CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020632

ADMINISTRATIVE DOCUMENTS

MERIDIA™ (sibutramine hydrochloride monohydrate) Capsules
NDA 20-632
Section 13 - Patent Information

PATENT INFORMATION

Knoll Aktiengesellschaft of Ludwigshafen, Germany (Knoll AG) and Knoll Pharmaceutical Inc. of Mt. Olive, New Jersey are the owners as indicated of the following United States patents relating to sibutramine which are relevant under 21 USC 355 (b):

US Patent No:	Assignee:	Expiry Date
4,746,680	Knoll AG	11 June 2002
4,929.629	Knoll AG	29 May 2007
SN07/962,175	Knoll Pharmaceutical Company	2012 (precise date to be determined after issuance)

Patent No. 4,746,680 claims sibutramine per se.

Patent No. 4,929,629 claims sibutramine hydrochloride monohydrate.

Patent No. SN07/962,175 claims the use of sibutramine hydrochloride monohydrate in the treatment of obesity.

Thomas V. Allman
Vice President and Secretary

APPEARS THIS WAY
ON ORIGINAL

MERIDIA™ (sibutramine hydrochloride monohydrate) Capsules
NDA 20-632
Section 14 - Patent Certification

PATENT CERTIFICATION

Knoll Pharmaceutical Company, Mt. Olive, NJ, certifies that United States Patent Numbers 4,746,680 and 4,929,629 cover the composition of sibutramine or sibutramine hydrochloride monohydrate and Patent Application Serial Number 0/962,175 covers a method of use of sibutramine hydrochloride monohydrate. Sibutramine is the subject of this application for which approval is sought.

Thomas Y. Allman
Vice President and Secretary

APPEARS THIS WAY
ON ORIGINAL

EXCLUSIVITY SUMMARY for NDA # 20-632 SUPPL # _____

Trade Name Meridia Capsules Generic Name _____

Applicant Name Knoll Pharmaceuticals HFD-510

Approval Date November 22, 1997

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

   a) Is it an original NDA?

   YES /✓/ NO /___/

   b) Is it an effectiveness supplement?

   YES /___/ NO /✓/

   If yes, what type? (SE1, SE2, etc.) _____

   c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

   YES /✓/ NO /___/

   If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

   _____

   _____

   If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

   _____

   _____

d) Did the applicant request exclusivity?

YES /___/ NO /___/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

_____

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use?

YES /___/ NO /___/

If yes, NDA # _____ Drug Name _____

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /___/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

APPEARS THIS WAY ON ORIGINAL

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /___/ NO /✓/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # _____ _____

NDA # _____ _____

NDA # _____ _____

2. Combination product. N/A

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # _____ _____

NDA # _____ _____

NDA # _____ _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. IF "YES," GO TO PART III.

PART III **THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS**

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /___/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

   For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

   (a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /___/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:**

_____

_____

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /___/ NO /___/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /___/

If yes, explain: _____

_____

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /___/

If yes, explain: _____

_____

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1, Study # _____

Investigation #2, Study # _____

Investigation #3, Study # _____

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

Investigation #3 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

NDA # _____ Study # _____

NDA # _____ Study # _____

NDA # _____ Study # _____

b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

Investigation #3 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

NDA # _____ Study # _____

NDA # _____ Study # _____

NDA # _____ Study # _____

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation #__, Study # _____

Investigation #__, Study # _____

Investigation #__, Study # _____

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND # _____ YES /___/ ! NO /___/ Explain: _____

! _____

Investigation #2

IND # _____ YES /___/ ! NO /___/ Explain: _____

! _____

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1

YES /___/ Explain _____ ! NO /___/ Explain _____

_____ ! _____

_____ ! _____

Investigation #2

YES /___/ Explain _____ | NO /___/ Explain _____

_____ | _____

_____ | _____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /___/

If yes, explain: _____

_____

_____

_____

_____ 9/20/96

Signature Date

Title: Consumer Safety Officer

_____ 11/1/96

Signature of Division Director Date

APPEARS THIS WAY ON ORIGINAL

cc: Original NDA Division File HFD-85 Mary Ann Holovac

DRUG STUDIES IN PEDIATRIC PATIENTS
(To be completed for all NME's recommended for approval)

NDA # 20-632 Trade (generic) names Meridia (sibutramine hydrochloride monohydrate) / Capsules

Check any of the following that apply and explain, as necessary, on the next page:

____ 1. A proposed claim in the draft labeling is directed toward a specific pediatric illness. The application contains adequate and well-controlled studies in pediatric patients to support that claim.

____ 2. The draft labeling includes pediatric dosing information that is not based on adequate and well-controlled studies in children. The application contains a request under 21 CFR 210.58 or 314.126(c) for waiver of the requirement at 21 CFR 201.57(f) for A&WC studies in children.

____ a. The application contains data showing that the course of the disease and the effects of the drug are sufficiently similar in adults and children to permit extrapolation of the data from adults to children. The waiver request should be granted and a statement to that effect is included in the action letter.

____ b. The information included in the application does not adequately support the waiver request. The request should not be granted and a statement to that effect is included in the action letter. (Complete #3 or #4 below as appropriate.)

____ 3. Pediatric studies (e.g., dose-finding, pharmacokinetic, adverse reaction, adequate and well-controlled for safety and efficacy) should be done after approval. The drug product has some potential for use in children, but there is no reason to expect early widespread pediatric use (because, for example, alternative drugs are available or the condition is uncommon in children).

____ a. The applicant has committed to doing such studies as will be required.

____ (1) Studies are ongoing.
____ (2) Protocols have been submitted and approved.
____ (3) Protocols have been submitted and are under review.
____ (4) If no protocol has been submitted, on the next page explain the status of discussions.

____ b. If the sponsor is not willing to do pediatric studies, attach copies of FDA's written request that such studies be done and of the sponsor's written response to that request.

✓ ____ 4. Pediatric studies do not need to be encouraged because the drug product has little potential for use in children.

____ 5. If none of the above apply, explain.

Explain, as necessary, the foregoing items: _____

Signature of Preparer

Date 9/30/96

cc: Orig NDA
HFD-510/Div File
NDA Action Package

APPEARS THIS WAY
ON ORIGINAL

XVI. Certification by Sponsor

The sponsor, Knoll Pharmaceutical Company (formally Boots Pharmaceuticals, Inc.), certifies that the services of persons debarred under subsections (a) or (b) of Section 306(a) or (b) of the Generic Drug Enforcement Act of 1992 [21 U.S.C. 335a(k) (1)] have not and will not be used in connection with this application.

In addition, neither Knoll Pharmaceutical Company nor any affiliated persons responsible for the development or submission of this application has had any convictions as described in Section 306(a) and (b) of the Act within the last five years of the date of this application.

APPEARS THIS WAY
ON ORIGINAL

Abraham Varghese, Ph.D.
Manager, Regulatory Affairs

APPEARS THIS WAY
ON ORIGINAL

November 18,1997
Memorandum
To the File: NDA 20-632 Meridia capsules
(sibutramine hydrochloride monohydrate capsules)
From: Solomon Sobel M.D. Director, Division of Metabolic and Endocrine Drug Products 11-18-97
Subject: Approvable status of Meridia

This application remains in approvable status (The sponsor had previously received an approvable letter in November of 1996).

We believe that the issue of hypertension while on this drug can be managed by careful dose titration with monitoring and withdrawing medication from patients who show a significant increase in blood pressure. The revised labeling gives greater emphasis to this issue in both the Warning Section and the Dosage and Administration Section.

The sponsor has also agreed to eliminate the 20 mg capsule and has advised that doses exceeding 15 mg in total daily dosage are not recommended. Our analysis showed that limiting the dosage to 15 mg will significantly decrease the number of patients who experience hypertension. This increase in safety will be accomplished with only a small loss in efficacy.

The reason we cannot proceed to a full approval at this time is that the scheduling of this drug under DEA provisions has not yet been accomplished. The scheduling must await approval of the drug. The final actions in respect to scheduling and approval apparently must proceed simultaneously.
When DEA is close to scheduling they will call us and we will coordinate the letters.
We have also recommended that the sponsor shorten, considerably, the Patient Package Insert and give greater emphasis to the information about hypertension. The information about hypertension should be placed at the beginning of the PPI.
We also informed the sponsor that the PPI will be reviewed by DDMAC. The sponsor stated, today, that they will submit the results of a test survery that addressed the issue of understandability of the PPI. We also outlined ,today, what the major components of the Phase 4 study should be.

Conclusion: The application is Approvable at this time. The final approval letter will issue after the above mentioned steps are accomplished.

Solomon Sobel

cc: NDA 20-632 Arch
HFD-510 / Div File
HFD-510/ Sobel, Troendle, Colman, Stadel, Haber, Moore, Hertig, Stelgerwalt, Fossler, Jones, Ahn, Phan, Nevius

November 1, 1996
Division Director's Memo
To the File: NDA 20-632 sibutramine hydrochloride monohydrate
(Meridia Capsules)
From: Solomon Sobel M.D. Director, Divison of Metabolic and
Endocrine Drug Products 11-1-96
Subject: the approvability of the NDA

The Division recommends that this NDA receive an approvable letter rather than a full approval at this time.
There are several areas which we wish to explore and refine before a full approval is granted.

The main concern surrounding this drug was its effect on blood pressure. This effect is attributed to increased sympathetic activity which results in rises in both systolic and diastolic blood pressure as well as rises in pulse rate.

The mean rises in blood pressure are in the range of 2 to 4 mmHg. However, there is a significantly greater number of patients in the drug group that have considerably larger rises in blood pressure than in the the placebo group.

At the Advisory Committee meeting, this change in blood pressure was deemed to constitute a safety risk and by a small margin the committee voted to recommend against approval.

Since the Advisory Committee meeting the Division has explored ways to detect those patients who are likely to have rises in blood pressure early in the course of therapy. This approach is promising in eliminating patients who will have significant elevations at later time points. It was also noted in our preliminary analysis that by using a "blood pressure screen" patients destined to have a significant blood pressure rise could be removed from treatment but the favorable effect on weight loss in patients remaining on treatment for the most part would be maintained.
One of the problems of the screen which was employed is its sensitivity which removed approximately the same numbers of placebo and treated patients when systolic pressure was used (two measurements of systolic blood pressure of 10 mmHg above baseline on 2 consecutive visits).
There was a somewhat better specificity for patients on sibutramine when a diastolic pressure was used (i.e two measurements of diastolic blood pressure 10mmHg above baseline on 2 consecutive visits)

During the next several months we hope to refine methods of blood pressure screening by careful reanalysis of existing data.

2. There is an issue of the appropriate scheduling of this drug under the Controlled Substances Act. We have met with the appropriate FDA Division and we will forward recommendations to the company in respect to this issue.

3. We may also wish to make further recommendations in respect to the upper limit of daily dosing . Some reviewers believe that 15 mg/day will be a safer dose than 20 mg/day and that there will be only a small loss in potential efficacy with this dose limitation.

4. There have been several suggestions in respect to possible phase 4 commitments

This suggestion is being discussed within the Division.

5. Also, we will ask for a commitment for the development of a patient information insert which will help the patient in the proper and safe use of this drug.

After, the above issues are addressed we believe we can recommend approval.
I believe that this approach would be sufficient to change the vote of the Advisory Committee to approval. We will discuss these approaches with our Advisory Committee menmbers.

Recommendation: This NDA is approvable.

cc:
NDA 20-632 Arch
HFD-510 Div. File
HFD-510/Sobel, Galliers, Colman, Troendle, Haber, Moore, Hertig, Steigerwalt, Fossler, Jones, Ahn, Pian, Marticello

APPEARS THIS WAY
ON ORIGINAL

NDA 20632 Knoll Pharmaceutical
Sibutramine October 11, 1996

Sibutramine is a **norepinephrine and 5-hydroxytryptamine reuptake inhibitor** which reduces appetite and is offered for weight loss. Efficacy is not an issue except as it is borderline and must be considered in the benefit-to-risk determination. Two studies, BPI 852 (24 wk) and SB 1047 (12 mo), were identified as meeting Agency criteria for adequate and well controlled. They are the only controlled studies that were longer than 12 wk.

BPI 852: 24 wk,Double-blind, placebo-controlled, dose-ranging.
End points: Changes in body weight (% of baseline), vital signs, Waist and hip circumferences.
1047 subjects were randomized and **684 (65%) completed 24 wk** (824, 79%, completed 12 wk).
In the following table, the fourth column shows the percent of subjects who lost 5 and 10% of initial body weight, and then the percent who **lost 5% minus the 12% that was lost by placebo subjects**. Since there were no 10% losers in the placebo group, the entire fraction can be attributed to drug. In () is the fraction of 5% losers that is not attributable to drug, but to placebo (12%, which is placebo-induced/total fraction that are 5% losers or, for 30 mg group, 12%/62%=19%). In the last column, the percent of subjects who had **dose reduction due to blood pressure systolic >160 or diastolic >95**, /followed by the percent who had **dose reduction due to pulse >100**, and then /those who were **discontinued from the trial due to blood pressure**.

Dose	N	Wgt Lost kg	%who lost 5%/10%/-P	% of pts who had dose reduced BP/P/DC
Placebo	148	1.3	12/ 0	3/1/1
1 mg	149	2.4	18/ 7/ 6 (67%)	1/1/0
5 mg	151	3.7	31/ 9/19 (39%)	1/1/1
10 mg	150	5.7	45/12/33 (27%)	3/0/0
15 mg	151	7.0	52/23/40 (23%)	4/3/2
20 mg	146	8.2	51/25/39 (24%)	3/8/3
30 mg	151	9.0	62/35/50 (19%)	9/3/7

Weight loss increased with dose, as did the percent who lost 5 and 10% of initial body weight, and dose reductions for BP and for P and the percent who were discontinued for BP.
The two highest doses (20 and 30 mg/d) meet our suggested weight loss criteria of 5% greater mean weight loss in drug than in placebo groups by LOCF analysis.
By ITT analysis 38, 41, 45, and 48% of patients on 10, 15, 20 and

30 mg doses lost at least 5% of initial body weight, all were significantly different from placebo, but 20 and 30 mg were not consistently different from each other.
Of completers, a significantly greater proportion of patients lost at least 5% of body weight in the 15-30 mg drug groups than in the placebo group.

In spite of greater numbers who lost weight, only 9% of drug groups had -10-0 mmHg change of blood pressure compared to 21% of placebo patients.
Twelve sibutramine and 1 placebo patient had increases of standing diastolic pressure to more than 100. The abnormal values ranged from 106 to 110 and represented increases of 16 to 48 mmHg above baseline values. The placebo patient had DBP 108, an increase of 16mmHg.

SB 1047: Double-blind, placebo-controlled, 2 dose (10 and 15mg) for 12 mo.
End points: Changes in body weight (% of baseline), vital signs, Waist and hip circumferences.
485 randomized and **256 (65%) completed 12 mo, 80/163 P, 82/161 10mg, and 94/161 15mg.**
Completers only, weight lost, difference from placebo in percent change from baseline, and in proportion who lost at least 5%:

Month\Dose	**10 mg**	**15 mg**	**Pts\weight loss/dose**	**10 mg**	**15 mg**
3	3.5	5.8	Patients(completers) who **lost 5% or more at 6 mo.**	31%	43%
6	4.4	6.8			
9	4.6	6.9	Patients(completers) who **lost 5% or more at 12 mo. (endpoint)**	27% (19%)	36% (37%)
12	3.6	5.3			

The 6 mo weight loss was better than the 12 month weight loss, indicating **some regain** is likely. It would be very useful to know how much of the original loss was still present at 24 months.

Other studies were generally supportive of weight loss (drug groups at doses of 5-30 mg/day) that was significantly greater than in placebo groups. In 4 studies, pulse was significantly different in drug and placebo patients, and in one, BP was significantly increased. In 2, waist circumference decreased.

In the following table, these controlled studies are listed with **duration** (wks), **population** studied (Popul), percent who were **males** (%M), and **numbers** by dose in mg. The population of all of the studies were obese subjects, NDA = otherwise healthy obese subjects in the two studies identified as pivotal, Obese = other studies of uncomplicated obese subjects, DM = obese subjects with diabetes, HBP = obese sujects with hypertension.

Study	wks	Popul	%M	0	1	5	10	15	20	30
BPI 852 N	**24**	**NDA**	20	148	149	151	150	152	146	151
BPI 850 N	8	**Obese**	30	20		19			21	
BPI 851 N	12	**Obese**	12	16			17			
BPI 853 N	12	**DM**	22	6					6	
BPI 855 N	8	**HBP**	20	10					10	
SB 1047 N	52	**NDA**	20	163			161	161		
SB 1042 N	12	**Obese**	11	51	50		56		49	
SB 1043 N	12	**Obese**	13	59		56	59	62		
SB 1052 N	12	**DX**	20				26			
SB 3051 N	12	**DM**	47	44				47		
SB 2057 N	12	**HBP**	32	59			54			
SB 2053 N	12	**DX**	8	114			112			
Total N				690	199	226	**635**	**422**	232	151

For the most part these studies were negative, except for weight loss. Unfortunately, the usual benefits of weight loss were not seen. It would be interesting to separate patients by weight lost (more or less than the median), and see how they compare for risk factors.

Sibutramine has the minimum efficacy required, if only the two studies identified by the company as pivotal are looked at, and if categorical analyses are used. I am not sure how the other studies do on categorical analysis. Mean weight loss consistently favors drug.

In the following table, all studies were randomized and double-blind, and had placebo controls (two had dexfenfluramine comparison). Weight lost is for placebo the actual lost, and for others placebo-subtracted weight loss. In the last column, W is for **waist circumference**, F for **body fat** as measured in studies of body composition, BP for **blood pressure**, P for **heart rate**, L for **lipids**, G for **glucose/insulin/metabolic control**. - follows letters where measurement was done and no significant effect was seen; + follows where an effect was found; ? was used for one instance where lipid response was mixed.

Weight-loss efficacy					
Study	Duration	Dose	N	Wgt loss	Other
SB 1042	12	0	51	3.4k	W-BP-**P+**
		1	50	0.0k	
		10	56	2.5k	
		20	49	3.9k	
BP 850	8	0	20	1.3%	L-**BP+**
		5	19	1.7%	
		20	21	3.8%	
BPI 851	12	0	11	3.2k	%F-L?BP-
		10	16	2.4k	**P+**
SB 1043	12	0	59	1.6k	**W+**
		5	56	1.2k	L-BP-**P+**
		10	59	3.6k	
		15	62	3.5k	
NIDDM					
BPI 853	12	0	6	0.5k	G-BP-L-
		30/20	9	2.1k	
SB 3051	12	0	44	0.2k	W-F+G-BP-
		15	47	2.1k	**P+**
Hypertension					
BPI 855	8	0	10	loss not	See below
		20	9	intended	
SB 2057	12	0	127	2.3k	**W+**BP-L-
		10		2.4k	
Compare with Dexfenfluramine					
SB 2053	12	10	112	4.6	W-L-
		30 DXF	114	3.4k	
SB 1052	12	0	24	2.9k	W-L-BP-P-
		10	26	1.2k	
		30 DXF	25	2.3k	

Weight gain in patients with NIDDM was only 2.1 kg greater than placebo.

BPI 855: 24 hr BP monitoring. Wgt loss was not intended, but loss of 1.7 kg occurred. Heart rate increased in sibutramine compared to placebo groups. In placebo patients, SBP was decreased at hours 12 and 16 (nighttime) on week 4 and hour 16 on week 8 by 24.8 to 30.2 mmHg, but **sibutramine patients SBP was increased 3 to 13.4, so differences were 27.8 to 43.6 mmHg.** 16-hour values were statistically significant. DBP showed less decrease (21.5 and 38.9 at 24 hr on weeks 4 and 6), but sibutramine increased 3.9 & 7.8 at 20 hr, 3.9 and 1.9 at 24 hr. Differences were significant at several time points. Other time points and mean arterial pressures showed trend toward significant. Where blood pressure was not significantly increased by drug, trends are consistently in that direction.

The Advisory Committee was **concerned about the increase in blood pressure**, and the **failure to show benefits in terms of cardiovascular risk factors.** In particular the lack of a normal diurnal decrease in blood pressure was of concern. In study BP 850, bpm increase in pulse rate were 5.3 and 4.5 in the 5 and 20 mg groups respectively. In general, pulse and blood pressure increases were not dose-related. Increased pulse rate was a consistent finding and seen in most studies.

Placebo weight loss is large enough that it is important that placebo responders cannot be identified so that they need not be exposed to drug.

In a summary of 54 clinical trials, **tachycardia** was reported as an adverse event in 0.3% of placebo and 2.5% of drug-treated patients. In depression studies, tachycardia was reported in 0.9% of placebo and 3.4% of drug patients; palpitations in 1.7 and 4.6%; and hypotension in 0.3 and 1.7%, respectively. **Blood pressure was significantly increased**, generally by 3-5 mmHg at doses of 5 mg or more. In placebo-controlled studies of obese normotensive subjects, **placebo-subtracted mean changes in systolic pressure ranged up to 4.7 mmHg.** There was not a clear dose relationship, but there did seem to be a tendency to more change with higher doses. Hypertensive patients tended to show a small decrease, but BP decreases on placebo were even greater, so that placebo-subtracted differences favored placebo. This decrease may be due to regression to the mean since patients were separated for analysis on the basis of their initial blood pressure. BP is expected to decline somewhat from baseline as a result of initial tension. Similar results were seen in systolic and diastolic pressures. Over all controlled studies, about 50% of patients on drug had increases in SBP and 40% had decreases; on placebo, about 40% had increases in SBP and nearly 50% had decreases. In DBP, about 32% of drug patients had decreases while 50% had increases; in placebo patients 45 and 37% had

decreases and increases. In these controlled studies, **outliers** (systolic or diastolic BP increased at least 25mmHg at least at one visit) were about 28 to 38% percent of drug-treated patients (read off the histogram). In the 10-15 mg groups with 635 and 422 subjects, 28 and 37% were classified as outliers.

Of most concern are the few patients who do have a **sustained, substantial blood pressure elevation**. Also, even though not sustained, a spike of BP could potentially precipitate a stroke, as is thought to happen rarely with phenylpropanolamine. It is not possible to screen for this event, if it results in an excess risk on initial drug administration (also as is thought to happen with PPA).

Colman review p.157 has a table of SBP and DBP changes from baseline at 6, 12 and 18 mo in the 852 extension study, which shows in the "All Doses" column that patients who have been on study 18 mo have more change than those on study 12 mo (4.2 vs 1.8 diastolic and 7.6 vs 6.1 systolic), indicating that **BP continues up beyond the year that has been carefully studied** so far. Also, on p 158, the percent of patients with elevations **sustained for 3 consecutive visits is 6% for systolic and 4% for diastolic**, a fairly high number for the benefits obtained.

The sponsor proposes to screen patients for 8 weeks to detect any diastolic or systolic elevations of blood pressure on two consecutive visits (outliers). This method is said to identify 55 to 60% (study BPI 852) or 70 to 80% (study SB 1047) of eventual **hypertensive outliers**. If the actual detection may be as low as 55%, a great many patients with substantial elevations of blood pressure would be missed. Even a few percent of missed hypertensives would be too many, as they might end up with strokes, cardiac hypertrophy, myocardial infarction or heart failure. This is a **population prone to cardiovascular events and cardiovascular deaths**.

The time-course of BP elevations would be helpful, as would blood pressure relationship to demographic factors, and to drug-induced weight loss. There is enough evidence to be worrisome, particularly the nighttime differences in BP. At the same time the **health benefits were not demonstrated for insulinemia and glucose tolerance, or for lipids.**

Comments and summary:

1. There is indisputably a mean effect on body weight that provides small but nevertheless **adequate efficacy for approval** with the expectation that physicians and patients make the final decision about use of the drug in the individual patient.

