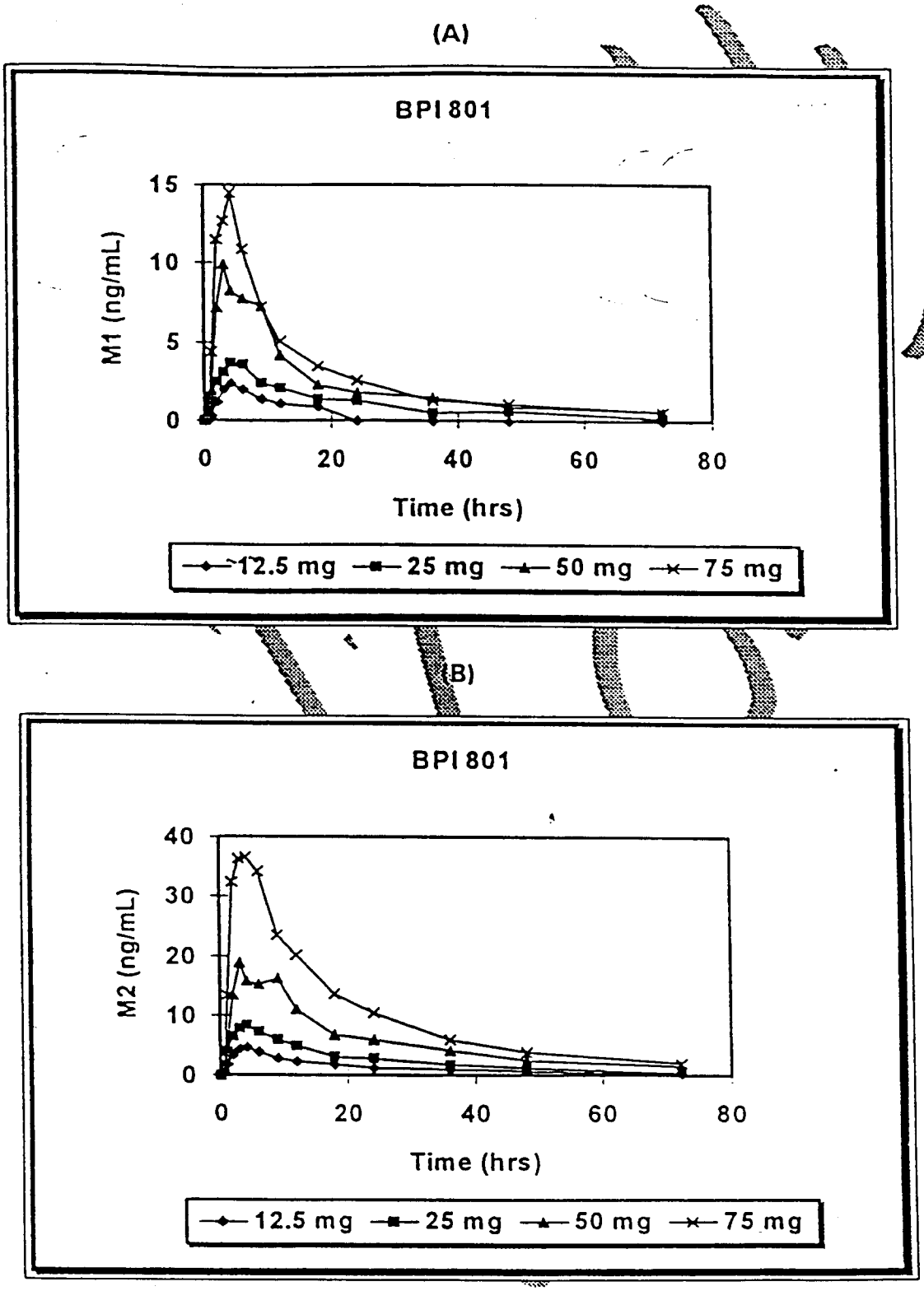
APPENDIX

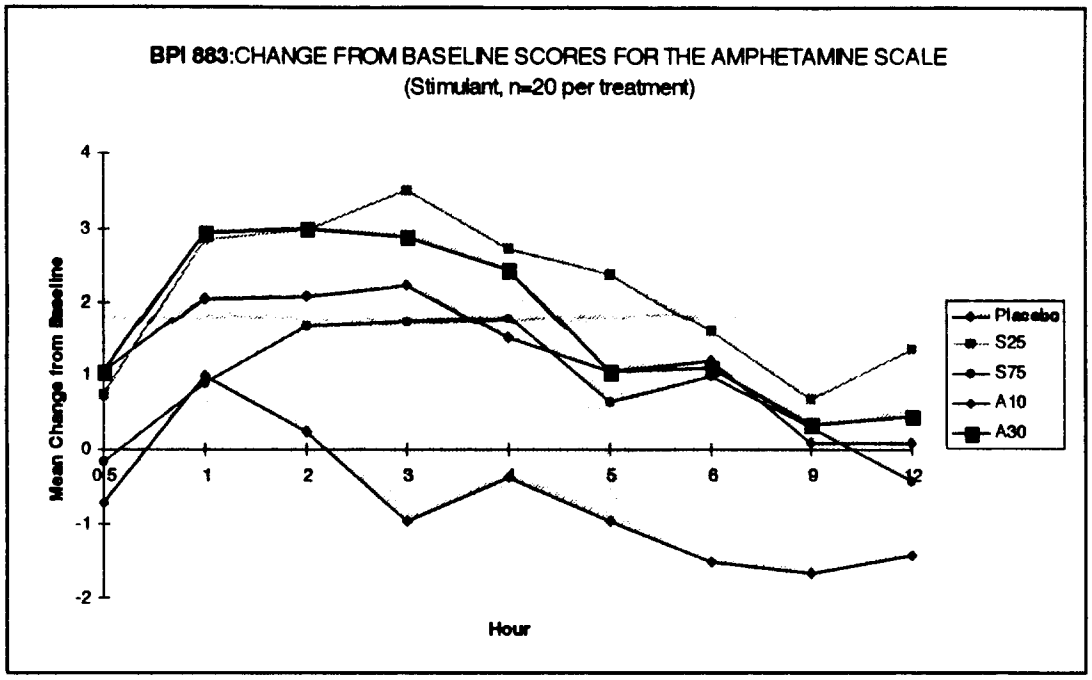
Figure 1: Mean plots of M1 (A) and M2 (B) after doses of 12.5, 25, 50 and 75 mg sibutramine to four different groups of male volunteers. (Study BPI 801).

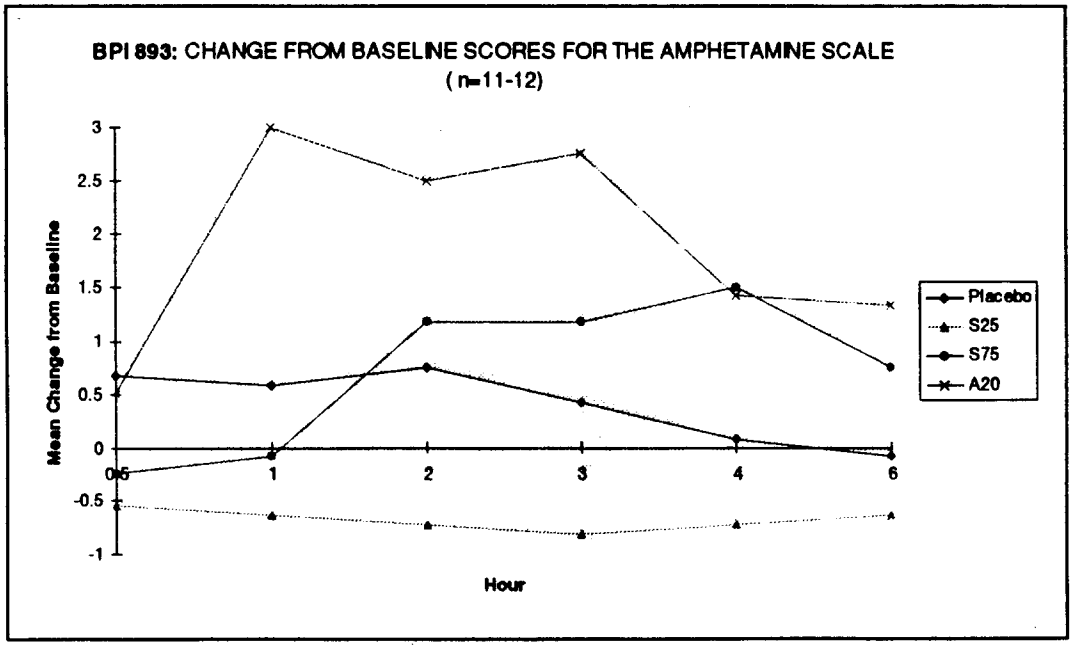


Assessment of the potential abuse liability of sibutramine hydrochloride. Studies BPI 883 and BPI 893.

	BPI 883	BPI 893
Objective	To assess the potential abuse liability of sibutramine hydrochloride (25 and 75 mg) compared to **dextroamphetamine (10 and 30 mg)** and placebo in diagnosed substance abusers	To assess the potential abuse liability of sibutramine hydrochloride (25 and 75 mg) compared to **dextroamphetamine (20 mg)** and placebo in recreational substance (stimulant) users
No. of subjects	20	17, 12 completed
Diagnosis and criteria for inclusion	Male and female subjects aged 21 to 45 years, with **history of psychoactive substance abuse of stimulants** as documented in the admission medical history and Addiction Severity Index, **who have used cocaine within 30 days prior to study**. Abstinent from all psychoactive, prescription, and nonprescription drugs for seven days before study entry, alcohol and psychoactive drugs throughout the study, and caffeine and smoking for 15 minutes before each assessment.	Male and female subjects aged 18 to 50 years, **with history of recreational psychomotor stimulant use** (on at least six occasions), but **without signs of dependence** or any past history of dependence to psychomotor stimulants
Test product, dose, batch No.	Sibutramine 5 mg, Lot no. JL04 Sibutramine 15 mg, Lot no. KG07 Sibutramine 25 mg **(5x 5mg +1 placebo)** Sibutramine 75 mg (5 x 15 mg + 1 placebo)	Sibutramine 10 mg, Lot no. HF01 Sibutramine 15 mg , Lot no. KG07 Sibutramine 25 mg **(1x 10 mg, 1x 15 mg + 3 pl.)** Sibutramine 75 mg (5 x 15 mg + 0 placebo)
Duration of treatment	Each subject received one of five medications on five separate days with each dose separated by a minimum **three-day washout period.**	Each subject received one of four medications on four separate days with each dose separated by a minimum **five-day washout period.**
Reference drugs	Dextroamphetamine 5 mg-Lot no JL02	Dextroamphetamine 5 mg-Lot no JL02 and **GA01**
Criteria for evaluation	• Addiction Research Center Inventory (ARCI) comprising the following subscales: •Amphetamine (Stimulant) •Benzedrine (Stimulant) •Morphine-Benzedrine (Euphoria) •Pentobarbital-Chlorpromazine-Alcohol (Sedation) •LSD (Dysphoria and Hallucination) • Drug Rating questionnaire •Felt the drug •Liked the drug •Disliked the drug •Felt high • Specific Drug Effect Questionnaire (22-item) • Drug Identification Questionnaire (If the drug studied felt like of certain drugs) • Street Value Assessment • Treatment Enjoyment assessment (Which one of the five medications they would enjoy taking again)	• Addiction Research Center Inventory (ARCI) comprising the following subscales: •Amphetamine (Stimulant) •Benzedrine (Stimulant) •Morphine-Benzedrine (Euphoria) •Pentobarbital-Chlorpromazine-Alcohol (Sedation) •LSD (Dysphoria and Hallucination) • Profile of Mood States • Visual Analog Scales • End of Session Questionnaire • Multiple Choice Procedure

Addiction Research Center Inventory. Amphetamine Scale (Stimulant)





