sibutramine during the extension study. Each patient was interviewed by a dietitian and was encouraged to follow specific dietary recommendations for diabetics. Assessments were made at weeks 16, 20, 24, and at 4-weeks post-active treatment.

## PROTOCOL

## POPULATION

**8.10.3.1** Upon completion of the double-blind, placebo-controlled, parallel-group core trial, SB 3051, patients were assessed for eligibility to continue into this extension trial. Eligible patients were of either sex, and between [redacted] years of age. Patients were not eligible to participate in the extension trial if they had a diastolic blood pressure greater than 110 mmHg or experienced a serious adverse event during the core trial.

## ENDPOINTS

**8.10.3.2** The primary endpoints of this extension study included change in body weight, waist and hip circumferences, body composition (DEXA), and blood pressure and pulse. A test meal with measurement of glucose and insulin concentrations was also an endpoint measured at week 24. The change in $HbA1_c$ levels was assessed at weeks 12 and 24. Changes in diabetic medication were also recorded.

## STATISTICAL CONSIDERATIONS

**8.10.3.3** The change in body weight, calculated on a last observation carried forward basis, from week 0 to week 24 for the group randomized to receive sibutramine in the core study (SB3051) and the corresponding changes from week 12 to week 24 within each group from SB 3051 were reported with 95% confidence intervals. One-way ANOVA with a factor for center was conducted to evaluate for consistency of any treatment effect between the two centers. It was not possible to accurately calculate the statistical power of the extension trial because it was unknown how many subjects would complete the core study. The changes in fasting glucose and insulin levels during the core trial did not follow a normal distribution, and therefore, the Hodges-Lehmann estimate of the median changes and the associated 95% confidence intervals were reported. Fasting insulin levels recorded below the detection range of the assay were reset to the lower assay limit, similarly, any value recorded above the detection range was reset to the upper detection limit. Changes in fasting insulin concentrations were analyzed for subgroups of

patients, as defined by the concomitant diabetic medication.

## RESULTS

## POPULATION ENROLLED/ANALYZED

**8.10.4.1** A total of 74 patients completed the core trial and continued into the extension trial. Of these, 67 patients completed the extension trial. Table 8.104.1.1 provides the baseline (week 12) characteristics of the two groups from the core study.

**TABLE 8.10.4.1.1**

| Variable | Sibutramine n=37 | Placebo n=37 |
|---|---|---|
| Age (yrs) | 53.3 | 54.5 |
| Male | 19 | 17 |
| Female | 18 | 20 |
| Weight (kg)+ | 81.8 | 83.9 |
| BMI ($kg/m^2$) | 29.5 | 31.0 |

+ median values

As expected, the individuals who received sibutramine in the core study weighed less than those who received placebo. This difference in body weight was more pronounced for the males (median weight 82.6 vs 87.7 kg for sibutramine vs placebo, respectively).

## EFFICACY ENDPOINT OUTCOMES

Body weight

**8.10.4.2** The mean actual change in body weight (kg) to endpoint for the groups by original treatment in the core study are shown in table 8.10.4.2.1

**TABLE 8.10.4.2.1**

| Previous tx | n | Change from wk 12 | 95% CI | n | Change from wk 0 | 95% CI |
|---|---|---|---|---|---|---|
| Sib 15 mg | 36 | -0.6 kg | -1.2,0.0 kg | 36 | -3.3 kg | -4.2,-2.3 kg |
| Placebo | 37 | -1.9 kg | -2.6,-1.3 kg | 37 | -2.5 kg | -3.3,-1.7 kg |

It should be noted that the absolute weight loss in the diabetics who received 15 mg QD of sibutramine from baseline to endpoint was a modest 3.3 kg.

Table 8.10.4.2.2 illustrates the mean percentage change in body weight to endpoint.

| TABLE 8.10.4.2.2 | | | | | | |
|---|---|---|---|---|---|---|
| **Previous tx** | **n** | **Change from wk 12** | **95% CI** | **n** | **Change from wk 0** | **95% CI** |
| Sib 15 mg | 36 | -0.7% | -1.4, 0.0 | 36 | -3.8% | -4.9, -2.8 |
| Placebo | 37 | -2.3% | -3.1, -1.5 | 37 | -3.0% | -3.9, -2.1 |

The results of the mean percentage change in body weight were similar for the completers dataset, and again, indicate that sibutramine caused a modest, but statistically significant reduction in percent body weight when administered for 24 weeks.

Body composition

The sibutramine group had a statistically significant reduction in waist circumference, whereas the placebo group did not. The change in waist circumference for the sibutramine group from week 0 to week 24 was -4.7 cm ( 95% CI -2.7, -6.6 cm).

The changes from week 0 to endpoint in body composition measured by DEXA are shown in table 8.10.4.2.3

| TABLE 8.10.4.2.3 | | |
|---|---|---|
| **Body Component** | **Sibutramine n=34** | **Placebo n=34** |
| Soft tissue mass (kg) | -3.2 (-4.2, -2.2) | -2.4 (-3.2, -1.5) |
| Fat mass (kg) | -2.7 (-3.6, -1.8) | -1.8 (-2.6, -1.1) |
| Lean mass (kg) | -0.5 (-1.1, 0.0) | -0.5 (-1.0, -0.1) |
| Percentage fat mass (%) | -1.9 (-2.7, -1.1) | -1.1 (-1.7, -0.5) |
| Bone mineral content (g) | -15.1 (-42.6, 12.5) | -8.3 (-23.9, 7.3) |

Values in parentheses represent the 95% CI

There were statistically significant reductions in fat mass and percentage fat mass in both groups. There was also a small reduction in lean mass in both groups; this reduction was statistically significant in the placebo group only.

Metabolic control

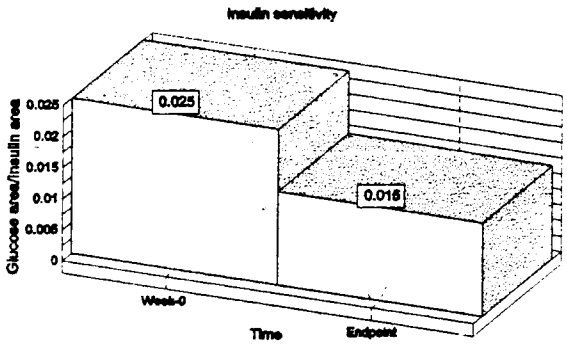
There were no statistically or clinically significant changes in fasting glucose or insulin levels during the extension study. Similarly, there were no significant changes in the levels of $HbA1_c$ in either group (95% CI for the change from week 0 to week 24: -0.5, 0.5% for the sibutramine

group and -0.2, 0.5% for the placebo group).

In general there were no significant changes in the fasting or post-test meal glucose concentrations in the sibutramine or placebo groups at endpoint. However, there was a statistically significant increase in the incremental AUC for insulin following a test meal in the sibutramine group from week 0 to endpoint (8.5 mmol/l.min) and week 12 to endpoint (12.3 mmol/l.min). The increase in insulin levels following treatment with sibutramine without a significant reduction in glucose concentrations raises the possibility that sibutramine treatment was associated with a decrease in insulin sensitivity.

The ratio of glucose to insulin concentration is a crude index of insulin sensitivity. Figure 8.10.4.2.1 illustrates the change in the ratio of the glucose to insulin area following a test meal in the sibutramine group. The decrease in the ratio of glucose to insulin again suggests a possible reduction in insulin sensitivity. The effect of sibutramine-induced weight loss on insulin sensitivity should be definitively examined by the hyperinsulinemic and hyperglycemic clamp techniques.

**Figure 8.10.4.2.1**








Subgroup analysis

Whereas, overall, there was no change in the mean $HbA1_c$ concentration in the sibutramine-treated subjects, the Sponsor reported that 13 subjects who were randomized to sibutramine treatment in the core study SB 3051 had reductions in $HbA1_c$ of > than 1.0%.

Table 8.10.4.2.4 provides the metabolic responses of the 13 subjects who had a favorable decrease in $HbA1_c$ levels.

| TABLE 8.10.4.2.4 | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **#subjects** | **Δ Weight** | **Δ $G_0$** | **Δ $I_0$** | **ΔG AUC** | **Δ I AUC** | **Δ SBP** | **Δ DBP** | **Δ P** |
| 13 | -4.5 | -2.6 | 0.7 | -0.17 | 9.1 | -0.8 | 1.6 | 6.5 |

Deltas represent the change from baseline to endpoint.
**Δ Weight** in kg; **Δ $G_0$** = change in fasting glucose level in mmol/l; **Δ $I_0$** = change in fasting insulin level in U/l; **ΔG AUC** = change in incremental area under the curve post-test meal for glucose in mol.l/min; **ΔI AUC** = change in incremental area under the curve post-test meal for insulin in mmol.l/min; **ΔSBP** = change in systolic blood pressure in mmHg; **ΔDBP** = change in diastolic blood pressure in mmHg; **ΔP** = change in pulse in beats per minute.

The metabolic responses in this subgroup of subjects who had a reduction in $HbA1_c$ of >1% were similar to those of the overall group, and indicate that post-load insulin levels increased, as did diastolic blood pressure and pulse rate following treatment with sibutramine. In sum, in this subgroup of patients, the favorable reduction in $HbA1_c$ levels was not accompanied by favorable changes in other metabolic or co-morbid conditions.

Change in antidiabetic medication

The changes in anti-diabetic therapy during the extension study categorized by treatment group in the core study are illustrated in table 8.10.4.1.2

| TABLE 8.10.4.1.2 | | | | | | |
|---|---|---|---|---|---|---|
| **Therapy** | **Reduction in dose** | | **Increase in dose** | | **No change in dose** | |
| | Sib | Pl | Sib | Pl | Sib | Pl |
| Insulin | 1 | 3 | 4 | 1 | 5 | 5 |
| Sulphonyl | 1 | 2 | 0 | 2 | 17 | 9 |
| Metformin | 0 | 0 | 0 | 0 | 8 | 14 |

It appears that more sibutramine-treated patients had an increase in their insulin dose than did placebo patients.

## SAFETY OUTCOMES

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Adverse events

**8.10.4.3** Adverse experience data are available for 73/74 subjects. The most common events were in the COSTART categories Body as a Whole, Digestive and Nervous Systems. The adverse events reported by greater than 5% of patients who received sibutramine are listed in table 8.10.4.3.1

| TABLE 8.10.4.3.1 | | | |
|---|---|---|---|
| **COSTART term** | **Placebo** | **Sibutramine❁** | |
| | **Weeks 12-24** | **Weeks 12-24** | **Weeks 0-24** |
| Asthenia | 4 | 1 | 2 |
| Headache | 8 | 4 | 9 |
| Infection | 1 | - | 9 |
| Pain | 5 | 1 | 2 |
| Abdominal pain | 3 | 1 | 1 |
| Back pain | - | - | 4 |
| Chest pain | 3 | 3 | 4 |
| Palpitation | 2 | - | 2 |
| Constipation | 8 | 4 | 17 |
| Dyspepsia | 1 | 2 | 4 |
| Nausea | 3 | - | 2 |
| Hyperglycemia | - | 3 | 6 |
| Hypoglycemia | 3 | 1 | 2 |
| Arthralgia | 1 | 3 | 6 |
| Dizziness | 4 | 4 | 9 |
| Dry mouth | 10 | 4 | 14 |
| Insomnia | 2 | 3 | 3 |
| Pharyngitis | 7 | 3 | 8 |
| Sweat | 2 | 2 | 7 |
| Albuminuria | 1 | - | 3 |

❁ includes adverse events reported in core trial

Two patients experienced serious adverse events. Both patients remained in the study. One patient, a 63 year old Black male, experienced mild chest pain following a fall in which his chest was injured. Angina was diagnosed by an exercise treadmill test; the patient did complete the study. The second patient, a 51 year old Caucasian male, was hospitalized for left knee arthroscopy. One patient started an antidepressant because of mild depression.

Six patients withdrew from the study because of an adverse event. These are summarized in table 8.10.4.3.2

| TABLE 8.10.4.3.2 | | | | | | |
|---|---|---|---|---|---|---|
| **Number** | **Age** | **Gender** | **Dose** | **Duration** | **Event** | **Comment** |
| 44 | 54 | M | 15 | 105 | severe abdominal pain | dx with constipation |
| 70 | 55 | F | 15 | 93 | worsening of diabetes | FBS of 23.4 mmol/l |
| 71 | 58 | M | 15 | 105 | severe hyperlipidemia IIB | cholesterol and TG levels rose significantly during the trial and decreased after drug stopped |
| 76 | 44 | M | 15 | 163 | ⇑ LFTs | ? relationship to drug |
| 104 | 41 | M | 15 | 121 | mild hyperglycemia | possible relationship to drug |
| 115 | 54 | F | 15 | 5 | headache | persisted 82 days post-withdrawal |

Clinical chemistries

There were two potentially significant clinical laboratory value changes during the study. One patient was receiving iron treatment for anemia. During the course of the core and extension studies her hemoglobin level decreased from 11.3 g/dl to 9.7 g/dl. No results were available from week 28. Another patient had an increase in urea and creatine levels at week 24 (9.3 mmol/l and 203 umol/l, respectively. The values returned to normal at the end of the study.

Lipoprotein lipids

There were no statistically significant changes in lipoprotein lipid levels in the group that received sibutramine in the core study and completed the 24 week extension study.

Vital signs

Table 8.10.4.3.3 illustrates the mean changes in blood pressure and pulse.

| TABLE 8.10.4.3.3 | | |
|---|---|---|
| **Variable** | **Mean change (95% CI) by previous treatment in core study** | |
| | **Placebo (week 12-24)** | **Sibutramine (week 0-24)** |
| | n=34 | n=33 |
| Systolic BP (mmHg) | 5.1 | 0.8 |
| Diastolic BP (mmHg) | 2.8 | 3.6 |
| Pulse rate (bpm) | 6.6 | 10.1 |

❁ statistically significant, $p<0.05$

As shown in the above table there were statistically significant increases in diastolic blood pressure and pulse rate in the patients who received sibutramine from week 0 to week 24.

Electrocardiograms

Aside from a mean increase in heart rate of 8 to 9 beats per minute, there were no clinically significant changes in the ECGs.

**8.10.5 SPONSOR'S CONCLUSIONS**

"Treatment with sibutramine 15 mg once-daily, for up to six months produced sustained weight loss in this type II diabetic patient population. Sibutramine did not appear to affect diabetic control or the management of these patients. From the first dose of sibutramine, there was a mean increase in heart rate during the initial 12 weeks of sibutramine treatment; those patients who received an additional 12 weeks of treatment had little further change in heart rate. Sibutramine was well tolerated for up to six months in this patient population."

**8.10.6 MEDICAL OFFICER'S SUMMARY AND CONCLUSIONS**

This Reviewer does not agree with the Sponsor's conclusions that sibutramine was well tolerated in this diabetic population. The rationale for this statement is as follows: In this 12 week open-label extension study of obese type II diabetics, 15 mg QD of sibutramine produced minimal to modest reductions in body weight and percent body fat. Despite a 3.3 kg reduction in weight, there were no improvements in glucose metabolism as assessed by $HbA1_c$ concentrations, and fasting and post-load glucose concentrations. Moreover, the data suggest the possibility of reduced insulin sensitivity following treatment with sibutramine, as the AUC for insulin following a test meal increased without a significant reduction in glucose levels in the drug-treated group. This issue should be further explored with more sensitive methodologies such as the hyperglycemic and hyperinsulinemic clamps.

Regarding other co-morbid conditions, 24-weeks of treatment with sibutramine increased diastolic blood pressure and pulse rate and did not improve lipoprotein lipid levels.

***HYPERTENSION***

**8.11 BPI 855**

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**OBJECTIVE/RATIONALE**

**8.11.1** The objective of this study was to assess the effects of 20 mg QD of sibutramine on blood pressure as measured by 24-hour ambulatory monitoring in obese, hypertensive patients

controlled by a single antihypertensive agent.

**DESIGN**

**8.11.2** This study was a single center, parallel-group, double-blind, fixed-flexible dose, placebo-controlled study of 20 patients (10 sibutramine and 10 placebo). Following a 7-day inpatient phase during which time the subjects received sibutramine or placebo starting on day 1, the subjects were discharged and continued their dosing for an additional 7 weeks. During the outpatient phase, the subjects were allowed to reduce their dose from 20 mg QD to 10 mg QD if they developed intolerable side effects. Assessments were conducted at weeks 2, 4, 6, 8, and 9.

**PROTOCOL**

**POPULATION**

**8.11.3.1** Inclusion criteria:
1. Male or female patients between the ages of_____ years.
2. Body weight between
3. Documented history of essential hypertension (untreated diastolic blood pressure greater than 90 mmHg), or hypertension treated for at least 6 weeks prior to screening with the same dose of a single antihypertensive agent (calcium channel blocker, ACE inhibitor, or diuretic), and have a supine diastolic blood pressure of 95 mmHg or less on 2 successive occasions.

Exclusion criteria:
1. Thyroid hormone replacement therapy, beta-blockers, centrally acting sympathetic agents, alpha-2-agonists, and ganglionic blocking agents.

**ENDPOINTS**

**8.11.3.2** Twenty-four hour ambulatory blood pressure monitoring (ABPM) was performed during screening, inpatient day 0, inpatient day 3, outpatient week 4, and outpatient week 8. In addition to the standard laboratory measurements, the patients had measurements for 24-hour urinary VMA, plasma catecholamines, and plasma drug levels. Changes in vital signs, Appetite scales, and the Modified Norris Assessment scores were measured. During the screening phase patients recorded food intake for 4 days and received counseling from a dietitian to ensure intake of appropriate calories so that **weight loss would be minimized** and the effects of the drug on blood pressure would not be confounded by weight loss.

**STATISTICAL CONSIDERATIONS**

**8.11.3.3** The study report states that all comparisons between groups were conducted with t-tests. There is no mention of correction for multiple t-tests. The descriptive statistics for the observed body weights and their change from baseline were calculated and one-way ANOVAs

performed for the changes from baseline values, by visit. A repeated-measures ANOVA was performed for the changes from baseline values; the factors were visit, treatment, treatment by visit interaction, and patient within treatment. Because of the sizable treatment difference with respect to weight at baseline, analyses of covariance were completed for weight change, by visit. The factors in the ANCOVAs were treatment and baseline weight. Fisher's Exact Test was performed to determine whether or not there were treatment differences with respect to the number of patients reporting adverse experiences during the study.

## RESULTS

## POPULATIONS ENROLLED/ANALYZED

**8.11.4.1** Twenty patients were enrolled in the study and 19 completed the study. Subject # 18 in the sibutramine group withdrew from the study after 4 weeks because of fatigue, dry mouth, and increased perspiration.

Table 8.11.4.1.1 provides the baseline demographic information for the two groups.

**TABLE 8.11.4.1.1**

| Demographic Characteristic | Placebo n=10 | Sibutramine n=10 |
|---|---|---|
| Age (yrs) | 51.8 ± 6.7 | 49.9 ± 5.9 |
| Weight (kg) | 105.6 ± 18.5 | 93.5 ± 11.5 |
| Male | 4 | 0 |
| Female | 6 | 10 |
| Black | 4 | 5 |
| Caucasian | 6 | 5 |
| Supine systolic blood pressure (mmHg) | 131.0 ± 11.9 | 127.8 ± 13.4 |
| Supine diastolic blood pressure (mmHg) | 83.8 ± 8.0 | 81.0 ± 5.8 |
| Supine pulse rate (bpm) | 77.6 ± 8.0 | 78.4 ± 5.1 |

Values are means ± SD

There were significant differences between the two groups with respect to baseline sex distribution (p=0.04) and near significant differences with respect to baseline body weight (p=0.10). The calculated BMIs for the placebo and sibutramine groups are 41.4 $kg/m^2$ and 32.5 $kg/m^2$.

Table 8.11.4.1.2 summarizes the concurrent antihypertensive therapy for the two groups at baseline.

| TABLE 8.11.4.1.2 | | | |
|---|---|---|---|
| **Anti-hypertensive agent** | **Dose range** | **Placebo** | **Sibutramine** |
| Calcium Channel Blocker | 5-180 mg | 2 | 2 |
| Diltiazem | | 1 | 0 |
| Isradipine | | 1 | 1 |
| Nifedipine — | | 0 | 1 |
| ACE inhibitor | 5-10 mg | 1 | 1 |
| Enalapril | | 1 | 1 |
| ACE Inhibitor + diuretic | unknown | 2 | 0 |
| Captopril + hydrochlorothiazide | | 1 | 0 |
| Enalapril + hydrochlorothiazide | | 1 | 0 |
| Diuretic | 25-100 mg | 5 | 7 |
| Furosemide | | 1 | 0 |
| Hydrochlorothiazide | | 1 | 3 |
| Spironolactone | | 1 | 0 |
| Triamterene + hydrochlorothiazide | | 2 | 4 |

The anti-hypertensive treatments were similar for the two groups.