2. There is a small mean **increase in blood pressure** that is statistically significant, but clinical importance is not known.

3. There are a substantial number of patients who have an **increase in blood pressure** of a degree that is probably **clinically significant**.

4. The ability to **screen for blood pressure elevations** and to eliminate those patients for whom risks are substantial is hard to evaluate.

   a. One difficulty with screening blood pressures in order to eliminate those who get substantial BP changes is the finding that **nocturnal blood pressures** in drug treated patients are significantly higher relative to baseline than pressures in placebo patients. Daytime screening may screen out nocturnal effects only if they are highly correlated with convenient daytime BP determinations.

   b. Also, it is not clear that blood pressure **elevations of 8 weeks duration** are unlikely to pose a serious risk.

   c. And, the **false negatives appear to be unacceptably high** for us to recommend that care providers apply the proposed screen with any assurance of preventing cardiovascular events.

5. Lastly, the **absence of other beneficial changes** in cardiovascular risk factors, particularly glucose tolerance raises the question of why there is a disconnect between weight loss and insulin/glucose metabolism, and just what this disconnect does to CV risks. Could it increase the risks?

Recommendations:

1. Exploration of methods that could provide feasible and **effective screening** of patients for cardiovascular risk from the pressor effects of sibutramine should be undertaken by the sponsor.

2. Without some information allowing reasonably **accurate identification of patients** likely to develop substantial blood pressure elevations on this drug, it should be regarded as not approvable.

3. **Benefits have not been shown to outweigh risks**, and it seems unlikely that acceptable screening can be developed from the information now available.

4. Because of the short time available to meet User Fee Goals, this drug is **not approvable** for an indication of weight control at this time.

Gloria Troendle/10/11/96
cc:NDA 20632
Div File
HFD-510/GTroendle/EColman

APPEARS THIS WAY
ON ORIGINAL

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ON ORIGINAL

MEMORANDUM

DATE: 25 March 1997

TO: Eric Colman, MD
Medical Officer/Metabolic-Endocrine Group 2

FROM: Bruce V. Stadel, MD, MPH
Medical Officer/Epidemiology

SUBJECT: Sibutramine and blood pressure
NDA 20-632/Meridian (sibutramine)/Knoll Pharmaceutical Company

This replies to your request for consultation regarding the effects of sibutramine on blood pressure, and is based on: (1) the Medical Officer's 10 May 1996 Review of the NDA, pages 10 and 26; (2) the Sponsor's 3 January 1997 Amendment to the NDA, Attachment 1, called "Outliers: Time Course of Blood Pressure Changes in Outliers;" (3) the Sponsor's 23 January 1997 submission to the NDA called "Response to Facsimile of January 17, 1997;" (4) the 11 March 1997 and 13 March 1997 Memoranda of Consultation by Dr. Lee-Ping Pian, Division of Biometrics 2 -- copies attached.

BACKGROUND

The findings below refer to the main clinical trials of sibutramine, Studies BPI 852 and SB 1047. Study BPI 852 was conducted in the U.S. and was six months long: of patients randomized, 80% were women and 78% were Caucasian, 15% Black, and 7% Mexican-American; the age range was mean = 44. Study SB 1047 was conducted in the U.K. and was a year long: of patients randomized, 80% were women, and >98% were Caucasian; the age range was mean = 42.

FINDINGS

Table 1 gives an overview of how often patients in Studies BPI 852 and SB 1047 , on placebo and on sibutramine 5, 10, 15, or 20 mg per day , had at least two consecutive systolic blood pressures on-study that exceeded baseline by 10+, !5+, or 20+ mm Hg -- and Table 2 gives an overview of how often patients in the two studies had at least two consecutive diastolic blood pressures that exceeded baseline by 5+, 10+, or 15+ mm Hg.

Attachments 1 and 2 present statistical analyses of the data in Tables 1 and 2, and all p-values cited below are from Attachments 1-2 (Note: Attachment 1 includes data on systolic and diastolic blood pressures that exceeded baseline by 8+ and 12+ mm Hg because these analyses were done before I simplified the presentation).

Finally, Figures 1-4 show that: (1) the blood pressure effects of sibutramine in Studies BPI 852 and SB 1047 appeared over an interval of about 4-16 weeks, and that (2) the criterion of "at least two consecutive blood pressures on-study that exceeded baseline." by the amount described above, provides a reliable guide to substantial increases in mean placebo-subtracted systolic and diastolic blood pressure over the course of Studies BPI 852 and SB 1047.

DISCUSSION

1. Tables 1 and 2 show that the effects of sibutramine on blood pressure in Studies BPI 852 and SB 1047 were generally similar across the dose range 5-15 mg per day (20 mg per day was given only in Study BPI 852). This is not surprising since the two studies involved similar patient populations and because the blood pressure effects of sibutramine appeared over an interval of about 4-16 weeks, or less than the six months' length of Study BPI 852, which was the shorter of the two. I think the generally similar findings across the dose range 5-15 mg per day make it reasonable to use meta-analytic methods on these data.

   1.1 In Study BPI 852, 40% of patients on sibutramine 5-15 mg per day versus 29% of patients on placebo had at least two systolic blood pressures on-study that exceeded baseline by 10+ mm Hg, p =0.02. In Study SB 1047, 41% of patients on sibutramine 10-15 mg per day versus 34% of patients on placebo had at least two systolic blood pressures on-study that exceeded baseline by 10+ mm Hg, p=0.18.

   Combining the above findings by meta-analysis, p = 0.008. I conclude that sibutramine increased the frequency of two consecutive systolic blood pressures on-study that exceeded baseline by 10+ mm Hg, from about for patients on placebo to about for patients on sibutramine 5-15 mg per day, and that the finding is significant statistically.

   1.2 In Study BPI 852, 45% of patients on sibutramine 5-15 mg per day versus 37% of patients on placebo had at least two diastolic blood pressures on-study that exceeded baseline by 5+ mm Hg, p = 0.09. In Study SB 1047, 42% of patients on sibutramine 10-15 mg per day versus 29% of patients on placebo had at least two diastolic blood pressures on-study that exceeded baseline by 5+ mm Hg, p= 0.004.

   Combining the above findings by meta-analysis, p = 0.001. I conclude that sibutramine increased the frequency of two consecutive diastolic blood pressures on-study that exceed baseline by 5+ mm Hg from about for patients on placebo to about of patients on sibutramine 5-15 mg per day, and that the difference is significant statistically.

2. Tables 1 and 2 also show that sibutramine 20 mg per day had a greater blood pressure effect than sibutramine 5-15 mg per day:

   2.1. In Study BPI 852, 16% of patients on sibutramine 20 mg per day, 10% of patients on sibutramine 5-15 mg per day, and 7% of patients on placebo had at least two systolic blood pressures on-study that exceeded baseline by 20+ mm Hg. For the comparison of sibutramine 20 mg per day to placebo, $p = 0.0094$. For the comparison of sibutramine 5-15 mg per day to placebo, $p = 0.19$.

   2.2 In Study BPI 852, 10% of patients on sibutramine 20 mg per day, 7% of patients on sibutramine 5-15 mg per day, and 4% of patients on placebo had at least two diastolic blood pressures on study that exceeded baseline by 15+ mm Hg. For the comparison of sibutramine 20 mg per day to placebo, $p = 0.0395$. For the comparison of sibutramine 5-15 mg per day to placebo, $p = 0.22$.

RECOMMENDATIONS

I recommend that:

1. Approval to market sibutramine for weight loss be limited to < 20 mg per day.

2. The label should convey information about the blood pressure effects in the section on "Warnings." For example:

   Sibutramine substantially increases blood pressure in some patients, and this effect is similar in magnitude across the dosage range of 5-15 mg per day. Blood pressure should be measured and recorded before sibutramine is started and at regular intervals during the first three months of treatment. Benefit/risk should be weighed carefully for patients with substantial, persistent increases in systolic or diastolic blood pressure.

   In the two main clinical trials of sibutramine, doses of 5-15 mg per day increased the frequency of at least two consecutive systolic blood pressures on-drug that exceeded pre-drug baseline by 10+ mm Hg from about for patients on placebo to about 40-41% for patients on active drug ($p = 0.008$ for meta-analysis of the two trials), and increased the frequency of at least two consecutive diastolic blood pressures on-drug that exceeded pre-drug baseline by 5+ mm Hg for about for patients on placebo to about for patients on active drug ($p = 0.001$ for meta-analysis of the two trials).

Bruce V. Stadel, MD, MPH

cc:

Archive: NDA 20-632
HFD 510: SSobel
Gtroendle
Bstadel
HFD 715: DMartricello
Lpian

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TABLE 1

PERCENT OF PATIENTS WITH AT LEAST TWO CONSECUTIVE SYSTOLIC BLOOD PRESSURES ON STUDY THAT EXCEEDED BASELINE BY:

	MM OF MERCURY 10+	15+	20+
STUDY BP852 UNITED STATES 6 MONTHS			
PLACEBO (N=148)	29	12	7
SIBUTRAMINE			
5 MG (N=151)	41	14	9
10 MG (N=150)	46	22	11
15 MG (N=152)	34	17	12
5-15 MG (N=453)	40	18	10
20 MG (N=146)	49	27	16
STUDY BP1047 UNITED KINGDOM 12 MONTHS			
PLACEBO (N=163)	34	18	13
SIBUTRAMINE			
10 MG (N=161)	39	22	17
15 MG (N=161)	42	24	19
10-15 MG (N=322)	41	23	18

TABLE 2

PERCENT OF PATIENTS WITH AT LEAST TWO CONSECUTIVE DIASTOLIC BLOOD PRESSURES ON STUDY THAT EXCEEDED BASELINE BY:

	MM OF MERCURY 5+	10+	15+
STUDY BP882			
UNITED STATES			
6 MONTHS			
PLACEBO (N=148)	37	20	4
SIBUTRAMINE			
5 MG (N=151)	44	29	7
10 MG (N=150)	45	29	7
15 MG (N=152)	48	22	6
5-15 MG (N=453)	45	27	7
20 MG (N=146)	59	36	10
STUDY 1047			
UNITED KINGDOM			
12 MONTHS			
PLACEBO (N=163)	29	16	6
SIBUTRAMINE			
10 MG (N=161)	43	30	10
15 MG (N=161)	42	26	7
10-15 MG (N=322)	42	28	9

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MEMORANDUM

DATE: 10/11/96

FROM: Eric Colman, M.D 10/11/96

TO: NDA 20-632 file

CC: Maureen Hess, R.D., MPH
Gloria Troendle, M.D.
Bruce Stadel, M.D., MPH
Solomon Sobel, M.D.

SUBJECT: Sibutramine Review

In May of 1996 I completed the medical review of Sibutramine Hydrochloride. In June of 1996 I reviewed the results of 2 additional studies submitted to the NDA. I recommended nonapproval of the drug for the long-term treatment of obesity. The principal reason for my decision was the evidence of Sibutramine's pressor effect. In addition, the data in the NDA did not support the notion that the potential risk associated with the drug's pressor effect would be offset by improvements in lipoprotein lipid levels, as the Sponsor proposed. The effect of Sibutramine on lipoprotein lipid levels — expressed as mean changes from baseline — was variable across studies. The data did not demonstrate that Sibutramine-treated patients had consistent improvements in lipid levels when compared to placebo-treated subjects.

On September 26, 1996 an Advisory Committee meeting was held to discuss the Sibutramine application. During the meeting the Sponsor presented the results of a meta-analysis of the lipid data in the NDA. These data suggested that there were improvements in some lipid parameters in sibutramine-treated patients who achieved at least a 5% reduction in body weight. The details of this meta-analysis were submitted to the Division for review on 10/9/1996. Final conclusions regarding the validity of the results of this meta-analysis cannot be made until the data are reviewed by Dr. Lee Pian, an Agency statistician.

In any event, my primary concern continues to be the effect of Sibutramine on blood pressure. The need for an effective screening process to identify subjects, early after initiation of treatment, who experience significant increases in blood pressure was voiced at the Advisory Committee meeting. The Sponsor submitted, on 10/9/1996, an analysis of the time to first occurrence of clinically significant elevations in blood pressure. Time has allowed for only a cursory review of these data. The Sponsor states that approximately 60% of the patients on Sibutramine who were destined to experience a clinically significant increase in systolic or diastolic blood pressure (increase of $\geq$ 10 mmHg on 2 consecutive visits) at any time during the course of studies BPI 852

and SB 1047 could be identified by 4-8 weeks of treatment. While these results are encouraging and the Sponsor should be commended for pursuing such analyses, a number of important issues remain:

1. Is the use of an increase in SBP or DBP of ≥ 10 mmHg on 2 consecutive visits the best criterion to identify subjects who will have clinically significant drug-induced increases in blood pressure?

2. Is the identification of approximately 60% of the subjects by week 8 of treatment sufficient from a safety standpoint? Do the remaining 40% of the patients who develop a clinically significant increase in blood pressure after week 8 have an equal, greater, or lesser magnitude of change in BP when compared to the 60% of subjects identified within the first 8 weeks?

3. Is the drug's "efficacy" reduced after the subjects with clinically significant increases in blood pressure are removed from the analyses?

4. The results of these retrospective analyses might be considered hypothesis generating; they should to be tested in a prospective study.

Additional concern regarding blood pressure comes from study BPI 855. In this study, twenty-four hour ambulatory blood pressure monitoring indicated that 20 mg qd of Sibutramine not only eliminated the expected nocturnal reduction in blood pressure, but in fact, the drug increased nocturnal blood pressures when compared to the response in placebo patients. I think the results of this study are potentially of great importance and merit further study.

RECOMMENDATIONS

The pressor effect of Sibutramine is not well characterized. The extended use of Sibutramine as currently proposed by the Sponsor, I feel, may likely subject a significant portion of relatively healthy, overweight individuals to substantial risk for cardiovascular events. I recommend that the following phase 3 studies be conducted to better characterize the effects of this drug on blood pressure.

1. A 12-week, randomized, double-blind, placebo-controlled study to test the hypothesis that the majority of subjects destined to develop clinically significant increases in blood pressure can be identified within 4-8 weeks of treatment. Weight loss should also be a primary efficacy endpoint.

2. A randomized, double-blind, placebo-controlled study in which the effects of Sibutramine on nocturnal blood pressure are examined. This study should be larger than Study BPI 855 (n=20) and should be conducted in obese individuals without a history of hypertension. Weight loss should be a primary objective.

10/11/96

Eric Colman, M.D.

10-11-96

DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION **Public Health Service**

Division of Cardio-Renal Drug Products

Memorandum

DATE : SEP 16 1996

FROM : Director, Division of Cardio-Renal Drug Products, HFD-110

SUBJECT: Consultation regarding blood pressure effects of sibutramine, NDA 20-632, Knoll Pharmaceutical Company

TO : Maureen Hess, Consumer Safety Officer
Division of Metabolic and Endocrine Drug Products, HFD-510
Eric Colman, M.D., Medical Officer
Division of Metabolic and Endocrine Drug Products, HFD-510

This is a cover memorandum to the attached review which was conducted by Dr. Norman Stockbridge, Medical Group Leader in the Division of Cardio-Renal Drug Products (dated September 11, 1996).

I agree with the overall conclusion. Namely that one could evolve a risk/benefit analysis (gain from weight loss vs risk of stroke) along the lines outlined by Dr. Stockbridge and that decision making should be based upon such an analysis. Consequently, although sibutramine raises blood pressure (and that is clear enough from the data reviewed by Dr. Stockbridge), that fact alone is an insufficient cause for rejecting sibutramine as an appropriate anti-obesity agent.

The model proposed for use in the review is data based with respect to the effects of blood pressure and its relationship to the risk of stroke. The model presented is not data based (Dr. Stockbridge did not have access to data relevant to the morbid/mortal effects of obesity) with respect to the effect of body weight on the risk of morbid/mortal events (presumably such data are available, but they were not available to us). Thus, one quantitative component of data needed to perform the analysis suggested is not present in the review. The approach is clear enough and such analysis could be done.

Presumably, sibutramine is a mixed (direct and indirect) acting sympathomimetic amine (data that would address this question were not available for our review). If so, one could realistically expect that tolerance or tachyphylaxis would be a part of the description of its hemodynamic actions; since the 2 other (immediately remembered) drugs of this type (metaraminol and phenylpropanolamine) clearly exhibit such behavior in man and others of similar type exhibit the same property in animal models.

Along those lines, no data that reflect the effects of the 1st dose of sibutramine in man were available for review. Absent such data, it is not possible to deduce that tolerance/tachyphylaxis in man is (or is not) a property of sibutramine. It is possible that the 1st dose has much greater effects than those documented after multiple dosing. This is certainly a remediable defect in the description of the clinical pharmacology of sibutramine in man, but is not critical to the decision of approval/non-approval. It would be useful information that could contribute substantively with respect to Instructions for Use and to Clinical Pharmacology. I would encourage getting such data.

It is not at all clear, lacking individual data (having only group means to review), that each individual has a rise in blood pressure over the dose ranges tested. Moreover, it is not clear what the dose-response (single or multiple dosing) for blood pressure looks like. That a group's blood pressure (on multiple dosing) is raised in a dose-related fashion, is clear enough. But the group elevations described are modest and what dose would cause substantive changes in blood pressure is a sheer guess. Intersubject variability cannot be estimated. If all patients had blood pressure elevations like those depicted in Figure 6 of the review, one might view the effects along the lines of blood pressure elevations associated with

exercise (although somewhat more sustained associated with sibutramine than that associated with exercise). If only 2 of the 10 subjects in Study BPI 855 brought the group mean up, one could draw an entirely different conclusion. It would seem reasonable to resolve such questions.

We hope that these considerations are useful to your deliberation and would be pleased to discuss it further, should you so desire.

APPEARS THIS WAY
ON ORIGINAL

Norman Stockbridge, M.D., Ph.D.
Division of Cardio-Renal Drug Products, HFD-110

Food and Drug Administration
Rockville, MD 20857

5600 Fishers Lane
Tel (301) 594-5329 FAX: (301) 594-5494

Memorandum

DATE: Wednesday, September 11, 1996

TO: Maureen Hess, CSO, HFD-510
Eric Colman, MD, MO, HFD-510

THROUGH: Ray Lipicky, Director, DCRDP

Robert Temple, Director, ODE-I

SUBJECT: Effects of sibutramine on blood pressure

1. Consult request

This memo is a response to a consult request dated 5 August 1996. It is understood that NDA 20-632 (sibutramine for weight loss) is scheduled to go before an Advisory Committee on 26 September. The consult request reads as follows:

> *Please review: 1) Overview of BP data, hard copy and disk 2). Original protocol and results of BPI 855-A study using 24 hour ambulatory BP monitoring plus; revisal data on hardcopy. Sibutramine- anti-obesity agent, inhibitor of reuptake of NE and Serotonin.*

2. Material submitted

The material reviewed consists of two submissions by Knoll Pharmaceutical Company to NDA 20-632. The first is dated 19 July 1996. It consists of a two-page description of (quite reasonable sounding) data handling procedures for ABPM data in the clinical study BPI 855, followed by 84 pages of graphical and tabular data from this study. The second piece is dated 1 August 1996. It consists of a 13-page document outlining the sponsor's view of effects of sibutramine on blood pressure in placebo-controlled studies. This submission is accompanied by two diskettes, each of which contains a single WordPerfect 6.1 document. One electronic document appears to be identical in content to the 1 August 1996 paper document (but without figures). The other electronic document is the original "final study report" for study BPI 855, dated 23 February 1994, missing figures and some tables.

Thus, the material to review contains no original study protocols. The only trial with any detailed description is that for the ABPM study. There were no machine-readable data provided. Some of the hourly averaged ABPM data were keyed in from 19 July submission, but there were no raw data from individual subjects available in any form.

A copy of the draft medical review was requested on 3 September 1996 and delivered on 10 September 1996.

3. Non-ABPM blood pressure data

3.1. Summary of data in non-hypertensive subjects

3.1.1. Dose-response

Table 1 below and Figure 1 below are derived from the sponsor's summary data of effects of sibutramine on blood pressure in placebo-controlled studies. These are changes from baseline to the last on-treatment visit in studies of subjects with "uncomplicated" obesity. It is not stated how long the double-blind treatment period was, what was the temporal relationship between dosing and assessment of blood pressure, or the number of subjects in each active dose group. It is understood from conversation with Dr. Colman that these were randomized fixed-dose studies.

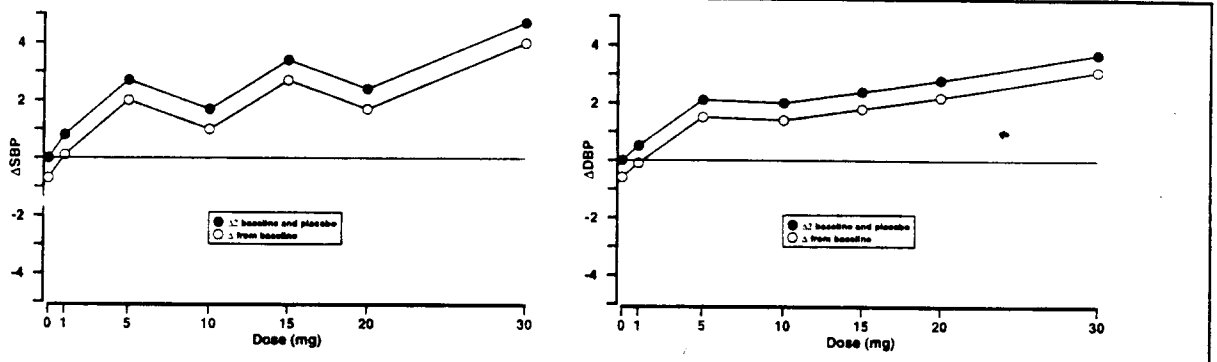

Figure 1. Effects on in-clinic blood pressure in placebo-controlled studies.

Table 1. Effects on in-clinic blood pressure in placebo-controlled studies.

	Plcbo n=469	Sibutramine (mg) n=1606					
		1	5	10	15	20	30
Systolic	-0.7	0.1	2.0	1.0	2.7	1.7	4.0
≤120 mmHg	4.0	2.3	6.3	6.4	7.6	6.1	6.5
>120 mmHg	-5.8	-4.0	-5.5	-5.2	-2.4	-5.6	-2.6
Diastolic	-0.6	-0.1	1.5	1.4	1.8	2.2	3.1
≤80 mmHg	1.2	1.9	2.8	3.1	3.7	3.5	4.7
>80 mmHg	-4.7	-5.2	-4.0	-2.2	-2.7	-2.8	-2.8

The table shows stratification based on baseline blood pressure. It is unstated how many subjects were in each stratum. Presumably the stratification was part of the analysis rather than part of the randomization procedure. The differences between the strata are apt to be the result of regression to the mean: subjects stratified on the basis of a spurious measurement below their true mean tend to rise while those stratified on the basis of a spurious measurement above their true mean tend to fall.

Without knowing whether they were gathered at the time of the peak effect or at trough, these data cannot conclusively be said to establish the foot of the dose-response curve. It seems likely at least that the 5-mg dose has an appreciable effect and that the 30-mg dose is not on the plateau.

3.1.2. Shifts

The proportions of subjects whose blood pressure rose, fell, or remained the same is shown in Figure 2 below. It is a little surprising that, for a continuous measurement, of subjects are shown as having no change.