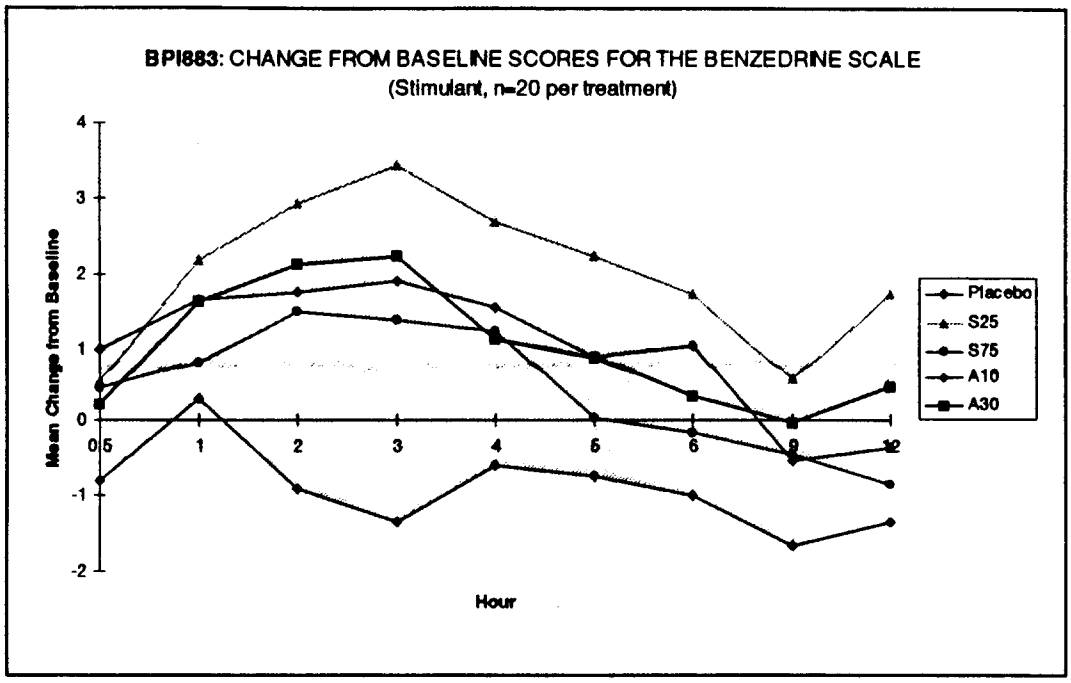
BPI 883: Peak changes were noted at 3 hours after dosing with sibutramine 25 mg and at 4 hours after dosing with sibutramine 75 mg. Scores for sibutramine 25 mg were significantly greater than placebo at 3 and 4 hours and scores for sibutramine 75 mg were significantly greater than placebo at 3 hours. Numerically, the scores for sibutramine 25 mg were higher than the scores for sibutramine 75 mg. Positive values indicate a subjective stimulant response. The peak for dextroamphetamine 10 mg was noticed at 3 hours after dosing and at 2 hours after dosing with 30 mg.

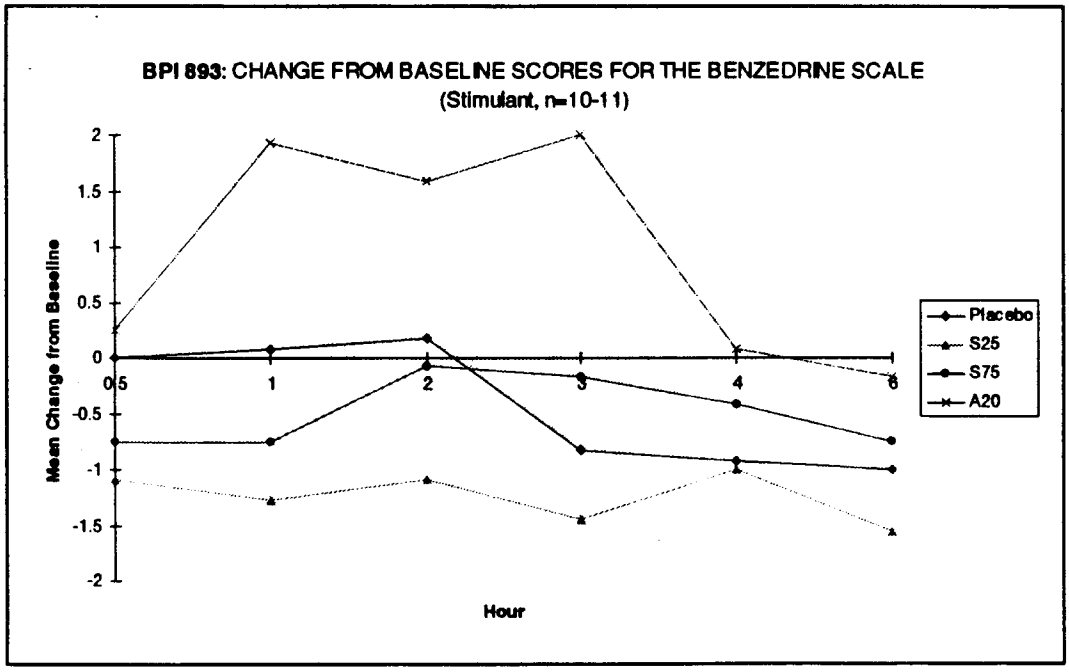
BPI 893: Peak changes were noted at 3 hs after dosing for sibutramine 25 mg and 4 hours after dosing for sibutramine 75 mg. Scores were indistinguishable from placebo at both doses. The peak change for dextroamphetamine 20 mg was noted at 1 hour after dosing and was statistically significantly greater than placebo

Comments: In both studies Peak changes were noted at 3 hours after dosing with sibutramine 25 mg and at 4 hours after dosing with sibutramine 75 mg. In BPI 883 the scores were distinguishable from placebo at 3 hours in BPI 893 at both doses the scores were indistinguishable from placebo. In BPI 883 numerically the scores for sibutramine 25 mg were higher than the scores for sibutramine 75 mg. The latter was not the case in BPI 893.

APPEARS THIS WAY
ON ORIGINAL

Addiction Research Center Inventory. Benzedrine Scale (Stimulant)





Positive values indicate a subjective stimulant response

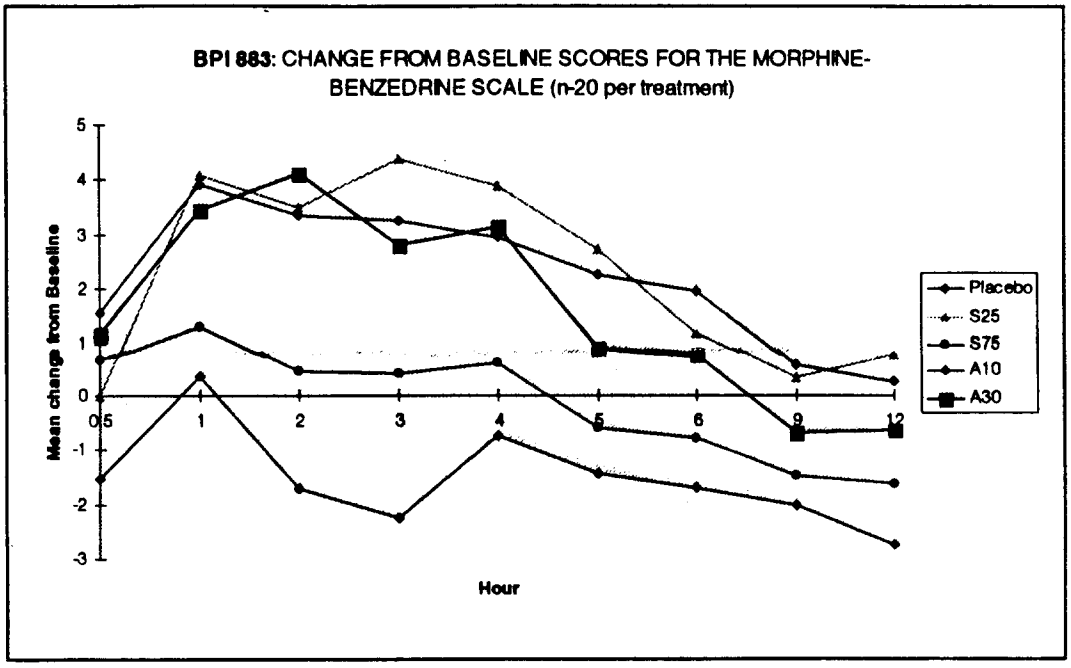
BPI 883: Peak changes for both doses of dextroamphetamine were noted at 3 hours after dosing. Peak changes for both doses of sibutramine were also noted at 3 hours after dosing. Scores for both doses of dextroamphetamine were significantly greater than placebo at 3 hours. The response for sibutramine 25 mg was significantly greater than placebo at 3 hours, but scores for sibutramine 75 mg was not greater than placebo. Sibutramine 25 mg produced numerically higher scores than the 75 mg dose.

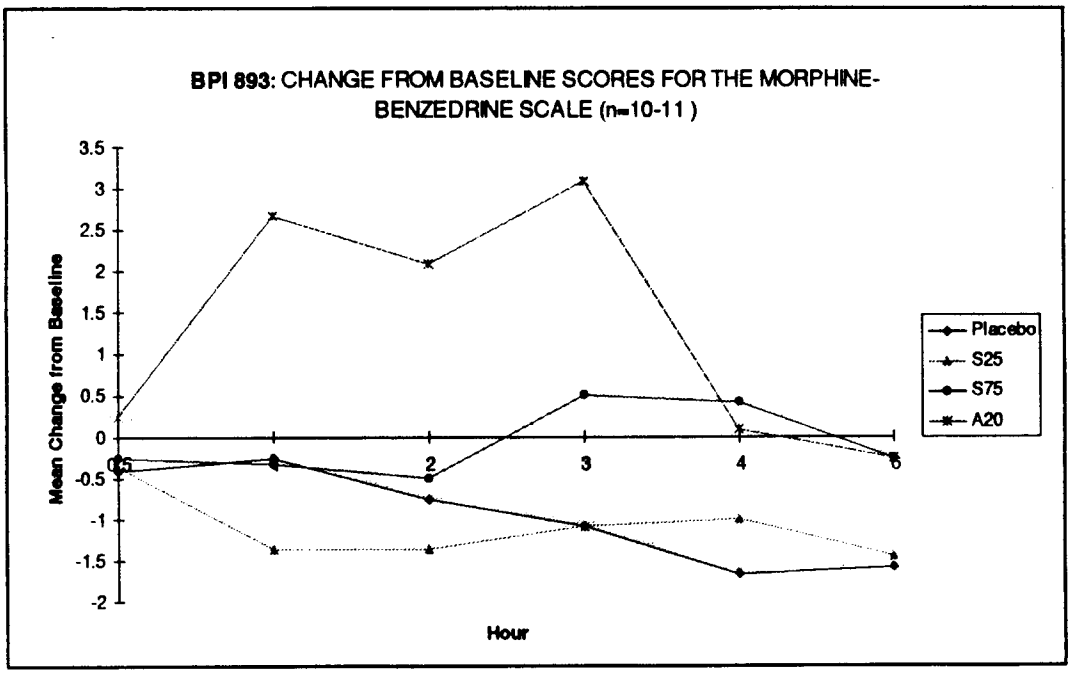
BPI 893: Peak changes for dextroamphetamine 20 mg was noted at 1.5 and 3 hours after dosing. Negative peak changes were noted at 6 hours after dosing for sibutramine 25 mg and at 1.5 hours after dosing for sibutramine 75 mg. Scores for dextroamphetamine 20 mg were statistically significantly greater than placebo. Both doses of sibutramine were indistinguishable from placebo.

Comments: Positive scores were noted for both doses of sibutramine in BPI 883. In this study sibutramine 25 mg gave a significantly greater response than placebo at 3 hours. In BPI 893, sibutramine 25 mg and 75 mg gave negative scores that they were indistinguishable from placebo.