## EFFICACY ENDPOINT OUTCOMES

**8.11.4.2** Weight loss was not an intended outcome of this study; and although there was a small mean reduction in body weight in the sibutramine group (-1.7 kg) and a small increase in the placebo group (0.2 kg) the difference was not statistically significant. The ANCOVA analysis results were the same as the ANOVA assessment and confirmed that there were no significant differences between the two groups.

## SAFETY OUTCOMES

Blood pressure

**8.11.4.3** The following tables illustrate the time points at which there were significant or nearly significant ($0.1>p>0.5$) treatment differences for the change in blood pressure from baseline as measured by 24-hour ambulatory monitoring.

| TABLE 8.11.4.2.1 | | | |
|---|---|---|---|
| 24-Hour Ambulatory Systolic Blood Pressure Change from baseline (mmHg) | | | |
| Time Point | Placebo | Sibutramine | p-value |
| Day 3/Hour 24 | 0.7 | -15.4 | 0.08 |
| Week 4/Hour 2 | -9.0 | 13.2 | 0.09 |
| /Hour 12 | -24.8 | 3.0 | 0.08 |
| /Hour 16 | -29.2 | 8.9 | 0.04 |
| Week 8/Hour 16 | -30.2 | 13.4 | 0.05 |

| TABLE 8.11.4.2.2 | | | |
|---|---|---|---|
| 24-Hour Ambulatory Diastolic Blood Pressure Change from baseline (mmHg) | | | |
| Time Point | Placebo | Sibutramine | P-value |
| Day 3/Hour 16 | 0.0 | 9.4 | 0.02 |
| Week 4/Hour 2 | -12.5 | 4.3 | 0.03 |
| /Hour 16 | -16.2 | 10.0 | 0.0001 |
| /Hour 20 | -6.7 | 3.9 | 0.09 |
| /Hour 24 | -21.5 | 3.9 | 0.08 |
| Week 4/Overall | -8.0 | 2.2 | 0.03 |
| Week 8/Hour 4 | -9.0 | 4.3 | 0.05 |
| /Hour 16 | -14.8 | 7.5 | 0.004 |
| /Hour 20 | -17.9 | 7.8 | 0.06 |
| /Hour 24 | -38.9 | 1.9 | 0.08 |
| Week 8/Overall | -7.7 | 3.7 | 0.04 |

| TABLE 8.11.4.2.3 | | | |
|---|---|---|---|
| 24-Hour Ambulatory Mean Arterial Pressure Change from baseline | | | |
| Time Point | Placebo | Sibutramine | p-value |
| Week 4/Hour 2 | -11.3 | 7.2 | 0.04 |
| /Hour 12 | -15.4 | -0.9 | 0.09 |
| /Hour 16 | -20.5 | 9.6 | 0.0004 |
| Week 4/Overall | -8.7 | 2.6 | 0.07 |
| Week 8/Hour 4 | -7.1 | 5.8 | 0.06 |
| /Hour 16 | -20.0 | 9.5 | 0.009 |
| /Hour 20 | -16.0 | 9.8 | 0.07 |
| Week 8/Overall | -5.6 | 5.5 | 0.10 |

It is clear from the above data that treatment with sibutramine was associated with elevations in blood pressure when compared to the blood pressure response in the placebo subjects.

It is interesting and important to note that there were statistically and clinically significant increases in mean arterial blood pressure in the sibutramine group during the hours 10:00 pm to 6:00 am for week 4 (-14 vs 4.0 mmHg; placebo vs sibutramine, $p<0.05$) and week 8 (-16.0 vs 8.0 mmHg, $p<0.05$).

Blood pressure was also measured with a sphygmomanometer and no significant differences were noted between the two groups. A repeated measures ANOVA did not reveal any statistically significant differences between the two groups for any of the manually-measured blood pressure parameters.

In general, heart rates were increased above baseline in both treatment groups at all times. Table 8.11.4.2.4 illustrates the time points for the significant or nearly significant treatment differences for the change in pulse rate from baseline.

TABLE 8.11.4.2.4

24-Hour Ambulatory Heart Rate Change from baseline (bpm)

| Time Period | Placebo | Sibutramine | p-value |
|---|---|---|---|
| Day 3/Hour 16 | 2.4 | 7.5 | 0.08 |
| /Hour 20 | -3.7 | 4.5 | 0.01 |
| Week 4/Hour 24 | -1.1 | 10.9 | 0.1 |
| Week 8 /Hour 1 | 4.1 | 23.0 | 0.02 |
| /Hour 3 | 3.4 | 25.8 | 0.02 |
| /Hour 4 | 5.7 | 16.9 | 0.006 |
| /Hour 5 | 5.7 | 22.9 | 0.003 |
| /Hour 12 | -2.0 | 10.7 | 0.07 |
| /Hour 24 | -3.4 | 12.7 | 0.004 |
| Overall | 3.5 | 15.1 | 0.01 |

Adverse events

The most commonly reported adverse events were headache (7 in sibutramine and 4 in placebo), infection (3 in sibutramine and 4 in placebo), constipation (4 in sibutramine and 2 in placebo), and anorexia (3 in sibutramine and 3 in placebo). There were no statistically significant differences between the two groups with respect to incidence of reported adverse events.

Clinical chemistries

There were no significant changes in hematology parameters noted during the study. There were also no clinically significant changes in serum chemistry values during the study. There were no significant changes in urinary VMA concentrations in the two groups. The treatments did not have any effect on thyroid function parameters.

Lipoprotein lipids

The changes in lipoprotein lipid levels were minor and similar in the two groups.

Plasma catecholamine levels

The plasma norepinephrine level increased in the placebo group (62.8 pg/ml) and in the sibutramine group (18.4 pg/ml). The numbers of measurements of epinephrine and dopamine were insufficient to make comparisons.

Electrocardiograms

In general, there were nonsignificant differences in ECG parameters, including heart rate, PVCs and PACs between the two groups.

Appetite and Mood assessment

The two groups did not differ with respect to components of appetite. No differences in compliance were observed (except week 8); the distribution of successful and unsuccessful dietary compliance across the treatment groups was almost identical. There were no clear differences between the two groups with respect to mood as assessed by the Modified Norris Assessment with the exception of alertness, excitement, and energy, which showed favorable trends in the sibutramine group.

## 8.11.5 SPONSOR'S CONCLUSIONS

"In general, few significant treatment differences were demonstrated in this small pilot study comparing the effect of sibutramine vs. placebo in a population of obese hypertensive patients whose hypertension was adequately controlled by available oral agents, although modest increases in heart rate and nocturnal blood pressure were apparent.

Sibutramine 20 mg daily appeared to be well tolerated and did not affect the frequency of adverse experiences. Laboratory values, vital signs, ECG measurements, and physical examination parameters appeared to be similar for the sibutramine and placebo groups."

## 8.11.6 MEDICAL OFFICER'S CONCLUSIONS

Although this study was conducted in a small number of hypertensive subjects it is a valuable

study because of the use of 24-hour ambulatory blood pressure monitoring, a technique that reduces measurement error and provides an integrated assessment of blood pressure.

This Reviewer does not agree with the Sponsor's statement that "**modest** increases in heart rate and nocturnal blood pressure were apparent." While manually-measured blood pressures were not statistically significantly different between the sibutramine and placebo groups, the 24-hour ambulatory blood pressure data indicated that the use of sibutramine significantly increased blood pressure and pulse. In particular, nocturnal blood pressure tended to be higher in the sibutramine group compared to the placebo group.

There were two disconcerting findings from this study. The first is the paradoxical increase in nocturnal blood pressure in the sibutramine-treated subjects. The second is the discrepancy between the results obtained by 24-hour ambulatory blood pressure monitoring with the results from the manually-measured blood pressures. Collectively, the results of this study suggests that 24-hour ambulatory blood pressure monitoring should be used in a larger group of hypertensive patients in which weight loss is a therapeutic goal.

**8.12 SB 2057**

**OBJECTIVE/RATIONALE**

**8.12.1** The objectives of this study included comparing the efficacy, safety, and tolerability of 10 mg QD of sibutramine to placebo in obese, hypertensive patients for 12 weeks. An additional objective was to assess the effect of sibutramine-induced weight loss on blood pressure.

**DESIGN**

**8.12.2** This study was a double-blind, parallel-group, placebo-controlled 12 week study of 113 patients. There was a 3-week washout period during which time patients received dietary advice. Subjects were randomized to 10 mg QD of sibutramine or placebo (taken in the morning) for 12 weeks and then followed-up for one month following cessation of therapy.

**PROTOCOL**

**POPULATION**

**8.12.3.1** Inclusion criteria included:

1. Male or female patients
2. Age
3. BMI of
4. Resting diastolic blood pressure within the range mmHg; during the screening phase blood pressure was measured in the supine and standing positions and 3 measurements were taken.

5. The use of antihypertensive medication was allowed. Subjects were allowed to take 2 antihypertensive agents if the dosage had been maintained for a minimum of 4 weeks prior to screening.

## ENDPOINTS

**8.12.3.2** Endpoints included change in body weight, waist and hip circumferences, diastolic and systolic blood pressure (measured 3 times while subjects were supine and standing) and heart rate. The change in Clinical Global Impression Scale, change in use of tobacco and alcohol, change in dietary compliance and hunger, satiety, appetite, craving and snacking scales were also assessed.

## STATISTICAL CONSIDERATIONS

**8.12.3.3** Differences between treatment groups were tested using repeated measures ANOVA, including factors for treatment group, center, the treatment group-by-center interaction, time and the time-by-treatment group interactions. The repeated measures ANOVA was conducted on four datasets:

1. Unbalanced set
2. Balanced set (missing values replaced by predicted values calculated from the model fitted to the available data.
3. LOCF for both between and within treatment group tests.
4. Completers; missing values were interpolated to ensure complete patient profiles.

Changes in diastolic blood pressure over the course of the study were analyzed in a similar manner to the change in body weight. The proportion of patients losing greater than 5% of baseline body weight at endpoint and over 12 weeks was compared between treatment groups using logistic regression with factors for treatment, center and the treatment group-by-center interaction. The study was powered to detect a 2.7 kg difference in bodyweight between the two groups. Differences in the proportion of patients reporting adverse events in each treatment group was analyzed using the Chi-square test. An intent-to-treat analysis was also performed for subjects who took at least one dose of study medication and had at least one post-baseline assessment.

## RESULTS

## POPULATIONS ENROLLED/ANALYZED

**8.12.4.1** Overall, 131 patients were screened for the study; four subjects withdrew during the washout period and 127 patients were randomized to treatment. Of these patients, 14 were given study medication in error (all from center 2), by the investigator during the washout period. These subjects were withdrawn from the study. Thus, 113 patients entered the double-blind phase of the study. During the double-blind phase, 7 subjects withdrew and thus 106 patients

completed the study. A total of 127 patients received at least one dose of study medication and were included in the intent-to-treat analyses of the principal efficacy measures. Of these, 14 patients who were recruited at center 2 failed to undergo a washout and were therefore excluded from the modified intent-to-treat analyses.

Table 8.12.4.1.1 provides the baseline demographic characteristics for all patients (excluding center 2).

| TABLE 8.12.4.1.1 | | |
|---|---|---|
| **Demographic variable** | **Sibutramine n=54** | **Placebo n=59** |
| Age (yrs) | 47.7 | 48.1 |
| Male | 18 | 20 |
| Female | 36 | 39 |
| Caucasian | 53 | 57 |
| Weight (kg)+ | 93.6 | 97.0 |
| BMI ($kg/m^2$) | 33.5 | 33.8 |

+ median values

The treatment groups were comparable for age, sex, and race. The placebo group had a higher median body weight at baseline; however, the BMIs were similar. Baseline blood pressure values were similar for the two groups.

All patients were hypertensive as required by the protocol; however, only 33% were taking anti-hypertensive drug therapy. Table 8.12.4.1.2 illustrates the anti-hypertensive medications taken by the patients in the two groups.

| TABLE 8.12.4.1.2 | | |
|---|---|---|
| **Anti-hypertensive agent** | **Placebo** | **Sibutramine** |
| ACE inhibitor | 9 | 6 |
| β-blockers | 7 | 6 |
| Calcium channel blocker | 7 | 4 |
| Diuretics | 9 | 8 |

## EFFICACY ENDPOINT OUTCOMES

Body weight

**8.12.4.2** The results of the analyses on the four datasets were, in general, similar. There was a statistically significant treatment group effect for the repeated measures ANOVA, as well as significant week and treatment group-by-week effects were also detected.

**Figure 8.12.4.2.1**

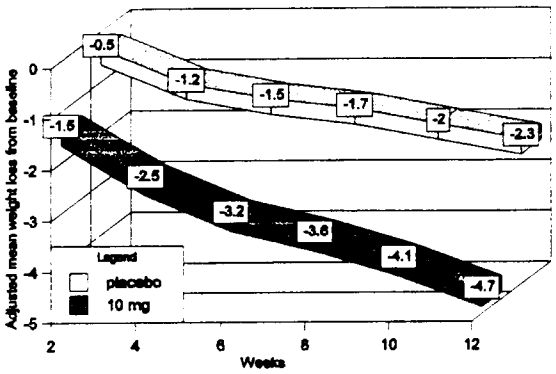
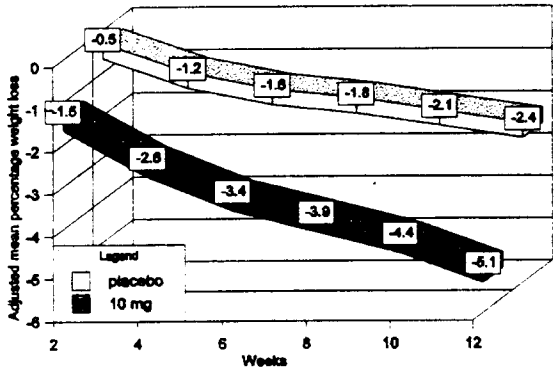



Figure 8.12.4.2.1 shows the adjusted (for center and treatment group-by-center interaction) mean change in body weight (kg) for the completers. The sibutramine group lost significantly more weight than the placebo group at weeks 2-8 ($p<0.001$) and weeks 10 and 12 ($p<0.01$).

Figure 8.12.4.2.2 illustrates the adjusted (for center and treatment-by-center interaction) mean percentage change from baseline in body weight for the completers.

**Figure 8.12.4.2.2**




At every time point the sibutramine group lost a significantly greater percentage of bodyweight compared to placebo ($p<0.001$).



The proportion of subjects losing greater than 5% of baseline body weight in the sibutramine group was significantly higher than the proportion in the placebo group (44 vs 17% respectively, $p=0.002$).

Waist circumference

Waist circumference was reduced by 4.0 cm in the sibutramine group and by 1.8 cm in the placebo group.

Compliance and appetite

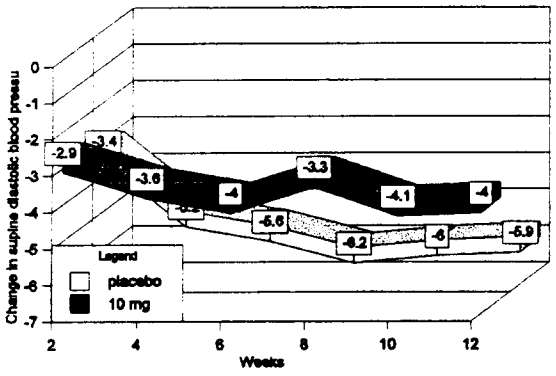
There were no statistically significant differences between the treatment groups in dietary compliance or in the hunger, appetite, satiety, snacking and craving visual analogue scales.

Blood pressure and pulse

For both treatment groups, diastolic and systolic blood pressures (supine and standing) were reduced; the differences between the groups, however, were not statistically significant.

Figure 8.12.4.2.3 provides the change from baseline in supine diastolic blood pressure for the completers.

**Figure 8.12.4.2.3**




It is interesting to note that although the sibutramine group lost significantly more weight during the study than the placebo group, the reductions in blood pressure were smaller in the sibutramine group compared to the reductions in the placebo group.

The change from baseline in supine pulse rate was -4.3 bpm in the placebo group and 2.4 bpm in the sibutramine group ($p<0.001$). The change from baseline in standing pulse rate was -5.8 bpm in the placebo group and -0.6 bpm in the sibutramine group ($p<0.01$).

**SAFETY OUTCOMES**

Adverse events

**8.12.4.3** There were no statistically significant differences between the groups with respect to the incidence of reported adverse events. The most common events in the COSTART categories

were Body as a Whole, Digestive, and Nervous System. The most common events (reported by > 5% of patients) were constipation (4 placebo and 6 sibutramine), dry mouth (2 placebo and 8 sibutramine), and nervousness (5 placebo and 1 sibutramine). Two subjects in the placebo group were withdrawn from the study: one because of distention of the abdomen and one because of fever. Two sibutramine subjects were also withdrawn from the study: one because of obsessive behavior and one because of nausea and constipation. There were no reported adverse events during the 1-month follow-up period.

Clinical chemistries

The platelet count increased from baseline in the sibutramine group (14.24 × $10^9$/l) and decreased in the placebo group (-0.46 × $10^9$/l) ($p<0.01$). The creatine concentration was reduced in the sibutramine group (-4.40 umol/l) and decreased in the placebo group (-0.86 umol/l) ($p=0.03$). These changes were not clinically significant.

Lipoprotein lipids

The total cholesterol level decreased by 0.40 mmol/l in the sibutramine group and decreased by 0.21 mmol/l in the placebo group ($p=0.04$).

Electrocardiograms

The results of the analysis of change in heart rate from the ECG were similar to the changes observed with the manually-measured pulse rates. The QT interval was reduced in the sibutramine group (-9.3 ms) and the placebo group (-2.4 ms), ($p=0.02$); these changes were not clinically meaningful.

**8.12.5 CONCLUSIONS**

In this study of obese hypertensive patients, 10 mg QD of sibutramine led to a statistically significantly greater degree of weight loss than did placebo (-4.7 vs -2.3 kg, $p<0.01$). However, despite a greater reduction in body weight in the sibutramine group, the placebo group had a greater reduction in diastolic blood pressure (supine and standing). In contrast to the effect of sibutramine on blood pressure, total cholesterol levels were favorably affected by drug treatment. There were no clinically significant changes in serum chemistries noted during the study (the LFTs are not reported).

**8.13. SB 3069**

**OBJECTIVE/RATIONALE**

**8.13.1** The primary objective of this open-label extension study of core trial SB2057 was to assess the long-term (6 months) efficacy, safety and tolerability of sibutramine in mild to

moderately obese, hypertensive subjects.

**DESIGN**

**8.13.2** This study was a 12-week multicenter, open-label extension trial following the 12- week core study SB 2057, in which hypertensive patients received placebo or 10 mg QD of sibutramine. All patients regardless of receiving active drug or placebo in the core study received 10 mg QD of sibutramine during this trial.

**PROTOCOL**

**POPULATION**

**8.13.3.1** Only those patients who completed SB 2057 were eligible for SB 3069. The inclusion criteria included:

1. Age _____
2. Male of female.
3. Subjects were allowed to take up to two anti-hypertensive agents.

Exclusion criteria included:

1. Diastolic blood pressure of greater than 125 mmHg.
2. Patients who had experienced a serious adverse event in study SB 2057.
3. Patients who violated the protocol of study SB 2057.

**ENDPOINTS**

**8.13.3.2** The primary endpoints were the change in body weight and diastolic blood pressure. The major assessments were conducted at weeks 16, 20, 24, and 28. Blood pressure was recorded as the mean of three measurements.

**STATISTICAL CONSIDERATIONS**

**8.13.3.3** The principle measure of efficacy was the change in body weight calculated on a last observation carried forward basis. The change from week 0 to week 24 for the group randomized to sibutramine in SB 2057 and the corresponding changes from week 12 to week 24 within each of the treatment groups from SB 2057 were reported with 95% confidence intervals. Changes in diastolic blood pressure over the course of the study were analyzed in a similar manner to body weight.

**RESULTS**

**POPULATIONS ENROLLED/ANALYZED**

**8.13.4.1** Overall, 103 patients (113 entered SB 2057) entered into the trial between 10/93 and 5/94. Of these, 100 patients completed the study to week 24. Table 8.13.4.1.1 illustrates the baseline demographic characteristics.

| TABLE 8.13.4.1.1 | | |
|---|---|---|
| **Variable** | **Previous treatment** | |
| | **Sibutramine, n=49** | **Placebo, n=54** |
| Age (yrs) | 48.3 | 47.6 |
| Male | 17 | 19 |
| Female | 32 | 35 |
| Caucasian | 49 | 53 |
| Weight (kg)❂ | 88.9 | 91.8 |
| BMI ($kg/m^2$) | 31.6 | 32.5 |

❂ median values

Table 8.13.4.1.2 provides the anti-hypertensive agents taken by the subjects in each baseline group. Fifty-four percent of the subjects were taking an anti-hypertensive agent.

| TABLE 8.13.4.1.2 | | |
|---|---|---|
| **Anti-hypertensive therapy class** | **Previous treatment group** | |
| | **Placebo** | **Sibutramine** |
| ACE-inhibitor | 9 | 5 |
| β-blocker | 7 | 7 |
| Calcium channel blocker | 7 | 4 |
| Diuretics | 2 | 3 |
| Thiazide | 6 | 4 |
| Clonidine | 1 | 0 |

The two groups were well matched for use of antihypertensive therapy at baseline.