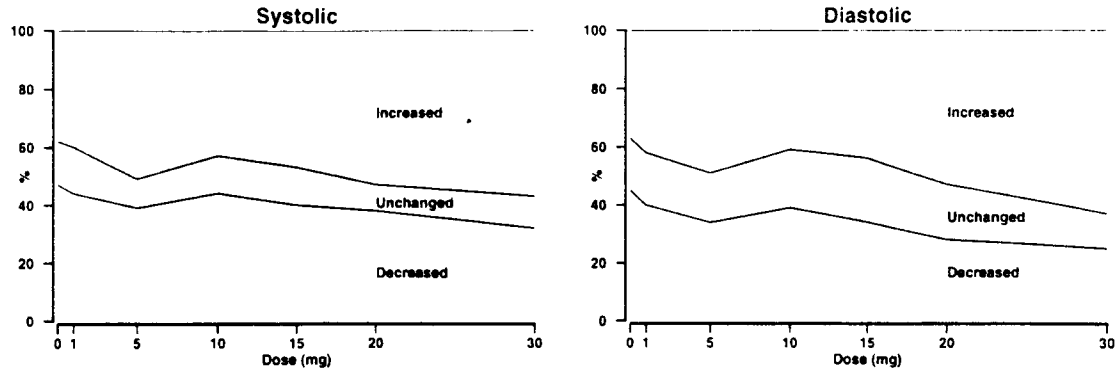

Figure 2. Proportions of subjects with shifts in blood pressure in placebo-controlled studies.

The amount of shift in blood pressure was also analyzed by the sponsor for placebo-controlled studies, as shown in Figure 3 below[1]. The curves are evidently fitted estimates based upon the 10-mmHg histogram bins, so it is prudent not to read too much into the details of the shapes. However, the curves are suggestive that the distribution tends to flatten out (the standard deviation tends to increase) at higher doses.

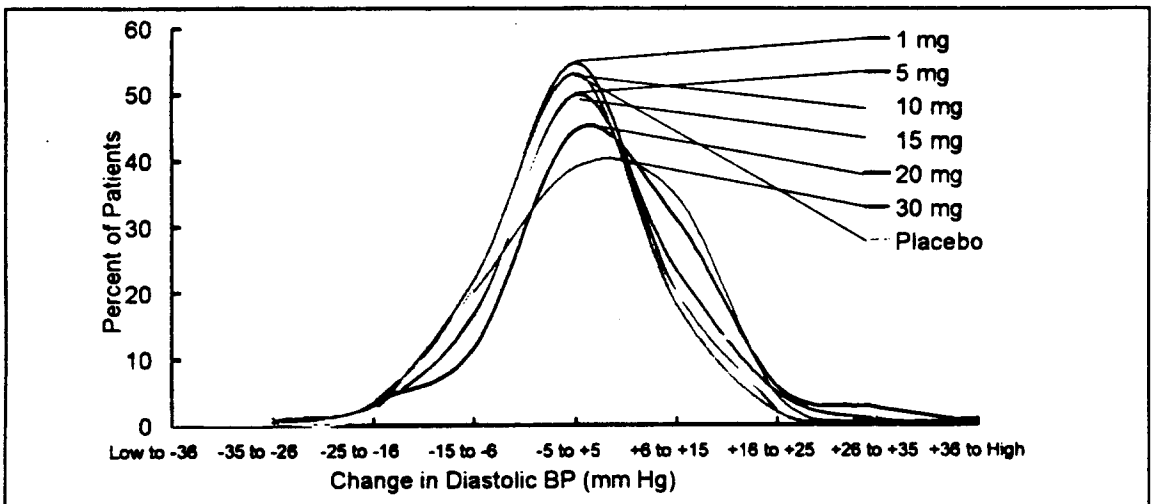

Figure 3. Frequency distribution for shifts in blood pressure in placebo-controlled studies.

3.1.3. Outliers Dose-response data are summarized for several measures of outlier responses in placebo-controlled studies in Figure 4 below.

3.2. Experience with hypertensive subjects

3.2.1. Study SB 2057 The sponsor also provided data from study SB 2057, conducted among obese hypertensive subjects. This 12-week study compared blood pressure responses between placebo (n=59) and sibutramine 10 mg (n=53). The enrollment criteria are not described. The results are presented with stratification by use or non-use of antihypertensive agents, but it is unstated whether such stratification was part of the study design or just part of the analysis. The magnitude of baseline- and placebo-subtracted response was similar to that described for non-hypertensives: +1.1/+1.4 mmHg. Subjects who were on antihypertensive therapy (n=37) had placebo- and baseline-corrected shifts of +4.5/+1.4 mmHg.

[1] The curves for the 10 and 15 mg doses were lost in monochrome scanning of the color original.

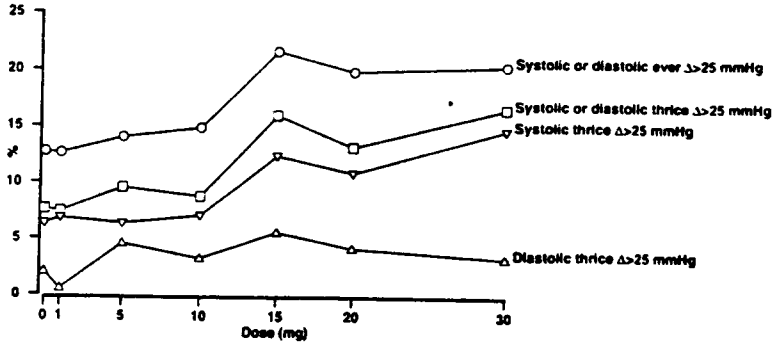

Figure 4. Outliers for increases in blood pressure in placebo-controlled studies.

3.2.2. Other hypertensives

Some studies did not recruit for, but did not exclude, obese subjects who were hypertensive. The sponsor summarized data from such subjects on placebo (n=97), and sibutramine 10 mg (n=65) and 15 mg (n=77). Mean double differences from baseline and placebo were +3.1/+1.2 for the 10 mg cohort and +2.9/+2.5 for 15 mg. Subjects (n=89) who were on antihypertensive treatment had mean placebo- and baseline-corrected shifts of +4.8/-4.1 (10 mg) and +2.9/+0.4 mmHg (15 mg).

4. Study BPI 855

4.1. Basis for review

Review of the study design was based upon an electronic document described in section 2 on page 1, and not the original study protocol. Study results were based upon the revised hardcopy data tables provided in the submission of 19 July 1996.

4.2. Title

A double-blind study to evaluate the effects of sibutramine hydrochloride versus placebo in an obese, controlled hypertensive population.

4.3. Conduct

This study was performed between June and November 1991. There was a single site and clinical investigator (DH Sugimoto, .).

4.4. Subjects

Subjects were to be males and postmenopausal or surgically sterile females, with a documented history of diastolic pressure >90 mmHg, on a stable dose of one antihypertensive agent (calcium channel blocker, ACE inhibitor, or diuretic) for 6 weeks. Exclusion criteria were (1) significant physical illness or clinical findings affecting absorption, metabolism, or excretion, (2) history or findings of alcohol or drug abuse, (3) significant neurological or psychiatric illness, (4) need for thyroid replacement therapy, other antihypertensive agents, or drugs affecting assay of urinary VMA, and (5) technically inadequate screening ABPM.

4.5. Study procedures

This was a randomized, double-blind, parallel-group, placebo-controlled study. There was no specified primary hypothesis. Subjects were randomized to receive either placebo or sibutramine 20 mg once in the morning daily for up to 8 weeks. The first week was conducted in clinic. Follow-up continued for 1 week after drug withdrawal.

Antihypertensive treatment was allowed to be modified as indicated.

Supine and standing vital signs were recorded (cuff) at 0, 4, 8, and 16 hours on days 0 to 4; on day 5; and at the end of 2, 4, 6, 8, and 9 weeks. Twenty-four hour ABPM data were recorded on days 0 and 3, and at the end of weeks 4 and 8.

Blood samples were obtained for assay of plasma sibutramine at baseline, days 4 and 5, and at the end of weeks 2, 4, and 8.

4.6. Results

4.6.1. Study conduct

Twenty subjects were randomized and 19 subjects completed study. Ten subjects were randomized to each treatment group.

Baseline data were comparable with the following exceptions. All 4 male subjects were randomized to placebo ($p<0.05$). Subjects in the placebo group were on average 12 kg heavier ($p=0.1$) and had supine blood pressure +3/+3 mmHg greater[2] than those on active treatment. Two subjects in the placebo group were on an ACE inhibitor plus diuretic, in violation of the study protocol.

Compliance (by capsule count) was, on average, in both treatment groups for the first and last two-week periods. One sibutramine subject withdrew after 4 weeks of treatment.

4.6.2. Cuff blood pressure

Mean changes in cuff measurements of blood pressure, supine and standing, are shown in Figure 5 below. Data from the 4-, 8-, and 16-hour time points on days 0 to 4 were apparently not collected systematically and so were not analyzed by the sponsor.

4.6.3. Ambulatory blood pressure

Ambulatory blood pressure data were presented as hourly means. Raw records were not available for review. Figure 6 below shows several views of the diastolic pressure data, as the reported averages, as changes from baseline, and as double differences; i.e., changes from baseline and placebo. No similar analyses of systolic pressure or heart rate were performed as part of this review.

These same data were smoothed by a center-weighted, moving-bin scheme[3]. The resulting curves are laid upon the unaltered data points in Figure 7 below.

From the ambulatory data, it can be seen that the placebo and active treatment groups were not especially well matched with regard to baseline diastolic pressure. It is several mmHg lower in the active treatment group.

At day 3 and week 4, the diastolic pressure in the placebo group declines from baseline. How much of this change, or the apparent rise between weeks 4 and 8, can be attributed to chance variation, to changes in antihypertensive medications, or other factors cannot be determined.

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[2] The difference was said not to be statistically significant.

[3] The value at each time point t was computed as:

$$x_t = \frac{(x_{t-1} + 2x_t + x_{t+1})}{4}$$

with appropriate adjustments at the end points.

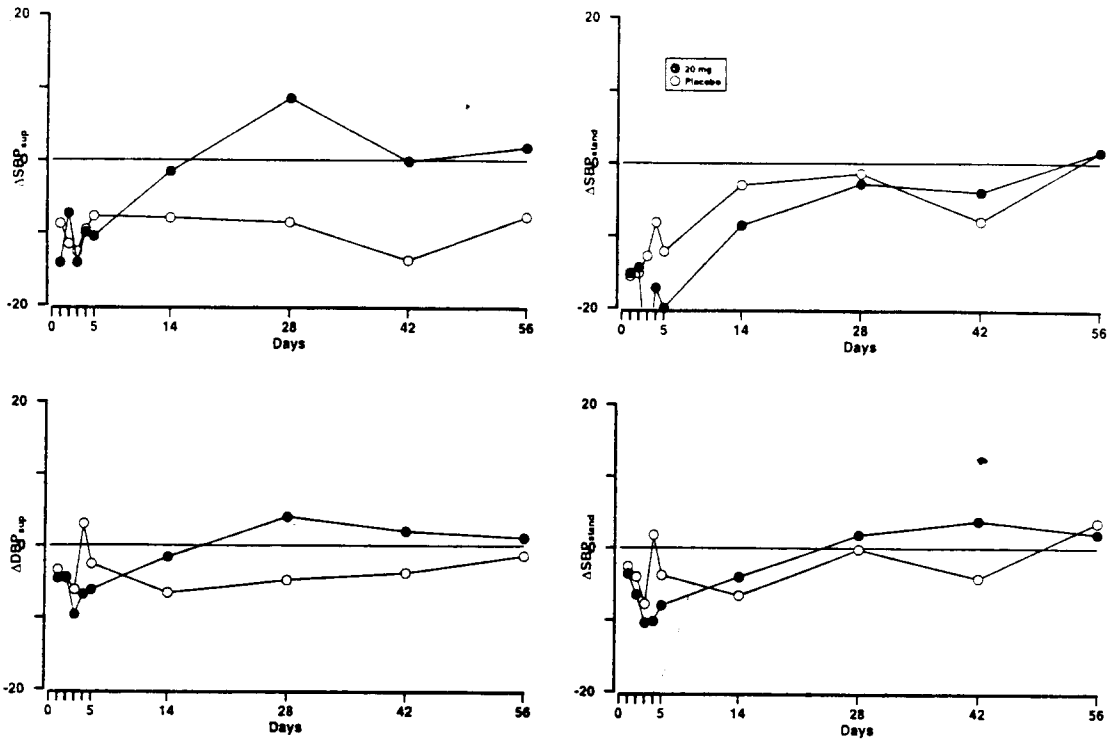

Figure 5. Changes in cuff blood pressures in study BPI 855

At each post-baseline measurement, the mean effect of active treatment was to increase diastolic pressure above that seen in the placebo group. Changes from baseline and placebo reveal some other systematic effects, as well. The most prominent effect, seen on all three post-baseline measurements, is a particularly large increase in the nighttime diastolic pressure. The effect is not an actual reversal of the normal nighttime fall in blood pressure, but it is a significant reduction in the magnitude of the fall.

An effect of treatment seems clearly established by day 3. Particularly without correlated data on changes in antihypertensive medications[4], the data are not adequate to conclude that the effect seen at 4 or 8 weeks represents the full effect of treatment.

The data on plasma drug levels do not appear in the study report, so the relationship between the apparent time course of drug effect and plasma level cannot be addressed.

5. Summary, discussion, and recommendations

5.1. Effects of sibutramine on blood pressure

The effects of sibutramine on blood pressure were not well characterized by the data presented for review.

[4] Changes in blood pressure medication were permitted by the protocol. However, a description of such changes as occurred were not in final study report.

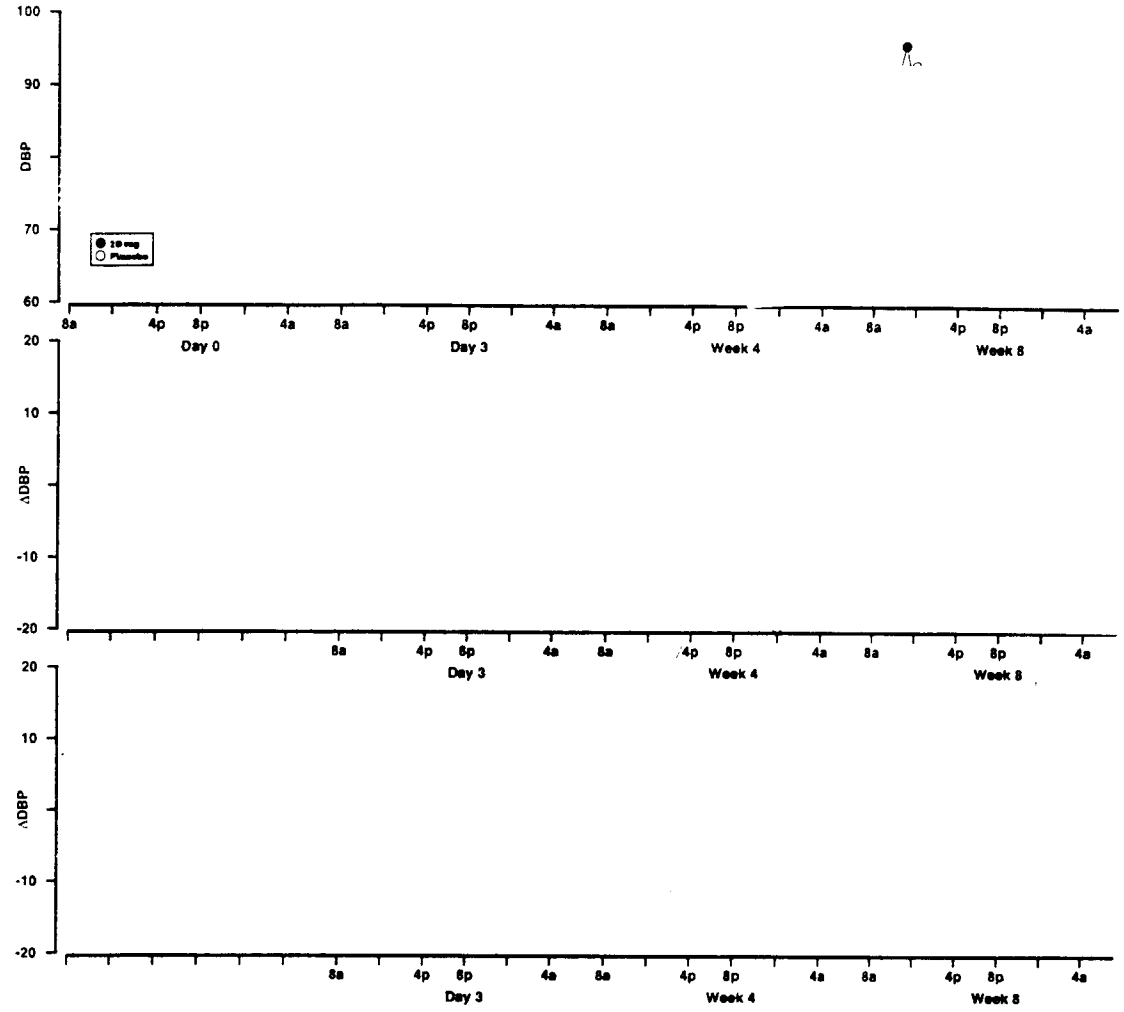

Figure 6. Hourly blood pressures in study BPI 855

The time course of changes in blood pressure following a dose of sibutramine can best be inferred from changes from baseline and placebo in ambulatory blood pressure. These data suggest that there are substantial mean effects during the nighttime, i.e., some s after dosing[5]. Study BPI 855 could have provided additional insight into the development of blood pressure effects had protocol-specified cuff data been obtained at periods of hours after dosing on the first few clinic days.

There are some data from which to assess the time course for development of hypertensive effects following repetitive dosing. These data, collected from the small number of subjects in Study BPI 855 do not rule out the possibility that blood pressure continues to rise after this time.

There are no available data from which to assess the time course of a return to normal blood pressure following a period of weeks or months of treatment.

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[5] The differences in response seen with cuff measurements supine and standing (Figure 5) are consistent with the apparent night-time effect being attributable to the supine position.

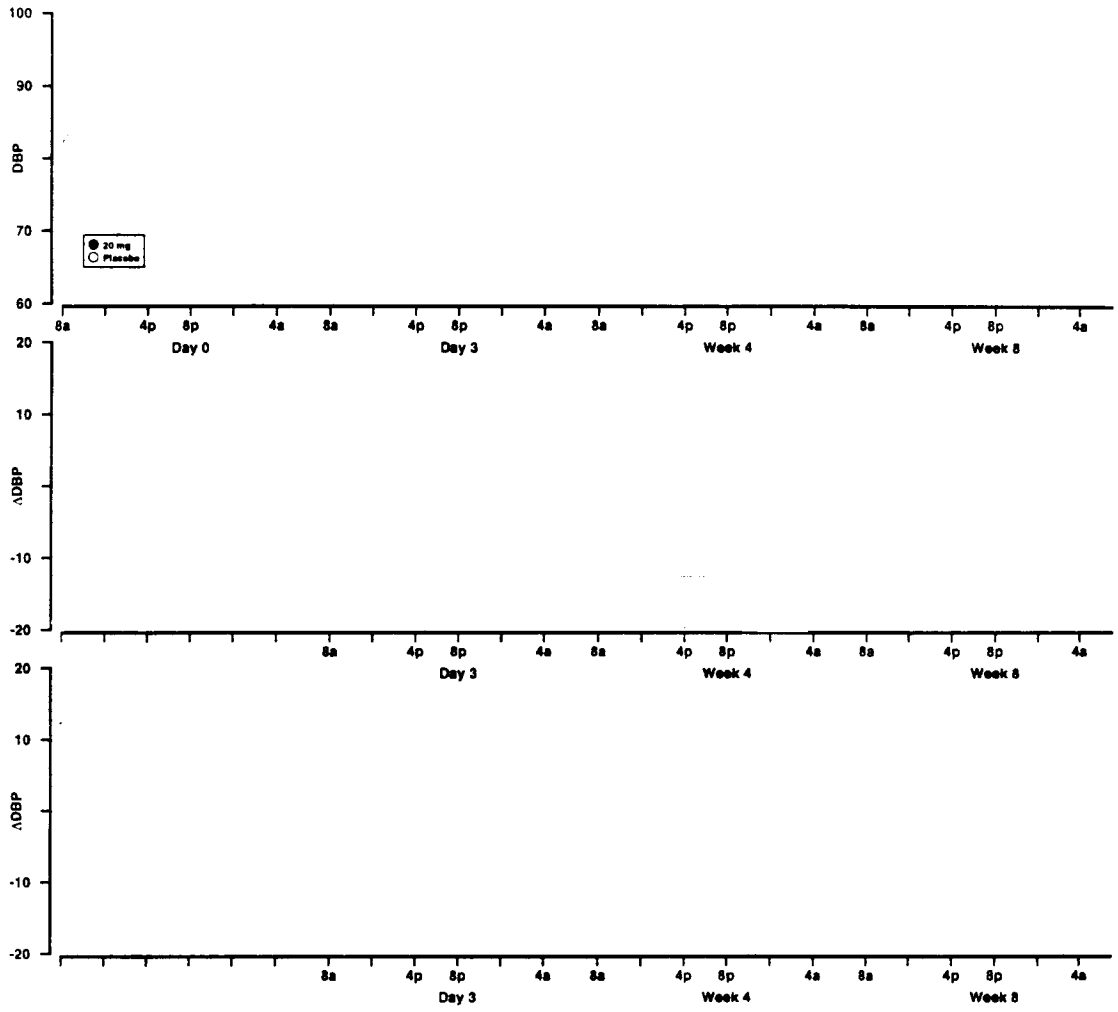

Figure 7. Smoothed blood pressures in study BPI 855.

The sponsor has provided some information with regard to the relationship between dose and mean changes in blood pressure. It needs to be clarified what the timing was for these measurements in comparison with the last dose. Doses substantially greater than 30 mg (the highest dose for which data were provided) would be necessary to assess the mean plateau response.

No individual subject data were provided for review. Group mean changes in blood pressure were modest, but it is not clear whether this represented the outlying responses of a small number of individuals or a shift by, more or less, the entire treatment group, superimposed, in either case, on normal diurnal and day-to-day changes in blood pressure. Were the same subjects response outliers at 4, 6, and 8 weeks in Study BPI 855? Figure 4 shows that a large proportion of subjects who ever showed a change in systolic or diastolic pressure >25 mmHg showed that finding on 3 successive occasions, raising the prospect that the greatest responders can be identified.

5.2. Algorithm for estimating net clinical benefit

Chronic elevation of blood pressure carries with it the risk of catastrophic cardiovascular events. In the relatively young population apt to receive sibutramine, the risk is predominantly that of stroke. Blood pressure elevation for the expected period of treatment might carry a less-than-proportional risk, but the observation that the risk of stroke is rapidly reduced fully in proportion to the change in blood pressure wrought by an antihypertensive drug suggests that there is little accumulation of risk.

The function which relates blood pressure to the risk of cardiovascular mortality or stroke is moderately well characterized. It is a function with no threshold; the lowest blood pressures carry the lowest risks, probably right up to the point where one cannot sit upright or stand. The risk is about twice as high in men as in women, but the increment in risk associated with hypertension is about twice as great in women. The data in Figure 8 below, from the 361,000 men in the Multiple Risk Factor Intervention Trial, are illustrative of the kind of data that are available.