APPEARS THIS WAY
ON ORIGINAL

Addiction Research Center Inventory. Morphine-Benzedrine Scale (Euphoria)





Positive values indicate a subjective euphoric response

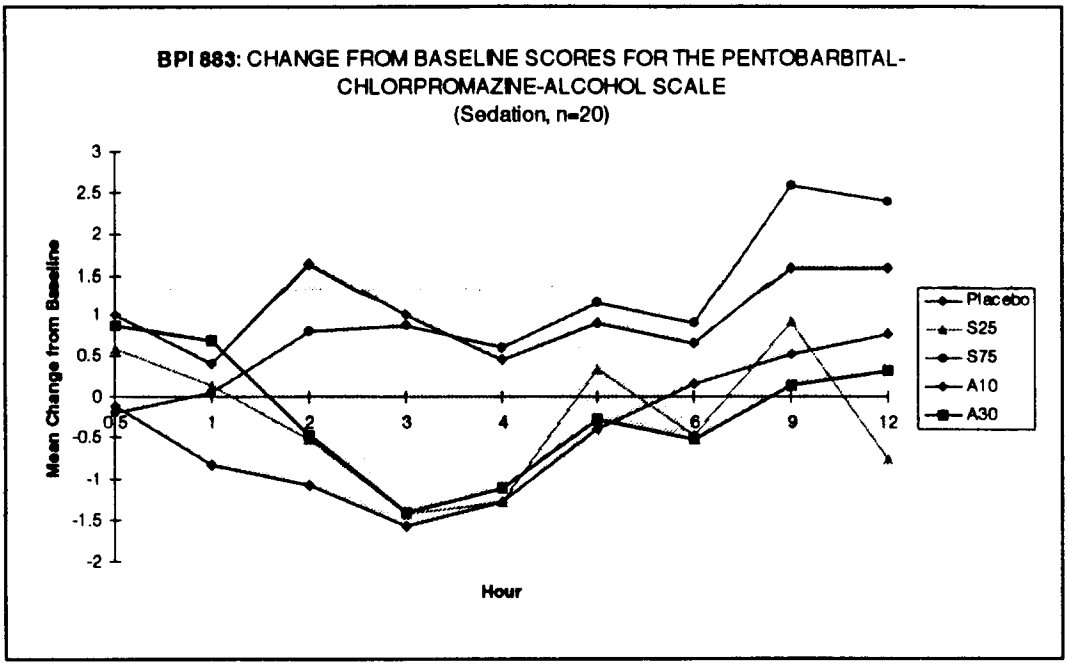
BPI 883: Peak changes for dextroamphetamine were noted at 1 hour after dosing for the 10 mg dose and at 2 hours for the 30 mg dose. Peak changes for sibutramine were noted at 3 hours after dosing for 25 mg dose and at 1 hour for the 75 mg dose. Scores for both dextroamphetamine groups were significantly greater than placebo at 3 hours after dosing . At 3 hours, the response for sibutramine 25 mg was statistically significantly greater than placebo, but the score for sibutramine 75 mg was not. As was the case for the stimulant scales the 25 mg dose of sibutramine produced numerically higher and positive scores than sibutramine 75 mg.

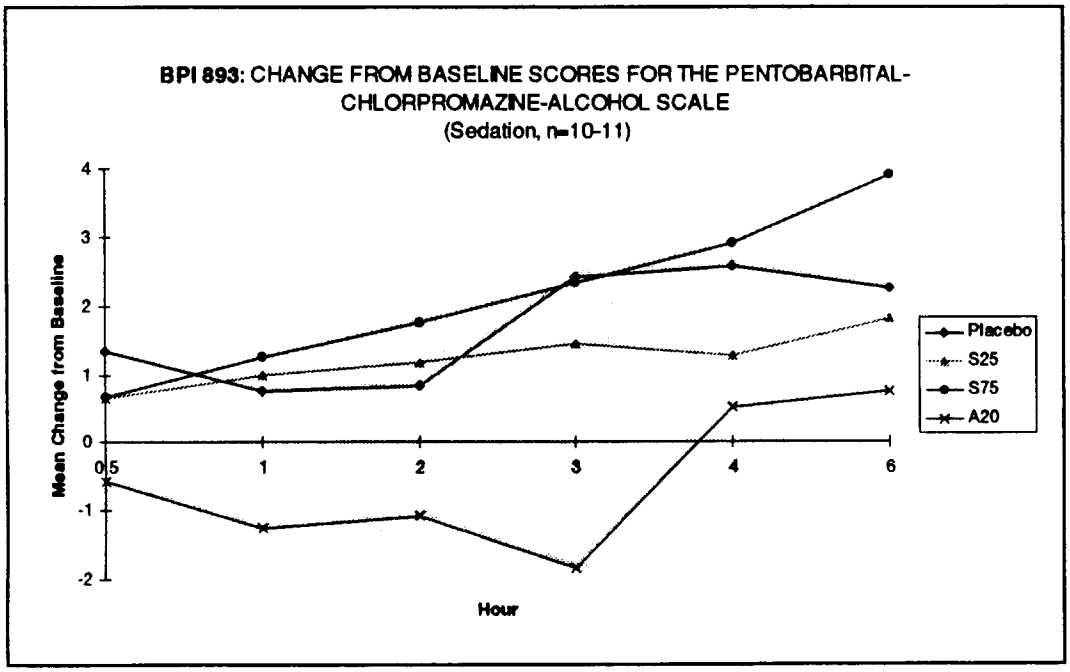
BPI 893: Peak change for dextroamphetamine 20 mg was noted at 3 hours after dosing. Negative peak changes were noted at 6 hours for sibutramine 25 mg and at 2 hours for sibutramine 75 mg. A positive score was noted for sibutramine 75 mg at 3 hours. The scores for dextroamphetamine were significantly greater than placebo. Both doses of sibutramine were indistinguishable from placebo.

Comments: Positive scores were noted for both doses of sibutramine in BPI 883. In this study sibutramine 25 mg gave a significantly greater response than placebo at 3 hours. In BPI 893, sibutramine 25 mg and 75 mg gave negative scores that they were indistinguishable from placebo.

APPEARS THIS WAY
ON ORIGINAL

Addiction Research Center Inventory. Pentobarbital-Chlorpromazine-Alcohol Scale (Sedation)





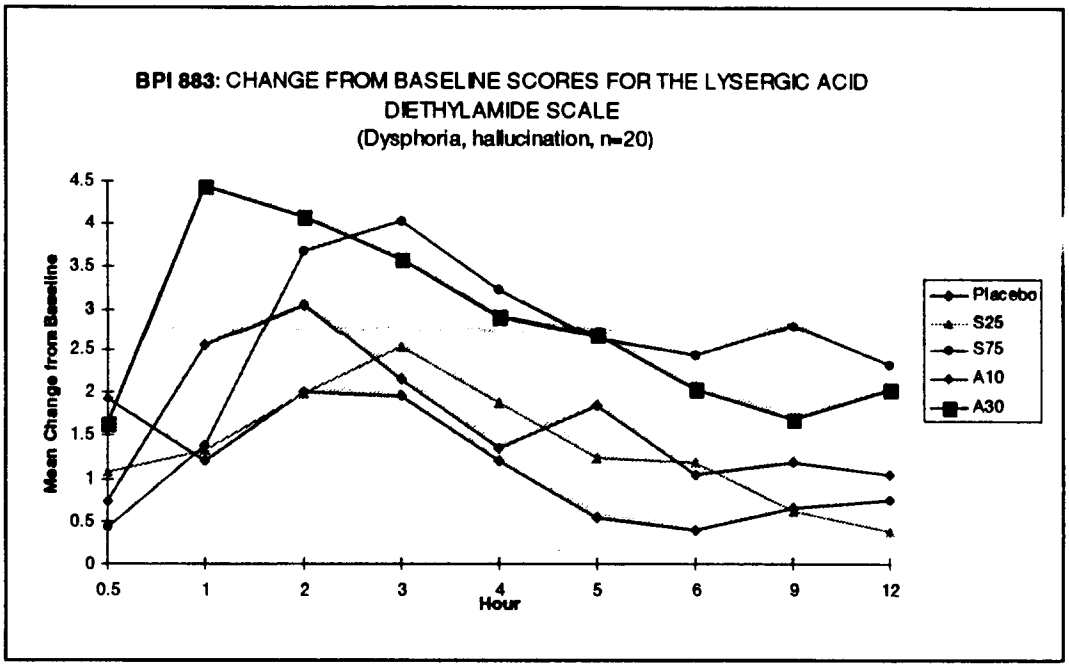
Positive scores indicate a subjective sedative response

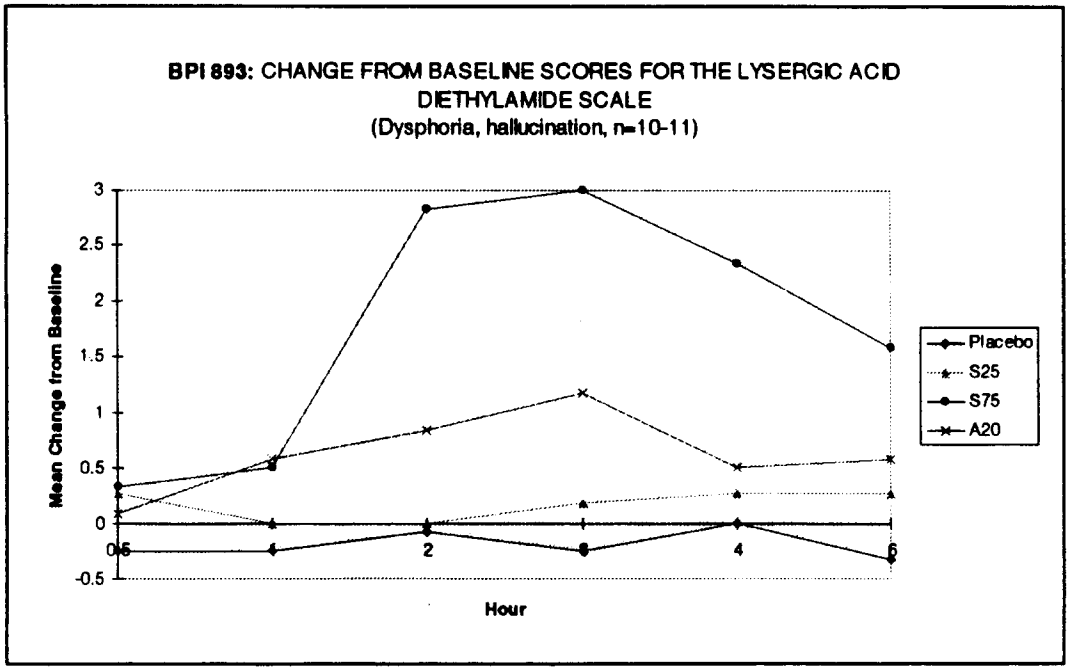
BPI 883: The overall treatment p-value did not reach statistical significance at any time point, therefore, multiple comparisons were not performed.

BPI 893 : A negative value peak change for dextroamphetamine 20 mg was noted at 3 hours after dosing. Peak changes were noted at 6 hours after dosing for sibutramine 25 mg and 75 mg. Peak scores for dextroamphetamine were significantly different from placebo. Both doses were indistinguishable from placebo.

Comments: In both studies sibutramine 25 mg and 75 mg gave scores indistinguishable from placebo.

Addiction Research Center Inventory. Lysergic Acid Diethylamine Scale (Dysphoric-Hallucination)





Positive values indicate a subjective dysphoric or hallucinatory response

BPI 883 :Peak changes for dextroamphetamine were noted at 1 hour after dosing for 30 mg dose and at 2 hours for the 10 mg dose. Peak changes for both sibutramine doses occurred at 3 hours. The overall treatment p-value did not reach statistically significance at any point, therefore multiple comparisons were not performed.

BPI 893 : The peak (positive) for dextroamphetamine 20 mg was noted at 3 hours after dosing. Peak changes were noted at 3 hours after dosing for sibutramine 75 mg, being the scores statistically significantly greater than placebo. There were not statistically significant differences between dextroamphetamine , sibutramine 25 mg and placebo.

Comments: In BPI 883 none of the drugs studied indicated to have a dysphoric or hallucinatory effect. On the hand in BPI 893 sibutramine 75 mg showed dysphoric or hallucinatory effect at 2 through 4 hours after dosing.

APPEARS THIS WAY
ON ORIGINAL

BPI 883, DRUG RATING QUESTIONNAIRE.