## EFFICACY ENDPOINT OUTCOMES

### 8.13.4.2 Body weight

Table 8.13.4.2.1 illustrates the mean change in absolute body weight (kg) to endpoint - LOCF.

| TABLE 8.13.4.2.1 | | | | | |
|---|---|---|---|---|---|
| **Previous treatment** | **n** | **Change from week 12 (range)** | **95% CI** | **Change from week 0 (range)** | **95% CI** |
| Placebo | 54 | -3.4 | -4.2, -2.7 | -5.8 | -4.5, -7.1 |
| Sibutramine | 49 | -1.2 | -2.0, -0.5 | -5.7 | -7.2, -4.2 |

Of the 49 patients who previously received sibutramine, 16 gained weight (0.1-3.2 kg) but the majority lost weight; with 13 patients losing more than 3 kg of their week 12 body weight. Similar results were reported in the completers dataset.

Table 8.13.4.2.2 provides the mean percent change in body weight (kg) at endpoint - LOCF.

| TABLE 8.13.4.2.2 | | | | | |
|---|---|---|---|---|---|
| **Previous treatment** | **n** | **Change from week 12 (range)** | **95% CI** | **Change from week 0 (range)** | **95% CI** |
| Placebo | 54 | -3.7 | -4.5, -3.0 | -6.0 | -7.3, -4.7 |
| Sibutramine | 49 | -1.4 | -2.3, -0.6 | -6.1 | -7.6, -4.5 |

The results were essentially the same for the completers analysis and indicate that 24 weeks of treatment with sibutramine led to a statistically significant reduction in body weight.



**Figure 8.13.4.2.1**

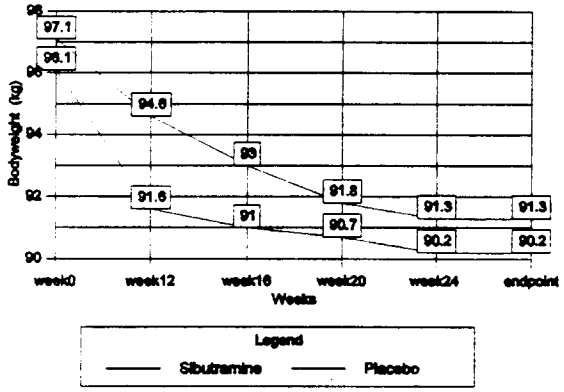



Figure 8.12.4.2.1 illustrates the absolute change in body weight for the sibutramine and placebo groups. It must be kept in mind that the placebo group received placebo from week 0 to week 12 at which time they began 10 mg QD of sibutramine.

Figure 8.13.4.2.1 illustrates that the greatest rate of weight loss (steepest slope of line) occurs during the first 12 weeks of drug treatment.

It is interesting to examine the proportion of patients who lost greater than 5% of week-0 and

week-12 body weight. These data are shown in table 8.13.4.2.3.

| TABLE 8.13.4.2.3 | | | | | |
|---|---|---|---|---|---|
| **Target** | **Change from** | **Previous tx** | **n** | **%** | **95% CI** |
| >5% of week0 weight | week 0 to endpoint | sibutramine | 49 | 59 | 45, 73 |
| | | placebo | 54 | 57 | 44, 71 |
| >5% of week12 weight | week 12 to endpoint | sibutramine | 49 | 8 | 0.5, 16 |
| | | placebo | 54 | 28 | 16, 40 |

These data suggest that the majority of the weight loss effect of the drug is present by week 12 of treatment.

Waist circumference

In the week 0 to endpoint analysis, the sibutramine group had a 5.1 cm reduction in waist circumference and the placebo group lost 5.0 cm from their waist circumference. These were both statistically significant within group changes.

Blood Pressure

The changes in diastolic blood pressure (DBP) in the completers dataset are shown in table 8.13.4.2.4.

| TABLE 8.13.4.2.4 | | |
|---|---|---|
| **Variable** | **Mean change (95% CI) by previous treatment** | |
| | **Placebo n=53** | **Sibutramine n=47** |
| Week 12 to week 24 | | |
| Supine DBP (mmHg) | -0.9 | -2.5 |
| Standing DBP (mmHg) | -0.2 | -3.6 |
| Week 0 to week 24 | | |
| Supine DBP (mmHg) | -7.4 | -6.1 |
| Standing DBP (mmHg) | -6.7 | -7.1 |

In the completers dataset, from week 0 to week 24, the reductions in diastolic blood pressure were similar for the placebo and sibutramine groups. The results for systolic blood pressure were similar.

It is interesting to note that, whereas there were statistically significant correlations between the reduction in body weight and the reduction in systolic and diastolic blood pressures in the sibutramine-treated subjects in the core study SB2057, these correlations were no longer significant when analyzed at endpoint in the extension study SB3069. The correlation coefficients for the change in body weight vs the change in blood pressure are depicted below in table 8.1.4.2.5.

| TABLE 8.13.4.2.5 Correlation between the Δ in body weight vs the Δ in blood pressure at endpoint | | | | |
|---|---|---|---|---|
| **Blood pressure** | | **Core study SB2057** | | **Extension study SB3069** |
| | | Sibutramine | Placebo | Sibutramine● |
| Supine | DBP | 0.36 p=0.007 | 0.39 p=0.002 | 0.19 p=0.2 |
| | SBP | 0.28 p=0.04 | 0.34 p=0.008 | 0.15 p=0.3 |
| Standing | DBP | 0.37 p=0.006 | 0.39 p=0.002 | 0.14 p=0.3 |
| | SBP | 0.27 p=0.05 | 0.32 p=0.01 | 0.20 p=0.2 |

● individuals randomized to sibutramine in the core study SB2057 and continued into SB3069

Pulse rate

The changes in pulse rate during the study are shown in table 8.13.4.2.6

| TABLE 8.13.4.2.6 | | |
|---|---|---|
| **Variable** | **Mean change (95% CI) by previous treatment** | |
| | **Placebo n=53** | **Sibutramine n=47** |
| Week 12 to week 24 | | |
| Supine pulse rate (bpm) | 6.7 | 2.1 |
| Standing pulse rate (bpm) | 5.5 | 1.6 |
| Week 0 to week 24 | | |
| Supine pulse rate (bpm) | 2.0 | 4.3 |
| Standing pulse rate (bpm) | -0.3 | 0.3 |

The results of the completers dataset analyses were similar to the above endpoint analyses and indicate that sibutramine treatment increases pulse rate.

## SAFETY OUTCOMES

**8.13.4.3** Adverse Events

As expected, the number of patients who reported an adverse event was greater in the sibutramine group from week 0 to week 24 (61%) compared to the sibutramine group from week 12 to week 24 (37%). Thirty-seven patients who received placebo during the core study and sibutramine from week 12 to week 24 reported an adverse event. The most common body systems by COSTART included Body as a Whole, Cardiovascular, and Nervous Systems. The individual complaints by group and week of drug ingestion are not compared statistically. Dry mouth and back pain were reported by more than 5% of patients (six patients in each case).

Seven potentially serious adverse events were reported; all of these patients completed the trial. Details of these events are shown in table 8.13.4.3.1

**TABLE 8.13.4.3.1**

| Number | Gender | Age | Duration | Event | Comment |
|---|---|---|---|---|---|
| 3 | F | 64 | 84 | LBBB on ECG | possible silent MI? |
| 22 | M | 47 | 148 | A Fib dx from ECG | RBBB also present, LAHB on screening ECG |
| 29 | M | 51 | 84 | Repolarization abnormality on ECG | Outcome of event unknown |
| 60 | F | 54 | 148 | Sciatica | had surgery and recovered |
| 65 | M | 38 | 5 | Lumbago | corrective surgery was performed |
| 93 | M | 63 | 44 | Pernicious anemia | treated with Vitamin $B_{12}$ |
| 116 | M | 61 | 79 | Syncope | medical hx of cerebral infarction, aortic aneurism, tension headaches |

Three patients were withdrawn from the study because of an adverse event. The details of these withdrawals are provided in table 8.13.4.3.2

**TABLE 8.13.4.3.2**

| Number | Gender | Age | Duration | Event | Comment |
|---|---|---|---|---|---|
| 33 | F | 34 | 1 | nausea | resolved when drug stopped |
| 38 | F | 37 | 112 | insomnia | resolved when drug stopped |
| 138 | M | 37 | 84 | gastric pain | resolved when drug stopped |

One serious post-study event was recorded. Patient # 138, a 37 year old male, suffered a myocardial infarction and died from ventricular fibrillation. The death occurred two weeks and one day after being withdrawn from the extension trial at week 24 because of stomach pains. He had a history of stenosis of the left anterior descending coronary artery treated with PTCA one year previously.

Clinical laboratory evaluation

The statistically significant changes in laboratory assessments after 24 weeks of treatment with sibutramine are shown in table 8.13.4.3.3

**TABLE 8.13.4.3.3**

| Variable | Number of patients | Mean change from baseline | 95% CI |
|---|---|---|---|
| Hemoglobin (mmol/L) | 47 | -0.13 | -0.23, -0.03 |
| Mean cell volume (fl) | 43 | 1.74 | 0.35, 3.14 |
| Platelets ($\times 10^9$/L)O | 47 | 9.00 | 2.50, 14.50 |
| Chloride (mmol/L) | 47 | -2.02 | -2.96, -1.08 |
| Creatine (umol/L)O | 47 | -3.00 | -6.00, -1.00 |
| Total protein (g/L) | 46 | -2.67 | -3.64, -1.70 |
| Albumin (g/L) | 46 | -1.09 | -1.90, -0.28 |
| AST (U/L)O | 46 | 6.50 | 4.50, 9.00 |

O Hodges-Lehmann estimate of median change

None of the above changes were clinically significant.

Lipoprotein Lipid Levels

A summary of the changes in lipid levels is provided in table 8.13.4.3.4

**TABLE 8.13.4.3.4**

| Lipid Level (mmol/L) | Mean change (95% CI) from baseline to endpoint by previous treatment | |
|---|---|---|
| | Placebo n=53 | Sibutramine n=47 |
| Total cholesterolO | -0.05 | -0.20 |
| LDL cholesterol | 0.02 | -0.07 |
| HDL cholesterol | 0.03 | 0.01 |

| TABLE 8.13.4.3.4 | | |
|---|---|---|
| Lipid Level (mmol/L) | Mean change (95% CI) from baseline to endpoint by previous treatment | |
| | Placebo n=53 | Sibutramine n=47 |
| Triglycerides✪ | 0.00 | -0.45 |
| VLDL | -0.03 | -0.17 |

✪ Hodges-Lehmann estimate of median change

There were statistically significant reductions in total cholesterol, triglycerides, and levels of VLDL in the group that received sibutramine for 24 weeks

Electrocardiograms.

Other than an increase in heart rate, there were no clinically significant changes in ECG parameters.

## 8.13.5 SPONSOR'S CONCLUSIONS

"The changes observed in this study support the conclusion of the core study. Continued therapy with sibutramine 10 mg induced further weight loss without increasing blood pressure and therefore did not adversely affect the management of hypertension in this patient population. Overall, the small increase in pulse rate was not considered to be clinically significant and sibutramine was well tolerated."

## 8.13.6 MEDICAL OFFICER'S CONCLUSIONS

The mean absolute weight loss (kg) from week 0 to week 24 in the sibutramine group was statistically significant: 5.7 kg; the 95% CI was -7.2, -4.2 kg with a range of
These findings indicate that 10 mg QD of sibutramine may produce significant weight loss in a subset of hypertensive patients with the maximum effects occurring during the first 12 weeks of therapy. In terms of blood pressure control, the group treated with sibutramine for 24 weeks had a 6.5 mmHg reduction in diastolic blood pressure. The direct correlation between sibutramine-induced weight loss and the reduction in blood pressure was evident at completion of the 12-week core study SB2057, but was absent in the extension study. These data underscore sibutramine's inability to consistently reduce both body weight and blood pressure. The increase in pulse rate of approximately 4 bpm may have been attenuated by the concomitant use of calcium channel and β-blockers.

In general, the adverse events reported were not serious and were consistent with those reported in the other trials. However, in this group of higher-risk individuals, by nature of their hypertension, four serious cardiovascular events were reported: three during the trial and one following the trial. These events were: 1) new LBBB; 2) atrial fibrillation; 3) a new

repolarization abnormality on ECG; and 4) a death from an acute myocardial infarction in a 37 year old male with a history of coronary artery disease. The patient suffered the infarction 15 days post-study. The enhanced sympathetic tone induced by sibutramine may represent a potential risk in obese individuals with cardiac disease.

*COMPARATIVE STUDIES*

**8.14 SB 2053**

**OBJECTIVE/RATIONALE**

**8.14.1** The principle objective of this study was to compare the efficacy and tolerability of 10 mg QD of sibutramine to 15 mg BID of dexfenfluramine in obese subjects.

**DESIGN**

**8.14.2** This study was a 12-week, multicenter, randomized, double-blind, parallel-group comparison of sibutramine with dexfenfluramine in 237 obese patients. There was a 1 to 2 week wash-out period followed by a 12-week double-blind treatment phase. There was also a 4-week follow-up phase following active treatment.

**PROTOCOL**

**POPULATION**

**8.14.3.1** Entry criteria for this study included patients aged _____years, male or female, and obese with a BMI $\geq$ 27 kg/m$^2$. Relevant exclusion criteria included patients with IDDM or insulin-requiring NIDDM, patients taking anorectic agents or antidepressants, antiserotoninergics, barbiturates, and neuroleptics.

**ENDPOINTS**

**8.14.3.2** The endpoints included changes in body weight, waist and hip circumferences, vital signs, serum chemistries, measures of appetite, and documentation of any adverse events.

**STATISTICAL CONSIDERATIONS**

**8.14.3.3** In the analyses of actual weight loss, the equivalence parameter was 2 kg (i.e. the treatments will be considered equivalent if the difference between the two groups in less than 2 kg). For percentage weight loss, the equivalence range was the arithmetic difference of 2.5%. Differences between treatment groups in the change from baseline in body weight was analyzed using repeated measures ANOVA including factors for treatment group, time, and the treatment group-by-time interaction.There were 4 datasets:

1. Unbalanced analysis-all available data with no account taken of missing values.
2. Balanced analysis-all available data with the addition that for the within group tests, the missing values are replaced by predicted values calculated from the model fitted to the data.
3. LOCF.
4. Completers-patients who complete the 12 week treatment phase.

For the secondary measures of efficacy, the results were presented as 95% confidence intervals for the difference between the two treatment groups. The overall percentages of patients reporting adverse events in each treatment group were compared using the 90% confidence interval based on the Chi-square test. The 95% confidence intervals for the difference based on two sample t-tests were used to assess the change to endpoint and week 12 for blood pressure and pulse.

## RESULTS

## POPULATIONS ENROLLED/ANALYZED

**8.14.4.1** Two-hundred thirty-seven patients were screened into the study at 38 centers. Eleven patients withdrew before the baseline visit; 226 patients were entered into the double-blind phase. One-hundred twelve subjects were randomized to sibutramine and 114 were randomized to dexfenfluramine. One-hundred two subjects completed the study in the sibutramine group and 95 completed in the dexfenfluramine group. There was a statistically significantly lower risk of withdrawal in the sibutramine group compared to the dexfenfluramine group (90% CI 0.28, 0.95). Table 8.14.4.1.1 provides the baseline characteristics for the two groups.

**TABLE 8.14.4.1.1**

| | **Sibutramine n=112** | **Dexfenfluramine n=114** |
|---|---|---|
| Age (yrs) | 38.9 | 38.8 |
| Gender | 101 female | 106 female |
| Race | 111 Caucasian | 111 Caucasian |
| Weight (kg) | 84 | 86 |
| BMI* (kg/m$^2$) | 33.3 | 33.7 |

Values in parentheses are ranges
* represent median values
* baseline BMI was 40.2 kg/m$^2$ for the sibutramine males and 34.2 kg/m$^2$ for the males in the dexfenfluramine group.

There were 9 subjects in the dexfenfluramine group and 4 subjects in the sibutramine group taking antihypertensive agents at baseline. Six of the dexfenfluramine and 2 of the sibutramine subjects were taking diuretics and antidiuretics. Fourteen sibutramine and 7 dexfenfluramine subjects were taking estrogens at baseline. Five dexfenfluramine and 1 sibutramine subject were

taking hypoglycemic agents. During the study, 11 sibutramine and 2 dexfenfluramine subjects started laxatives.

The withdrawal rates and reasons for withdrawal are summarized in table 8.13.4.1.2

| TABLE 8.13.4.1.2 | | |
|---|---|---|
| Reason for withdrawal | Sibutramine n=112 | Dexfenfluramine n=114 |
| Adverse events | 6 | 11 |
| Lack of efficacy+ | 2 | 3 |
| Withdrew consent | 2 | 4 |
| Unable to attend | 0 | 1 |

+The two patients in the sibutramine group that withdrew because of lack of efficacy lost -5.4 and -2.0 kg of weight at 74 and 39 days, respectively. The 3 subjects who withdrew in the dexfenfluramine group gained 1.5, 3.5, and 1.0 kg of weight at 47, 45, and 47 days, respectively.

## EFFICACY ENDPOINT OUTCOMES

Body weight

**8.13.4.2** Table 8.13.4.2.1 illustrates the actual change in body weight (kg) by treatment group for intent-to-treat patients included in the balanced dataset.

| TABLE 8.13.4.2.1 | | | | | |
|---|---|---|---|---|---|
| **Variable** | **Week** | **Treatment group** | | | |
| | | **Sibutramine** | | **Dexfenfluramine** | |
| Weight (kg) | | N | Mean | N | Mean |
| | Baseline | 112 | 89.1 | 112 | 88.5 |
| | 4 | 112 | -2.8 | 112 | -2.0 |
| | 8 | 112 | -4.0 | 112 | -2.9 |
| | 12 | 112 | -4.6 | 112 | -3.4 |
| | overall change | 112 | -3.8 | 112 | -2.8 |
| 90% CI for difference -1.6,-0.4◇ | | | | | |

◇Equivalence interval is -2kg, +2kg

The results of all the analyses comparing the amount of weight lost in the two groups were very similar. In general, it could not be concluded that one drug was more efficacious than the other.

The results of the percentage change in body weight were similar to the analysis of the change in absolute body weight: the sibutramine group lost approximately 4.3% of baseline body weight and the dexfenfluramine group lost approximately 3.2 %. These differences were not statistically significant.

In the completers dataset, 48% of the sibutramine subjects lost >5% of baseline body weight and 38% of the dexfenfluramine subjects met this goal.

Waist circumference

Waist circumference decreased by 4.3 cm in the sibutramine group and by 4.0 cm in the dexfenfluramine group.

Consummatory behavior

There were no statistically significant differences between the groups for the visual analogue scales. The reduction in the number of calories consumed and reductions in calories from carbohydrates, protein, fat, and alcohol were similar for the two groups.

**SAFETY OUTCOMES**



Adverse events

**8.13.3** Table 8.6.4.3.1 provides the number of patients in each group reporting the most common (reported by 5% of subjects) adverse event by COSTART system.