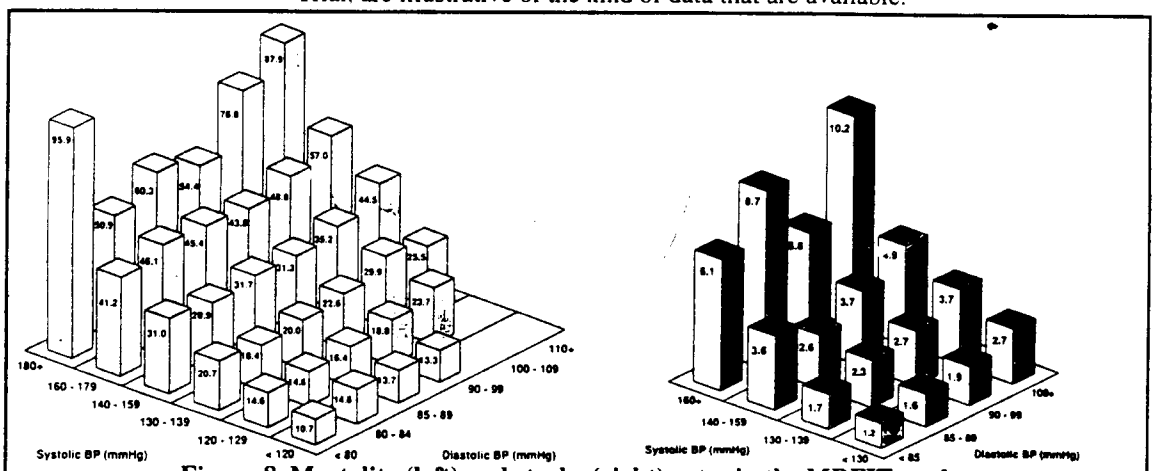

Figure 8. Mortality (left) and stroke (right) rates in the MRFIT study.

Although it is beyond the scope of this review, it is certainly feasible to work out a reasonable model of the risk per unit time associated with a given weight and blood pressure. Such a model will need to have a few other risk factors incorporated as well—gender, age, and smoking history, for example. With such a model, physicians and patients can make rational decisions regarding the use of sibutramine for weight loss. The basis for making such decisions is outlined below.

For simplicity, it is assumed that (a) sibutramine has no adverse effects other than blood pressure elevation, (b) the risk per unit time associated with blood pressure is independent of the mechanism (endogenous or drug-mediated) which sets it and independent of the amount of time at that blood pressure, and (c) the risk per unit of time associated with weight is also independent of the mechanism (endogenous or drug-mediated) which sets it and independent of the amount of time at that weight.

When other risk factors have been modeled, one can derive an individual's estimated mortal risk per unit of time as a function of weight and systolic or diastolic pressure. Such a surface would look similar to that shown in left-hand panel of Figure 9 below[6]. The right-hand panel of Figure 9 shows a contour plot of the same function; lines of equal risk are separated by equal increments in risk.

Sibutramine produces a quicker change in blood pressure than in weight. Thus, initiation of treatment would be expected to increase acutely a patient's risk of cardiovascular death. However, a net benefit can be achieved (in a probabilistic sense)

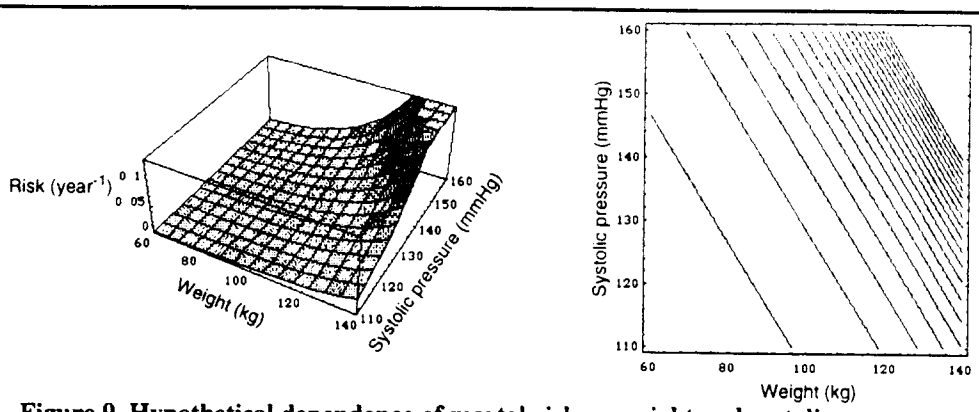

Figure 9. Hypothetical dependence of mortal risk on weight and systolic pressure.

over time if the patient's trajectory on this risk surface, on or off treatment, moves him into a region of lower risk.

Then, the question becomes how long one must sustain the new lower weight in order to offset the incremental risk associated with the process of achieving that lower weight. Arrows in Figure 10 below show progress in a hypothetical course of sibutramine. Initiation of treatment is associated with an immediate shift in systolic pressure. Thereafter, weight loss proceeds asymptotically to a new, lower steady-state. Then the drug is discontinued, and systolic pressure readjusts. The total risk associated with the drug treatment can be calculated as the sum of the risks-per-week. In this case, the patient went from a baseline risk of 0.045 year^{-1} to a final risk of 0.026 year^{-1}. Weight loss was 11 kg over 10 weeks, great enough that, if sustained, it would have made the shift in blood pressure worthwhile, even if the drug use was maintained indefinitely. In contrast, a subject starting from the same place and experiencing the same initial blood pressure change, followed by a drop in weight of only 2 kg over 10 weeks, would, according to this model, need to maintain the weight loss for some 10 months, off of sibutramine, to justify the mortal risk of treatment.

5.3. Recommendation

Were sibutramine's effects on blood pressure the only basis for considering non-approval, such a decision would seem to be a mistake, because potential long-term benefits of weight reduction could outweigh short-term risks of blood pressure elevation.

This review outlines a rational basis by which a physician and patient could evaluate the relative merits of the use or non-use of sibutramine for weight loss. The details of a plan could be developed from available epidemiologic data and incorporated in the label's instructions for use.

How closely patients would need monitoring is not clear from the data made available for this consultative review. If a patient's long-term blood pressure response (as distinct from the population's mean response) can be predicted from several short-term measurements, then the need for close monitoring for the duration of treatment would be reduced.

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6. The relationship between systolic pressure and risk is a reasonable approximation to the MRFIT data. The relationship between weight and risk is purely speculative, as is the interaction between weight and systolic pressure. The surface modeled was given by

$$r(w,s) = r_0 e^{(w-w_0)/\omega} e^{(s-s_0)/\sigma}$$

where r_0 is a base risk rate, w_0 and s_0 define the weight and systolic pressure to which the base rate corresponds, and ω and σ set weight and systolic pressure changes necessary to produce an e-fold change in risk.

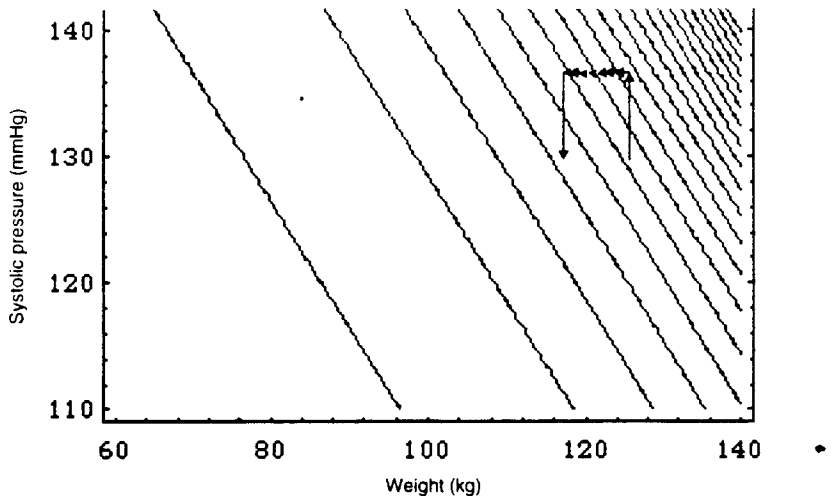

Figure 10. Risk changes associated a hypothetical course of sibutramine.

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M E M O R A N D U M

DATE: 30 August 1996

FROM: Bruce V. Stadel, MD, MPH
Medical Officer/Epidemiology

SUBJECT: Benefit/Risk Evaluation of Sibutramine
NDA 20-632/ Knoll Pharmaceutical Company

TO: Eric Colman, MD
Medical Officer
Metabolic-Endocrine Group 1

This replies to your request for review of the "Benefit/Risk Evaluation of Sibutramine" in the submission by Knoll dated 7 August 1996.

The model has two parts. The first part uses data from the Framingham Heart Study (FHS), which show that small differences in blood pressure and lipid levels at baseline in the FHS were predictive of substantial differences in the later occurrence of coronary heart disease and other cardiovascular disorders.

I have no reason to question the validity of the FHS itself. However, I think it needs to be emphasized that the relevance of FHS data to sibutramine is critically dependent on the extent to which:

(1) sibutramine has been shown to cause changes in blood pressure and lipid levels that are similar in magnitude and statistical significance to the naturally-occurring variations in baseline blood pressure and lipid levels that are used in the FHS part of the model, and

(2) changes in blood pressure and lipid levels that are caused by sibutramine have the same meaning biologically as the naturally-occurring variations in baseline blood pressure and lipid levels that are used in the FHS part of the model.

With regard to item (1) above, the 7 August 1996 submission by Knoll states on page 6 that "scenarios...were developed...using the actual mean changes seen in the sibutramine studies for diastolic blood pressure, cholesterol, and HDL cholesterol." However, the specific "sibutramine studies" that were used are not cited and nothing is said about the statistical significance of "the actual mean changes."

With regard to item (2) above, it is generally accepted that some drugs alter the occurrence of coronary heart disease and other cardiovascular disorders by altering blood pressure or lipid levels -- however, there are no data specific to sibutramine or other weight-loss drugs.

The second part of the model uses data from the Nurse's Health Study (NHS), which show that moderate differences in Body Mass Index (BMI) at baseline in the NHS, when the women were 30-55 years of age, were predictive of substantial differences in later rates of all-cause mortality and cardiovascular disease mortality. [BMI is defined as weight in kilograms divided by (height in meters)^2]

The limitations of the NHS part of the model are similar to those of the FHS part, i.e., the relevance of NHS data to sibutramine is critically dependent on the extent to which:

(1) sibutramine has been shown to cause changes in BMI that are similar in magnitude and statistical significance to the naturally-occurring variations in baseline BMI that are used in the NHS part of the model, and

(2) changes in BMI that are cause by sibutramine have the same meaning biologically as the naturally-occurring variations in baseline BMI that are used in the NHS part of the model.

With regard to item (1) above, I think the NHS part of the model applies the SB 1047 study findings for sibutramine 15 mg per day to the NHS data in a generally reasonable way. Placebo had only a small weight-loss effect in the SB 1047 study, so it is of no practical importance that the findings for placebo have not been subtracted from the findings for sibutramine (Tables 1 & 2). Also, it has been suggested that placebo effects in randomized double-blind clinical trials are due to participation in the trials, and would not otherwise occur (personal communication, Dr. Gerald Faich). Although I have not myself seen studies in support of this opinion, I think it is likely to be at least partly true.

With regard to item (2) above, I know of only one study that has investigated the relationship between intentional weight loss and subsequent mortality in women: Williamson DF, Pamuk E, Thun M, et al. Prospective study of intentional weight loss and mortality in never-smoking overweight U.S. women aged 40-64 years. Am J Epidemiol. 1995;141:1128-41. This observational follow-up study shows a decrease in all-cause mortality, after intentional weight loss, for the 35% of women who had obesity-related disorders prior to the weight loss; there is no decrease in all-cause mortality for the 65% without prior obesity-related disorders.

Among the 35% of women in the Williamson et al. study who had prior obesity-related disorders, the decrease in all-cause mortality after intentional weigh loss was 20% for a loss of 1-19 pounds and 19% for a loss of 20 pounds or more, i.e., the decrease in mortality was not clearly related to the amount of weight loss. I think this suggests that the decrease in all-cause mortality among women who lost weight intentionally involved lifestyle changes, such as increased exercise, in addition to weight loss itself.

CONCLUSIONS AND RECOMMENDATIONS

The "Benefit/Risk Evaluation of Sibutramine" model is based on relationships between naturally-occurring variations in BMI and subsequent rates of mortality and morbidity. These relationships suggest that weight loss caused by sibutramine or other drugs might reduce later mortality and morbidity, but do not meet the standard of evidence causality required for drug approval.

cc:

NDA 20-632
HFD 510 Sobel/Troendle/Stadel/Hess

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TABLE 1

SIBUTRAMINE STUDY 1047

PERCENT OF PATIENTS COMPLETING STUDY
BY WEIGHT CHANGE FROM BASELINE
AND TREATMENT GROUP

WEIGHT CHANGE FROM BASELINE	SIBUTRAMINE 15 MG (N=93)	PLACEBO (N=76)
LOSS		
< 5%	22	36
5 to <10%	26	21
10 to <15%	24	5
≥15%	15	2
GAIN		
< 5%	9	30
5 to <10%	5	5
10 to <15%	0	0
≥15%	0	0

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TABLE 2

SIBUTRAMINE STUDY 1047

PERCENT OF PATIENTS RANDOMIZED IN STUDY
BY WEIGHT CHANGE FROM BASELINE
AND TREATMENT GROUP

WEIGHT CHANGE FROM BASELINE	SIBUTRAMINE 15 MG (N=161)	PLACEBO (N=163)
LOSS		
< 5%	13	21
5 to <10%	15	10
10 to <15%	14	2
≥15%	9	1
GAIN		
< 5%	5	14
5 to <10%	3	2
10 to <15%	0	0
≥15%	0	0

OCT -7 1997

DIVISION OF ANESTHETIC, CRITICAL CARE
AND ADDICTION DRUG PRODUCTS

HFD-510 CONSULT
ABUSE LIABILITY ASSESSMENT

NDA #:	**20-632**
SPONSOR:	**Knoll Pharmaceutical Company**
PRODUCT:	**Meridia®**
GENERIC NAME:	**Sibutramine Hydrochloride Monohydrate**
CHEMICAL NAME:	**Cyclobutanemethanamine, 1-(4-chlorophenyl)-N, N-dimethyl-(2-methylpropyl)-hydrochloride, monohydrate, (±)**
DOSAGE FORM:	**Capsules**
CLINICAL DOSAGE:	**5, 10, and 15 mg**
INDICATION:	**Long-term treatment of obesity**
REVIEWERS:	**BeLinda A. Hayes, Ph.D. , Michael Klein, Ph.D., and Silvia Calderon, Ph.D.**
REVIEWERS DATE:	**October 6, 1997**

BACKGROUND.

Knoll Pharmaceutical Company has submitted NDA 20-632 for Sibutramine hydrochloride monohydrate capsule to Food and Drug Administration Division of Metabolism and Endocrine Drug Products. Sibutramine hydrochloride monohydrate, Meridia®, is indicated for the long-term treatment of obesity. Meridia® will be marketed as 5, 10, and 15 mg capsules. The recommended starting dose is 5 mg per day; the dose can be adjusted, as needed, to a maximum of 20 to 30 mg.

When developing a new pharmaceutical product, which demonstrates structural similarity and/or a similar pharmacological profile with a known drug of abuse, FDA requires the sponsor to submit an abuse liability assessment package and scheduling proposal [21CFR § 314.50 (5)(vii)] with their NDA submission. Sibutramine meets the requirement for evaluation in accordance to the Controlled Substance Act (CSA). Issues relating to drug abuse and the appropriate scheduling of the drug under the CSA are the responsibilities of the Division of Anesthetic, Critical Care, and Addiction Drug Products' Controlled Substance Evaluation Team. The abuse liability assessment is based upon the evaluation of all available data on the chemistry, pharmacological (both preclinical and clinical), pharmacokinetic, and pharmacodynamic profiles of the compound, and the adverse effects associated with the compounds. According to the sponsor, Sibutramine's abuse potential is currently being evaluated in Europe.

Sibutramine is subjected to extensive first-pass metabolism resulting in the formation of M1 and M2. Single-dose study in normal volunteers show that the kinetics of M1 and M2 are linear in the range Mean $t_{1/2}$ of M1 was 12.6 hours and that M2 was 13.3 hours Overall plasma concentrations of M2 were 2-3 times higher than M1 concentrations. Peak concentrations were reached for M1 and M2 around 4-6 hours post-dose. After a single 15 mg dose, increased levels of M1 were observed in the obese subjects as compared to normal controls, which a corresponding decrease in the M2 metabolite. The combined M1 and M2 profiles for the 2 groups are superimposable. Because M1 and M2 are the active forms, and sibutramine is only sporadically detected in human plasma after administration of clinically relevant doses. Also, the (+) stereoisomers of M1 and M2 are about -10 times more potent (in rats) at reducing food intake than the (-) stereoisomers.

Sibutramine biochemical profile is similar to that of marketed antidepressants and anoretics. Sibutramine is a monoamine reuptake inhibitor which down regulates (i.e., sensitizes) α_2 and β adrenoceptors. Sibutramine's and its primary and secondary amines metabolites reuptake inhibition profile has been evaluated in both *in vitro* and *ex vivo* studies in rats and/or humans. Results from these studies have shown that both BTS 54 354 and BTS 54 505 are potent monoamine reuptake inhibitors of noradrenaline, 5-hydroxytryptamine (5-HT) and dopamine in comparison to sibutramine.

the affinity of sibutramine, BTS 54 354 and BTS 54 505 for the monoamine reuptake sites and other CNS receptors were examined in rat, pig or guinea pig tissues and post-mortem human brain. Uptake inhibition for noradrenaline, serotonin and dopamine were measured using [^{3}H]nisoxetine, [^{3}H]paroxetine and [^{3}H]GBR 12935 as ligands in rat (frontal cortex and striatum) and in post mortem human brain (thalamus and putamen). From the *in vitro* data it could be concluded that sibutramine is only weakly active as a monoamine reuptake inhibitor. However, its metabolites BTS 54354 and BTS 54505, are extremely powerful inhibitors of monoamine reuptake. In human brain tissue, these metabolites are equipotent and both compounds have K_i's of approximately 20 nM for noradrenaline and 5-HT reuptake sites with 2 to 3 fold less affinity for dopamine sites. In rat brain, these metabolites show preferential actions as noradrenaline reuptake inhibitors, with approximately 5 fold lower potency versus both 5-HT and dopamine. K_i values for sibutramine, BTS 54354 and BTS 54505 for serotonin, noradrenaline and dopamine reuptake sites both in rat and in man are summarized in **Table 1**. These values were extracted from study BL94024

This study also demonstrated that neither sibutramine nor its two amine metabolites exhibited affinity for 5-HT (5-HT_1, 5-HT_{1A}, 5-HT_{1D}, 5-HT_{2A}, 5-HT_{2c}), adrenergic (β_1, β_2,α_1,α_2), dopaminergic (D_1, D_2), muscarinic, histamine or benzodiazepine receptors in rat, pig or guinea pig tissue (K_is > 1 μM). Sibutramine and its metabolites did not show any significant affinity for 5-HT, adrenergic, dopaminergic, muscarinic, histamine (H_1) and benzodiazepine receptors in rat, pig or guinea pig tissue and human brain.

Table 1. ***In vitro*** **binding to monoamine uptake sites for sibutramine, BTS 54354 and 54505 in rat (frontal cortex and striatum) and in post mortem human brain (thalamus and putamen) using [^{3}H]nisoxetine, [^{3}H]paroxetine and [^{3}H]GBR 12935 as ligands.**

COMPOUND	Ki (nM) ± SEM					
	RAT			HUMAN		
	5-HT	NE	DA	5-HT	NE	DA
Sibutramine	2135 ± 137	86 ± 10	3072 ± 50	298 ± 65	5451 ± 1160	943 ± 64
BTS 54 354	19 ± 1	12 ± 1	60 ± 2	15 ± 3	20 ± 8	49 ± 9
BTS 54 505	18 ± 2	14 ± 3	50 ± 2	20 ± 3	15 ± 3	42 ± 5

Results obtained from monoamine uptake studies are consistent with sibutramine and its metabolites affinity for the monoamine reuptake receptors

BTS 54354 and BTS 54505 were considerably more potent inhibitors of [^{3}H] monoamine uptake than the parent compound, sibutramine. Both metabolites were in fact potent NA, 5-HT and DA uptake inhibitors. Their ability to inhibit NA uptake was comparable with desipramine and with imipramine at 5-HT reuptake sites and they appeared to be approximately 4 times more potent than nomifensine and 10 fold higher than cocaine as DA uptake inhibitors. A summary is shown in **Table 2.** Relative to their effects on noradrenergic reuptake, BTS 54 505 and BTS 54 354 were 6- and 9-fold less potent as inhibitors of [^{3}H]-DA uptake into rat synaptosomes, respectively.

Table 2: **The effect of Sibutramine, BTS 54354, BTS 54505 compared to other antidepressants, weight modifiers with abuse potential and other stimulant drugs of abuse on [^{3}H]monoamine uptake into rat brain synaptosomes. (Data taken from P93045 and BL96008).**

Compounds	K_i (nM)		
	[^{3}H]NA	[^{3}H]5-HT	[^{3}H]DA
Sibutramine	283	3131	2309
BTS 54354	3	18	24
BTS 54505	5	26	31
Desipramine	1.7	200	4853
Imipramine	29	31	6914
Nomifensine	8.0	2660	88
d-Amphetamine	45	1441	132
Methamphetamine	73	2919	114
Mazindol	1	79	28
Cocaine	85	135	250
Methylphenidate	52	14894	110
Bupropion	2590	18312	409
Fluoxetine	320	11	2025
Venlafaxine	196	26	2594

Plasma, obtained from healthy male volunteers, during and after sibutramine treatment (single dose, 12.5 or 50 mg; repeated dosing, 5 - 20 mg/daily or 15 mg twice daily) or placebo treatment, was assayed *in vitro* for its ability to inhibit [^{3}H]-NA uptake by rat cortical synaptosomes, [^{3}H[-5-HT uptake by human platelets and [^{14}C]-DA by rat striatal synaptosomes (Luscombe *et al.*, *Psychopharmacology*, 100: 345-349, 1990). Plasma obtained from healthy male volunteers receiving single or repeated dosing with sibutramine produced an inhibitory effect on monoamine uptake *in vitro*.

The primary and secondary metabolites may have contributed to these effects since peak effects did not occur until 3 hours after a single dose of 50 mg sibutramine or 4 to 6 days after initiation of repeated dosing. These results are also consistent with the pharmacokinetic profile of sibutramine.

Binding parameters of adrenoceptors in rat brain membrane preparations have been evaluated in rats receiving repeated dosing of sibutramine (Buckett *et al.*, 1988; Heal *et al.*, 1989) or BTS 54 354 and BTS 54 505 (Luscombe *et al.*, 1989). Sibutramine rapidly and potently down-regulated rat cortical β-adrenoceptors; after 3 days of oral dosing with 1.0 or 3.0 mg/kg of sibutramine, the number of β adrenoceptors were significantly ($p<0.01$) reduced by 21% and 29%, respectively (Buckett *et al.*, 1988).

Heal and colleagues (1988) reported similar results following oral administration of sibutramine (3 mg/kg) for 10 days. The total number of β adrenoceptors present in the rat cortex was significantly decreased; a 38% reduction in the total number of β adrenoceptors was observed. This reduction was shown to be due to a decrease in the number of β_1 adrenoceptors population. Similar results were observed with the antidepressants amitriptyline (10 mg/kg, p.o.), and desipramine (10.0 mg/kg, p.o.). The primary and secondary metabolites of sibutramine also rapidly and potently induced down-regulation of the β adrenoceptors. Rats dosed for 3 consecutive days with 1.8 mg of BTS 54 354 or 3.3 mg/kg of BTS 54 505, decreased the numbers of β adrenoceptors by 19% and 24%, respectively (Luscombe *et al.*, 1989).

The ability of sibutramine and its primary and secondary amine metabolites, BTS 54 505 and BTS 54 354, to affect the release of [^{3}H]-noradrenaline from rat brain slice *in vitro* was compared with those of d-fenfluramine, d-norfenfluramine and d-amphetamine. In contrast to results observed with d-fenfluramine (10^{-5}M), d-norfenfluramine (10^{-5}M) and d-amphetamine (10^{-6} and 10^{-5}M), sibutramine, BTS 54 354 and BTS 54 505, at concentrations of 10^{-7} - 10^{-5}M, had no significant effect on the basal release of [^{3}H]NA from rat cortical slices.