The drug rating questionnaire used in BPI 883 is a four-item questionnaire where the subject has to if she/he: felt the drug, liked the drug, disliked the drug or felt high. For each item the subject was to indicate how she/he felt at the time darkening a circle along a continuous line of 42 circles (equivalent to a 100-mm visual scale). The scale was anchored with descriptors "not at all" and "awful a lot".The observer used the same scale to rate wether the subject felt the drug. For the question " Do you feel a drug effect now", dextroamphetamine 30 mg had significantly greater drug effects than placebo at 1 and 5 hours. Sibutramine 75 mg had significantly greater effects than placebo at 3 and 6 hours. Sibutramine 25 mg had significantly greater effects than placebo at 5 and 6 hours. For the same question the observer judged the same effects.

For the question "Do you like the drug effect you are feeling now", the effects of dextroamphetamine were liked significantly more than those of placebo at 2 and 3 hours after doing. The responses for both doses of sibutramine were indistinguishable from placebo. No statistically significant value was obtained at any point from the observer side.

For the question "Do you dislike the drug effect you are feeling now",effects of sibutramine 75 mg were disliked significantly more than those of placebo at 2, 6 and 12 hours after dosing. For sibutramine 25 mg the effects were disliked more than those of placebo at 5 hours. Observer concur.

For the question "Are you high now", the responses of sibutramine were indistinguishable from placebo at all time points.

BPI 883, SPECIFIC DRUG EFFECT.

This is 22-item asked the subject if the drug was producing certain effects (e.g., skin itching, sleepiness, nervousness, etc.). For each item, the subject was to select the response that best described how she/he felt at the time. There were no apparent overall trends in the change from baseline scores

BPI 883, END OF SESSION QUESTIONNAIRE.

Subjects were asked to identify the drug they just received either as placebo , stimulant or depressant. In this study most of the subjects correctly identified dextroamphetamine and most correctly identified placebo. Sibutramine was identified as placebo by more than half of the subjects. Sibutramine was identified as stimulant by 9 out of 12 subjects, the other three believed they had a depressant substance.

BPI 883, DRUG IDENTIFICATION QUESTIONNAIRE.

This is ten-item questionnaire where the subject is asked if the drug felt like other certain drug (e.g. morphine, chlorpromazine, barbiturate, etc). All treatment groups, including placebo showed a trend toward having their drug effect described being similar to those of stimulants.

BPI 883, STREET VALUE.

Although, in this study there were no statistically significant differences among the treatment groups at any time point, dextroamphetamine 30 mg show numerically higher "street value" than any other drug.

BPI 893, PROFILE OF MOOD STATES (POMS)

This is a 72 item questionnaire commonly used to described mood states. Dextroamphetamine made the subjects feel invigorated, friendly, elated aroused and in a positive mood, sibutramine did not produce this effects
There were no apparent overall trends in the change from baseline

BPI 893, VISUAL ANALOG SCALES.

The visual analog scales (VAS) consist of a series of 19 horizontal 100 mm lines, each labeled with and adjective describing the mood or a feeling (good drug effect, bad drug effect, drug liking, stimulated high, down, miserable and others) measuring from "not at all" to "extremely"

Dextroamphetamine was positive on the Good Drug Effect, Drug Liking, High, Alert, and Social Scales; sibutramine was not with the exception of a one time point where sibutramine 25 mg was positive in the Social Scale

Scores for sibutramine 75 mg were statistically significantly greater than dose for placebo and dextroamphetamine in the "Bad drug effect".

APPEARS THIS WAY
ON ORIGINAL

CONCLUSIONS.

Sibutramine, a 4-chloro-substituted phenylethylamine derivative, is structurally related to the stimulants d-amphetamine, methamphetamine, phenylethylamine, fencamfamine, and methylphenidate. Sibutramine is a pro-drug. Its pharmacological activity is primarily through the actions of its demethyl metabolites, primary (M1: BTS 54, 505) and secondary (M2: BTS 54 354). *In vitro* binding studies have demonstrated that sibutramine is a weak monoamine reuptake inhibitor, while irs metabolites BTS 54 354 and BTS 54 505 are potent monoamine reuptake inhibitors.

To evaluate the dependence potential of sibutramine, preclinical and clinical studies were conducted. The subjective effects and ability to function as a positive reinforcer were evaluated in preclinical drug discrimination studies and a primate self-administration study, respectively. Results from the drug discrimination studies suggested that sibutramine and its metabolites did not possess amphetamine-like or MDMA-like discriminative stimulus effects (i.e., subjective effects). However, the validity of these results are questionable. In both drug discrimination studies conducted by the sponsor, there were some technical concerns.

However, evaluation of sibutramine's dependence potential in preclinical self-administration study and clinical studies has suggested that its dependence capacity is equivalent to that of CNS stimulants. Results from the self-administration study demonstrated that sibutramine does possess reinforcing properties (i.e., functioned as a positive reinforcer) in primates. Sibutramine was substituted for cocaine in some of the primates trained to self-administer cocaine. However, the reinforcing efficacy of sibutramine was lower than that of cocaine. Results from this study also demonstrated that sibutramine was capable of functioning as a positive reinforcer in monkeys with extensive experience in self-administering abusable drugs and in naive monkeys with no experience.

Human abuse liability testing indicated that sibutramine has an abuse potential that is greater than placebo and less than amphetamine. Sibutramine was shown to have amphetamine-like pharmacological effects in volunteers with stimulant experience. Analysis of subjects that withdrew from the weight loss trial was due to amphetamine-like adverse effects. Consistent with an amphetamine-like adverse effect profile, adverse events that resulted in patient withdrawal included: nervousness, hyperactivity, increased energy, anxiety, increased insomnia, asthenia, tremor, dry mouth, and speedy feeling.

RECOMMENDATION.

FDA Division of Anesthetic, Critical Care, and Addiction Drug Products (HFD-170) recommends that sibutramine (MERIDIA®) be controlled in Schedule IV of the Controlled Substances Act.

HFD-170, also, recommends the following as the proposed label for MERIDIA®:

DRUG ABUSE AND DEPENDENCE

Sibutramine MERIDIA® (sibutramine hydrochloride) is controlled in Schedule IV of the Controlled Substances Act (CSA).

MERIDIA® produces amphetamine-like effects. As with any CNS active drug, physicians should carefully evaluate patients for history of drug abuse and follow such patients closely, observing them for signs of misuse or abuse (e.g., drug development of tolerance, incremantation of dose, drug seeking behavior).

APPEARS THIS WAY
ON ORIGINAL

BeLinda A. Hayes, Ph.D. — Date: 10/7/97

Silvia Calderon, Ph.D. — Date: 10-7-97

Concurred by Acting Team Leader:

Michael Klein, Ph.D. — Date: 10-7-97

cc: NDA 20-632
HFD-510/Div. File
HFD-510/MHess/EColman

APPEARS THIS WAY
ON ORIGINAL

Memorandum

From: Curtis Wright MD MPH, Acting Director,
Division of Anesthetics, Critical Care, and Addiction Drug Products, HFD-170

To: Director, Division of Metabolic and Endocrine Drug Products (HFD-510)

Date: 10/24/96 10/24/96

Subject: Abuse Liability of Sibutramine

NDA: 20-632
Sponsor: Knoll
Drug: Meridia (Sibutramine Hydrochloride)
Type of Submission: Consult
Proposed Indication: Anorectic
Reviewer: B. Hayes PhD
Peer Reviewer: M Klein PhD
CSO: C Moody

Summary: I concur with the recommendation of Dr's Hayes and Klein that the abuse liability evaluation of this drug is insufficient to permit its classification under the Controlled Substances Act. In the opinion of the Division no valid decision regarding its abuse liability may be made until more information is received by the Agency.

Text: Sibutramine is a relatively inactive compound (uptake constants in human and animal brain in the micromolar region (10^{-6})) that has two active metabolites, BTS 54-354 & BTS 505. These metabolites have nanomolar (10^{-9}) affinities for serotonin, dopamine, and nor-epinephrine uptake sites. Sibutramine was tested in an intraperitoneal drug discrimination protocol in rats against amphetamine and in a human oral drug discrimination protocol against amphetamine. Both studies were flawed (see the primary review conclusions), but more importantly missed the point.

These studies were conducted by the sponsor in a difficult area of behavioral pharmacology without consulting the Aagency. That the studies are insufficient is shown by the additional studies that the sponsor currently has underway (see supplemental review of protocols dated 8/6/96). It would be most inadvisable to make a regulatory decision without more information from the ongoing studies.

The crux of the problem is that phenylethylamines with this spectrum of action are more likely to be hallucinogenic-dysphoriants than amphetamine-like drugs. While this provides some reassurance to normal users of the compounds, the recent epidemic of MDMA use and the resurgence of LSD provide quite clear evidence that a new, legal, hallucinogen unfettered by the Controlled Substances Act would have a negative impact on the public health.

Thus while I agree with the sponsor that this drug and its metabolites are probably not amphetamine-like stimulants in oral use at the doses tested, I also agree with the primary review team that the abuse liability of this drug has not been adequatrely established, and more information is needed.

(continued)

The sponsor is strongly urged to meet with the staff of HFD-170 so that we may provide all possible assistance in helping them resolve this problem.

Curtis Wright
Acting Director, HFD-170

cc: NDA Arch
HFD-510
HFD-510/EColman/GTroendle/MHess

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

NDA #: 20-632
Sponsor: Knoll Pharmaceutical Company
Product: Meridia®
Generic: Sibutramine hydrochloride monohydrate
Dosage Form: Capsules
Clinical Dosage: 5, 10, 15 mg
Indication: Treatment of Obesity

Reviewers: Michael Klein, Ph.D.

BeLinda Hayes, Ph.D.

October 16, 1996

In order for a new drug that has no marketing history to be scheduled under the Controlled Substances Act (CSA), data from preclinical and clinical studies must show that the drug is active in the central nervous system, is likely to be used outside of medical administration in increasing and excessive amounts and that it is likely to create dependence.

All of these criteria have not yet been demonstrated for sibutramine (Meridia®) in the studies conducted and submitted for review. Protocols for long term placebo-controlled studies for sibutramine were reviewed. Whereas the adverse events after long term use were investigated, the development of a withdrawal syndrome was not probed in these studies, nor were the characteristics of a potential withdrawal syndrome.

The following protocols were reviewed:

1. **Clinical Protocol BPI 850 (7-26-89)** A double-blind, placebo-controlled pilot study to evaluate the weight reducing efficacy, safety and tolerability of sibutramine 5 and 20 mg daily in obese subjects.

   Objectives:

   A. To assess the weight reducing effects of 5 and 20 mg oral daily doses of sibutramine, and placebo, when given in conjunction with modest caloric restriction, exercise, and behavior modification.
   B. To assess the anorectic and satiety inducing effects of sibutramine.
   C. To evaluate the safety and tolerability of sibutramine in an obese population.

2. **Clinical Protocol BPI 851 (3-23-89)** A Double-Blind, Placebo-controlled Pilot Study to Evaluate the Weight-Reducing and Anorectic Activity and Safety of Sibutramine 10 mg per day in Obese Subjects

   Objectives:

   A. To evaluate the weight reducing ability of sibutramine 10 mg and placebo administered to obese subjects over a 12-week period in single oral morning doses.
   B. To evaluate aspects of sibutramine vs placebo on appetite, food intake, percent body fat, metabolic rate, thyroid function, and serum lipids.
   C. To evaluate tolerability and safety of sibutramine 10 mg relative

to placebo when administered to obese subjects over a 12 week period.

3. **Clinical Protocol BPI 852 (3-30-92)** A Multicenter, double-blind, repeated-dose, placebo-controlled, parallel-group, dose-ranging study to evalute 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.

   Objectives:

   A. To compare the effects of the following doses of sibutramine (1,5,10,15,20 mg or 30 mg) or placebo on weight loss in obese patients when given in conjunction with modest caloric restriction, exercise, and behavior modification for up to 12 weeks.
   B. To assess the effects of the following doses of sibutramine (1,5,10,15,20 or 30 mg) or placebo on supine and standing heart rate in obese patients after 2 and 12 weeks.
   C. 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.

   Secondary Objective:

   A. To assess the efficacy, safety and tolerability of sibutramine (1,5,10,15,20 or 30 mg) for up to 24 weeks in obese patients.