**TABLE 8.13.3.1**

| COSTART term | Sibutramine n=112 | Dexfenfluramine n=114 |
|---|---|---|
| Asthenia | 7 | 16 |
| Flu syndrome | 18 | 11 |
| Headache | 15 | 13 |
| Infection | 3 | 10 |
| Abdominal pain | 6 | 8 |
| Constipation | 18 | 4 |
| Diarrhea | 1 | 12 |
| Nausea | 6 | 7 |
| Dry mouth | 15 | 11 |

| TABLE 8.13.3.1 | | |
|---|---|---|
| **COSTART term** | **Sibutramine n=112** | **Dexfenfluramine n=114** |
| Insomnia | 6 | 9 |
| Pharyngitis | 6 | 6 |

Fourteen patients were withdrawn from the study due to an adverse event. Details of these events are provided in Table 8.13.3.2

| TABLE 8.13.3.2 | | | | | | |
|---|---|---|---|---|---|---|
| **Number** | **Sex** | **Age** | **Drug** | **Duration** | **Event** | **Comment** |
| 31 | F | 51 | Sib | 28 | severe migraine | resolved with acetylsalicylate |
| 34 | F | 48 | Sib | 77 | severe nausea and headache | remained six weeks post-withdrawal |
| 72 | F | 28 | Sib | 63 | moderate depression | recovered 1-week after withdrawal |
| 147 | F | 35 | Sib | 56 | headaches | resolved 1-day after withdrawal |
| 199 | F | 48 | Sib | 6 | urticaria | resolved 2-weeks after withdrawal |
| 231 | F | 27 | Sib | 49 | abdominal pain flushing | resolved 1-week after withdrawal |
| 13 | F | 38 | Dex | 33 | severe headaches | resolved 2-days after withdrawal |
| 27 | F | 27 | Dex | 26 | headaches, epigastric pain | resolved 1-day after withdrawal |
| 37 | F | 33 | Dex | 28 | palpitations, orthostatic hypotension | resolved 1-month after withdrawal |
| 62 | F | 29 | Dex | 35 | asthenia, diarrhea | ? |
| 75 | F | 24 | Dex | 16 | nausea, vomiting | ? |
| 94 | F | 40 | Dex | 6 | headache, nausea, vomiting | resolved 2-days after withdrawal |
| 139 | F | 22 | Dex | 22 | facial erythema | resolved 5-days after withdrawal |
| 186 | F | 33 | Dex | 7 | dizziness | resolved 1-day after withdrawal |

Clinical chemistries

There were no clinically significant changes in the serum chemistry values for either group.

Lipoprotein lipids

Total cholesterol decreased by -4.43% and -6.33% in the sibutramine and dexfenfluramine groups, respectively. The mean percent change from baseline in triglyceride levels were -13.99% and -8.55% for the sibutramine and dexfenfluramine groups, respectively. These differences were not statistically significant.

Vital signs

There were statistically significant differences in the changes in diastolic blood pressure and pulse rate between the two groups. Diastolic blood pressure increased by 1.9 mmHg in the sibutramine group and decreased by 1.5 mmHg in the dexfenfluramine group. The pulse rate increased in the sibutramine group 3.6 bpm and decreased by 0.9 bpm in the dexfenfluramine group.

Electrocardiograms

There were no significant changes in the ECG parameters in either group.

Post-treatment follow-up

Spontaneous reporting during the 4-week follow-up period did not reveal any evidence of withdrawal phenomena for either drug.

## 8.13.5 SPONSOR'S CONCLUSIONS

"Weight loss occurred with both treatments and this study demonstrated that sibutramine 10 mg given once-daily and dexfenfluramine 15 mg twice-daily were equivalent in terms of both actual and percentage weight loss in obese patients. Both drugs had similar safety profiles with the exception of statistically significant increases in mean pulse rate and standing diastolic blood pressure with sibutramine compared to dexfenfluramine."

## 8.13.6 MEDICAL OFFICER'S CONCLUSIONS

This Reviewer agrees with the Sponsor's conclusions.

In this 12-week study of obese, primarily Caucasian women, 10 mg QD of sibutramine produced an equivalent amount of weight loss as 15 mg BID of dexfenfluramine. Despite similar degrees of weight loss, sibutramine produced elevations in mean pulse rate and standing diastolic blood

pressure. The reported adverse events were consistent with the known pharmacological effects of the two drugs.

**8.14 SB 1052**

**OBJECTIVE/RATIONALE**

**8.14.1** The objective of this 12-week study was to compare the efficacy and the tolerability of 10 mg QD of sibutramine with 30 mg QD of dexfenfluramine and placebo in moderately obese subjects.

**DESIGN**

**8.14.2** This was a 12-week multicenter, double-blind, randomized, placebo-controlled, parallel-group study of 75 obese subjects: 25 subjects in each treatment arm. There was a 1- week washout phase during which time the subjects received general written and verbal dietary instructions. The 12-week active-treatment phase was followed by a 4-week follow-up visit. Because of reports of depression associated with abrupt withdrawal of dexfenfluramine, a protocol amendment dated September 4, 1992 stated that during week 11 the dexfenfluramine subjects take only 15 mg QD of the drug.

**PROTOCOL**

**POPULATION**

**8.14.3.1** Entry criteria for the study included obesity:BMI kg/m$^2$, male and female subjects aged years and in a good state of health. Subjects controlled on a hypertensive agent(s) during the preceding 6 months were allowed to participate in the study.

**ENDPOINTS**

**8.14.3.2** The primary endpoint was the change in body weight from baseline; weight was measured at screening, and baseline, and every week during the 12-week active phase, as well as at week 16. Waist and hip circumferences were measured at baseline and again at week 12. The CGI depression scale, alcohol usage, tobacco usage, laboratory assessments, patient self-assessments of hunger and appetite, and vital signs were examined at regular intervals during the study.

**STATISTICAL CONSIDERATIONS**

**8.14.3.3** As with previous studies, the original protocol does not detail the statistical procedures. The study was planned to detect a difference between treatment groups in mean change in body weight to endpoint of 3.8 kg. For the primary efficacy parameter, change in weight from

baseline, repeated measures ANOVA was performed with several interaction terms. Fisher's protected LSD method was used to compare differences between groups when an overall effect was confirmed. The repeated measures ANOVA was performed on 4 datasets:
1). Unbalanced analysis
2). Balanced analysis
3). LOCF
4). Completers

Heterogeneity of variances was documented for the weight loss data and therefore compensation was made when conducting multiple comparisons. In addition, an imbalance was found in baseline body weight between the groups. The correlation between the change in weight from baseline to endpoint and the average of the baseline and endpoint values was examined and found to be -0.08, p=0.56. Thus, a simple change model was therefore considered to be appropriate. The Mantel-Haenszel Test was used to compare the proportion of patients with a reduction of greater than 5% of baseline weight at endpoint and at week 12.

## RESULTS

## POPULATIONS ENROLLED/ANALYZED

**8.14.4.1** Overall, 77 patients were screened for entry into the study. Two patients withdrew during the washout phase, thus, 75 patients entered the double-blind phase: 24 to placebo, 25 to dexfenfluramine, and 26 to sibutramine. A total of 52 patients completed the 12 week study: 17/24 placebo, 16/25 dexfenfluramine, 19/26 sibutramine. Table 8.14.4.1.1 illustrates the reason for withdrawal from the study by treatment group.

**TABLE 8.14.4.1.1**

| Reason for withdrawal | Placebo | Dexfenfluramine | Sibutramine |
|---|---|---|---|
| | n=24 | n=25 | n=26 |
| Adverse event | 2 | 2 | 0 |
| Lack of efficacy | 1 | 0 | 0 |
| Lost to follow-up | 3 | 5 | 4 |
| Protocol violation• | 0 | 2 | 1 |
| Withdrew consent | 1 | 0 | 2 |
| Total withdrawn | 7 (29%) | 9 (36%) | 7 (27%) |

There were no statistically significant differences between the groups for withdrawal rates
• did not attend follow-up visits

There were a number of protocol violations, compliance violations and discrepancies in timing

of assessments in all groups. They appeared to be balanced among treatment groups and it is unlikely that they affected the study results.

Two patients (placebo group) did not provide a post-baseline assessment of body weight and were not included in any of the efficacy analyses. Sixty-nine patients provided an assessment of body weight after week 2 and were included in the primary measures efficacy analyses. Four patients were withdrawn during the follow-up period, but provided an assessment of body weight at week 12.

Table 8.14.4.1.2 provides the baseline demographic variables for the 3 groups.

**TABLE 8.14.4.1.2**

| Variable | Placebo | Dexfenfluramine | Sibutramine |
|---|---|---|---|
| | n=24 | n=25 | n=26 |
| Age (yrs) | 41.4 | 42.1 | 41.9 |
| Sex (% female) | 88% | 80% | 73% |
| Race (% Caucasian) | 100% | 100% | 100% |
| Weight (kg)✚ | 84.5 | 87.6 | 87.4 |
| BMI (kg/m$^2$) | 32.5 | 33.7 | 33.6 |

✚ median values

The men in the dexfenfluramine group had a higher baseline BMI: 35.3 kg/m$^2$; compared to placebo subjects: 31.3 kg/m$^2$; and sibutramine-treated individuals: 34.6 kg/m$^2$.

## EFFICACY ENDPOINT OUTCOMES

### Body weight

**8.14.4.2** It should be noted that for the completers dataset there was no statistically significant week-by-treatment group interaction. The results of the unbalanced dataset analysis for actual weight loss at each time point during the study for the 3 groups are shown in Table 8.14.4.2.1

**TABLE 8.14.4.2.1**

| Week | Group | n | Adjusted mean change (kg) |
|---|---|---|---|
| 2 | Pl | 21 | -0.7 |
| | Dex | 23 | -1.8** |
| | Sib | 24 | -2.0** |

| TABLE 8.14.4.2.1 | | | |
|---|---|---|---|
| **Week** | **Group** | **n** | **Adjusted mean change (kg)** |
| 4 | Pl | 22 | -1.1 |
| | Dex | 23 | -3.0** |
| | Sib | 24 | -2.8** |
| 6 | Pl | 20 | -1.0 |
| | Dex | 20 | -4.0*** |
| | Sib | 20 | -3.7*** |
| 8 | Pl | 18 | -1.4 |
| | Dex | 22 | -3.8** |
| | Sib | 22 | -4.0** |
| 10 | Pl | 17 | -2.1 |
| | Dex | 19 | -3.7 |
| | Sib | 21 | -4.8** |
| 12 | Pl | 15 | -2.9 |
| | Dex | 18 | -4.1 |
| | Sib | 20 | -5.2 |

** $0.05 \leq p < 0.01$ *** $0.001 \leq p < 0.01$ compared to placebo
Pl=placebo, Dex=dexfenfluramine, Sib=sibutramine

The results of the analysis on the balanced dataset was similar to the unbalanced dataset analysis.

**Figure 8.14.4.2.1**

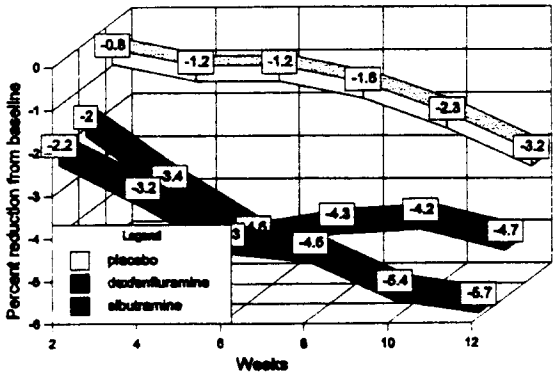



Figure 8.14.4.2.1 illustrates the adjusted mean change in percentage weight loss from baseline.

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There were no statistically significant differences in weight loss between patients who received sibutramine and those who received dexfenfluramine. The sibutramine group had a statistically significantly greater percentage weight loss than placebo patients at all weeks except week 12. The adjusted mean percentage weight loss at endpoint was 4.8% for the sibutramine group, 4.5% for the patients who received dexfenfluramine, and 2.4% for placebo patients; these differences were not statistically significant.

There were no statistically significant differences among the three groups with respect to the proportion of patients losing greater than 5% of baseline body weight (completers dataset at week 12: 40%, 41%, and 55% for the placebo, dexfenfluramine, and sibutramine groups, respectively).

Waist circumference

In an endpoint analysis, the reduction in waist circumferences were 4.0, 4.6, and 2.5 cm in the sibutramine, dexfenfluramine, and placebo groups, respectively.

Consummatory behavior

There were no statistically significant differences among the treatment groups for the changes to endpoint in the hunger, appetite, and eating visual analogue scales. There were no differences among the groups with respect to changes in dietary compliance.

## SAFETY OUTCOMES

Adverse events

**8.14.4.3** There were no statistically significant differences in the proportions of patients in each group reporting an adverse event. However, the dexfenfluramine group reported significantly more adverse events in the digestive system (diarrhea) compared to the sibutramine or placebo groups. Reports in Body as a Whole (infections) and Nervous System (dry mouth) were significantly greater in the dexfenfluramine and sibutramine groups than in the placebo group. There did not appear to be any significant differences among the groups in the percentage of patients reporting severe adverse events.

Table 8.14.4.3.1 provides the details of the patients who withdrew from the study.

**TABLE 8.14.4.3.1**

| Number | Sex | Age | Drug | Duration | Event | Comment |
|---|---|---|---|---|---|---|
| 59 | F | 44 | Pl | 77 | stroke | recovered |
| 16119 | M | 43 | Dex | 42 | renal calculus | recovered |

| TABLE 8.14.4.3.1 | | | | | | |
|---|---|---|---|---|---|---|
| **Number** | **Sex** | **Age** | **Drug** | **Duration** | **Event** | **Comment** |
| 57 | F | 58 | Pl | 42 | blackout, amnesia | recovered |
| 30 | F | 20 | Dex | 77 | hot flashes, dizziness | recovered |
| 38— | F | 24 | Sib | 36 | daughter ingested 8 capsules | recovered without event |

Serum chemistries

The only statistically significant change in a serum chemistry value was a mean increase of 14.1 U/l in creatinine kinase in the sibutramine group and a mean decrease of 20.4 U/l in the dexfenfluramine group. These changes were not clinically significant.

Lipoprotein lipids

There were no statistically significant differences in the changes in lipid levels among the groups.

Vital signs and electrocardiograms

There were no statistically significant differences among the three groups with respect to blood pressure, heart rate, or ECG parameters.

Clinical Global Impression

There were no significant group changes in depressive symptoms as measured by the Clinical Global Impression scale at week 12. The week 16 values are not reported.

## 8.10.5 SPONSOR'S CONCLUSIONS

"This study clearly demonstrated significantly greater weight loss during treatment with sibutramine and dexfenfluramine compared to placebo with no statistically significant differences between the two active treatments. Safety and tolerability of the two treatments were acceptable."

## 8.10.6 MEDICAL OFFICER'S CONCLUSIONS

This Reviewer concurs with the Sponsor's conclusions.

This 12-week study comparing the efficacy of 10 mg QD of sibutramine with 30 mg QD of dexfenfluramine and placebo reported that the active-drug treatments were comparable and both produced significantly more weight loss than placebo. There were no significant changes in serum chemistry values or vital signs during the study. There were no significant adverse events reported with the use of sibutramine, and in general, the drug was well tolerated.



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## 9. OVERVIEW OF EFFICACY

Table 9.1 Results of the pivotal studies conducted in patients with uncomplicated obesity.

| TABLE 9.1 | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Study | Dose | Duration | % completed | Δ % Wt | 5% responders | ΔSBP | ΔDBP | ΔPulse |
| **PIVOTAL - UNCOMPLICATED OBESITY STUDIES** | | | | | | | | |
| 852 | Pl | 6 months | 55 | -1.3 | 20% | 1.7 | 0.8 | 0.6 |
| | 1mg | | 65 | -2.8 | 25% | 1.2 | 0.3 | 0.3 |
| | 5mg | | 70 | -3.7 | 37% | 2.5 | 2.1 | 3.3 |
| | 10mg | | 63 | -5.8 | 60% | 4.2 | 2.8 | 6.0 |
| | 15mg | | 60 | -7.4 | 67% | 3.4 | 2.7 | 6.1 |
| | 20mg | | 58 | -8.6 | 72% | 5.0 | 4.0 | 7.0 |
| | 30mg | | 55 | -9.4 | 77% | 4.1 | 3.3 | 5.3 |
| 1047 | Pl | 12 months | 50 | -1.9 | 29% | -0.9 | 0.1 | -0.2 |
| | 10mg | | 51 | -5.5 | 56% | -0.3 | -0.2 | 0.4 |
| | 15mg | | 59 | -7.2 | 65% | 2.7 | 2.0 | 1.5 |
| 852X• open label study | 15mg | 12 months | 56 | Na | Na | 6.2 | 1.8 | 4.7 |
| | 20mg | | | Na | Na | 6.6 | 3.1 | 8.4 |
| | 25mg | | | Na | Na | 6.8 | 2.2 | 8.0 |
| | 30mg | | | Na | Na | 6.1 | 1.3 | 7.8 |
| | 15mg | 18 months | 38 | Na | Na | 5.9 | 5.3 | 8.4 |
| | 20mg | | | Na | Na | 10.8 | 8.4 | 7.8 |
| | 25mg | | | Na | Na | 7.2 | 2.7 | 7.6 |
| | 30mg | | | Na | Na | 7.8 | 3.0 | 6.9 |

SBP=systolic blood pressure and DBP=diastolic blood pressure in mm Hg; pulse in beats per minute.
• doses represent modal dose = dose most frequently taken
Na=not available

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Table 9.2 Results of short-term studies in patients with uncomplicated obesity.

| TABLE 9.2 | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Study | Dose | Duration | % completed | Δ % Wt | 5% responder | Δ SBP | Δ DBP | Δ Pulse |
| **NON-PIVOTAL - UNCOMPLICATED OBESITY STUDIES** | | | | | | | | |
| 1042 | Pl | 12 weeks | 47 | -4.0 | 42% | -7.4 | -2.8 | -1.5 |
| | 1mg | | 38 | -4.3 | 44% | -3.0 | -1.0 | 1.7 |
| | 10mg | | 48 | -7.7 | 74% | -3.8 | -0.9 | 0.0 |
| | 20mg | | 61 | -9.1 | 83% | -7.6 | -4.4 | -1.1 |
| 850 | Pl | 8 weeks | 95 | -1.3 | Na | 5.8 | 0.8 | -1.4 |
| | 5mg | | 95 | -3.0 | Na | 5.2 | 3.4 | 2.7 |
| | 20mg | | 88 | -5.0 | Na | 4.2 | 3.7 | 3.6 |
| 851 | Pl | 12 weeks | 69 | - | Na | 3.2 | -1.4 | -7.5 |
| | 10mg | | 94 | - | Na | -2.4 | 0.9 | 1.3 |
| 1043 | Pl | 12 weeks | 80 | -1.7 | 19% | -1.2 | 0.5 | -2.0 |
| | 5mg | | 84 | -3.1 | 23% | 3.4 | 0.5 | 1.2 |
| | 10mg | | 83 | -6.1 | 53% | 0.9 | 2.2 | 3.8 |
| | 15mg | | 84 | -5.8 | 58% | 0.6 | 0.4 | 4.2 |

Na = not available

The efficacy evaluation for obesity drugs as outlined in the Guidance for the Clinical Evaluation of Weight-Control Drugs include several potential parameters: (1) The mean weight loss in the drug-treated subjects must be statistically significantly different from the mean weight loss in subjects receiving placebo; (2) the drug-treated patients must have a mean percent weight loss from baseline that is 5% greater than the mean percent loss of the placebo group; (3) alternatively, it may be shown that the proportion of subjects who reach and maintain a loss of at least 5% of initial body weight is greater in subjects on drug compared to those receiving placebo.

The data from the two pivotal studies indicate that: (1) doses of 15-30 mg QD of sibutramine are associated with a mean percent weight loss from baseline that is at least 5% greater than that achieved with placebo and is statistically significantly different; and (2) a greater percentage of patients taking 5-30 mg QD of sibutramine achieve a loss of at least 5% of initial body weight when compared to placebo subjects. Thus, the submitted data support the "efficacy" of sibutramine, as defined in the Guidance.

Table 9.3 Results from studies of obese patients with non-insulin dependent diabetes mellitus and hypertension.

| TABLE 9.3 | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Study | Dose | Duration | % completed | Δ % Wt | Δ SBP | Δ DBP | Δ Pulse | Δ HbA1c | Δ fasting G | Δ G area | Δ I area |
| — | | | **NON-INSULIN DEPENDENT DIABETES MELLITUS STUDIES** | | | | | | | | |
| 853 | Pl | 12 weeks | 100 | -1.0 | 5.3 | 1.7 | -1.7 | 0.1 % | 22 mg/dl | Na | Na |
| | 20mg | | 75 | -3.0 | 4.8 | -0.6 | 6.2 | 0.1 % | 9 mg/dl | Na | Na |
| 3051 | Pl | 12 weeks | 91 | -0.3 | -0.1 | 2.1 | 0.5 | 0.1 % | 14 mg/dl | Na | Na |
| | 15mg | | 91 | -2.8 | -0.3 | 3.1 | 7.3 | -0.3 % | -5 mg/dl | Na | Na |
| 3068x | 15mg | 6 months | 70 | -3.8 | 0.8 | 3.6 | 10 | 0.0 % | -3.6 mg/dl | -0.15 | 8.5 |
| | | | **HYPERTENSION STUDIES** | | | | | | | | |
| 855● ◆ | Pl | 8 weeks | 100 | - | -1.8 | -7.7 | 3.5 | NA | NA | NA | NA |
| | 20mg | | 90 | - | 8.9 | 3.7 | 15.1 | NA | NA | NA | NA |
| 2057 | Pl | 12 weeks | 93 | -2.4 | -5.6 | -5.4 | -4.3 | NA | NA | NA | NA |
| | 10mg | | 95 | -5.1 | -5.5 | -3.7 | 2.4 | NA | NA | NA | NA |
| 3069x | 10mg | 6 months | 87 | -6.1 | -6.1 | -2.5 | 4.3 | NA | NA | NA | NA |

ΔG area = the change in incremental fasting glucose levels in mol/l.min; ΔI area = the change in incremental fasting insulin levels in mmol/l.min.