Using similar methodology, the ability of BTS 54 524, BTS 54 505 and BTS 54 354 to stimulate the release of [^{3}H]DA from rat striatum slices was compared to that of the methamphetamine (10^{-8} - 10^{-4}M), dexamphetamine (10^{-7} - 10^{-5}M), methylphenidate (10^{-7} - 10^{-5}M), fencamfamine (10^{-7} - 10^{-5}M) , nomifensine (10^{-7} - 10^{-5}M), bupropion and GBR 12909 (10^{-7} - 10^{-5}M). Methamphetamine (10^{-8} - 10^{-4}M) and dexamphetamine (10^{-7} - 10^{-5}M) produced concentration-dependent increases in the release of [^{3}H]DA from striatal slices. Methamphetamine and dexamphetamine enhanced the release of dopamine by 140% and 138%, respectively, at 10^{-5} M and this effect was also detectable at the lowest drug concentration tested (27% at 10^{-8} M and 56% at 10^{-7} M respectively). Methylphenidate (10^{-7} - 10^{-5}M) and fencamfamine (10^{-7} - 10^{-5}M) and the dopamine reuptake inhibitors nomifensine (10^{-7} - 10^{-5}M) and GBR 12909 (10^{-7} - 10^{-5}M) significantly increased the release of [^{3}H]DA release at the highest concentration (10^{-5}M). The secondary active amine, BTS 54354, increased the release of [3H]dopamine in a 30 % at 10^{-5} M. This is not a large effect and only occurred at high concentration. Sibutramine and BTS 54 505 were inactive at concentrations as high as 10^{-5}M.

In the unilateral nigrostriatal lesioned rats, which is an *in vivo* model of a drug action on brain dopamine action, methamphetamine (4.2 mg/kg), methylphenidate (100.0 mg/kg) and fencamfamine (10 mg/kg) all induced significant ipsilateral circling that diminished after 4-5 hrs. Apomorphine, dopamine agonist, induced contralateral circling within 1 hr. Under the same conditions, sibutramine at a high oral dose (30.0 mg/kg) induced significant ipsilateral, which is probably due to its dopamine reuptake blockade ability. At a lower dose of 6.0 mg/kg administered orally, this effect was observed 4-5 hrs after treatment. The active metabolites at 6.0 mg/kg dose did not induce a significant change in circling behavior from control when administered orally. At 5.0 mg/kg (i.p.), the primary amine BTS 54 505, produced effects comparable to the effects elicited by the oral administration of 14.3 mg/kg cocaine. This effect was still evident 4 to 5 hours post-treatment.

Table 3: **Comparison of the effects on ipsilateral circling in unilateral nigrostriatal-lesioned rats of sibutramine, BTS 54354, BTS 54505, other weight modifiers and other stimulant drugs of abuse. (Data taken from Research Report BL96008)**

Drug	Dose (mg/kg)	Route	Circling (turns/min) 0.1-1h	Circling (turns/min) 4-5h
Sibutramine	6 30	PO PO	0.2 ± 0.1 3.0 ± 0.6	1.1 ± 0.3 6.7 ± 1.4
BTS 54354	6 5	PO IP	0.1 ± 0.1 0.9 ± 0.3	0.6 ± 0.1 0.8 ± 0.3
BTS 54505	11 5	PO IP	0.8 ± 0.6 1.7 ± 0.2	3.0 ± 0.7 1.4 ± 0.2
d-Amphetamine	1.8 6	PO PO	4.3 ± 1.0 7.8 ± 0.8	0.7 ± 0.3 1.9 ± 0.8
Methamphetamine	0.42 4.2	PO PO	0.6 ± 0.2 8.4 ± 0.7	0.2 ± 0.1 0.9 ± 0.3
Mazindol	4	PO	1.9 ± 0.6	0.1 ± 0.0
Cocaine	14.3 43	PO PO	1.8 ± 0.5 3.0 ± 1.1	0 ± 0 0 ± 0
Fencamfamine	3 10	PO PO	1.3 ± 0.4 5.4 ± 1.1	0.6 ± 0.2 1.1 ± 0.2
Methylphenidate	40 100	PO PO	9.3 ± 1.8 10.4 ± 2.2	0.8 ± 0.4 3.4 ± 0.4
Bupropion	30 100	PO PO	1.8 ± 0.4 5.8 ± 1.1	0.2 ± 0.1 0.9 ± 0.2
Nomifensine	3.3 11	PO PO	0.4 ± 0.1 5.7 ± 1.6	0.3 ± 0.2 2.0 ± 0.6
Desipramine	18 20	PO IP	0.3 ± 0.3 0.1 ± 0.1	0.2 ± 0.1 0 ± 0
Venlafaxine	306	PO	0.2 ± 0.1	0.1 ± 0.1

The *in vivo* behavioral and pharmacological profile of sibutramine is consistent with that of clinically effective antidepressants. As depicted in Table 4, sibutramine exhibited potent activity in the standard antidepressant screens.

Table 4. Sibutramine activity in the standard antidepressant screens.

COMPOUND	ED_{50} (mg/kg, p.o.)		
	RESERPINE REVERSAL (mice)	PORSOLT TEST (mice)	RESERPINE PREVENTION (rats)
Sibutramine	1.8	10.0	0.6
Nomifensine	2.2	10.0	1.1
Imipramine	71.0	30.0	10.0
Amitriptyline	5.8	10.0	70.0
Desipramine	6.0	30.0	1.8

CHEMISTRY

Sibutramine hydrochloride monohydrate is a white to cream crystalline powder, soluble in water below pH 5

It is a racemic compound with one asymmetric center and is not polymorphic.

Scheme 1

PRECLINICAL ABUSE LIABILITY ASSESSMENT

In evaluating the abuse potential of sibutramine, the sponsor conducted the following studies:

Report No. P88019: "The dextroamphetamine cued drug discrimination test - New criteria for the evaluation of results."

STUDY DESIGN.

The drug discrimination study in rats was conducted at
In this study, rats were trained to discriminate between the stimulus effects of dextroamphetamine (0.5 mg/kg, i.p., 15 minutes pretreatment) and saline in a two-lever drug discrimination paradigm according to a FR-5 schedule of sweet milk reinforcement. On days when dextroamphetamine was administered, one of the two response levers was designated as correct and resulted in sweet milk delivery. On days when saline injections were administered, the other lever was designated as correct. After attaining discrimination criteria (i.e., ≥ 75% correct lever responses during a 3 month training period), each rat was tested with the following drugs: methamphetamine (i.p.); fencamfamine (i.p.); methylphenidate (0.1 - 3.0 mg/kg, i.p.); d-amphetamine (0.03 - 0.3 mg/kg, i.p.); nomifensine (i.p.); bupropion (i.p.); BTS 54 524 (Sibutramine; i.p.); BTS 54 354 (i.p.); and BTS 54 505 (i.p.). Each dose level of the test drug was evaluated in a minimum of five rats.

Data analyses. The data was expressed two ways; results for each individual rat and as cumulative results. The total number of responses on either the drug-lever or the saline-lever and the rat's lever pressing behavior were determined. Normal or acceptable lever pressing behavior was defined as: mean total lever presses from eight consecutive amphetamine tests minus one standard deviation. Each rat overall performance was classified as follows in Table 1:

Table 1. **Classification of the subjects overall performance in the drug discrimination study.**

CLASSIFICATION OF RESPONSE BY AN INDIVIDUAL RAT	
TYPE OF RESPONSE	**RESPONSE DEFINED**
Amphetamine	≥ 75% of total responses occurred on the amphetamine lever Lever Pressing was at normal performance level or above
Saline	≥ 75% of total responses occurred on the saline lever Lever pressing was at normal performance level or above
No Preference	< 75% of the total responses occurred on either lever Lever pressing was at normal performance level or above
Invalid Response	Lever pressing was below normal performance level
CLASSIFICATION OF CUMULATIVE RESULTS	
Amphetamine	Majority of the rats selecting the amphetamine lever
ANO	Divided Group: Some of the rats selecting the amphetamine lever and some rats showing no preference
NOP	Majority of the rats showing no preference
SNO	Divided Group: Some of the rats selecting the saline lever and some rats showing no preference
SAL	Majority of the rats selecting the saline lever

Results. The individual and group data are summarized in Table 2. The stimulants d-amphetamine, methamphetamine, fencamfamine, methylphenidate elicited d-amphetamine-like discriminative stimulus effects in all rats treated with the highest dose. The antidepressant nomifensine and bupropion also produced d-amphetamine appropriate responding in 83% and 100% of the subjects tested at the highest dose, respectively. In contrast, sibutramine (BTS 54 524) and its metabolites BTS 54 354 and BTS 54 505 did not evoke d-amphetamine-appropriate responding in the subjects; indecisive results (i.e., SNO, NOP) were observed at 3.0 mg/kg. At the highest dose tested, behavioral disruption was observed in 94 to 100% of the subjects.

Table 2. **Individual data and group data for test drugs in rats trained to discriminate d-amphetamine (0.5 mg/kg, i.p.) from saline.**

DRUG	DOSE (mg/kg, i.p.)	NUMBER OF RATS RESPONDING IN EACH RESPONSE CATEGORY				% DISRUPTIONS	GROUP RESPONSE CATEGORY (% OF SUBJECTS RESPONDING)
		AMPHETAMINE	SALINE	NO PREFERENCE	INVALID		
Dextroamphetamine	0.03	0	5	0	0	0	SAL (100%)
	0.1	0	5	1	0	0	SAL (83%)
	0.3	6	0	0	0	0	AMPH (100%)
Methamphetamine	0.03	0	5	0	0	0	SAL(100%)
	0.1	0	5	0	0	0	SAL (100%)
	0.3	4	0	1	1	17	AMPH (80%)[a]
	0.5	6	0	0	0	0	AMPH (100%)
Fencamfamine	0.1	0	5	0	0	0	SAL (100%)
	0.3	0	5	0	1	17	SAL (100%)[a]
	1.0	0	4	4	1	11	SNO
	3.0	5	0	0	0	0	AMP (100%)
Methylphenidate	0.1	0	5	0	0	0	SAL (100%)
	0.3	0	5	0	0	0	SAL (100%)
	1.0	0	6	2	0	0	SAL (100%)
	3.0	6	0	0	0	0	AMP (100%)
Nomifensine	0.1	0	5	0	0	0	SAL (100%)
	0.3	0	5	0	0	0	SAL (100%)
	1.0	1	1	2	1	20	NOP (50%)[a]
	3.0	5	0	1	0	0	AMP (83%)
Bupropion	3.0	0	6	0	0	0	SAL (100%)
	10.0	0	5	0	0	0	SAL (100%)
	30.0	5	0	0	2	29	AMP (100%)[a]
Sibutramine (BTS 54 524)	0.3	0	5	0	0	0	SAL (100%)
	1.0	0	5	0	0	0	SAL (100%)
	3.0	0	5	3	2	20	SNO
	5.0	0	0	0	6	100	DIS
BTS 54 354	0.3	0	5	1	0	0	SAL (83%)
	1.0	0	6	4	0	0	SNO
	3.0	1	1	10	2	14	NOP (83%)[a]
	10.0	0	0	0	4	100	DIS
BTS 54 505	0.3	0	5	0	0	0	SAL (100%)
	1.0	0	7	2	2	18	SAL (78%)[a]
	3.0	0	5	4	5	36	SNO
	5.0	0	0	1	17	94	DIS

[a]: Rats displaying lever pressing behavior classified as invalid (i.e., below normal) were not included in the calculation of % subjects responding.

Conclusions and Comments. While these results suggest that sibutramine and its metabolites do not possess d-amphetamine-like stimulus properties, it is difficult to conclusively conclude that sibutramine and its metabolites do not share some commonality with d-amphetamine. No definite conclusion can be made on the discriminative stimulus profile of sibutramine and its metabolite because of the study design and approach the sponsor selected in summarizing the data.

In this drug discrimination study, the rats were pre-injected with sibutramine fifteen minutes prior to a 2.5 minute test session. Using such a short pre-injection time, the discriminative stimulus effects of sibutramine and its metabolites could have been missed at the doses that did not produce behavioral disruption. Also using a larger subject population would be helpful; ten subjects per dose would be ideal.

By selecting to present the data as amphetamine-like, saline-like or no preference, a quantitative analysis (i.e., the mean percent amphetamine-appropriate responding and mean overall response rate) of the data was not made available. A quantitative analysis of the data allows one to assess whether or not the test drug has multiple discriminative stimulus properties (i.e., sharing some similarity with the training drug but also having a component of its stimulus effect that differ from the training drug) and quantify the dose-response relation in terms of percent drug-lever responding and overall response rate. This analysis is very critical for drugs like sibutramine and its metabolites which possess both dopaminergic, serotoninergic and noradrenergic properties. By using this approach in analyzing the discriminative stimulus properties of 3,4-methylenedioxymethamphetamine (MDMA), an amphetamine-like hallucinogen, it was shown to possess both amphetamine-like and LSD-like discriminative stimulus effects.

Report Nº BI97021: Evaluation of the abuse liability of sibutramine, BTS 54 354, BTS 54 505 and various reference drugs in the rat MDMA-cued drug discrimination model.

Because the sponsor maintained that sibutramine has more sertoninergic activity than dopaminergic activity, one may speculate that it may possess more hallucinogenic activity and may have an abuse profile similar to the hallucinogens. Henceforth, in our initial abuse liability assessment, it was strongly recommended that the sponsor evaluate the discriminative stimulus effects of sibutramine, amphetamine and another anoretic (e.g., fenfluramine) in rats trained to discriminate MDMA from vehicle. In response to the agency request, the sponsor conducted the following drug discrimination study in rats trained to discriminate 1.5 mg/kg MDMA from saline.

METHODS.

Subjects. Six female PVG rats served as subjects. At the start of the study, the rats weighed between 120 to 150 g.

Procedure. In this study, rats (n=6) were trained to discriminate the stimulus effects of MDMA (1.5 mg/kg, i.p., 15 minutes pretreatment) and saline (1 ml/kg, i.p., 15 minutes pretreatment) in a two-lever drug discrimination paradigm according to a FR-5 schedule of reinforcement. On days when MDMA was administered, one of the two response levers was designated as correct and resulted in delivery of a reward. On days when saline injections were administered, the other lever was designated as correct. Training and test sessions lasted 10 minutes. During the 10 minute test session, no reinforcement was delivered for responding on either lever during the first 2.5 minutes of the test session. For the remaining 7.5 minutes of the test session, responding on either lever delivered reinforcement.

After attaining discrimination criteria (i.e., $\approx$ 60% correct lever responses on most trials), the rats were tested with saline and MDMA under test session conditions. The testing phase was not entered until the rat had completed $\geq$4 correct consecutive saline and MDMA tests. Substitution tests were conducted with Metabolite 1:BTS 54 354 (1.0, 3.0, and 10.0 mg/kg, i.p., 15 min. pretreatment); Metabolite 2: BTS 54 504 (1.0, 3.0, and 10.0 mg/kg); and sibutramine (1.0, 3.0, and 10.0 mg/kg, i.p., 1 hr pretreatment).

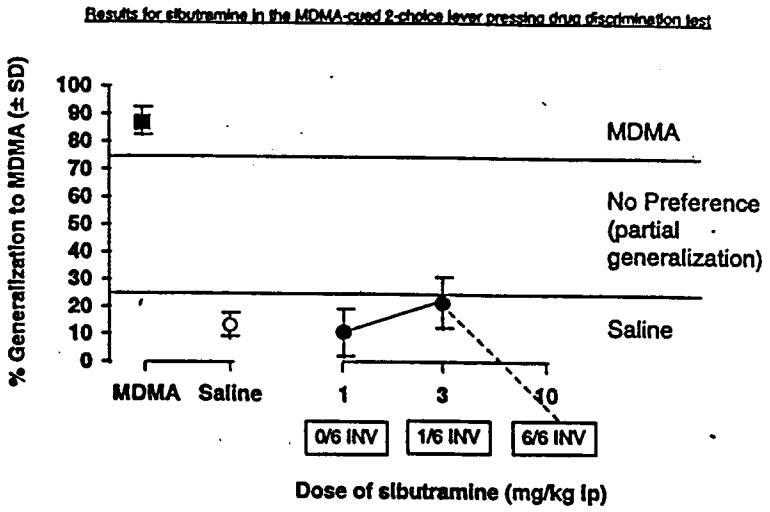
Data Analyses. For each test session, the data was expressed as: 1) The total number of responses on either the drug-lever or the saline-lever and the rats' lever pressing behavior were determined.; 2) Mean percentage of MDMA lever responding. Each overall performance was classified as follows in Table 1.

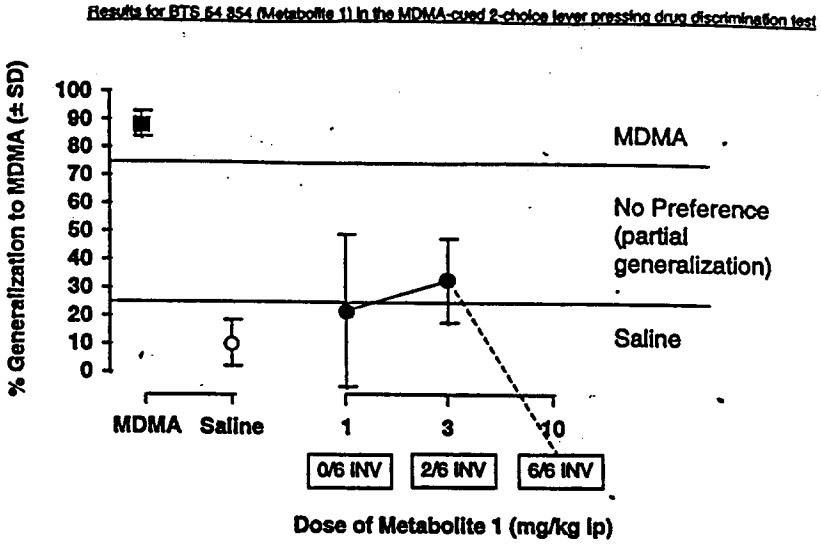
Table 1. **Classification of the subjects overall performance in the drug discrimination study.**

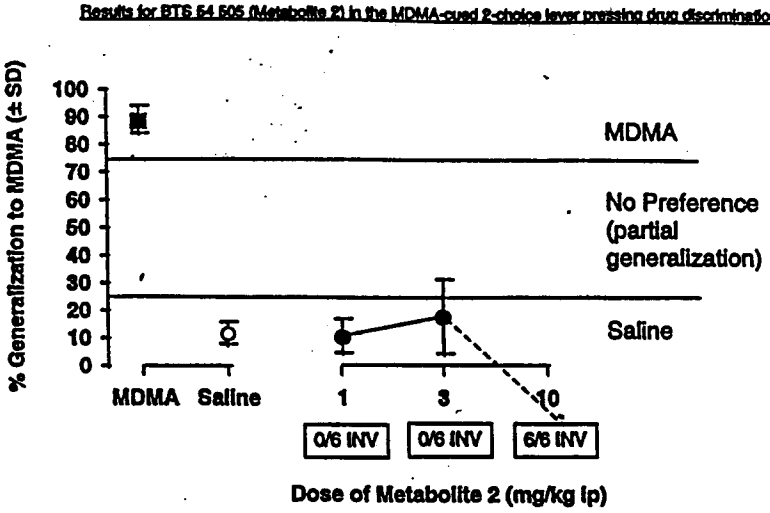
CLASSIFICATION OF RESPONSE BY AN INDIVIDUAL RAT	
TYPE OF RESPONSE	**RESPONSE DEFINED**
MDMA	≥ 75% of total responses occurred on the MDMA lever Lever Pressing was at normal performance level or above
Saline	≥ 75% of total responses occurred on the saline lever Lever pressing was at normal performance level or above
No Preference	< 75% of the total responses occurred on either lever Lever pressing was at normal performance level or above
Invalid Response	Lever pressing was below normal performance level
CLASSIFICATION OF CUMULATIVE RESULTS	
MDMA	Majority of the rats selecting the MDMA lever
MDMANO	Divided Group: Some of the rats selecting the MDMA lever and some rats showing no preference
NOP	Majority of the rats showing no preference
SNO	Divided Group: Some of the rats selecting the saline lever and some rats showing no preference
SAL	Majority of the rats selecting the saline lever
DIS	≥ 50% of tested rats showing invalid responses indicating behavioral disruption

Results. Results are presented in Figure 1 and Table 2. Figure 1 shows the effects of substitution tests with sibutramine, BTS 54 354 and BTS 54 505. Neither sibutramine nor its active metabolites substituted for MDMA in all rats. Behavioral disruption (i.e., suppressed rate of responding) was noted at the highest dose (10.0 mg/kg) tested in 100% of the subjects. The sponsor reported that this behavioral disruption was not the consequence of immobility, stereotypy or other pronounced behavioral abnormalities. Saline-appropriate responding was elicited in 100% of the subjects tested with 1.0 mg/kg of sibutramine and BTS 54 505 (Table 1). MDMA-appropriate responding was elicited by one rat tested with 1.0 mg/kg of BTS 54 354; the other five rats elicited saline-appropriate responding. Consistent with the results observed in d-amphetamine trained rats, sibutramine, and its metabolites BTS 54 354 and BTS 54 505 produced indecisive results (i.e., SNO, and NOP) at a dose of 3.0 mg/kg.

Figure 1. Dose-response curves with sibutramine, BTS 54 354, and BTS 54 505 in rats trained to discriminate MDMA (1.5 mg/kg, IP) from saline under a FR schedule.







INV = No of rats showing invalid, ie suppressed lever press responding.

Table 2. **Individual data and group data for test drugs in rats trained to discriminate MDMA (1.5 mg/kg, i.p.) from saline.**

DRUG	DOSE (mg/kg, i.p.)	NUMBER OF RATS RESPONDING IN EACH RESPONSE CATEGORY				% DISRUPTIONS	% MDMA-LEVER RESPONDING (MEAN ± SD)	GROUP RESPONSE CATEGORY (% OF SUBJECTS RESPONDING)
		MDMA	SALINE	NO PREFERENCE	INVALID			
Sibutramine	1.0					0	11.2 ± 6.8	SAL (100%)
	3.0					17	22.2 ± 8.7	SNO
	10.0					100	NA	DIS (100%)
BTS 54 354	1.0					0	22.8 ± 28.4	SAL (83%)
	3.0					33	32.3 ± 16.0	NOP(75%)[a]
	10.0					100	NA	DIS (100%)
BTS 54 505	1.0					0	10.4 ± 5.4	SAL (100%)
	3.0					0	18.5 ± 13.2	SNO
	10.0					100	NA	DIS (100%)

a: Rats displaying lever pressing behavior classified as invalid (i.e., below normal) were not included in the calculation of % subjects responding.

NA: Not applicable because of behavioral disruption.

Conclusions and Comments. The present results suggest that sibutramine and its metabolites do not possess MDMA-like discriminative stimulus effects in rats. However, the study design raises some concerns about the validity of these results. The basis for these concerns are as follows:

1. **Performance level of the rats.** The discrimination criteria selected by the sponsor is much lower than what is customarily used in this area of research. The sponsor used a discrimination criteria of 60% correct lever responses on most trials for this study. Researchers in this area customarily uses a criteria of ≥ 80% of the total responses being emitted on the appropriate lever or correctly choosing the correct lever appropriate for the injection received in 8 of 10 consecutive sessions, twice (this represents at least an 80% performance level being required before commencing with the dose-response testing). Also, this criteria is lower than the discrimination criteria the sponsor used in their d-amphetamine drug discrimination study; a ≥ 75% criteria was used in that study.