4. **Study Number SB 1042 (11-22-91)** A Double Blind, placebo Controlled Dose Ranging Study to Evaluate the Weight Reducing and Anorectic Activity of Sibutramine Hydrochloride in Obese Patients.

   Objectives:

   A. To assess the weight reducing effects of 1, 10, and 20 mg once daily doses of sibutramine and placebo in order to explore the extremes of the dose range with reference to an intermediate dose.
   B. To evaluate the safety and tolerability of sibutramine in an obese population.
   C. To examine the procedural and practical aspects of facsimile monitoring by comparing centers monitored using the new system with those monitored using existing methods.

5. **Study Number SB 1043 (11-22-91)** A Double Blind, Placebo Controlled Dose Ranging Study to Evaluate the Weight Reducing Activity of Sibutramine Hydrochloride in Obese Patients.

   Objectives:

   A. To assess the weight reducing effects of 5, 10, and 15 mg once daily doses of sibutramine and placebo in order to establish the optimum anorectic dose.
   B. To evaluate the safety and tolerability of sibutramine in an obese population.

6. **Study Number SB 1047 (3-19-92)** Long Term Treatment of Mild to Moderately Obese Patients with Sibutramine

Objectives:

A. To assess the long term efficacy and tolerability of sibutramine in the treatment of mild to moderate obesity
B. To assess the long term safety of sibutramine in mild to moderate obesity.

7. **Study Number SB1049 (11-8-93)** Efficacy and tolerability of sibutramine versus placebo in maintenance or improvement of weight loss, in obese patients, following a very low calorie diet.

Objectives:

A. To evaluate the efficacy of long term treatment with sibutramine in maintaining or improving weight loss in obese subjects who have successfully lost weight on a VLCD.
B. Safety and tolerability will be monitored by recording all adverse events and by regular laboratory investigations and ECGs.

8. **Study Number SB1052 (5-27-92)** A Double Blind, Placebo Controlled Multicentre Study to Evaluate the Weight Reducing and Anorectic activity of Sibutramine in Comparison with Dexfenfluramine in Obese patients.

Objectives:

A. To assess the efficacy of sibutramine in the treatment of obesity in comparison with dexfenfluramine within a 12 week period.
B. To assess the safety and tolerability of sibutramine in mild to moderate obesity.

9. **Study Number SB 2053 (7-16-93)** Efficacy and Tolerability of Sibutramine versus Dexfenfluramine in Obese Patients.

Objectives:

A. To compare the efficacy of sibutramine and dexfenfluramine in obese patients during a 3 months treatment period.
B. Principal measure of efficacy will be the weight loss achieved by each group after 3 months treatment.
C. Safety and tolerability of sibutramine and dexfenfluramine will be monitored by recording all adverse events, laboratory investigations and ECGs.

ABUSE LIABILITY STUDIES

After review of the preclinical and clinical abuse liability studies (attached) in NDA #20-632, HFD-170 was provided two new clinical protocols for review (BPI 883 and BPI 893). These protocols were reviewed and comments were submitted to the sponsor. On August 23, 1996, the sponsor responded to our comments. Our responses to those comments are also attached.

In addition to the clinical trials, we have been informed by the sponsor that an additional preclinical primate self-administration study is being conducted at the University of Mississippi under the direction of Dr. William Woolverton. This protocol and any results have not been submitted for review, but is certainly relevant to the abuse liability assessment.

In addition to the above three ongoing studies, we are recommending that two additional preclinical studies be conducted. The first request is based on the use of a hallucinogenic comparator, MDMA, which has both potent serotonergic and dopaminergic activity, as seen with sibutramine and its metabolites, and is probably a more appropriate positive control than d-amphetamine. Also, the individual contributions of the active metabolites to the drug's effects will be investigated. The second preclinical study is to attempt to acquire data on the characteristics of a possible withdrawal syndrome resulting from long term use of the drug.

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

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

Consistent with these preclinical findings, results from the clinical trial conducted by J. Cole (McLean Hospital) suggested that sibutramine may possess hallucinogenic properties. Healthy male volunteers receiving 30 mg sibutramine produced statistically significant effects on the LSD Group of the ARCI. Sibutramine's active metabolites have been shown to have a neurochemical profile similar to that of MDMA. As such, they may elicit MDMA-like discriminative stimulus responses. To test this hypothesis, the following drug discrimination study is proposed:

Protocol for evaluation of the discriminative stimulus effects of sibutramine.

Subjects. Ten male Sprague Dawley rats that are 3 months of age at the start of the study are appropriate subjects. The animals should be maintained at 85% of their free-feeding body weight by feeding a limited amount of rat chow following each daily training session.

Training Procedure. The rats will be trained during daily experimental sessions to respond to food pellet delivery according to a FR-32 schedule of reinforcement. Sessions will end after 30 minutes. The rats will be trained to discriminate 1.5 mg/kg i.p. MDMA (corresponding to a dose that has been demonstrated to serve as a discriminative stimulus in rats by Glennon *et al.*, Medical College of Virginia) from saline. A double alternation schedule (i.e., MDMA, MDMA, saline, saline, MDMA, MDMA, saline, saline, etc.) Should be employed. On days when MDMA is administered, one of the two response levers will be designated correct and will

result in food pellet delivery. On days when saline injections are given, the other lever will be designated as correct. Five of the rats will be trained to press the left lever after receiving MDMA for food reinforcement and the right lever after saline injections. The remaining five rats will be trained to press the right lever after receiving MDMA for food reinforcement and the left lever after saline injections.

Rats are initially trained to lever press under a FR1 schedule of food reinforcement with responses on either lever being reinforced. After 6 to 10 sessions, or when rats are reliably responding on either lever, discrimination training should be initiated. Fifteen minutes before the training sessions, the rats will be injected with 1.5 mg/kg i.p. of MDMA or saline according to the double alternation schedule. The rats are returned to their home cages after the injection. Fifteen minutes later, the rats are placed in the operant chambers. Sessions are started shortly after placing the rats in the chambers. The FR requirement on the correct lever should be gradually increased over a number of sessions (10-15) to a value of 32. Responses on the incorrect lever will reset the FR requirement on the correct lever. After each session, the rats are caged and fed.

Training continues until subjects consistently make 90% of their responses on the correct lever and respond with overall rates greater than 0.5 responses/sec. Tests for discriminative control by the injections are then conducted.

Stimulus Generalization Tests. Test sessions will be identical to training sessions except that 32 consecutive responses on either lever will result in food reinforcement. Test sessions will be conducted on Tuesdays and Fridays if the rats met the following criteria on the day before testing. The first completed FR was made on the correct lever, response rates were above 0.5 responses/sec; 90% correct-lever responding was maintained throughout the session. In addition, the rats must complete the first FR on the correct lever on both preceding MDMA and saline days.

After discriminative stimulus control by MDMA and saline injections have been demonstrated, generalization tests with the following drugs should be conducted: MDMA if 3.0 mg/kg does not significantly suppress rate of responding, a higher dose should be tried); sibutramine BTS 54 354 ; BTS 54 505 . Between testing of each of these test drugs, control tests with the training drug of MDMA and saline should be conducted. Drugs should be administered intra peritoneally.

To determine the correct pre-injection time to use with sibutramine and its metabolites, a time course study should be conducted. It is recommended that an ED_{50} dose of sibutramine tested at pre-session injection times (ranging from 0 to 420 minutes) be evaluated.

Data Analysis. Percentage of MDMA-lever responding should be averaged at each dose for all ten rats. When responses are less than 0.05 responses/sec, percentage of MDMA-lever responding for

that test will not be included in the group data analysis. Response rate are calculated as mean responses per second. ED_{50} values for percentage of MDMA-lever responding and overall response rate is calculated using least-squares linear regression on the linear portion of the dose effect curves after log_{10} transformation of response rate to percentage of vehicle control response rates and after log_{10} transformation of dose.

3. **Physical dependence producing potential of sibutramine.** Abstinence-associated withdrawal signs, which are the consequence of physical dependence, is a frequent motivator of continued drug intake. The following preclinical protocol or reasonable facsimile can be considered for assessing the physical dependence potential of sibutramine in primates:

Subjects. Three male and three female rhesus monkeys are proposed subjects for the study. All animals should be individually housed with continuous access to water; a complete diet of primate diet should be made available once daily.

Dose Selections. A preliminary acute behavioral study should be conducted to select the appropriate doses to use for the physical dependence study. The route of drug administration for the study is oral. Two doses should be selected for the physical dependence study: the lowest dose that elicits mild-to-moderate neuro-effective signs and the next highest tolerated dose without significant neuro-effective signs.

Experimental Procedure and Design. The monkeys will be dosed twice daily between 9:30 - 10:30 AM and 4:00 - 5:00 PM. All monkeys will be dosed seven days per week.

The starting dose of sibutramine administered orally twice daily will be the lowest dose causing mild to moderate behavioral signs. The animals will be treated with this dose for the first 28 days of the study. Diminished response from the drug dose should be continually assessed. During week 5 of the study, treatment will be stopped and the monkeys observed daily for signs of withdrawal.

Dosing should recommence on Week 6 for a further 4-week period during which the sibutramine dose should be increased to the next highest tolerated dose. The monkeys will be dosed twice daily. Treatment should be discontinued during Week 10 and monkeys observed for signs of abstinence.

Withdrawal Observation. The following observations and records should be made during the study.

a. **General Clinical Signs**
Animals are observed twice daily after dosing throughout study for behavioral changes and signs of ill health.

b. During Week 5 and 10, when treatment is discontinued, monkeys are observed, in order to assess development of abstinence. During withdrawal periods, monkeys should be observed for 30 minutes twice daily after 10:30 AM and 4:00 PM. The potential withdrawal signs precipitated by cessation of sibutramine administration

should be assessed using a combination of abstinence signs routinely used to assess the physical dependence liability of other compounds which are more frequently assessed in this sort of study (e.g., opiates or benzodiazepines or barbiturate). The withdrawal signs should be graded in order of severity as proposed in the table below.

c. **Rectal Temperature Measurements**
Pre-dosing rectal temperature should be determined just prior to the first day of dosing of the test compound. During drug treatment, rectal temperatures should be taken once a week, on the fifth day of each dose week immediately prior to administration of the morning dose. During the withdrawal phase of the study, the rectal temperatures should be recorded daily.

d. **Body weight.** Bodyweight should be recorded in the morning (at the same time of day) during the week prior to commencement of dosing and then on the fifth day of each treatment week. During the withdrawal period of the study, the body weight will be recorded daily.

e. **Food Consumption.** The quantity of food consumed by each monkey will be recorded daily throughout the study and total food consumption for each 7-day dosing period will be calculated.

f. **Blood Sampling.** The drug and metabolites plasma levels should be determined on day 10 of the study. Blood will be drawn from the femoral vein prior to the morning dosing and 1 hour post-dosing, before dosing at 4:00 PM and 1-hour post-dosing. Blood will be drawn prior to the morning treatment on day 11. Blood will be drawn again on study days 45 and 46 of the second 28-day dosing period.

MILD	MODERATE	MARKED	SEVERE
Yawning	Agitation	Extreme Restlessness	Marked Apathy
Shivering	Tremor	Cramps	Persistent Prostration
Perspiration on face	Bared Teeth	Vomiting	Dyspnea
Stretching	Exaggerated Response	Persistent Vocalization	Pallor
Scratching	Occasional Shrill or guttural	Occasional Prostration	Collapse
Head shaking	Restlessness	Ptosis	Coma
Piloerection	Unusual Postures	Spasticity	Convulsions
Mild Tremor	Coughing	Impaired Motor Function	Delirium
Mild agitation	Retching	Hyperventilation	Hallucination
	Vocalization		Dissociation
			Nystagmus
			Death

CONCLUSION:

As the sponsor is currently conducting one preclinical and two clinical abuse liability studies, and HFD-170 has suggested with justification the need for two additional preclinical studies, results of these studies are not available for review. As such, there is currently insufficient data to make a recommendation on the appropriateness of scheduling or not scheduling sibutramine.