● Subjects were told to maintain body weight

◆ Blood pressure and pulse data are the week 8 overall values from 24-hour ambulatory monitoring.

Na = not available; NA = not applicable

The short-term use of 15 and 20 mg QD of sibutramine in non-insulin dependent diabetic patients was associated with clinically insignificant amounts of weight loss. The use of 15 mg QD of sibutramine for 6 months (3 months placeo-controlled and 3 months open-label) resulted in a mean percent reduction in body weight of 3.8% compared to an approximate 7 to 8% reduction in weight in obese nondiabetic patients taking 15 mg QD in the pivotal studies.

Obese, hypertensive subjects who recieved 10 mg QD of sibutramine for up to 6 montsh lost a similar percentage of weight (-5.1%) as obese, normotensive subjects taking the same dose in the pivotal studies.

Thus, whereas the data support sibutramine's efficacy in obese, hypertensive patients, there is no evidence that sibutramine is an effective weight-loss agent in non-insulin dependent diabetic patients.

Table 9.4 Results of studies comparing sibutramine with dexfenfluramine.

| TABLE 9.4 | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Study | Dose | Duration | % completed | Δ % Wt | 5% responders | Δ SBP | Δ DBP | Δ Pulse |
| **ACTIVE CONTROL STUDIES** | | | | | | | | |
| 2053 | 10mg Sibutramine | 12 weeks | 91 | -4.3 | 48% | 0.7 | 2.3 | 3.4 |
| | 30mg Dex | | 83 | -3.2 | 38% | 0.7 | -2.0 | -1.3 |
| 1052 | 10mg Sibutramine | 12 weeks | 73 | -5.7 | 55% | 1.0 | 1.2 | 1.9 |
| | 30mg Dex | | 64 | -4.7 | 41% | -0.7 | -1.7 | -4.2 |
| | Pl | | 71 | -3.2 | 40% | -4.9 | -5.1 | -3.6 |

The data from the two comparative studies indicate that 10 mg QD of sibutramine and 30 mg QD of dexfenfluramine are equivalent in terms of weight loss efficacy.



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## 10. OVERVIEW OF SAFETY

### 10.1.1 Exposure and Demographics

Table 10.1.1 illustrates the number of unique subjects exposed to sibutramine as of September 30, 1994.

| TABLE 10.1.1 | | | |
|---|---|---|---|
| **Study population** | **US studies** | **European studies** | **Total** |
| All obese patients | 1051 | 991 | 2042 |
| Depressed patients | 831 | 194 | 1025 |
| Volunteers | 170 | 260 | 430 |
| All subjects | 2052 | 1445 | 3497 |

Exposure denominators

A patient who received sibutramine in either of the European placebo-controlled studies SB 2057 and SB 3051, who also received sibutramine in the open extension studies SB 3069 and SB 3068, respectively, was counted once, since there was little or no interruption of therapy between studies. In addition, a patient who received sibutramine in either of the US placebo-controlled studies BPI 852 or BPI 806, who also received sibutramine in the open extension study BPI 852X or BPI 806X, was counted twice (as two sibutramine exposures), due to an interruption in therapy between the studies (at least 6 weeks for BPI 852; and approximately 10 days for BPI 806). This Reviewer does not believe that these subjects should be counted as two unique exposures.

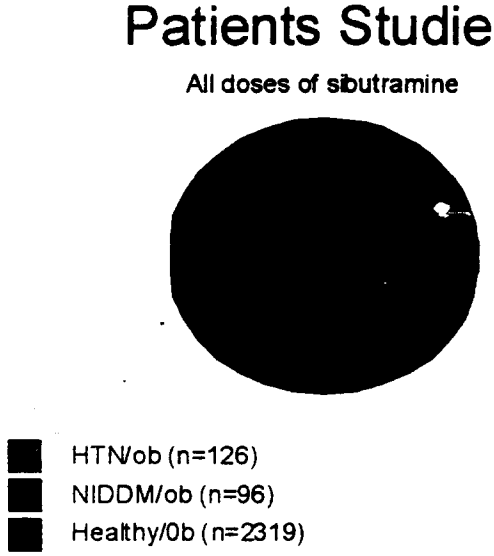
Table 10.1.2 provides the number of subjects exposed to sibutramine as of September 30, 1994 by mean daily dose.

| TABLE 10.1.2 | | | | | | | |
|---|---|---|---|---|---|---|---|
| **Study population** | **< 5 mg** | **5-9 mg** | **10-14 mg** | **15-19 mg** | **20-29 mg** | **≥ 30 mg** | **All doses** |
| Obese | 198 | 249 | 628 | 617 | 520 | 107 | 2319 |
| Obese/HTN | 0 | 0 | 116 | 0 | 10 | 0 | 126 |
| Obese/NIDDM | 0 | 0 | 1 | 84 | 11 | 0 | 96 |
| All obese | 198 | 249 | 745 | 701 | 541 | 107 | 2541 |
| Depressed | 22 | 307 | 460 | 404 | 12 | 3 | 1208 |

| TABLE 10.1.2 | | | | | | | |
|---|---|---|---|---|---|---|---|
| **Study population** | **< 5 mg** | **5-9 mg** | **10-14 mg** | **15-19 mg** | **20-29 mg** | **≥ 30 mg** | **All doses** |
| Volunteers | 15 | 35 | 16 | 122 | 201 | 68 | 457 |
| All subjects | 235 | 591 | 1221 | 1227 | 754 | 178 | 4206 |

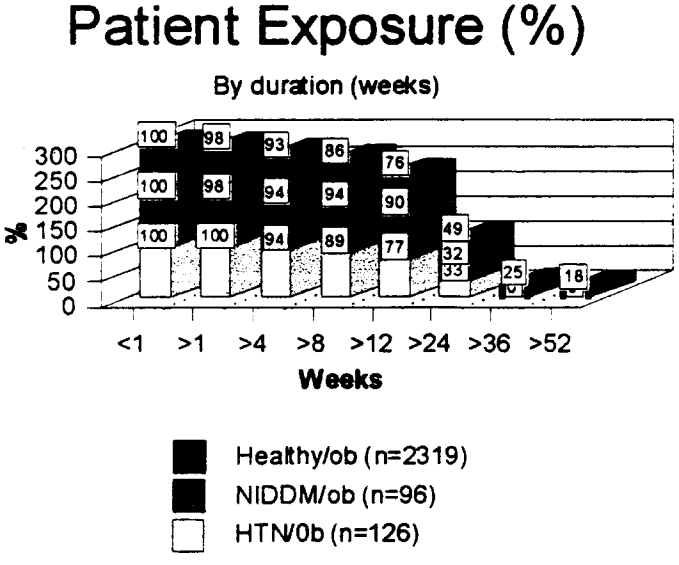
The below figure illustrates the percentage of subjects studied by patient population.

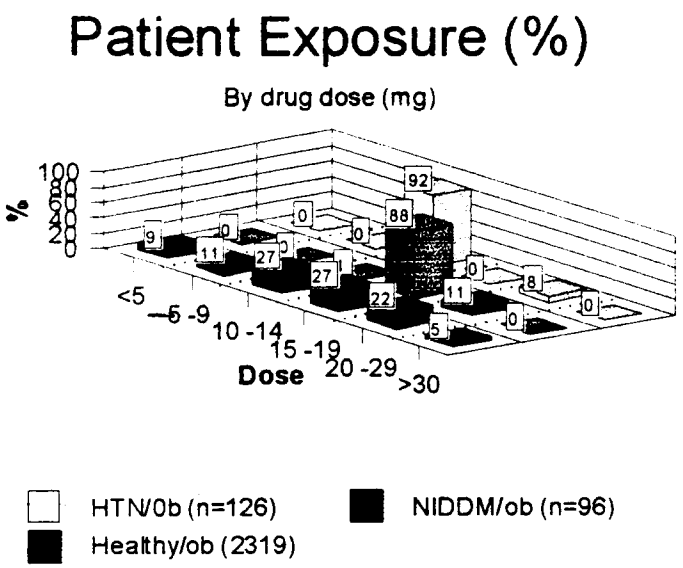







The below figures illustrate the percentage of healthy, hypertensive, and diabetic obese patients exposed to sibutramine by duration and dosage, respectively.



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The above data illustrate that the majority of the healthy obese subjects studied were taking 10-20 mg QD of sibutramine for an average of less than 24 weeks. In the obese hypertensive patients, over 90% of the subjects studied were taking 10-15 mg QD of sibutramine with an average exposure time of approximately 4-6 weeks. In the obese NIDDM patients, the vast majority were taking 15-20 mg of sibutramine, with an average exposure time of approximately 6 weeks.

Baseline demographics

The majority (80%) of the obese subjects studied were between the ages of_____, years, approximately 80% were female, and roughly 87% were Caucasian and 10% African-American. Only 1% of the subjects were over the age of 65 years. In general, the subjects in the hypertension and NIDDM studies were older and there were more males compared to the subjects in the healthy obese studies. The mean BMI of the sibutramine subjects was 33.8 $kg/m^2$. The majority of the subjects had an upper body distribution of fat as indicated by a mean waist to hip ratio of 1.0 and 0.8 for the men and women, respectively.

Premature discontinuations

In the placebo-controlled studies of all obese subjects, 10.2% of the sibutramine subjects and 8.4% of the placebo subjects withdrew because of an adverse event. Of the obese, hypertensive subjects 4.2% of the sibutramine subjects and 2.7% of the placebo subjects withdrew due to an adverse event. And of the obese diabetic subjects, 6.8% of the sibutramine subjects and 4.0% of the placebo subjects withdrew because of an adverse event.

Dose reductions due to adverse events

The majority of patients with dose reductions were from BPI 852. In this study, if a patient experienced either an intolerable adverse event, or had two mean supine pulse rates greater than 100 beats per minute, or a systolic blood pressure greater than 160 mmHg or a diastolic pressure greater than 95 mmHg, the patient's dose was reduced. Overall, 65 of 899 (7.2%) sibutramine-treated patients had their dose permanently reduced due to intolerable adverse events.

Table 10.1.7 provides the number of subjects at each dose who had a permanent dose reduction.

**TABLE 10.1.7**

| | **Placebo n=148** | **1mg n=149** | **5mg n=151** | **10mg n=150** | **15mg n=152** | **20mg n=146** | **30mg n=151** |
|---|---|---|---|---|---|---|---|
| Adverse event | 3 | 7 | 4 | 10 | 6 | 15 | 23 |
| Blood pressure | 5 | 1 | 1 | 4 | 6 | 5 | 13 |
| Pulse rate | 1 | 1 | 2 | 0 | 4 | 11 | 4 |
| Other | 0 | 1 | 6 | 3 | 4 | 1 | 3 |
| Unknown | 0 | 0 | 1 | 1 | 0 | 1 | 1 |
| Total # | 9 | 10 | 14 | 18 | 20 | 33 | 44 |
| **Percentage** | **6%** | **7%** | **9%** | **12%** | **13%** | **23%** | **29%** |

Clearly, more subjects in the 20 and 30 mg groups had permanent dose reductions because of an adverse event and there were significantly more dose reductions due to an increase in blood pressure in the 30 mg group.

The adverse events associated with permanent dose reductions included asthenia, headache, chest pain, hypertension, palpitations, tachycardia, anorexia, nausea, agitation, anxiety, dizziness, dry mouth, hyperkinesia, insomnia, nervousness, tremor, rash, and dyspnea. Of note,

**10.2**

### 10.2.1 Significant/Potentially Significant Adverse Events

The majority of the adverse event data are from studies in obese patients with an occasional reference to subjects from depression studies.

Cardiovascular adverse events

Table 10.2.1 illustrates the cardiovascular events that occurred more frequently in the sibutramine-treated patients compared to the placebo subjects.

| TABLE 10.2.1 | | |
|---|---|---|
| **Adverse event** | **Sibutramine** | **Placebo** |
| Tachycardia | 2.8% | 0.5% |
| Palpitations | 3.1% | 1.2% |
| Hypertension | 2.1% | 0.8% |
| Vasodilatation | 2.6% | 0.8% |

These events were also among those that most frequently led to premature termination of treatment in sibutramine-treated patients.

Of concern are the potential effects of sibutramine on cardiac conduction (i.e. arrhythmias). Sibutramine's inhibition of the reuptake of norepinephrine and resultant increase in sympathetic tone provide the pharmacological basis for this concern. The Knoll medical monitor determined that 31 last on-treatment ECGs from 2473 patients had clinically significant changes from their respective baseline ECGs. Twenty-eight of the 31 abnormalities were from subjects taking sibutramine and 3 were from placebo patients. The ratio of subjects taking sibutramine to those on placebo was 3.0, whereas, the ratio of clinically significant ECG changes in the sibutramine to placebo group was 9.0. The majority of these abnormalities were arrhythmias. A consultant cardiologist felt that 5 of the 28 ECGs represented clinically significant changes. These changes included frequent ventricular ectopic beats, atrial fibrillation, left bundle branch block, and T-wave changes. Although the precise number of subjects who had sibutramine-induced ECG abnormalities is difficult to determine with great precision, the drugs effect on pulse and blood pressure raise concern if the drug is taken by a large number of obese subjects, many of whom have occult coronary artery disease.

Dyspnea

In placebo-controlled studies involving obese and depressed patients, 29 sibutramine-treated patients (1.1%) reported dyspnea compared to one placebo-treated patient. One patient (#6015 from BPI 852X), a 54 year old Caucasian female was withdrawn from the study because of scleroderma and Raynaud's phenomenon. She had taken 20 mg QD of sibutramine for 24 weeks in BPI 852 and 15 mg QD for 14 weeks and then 20 mg QD for 14 weeks in BPI 852X. The scleroderma was diagnosed 10 weeks prior to her withdrawal. She experienced dyspnea 5 months prior to the diagnosis of scleroderma and felt to be secondary to pulmonary hypertension. A review of 22 case report forms from patients who complained of dyspnea revealed that 21 patients had spontaneous recovery of their shortness of breath. One subject was evaluated in an emergency room for her complaint of dyspnea. A complete cardiopulmonary

work-up was negative. This patient was eventually withdrawn from the study; her dyspnea resolved after she stopped the study medication. Of note, the majority of the cases of dyspnea occurred in subjects enrolled in depression studies.

An association between anorexic agents and primary pulmonary hypertension (PPH) was reported decades ago and the recently reported findings from the International Primary Pulmonary Hypertension Study confirm that the risk of developing primary pulmonary hypertension (PPH) is increased in individuals taking anorexigens for more than 3 months. It is not unreasonable to consider sibutramine as an anorexigen and as such, the risk for PPH may be increased with prolonged intake. This issue should be considered in the labeling if the NDA is approved.

CNS adverse events

Several CNS adverse events were recorded with a higher frequency in the sibutramine group compared to the placebo group. These included dry mouth, sweatiness, insomnia, and dizziness. In general, these symptoms were mild and not life-threatening. Three obese subjects (0.2%) treated with sibutramine in placebo-controlled studies reported seizure activity. One subject was diagnosed with a brain tumor, one subject had a history of epilepsy, and the third subject experienced a seizure-like event out of the hospital and a confirmed seizure while in the hospital. the relationship to the study medication (20 mg ) was judged as possible. There were two reported cerebrovascular accidents and one report of a suspected subarachnoid hemorrhage. All subjects were female and taking 15 mg QD of sibutramine. The first subject had no history of hypertension and the event was recorded as possibly related to the study medication. The second subject was 52 years old and had a history of hypertension treated with medication. She received 15 weeks of drug treatment at the time of her stroke. Of note, her systolic blood pressure had increased 10 mmHg from baseline during the study without a change in the dose of her antihypertensive medication The third subject had a long history of hypertension controlled with amlodipine and atenolol. She did not have an increase in her blood pressure during the study and eventually completed the study on 15 mg QD of drug.

Acute interstitial nephritis

A 67 year old Caucasian female took 10 mg QD of sibutramine for 6 months in BPI 852 and then entered the open extension (BPI 852X) at daily doses of 15 mg for 4 weeks, increasing up to 20 mg for 4 weeks, 25 mg for 10 weeks, and 30 mg for 18 weeks. At the time of the event, the patient had been on 15 mg for approximately 2 weeks. She was withdrawn from the study because of increasing BUN and creatinine levels. A diagnosis of acute interstitial nephritis, possibly drug related was made on renal biopsy. The patient was treated with corticosteroids and underwent dialysis. Follow-up renal function evaluation showed complete recovery. The event was recorded as a probable drug-related event.

Thrombocytopenia

Four subjects (2 in depression studies) experienced thrombocytopenia during or shortly after discontinuation from a sibutramine study. A 61 year old female with depression took 5 mg of sibutramine for 2 weeks followed by 10 mg for 1 week and was found to have a platelet count of on routine laboratory examination. Her platelet count returned to normal within 3 weeks of the event. The event was recorded as probably related to sibutramine. In another depression study, a patient had an initial platelet count of , which decreased to after 12 days of treatment with 10 mg of sibutramine. The platelet count was 10 days after treatment was discontinued. No follow-up was available. A 39 year old male patient developed mild thrombocytopenia , 10 days after stopping sibutramine 10 mg. The patient did not return for 15 weeks at which time the platelet count had normalized The event was recorded as possibly related to the study drug. And the fourth subject experienced mild thrombocytopenia at the end of a 14-day treatment period with 20 mg of the drug. The platelet count returned to normal within 2 days of stopping the drug.

Ecchymosis and disorders of hemostasis

Serotonin is involved in platelet aggregation and in the regulation of blood vessel constriction and dilatation. Sibutramine inhibits the reuptake of serotonin and therefore it would not be unusual to find an increase in the incidence of ecchymosis or bruising with the use of this drug. Abnormal hemostasis has been reported with other drugs that inhibit the reuptake of serotonin such as fluoxetine and paroxetine. Treatment-emergent ecchymosis was reported in 1.2% of sibutramine-treated patients and in 0.2% of placebo patients. In seven of the 14 cases in placebo-controlled studies in obese patients, bruising occurred spontaneously and all the patients were females taking NSAIDs or aspirin. There was no associated decrease in platelet count. There was an excess of adverse events suggestive of abnormalities of hemostasis in patients treated with sibutramine in placebo-controlled studies compared to placebo subjects. These events were coded under the COSTART terms hemorrhage vaginal, GI, gum, rectal, eye, subarachnoid, hematuria, hemoptysis, ecchymosis, epistaxis, petechia, menorrhagia, and metrorrhagia.

Paresthesia/peripheral neuropathy

Paresthesia was reported by 52 sibutramine-treated patients (2.0%) compared to 7 placebo patients (0.7%). Tenosynovitis was reported by 23 sibutramine-treated patients (1.3%) and 2 placebo patients (0.3%). Many subjects had their symptoms categorized as carpal tunnel syndrome, however, review of these reports by the Sponsor indicated that in several cases the events may have represented a paresthesia. A 63 year old Caucasian male who received sibutramine 15 mg QD for one year developed paresthesias of the toes. He was subsequently diagnosed with early neuropathy on the basis of sensory deficits.

Pain and related adverse events

Pain events occurred more frequently in patients treated with sibutramine than with placebo. The

excess of treatment-emergent events was accounted for by back pain, pain in the thighs, legs or feet, generalized aches and pains, pains in the teeth and jaw, dysmenorrhea and abdominal pain. Many subjects reported headache. It is possible that sibutramine heightens the awareness of such events due to it effect on the autonomic nervous system. Headaches may be related to sibutramine's effects on cranial blood vessel reactivity, and dysmenorrhea due to effects on uterine muscle and blood vessels, both secondary to the inhibition of serotonin reuptake. The abdominal pain was frequently associated with either constipation or diarrhea, nausea or vomiting, indigestion, eructation or flatulence.

Infection and flu syndrome

Infection, and the possibly related adverse events such as laryngitis, pharyngitis, rhinitis, sinusitis, ear disease and flu syndrome, were more frequently reported treatment-emergent events in sibutramine-treated obese patients than in placebo-treated patients. Approximately 90% of the infections reported by sibutramine-treated patients were upper respiratory tract infections, including cold and cold symptoms. Sibutramine, like other SSRIs, appears to be associated with a "flu syndrome" and symptoms which could be described as flu-like (backache, myalgia, arthralgia, and headache).