2. **Ability to discriminate MDMA.** In drug discrimination studies it is common practice to test several doses of the training drug in the subjects in order to characterize the dose-response function. This is very useful in making potency comparison to the training drug and the test drug. In the letter dated November 8, 1996, the agency asked that the sponsor test MDMA, sibutramine, BTS 54 354 and BTS 54 505 in rats trained to discriminate MDMA.

3. **Lack of Positive Control.** To verify that the performance level of the rats would ensure that they can generalize to drugs that are known to elicit MDMA-like discriminative stimulus effects, at least one positive control should have been substituted for MDMA in this study. In the agency letter dated June 5, 1996, it was recommended that amphetamine and another anorectic (e.g. fenfluramine) be tested in the proposed study.

Report: **Evaluation of the reinforcing effects of sibutramine and nomifensine in rhesus monkeys.**

Investigator: **William L. Woolverton, James K. Rowlett, and Kristin M. Wilcox**

Site: **Department of Psychiatry and Human Behavior, University of Mississippi Medical Center, Jackson, Mississippi**

Objectives: **Evaluate the reinforcing effects of sibutramine and nomifensine.**

INTRODUCTION.

The self-administration paradigm is widely used to determine whether or not a drug can control behavior (that is function as a positive reinforcer) and to evaluate the abuse potential of the substance. Self-administration studies using nonhuman primates and rats have been shown to be a valid and reliable prediction of the potential of a compound to result in drug dependence (i.e., addiction). There is a strong concordance between the types of drugs that serve as reinforcers in animals and the many illicit drugs associated with problems of addiction, dependence or abuse by man (Johanson and Balster, 1978; Griffiths *et al.*, 1980; Woolverton and Nader, 1990).

The reinforcing effects of sibutramine were evaluated and compared to that of nomifensine in rhesus monkeys experienced in self-administering cocaine intravenously under a fixed ratio 10 schedule of reinforcement. Nomifensine is an antidepressant which mediates its effects through both the dopaminergic and noradrenergic neuronal system. Nomifensine is a selective inhibitor of dopamine and norepinephrine transporters. Preclinical studies have demonstrated that nomifensine can function as a positive reinforcer and possesses both amphetamine-like and cocaine-like discriminative stimulus effects (i.e., subjective effects). When nomifensine was substituted in baboons (Lamb, R.J., and Griffiths, R.R., Psychopharmacology-Berl, 102(2):183-190, 1990), squirrel monkeys (Bergman, J. *et al.*, J. Pharmacol. Exp. Ther., 251(1):150-155, 1989) and rhesus monkeys (Winger, G., *et al.*, Drug Alcohol Depend., 24(2):135-142, 1989) in which baseline responding was maintained by intravenous injections of cocaine, self-administration behavior was maintained at levels above vehicle. Self-administration studies performed with rats have demonstrated that nomifensine can initiate and maintain intravenous self-administration (Spyrake, C., and Fibiger, H.C., Science, 212:1167-1168, 1981) and self-injection into the nucleus accumbens (Caarlezon, W.A., *et al*, Psychopharmacology-Berl, 122(2):194-197, 1995).

METHODS.

Subjects. Six adult rhesus monkeys (5 ♂, and 1 ♀) weighing between 4.0 and 11.0 kg during the study served as subjects for this study. Each monkey was fitted with a stainless-steel restraint harness and spring arm which was attached to the rear of the experimental chamber in which the monkey resided in for the duration of the experiment. The subjects' history is summarized in Table 1 below:

Table 1. Previous drug exposure and the experimental conditions for the monkey in the present study (As copied from the sponsor submission).

MONKEY I.D. (GENDER)	DRUG EXPOSURE PRIOR TO THE PRESENT STUDY	TIME OF EXPOSURE	FIRST TEST COMPOUND (dose range, mg/kg/injection, # tested)	SECOND TEST COMPOUND (doses, mg/kg/injection, # tested)
AL99 (♂)	Cocaine	≈ 3 months	Sibutramine	Nomifensine
18108 (♀)	Cocaine	≈ 1 month	Sibutramine	Nomifensine
L638 (♂)	Naive	-	Sibutramine	Not Tested
MO54 (♂)	Naive	-	Nomifensine	Sibutramine
L701 (♂)	Naive	-	Nomifensine	Sibutramine
13596 (♂)	Cocaine, Heroin	≈ 24 months	Nomifensine	Sibutramine

Procedure. Prior to the initiation of the self administration study, the monkeys were surgically prepared with a chronic, indwelling intravenous catheter into a major vein. The catheter was inserted into either the internal jugular, external jugular, femoral vein or brachial vein.

The catheter is then threaded subcutaneously to an opening in the skin on the back of the subject. To protect the catheter, the subject is fitted with a harness or vest with an attached tether for restraint. The restraint tether is attached to the experimental chamber in which the animal is housed and allows for freedom of movement within the chamber. The catheter is threaded through the tether and attached to an automatic injection pump.

Drug injections are made contingent upon a behavioral response under conditions that are controlled with electronic programming equipment. After catheter implantation and recovery from surgery, the monkeys were trained to respond on the right lever for cocaine injections (0.1 mg/kg/injection) on an FR 1 schedule. Once responding was established, the training dose of cocaine was reduced to 0.03 mg/kg/injection and the FR requirement was gradually brought up to an FR 10. Daily sessions were 120 minutes. When stable FR 10 responding ensued for cocaine in all monkeys (less than 15% variation in number of injections per session for at least 3 consecutive sessions with no trends), saline was substituted for cocaine until responding declined to low levels and was again stable.

Following this saline substituted, the monkeys were returned to the cocaine baseline condition (0.03 mg/kg/injection) for at least 3 sessions or until responding was stable. Once stable responding occurred doses of sibutramine and nomifensine were substituted for cocaine injections for at least the same number of sessions required for responding to decline to low levels when saline was available or until responding was stable. If responding had not stabilized after 30 consecutive sessions, substitution testing of that dose was ceased. Following each dosage substitution, the monkeys were returned to cocaine for at least three days or until stable responding occurred.

Following each behavioral session, each monkey was observed using a behavioral rating scale to assess the psychomotor stimulant-like behavioral effects of sibutramine. The monkeys were observed for 1 minute by a trained observer for the following behaviors (Table 2):

Table 2. Behavioral rating Scale

BEHAVIORAL CATEGORY	OBSERVATION
Locomotor Activity	• Translocation in cage: leg or whole body movement; large swings of the upper body
Grooming/Bug Picking	• Repetitive petting or picking at hair or skin
Visual Checking	• Rapid, continuous shifts of visual field resulting from repetitive eye and/or head movements
Visual Tracking	• Continuous, slow searching of the visual field for apparently nonexistent objects, often accompanied by staring
Buccal Movement	• Repetitive movements of the tongue or lips
Splayed Legs	• Legs spread apart and turned outward, often accompanied by swaying

Each behavior was scored as following: 1 = present ; 0 = absence; total = sum of all scores.

Data Analysis. The mean number of injections of sibutramine and nomifensine for the last 3 days of substitution was calculated for each dose for each monkey. A dose of a test drug was considered to be functioning as a reinforcer if mean rates of self-administration exceeded saline rates and the ranges did not overlap. The within-session distributions of injections for cocaine, sibutramine and nomifensine were calculated as the mean percentages of total number of injections per 30-min session segment for all six monkeys.

RESULTS.

The sibutramine dose-response curves and control rates are presented in Figure 1. The mean number of cocaine injections per session varied between 40 and 92 injections in individual monkeys. Saline substitution resulted in low levels of self-administration with injection rates of 1 to 10 injections per session (points above "S1"). When sibutramine was substituted for cocaine intersubject variability was evident. For subjects AL99, and 18108, substitution of doses of sibutramine . did not substitute for cocaine (Fig 1, upper panel).

For monkey L638, maximum rates of sibutramine self-administration occurred at 0.03 mg/kg/injection. As depicted in Figure 1, sibutramine clearly maintained higher rates of self-administration than did the first saline determination. In comparison to the second saline determination, the number of sibutramine injections per session (35/session) was slightly above this monkey's second saline determination (27 injections/session). Also, it should be pointed out that the range for sibutramine overlapped with the range for saline Because of this ambiguous finding, monkey L638 was retested with 0.03 mg/kg/injection of sibutramine. Again sibutramine maintained self-administration behavior in this monkey; the mean number of injections was 19 for the last three sessions over the four test sessions. Testing was terminated before stable responding was obtained because of the appearance of blood in the monkey urine.

For monkey M054, sibutramine at doses up to 0.1 mg/kg/injection did maintain self-administration; the number of injections per session were within the range observed with saline for this monkey. When 0.3 mg/kg/injection was substituted for cocaine, this dose of sibutramine was self-administered by M054. However, stable responding was not reached because the subject was withdrawn from the study on the seventeenth day of testing because of health concerns. Like monkey L638, he developed hematuria. At the time he was withdrawn from the study, this monkey mean number of injections per session was 60).

When sibutramine was substituted for cocaine in monkeys 13596 and L701, sibutramine produced injection rates substantially greater than saline at one or more doses, where the ranges of rate did not overlap the range of saline rates. For subject L701, the characteristic inverted "U" shaped dose response function was obtained. Sibutramine at doses of 0.01, 0.03, and 0.1 mg/kg/injections clearly functioned as a positive reinforcer in this monkey. Maximum rates of sibutramine self-administration occurred at 0.01 mg/kg/injection. For monkey 13596, maximum rates of sibutramine self-administration occurred at 0.3 mg/kg/injection. Substitution testing with 1.0 mg/kg/injection was terminated after the third session because of concerns over the health of the monkey; blood was detected in the urine. However, the mean number of injections over these three sessions was 16 injection/session (range = 10-22).

The nomifensine dose-response curves and control rates are presented in Figure 2. The mean number of cocaine injections for individual monkeys ranged from 30 to 98 injections per session. Saline substitution resulted in low levels of self-administration with an average injection rates of 1 to 15 injections per session (Fig. 2 , points above "S1"). Substitution of doses of nomifensine produced inverted "U" shaped dose-response function with at least two doses in all monkeys maintaining responding above saline levels where the ranges did not overlap.

Doses of nomifensine that maintained self-administration behavior are summarized in Table 3. Self-administration was maintained by 0.001 mg/kg/injection of nomifensine in monkeys L701, and AL99. Nomifensine at a dose of 0.003 mg/kg/injection and 0.1 mg/kg/injection maintained maximal responding in monkeys M054, L701, AL99, 18108, and 13596 and in monkey 18108, respectively.

Figure 1. The mean number of injection of each dose of sibutramine self-administered by each monkey. Points above C and S represent the mean number of self-administered injection of cocaine and saline, respectively. The mean is based on the last three days of each dosage substitution.

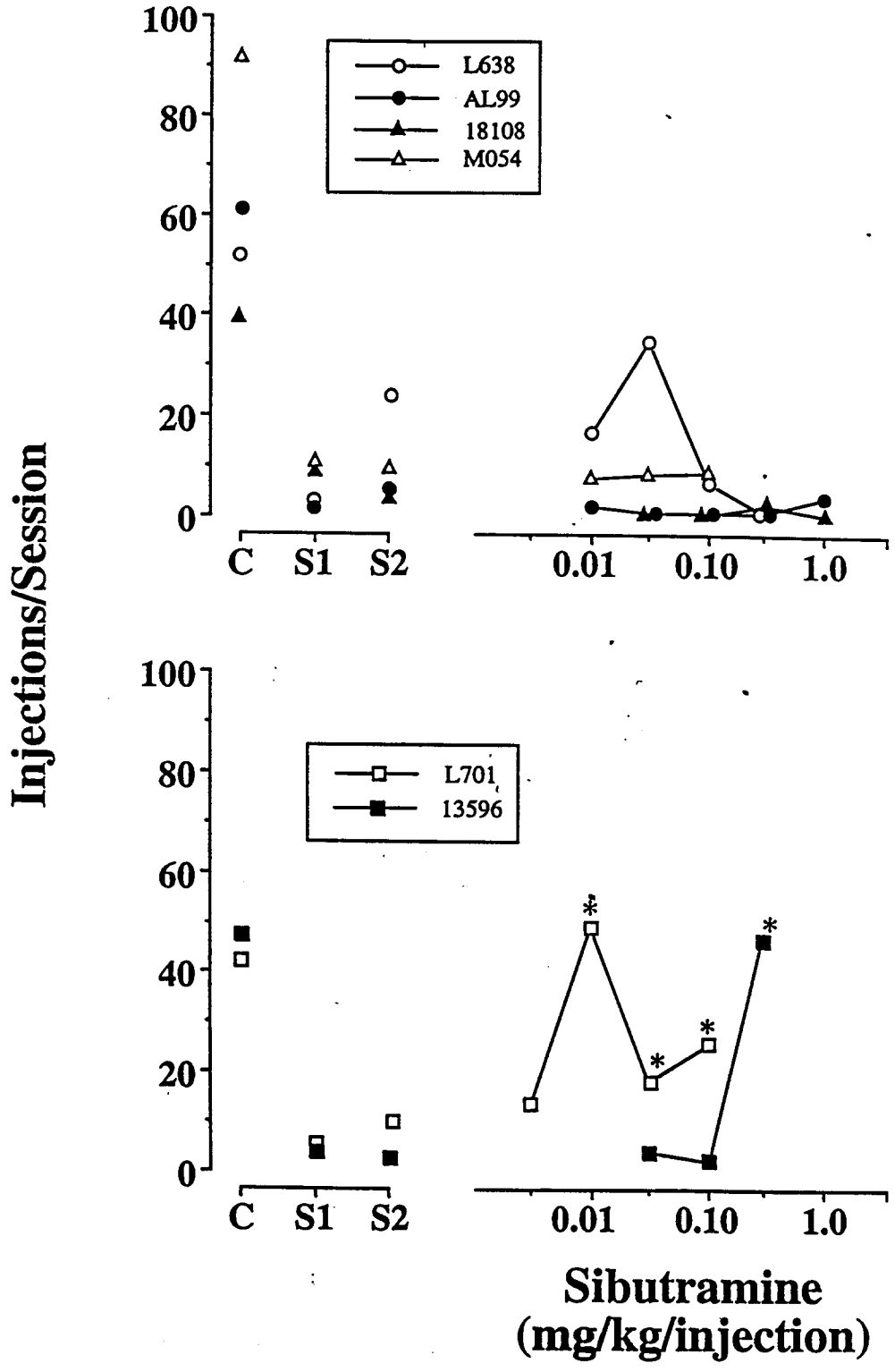


Figure 2. The mean number of injection of each dose of nomifensine self-administered by each monkey. Points above C and S represent the mean number of self-administered injection of cocaine and saline, respectively. The mean is based on the last three days of each dosage substitution.

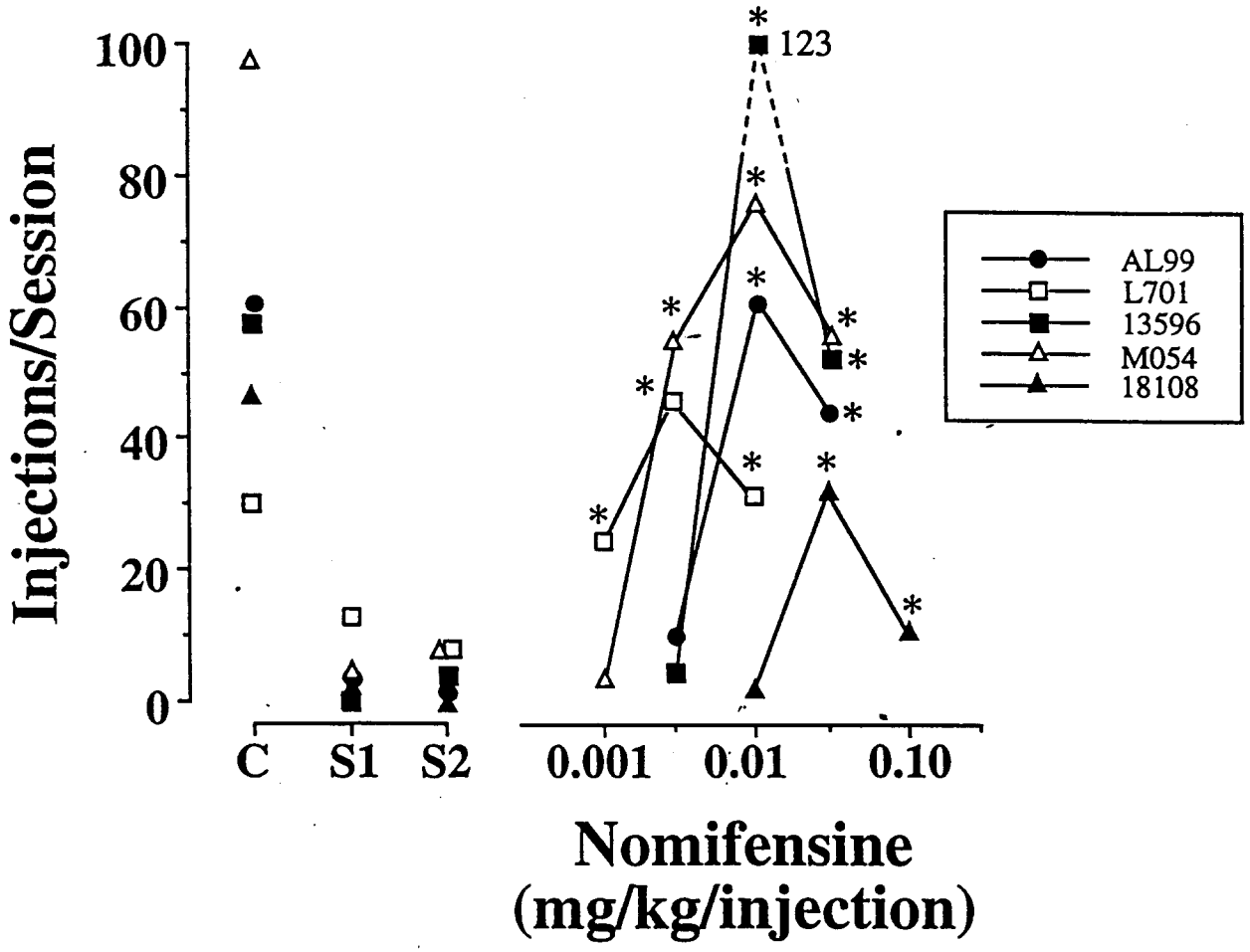


Table 3. **Doses of sibutramine and nomifensine that maintained self-administration in monkeys trained to self-administer cocaine.**

MONKEY Nº	DOSE(S) THAT MAINTAINED SELF-ADMINISTRATION	
	NOMIFENSINE (mg/kg/injection)	SIBUTRAMINE (mg/kg/injection)
M054	0.003, 0.03, and 0.03	0.3 (terminated early due to hematuria)
L701	0.001, 0.003, and 0.01	0.01, 0.03, and 0.1
AL99	0.01, 0.03	-
18108	0.03, and 0.1	-
13596	0.01, 0.03	0.3, and 1.0 (terminated early due to hematuria)
L638	Not tested	0.03

Conclusion. Sibutramine was shown to maintain fixed-ratio 10 responding in three of the six monkeys tested. In two of these monkeys (L701, 13596), one or more doses of sibutramine maintained responding. When sibutramine was available, the biphasic, inverted U-shape dose-response function that is characteristic of drugs that function as a positive reinforcer was observed. In the third monkey (L638), sibutramine (0.03 mg/kg/injection) maintained self-administration above levels of the first saline self-administration determination. However, when saline was made available after the sibutramine substitution test, the number of saline injections had increased such that sibutramine self-administration and saline self-administration overlapped. Henceforth, according to the definition of a positive reinforcer, sibutramine failed to function as a positive reinforcer in this monkey. When this dose was being retested in this subject, the monkey was self-administering this dose of sibutramine; but testing was aborted before stable responding was obtained because of health reasons.

Nomifensine maintained FR 10 responding at rates that exceeded saline self-administration at two or more doses in all six monkeys.

In conclusion, the results from this study have clearly shown that sibutramine can function as a positive reinforcer in some monkeys trained to self-administer cocaine as their baseline drug. Sibutramine clearly functioned as a positive reinforcer in one monkey with an extensive drug history (13596) and in one monkey with no prior drug history (L701). This observation suggests that sibutramine has the potential to be a drug of abuse in people with a history of stimulant abuse and may become a drug of abuse in people with no history of substance abuse.

The fact that some monkeys self-administered sibutramine and some did not raises the question "What is unique about these subjects?" The three monkeys that clearly did not self-administer sibutramine, may be slow metabolizer. Sibutramine is a prodrug. To alleviate this variable, it would had been interesting to see whether or not the active metabolites would maintain self-administration behavior. Also, could these animals have experienced a dysphoric effect to the drug and avoided self-administration. Subjects in clinical abuse liability studies have reported dysphoria. Dysphoric drugs usually are not self-administered by primates. Of particular interest is that most of the monkeys that self-administered sibutramine experienced ill health; they developed hematuria.

Title: **BTS 54 524 - 13 week, oral (Gavage) toxicity study in the monkey, with a 6-week treatment-free period.**

Study Report

Background.

In addition to the primary reinforcing effects, other factors come into play that can profoundly affect the drug pattern of use and the likelihood that the drug use will be continued. Among these factors are the capacities of some drugs to produce tolerance and/or physical dependence. Tolerance develops when, after repeated administration, a given dose of a drug produces a decreased effect resulting in increasing larger doses being administered in order to obtain the desired effect. Physical dependence refers to an altered physiological state resulting from the repeated administration of a drug, which necessitates the continued use of the drug in order to prevent the appearance of the withdrawal syndrome characteristics for the particular drug.

The propensity to cause physical dependence can be examined in animal studies. There are three types of animal models for assessing the drug's ability to induce physical dependence. The first study is called the substitution study. In this model, a single dose of the test drug will be substituted in animals (rats or primates) that have been made physically dependent on a drug (i.e., an opiate or a barbiturate) known to produce physical dependence. The drug is substituted when the animal is beginning to show signs of withdrawal. The second model is known as precipitated withdrawal study. In this assay, the ability of the drug to precipitate withdrawal in opiate- or barbiturate-dependent animals is evaluated. The third animal study is known as the primary dependence test. In this assay, drug-naive animals are given repeated administration of the test drug for periods of a few weeks to a few months. The dependence potential of the test drug can be evaluated by administering an antagonist and/or by abrupt cessation of the drug. The animals are observed for physical signs and symptoms of withdrawal.

In the agency letter dated November 8, 1996, it was recommended to the sponsor that they evaluate the physical dependence potential of sibutramine in primates. We suggested a 10-week, 2-dose study (i.e., primary dependence study) in 3 males and 3 females rhesus monkeys. In response to this request, the sponsor submitted results from a 13 week oral dosing study. The results from this study will be described.

STUDY DESIGN.

The 13-week oral toxicity study in cynomolgus monkeys (Maca fascicularis) was conducted at during the period of December 7, 1988 to April 20, 1989. The study was conducted in compliance with the Good Laboratory Regulation.

Fourty cynomolgus monkeys were used as subjects in this study. The monkeys were randomly (stratified by body weight) assigned to the following four treatment groups: Group 1: 0 mg/kg/day; Group 2: 1.0 mg/kg/day; Group 3: 3.0 mg/kg/day; and Group 4: 10.0 mg/kg/day. Group 1 and Group 4 were composed of 4 ♂\group and 4 ♀/group that were humanely sacrificed after the last dose on the last day of week 13 and 4 ♂/group and 4 ♀/group that were maintained untreated for 6 weeks. Group 2 and Group 3 consisted of 4 ♂/group and 4 ♀/group that were sacrificed after the last dosing of the study.