10-16-96

Michael Klein, Ph.D. 10-16-96

APPEARS THIS WAY
ON ORIGINAL

10/16/96

BeLinda Hayes, Ph.D. 10-16-96

APPEARS THIS WAY
ON ORIGINAL

SIBUTRAMINE (MERIDIA) CAPSULES

NDA 20-632 CLINICAL ABUSE POTENTIAL PROTOCOLS (BPI 883 AND BPI 893)

KNOLL PHARMACEUTICAL COMPANY, 3000 CONTINENTAL DRIVE, NORTH MOUNT OLIVE, NJ 07828-1234

CLINICAL PROTOCOL BPI 863
8-23-96 SUBMISSION WITH RESPONSES TO COMMENTS SUBMITTED TO SPONSOR IN JUNE 5, 1996 CORRESPONDENCE. HFD-170 RESPONSE TO EACH SPONSOR COMMENT (8-23-96) IS INDICATED BELOW:

3.a. Protocols BPI 883 and BPI 893, represent major new clinical abuse liability studies, were submitted to HFD-170 for review after submission of NDA 20-632 to the Agency. BPI 893 is and is dated 6-13-96. BPI 883 has the same and is dated 11-21-95. The new protocols were reviewed by HFD-170 and comments were provided to sponsor. Dose of sibutramine has been increased to 75 mg, but positive control dextroamphetamine is unlikely to be the appropriate positive control.

b. BPI 863 only included males. Sponsor has made the commitment that both males and females are being randomized according to Protocols BPI 893 and BPI 883.

c. Study Protocols are being conducted up to 6 hours, which is certainly more likely to result in successful contribution of peak responses corresponding to formation of the active metabolites. Although it is generally believed that the abuse potential of a substance is related to its rate of onset, this is not always the case and there are many factors - such as the uncontrolled availability of a drug on the market when all competing therapeutic agents are subjected to some level of control under the Controlled Substances Act - that contribute to abuse of a drug.

d. Sponsor provided clarification.

e. Sponsor provided clarification. Individuals who were identified as preferring hallucinogens, however, they may have been primarily abusers of marijuana, which would not necessarily be the most appropriate study population. However, we recognize and appreciate the investigators' difficulties in obtaining a pure stimulant abusing group.

f. Sponsor noted that in one of the new studies, BPI 893, subjects are separated from each other to some extent.

g. ARCI scores and summaries were provided. On the ARCI Pentobarbital-Chlorpromazine-Alcohol Scale, 30 mg sibutramine was statistically significant from placebo at 1, 3 and 4 hours. On the ARCI LSD Scale, 30 mg sibutramine was statistically significant from placebo at 1, 2, and 3 hours. On the ARCI MBG scale, sibutramine 20 mg was not statistically significant from 30 mg, nor was there consistent statistical difference between 20 mg and 30 mg

sibutramine vs. amphetamine 20 mg.

BPI 883: HFD-170 responses to each of the sponsor's comments below:

1. Investigator believes that the sequence of drug administration should not affect overall study results. No further comment.

2. Ample justification for doses used in study was provided.

3. Investigator may have some problems in recruiting females for the study. Statistical data should be provided for females, since they represent the majority of those who are likely to use the drug.

4. Investigator does not recognize that benzoylecgonine is a common artifact in illicit cocaine.

BPI 893: HFD-170 responses to each of the sponsor's comments below:

1. Investigator may have some problems in recruiting females for the study. Statistical data should be provided for females, since they represent the majority of those who are likely to use the drug.

2. The immediate gratification theory is not always relevant as has been seen in the past for other drugs. See comments under 3.c. (above) for BPI 863.

3. Amendment 1 of the protocol is satisfactory. A copy has been provided.

4. Satisfactory response is not the same as that of PI for BPI 883 (see 4 above for BPI 883).

5. There is probably a semantical difference in what is meant by "current recreational drug use." The phrase should not mean "concomitant drug use while on study."

6. PI should have some knowledge of whether subject routinely participates in this sort of trial.

7. It would be expected that an inpatient study would result in less abuse of other street drugs that may be available.

10-16-96

Michael Klein, Ph.D. 10-16-96

APPEARS THIS WAY
ON ORIGINAL

10/16/96

BeLinda Hayes, Ph.D. 10-16-96

AUG - 6 1996

SIBUTRAMINE (MERIDIA) CAPSULES (5,10, 15,20 mg capsules for oral use)
NDA #20-632 REVIEW OF CLINICAL ABUSE LIBILITY PROTOCOLS

Sponsor: Knoll Pharmaceutical Company, 3000 Continental Drive, North Mount Olive, NJ 07828-1234

Summary: Many of our questions relative to the following clinical abuse liability studies result because sibutramine appears to be a prodrug for active metabolites that seem to be largely responsible for the drug's activity. The active metabolites appear to be functionally different from the parent drug. We are concerned that the dose is not sufficiently high to pick up the effects of the active metabolites and that their effects which peak several hours after the peak of dextroamphetamine (the positive control) might not be discerned.

Finally, dextroamphetamine is pharmacologically distinct from sibutramine, but not from the active metabolites and therefore should be compared directly with the metabolites. Results from the study conducted by J. Cole (McLean Hospital) suggested that sibutramine may possess hallucinogenic properties; healthy male volunteers receiving 30 mg parent drug produced statistically significant effects on the LSD Group of the ARCI. Reasonable preclinical drug discrimination studies could be designed to provide useful information for selection of appropriate candidates to be used as positive comparators.

1. CLINICAL PROTOCOL BPI 883 (11-21-95)

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 Hcl 25 and 75 mg compared to dextroamphetamine 10 and 30 mg and placebo in diagnosed substance abusers.

PI: Donald Jasinski M.D.

Objectives: To assess the potential abuse liability of sibutramine 25 and 75 mg when compared to dextroamphetamine 10 and 30 mg and placebo in diagnosed substance abusers.

Questions: 1. What drugs do the study subjects abuse regularly? Are they stimulant abusers? Are you selecting subjects that have used a stimulant one time in their life or "X" number of times per week, month, or year, etc.? What is the likelihood that the sequence of drug administration could affect the study results?

2. Are the right doses being tested and compared?: Recommend doing a computer simulation of blood levels for parent drug and metabolites with time periods. This ties in to predicting the dose that would have positive effects.

3. Is there a statistically significant sample for Females?

4. Recommend not using subjects who test positive for both cocaine or benzoylecgonine. What is justification for only excluding positive test for cocaine parent compound but not benzoylecgonine presence.

2. CLINICAL PROTOCOL BPI 893

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

PI: Charles Schuster, Ph.D. and John Hopper, M.D.

Objectives: To assess the potential abuse liability of sibutramine 25 and 75 mg when compared to dextroamphetmaine 20 and placebo, in recreational substance (stimulant)users.

Questions: 1. Do the sponsor and the PIs expect that we will be able to make statistically significant conclusions relative to gender or racial composition based upon the study?

2. Physiological and subjective effects scales will be completed on the prodrug up to 6 hours after its administration. Is this long enough to adequately measure the response of the active metabolites?

3. Study sessions will take place in the University's human psychopharmacology laboratory. 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. Is this adequate to prevent the subjects from discussing the drugs and their effects, thus having an effect on the responses of other study subjects?

4. A positive urine drug screen is one of the exclusion criteria. Subjects testing positive for cocaine are excluded, but testing positive for cocaine metabolites are eligible. What is the rationale for this? Afterall, frequently benzoylecgonine is a major impurity and hydrolysate of cocaine.

5. Current recreational drug use is allowed if the candidate can produce a negative urine sample. Justify.

6. Are subjects experienced in these sort of studies? How many have they participated in?

7. Are the results of an outpatieht study adequate?

Michael Klein, Ph.D. (HFD-170) 8-6-96

BeLinda Hayes, Ph.D. (HFD-170) 8/6/96

APPEARS THIS WAY
ON ORIGINAL

MAY 16 1996

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. and Michael Klein, Ph.D.**
REVIEWERS DATE:	**May 16, 1996**

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 with their NDA submission. Sibutramine meets the requirements 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. 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 the United Kingdom, relative to its consideration as a potential controlled drug as defined by the Misuse of Drugs Act of 1971.

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 hour range), 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, with 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. **(See attached Figure 1 from the Biopharmaceutics review of Drs. Jones and Fossler).**

Sibutramine's biochemical profile is similar to that of marketed antidepressants and anorectics. Sibutramine is a monoamine reuptake inhibitor which down-regulates (i.e., sensitizes) α_2 and β adrenoceptors. Sibutramine's and its primary and secondary amine metabolites reuptake inhibition profiles have 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 inhibitors of noradrenaline, 5-hydroxytryptamine (5-HT) and dopamine relative 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. In both rat and human brain tissues, BTS 54 354 and BTS 54 505 exhibited high affinity for both the 5-HT and NA reuptake sites (Table 1). Both metabolites were equipotent. On the other hand, sibutramine displayed weak and moderate affinity for the noradrenaline reuptake site in human and rat brain, respectively. The metabolites also displayed moderate affinity for the dopamine reuptake sites in both species; their affinity for the dopamine sites was 2 to 3 fold less than that observed with the noradrenaline site. 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.

Results obtained from monoamine uptake studies are consistent with sibutramine and its metabolites affinity for the monoamine reuptake receptors. In rat brain synaptosomes, the primary metabolite BTS 54 505 and the secondary metabolite 53 354 were potent inhibitors of [^{3}H]NE and [^{3}H]-5-HT uptake (Table 2). BTS 54 505 and BTS 54 354 inhibitory effects on [^{3}H]NE uptake were equivalent with K_i's of 4.9 and 2.7 nM, respectively. However, BTS 54 505 and BTS 54 354 were 6- and 5-fold less potent as [H]-5HT inhibitors, respectively. With a K_i value of 282 nM, sibutramine was a weak inhibitor of [^{3}H]-NE uptake into rat synaptosomes. In comparison to sibutramine, the hydroxylated primary amine metabolites BTS 64 472 and BTS 65 400 were more potent [^{3}H]-monoamine uptake inhibitors than sibutramine. BTS 54 505 and BTS 54 354 were also potent inhibitors of [^{3}H]-5-HT and [^{3}H]-DA uptake into rat synapatosomes.

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.

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.*, 1990). Plasma obtained from healthy male volunteers receiving single or repeated dosing with sibutramine produced an inhibitory effect on monoamine uptake *in vitro*. The rank order of uptake inhibition was: [^{3}H]-NA >[^{3}H]-5-HT > [^{14}C]-DA. 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.), 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 methamphetamine dexamphetamine, methylphenidate, fencamfamine, nomifensine, bupropion and GBR 12909. 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. 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). Similar results were elicited by the secondary metabolite of sibutramine (BTS 54 354) and at a concentration of 10^{-5}M. Sibutramine and BTS 54 505 were inactive at concentrations as high as 10^{-5}M.

Table 1. **Sibutramine and its metabolites affinity for the serotonin (5-HT), noradrenaline (NE) and dopamine (DA) reuptake sites in rat and human brain.**

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

Table 2. **The effect of sibutramine and its metabolites on [^{3}H]monoamine uptake into rat synaptosomes.**

COMPOUND	K_i (nM)		
	NA	5-HT	DA
Sibutramine	283 ± 25	3131 ± 193	2309 ± 104
BTS 54 354	2.7 ± 0.3	18 ± 2	24 ± 1
BTS 505	4.9 ± 0.3	26 ± 1	31 ± 2
BTS 64 472	55 ± 3	581 ± 51	31 ± 2
BTS 64 473	438 ± 33	2963 ± 97	3012 ± 126
BTS 65 400	11 ± 1	31 ± 3	55 ± 6

Values are means ± SEM for 3 independent determinations

The *in vivo* behavioral and pharmacological profile of sibutramine is consistent with that of clinically effective antidepressants. As depicted in Table 3, sibutramine exhibited potent activity in the standard antidepressant screens.

Table 3. Comparison of sibutramine's activity with standard antidepressants in routine antidepressant models.

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

ABUSE LIABILITY STUDIES.

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 designed as correct and resulted in sweet milk delivery. On days when saline injections were administered, the other lever was designed 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 (i.p.); d-amphetamine (, i.p.); nomifensine (i.p.); bupropion (, i.p.); BTS 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 individual rats' and groups' overall performance were classified as follows in Table 4:

Table 4. Classification of individual rats' and group overall performance.