Impotence and urinary retention

Impotence and urinary retention were observed primarily in the sibutramine-treated depressed patient population. In placebo-controlled studies of depressed patients, impotence was observed in 1.7% of sibutramine-treated patients and in 0.3% of the placebo patients. Urinary retention was observed in 1.1% of the sibutramine-treated patients and in no placebo subjects. In comparison, in sibutramine-treated obese patients the incidence of impotence and urinary retention were 0.2% and 0.1%, respectively for the active-drug group and no reports of either-symptom in the placebo subjects. The decreased reporting of impotence in the obesity studies may reflect the preponderance of female patients in these studies. Impotence and urinary retention have been reported with other serotonin and norepinephrine reuptake inhibitors, such as venlafaxine.

**10.2.2 Deaths**

There were 2 deaths by suicide in depression studies. There was one death in the obesity studies. This 37 year old Caucasian male had a history of coronary artery disease and hypertension and suffered a myocardial infarction 15 days after completing treatment with 10 mg QD of sibutramine for 12 weeks. The subject's completion ECG did not differ from his baseline tracing.

**10.2.3 Overdose Exposure**

An overdose exposure occurred in a 2 year old daughter of a study participant. This girl ingested up to eight 10 mg capsules of sibutramine. The child was observed in the hospital and did not

experience any complications. Telephone follow-up 5 weeks after the event confirmed that the child did not have any permanent sequela.

A 30 year-old male patient in a depression study attempted suicide by taking an overdose of his study medication along with alcohol. He ingested approximately 100 mg of sibutramine. The patient recovered without serious sequela. No laboratory or ECG abnormalities were noted.

## 10.3 Other Safety Findings

### 10.3.1 Adverse events

Adverse events occurring during the active-treatment period, within 6 days of discontinuing the study medication, or present at baseline but worsening during the course of the study were considered to be treatment-emergent.

Adverse drug incidence tables

The percentage of **all** obese patients reporting adverse events in placebo-controlled studies with an incidence of > 1% in the sibutramine group and the difference compared to placebo was statistically significant or near significant are shown in table 10.1.7

| TABLE 10.3.1 | | |
|---|---|---|
| **COSTART body system** | **Placebo n=605** | **OSibutramine n=1766** |
| Infection | 12.7 | 22.8 |
| Abdominal pain | 3.3 | 4.8 |
| Vasodilatation | 0.8 | 2.6 |
| Tachycardia | 0.3 | 2.5 |
| Anorexia | 4.3 | 14.1 |
| Constipation | 6.1 | 11.4 |
| Appetite increase | 2.8 | 9.3 |
| Nausea | 3.0 | 5.9 |
| Tenosynovitis | 0.3 | 1.3 |
| Joint disorder | 0.3 | 1.1 |
| Dry mouth | 4.8 | 18.2 |
| Insomnia | 4.6 | 10.8 |
| Dizziness | 3.6 | 7.3 |

| TABLE 10.3.1 | | |
|---|---|---|
| **COSTART body system** | **Placebo n=605** | **OSibutramine n=1766** |
| Paresthesia | 0.7 | 2.1 |
| Dyspnea | 0.0 | 1.0 |
| Rhinitis | 8.9 | 11.2 |
| Sweat | 0.7 | 2.5 |
| Taste perversions | 1.0 | 2.4 |
| Ear disorders | 0.5 | 2.0 |
| Dysmenorrhea | 1.0 | 3.5 |

O all doses combined

Adverse events that appeared to be dose-related include vasodilation, tachycardia, palpitations, anorexia, nausea, dry mouth, taste perversion, and possibly dyspnea.

Although no statistical analyses were provided by the Sponsor, the following tables provide the adverse events (% of subjects) that occurred in ≥ 2% of the obese hypertensive and diabetic populations and were numerical greater than the percentage in the placebo patients.

| TABLE 10.3.2 OBESE HYPERTENSIVE PATIENTS | | |
|---|---|---|
| **COSTART term** | **Sibutramine n=72** | **Placebo n=75** |
| Chills | 2.8 | 0.0 |
| Headache | 11.1 | 6.7 |
| Neck pain | 2.8 | 0.0 |
| Tachycardia | 2.8 | 0.0 |
| Constipation | 13.9 | 9.3 |
| Nausea | 6.9 | 2.7 |
| Dry mouth | 16.7 | 2.7 |
| Insomnia | 5.6 | 0.0 |
| Increased sweating | 5.6 | 2.7 |
| Urinary tract infection | 2.8 | 0.0 |

| TABLE 10.3.3 OBESE DIABETIC PATIENTS | | |
|---|---|---|
| **COSTART term** | **Sibutramine n=59** | **Placebo n=50** |
| Infection | 16.9 | 2.0 |
| Malaise | 3.4 | 2.0 |
| Abdominal pain | 8.5 | 4.0 |
| Constipation | 27.1 | 26.0 |
| Dyspepsia | 8.5 | 4.0 |
| Nausea | 10.2 | 4.0 |
| Rectal disorder | 3.4 | 0.0 |
| Arthralgia | 10.2 | 8.0 |
| Joint disease | 3.4 | 2.0 |
| Dry mouth | 18.6 | 10.0 |
| Nervousness | 3.4 | 2.0 |
| Bronchitis | 3.4 | 0.0 |
| Pharyngitis | 18.6 | 12.0 |
| Sinusitis | 3.4 | 0.0 |
| Nail disorder | 3.4 | 0.0 |
| Increased sweating | 11.9 | 4.0 |
| Dysuria | 3.4 | 0.0 |
| Urinary tract infection | 5.1 | 2.0 |
| Urinary frequency | 3.4 | 0.0 |

It is of interest to note that the incidence of infections is dramatically higher in the obese diabetic patients compared to the controls. The Sponsor states that the majority of the infections were classified as upper respiratory infections.

Time to onset of first report of an adverse event

Most adverse events in the obese population occurred either during the first 4 weeks of treatment, or occurred with a relatively even distribution throughout the treatment period. Dry mouth, anorexia, and insomnia were reported at a higher incidence in the first week, but the number of new reports decreased thereafter. Anxiety appeared to have occurred more frequently as the duration of treatment increased.

Duration of adverse events

Adverse events with a short duration (within 7 days) included nausea, dysmenorrhea, dizziness, palpitations, and abdominal pain. Adverse events with a longer duration (at least 15 days) included constipation, paresthesia, anxiety, sweating, anorexia, increased appetite, dry mouth, and taste perversion. It is important to known how many subjects dropped out of the study due to an adverse event early in the study, as this could affect the pattern of occurrence of adverse events.

Adverse event by total daily dose at the time of the event

The events that appeared to be dose-related included palpitations, tachycardia, vasodilatation, anorexia, nausea, dry mouth, taste perversion, insomnia, and nervousness.

Post-treatment adverse events

The most frequently reported post-treatment adverse event was headache. This adverse event was reported by 3.2% of sibutramine subjects compared to 0.3% of the placebo subjects.

Withdrawals due to an adverse event

In the placebo-controlled studies of obese patients, 9.9% of the sibutramine subjects and 8.4% of the placebo subjects were withdrawn due to an adverse event. More nervous system and cardiovascular system events led to withdrawals from sibutramine treatment compared to treatment with placebo. Table 10.3.4 illustrates the percentage of obese patients withdrawn from placebo-controlled studies due to adverse events with a sibutramine-withdrawal rate ≥ 0.5% and greater than the placebo-withdrawal rate.

**TABLE 10.3.4**

| COSTART term | Placebo n=605 | Sibutramine n=1766 |
|---|---|---|
| Hypertension | 0.3% | 1.0% |
| Insomnia | 0.3% | 0.8% |
| Depression | 0.5% | 0.7% |
| Dizziness | 0.3% | 0.6% |

### 10.3.2 Laboratory findings

Laboratory data are presented in 3 formats. First, the mean percentage change from baseline is presented for each dosage group as well as for all dosage groups combined. Second, shift tables

indicate the number of patients who had normal baseline values and shifted into the high or low ranges based on the normal ranges for that particular study and laboratory. And third, the absolute number and percentage of laboratory values considered clinically significant (neuropharmacology guidelines) are presented.

Hematology

Table 10.3.2.1 illustrates the mean percent change from baseline to the last observation in healthy obese subjects in placebo-controlled studies.

**TABLE 10.3.2.1**

| | **Placebo** | **Sibutramine** |
|---|---|---|
| Hemoglobin | -0.4 (386) | -0.2 (1427 |
| Hematocrit | -0.1 (386) | 0.7 (1427) |
| RBC | 0.7 (223) | -0.7 (535) |
| WBC | 0.9 (386) | -2.0 (1426) |
| Neutrophils | 1.1 (373) | -0.3 (1409) |
| Lymphocytes | 2.5 (386) | 3.5 (1426) |
| Monocytes | 6.3 (373) | 7.4 (1408) |
| Eosinophils | 17.1 (373) | 22.3 (1407) |
| Basophils | 9.9 (368) | 9.4 (1402) |
| Platelets | -1.7 (386) | 1.9 (1425) |

values in parentheses represent the number of patients

There was a greater percentage of sibutramine patients who had normal baseline WBCs with high on-treatment values compared to placebo-treated subjects (5.6% vs 3.5%, respectively). The Sponsor states that the majority of these high on-treatment values in the sibutramine group were isolated events and the last on-treatment value returned to within the normal range. Similarly, a larger percentage of sibutramine-treated patients with normal platelet counts at baseline had shifts to high on-treatment values compared to placebo (3.8% vs 1.6%, respectively). No patient had a platelet count above 700,000/mm$^3$.

Serum chemistry

Electrolytes

Table 10.3.2.2 illustrates the mean percentage change in electrolytes in uncomplicated obese patients in placebo-controlled studies.

| TABLE 10.3.2.2 | | |
|---|---|---|
| **Parameter** | **Sibutramine** | **Placebo** |
| Sodium | -0.2 (390) | -0.2 (1444) |
| Chloride | -0.4 (389) | -0.6 (1443) |
| Potassium | 0.8 (391) | -0.3 (1441) |
| Phosphate | 2.4 (163) | 0.1 (896) |
| Calcium | -0.1 (391) | -0.5 (1443) |

values in parentheses represent the number of patients

There were 2.3% of the placebo group and 5.0% of the sibutramine-treated group that had normal baseline calcium levels with and on-treatment low value.

Uric acid

There was a possible dose-related effect of sibutramine on serum uric acid levels. The mean change from baseline to last recorded observation for healthy obese patients in placebo-controlled studies was 0.023% for the placebo group and -8.298% for the 30 mg sibutramine group. It is unlikely that these reductions in serum uric acid are clinically relevant.

Glucose

In placebo-controlled studies, the mean percentage change from baseline in plasma glucose was -1.1% (n=1443) in the sibutramine-treated group and 0.2 (391) in the placebo-treated group. There were no clinically significant differences between the sibutramine and placebo groups with respect to the percentage of patients who had clinically significant values (<50 mg/dl or >180 mg/dl). In a population of uncomplicated obese subjects, sibutramine did not appear to adversely affect glucose concentrations. The values presented by the Sponsor were a combination of fasting and non-fasting values.

Albumin and total protein

There were no clinically significant changes in albumin or total protein in sibutramine-treated patients.

Creatine kinase and creatine kinase MB

The mean percentage increase from baseline in creatine kinase in uncomplicated obese patients was 11.5% for the sibutramine-treated group and 2.9% for the placebo group. In addition, 3.9% of sibutramine-treated patients had values outside the upper limit of normal compared to 2.5% of

the placebo-treated subjects. None of the uncomplicated obese patients had clinically significant values while receiving treatment. The mean percentage change from baseline in CKMB values were similar for the sibutramine and placebo groups (-3.9% and -3.1%, respectively). The percentage of patients with shifts outside the normal range was also similar in the two groups. These changes do not appear to be clinically significant.

BUN and creatinine

The mean percentage change in BUN in the uncomplicated obese subjects was 1.3% for the sibutramine-treated group and 1.2% for the placebo-treated subjects. For creatinine, the mean percentage changes were 0.1% and -0.8% for the sibutramine and placebo subjects, respectively. For BUN and creatinine, the number of subjects with values that shifted outside of the normal range were similar in the sibutramine and placebo groups. Clinically significant values were seen in 0.4% or less of the sibutramine and placebo subjects.

Urinalysis

Six percent and 3% of sibutramine-treated patients had clinically significant changes in values for ketone and hemoglobin, respectively, compared with 3% and 0% in the placebo subjects. In addition, 4.3% of sibutramine-treated individuals and 2.2% of placebo subjects had clinically significant changes in values for protein in the urine.

Liver function tests (ALT, AST, GGT, Alk Phos, LDH, and bilirubin)

Abnormal liver function tests were reported as adverse events in 1.2% of sibutramine-treated patients in placebo-controlled obesity studies, compared to 0.5% in placebo subjects. In placebo-controlled depression studies, 0.9% of sibutramine-treated subjects had abnormal LFT's compared with 0.6% of placebo subjects.

Table 10.3.2.3 provides the mean percentage change from baseline in liver function tests in uncomplicated obese patients in placebo-controlled studies.

**TABLE 10.3.2.3**

| Parameter | Placebo | Sibutramine |
|---|---|---|
| Bilirubin | 15.9 (391) | 10.4 (1442) |
| ALT | 11.5 (390) | 9.4 (1445) |
| AST | 6.3 (389) | 11.2 (1445) |
| GGT | 0.8 (227) | -1.4 (546) |
| Alk Phos | -0.7 (391) | 1.5 (1442) |

| TABLE 10.3.2.3 | | |
|---|---|---|
| **Parameter** | **Placebo** | **Sibutramine** |
| LDH | -0.9 (377) | -1.0 (1424) |

values in parentheses represent the number of patients

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The only liver function test that was increased significantly when compared to the placebo group was AST (11.2% vs 6.3%, sibutramine vs placebo).

Table 10.3.2.4 illustrates the percentage of uncomplicated obese patients in placebo-controlled studies with an on-treatment value for liver function tests that exceeded the upper limit of normal.

| TABLE 10.3.2.3 | | |
|---|---|---|
| **Parameter** | **Placebo** | **Sibutramine** |
| Bilirubin | 1.6 (386) | 2.3 (1421) |
| ALT | 9.2 (349) | 12.7 (1280) |
| AST | 3.5 (367) | 6.0 (1370) |
| GGT | 3.8 (212) | 2.7 (518) |
| Alk Phos | 2.4 (379) | 3.8 (1383) |
| LDH | 4.8 (354) | 5.2 (1378) |

values in parentheses represent the number of patients

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The percentage of sibutramine-treated patients with clinically significant changes in laboratory values was < 0.5%. The data do not rule out the possibility of a drug-related increase in bilirubin, ALT, and in particular, AST.

Table 10.3.2.3[a] details the information associated with patient withdrawal from obesity and depression clinical studies because of an abnormal LFT value.

| TABLE 10.3.2.3[a] | | | | | | |
|---|---|---|---|---|---|---|
| **Indication** | **Sex** | **Age** | **Dose** | **Duration** | **Event** | **Comment** |
| Obesity | M | 47 | 10mg | 14 d | raised Alk Phos and GGT | raised at baseline and increased during trial |
| Depression | M | 28 | 10mg | 6 d | raised LDH, AST, and ALT | evidence of heavy ETOH use |
| Depression | M | 33 | 10mg | 5 d | elevated biliburin | screening was _ which increased to |

| TABLE 10.3.2.3[a] | | | | | | |
|---|---|---|---|---|---|---|
| **Indication** | **Sex** | **Age** | **Dose** | **Duration** | **Event** | **Comment** |
| Obesity | ? | ? | 15mg | 163 d | raised GGT at baseline | further increases in GGT, AST, and ALT |
| Depression | ? | ? | 10mg | 100 d | raised AST and ALT | also taking tetracycline |
| Obesity | F | 58 | 15mg | 207 | raised ALT and GGT | returned to normal 10 weeks post-treatment |
| Obesity | M | 34 | 20-10mg | 121 d | raised AST, ALT, and LDH | returned to normal 30 days post-treatment |
| Depression | F | 44 | 10-20mg | 42 d | raised Alk Phos, AST, and ALT | outcome ? |
| Depression | F | 53 | 10-20mg | 27 d | raised Alk Phos, AST, and ALT | resolved within 1 month |

Thyroid function tests

There were no clinically significant changes from baseline in the values for the thyroid function tests in the sibutramine-treated subjects when compared to the control subjects.

Plasma lipoprotein lipids

The lipoprotein lipid data represent a combination of fasting and non-fasting samples; therefore, the accuracy of the measurements, particularly high density lipoprotein lipids and triglycerides are questionable.

Table 10.3.2.4 provides the mean percentage change from baseline to endpoint in plasma lipid levels in uncomplicated obese patients in placebo-controlled studies.

| TABLE 10.3.2.4 | | |
|---|---|---|
| **Parameter** | **Placebo** | **Sibutramine** |
| Total cholesterol | -1.7 (360) | -3.4 (1297) |
| Triglyceride | 0.2 (360) | -8.9 (1296) |
| LDL | -1.0 (121) | -4.2 (729) |
| HDL | -0.2 (133) | 3.1 (749) |

values in parentheses represent the number of patients

Vital signs

Table 10.3.2.5 provides the criteria for clinically significant (FDA Neuropharmacology guidelines) and borderline clinically significant (Sponsor's guidelines) abnormal vital signs. In order to be identified as clinically significantly abnormal, an on-drug value needed to meet the criterion value, and also represent a change of at least the magnitude noted in the change relative to baseline column. Baseline measurements were defined as those nearest in time prior to the first dose of study medication. Mean changes from baseline were calculated for subjects with baseline data and at least one on-therapy value.

**TABLE 10.3.2.5**

**Criteria for Clinically Significant Abnormal Vital Signs**

| Variable | Criterion Value | Change relative to Baseline |
|---|---|---|
| Systolic BP (mmHg) | ≥ 180 | Increase of ≥ 20 |
| | ≤ 90 | Decrease of ≥ 20 |
| Diastolic BP (mmHg) | ≥ 105 | Increase of ≥ 15 |
| | ≤ 50 | Decrease of ≥ 15 |
| Heart rate (beats/min) | ≥ 120 | Increase of ≥ 15 |
| | ≤ 50 | Decrease of ≥ 15 |
| **Criteria for Borderline Clinically Significant Abnormal Vital Signs** | | |
| Systolic BP (mmHg) | ≥ 140 | Increase of ≥ 10 |
| | ≤ 100 | Decrease of ≥ 10 |
| Diastolic BP (mmHg) | ≥ 90 | Increase of ≥10 |
| | ≤ 60 | Decrease of ≥ 10 |
| Heart rate (beats/min) | ≥ 100 | Increase of ≥ 10 |
| | ≤ 60 | Decrease of ≥ 10 |

Blood pressure: Mean change from baseline.

Table 10.3.2.6 illustrates the mean change from baseline in systolic and diastolic blood pressure (mmHg) in uncomplicated obese patients in placebo-controlled studies by dose.

**TABLE 10.3.2.6**

| Measurement | Placebo | < 5mg | 5-9 mg | 10-14 mg | 15-19 mg | 20-29 mg | ≥ 30 mg | All doses |
|---|---|---|---|---|---|---|---|---|
| Resting SBP | -0.7 | 0.1 | 2.0* | 1.0 | 2.7* | 1.7* | 4.0* | 1.7* |

| TABLE 10.3.2.6 | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **Measurement** | **Placebo** | **< 5mg** | **5-9 mg** | **10-14 mg** | **15-19 mg** | **20-29 mg** | **≥ 30 mg** | **All doses** |
| Standing SBP | 0.9 | 1.2 | 1.1 | 3.1 | 3.3 | 3.5 | 1.2 | 2.3 |
| Resting DBP | -0.6 | -0.1 | 1.5* | 1.4* | 1.8* | 2.2* | 3.1* | 1.5* |
| Standing DBP | 0.5 | -1.3 | 0.6 | 1.7 | 4.0* | 2.6 | 2.3 | 1.7 |

* $p \leq 0.05$ compared to placebo

These data affirm that doses of 5 mg and higher are associated with elevations in blood pressure. It should be kept in mind that doses of 5 mg and above are associated with reductions in bodyweight, thus an increase in blood pressure is clearly an undesirable drug effect.

Following cessation of therapy (4 and 6 weeks) in the 6 and 12 month studies mean changes from baseline in systolic and diastolic blood pressure were elevated compared to baseline but were trending down.