The study included daily observations for changes in appearance and/or behavior, body weight (pre-dose, weekly), food consumption (daily), ophthalmoscopy (pre-dose, weeks 6 and 13), electrocardiography (pre-dose, and before daily dosing once in weeks 6 and 13), standard hematology parameters (pre-dose, and

in weeks 6 and 13), standard clinical chemistry parameters (pre-dose, and in weeks 6 and 13), urine analysis (pre-dose, and weeks 6 and 13), macroscopic and microscopic analysis (week 13, and after treatment-free period of study).

RESULTS.

No overt signs of behavioral toxicity were observed in either the male or female monkeys following 1.0 or 3.0 mg/kg/day of BTS 54 524 (sibutramine). These doses also did not induce any significant changes in body weight, or food consumption. Some incidences of toxicity were observed in the high dose group. There was an increase incidence of vomiting immediately following the administration of 10.0 mg/kg. Also, an initial loss of body weight was seen in most animals receiving this high dose of sibutramine; however, the weight changes over the 13-week treatment period were comparable to the controls. There were no treatment-related changes in the hematological, clinical chemistry and urine parameters. Also, no treatment-related ocular changes were observed.

During the treatment-free period, the body weight of the high dose subjects were comparable to the control monkeys. In their submission, the sponsor did not submit data on food consumption or report that there were any observed signs of a withdrawal syndromes. The only reported clinical observations were: soft feces (1♂), menses (1 ♀), and hair loss (2 ♀).

CONCLUSIONS.

The findings from this study suggest that sibutramine does not produce physical dependence in cynomolgus monkeys. However, one can not conclude that sibutramine is void of physical dependence potential because this study was designed to evaluate toxicity associated with oral administration of sibutramine and not to observe and rate behaviors commonly associated with a withdrawal syndrome. In fact, it was surprising that no signs of withdrawal were observed during the first few days after cessation of treatment.

CLINICAL ABUSE LIABILITY ASSESSMENT

The abuse potential of sibutramine was evaluated in the following clinical trials:

STUDY № BPI 863: A single-center, double-blind, single-dose, placebo-controlled, randomized, latin square, crossover study to evaluate the potential abuse liability of sibutramine hydrochloride (20 and 30 mg) compared to dextroamphetamine (20 and 30 mg) and placebo in recreational stimulant users.

CLINICAL INVESTIGATOR: Jonathan O. Cole, M.D.

SITE: McLean Hospital, S. Belnap III 115 Mill St., Belmont MA 02178

OBJECTIVES: To compare the abuse potential of sibutramine hydrochloride (20 and 30 mg) to that of dextroamphetamine (20 and 30 mg) and placebo in recreational stimulant users.

PROTOCOL.

Study Design. A single-center, single daily dose, double-blind, active reference, placebo-controlled, Latin Square crossover study.

Duration of study. The duration was approximately 43 days consisting of four phases: screening evaluation period, an initial washout period (2 weeks), five treatment sessions followed by a five day washout period and a post-study evaluation (5 days post-treatment)

Subjects: 30 healthy male volunteers; *INCLUSIONS CRITERIA:* 1) 2) body weight within the range -15% to +50% of ideal weight according to the Modified 1983 Metropolitan Height and Weight Table; 3) competent to understand the study, to give written consent and able to communicate with the investigators; 4) without major psychiatric and medical problems; 5) history of recreational stimulant use (at least on 6 occasions) ; 6) willing to abstain from all psychoactive drugs for 48 hours, alcohol for 24 hours, caffeine for 6 hours and food for 2 hours prior to each study session; 7) willing to abstain from cigarette smoking for 30 minutes prior to each session.

Subjects that met any of the following criteria were excluded from the study: 1) diagnosis with psychoactive substance abuse according to the DSM III-R within twelve months of study enrollment; 2) history of seizure disorder, severe cerebral trauma or stroke; 3) history of cardiac disease; 4) known hypersensitivity to antidepressants or multiple drugs; 5) immediate family history of mental disorders; 6) on prescribed psychotropic agents, thyroid hormones, beta-blockers, anticholinergics, antiasthmatics, barbiturates, reserpine, or cyclobenzaprine; 7) used any investigational drug within 30 days of the initiation of treatment.

Study Site: Study sessions occurred in a living room-like setting in a psychopharmacology unit. Subjects were allowed to interact freely among themselves during the study. However, when completing the self-report instrument, subjects sat apart from one another with no interaction until all subjects in the group completed these instruments. Subjects were not allowed to leave the unit until all symptoms of drug-induced changes had resolved.

Study Plan: **Treatment Phase**. Five treatment sessions, at five day intervals, were approximately 5 hours in duration. During each session, the subjects were evaluated in groups of 5 (i.e., six subjects per each treatment condition per session). All subjects received each treatment condition. Prior to receiving his designated session's medication, each subject was required to have a drug-free urine sample, complete the Addiction Research Center Inventory (ARCI), Feelings Statement Scale with a favorite drug selection (session 1 only), Highness Section, a Modified Norris Assessment questionnaire and have blood pressure, heart rate and body weight measured. Subjective response measures included: ARCI at 1, 2, 3, and 4 hours post-treatment, treatment identification (i.e., identify which treatment they think they received) at 2 and 4 hours post-medication, enjoyment identification selection (i.e., rating of how much the drug was liked) evaluated at 4.5 hours after dosing during session 5 only, estimation of the "street value" of the treatment at 4.5 hours, a Highness Section at 1, 2, 3 and 4 hours post-treatment and the Modified Norris Assessment (rating of feelings such as mental and physical sedation, tranquility and other attitudes) was performed at 3 hours post-dosing. Physiological measures included: Blood pressure and heart rate measures at 1, 2, 3, and 4 hours post-dosing. Side effects associated with the treatment was assessed every hour for up to 4.5 hours after treatment. **Post-treatment Evaluation**. Five days after their last treatment, the subjects returned to the psychopharmacology unit for the post-treatment evaluation phase. Physical examination, blood pressure, heart rate, body weight, electrocardiogram, hematology, serum chemistry, urinalysis, thyroid function and adverse events were assessed.

Study Medications. Dextroamphetamine tablets (Dexedrine®) (5 mg) and sibutramine capsules (10 mg) were the active drugs for the study. Dextroamphetamine tablets were encapsuled in capsules. The active drug capsules were not identical. Sibutramine hydrochloride capsules were white opaque while the dextroamphetamine capsules were light blue opaque in appearance. Each active drug had a corresponding placebo capsules that was identical in appearance. At each of the five treatment sessions, each subject received 9 capsules in a single oral dose. The five treatment conditions are listed in Table 1 below:

Table 1. Treatment conditions for the study.

TREATMENT	# OF ACTIVE CAPSULES[a]	# OF SIBUTRAMINE MATCHING PLACEBO CAPSULES	# OF D-AMPH MATCHING PLACEBO CAPSULES
A: 20 mg Sibutramine	2	1	6
B: 30 mg Sibutramine	3	0	6
C: 20 mg d-AMPH	4	3	2
D: 30 mg d-AMPH	6	3	0
E: Placebo	0	3	6

a: Sibutramine HCl 10 mg or dextroamphetamine (D-AMPH) 5 mg

Data Analysis. Assessments examined include: **Analysis of abuse potential (i.e., ARCI, Modified Norris Assessment, "highness", treatment identification, "street value", enjoyment selection)**. ANOVA (with $\alpha = 0.05$) was used to assess treatment differences. When the ANOVA showed statistically significant treatment differences, then multiple comparisons were performed using Fisher's LSD method to show specific differences. Results from the "street value" analysis and treatment identification were analyzed using the Generalized Mantel-Haenszel to assess treatment differences. A chi-square goodness-fit test was used to determine treatment difference with enjoyment section. **Physiological Effects**. Descriptive statistics (number of observations, mean, standard deviations, median and range) was used to report changes from baseline for vital signs and body weight. An ANOVA for continuous variables was used to analyze differences from baseline. **Adverse Effects**. Adverse effects were categorized as pre-treatment,

treatment-emergent, or post-session according to their start date. The adverse effects were summarized by number of subjects and occurrence counts, treatment and body system affected and COSTART terms.

RESULTS.

Results from this study suggest that there are some differences and similarities in the subjective effects profile of sibutramine with that of dextroamphetamine. On the ARCI, scales measuring amphetamine-like activity (i.e., Amphetamine Scale and Benzedrine Scale) and euphoria (Morphine-Benzedrine Scale), dextroamphetamine (20 and 30 mg) had a significantly greater stimulant effect than placebo and sibutramine for the majority of the timepoints ($p<0.05$, Fisher's LSD). Peak effects for dextroamphetamine's amphetamine-like activity and euphoria occurred at 2 and 3 hours, respectively. In contrast, the responses elicited by 20 and 30 mg of sibutramine were indistinguishable from placebo at all timepoints.

Like dextroamphetamine, sibutramine displayed a significant response on the scales measuring sedation (Pentobarbital-Chlorpromazine-Alcohol Scale) and dysphoria (Lysergic Acid Diethylamide Scale). At the highest dose (30 mg) tested, sibutramine produced significant ($p<0.05$, Fisher's LSD) sedative and dysphoric effects; however, responses for the 20 mg dose were similar to that of placebo. Dextroamphetamine showed significantly greater response at 20 and 30 mg.

Sibutramine was rated by the subjects as less than dextroamphetamine in the categories of drug enjoyment and street value. The mean dollar of street value for dextroamphetamine (20 mg, $2.82; 30 mg, $3.32) were significantly greater than placebo ($0.17, $p<0.05$). In contrast, the street-estimated value for both sibutramine doses did not separate from placebo; 20 mg and 30 mg street value was $0.50 and $0.67, respectively. The rank order of session was: 30 mg dextroamphetamine > 20 mg dextroamphetamine > placebo > 30 mg sibutramine > 20 mg sibutramine. Percentages of the subjects enjoying each treatment were: 45% for 30 mg dextroamphetamine; 28% for 20 mg dextroamphetamine; 14% for placebo; and 5% for 30 mg sibutramine and 0% for 20 mg sibutramine.

As measured in the "Highness Section", both dextro-amphetamine- and sibutramine-induced mental and physical high/experience were perceived as being different from the subjects' previous experience with stimulants and their favorite drug of abuse.

Table 2 shows the results of the subjects' rating of their feelings about the treatment. The results show a clear difference in sibutramine-induced and dextroamphetamine-induced feelings. Sibutramine elicited feelings of mental and physical sedation at the 20 mg dose and a feeling of tranquility at the 30 mg dose. In contrast, dextroamphetamine did not elicit feelings of sedation.

Table 2. Results from the Modified Norris Assessment Questionnaire.

	MEAN CHANGE FROM BASELINE				
MODIFIED NORRIS FACTOR	PLACEBO	SIBUTRAMINE (20 MG)	SIBUTRAMINE (30 MG)	D-AMPHETAMINE (20 MG)	D-AMPHETAMINE (30 MG)
Mental Sedation	0.44	2.23	0.35	-1.38	-4.80*
Physical Sedation	0.31	2.96	0.68	-0.11	-2.99*
Tranquilization	0.70	-1.90	1.14	-1.68	-2.00
Other Types of Feelings or Attitudes	1.44	2.80	0.98	-1.04[b]	-3.28*

Both doses of sibutramine and dextroamphetamine tended to show dose-related increases in blood pressure and pulse rat, but the effects were generally greater with dextroamphetamine. Respective maximum mean increases from baseline for systolic and diastolic blood pressure and pulse rate (supine or standing) for treatments were: dextroamphetamine (both doses), +20.7 and +9.0 mm HG and +12.4 bpm; sibutramine (both doses), +9.9 and +6.3 mm HG and +9.0 bpm and placebo +4.9 and +3.5 mm HG and -0.1 bpm.

No deaths or premature withdrawals due to ADEs were reported.

Conclusion and Comments. The results from this study suggest that sibutramine is not amphetamine-like in healthy male volunteers. At the doses tested in this study, results from the Modified Norris Assessment Questionnaire, sibutramine showed sedative and tranquilizing-like effects. Results from the LSD Group of the ARCI suggest that sibutramine may possess hallucinogenic effects at 30 mg. However, these results lack value in contributing to the abuse liability assessment of sibutramine because of the following study deficiencies:

1. Only two doses of sibutramine were evaluated and they were within the recommended therapeutic dose range. These doses were not high enough to allow full evaluation of peak effects of the active metabolites BTS 54 354 and BTS 54 505. Therapeutic agents that are abused are commonly taken in excess of the recommended therapeutic dose. Clinical trial assessing a drug abuse potential should evaluate doses that one would predict to occur within the "drug culture".

2. The subjects selected for the study were not a fair representation of the population that will be exposed to the drug. Females were excluded from this study, although they were included in the clinical efficacy trials. Females may seek this drug out more frequently than males and may be at a greater risk to abuse this drug.

3. The abuse liability assessments were hourly up to 4.5 hours. However, the peak response from the M1 and M2 metabolites occurred between 4 and 6 hours after the drug was taken. It is likely that the full response from the active metabolites has been missed.

4. It was unclear about the subjects drug history. Subjects that had used stimulants on six occasions were selected: Did this mean six times over a lifetime or six times within a certain timeframe (such as within 3 years prior to the study)?

5. The sponsor should have selected a subject population that was more experienced in stimulant abuse than the fairly inexperienced recreational stimulant abusers. In fact, only a small percentage of the subjects identified their favorite drug as being a stimulant; 12.9%, 71%, 3.2%, 6.5%, and 3.2% of the patient population selected stimulants, hallucinogens, opiates, sedatives and inhalants as their favorite recreational drug, respectively. Results observed in the treatment identification section will be strongly influenced on the subjects' drug abuse history. Experienced users will be better able to make subtle discrimination between drugs with similar effects.

6. Capsules for the different drugs in the study were not identical in color (blue or white). In abuse liability assessment studies, the treatment drugs should be identical in appearance so that the differences in capsules will not influence the subjects evaluation of the drug.

7. Subjects were in too close contact prior to and during drug evaluation period, able to discuss the drugs and their effects, thereby potentially influencing other subjects on the drug evaluations.

8. Data needs to be summarized and shown on charts for ARCI to include all ranges, means, and standard deviations for test results.

SIBUTRAMINE (MERIDIA) CAPSULES: CLINICAL PROTOCOL Nº BPI 883

Title: A single-center, **IN-PATIENT**, double-blind, single-dose, placebo-controlled, randomized, balanced, Latin square crossover study to evaluate the potential abuse liability of sibutramine hydrochloride 25 and 75 mg compared to dextroamphetamine 10 and 30 mg and placebo in diagnosed substance abusers.

Clinical Investigator: Donald Jasinski, M.D.

Site: Johns Hopkins Bayview Medical Center
Clinical Pharmacology Research
4940 Eastern Avenue, Room 1403 D-1-Center
Baltimore, MD 21224

Study Period: August 10, 1996 to December 24, 1996

Objective: This study is intended to confirm that sibutramine at 25 & 75 mg does not possess amphetamine-like abuse potential. The potential abuse liability of sibutramine hydrochloride (25 and 75 mg) will be compared to dextroamphetamine (10 and 30 mg) and placebo in diagnosed substance abusers.

STUDY DESIGN: A single-center, in-patient, single-dose, double-blind, active-reference, placebo-controlled, balanced Latin Square crossover study in 20 substance-abusing volunteers.

Each subject participates in 5 separate study sessions separated by 3-day washout periods. By the end of Session 5, each subject will have taken all 5 study medications: sibutramine 25 & 75 mg, dextroamphetamine 10 & 30 mg, and placebo. Sequence of the 5 study medications is determined by balanced Latin Square randomization. Subjects remain in residential research unit and are supervised 24 hours/day. On day 21, subjects are discharged if all clinically significant drug-induced changes are resolved. Post-study ADE follow-up visits are scheduled for subjects with ongoing ADEs at discharge.

During each 24-hour study session (Days 1, 5, 9, 13, and 17), vital signs and pupil size are measured and subjective scales completed 60 and 30 minutes prior to dosing and 0.5, 1, 2, 3, 4, 5, 6, 9, 12 and 24 hours afterwards. Subjective scales include the following evaluations: ARCI (subject), Drug Rating Questionnaire (subject & observer), Specific Drug Effect Questionnaire (subject & observer), and Drug Identification Questionnaire (subject). The Street Value Assessment is completed by the subject 2,4, and 6 hours after dosing. On Day 17 only, the Treatment Enjoyment Assessment is completed 2, 4, and 6 hours after dosing.

Each study session is followed by a 3-day washout period (Days 2-4, 6-8, 10-12, 14-16 and 18-20). During the washout periods, vital signs and pupil size are monitored and the subjective scales are completed at regularly scheduled intervals and sleep logs maintained. Urine drug screens are performed on the first day of each washout period (Days 2,6,10,14, and 18). Subjects do not begin another study session (i.e., dose again with study medication) until their supine systolic and diastolic blood pressures are $\leq$140 and 90 mm Hg, respectively; their pulse rate is $\leq$90 bpm; and, in the Investigator's opinion, their subjective scales and clinical profile no longer represent drug effect. Additional days may be added to the washout period.

On Day 21 (3 days after completing Session 5), subjects will be eligible for discharge from the research unit. No subject will be allowed to leave the unit until all clinically significant drug-induced changes have resolved.

STUDY MEDICATION.

DOSE: 5, 10, 15, and 20 mg capsules for oral use

The 5 different study medication cells in this trial are:

Cell A:	Sibutramine 25 mg as a single oral dose
Cell B:	Sibutramine 75 mg "
Cell C:	Dextroamphetamine 10 mg "
Cell D:	Dextroamphetamine 30 mg "
Cell E:	Placebo "

Fasted subjects will be administered medication under supervision with approximately 300 ml water.

SUBJECT SELECTION.

INCLUSION CRITERIA:

1. Medical history and clinical profile.
2. Males/Females
3.
4. -10% to +15% of ideal weight
5. Good physical and mental health
6. History of psychoactive substance abuse includes stimulants
7. Be will to remain in the research unit for 21 days.
8. Use of cocaine within 30 days of Day 1

EXCLUSION CRITERIA (ANY OF THE FOLLOWING):

1. Inpatients or scheduled for elective surgery during study
2. History: convulsions; seizures; severe cerebral trauma; stroke.
3. Clinically significant lab abnormality or organic disease that in opinion of Investigator, might create a risk for the subject, obscure effects of study medication, or interfere with drug's absorption, metabolism or excretion.
4. Clinically significant history of cardiac disease including hypertension, any abnormal cardiac condition or a pathologically abnormal ECG.
5. Significant immunologic, hepatic, renal, pulmonary or hematologic dysfunction.
6. History or current platelet count of less than 150,000/mm^3
7. Supine pulse rate >90 bpm or confirmed supine systolic or diastolic BP >140 or 90 mm Hg, respectively.
8. Need for any concomitant medication other than birth control
9. Thyroid dysfunction or any other significant endocrine abnormality (also type I or type II diabetes mellitus)

10. Demonstration of any of the following in reaction to a previously used CNS stimulant: ischemic ECG changes, clinically sign on cardiac arrhythmia or clinically significant manifestations of mitral valve prolapse.
11. History of hypersensitivity to antidepressants or multiple drug hypersensitivities.
12. Use of narcotics, narcotic antagonists, psychotropic drugs, or any recreational, Rx, or OTC drugs within 7 days of admission. Administration of any investigational drug within 30 days prior to admission. Prior administration of sibutramine at any time.
13. An acute illness within 7 days of admission
14. a positive urine drug screen on admission. Subjects testing + for cocaine are excluded. Subjects who test + for cocaine metabolite (in absence of parent compound) are eligible.
15. Any substance abuse or dependence requiring immediate medical treatment as evidence by Addiction Severity Index (AS).

ADDICTION SEVERITY INDEX: Standard battery of interview items to assess drug use by self-report.

SUBJECTIVE SCALES - SUBJECT RATINGS:

1. ARCI: 49 Item questionnaire contains 5 overlapping subscales derived from the original 102-item ARCI. Subject is instructed to select which of 5 responses best describes how he feels right now. Response for each item is: "not at all"(1), "maybe"(2), "a little"(3), "moderately"(4),"an awful lot"(5).

A. Morphine-Benzedrine Group (MBG) consisting of 16 items that identify drugs with euphoric properties. Scored from
B. Pentobarbital-Chlorpromazine-Alcohol Group (PCAG) consisting of 15 items that identify drugs with sedative properties. Scored from
C. LSD-Specific Group consisting of 14 items that identify drug with hallucinogenic and dysphoric properties. Scored from
D. Benzedrine Group (BG) consisting of 13 items that identify drugs with amphetamine-like properties. Scored from
E. Amphetamine Scale consisting of 11 items that measure amphetamine-like effects. Scored from

2. **DRUG RATING QUESTIONNAIRE:** 4-Item questionnaire will ask subject if he:
i. Feels the drug, **ii.** Likes the drug, **iii.** Dislikes the drug, or **iv.** Feels high. For each item subject will indicate how he feels right now by darkening a circle along a continuous line of 42 circles (equivalent to 100 mm visual analog scale). Scale is anchored with the descriptors "not at all" and "an awful lot". Scored from 1 to 42.

3. **SPECIFIC DRUG EFFECT QUESTIONNAIRE:** 22-Item questionnaire asks if drug is producing certain effects (i.e., skin itching, sleepiness, nervousness, dizziness, depression, hallucinations, etc.). For each item, subject will be instructed to select which of 5 responses best describes how he feels right now. Response for each item will be scored as follows:"not at all" (1); "maybe" (2); "a little" (3); "moderately" (4); "an awful lot" (5).

4. **DRUG IDENTIFICATION QUESTIONNAIRE:** 10-Item questionnaire will ask subject if the drug effect feels like that of certain drugs (i.e., placebo, morphine, Thorazine, barbiturates, LSD, Valium, amphetamines, PCP, etc.). For each item, subject is instructed to select which of 5 responses best describes how he feels right now. Response for each item is scores as follows: "not at all" (1), "maybe" (2), "a little" (3), "moderately" (4), "an awful lot" (5).

5. **STREET VALUE ASSESSMENT:** Subjects asked to estimate cash value ($0-$10) of the study drug they have just experienced were it to be offered illicitly on the street.

6. **TREATMENT ENJOYMENT ASSESSMENT:** Subject is asked to identify which one of the 5 study medications they would enjoy taking again.

SUBJECTIVE SCALES - OBSERVER RATINGS:

1. **DRUG RATING QUESTIONNAIRE:** 3-Item questionnaire asks the observer if subject feels the drug, likes the drug, or dislikes the drug. For each item, observer will indicate how subject feels right now by darkening a circle along continuous line of 42 circles (equivalent to a 100 mm VAS). Scale is anchored with descriptors "not at all" and "an awful lot". Scoring from 1 to 42.

2. **SPECIFIC DRUG EFFECT QUESTIONNAIRE:** 22-Item questionnaire asks observer if subject has certain drug effects (i.e.,skin itching, sleepiness, nervousness, dizziness, depression, hallucinations, etc.). For each item, observer will select which of 5 responses best describes how subject feels right now. Scoring is as follows: "not at all" (1), "maybe" (2), "a little" (3), "moderately" (4), "an awful lot"(5).

Profile of responses to sibutramine will be compared to both placebo and amphetamine.

The abuse potential of sibutramine will be judged by the degree of qualitative and quantitative similarity to the active reference, dextroamphetamine.

ADVERSE EVENTS:

Any reaction side effect, or other untoward event, regardless of relationship to the study drug, that occurs during the conduct of a clinical trial. Clinically significant adverse changes in clinical status, ECGs, routine labs, X-rays, physical examinations, etc., are considered adverse events.

SERIOUS ADVERSE EVENT:

Any experience that suggests a significant hazard, contraindication, side effect of precaution. a serious ADE includes any experience that:

1. Is life threatening or fatal
2. Is permanently disabling
3. Requires or prolongs hospitalization
4. Is a congenital anomaly.
5. Is cancer
6. Is an overdose (whether accidental or deliberate).