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 5. 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.

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.

Table 5. 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.

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) 18 to 30 years of age; 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 below in Table 6:

Table 6. The five treatment conditions for the clinical trial.

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 was perceived as being different from the subjects' previous experience with stimulants and their favorite drug of abuse.

Table 7 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 7. Results from the Modified Norris Assessment Questionnaire.

MODIFIED NORRIS FACTOR	MEAN CHANGE FROM BASELINE				
	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 time frame (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.

CONCLUSIONS AND RECOMMENDATIONS.

The sponsor has provided extensive information on the preclinical pharmacology of sibutramine and its structural similarity to other anorectics and stimulants. However, this information is only a portion of the abuse liability assessment. Therefore, a complete and comprehensive evaluation on the abuse potential of sibutramine and a decision on possible CSA scheduling cannot be made. In order for an evaluation to be made, the sponsor needs to address the following issues:

1. **Discriminative Stimulus Effects.** The submitted study did not thoroughly evaluate the discriminative stimulus effects of sibutramine. Because sibutramine has more serotoninergic activity than dopaminergic activity, it may possess more hallucinogenic activity and may have an abuse profile similar to the hallucinogens. Data that will be useful would be a comparison of its discriminative stimulus effects to the discriminative stimulus effects elicited by commonly abuse hallucinogens (e.g. MDMA (3,4-methylenedioxymethamphetamine), LSD, mescaline or MDA). Sometimes drugs may not fully generalize to the discriminative stimulus of a training drug, but may only partially generalize to the drug. Like sibutramine, MDMA is a monoamine releasing agent that is more potent as a serotoninergic releasing agent than as a dopamine releasing agent, and it is strongly recommended that sibutramine and its metabolites be tested in rats trained to discriminate MDMA from saline. When the anorectic fenfluramine was tested in animals trained to discriminate amphetamine from saline, it did not elicit amphetamine-like stimulus effects; however, when evaluated in rats trained to discriminate MDMA from saline, it generalized to MDMA in a dose-dependent manner (Schechter, 1986). Performing a drug discrimination study in humans would also be very valuable in assessing the abuse potential of sibutramine. It is well-established that humans can learn to discriminate amphetamine from placebo under controlled-laboratory conditions. Because sibutramine may be more MDMA-like in discriminative stimulus effects, it is strongly recommended that the subjects be trained to discriminate MDMA from placebo. After the subjects have met criteria, they should be tested with sibutramine, amphetamine, and other anorectics (e.g., fenfluramine).

2. **Reinforcing Efficacy.** Another important component of an abuse liability assessment is the evaluation of the drug's reinforcing efficacy. This is done in a standard self-administration paradigm utilizing primates and humans. The reinforcing efficacy of sibutramine should be performed in primates trained to self-administer cocaine and if possible MDMA.

3. **Clinical Subjective Effects Evaluation (No. BPI 863).** Issues outlined above need to be corrected.

4. **Epidemiology Data.** If marketed in the U.K. or any other country, actual usage data should be provided.

May 16, 1996

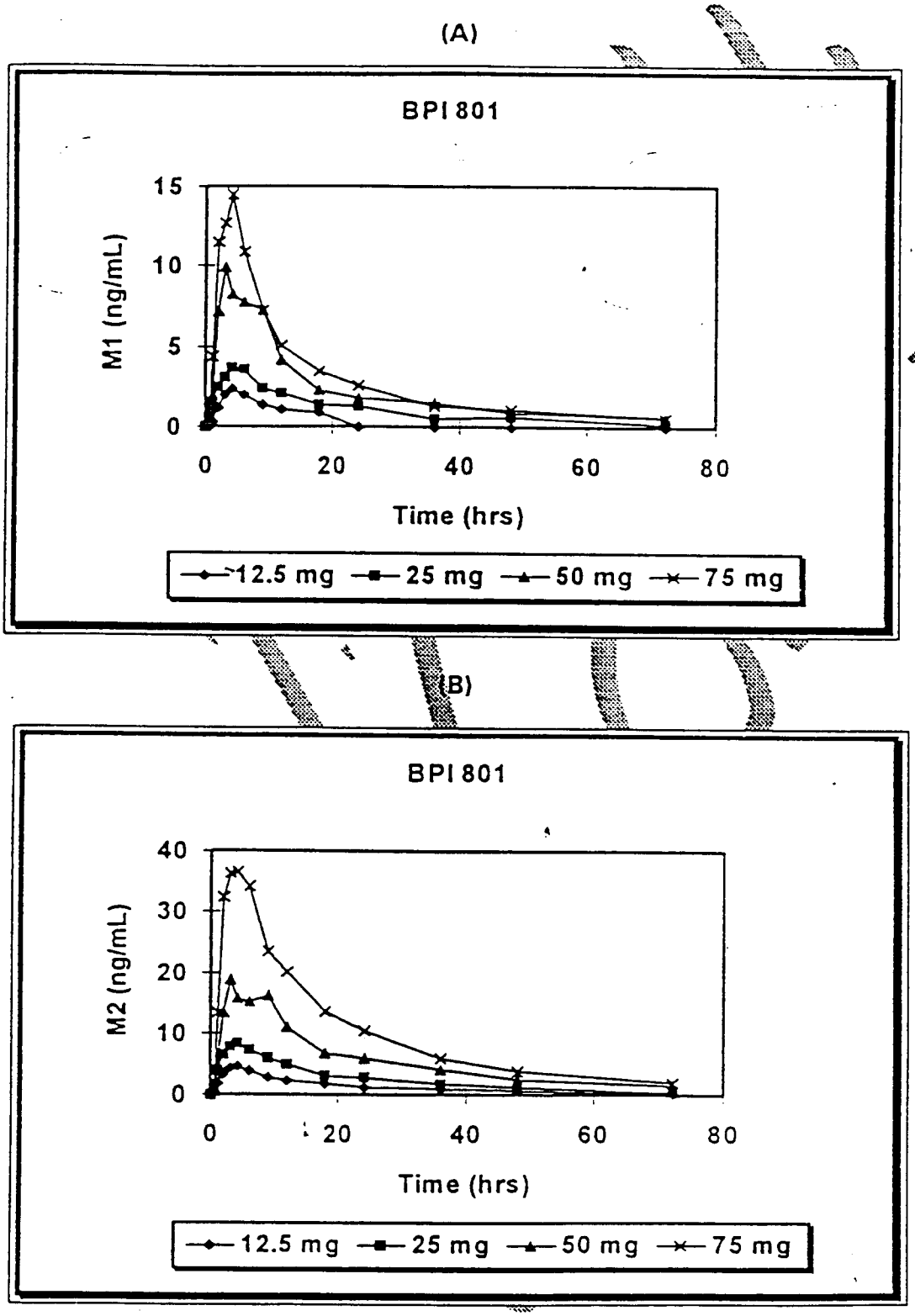
BeLinda A. Hayes, Ph.D. Date

Concurred by Acting Team Leader:

5-16-96

Michael Klein, Ph.D. Date

Figure 1: Mean plots of M1 (A) and M2 (B) after doses of 12.5, 25, 50 and 75 mg sibutramine to four different groups of male volunteers. (Study BPI 801).



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Heal D.J., Butler S.A., Hurst E.M. and Buckett W.R. (1989) Antidepressant treatments, including sibutramine hydrochloride and electroconvulsive shock decrease β_1- but not β_2-adrenoceptors in rat cortex. J. Neurochem. 53:1019-1025.

Luscombe G.P., Hopcroft R.H., Thomas P.C. and Buckett W.R. (1989) The contribution of metabolites to rapid and potent down-regulation of rat cortical β-adrenoceptors by the putative antidepressant sibutramine hydrochloride. Neuropharmacology 28:129-134.

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Schechter M.D. (1986) Discriminative profile of MDMA. Pharmacol. Biochem. Behav. 24:1533-1537.

RECORD OF TELEPHONE CONVERSATION/MEETING	**Date:** November 21, 1997
Re: Our 11/8/96 approvable letter I called Dr. Ashworth to clarify the items 9 & 10 on page 6 of our 11/8/96 AE letter. 1. Item # 9 recommended to include a warning to protect the capsules from heat and moisture in the carton, container, and the HOW SUPPLIED section of the labeling. We also recommended that the recommended storage temperature statement must be revised to conform to the USP 23 definition of either "controlled room temperature" or "room temperature." Dr. Ashworth stated that the following statement "Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F)[see USP controlled room temperature]. Protect capsules from heat and moisture" has been added to the labels. 2. Item #10 requested to submit draft carton labels for all sizes bottles and blister packs. Dr. Ashworth mentioned that there are no blister packs. He also mentioned that bottles are supplied without carton. cc:OrigNDA HFD-510/DivFile HFD-510/Haber/Hess APPEARS THIS WAY ON ORIGINAL **Name: Julie Rhee**	**NDA#:** 20-632 **Telecon/Meeting initiated by:** ○ Applicant/Sponsor ● FDA **By:** Telephone **Product Name:** Meridia (sibutramine HCl monohydrate) Capsules **Firm Name:** Knoll Pharmaceutical Company **Name and Title of Person with whom conversation was held:** Robert Ashworth, Ph.D. Director, Regulatory Affairs **Phone:** (973) 331-7570

RECORD OF TELEPHONE CONVERSATION/MEETING	**Date:** November 22, 1997 3:15 pm
Re: 11/22/97 patient package insert (PPI) I called Dr. Ashworth and requested the following changes in the 11/22/97 patient package insert: 1. On page 1, delete "MERIDIA comes in capsules form." 2. On page 2, change the heading from "**How should I take MERIDIA and when should I take it?**" to "**How and when should I take MERIDIA?**" 3. On page 7, make the following changes in the sentence in the middle of the page (addition, deletion): "If you experience an increase . . . , your doctor may decide to decrease the dose or discontinue MERIDIA 4. On page 9, "Check with your doctor . . . on a medically safe and effective birth control method while taking MERIDIA." 5. On page 10, "MERIDIA should be stored . . . room temperature (about 60 to). Never leave MERIDIA in hot or moist places." I asked Dr. Ashworth to submit the revised PPI as a Revision 2 to distinguish from an earlier fax. He agreed. cc:OrigNDA HFD-510/DivFile HFD-510/Hess **Name: Julie Rhee**	**NDA#:** 20-632 **Telecon/Meeting initiated by:** ○ Applicant/Sponsor ● FDA **By:** Telephone **Product Name:** Meridia **Firm Name:** Knoll Pharmaceutical Company **Name and Title of Person with whom conversation was held:** Robert Ashworth, Ph.D. Regulatory Affairs **Phone:** (973) 331-7570

DOCUMENTATION OF TELECONFERENCE

Date: 6th, November, 1997 10:05am - 10:15am

Between: FDA (HFD-170, Division of Anesthetics, Critical Care, and Addiction Drug Products).
Michael Klein, Ph.D. , Team Leader/CSET
CSO: Indira Kumar

And

Mel Spigelman, MD
Company Name: Knoll
Phone: 201-331-7600

Topic: Sibutramine hydrochloride (Meridia) Drug Abuse Labeling Issues.

Discussion:

The sponsor called to clarify issues regarding the labeling and marketing of Sibutramine hydrochloride (Meridia).

1. The Marketing division of their company is concerned about the use of the word ***"sympathomimetic"*** which is viewed unfavorably in many states (examples are New Jersey, Alabama, West Virginia, and Kansas). The company proposed the following word ***"noradrenergic like***" instead. They stated that this is not a scientific problem but is the states view toward the word. They also stated that the Goodman & Gillman definition of the words are similar. FDA recommended that the sentence be deleted from the label rather than inadequately describing the drug in the Drug Abuse Section. It was pointed out that a more thorough description of the drug's pharmacology was in other sections of the label, in any event.