Clinically significant and borderline clinically significant changes

Table 10.3.2.7 provides the percentage of patients with uncomplicated obesity in placebo-controlled studies with clinically significant and borderline clinically significant changes in systolic and diastolic blood pressure (mmHg).

| TABLE 10.3.2.7 | | | | |
|---|---|---|---|---|
| CLINICALLY SIGNIFICANT CHANGES | | | | |
| **Measurement** | **Direction** | **Position** | **Placebo** | **All doses** |
| Systolic BP | Increase | Resting | 0.9% | 1.0% |
| | | Standing | 0.0% | 0.0% |
| Diastolic BP | Increase | Resting | 0.2% | 1.4% |
| | | Standing | 0.6% | 1.2% |
| Systolic BP | Decrease | Resting | 1.3% | 2.0% |
| | | Standing | 2.6% | 5.8% |
| Diastolic BP | Decrease | Resting | 1.3% | 0.6% |
| | | Standing | 1.3% | 1.7% |
| BORDERLINE CLINICALLY SIGNIFICANT CHANGES | | | | |
| Systolic BP | Increase | Resting | 25.4% | 26.2% |
| | | Standing | 11.6% | 16.3% |

| BORDERLINE CLINICALLY SIGNIFICANT CHANGES | | | | |
|---|---|---|---|---|
| Systolic BP | Increase | Resting | 25.4% | 26.2% |
| Diastolic BP | Increase | Resting | 17.9% | 21.7% |
| | | Standing | 16.8% | 26.2% |
| Systolic BP | Decrease | Resting | 13.9% | 17.6% |
| | | Standing | 30.3% | 32.4% |
| Diastolic BP | Decrease | Resting | 13.4% | 13.6% |
| | | Standing | 11.0% | 13.4% |

Heart rate: Mean change from baseline

Table 10.3.2.8 illustrates the mean change in heart rate (bpm) from baseline in uncomplicated obese patients in placebo-controlled studies.

| TABLE 10.3.2.8 | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Measurement | Placebo | <5mg | 5-9mg | 10-14mg | 15-19mg | 20-29mg | ≥30mg | All doses |
| Resting HR | 0.0 | -0.1 | 2.9* | 3.6* | 3.9* | 3.5* | 5.1* | 3.2* |
| Standing HR | -1.4 | -1.2 | 1.7* | 3.0* | 2.9* | 4.7* | 5.0* | 2.5* |

* $p \leq 0.05$ compared to placebo

These data indicate that sibutramine is associated with an increase in pulse rate and the relationship is dose-related. The heart rate data obtained from ECGs were similar to that obtained by manual palpation, but the rates were, in general, 2-3 beats per minute higher.

As with blood pressure, at 4 and 6 weeks post-treatment the sibutramine subjects still had mildly, and dose-related elevations in heart rate.

Clinically significant and borderline clinically significant changes

Table 10.3.2.9 illustrates the percentage of patients with uncomplicated obesity from placebo-controlled studies with clinically significant or borderline clinically significant changes in heart rate.

| TABLE 10.3.2.9 | | | | |
|---|---|---|---|---|
| CLINICALLY SIGNIFICANT CHANGES | | | | |
| **Measurement** | **Position** | **Direction** | **Placebo** | **All doses** |
| Pulse rate | Resting | Increase | 0.0% | 0.3% |
| | Standing | | 0.0% | 1.2% |
| — | Resting | Decrease | 0.6% | 0.9% |
| | Standing | | 0.0% | 0.6% |
| BORDERLINE CLINICALLY SIGNIFICANT CHANGES | | | | |
| Pulse rate | Resting | Increase | 2.1% | 5.4% |
| | Standing | | 7.7% | 20.7% |
| | Resting | Decrease | 16.2% | 13.7% |
| | Standing | | 18.1% | 14.0% |

A greater percentage of sibutramine-treated patients reported an increase in heart rate or palpitations as an adverse event compared to placebo-treated patients (2.5% vs 0.3%, respectively for increase in heart rate and 2.3% vs 0.8%, respectively for palpitations).

Persistent hypertensive and tachycardic effects

Table 10.3.2.10 provides the percentage of patients whose vital signs met the borderline clinically significant criteria on three consecutive visits.

| TABLE 10.3.2.10 | | |
|---|---|---|
| **Parameter and position** | **Placebo** | **All doses** |
| **Systolic BP (mmHg)** | | |
| Resting | 4.9% | 5.7% |
| Standing | 0.0% | 1.5% |
| **Diastolic BP (mmHg)** | | |
| Resting | 1.5% | 3.5% |
| Standing | 0.0% | 3.1% |
| **Pulse rate (beats/min)** | | |
| Resting | 0.0% | 0.3% |
| Standing | 0.0% | 1.1% |

One percent of sibutramine-treated subjects were withdrawn from studies because of increased blood pressure compared to 0.4% of placebo subjects. Regarding the number of subjects who were withdrawn because of an elevated pulse rate: 0.4% and 0.2% of sibutramine and placebo-treated subjects, respectively were discontinued prematurely. Similar numbers were found for palpitations: 0.3% and 0.0% of sibutramine and placebo subjects, respectively were withdrawn prematurely for an increase in pulse rate.

Table 10.3.2.11 shows the percentage of patients in BPI 852 who had dose reductions, by initial dose, because of increased blood pressure or pulse.

**TABLE 10.3.2.11**

| **Reason for dose reduction** | **Placebo** | **1mg** | **5mg** | **10mg** | **15mg** | **20mg** | **30mg** |
|---|---|---|---|---|---|---|---|
| Blood pressure (mmHg) | 3.4 | 0.7 | 0.7 | 2.7 | 3.9 | 3.4 | 8.5 |
| Pulse (beats/min) | 0.7 | 0.7 | 1.3 | 0.0 | 2.6 | 7.5 | 2.6 |

Criteria for discontinuation: two mean supine pulse rates > 100 beats/min, or systolic blood pressure > 160 mmHg or diastolic > 95 mmHg.

Undoubtedly, a larger number of subjects would have required dose reductions if the cuffoff values for systolic and diastolic blood pressure were 140 and 90 mmHg, respectively.

Electrocardiograms

In general, sibutramine-treated individuals had minor reductions in their PR and QRS intervals and increases in their $QT_c$ intervals. These changes do not appear to be clinically significant.

The ECGs were categorized into one of three groups:

(1) Normal at baseline and on treatment.
(2) Abnormal at some stage during treatment but with the last recorded ECG either normal of no change from baseline.
(3) Normal at baseline with the last recorded ECG either abnormal or changed from baseline.

Eighty-five percent of the sibutamine and placebo ECGs were included in category 1. Approximately 10 % of the ECGs were included in category 2, and 4% were included in category 3. The ECGs from category 3 were reviewed by a Company medical monitor to determine whether the change following drug treatment was clinically significant. Thirty-one patients: 1.1% of the sibutramine-treated and 0.4% of the placebo-treated subjects were judged to have ECGs with a potentially clinically significant change from baseline. Of these 31 subjects, 28 received sibutramine and 3 placebo. A consulting cardiologist reviewed these 31 cases and determined that 5 of the 31 represented clinically significant changes and a drug-associated effect could not be ruled out. Of note, there were inconsistencies noted in the consultant

cardiologist's review of the EKGs. The Sponsor has been asked to address this issue. The response is pending.

**10.3.3 Special Studies**

Effects of alcohol and sibutramine

SB 2822

This was a double-blind, randomized, placebo-controlled, 4-way crossover study that investigated the psychomotor interactions between alcohol and 20 mg of sibutramine. The study participants were normal weigh, healthy male and female subjects, with a mean age of 27 years. Subjects received each of the following treatments:

1. Two placebo capsules and an alcoholic drink
2. Two sibutramine 10 mg capsules and a placebo drink
3. Two placebo capsules and a placebo drink
4. Two sibutramine 10 mg capsules and an alcoholic drink

The amount of alcohol in the drink was 0.5 g/kg of body weight diluted with 400 ml of ginger ale. The tasks that were performed at baseline and at 3, 4, 5, 6, and 10 hours after administration of the study capsules were:

1. Word presentation and immediate word recall
2. Picture presentation
3. Simple reaction time
4. Number vigilance
5. Choice reaction time
6. Visual tracking
7. Spatial memory
8. Memory scanning
9. Delayed word recall
10. Work recognition
11. Picture recognition
12. Body sway



Of the 156 summary measures of the psychomotor tasks, not surprisingly, 5% resulted in statistically significant sibutramine-by-alcohol interactions. These were confined to the word and picture recognition tasks.

The greatest percentage of reported adverse events were in the placebo plus alcohol group (80%) followed by the sibutramine plus alcohol (60%). There were no significant treatment effects on laboratory or vital sign parameters. It is of note to mention that the breath alcohol levels were 3.3 mg % lower with sibutramine treatment; the reason for this result is unknown.

In conclusion, in this small study of healthy young volunteers, 20 mg of sibutramine did not significantly alter the psychomotor response to a one-time ingestion of alcohol. The extremely large number of pairwise comparisons, without statistical correction, make it difficult to draw valid conclusions from this study.

Psychotrophic drug profile



BPI 802

In study BPI 802 12 healthy volunteers participated in a double-blind, single-dose crossover study in which the quantitative pharmacoelectroencephalographic effects of 5, 15, and 50 mg of sibutramine were compared to placebo and 50 mg of amitriptyline. Both 5 and 15 mg of sibutramine were categorized as antidepressants. The 50 mg dose was similar to CNS depressants, with secondary resemblance to cognitive activators.

Sleep effects

SSB 9045

In SSB 9045, the effect of 20 mg of sibutramine given once-daily in the morning for five days on sleep patterns and the distribution of rapid eye movements (REM) was investigated in 12 healthy volunteers. Similar to other antidepressants, sibutramine increased the time to onset of REM and decreased REM duration. There was also an increase in the time spent in Stage 1 of sleep.

Effect of sibutramine on cigarette usage

PSB 1898

This was a randomized, placebo-controlled, parallel-group study to examine the effects of 15 mg QD on the total number of cigarettes smoked and on the desire to smoke. The study had a baseline assessment week, a 2-week placebo run-in phase, and a 2-week double-blind treatment period. Twenty-four male subjects entered the run-in phase and all volunteers completed the study. There were no statistically significant differences in either the number of cigarettes smoked or the desire to smoke between the sibutramine and placebo groups. Similar adverse events were reported in the sibutramine and placebo groups, although the incidence of adverse events was higher in the sibutramine group than in the placebo group. There were no significant changes in body weight in either group.

Effect of sibutramine on the efficacy of the oral contraceptive pill

SB 4819

This was a single-blind, single-center study that compared the effects of 15 mg QD of sibutramine vs placebo on the efficacy of oral steroid contraceptives in 12 healthy female volunteers. The main variable measured was the change in plasma progesterone level. The study consisted of two study periods. In study period 1, all volunteers received placebo once-daily for 28 days (days -7 to 21) and their prescribed oral contraceptive for 21 days (days 1 to 21). Study period 2 started on day 22 and was the same as study period 1, with the exception that volunteers received sibutramine 15 mg QD instead of placebo. Eleven of 13 subjects completed the study; one dropped-out because of an adverse event (nausea and vomiting), and the other because of a protocol violation. There were no statistically significant differences between the sibutramine and placebo treatment periods for the change in plasma progesterone, FSH, and $EE_2$. The mean LH levels were 4.2 U/l in the placebo period and 4.7 U/l in the sibutramine period. This difference is not clinically significant. Headache was the most commonly reported event during both treatment periods.

Neurotoxicity

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See pharmacology review

No human data are presented on the potential for neurotoxicity. Animal data do not provide evidence that sibutramine depletes brain serotonin levels.

**10.3.4 Drug-Demographic Interactions**

**Adverse events**

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Age

The Sponsor did not provide an analysis of the effects of age on the incidence of adverse events.

Gender

Table 10.3.4.1 provides the percentage of adverse events thought to be sibutramine-related for all obese patients by gender. Sibutramine-related is defined as an adverse event occurring at a frequency $\geq$ 1%, and significantly ($p \leq 0.05$) or near-significantly ($p > 0.05$ and $\leq 0.1$) more than with placebo.

**TABLE 10.3.4.1**

| COSTART TERM | Male n=499 | Female n=2541 |
|---|---|---|
| Infection | 28 | 24 |
| Abdominal pain | 4 | 5 |
| Vasodilatation | 0.4 | 4 |

| TABLE 10.3.4.1 | | |
|---|---|---|
| COSTART TERM | Male n=499 | Female n=2541 |
| Tachycardia | 2 | 3 |
| Post-dose hypotension | 0.8 | 0.3 |
| Palpitations | 2 | 2 |
| Anorexia | 13 | 16 |
| Constipation | 8 | 12 |
| Appetite increase | 8 | 12 |
| Nausea | 3 | 6 |
| Joint disease | 0.4 | 1 |
| Tenosynovitis | 1 | 2 |
| Dry mouth | 13 | 21 |
| Insomnia | 8 | 12 |
| Dizziness | 5 | 7 |
| Paresthesia | 1 | 2 |
| Anxiety | 5 | 8 |
| Nervousness | 6 | 6 |
| Dyspnea | 0.4 | 1 |
| Rhinitis | 11 | 15 |
| Sweating | 2 | 3 |
| Taste perversion | 2 | 2 |
| Ear disorder | 1 | 2 |
| Dysmenorrhea | NA | 5 |
| Impotence | 1 | NA |
| Urinary retention | 0.4 | 0 |

NA = not applicable

The rate of infection was slightly higher in males, whereas nausea and dry mouth were more commonly reported by females. The smaller number of male subjects must be taken into account when analyzing these data.

Race

Eighty-six percent of the patients studied were Caucasian; 10% were African-American; and 4% were Oriental. Thus, it is difficult to draw firm conclusions regarding differences in the incidence of adverse events among the three racial group. Nevertheless, Caucasians reported abdominal pain, dizziness, and dysmenorrhea less frequently and African-Americans reported

insomnia less frequently.

**Laboratory values**

Gender

There were no obvious differences in the changes in serum chemistry, hematology, thyroid function, or urinalysis values when analyzed by gender. Males tended to have more favorable changes in triglyceride and high density lipoprotein lipid values. In general, males tended to lose more weight for a given dose of sibutramine compared to females; this may explain their more favorable lipid response.

Race

The value for the mean percentage change in AST was higher in Caucasians than in African-Americans (12.5 vs 5.1%, respectively). Caucasians also had a greater reduction in triglycerides compared to African-Americans (-9.4 vs -1.7%, respectively). There were no other obvious differences between the two racial groups.

**10.3.5 Drug-Disease Interactions**

Hepatic disease

The effects of a single 15 mg dose of sibutramine were investigated in an open-label, parallel-group study of 12 patients with normal liver function and 12 with impaired hepatic function. The mean age of these Caucasian males was approximately 50 years. Hepatic impairment was judged moderate by the Child-Pugh classification. The overall sibutramine concentrations were no higher, nor were they sustained for a longer time in the hepatically impaired subjects. The bioavailability of the two main active metabolites, $M_1$ and $M_2$ was increased by 24% in the hepatically impaired subjects.

Renal disease

The Sponsor has not submitted pharmacokinetic data from patients with renal disease.

**10.3.6 Drug-Drug Interactions**

Cimetidine

In study SB 4820, 12 healthy volunteers (6 male and 6 female) received a single oral dose of 15 mg of sibutramine, followed by repeated twice-daily doses of cimetidine 400 mg for 7 days. And on day 10 of the study subjects took a 15 mg dose of sibutramine with a single 400 mg dose of cimetidine. For the active metabolites, M1 and M2, there were statistically significant

differences between the two treatments. For M1, $C_{max}$ was 27% greater for the sibutramine/cimetidine treatment compared to sibutramine alone, whereas for M2, $C_{max}$ was 18% smaller for the sibutramine/cimetidine treatment. The AUC for M1 was 35% greater for the sibutramine/cimetidine treatment. When the data for M1 and M2 were combined for $C_{max}$ and AUC the difference between the two treatments was less than 8%.

Erythromycin

In study BPI 879, 12 obese patients received repeated, once-daily doses of sibutramine 20 mg for 7 days. This was followed by repeated once-daily doses of 20 mg of sibutramine plus repeated thrice-daily doses of erythromycin 500 mg for the next 7 days. The concomitant administration of sibutramine and erythromycin resulted in minor increases in steady-state plasma concentrations of active metabolite M2. In addition, there appeared to be an increase in pulse when subjects were administered the two drugs together.

Ketoconazole

In study BPI 880, 12 obese patients received once-daily doses of sibutramine 20 mg for 7 days. This was followed by repeated once-daily doses of sibutramine 20 mg plus repeated twice-daily doses of ketoconazole 200 mg for 7 days. The concomitant administration of these two drugs increased the concentrations of active metabolites M1 and M2 and increased heart rate.

The results of the aforementioned studies suggest that patients should be monitored closely when taking sibutramine with either cimetidine, erythromycin, or ketoconazole as well as other similarly metabolized drugs.

**10.3.7 Withdrawal Phenomena/Abuse Potential**

The most frequently reported post-treatment adverse event was headache. Of note, a 42 year old female Caucasian patient had an acute psychotic episode two days after being discontinued from study BPI 872. She was admitted to the hospital and treated with antipsychotic agents. The episode resolved within 5 days of treatment.

It is interesting to note that the drug Effexor, an antidepressant with similar pharmacological actions to that of sibutramine has been associated with a withdrawal syndrome during post-marketing spontaneous reporting. Headache is a component of the withdrawal syndrome of Effexor, and is the most commonly reported symptom following discontinuation of sibutramine.

Study BPI 863 was conducted to evaluate the abuse potential of sibutramine (20 and 30 mg) compared to placebo and dextroamphetamine (20 and 30 mg). The Addiction Research Center Inventory (ARCI) was administered pre-dose and hourly for 4 hours after the administration of the medications. For stimulation and euphoria, dextroamphetamine was significantly greater than placebo, whereas, the effects of sibutramine were indistinguishable from placebo. For scales

measuring dysphoria, both doses of dextroamphetamine and 30 mg of sibutramine produced greater responses when compared to placebo. The 20 mg sibutramine dose was the same as placebo. The rank order of treatment session enjoyment was dextroamphetamine 30 mg > dextroamphetamine 20 mg > placebo > sibutramine 30 mg > sibutramine 20 mg.

### 10.3.8 Human Reproductive Data

Five patients became pregnant while taking sibutramine. These cases are summarized in table 10.3.8.1

**TABLE 10.3.8.1**

| Patient # | Age | Dose | Duration | Outcome |
|---|---|---|---|---|
| 1067 | ? | 15mg | ? | ectopic pregnancy; laparotomy and salpingectomy |
| 0192 | 21 | 20mg | 9 wk | pregnancy was therapeutically terminated |
| 3150 | ? | 15mg | 2-3wks | normal child born |
| 0424 | 22 | 15mg | 19days | normal child born |
| 464 | ? | 15mg | 8wk | neonate had seizures; dx with viral meningitis |



## 10.4 SAFETY UPDATE

The Sponsor submitted a safety update on 12/19/95. This update includes five new studies and data from BPI 852X. The cutoff date for these data is 5/31/95. The five new studies are described in table 10.4.1

**TABLE 10.4.1**

| Placebo-controlled<br>Uncomplicated obese patients | | Dose range | Number Exposed | Planned Duration | Age Range |
|---|---|---|---|---|---|
| BPI 858 Metabolic study | Parallel group double-blind | Sibutramine 10-30mg | 33 Sib 16 Pl | 8 wks | |
| BPI 864 Feeding behavior study | Crossover double-blind | Sibutramine 10-30mg | 15 Sib 12 Pl | 12 wks | |
| **Uncontrolled** | | | | | |
| **Uncomplicated obese patients** | | | | | |
| BPI 872 Holter study | Single-treatment single-blind | Sibutramine 5-30mg | 21 | 10 wks | |
| **Volunteers** | | | | | |

| TABLE 10.4.1 | | | | | |
|---|---|---|---|---|---|
| Placebo-controlled<br>Uncomplicated obese patients | | Dose range | Number Exposed | Planned Duration | Age Range |
| BPI 870 Renal impairment study | Single-treatment open-label | Sibutramine 15mg | 6 | 1 day | |
| BPI 871 Bioequivalence study | Crossover Open-label | Sibutramine 30mg | 28 | 4 days | |

The data from these five studies have been combined an analyzed in a separate database. The data from BPI 852X have been combined with the previously reviewed data included in the ISS.

### 10.4.1 Overall Exposure

There have been a total of 2388 sibutramine exposures in patients with uncomplicated obesity as of the cutoff date of this update. Four-hundred-thirty-one patients received sibutramine for a duration of at least one year. At the time of the cutoff date, one patient in 852X had completed 102 weeks of sibutramine therapy.

### 10.4.2 Adverse Events

The most commonly reported adverse events in the five new studies were headache, anorexia, dry mouth, insomnia, increased appetite, dysmenorrhea, rhinitis, infection, nausea, CNS stimulation, and asthenia. These adverse events are representative of those reported in the integrated summary of safety (ISS).

Because of the small number of subjects in the five new studies and the differences in dose, duration, and monitoring of the patients, the remainder of this review will focus on data from BPI 852X, the long-term, open-label extension of the pivotal study BPI 852. In BPI 852X, 70% of the patients have withdrawn as of 5/31/95. Seventeen percent withdrew because of an adverse event and approximately 29% have withdrawn because of protocol violations.