RESULTS: The primary subjective measures followed were recognition by the Amphetamine scales, Benzedrine scales, the euphoria scales (MBG) and response to the question of liking the drug response. Separation from placebo of all three active drugs from placebo was indicated in drug liking and amphetamine scales. Sibutramine 25 mg & 75 mg overlapped with the lower dose of amphetamine. As is typical of these subjective scales, each time point offered large variabilities and standard deviations. Blood pressure increased with increasing dose of tested drug. See data summarized in the graphs, located in the Appendix, along with comparison to the following study (BPI893).

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CLINICAL PROTOCOL Nº BPI 893

Title: A four-period, double-blind, single-dose, placebo-controlled, randomized, balanced, Latin square crossover study to evaluate the potential abuse liability of sibutramine hydrochloride 25 and 75 mg was compared to dextroamphetamine 20 mg and placebo in recreational substance (stimulant) users.

Co-Principal Investigators: Charles R. Schuster, Ph.D. & John Hopper, M.D.

Site: Wayne State University School of Medicine
2761 E. Jefferson Avenue
Detroit, MI 48207.

Study Period: September 9, 1996 to February 20, 1997

Objective: To assess potential abuse liability of sibutramine 25 & 75 mg when compared to dextroamphetamine 20 mg & placebo, in recreational substance (stimulant) users.

Study Design. A single-center, OUT-PATIENT, double-blind, active-reference, placebo-controlled, balanced Latin Square crossover study conducted in 15 recreational substance (stimulant)using volunteers (to yield 12 completers) designed to examine abuse potential of sibutramine. Each subject will participate in a practice session and in four separate study sessions separated by at least 5-day washout periods. By the end of Session 4, each subject will have taken all four study medications: sibutramine 25 and 75 mg, dextroamphetamine 20 mg and placebo. Sequence of the four study medications are determined by balanced Latin Square randomization. Drug effects are assessed in each study session by subject reporting of subjective scales using subjective scales. After completion of all four drug sessions, participants return after a minimum 5-day washout period for a fifth (lottery) session. The purpose of this session is to allow subjects to actually receive one of two choices (drug or money) they made in the MCP in the study sessions, thereby ensuring that those choices are made carefully. a post-study visit is to take place 5-7 days later. Post-study Adverse Event Follow-Up Visits is to be scheduled for subjects who have ongoing adverse events at this visit. If a subject is replaced, the sequence of medications that a replacement subject receives will be identical to that of the subject dropped from study participation. Subjects prematurely terminating from the study are to complete all post-study procedures. Safety is monitored throughout study by physical examinations, vital signs measurements, laboratory safety analyses, and urine pregnancy tests (for women).

Study participants , are recreational psychomotor stimulant users, defined as those reporting using a psychomotor stimulant at least 6 times, but who have no signs of dependence. It is expected that the gender/race composition of the sample will approximate the proportions of individuals within Detroit area. Detroit is approximately 73% African-American, Hispanic and Native American, and the rest non-Hispanic White.

During practice session, participants become familiar with study procedures and practice the subjective effects as they would perform them in an experimental session. The four drug sessions (one each of 25 and 75 mg sibutramine and 20 mg d-amphetamine) will each be separated by a minimum 5 day washout period. There are also one lottery session and one post study follow-up session. During the drug sessions, medication will be administered in a single oral dose. Physiological and subjective (POMS, VAS, and ARCI) effects scales will be completed pre-drug and 0.5, 1, 1.5, 2, 2.5, 3, 4, and 6 hours post drug. The End of Session Questionnaire and MCP will be completed after the 6-hour assessment of physiological and subjective effects.

Study sessions take place in a living room-like setting in the . **Participants are allowed to interact among themselves; however, when completing the subjective effects instruments, they sit apart from each other and no interaction is allowed until all group members have completed the instruments.** Participants are not allowed to leave the laboratory until all symptoms of drug-induced changes have resolved. Participants remain for 24 hours, overnight for clinical observation, and then return after the 5 day washout periods. Urinalysis and hematology and breath alcohol tests were conducted when subjects returned after washout. There was no verification provided that other drugs of abuse were not taken after leaving unit where subjects were observed.

Study Medication. See above (Cell a, B, C, and D). Fasting (except for water) occurs from midnight the night before dosing until 2 hours post dosing on drug administration days. Medication (5 capsules) is administered under supervision, with approx. 300 mL water within a 2 min period.

SUBJECT SELECTION.

Inclusion Criteria (Require all):

1. Competent; **2.** Females (sterile or practicing birth control) or Males; **3.** 18-50 yoa; **4.** Within standard height & weight requirements; **5.** Good physical and mental health as confirmed by medical history, physical exam, lab testing and psychiatric interview; **6.** History of recreational psychomotor stimulant use (on at least 6 occasions), but without signs of dependence.

Exclusion Criteria (Any of the following):

1. Inpatient status or scheduled for elective surgery during course of study; **2.** History of any neurological disease (convulsions, head trauma, etc.); **3.** Any clinically significant lab abnormality or organic disease that could effect drug absorption, metabolism or excretion; **4.** Cardiac disease (hypertension, any abnormal cardiac condition or pathologically abnormal ECG); **5.** Immunologic, hepatic, renal, pulmonary or hematologic dysfunction; **6.** History or current platelet count $< 150{,}000/mm^3$; **7.** Supine pulse rate >90 bpm or supine systolic or diastolic BP >140 or 90 mmHg, respectively; **8.** Need to use any concomitant medications other than birth control; **9.** Thyroid dysfunction or any other significant endocrine abnormality (including Type I or Type II diabetes mellitus); **10.**Ischemic ECG changes, clinically significant cardiac arrhythmia, or clinically significant manifestations of mitral valve prolapse resulting from previously used CNS stimulant; **11.** History of hypersensitivity to antidepressants or multiple drug hypersensitivities; **12.** Use of narcotics, narcotic antagonists, psychotropics, or any recreational, Rx or OTC drugs within 7 days of study start without consent of investigator. Administration of any investigational drug within 30 days prior to study start. Prior ingestion of sibutramine at any time; **13.** An acute illness within 7 days of study start; **14.** a positive urine drug screen. Testing positive for presence of cocaine (parent) are excluded, but testing positive for cocaine metabolite are eligible. **15.** Past or current psychiatric illness; **16.** Current drug dependence; diagnosis of any type of drug or alcohol dependence within past year, other than nicotine, may not participate. Consuming >500 mg caffeine per day (5 cups brewed coffee) may not participate. Current recreational drug use is allowed if candidate can produce a negative urine sample or zero breathalyzer reading (alcohol) at the time of screening and at each session and is free of any signs/symptoms of withdrawal.

Description of Study Procedures:

1. Medical/psychiatric/medication history
2. Physical examination
3. Vital signs (BP, pulse rate, temperature, respiration rate)
4. Body weight & height
5. ECG
6. Clinical labs (hematology, serum chemistry, urinalysis, urine drug screen, breath alcohol test, pregnancy test).
7. Subjective/Mood Scales - Subject Ratings (ARCI, MBG, PCAG, LSD-specific group, POMS [Anxiety, Depression, Anger, Vigor, Fatigue, Confusion, Friendliness, Elation, Arousal and Positive Mood], VAS [good drug effect, bad drug effect, drug liking, stimulated, high, anxious, sedated, down, hungry, friendly, miserable, on edge, alert, tired, talkative, self-confident, social, irritable, and confused], End-of-Session Questionnaire [identify drug and rate their liking of drug's effects])

Treatment Days (Including Practice Session & Lottery Session)

Subjects will fast (except for water) from midnight the night before dosing until 2 hours postdose on drug administration days. Caffeine-containing beverages and smoking are prohibited for the 15 minutes before each vital sign measurement or rating scale evaluation. ADEs and concomitant medications (if required) are monitored and documented throughout the study period.

Heart rate and BP (supine) recorded 30 & 0 minutes prior to dosing (average is baseline) and **0.5, 1, 1.5, 2, 2.5, 3, 4 hours after dosing.** If supine pulse rates or systolic or diastolic BP $\geq$140 bpm or $\geq$180 or 110 mm Hg, subject will be discontinued. **Subjective scales (ARCI, POMS, VAS) will be completed within 30 minutes prior to dosing and 0.5, 1.5, 2, 2.5, 3, 4, and 6 hours after dosing (not required for Lottery Session). End of Session Questionnaire is completed at 6 hours postdose.**

Medications specifically excluded: Non-study Rx psychotropics, thyroid hormones, beta-blockers, antihypertensive agents, anticholinergics, antiasthmatics, cyproheptadine, sympathomimetics, oral hypoglucemics, barbiturates, reserpine, Flexeril (cyclobenzaprine), and any other medication on that may interfere with the study medication. Use of decongestants is strongly discouraged.

RESULTS.

The results of this study by evaluation and comparison with placebo and Amphetamine 20 mg of the data points for the Amphetamine Scale, Benzedrine Scale, MBG scale, and drug liking responses demonstrated minimal difference from placebo for sibutramine doses. Clear separation of the amphetamine 20 mg from the other drugs administered was observed. The major difference between this study and BPI883 (which showed greater similarity of sibutramine response with that of amphetamine 10 mg and greater separation from placebo) was that subjects were outpatients between doses. No clear cut verification of lack of drug abuse between doses was presented. Although the subjects remained inpatients during the periods of evaluation (24 hours following study drug administration), the washout period of 5 days between drug administration was potentially long enough for the subjects to abuse other drugs and/or alcohol and for the other drugs not to show up on the urine screens or breath alcohol measurements, but still to impact on subjects' response on subjective questionnaires.

The impact that population differences and differences in subjects' experience (BPI 883 & BPI 893) in participating in such studies remain unknown. See attached graphs for comparison with BPI 883 which follow.

EVALUATION OF SIBUTRAMINE'S ADVERSE EFFECTS

Adverse effects associated with sibutramine were assessed from several clinical trials. Sibutramine (5 and 20 mg) safety and efficacy as a weight loss agent was demonstrated in a 12 week placebo controlled, parallel group, double blind clinical trial, N=60 (Weintraub, *et al.*, Clin. Pharmacol. Ther., 50(3): 330-337, 1991). Difficulty sleeping was reported by 8 participants (7 from 20 mg sibutramine and 1 from 5 mg sibutramine and none from placebo). Six participants receiving 20 mg sibutramine complained of irritability, unusual impatience, or "excitation."

Cardiovascular, anticholinergic and CNS effects of single dose of 30, 45, and 60 mg of sibutramine hydrochloride were compared with amitriptyline (50 mg) and placebo given at weekly intervals in a randomized design to 6 healthy male volunteers (King and Devaney, Br. J. Clin. Pharmac., 26: 607-611, 1988). Adverse events were dry mouth, nervous feeling, tension, drowsiness. A small but statistically significant increase in supine heart rate in association with falls in both supine and standing systolic and diastolic blood pressure was also associated with sibutramine. Single doses of sibutramine had sympathomimetic effects on cardiovascular system but lacked clinically significant anticholinergic effects and was devoid of sedative effects.

Several large clinical studies to assess safety and efficacy of sibutramine as a weight loss drug were conducted. Approximately 1,700 subjects were assessed in these trials. Two pivotal trials were designated BPI 852 and SP 1047.

BPI 852 was a multi-center, double blind, repeated dose, placebo-controlled, parallel-group, dose-ranging study to evaluate the weight reducing efficacy, safety and tolerability of sibutramine hydrochloride 1, 5, 10, 15, 20 and 30 mg daily in obese patients for up to 24 weeks. A total of 899 patients participated in this trial.The primary objectives of this clinical study were: **1)** to compare the effects of each dose or placebo on weight loss in these subjects when given in conjunction with modest caloric restriction, exercise, and behavior modification for up to 12 weeks; **2)** to assess the effects of the tested doses on supine and standing heart rate in obese patients after 2 and 12 weeks; **3)** to assess the effects of the tested doses on supine and standing heart rate in obese patients after 2 and 12 weeks; **4)** to assess the effects of sibutramine on appetite, satiety, food, craving, and waist/hip ratio after treatment for up to 24 weeks in obese patients; **5)** and to assess the efficacy, safety and tolerability of sibutramine doses for up to 24 weeks in obese patients.

Adverse reactions that were reported were qualitatively similar to those of amphetamine and amphetamine-like drugs. In addition to hypertensive and tachycardia responses, a series of CNS stimulant responses mirroring those of amphetamine were observed. These are listed in the following Tables 1, 2, 3, 4, and 5 below.

Table 1. Number (%) of **obese** patients reporting adverse events in placebo-controlled trials and number of adverse events reported.

ADVERSE EVENT BY COSTART TERM	**All Obese** No. (%) patients		Healthy Obese No. (%) patients	
	Sibutramine (n= 1766)	Placebo (n=605)	Sibutramine (n= 1635)	Placebo (n=480)
AGITATION	9 (0.5)	0 (0.0)	9 (0.6)	0 (0.0)
AMNESIA	7 (0.4)	3 (0.5)	7 (0.4)	2 (0.4)
ANXIETY	75 (4.2)	18 (3.0)	75 (4.6)	16 (3.3)
ASTHENIA	108 (6.1)	32 (5.3)	100 (6.1)	23 (4.8)
CNS STIMULANT	17 (1.0)	3 (0.5)	17 (1.0)	1 (0.2)
CONFUSION	4 (0.2)	2 (0.3)	4 (0.2)	2(0.4)
CONVULSIONS	3 (0.2)	0 (0.0)	3 (0.2)	0 (0.0)
DEPRESSION	78 (4.4)	17 (2.8)	77 (4.7)	16 (3.3)
DEPRESSION PSYCHOTIC	2 (0.1)	0 (0.0)	2 (0.1)	0 (0.0)
DIZZINESS ✓	129 (7.3)	22 (3.6)	118 (7.2)	13 (2.7)
DREAM ABNORM.	6 (0.3)	0 (0.0)	6 (0.4)	0 (0.0)
DRY MOUTH ✓	322 (18.2)	29 (4.8)	299 (18.3)	22 (4.6)
EMOTION LABIL	26 (1.5)	5 (0.8)	26 (1.6)	5 (1.0)
EUPHORIA	1 (0.1)	2 (0.3)	1 (0.1)	2 (0.4)
HEADACHE ✓	577 (32.7)	131 (21.7)	552 (33.8)	105 (21.9)
HOSTILITY	3 (0.2)	0 (0.0)	3 (0.2)	0 (0.0)
HYSTERIA	1 (0.1)	0 (0.0)	1 (0.1)	0 (0.0)
INSOMNIA ✓	190 (10.8)	28 (4.6)	184 (11.3)	25 (5.2)
NERVOUSNESS ✓	100 (5.7)	22 (3.6)	97(5.9)	15 (3.1)
NEUROSIS	2 (0.1)	0 (0.0)	1 (0.1)	0 (0.0)
PARESTHESIA ✓	37 (2.1)	4 (0.7)	34 (2.1)	2 (0.4)
SUICIDE ATTEMPT	1 (0.1)	0 (0.0)	1 (0.1)	0 (0.0)
THINKING ABNORMAL	18 (1.0)	3 (0.5)	18 (1.1)	3 (0.6)
TREMOR	12 (0.7)	2 (0.3)	11 (0.7)	2 (0.4)

Table 2. ADVERSE EVENTS IN PLACEBO-CONTROLLED STUDIES WITH AN INCIDENCE OF ≥1% AND GREATER THAN PLACEBO INCIDENCE AND P-VALUES ≤ 0.05

TRIAL	Adverse Event by COSTART Preferred Term
ALL OBESE Sibutramine (n= 1766) Placebo (n= 605)	 DIZZINESS (p=0.0014) DRY MOUTH (p=0.0000) HEADACHE (p= 0.0010) INSOMNIA (p=0.0000) NERVOUSNESS (p=0.0516) PARESTHESIA (p=0.0195)

TABLE 3. Number (%) sibutramine-treated obese patients in placebo-controlled with treatment emergent adverse events by total daily dose at the time of the event. ADVERSE EVENTS THAT APPEARED TO BE DOSE-RELATED

COSTART TERM	Total Daily Dose (mg)		
	Placebo (n= 605)	10-14 (n= 582)	≥ 30 (n= 165)
ASTHENIA	32 (5.3)	27 (4.6)	17 (10.3)
HEADACHE	131 (21.7)	127 (21.8)	78 (47.3)
AGITATION	0 (0.0)	1 (0.2)	2 (1.2)
ANXIETY	18 (3.0)	17 (2.9)	13 (7.9)
CNS STIMULANT	3 (0.5)	1 (0.2)	5 (3.0)
DIZZINESS	22 (3.6)	31 (5.3)	15 (9.1)
DRY MOUTH	29 (4.8)	73 (12.5)	48 (29.1)
INSOMNIA	28 (4.6)	39 (6.7)	37 (22.4)
NERVOUSNESS	22 (3.6)	24 (4.1)	16 (9.7)
SLEEP DIS	1 (0.2)	1 (0.2)	2(1.2)
TREMOR	2 (0.3)	0 (0.0)	4 (2.4)

Table 4. **Listing of CNS Amphetamine-like treatment emergent adverse reactions from pivotal clinical efficacy trials following administration of sibutramine and placebo that resulted in withdrawal from the study.**

TRIAL	Nº OF SUBJECTS (N)	SIBUTRAMINE (N)	SIBUTRAMINE (%)	PLACEBO (N)	PLACEBO (%)
BPI 852	899	23	2.56%	4	0.45%
BPI 852X		29	3.22%		
SP 1047	322	14	4.35%	5	1.55%
TOTAL	1221	66	5.4%	9	0.74%

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Table 5. Reasons for Withdrawals

Patient withdrawals were tabulated according to the following categories:

1. Lack of effect; 2. Adverse event (including AEs with an outcome of death); 3. Lost to follow-up; 4. Protocol violation 5. Other

ADVERSE EVENT	PREVIOUS COSTART TERM	REVISED COSTART TERM	SUBJECT NUMBER
PANIC ATTACK/PANIC ATTACKS/PANICKY-SOMATIC ANXIETY	AGITATION	ANXIETY	BPI806X 2046, BPI806, 3473 BPI850, 0113 BPI852X 2122 BPI862 0014 SB1047 0181 SB1047 0234, SSB7601 0170
FLAT PERSONALITY	PERSON DIS	APATHY	BPI852X 6006
FLAT EMOTIONS/ FLATTER EMOTIONS	EMOTION LABILE	APATHY	BPI852 1102 BPI852 1129
FELT VERY ACTIVE FOR 2 HOURS AFTER DOSE	AESTHESIA	CNS STIM	MS86004 0021
FELT VERY ACTIVE FOR 2 HRS AFTER DOSE	HYPERKINESIA	CNS STIM	MS86004 0021
HYPER FEELING	NERVOUSNESS	CNS STIM	BPI806X 2076
HYPERACTIVE FEELING/ HYPER FEELING (HYPERACTIVE)/ FEELING HYPERACTIVE/ NERVOUS-HYPER/ OVERACTIVE HYPERACTIVITY/ INCREASED ENERGY	HYPERKINESIA	CNS STIM	BPI801 0063, BPI 805A 0503, BPI806 3328, BPI852: 1122, 1137,2029, 4001, 6012, 6025, 6073, 6130, 0008, MS85029 0008, BPI852X: 2032, 2001, 2037, 2048, 2055, 2068, 2105, 2116, 2135, 2149, 2152, 3017, 3047, 3048, 3050, 3064, 3088, 3089, 3091, 3103, 3117, 3133, 3145, 3147, 7028, 7127,7148
INCREASE OF THE PHYSICAL ACTIVITY & INTELLECTUAL ACTIVITY	CNS STIMULAT	CNS STIM	SB1043 0147
INCREASE OF THE PHYSICAL ACTIVITY & INTELLECTUAL ACTIVITY	HYPERKINESIA	CNS STIM	SB1043 0147
INCREASED ENERGY	CNS STIMULAT	CNS STIM	BPI850 0129
INCREASED ASSERTIVENESS	HOSTILITY	CNS STIM	BPI852X 3071
INCREASED ACTIVITY	HYPERKINESIA	CNS STIM	BPI852X 7106

ADVERSE EVENT	PREVIOUS COSTART TERM	REVISED COSTART TERM	SUBJECT NUMBER
INCREASED ASSERTIVENESS	REACT UNEVAL	CNS STIM	BPI852 3071
NERVOUSNESS/ HYPERACTIVITY	HYPERKINESIA	CNS STIM	BPI852 5170
OVERACTIVE	HYPERKINESIA	CNS STIM	MS85029 0008
PT FEELS "SPEEDY"/ PT FEELS LIKE SHE'S ON SPEED WHEN DRINKING COFFEE	NERVOUSNESS	CNS STIM	BPI852 1147, BPI1165
SPEEDING	EUPHORIA	CNS STIM	BPI863 1018
SPEEDY FEELING/ SPEEDINESS/ SPEEDY	HYPERKINESIA	CNS STIM	BPI852 1065, BPI852 4013
DISAPPOINTMENT	REACT UNEVAL	DEPRESSION	BPI852 1105
SHORT TEMPERED	HOSTILITY	EMOTION LABILE	BPI852X 1117
SLEEPLESSNESS	SOMNOLENCE	INSOMNIA	BPI822 0001
CHEWING ON TONGUE/FRUSTRATION	REACT UNEVAL	NERVOUSNESS	BPI806X 2132, BPI852 1053
IMPATIENT	ANXIETY	NERVOUSNESS	BPI850 0201
RETARDATION	THINKING ABNORMAL	THINKING ABNORM	SSB7601 0313
WORD/NAME FIND PROBLEMS/WORD-FIND DIFFICULTY	REACT UNEVAL	THINKING ABNORM	BPI852 1010, 1037, 1071, 1093, 1097, 1116, 1118, 1129, 1143

AMPHETAMINE (Adderall)

ADVERSE REACTIONS (LISTED IN PRODUCT LABELING):

1. **Cardiovascular:** Palpitations, tachycardia, elevation. Isolated reports of cardiomyopathy associated with chronic amphetamine use.

2. **Central Nervous System:** Psychotic episodes at recommended doses (rare), overstimulation, restlessness, dizziness, insomnia, euphoria, dyskinesia, dysphoria, tremor, headache, exacerbation of motor and phonic ticsband Tourette's syndrome.

3. **Gastrointestinal:** Dryness of the mouth, unpleasant taste, taste, diarrhea, constipation, other GI disturbances. Anorexia & weight loss may occur as undesirable effects when amphetamines are used for other than the anorectic effect.

4. **Allergic:** Urticaria

5. **Endocrine:** Impotence, changes in libido.

OVERDOSAGE:

1. Individual patient response to amphetamines varies widely.

2. **Symptoms:** Restless, tremor, hyperreflexia, rapid respiration, confusion, assaultiveness, hallucinations, panic, states, hyperpyrexia, and rhabdomolysis.

3. Fatigue & depression usually follow central stimulation.

4. Cardiovascular effects include arrhythmias, hypertension or hypotension and circulatory collapse.

5. Gastrointestinal symptoms include nausea, vomiting, diarrhea, and abdominal cramps. Fatal poisoning is usually preceded by convulsions and coma.

BOXED WARNING:

1. Amphetamines have a high potential for abuse.

2. Administration of amphetamines for prolonged periods of time may lead to drug dependence and must be avoided.

3. Particular attention should be paid to the possibility of subjects obtaining amphetamines for non-therapeutic use or distribution to others, and the drugs should be prescribed or dispensed sparingly.

CONCLUSIONS:

Sibutramine demonstrated a similar profile of pharmacological effects as evidenced by the Aes in sibutramine-treated subjects who withdrew from weight loss trials.