The most commonly reported adverse events (incidence $\geq$10%) were headache, infection, anorexia, rhinitis, dry mouth, increased appetite, anxiety, flu syndrome, pain, sinusitis, back pain, injury accident, insomnia, arthralgia, and pharyngitis. Overall, the incidence of these adverse events were very similar to those reported in the ISS.

Withdrawals due to Adverse Events

Table 10.4.2.1 provides the number and percentage of patients in BPI 852X who were withdrawn due to a treatment-emergent adverse events with a withdrawal rate of $\geq$ 0.5%.

| TABLE 10.4.2.1 | |
|---|---|
| **COSTART term** | **number and ( % ) of patients n=572** |
| Hypertension | 18 (3.2) |
| Depression | 13 (2.3) |
| Headache | 11 (1.9) |
| Insomnia | 8 (1.4) |
| Anxiety | 4 (0.7) |
| Dry mouth | 3 (0.5) |
| Emotional liability | 3 (0.5) |
| Nervousness | 3 (0.5) |
| Chest pain | 3 (0.5) |



Clinically Significant Adverse Events

A 26 year old male patient in BPI 852X had received sibutramine 15-25 mg for approximately 10 months when he developed fever, nausea, vomiting and a rash. His platelet count upon admission to the hospital was , followed by a drop to 8 hours later. He also had abnormal liver function tests. Sibutramine was discontinued and his platelet count returned to normal at the time of discharge. He was diagnosed with viral illness. After 4 months, the patient resumed sibutramine at doses of 20-25 mg with no further laboratory abnormalities.

A 53 year old female in study 852X was diagnosed with possible retinal melanoma after receiving sibutramine 15-30 mg for 9 months. The patient has refused to confirm the diagnosis.

### 10.4.3 Laboratory Parameters

Because of the relatively small sample sizes in this update, only those individuals with clinically significant changes in laboratory parameters are reported. The following data are from the five new studies as well as from 852X.

Table 10.4.3.1 provides the number of patients with clinically significant abnormal laboratory parameters with an incidence of approximately 1.0%.

| TABLE 10.4.3.1 | |
|---|---|
| **Parameter** | **Number of patients** |
| Hct < 32% females | 11/487 |
| TSH > 7.5 uIU/ml | 2/234 |
| TG > 250 mg/dl* | 81/565 |
| Total cholesterol > 300 mg/dl | 28/565 |
| HDL-C < 25 mg/dl | 17/565 |
| LDL-C > 160 mg/dl | 244/565 |
| Eosinophils > 10% | 5/588 |
| ALT > 3X ULN | 5/591 |

* lipid values are non-fasting

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### 10.4.4. Vital Signs and Electrocardiograms

Blood Pressure

The mean changes in blood pressure (mmHg) from baseline to 6, 12, and 18 months for subjects in 852X are shown in table 10.4.4.1

| TABLE 10.4.4.1 | | | | | |
|---|---|---|---|---|---|
| | **Sibutramine - modal dose✤** | | | | |
| Systolic BP | 15 mg | 20 mg | 25 mg | 30 mg | All Doses |
| month 6 | 6.7(91) | 7.1(90) | 8.4(86) | 5.0(157) | 6.5(439) |
| month 12 | 6.2(58) | 6.6(55) | 6.8(63) | 6.1(131) | 6.1(318) |
| month 18 | 5.9(36) | 10.8(35) | 7.2(38) | 7.8(93) | 7.6(210) |
| Diastolic BP | 15 mg | 20 mg | 25 mg | 30 mg | All Doses |
| month 6 | 2.7(91) | 4.4(90) | 3.3(86) | 2.0(157) | 3.0(439) |
| month 12 | 1.8(58) | 3.1(55) | 2.2(63) | 1.3(131) | 1.8(318) |
| month 18 | 5.3(36) | 8.4(35) | 2.7(38) | 3.0(93) | 4.2(210) |

✤modal dose represents the dose taken most frequently.
Numbers in parentheses represent the number of patients.

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An important issue related to blood pressure is the number of subjects with sustained increases in

blood pressure. Using the same criteria as defined in the ISS review, table 10.4.4.2 provides the number and percentage of subjects in 852X with sustained (3 consecutive visits) increases in systolic or diastolic blood pressure.

| TABLE 10.4.4.2 | | | | | |
|---|---|---|---|---|---|
| **Measurement** | **15 mg n=140** | **20 mg n=128** | **25 mg n=104** | **30 mg n=167** | **All Doses** |
| Systolic BP | 6 (4%) | 6 (5%) | 7 (7%) | 13 (8%) | 35 (6%) |
| Diastolic BP | 6 (4%) | 4 (3%) | 4 (4%) | 5 (3%) | 20 (4%) |

dose represent modal dose
n = number of patients with at least three consecutive visits

Table 10.4.4.3 provides the percentage of patients in 852X with an increase in resting blood pressure ≥ 30% from baseline to endpoint and months 6, 12, and 18.

| TABLE 10.4.4.3 | | | | |
|---|---|---|---|---|
| | **Sibutramine modal dose** | | | |
| | **15 mg** | **20 mg** | **25 mg** | **30 mg** |
| Systolic BP | | | | |
| Endpoint | 3% | 5% | 4% | 3% |
| Month 6 | 0% | 6% | 4% | 3% |
| Month 12 | 0% | 0% | 5% | 4% |
| Month 18 | 0% | 3% | 5% | 8% |
| Diastolic BP | | | | |
| Endpoint | 3% | 6% | 5% | 2% |
| Month 6 | 1% | 9% | 1% | 3% |
| Month 12 | 2% | 4% | 5% | 2% |
| Month 18 | 6% | 9% | 5% | 2% |

Pulse rate

The mean change in pulse rate from baseline to months 6, 12, and 18 in the subjects from 852X are shown in table 10.4.4.4

| TABLE 10.4.4.4 | | | | | |
|---|---|---|---|---|---|
| **Resting pulse** | **15 mg** | **20 mg** | **25 mg** | **30 mg** | **All Doses** |
| month 6 | 5.4 (91) | 6.4 (90) | 8.1 (86) | 7.2 (157) | 6.7 (439) |
| month 12 | 4.7 (58) | 8.4 (55) | 8.0 (63) | 7.8 (131) | 7.1 (318) |
| month 18 | 8.4 (36) | 7.8 (35) | 7.6 (38) | 6.9 (93) | 7.2 (210) |

dose represents the modal dose; values in parentheses are the number of subjects.



There were no subjects with a sustained elevation in supine pulse rate as defined by an increase in pulse rate of ≥ 100 bpm and an increase of ≥ 10 bpm above baseline. The Sponsor did not provide the data for resting or standing pulse.

Increases in resting pulse rate of ≥ 30% from baseline were observed in approximately 8-12% of the patients receiving modal doses of 15 mg or higher.

Electrocardiograms

In BPI 852X, the mean changes in heart rate from baseline to months 6, 12, and 18 as determined from ECGs were of a slightly greater magnitude than the changes noted by manual palpation. A dose-response relationship was also observed with modal doses of 15 mg and higher.

Safety update - 4/19/96

Two 10-day safety reports were submitted on 4/19/96. The first report was about a 65 year old female with a history of hypertensive cardiomyopathy and dyslipidemia, who was receiving 10-20 mg QD of sibutramine for one year and developed an intracerebellar hemorrhage. The patient's blood pressure, 220/110 on admission to the hospital was stabilized and she was discharged on a thiazide diuretic in addition to her captopril.The second report was about a 63 year old female with a history of asthma who was receiving 15 mg QD of sibutramine for 24 weeks. The patient developed sudden onset of palpitations and upon admission to the hospital had a heart rate of 150 bpm and a blood pressure of 160/100 mmHg. She was diagnosed with supraventricular tachycardia (SVT) and treated with verapamil. The cardiac work-up was normal. Of note: The patient's heart rate had increased by 13 bpm by the 20th week of treatment.

To date, there have been eight reported cerebrovascular accidents: Seven of these subjects were taking sibutramine and one was receiving placebo.

**Summary of Safety**

The data submitted in the integrated summary of safety and the safety update of 12/19/95 indicate that the common symptom-related adverse events associated with the use of sibutramine

(i.e. dry mouth, insomnia, nausea, etc) are, in general, not serious and reflect the pharmacodynamic actions of an inhibitor of serotonin and norepinephrine reuptake. However, the safety data indicate a possible to probable drug-related risk for several serious adverse events: cardiac arrhythmia, cerebrovascular accident, acute interstitial nephritis, thrombocytopenia, and bleeding disorders. Furthermore, the safety data highlight the paradoxical increase in blood pressure despite weight loss in sibutramine-treated patients.

## 11. DISCUSSION/CONCLUSIONS

The rationale for the treatment of obesity derives from the relationship between an excess level of body fat with numerous co-morbid conditions — the most common being hypertension,[1-4] non-insulin dependent diabetes mellitus,[5-9] and dyslipidemia.[10-14] The improvements in the major co-morbidities following the non-pharmacological treatment of obesity are well documented.[15-26]

As defined in the Guidance for the Clinical Evaluation of Weight-Control Drugs, an anti-obesity drug is considered efficacious if it is shown — after one year of treatment — to produce a mean percent loss of body weight that is 5% greater than the mean percent loss in the placebo group and the difference is statistically significant. Alternatively, a drug will be considered effective if the proportion of subjects who lose 5% of initial body weight is greater in the drug-treated group than the proportion in the placebo-treated subjects.

In the one-year pivotal study SB 1047, subjects were randomized to once-daily doses of 10 or 15 mg of sibutramine or to placebo. Less than 60% of the subjects randomized to each group completed the trial. Of these individuals, 65% of the subjects in the 15 mg group and 56% of the subjects in the 10 mg group lost 5% of initial body weight compared to 29% of placebo-treated subjects. However, only the 15 mg dose led to a mean percent weight loss that was 5% greater than the mean percent loss in the placebo group. The six-month dose-ranging study, BPI 852, reported that compared to placebo subjects, a greater percentage of subjects taking 5-30 mg QD of sibutramine lost 5% of initial body weight. On the other hand, only doses of 15-30 mg QD led to a percent weight loss that was 5% greater than the weight loss in the placebo group. The dose-response curve generated from BPI 852 suggests that weight loss is dose-dependent, with the steepest portion of the curve between the doses 5-20 mg.

Sibutramine's most worrisome safety issue centers on its effects on the major obesity-related co-morbidities, particularly blood pressure. A disturbing result of the dose-ranging study BPI 852, and its open-label extension 852X, was the paradoxical increase in blood pressure despite weight loss. Although the subjects in BPI 852 and 852X were normotensive at baseline, one would expect a reduction in blood pressure following weight loss in obese individuals.[27,28] In study SB 1047 a similar inverse relationship, albeit of a lesser magnitude, was observed between weight loss and blood pressure. In BPI 855, an eight-week study of obese, hypertensive patients taking 20 mg QD of sibutramine, a 1.7 kg reduction in body weight was associated with mean increases in systolic and diastolic blood pressures of approximately 9.0 and 4.0 mmHg, respectively. These changes were measured by 24-hour ambulatory monitoring — a measure of average daily blood pressure that correlates more closely with end-organ damage than manually-measured blood pressures[29,30] — and indicated that the overall increase in 24-hour blood pressure was due, in large part, to elevations in nocturnal pressures. In contrast to the results of the aforementioned studies, SB 3069, a six-month trial (three-months placebo-controlled and three-months open-label) of obese, hypertensive patients taking 10 mg QD of sibutramine, reported weight-loss

induced reductions in blood pressure. However, despite greater weight loss in the sibutramine group, the reductions in blood pressure were the same in the drug-treated and placebo patients. Moreover, there was no correlation between sibutramine-induced weight loss and a reduction in blood pressure following six months of drug treatment.

Given that small, sustained increases in blood pressure, even when within the normotensive range, are associated with an increased risk for cardiovascular disease,[31] the pressor effect of sibutramine is a significant safety concern. Furthermore, it is important to note that sibutramine's pressor effect does not appear to be dose-dependent. Consequently, restricting approval to the lower doses would not eliminate the potential for drug-induced increases in blood pressure.

Sibutramine was ineffective in the treatment of obese patients with non-insulin dependent diabetes mellitus. Six months of treatment with 15 mg QD resulted in only a 3.8% reduction in body weight. More importantly, the weight loss was associated with an increase in diastolic blood pressure, pulse, and post-load insulin levels, with no change in fasting glucose or $HbA1_c$ concentrations. In short, sibutramine worsened the risk factor profile of obese, non-insulin dependent diabetic patients.

With respect to lipoprotein lipids, in the one-year study SB1047, there were no statistically significant differences in the levels of total cholesterol or triglyceride between the drug-treated and the placebo-treated subjects at the completion of the trial. Pooled data from short and long-term studies suggest that sibutramine has a weak eulipemic effect. However, the Sponsor did not provide a statistical analysis of the pooled data, and therefore no valid conclusions can be made regarding the effect of sibutramine on lipoprotein lipid levels.

In summary, the 10 and 15 mg doses of sibutramine satisfy the minimum weight-loss criteria and duration of study as defined in the Guidance. However, sibutramine does not improve, and in some cases it aggravates, the major obesity-related co-morbidities.

## 13. RECOMMENDATIONS

**13.1** As discussed above, sibutramine has an unsatisfactory risk - benefit ratio, and therefore this Reviewer recommends non-approval of the original submission of NDA 20-632.

5/10/96

Eric Colman, M.D.
Medical Officer

Concurrent Review

cc: NDA Arch
Drs.GTroendle/SSobel

6-25-96

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**MEDICAL REVIEW of SAFETY UPDATE**

NDA #: 20-632

SPONSOR: Knoll

NOV 14 1997

DRUG: Sibutramine

DATE SUBMITTED: 10/20/97

DATE RECEIVED, M.O.: 10/25/97

DATE OF REVIEW: 11/5/97

## INTRODUCTION

This sibutramine safety update includes 11 studies which completed or had database lock since the second ISS was submitted in 2/97. Serious adverse events in ongoing studies reported to Knoll's safety group are current as of 9/1/97.

The 11 studies summarized in this report are as follows:

**BPI 873** - Single dose effects of renal dysfunction on the PK of sibutramine.

**BPI 881** - Effects of 12 weeks of 20mg qd of sibutramine on weight, BP, and pulse in patients with hypertension controlled with a beta-blocker, with or without concomitant diuretic therapy.

**BPI 883** - Single dose effects of sibutramine (25 to 75 mg) on abuse potential compared with dextroamphetamine in diagnosed substance abusers.

**BPI 893** - Single dose effects of sibutramine (25 to 75 mg) on abuse potential compared with dextroamphetamine and placebo in recreational stimulant users.

**SB 4070** - 12-week study of the effects of 15 mg qd of sibutramine in the treatment of obese patients with dyslipidemia.

**SB 4072** - 24-week study of the effects of 15mg qd of sibutramine on weight reduction in obese patients at risk for diabetes.

**SB 5076** - A single dose study of 30mg qd of sibutramine examining the effect on energy expenditure in normal males.

**SB 5079** - A single dose study of 15mg qd of sibutramine examining the effects on food intake and

hunger in normal males.

SB 5081 - A four-day treatment study of 10mg qd of sibutramine examining the effects on thermogenesis in obese patients.

SB 5083 - A 12-week study of 15 or 20mg qd of sibutramine examining the effects on heart rate variability in obese patients.

SB 5084 - An 8-week study of 15 mg qd of sibutramine examining the effects on energy expenditure in obese patients.

## EXPOSURE

Of the studies listed above, 394 patients have received sibutramine and 328 placebo. Including the entire database, a total of 4273 patients (73 patient-years) have been exposed to sibutramine as of 9/1/97.

## DEMOGRAPHICS

The majority of patients were female, the mean age ranges were from years, and of the subjects in the various studies were Caucasian.

## PREMATURE TERMINATIONS

Sixteen percent of sibutramine-treated patients and 18% of placebo-treated patients have terminated early. Adverse events were the reason for early withdrawal in 5.2% of sibutramine-treated subjects and 2.7% of placebo-treated patients.

## ADVERSE EVENTS

Adverse events that were recorded by a greater percentage of sibutramine- vs. placebo-treated patients and the differences were statistically significant include headache, palpitations, constipation, nausea, dry mouth, insomnia, and taste perversion.

Hypertension was reported as an adverse event in 1.0% of sibutramine-treated subjects vs. 1.2% of placebo-treated women. Tachycardia was reported as an adverse event in 2.3% and 0.4% of sibutramine- and placebo-treated patients, respectively.

## DEATHS

No deaths have been reported in subjects receiving sibutramine.

## OVERDOSE

A 45-year-old male was withdrawn after taking an overdose of diazepam on 8/12/97. He was started

on fluoxetine and lorazepam on 8/15/97. On the evening of 8/21/97, the patient took an overdose of sibutramine (20 x 20mg). He was hospitalized with a heart rate of 120bpm and was discharged the next day. Follow-up 19 days later indicated that he was clinically well.

## VITAL SIGNS

Relative to placebo, sibutramine treatment increased mean systolic blood pressure by 3.2 mmHg, increased diastolic blood pressure by 3.8 mmHg, and increased pulse rate by 5.4 bpm. In general, more sibutramine-treated patients compared with placebo-treated subjects had increases in systolic and diastolic blood pressure and pulse that were of borderline clinical significance (e.g., diastolic BP >90 mmHg and an increase of > 10 mmHg from baseline). Most of the exposures to sibutramine were with the 15-20mg qd doses. As reported in the previous safety update, the most consistent finding is the increase in resting pulse rate in sibutramine-treated subjects.

## MEDICAL OFFICER'S CONCLUSIONS

The data reported in this safety update are consistent with the findings from previous reports and indicate that the drug, particularly at doses greater than 15 mg qd, increases blood pressure and pulse.

11/13/97

Eric Colman, M.D.

cc: NDA Arch

11-14-97

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# MEDICAL REVIEW

**NDA #:** 20-632

**SPONSOR:** Knoll

**DRUG:** Sibutramine

**INDICATION:** Weight loss

**SUBJECT OF REVIEW:** Safety update

**DATE SUBMITTED:** 10/4/96



**DATE RECEIVED, M.O.:** 10/9/96

**DATE OF REVIEW:** 10/10/96

## BACKGROUND

This safety update includes data from 3 studies completed since the last safety update - December, 1995 - and represent data collected up to June 1, 1996. The studies are: SB 1049, SB 2056, and SB 2059. I reviewed the preliminary study reports for SB 1049 and SB 2059 in July, 1996.

A total of 254 subjects were randomized to sibutramine (10 mg qd) and 251 subjects were randomized to placebo in these 3 studies. The estimated patient years of exposure to sibutramine from these 3 studies is 120. The demographic characteristics of these patients reflect the demographic characteristics of the previously exposed patients: primarily middle-aged, Caucasian women with a mean BMI of $\approx$ 35.0 kg/m$^2$.



## ADVERSE EVENTS

In general, the adverse event profiles in these 3 studies were similar to the adverse events most commonly reported in the Integrated Summary of Safety (ISS) and do not represent serious conditions. The table below shows the adverse events that were reported with an incidence of > 1% and the difference between active and placebo-treated patients was statistically or nearly statistically significantly different.

| COSTART TERM | Sibutramine | Placebo | p value |
|---|---|---|---|
| Syncope | 1.2% | 0% | 0.08 |
| Constipation | 12% | 5% | 0.005 |
| Rectal disorder | 3% | 0.4% | 0.02 |

| COSTART TERM | Sibutramine | Placebo | p value |
|---|---|---|---|
| Dry mouth | 9% | 3% | 0.009 |
| Furunculosis | 1.2% | 0% | 0.09 |

The most frequent adverse event that led to premature discontinuation was depression in 0.8% of the Sibutramine-treated patients.

## SERIOUS ADVERSE EVENTS

Four Sibutramine-treated patients experienced serious adverse events during the time period 12/1/95 - 8/31/96 that were submitted as 10-day safety reports. One subject had a cerebrovascular disease of possible embolic origin; one subject had an intra cerebellar hemorrhage; one subject was diagnosed with a supraventricular tachycardia; and one subject complained of several neurological symptoms: paresthesia, dizziness, tremor, and visual blurring.

## VITAL SIGNS

There were no statistically significant differences in the changes in systolic or diastolic blood pressure between the drug or placebo-treated patients. The change in pulse rate from Baseline to Endpoint was 1.7 in the Sibutramine group and -1.8 in the placebo subjects ($p<0.01$).

## CONCLUSIONS

The data from the 3 studies included in this safety update are consistent with the findings reported in the ISS. No new safety issues appear to have emerged from these studies which included subjects taking 10 mg qd of Sibutramine.

10/11/96

Eric Colman, M.D.

cc: NDA Arch 10-11-96
Hess/Colman/Troendle

Please refer to pages 154-160 of Medical Officer's Review for safety update that was submitted 12/19/95.

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