2. There was a concern with the introductory statement, under the Drug Abuse and Dependence Category and it was decided that the statement should be standardized to read as follows ***"Sibutramine hydrochloride (Meridia) is controlled in Schedule IV of the Controlled Substances Act."***

3. The comment in the second paragraph "***as with all other CNS drugs***" should be removed and the paragraph should read as follows ***"Physicians should carefully evaluate patients for history of drug abuse and follow such patients closely, observing them for signs of misuse or abuse (e.g., development of tolerance, incrementation of doses, drug-seeking behavior)."***

Drafted by Indira Kumar 11/6/97 11:20am.

cc: Original NDA 20-632
HFD-510/Div Files
HFD-170/M.Klein
HFD-170/I.Kumar
HFD-170/C.P.Moody
HFD-510/M.Hess

AUG 27 1997

MEMORANDUM OF TELECON

DATE: August 27, 1997

APPLICATION NUMBER: NDA 20-632; Meridia (sibutramine)

BETWEEN:

Name: Dr. Bob Ashworth
Phone: (201) 331-7570
Representing: Knoll Pharmaceuticals

AND

Name: Maureen Hess, MPH, RD
Division of Metabolism and Endocrine Drug Products, HFD-510

SUBJECT: Request for data

Returned phone call to Dr. Bob Ashworth to inform him of conference room location for 9/10/97 meeting. Inquired if there are dissolution data available for the drug batches that were used for the clinical abuse studies (the latter studies). He stated that he was not sure and would have to check. I asked him that if such data are available, they should be submitted to the NDA. If such dissolution studies have not been conducted, these studies should be performed. He stated that he would get back to me.

Maureen Hess, MPH, RD
Consumer Safety Officer

cc: Original NDA 20-632
HFD-510/Div. File
HFD-510/MHess

TELECON

APPEARS THIS WAY
ON ORIGINAL

ORIGINAL

JUN 3 1997

10, 13, 14, 15, 16 Jan 97

Memorandum of Telephone Conversations

Between: Abraham Varghese, Ph.D. (201) 331-7561
Manager of Regulatory Affairs
Knoll Pharmaceutical Company
also
Dr. Hugh Morgan, Toxicologist, Knoll Pharmaceutical Company, United Kingdom - phone 011 44 1159 124455

and

David H. Hertig (301) 443-3520
Pharmacologist, HFD-510

Reference: NDA 20-632 Meridia (Sibutramine)

Subject: Carcinogenicity studies

10 Jan 97: Call to Dr. Varghese. He was not in.

p.m. - Dr Varghese called. I told him that all carcinogenicity studies must go through the Executive CAC (Carcinogenicity Assessment Committee) as a matter of course and that I had presented their studies for Sibutramine on 21 Jan 97. Hemangioma (benign) were seen in the uterus of two high dose females only. This showed a significant linear dose tumor-trend (Trend Test p = 0.0027). Dr. Varghese was asked if they have any historical data for this strain of mice. In addition could they provide any literature data on uterine hemangiomas in mice, especially this strain?

Dr. Varghese said that Dr Morgan their toxicologist was in Rockville and he would try to get in touch with him. He was unable to get in touch with him.

13 Jan 97: Dr. Hugh Morgan (United Kingdom) called.

The above request was repeated to Dr. Morgan.

14 Jan 97: Dr. Hugh Morgan called. He indicated that findings in their lab are not inconsistent with the open literature. He will fax reference and pertinent pages.

15 Jan 97: Voice Mail from Dr Varghese wishing to know if I received the fax and if it should be sent to the NDA.

16 Jan 97: Called Dr. Varghese and thanked him for the fax. Told him that I had talked to our team-leader (Dr. Ronald Steigerwalt) and he had indicated that it would not be necessary to formerly submit the fax to the NDA.

cc:
Original NDA 20-632;
HFD-345 HFD-510 NDA 20-632;
HFD-510 RSteigerwalt; MHess; DHertig

28 Aug 1996

Memorandum of Telephone Conversations

Between: Abraham Varghese, Ph.D. (201) 331-7561
Manager of Regulatory Affairs
Knoll Pharmaceutical Company

and

David H. Hertig (301) 443-3520
Pharmacologist, HFD-510 - 28 Aug 96

Reference: NDA 20-632 Meridia (Sibutramine)

Subject: GLP's; Requested neurotoxicity studies

22 Aug 96:

Returned Dr. Varghese's call of 21 Aug 96. He wished to tell us that the neurotoxicity studies requested by Dr. Joe Contrera looked favorable and that they would be submitted as soon as available. He indicated that they were mentioned in the Briefing Document (for Advisory Committee meeting) and should Dr. Contrera have any questions he could contact Dr. David Heal.

Dr. Varghese also asked if the requested Quality Assurance information that was submitted 1, 5 Aug 96 was satisfactory. I indicated that in general yes; however, there were still a couple of studies, especially the 6 month rat and 6 month dog studies, for which there were no QA inspection dates (they were however, signed by the Quality Assurance Manager as being carried out in compliance with FDA GLP's). He said that he would check into this.

[These studies were conducted in the mid-eighties at which time the sponsor has indicated that the reporting situation was different from that of today. - This situation has been brought to the attention of Dr. Earl Butler, DSI, HFD-345.]

28 Aug 96:

Dr. Varghese called to say that he had checked with the laboratory regarding the missing QA dates of inspection and that they did not exist. The only explanation was that which had been given in the above submission.

cc:
Original NDA 20-632;
HFD-24 JDeGeorge; HFD-400 JContrera
HFD-345 HFD-510 NDA 20-632; IND 27,264
HFD-510 RSteigerwalt; MHess; DHertig

AUG 14 1996

MEMORANDUM OF TELECON

DATE: August 13, 1996

APPLICATION NUMBER: NDA20-632; Meridia (sibutramine hydrochloride monohydrate) Capsules

BETWEEN:

Name: Abraham Varghese, Ph.D.
Phone: (201) 331-7561
Representing: Knoll

AND

Name: Maureen Hess
Division of Metabolism and Endocrine Drug Products, HFD-510

SUBJECT: Safety Update

Informed Dr. Varghese that the last safety update was 12/95 and that another safety update is needed. Informed Dr. Varghese that Dr. Colman stated that data from 12/95 to present would suffice. Informed him that the safety update is needed before the September 26, 1996 Advisory Committee Meeting.
Dr. Varghese stated that the Agency should have the safety update approximately the second week of September.

Maureen Hess, MPH, RD
Consumer Safety Officer

cc: Original NDA20-632
HFD-510/Div. File
HFD-510/MHess
HFD-510/EColman

TELECON

APPEARS THIS WAY
ON ORIGINAL

18 July 1996

Memorandum of Telephone Conversations

Between: Abraham Varghese, Ph.D. (201) 331-7561
Manager of Regulatory Affairs
Knoll Pharmaceutical Company
also
Hugh Morgan, Knoll Pharmaceutical Company (U.K.?)

and

David H. Hertig (301) 443-3520
Pharmacologist, HFD-510

10 Jul 96

Reference: NDA 20-632 Meridia (Sibutramine)

Subject: GLP's

15,16 Jul 96: Calls to Dr A. Varghese. He was not in.

16 Jul 96:
Dr. Varghese returned my call. Told him that under GLP's we require two statements for preclinical studies i.e. a Compliance Statement and a Quality Assurance Statement with dates of inspections and dates reported to management. This would also include mutagenicity studies.

18 Jul 96:
Hugh Morgan (Knoll Pharmaceutical Company, U.K.?) called. Dr. Varghese had called him but he was unclear of our request. I explained to him that under the GLP regulations we require two statements i.e. a Quality Assurance and a Compliance Statement. He stated that he was thoroughly familiar with this and that they were available but must have been inadvertently left out in assembly (of the NDA package). [I indicated that some were missing but did not elaborate as to which ones.] He indicated that the information would be assembled and submitted as a packet.

NOTE:
Information received: Submission 1,5 Aug 1996.

cc:
Original NDA 20-632;
HFD-24 JDeGeorge; HFD-400 JContrera
HFD-345 HFD-510 NDA 20-632; IND 27,264
HFD-510 RSteigerwalt; MHess; DHertig

Meeting Date: September 25, 1997 Time: 10:30 a.m. - 11:30 a.m. Location: PKLN1456

NDA 20-632 Meridia (sibutramine hydrochloride monohydrate) Capsules

Type of Meeting: General (Teleconference)

Meeting Chair: Dr. Solomon Sobel

External Participant lead: Dr. Mel Spigelman

Meeting Recorder: Ms. Maureen Hess

FDA attendees and titles:

Dr. Solomon Sobel, Director, DMEDP
Dr. Eric Colman, Medical Reviewer, DMEDP
Dr. Gloria Troendle, Deputy Director, DMEDP
Ms. Maureen Hess, CSO, DMEDP
Dr. Bruce Stadel, Medical Reviewer, DMEDP
Dr. Leo Lutwak, Medical Reviewer, DMEDP

External participant attendees and titles:

Dr. Mel Spigelman	Knoll, Vice President, Research and Development
Dr. Carl Mendel	Knoll, Director of Endocrine and Metabolism
Dr. Tim Seaton	Knoll, Senior Director, Endocrine and Metabolism
Dr. Bob Ashworth	Knoll, Director, Regulatory Affairs
Dr. Jeffrey Staffa	Knoll, Vice President, Scientific and Technical Affairs
Vaseem Iftekhar	Knoll, Associate Director, Project Management
Dr. Kenneth Kashkin	Knoll, Vice President, Clinical Research

Meeting Objectives:

Requested by the Agency to discuss the possibility of performing echocardiograms on study patients who have received or are currently receiving sibutramine in an attempt to rule out the possibility of valvulopathy.

Discussion Points:

- The firm began the teleconference by referring to the fax sent on 9/25/97 which contained summaries of echo data on 31 patients who received sibutramine. The patients received echocardiograms pre-treatment and at week 12 and there was no evidence of valvular dysfunction with sibutramine treatment. The Division inquired why the 31 patients received echocardiograms? The firm replied that it was done in an exploratory fashion in an attempt to recruit patients for a separate study. The Division inquired about the

sensitivity of the methods and what year they were done. The firm replied that the echo's were done in 1992 at Dr. George Bray's site, but is not sure about the technology of the equipment used. The Division stated that would be important to know to help interpret and evaluate the data. The firm replied that it will obtain that information.

- The Division stated that the data obtained on the 31 patients is a good start, but it is a preliminary one and 12 week data may not be reassuring. Also, patients in BPI 852 received low doses of sibutramine and given the sensitivity of the valvulopathy issue, need to look at how many patients should be evaluated, what dosages, etc. The firm stated that the studies are finished and they have lost control over the original study patients. However, they do have an ongoing study in Finland on diabetic patients which could be used as a resource for obtaining current echo data. The study contains 200 patients and is a 52 week, multi center, double-blind study that uses 15 mg sibutramine vs. placebo, followed by a 52-week open-label. Currently, there are 90 patients between week 0 and 24, 100 patients between week 24 and 52 and approximately 20 patients have already moved to the open label. Dr. Sobel asked how much could be done between now and the PDUFA goal date. The firm replied that they would not be able to do a comprehensive job before the goal date. Dr. Sobel stated that he is not sure if the Agency will have enough information at the goal date for approval; will have to consult with Dr. Bilstad. The firm asked the Division to elaborate its concerns. The Division replied that if the FDA had known that valvulopathy could occur with a class of drugs, valvular study would have been demanded during the trials. These agents maybe should be subjected to valvular study. Furthermore, the implication by the firm that fenfluramine and dexfenfluramine are unique and the problem of valvulopathy is unique to those drugs, is assuming too much at this time. The firm replied that PPH and valvulopathy may be a separate issue mechanistically, but the risk is associated with agents that release serotonin. The firm asked what they could do that would reassure the Division. The Division responded, a controlled study that contained a substantial population and dose, but is willing to accept the European data or go back to the NDA to accumulate a subset looking at different strata and doses.

- The Division asked if any power calculation had been performed on the Finish study. The firm stated that had not been done.

Action Items:

- None

Decisions (agreements) reached:

APPEARS THIS WAY
ON ORIGINAL

- None

Post meeting action items:

- Sponsor initiated echocardiograms on all patients in the Finish study in October, 1997.

Signature, minute's preparer:_____

Concurrence chair:_ /v _____

Concurrences:
BStadel/10.16.97/LLutwak/10.17.97/EColman/10.17.97/GTroendle/10.20.97/SSobel/10.21.97

cc: NDA 20-632
HFD-510/Div.File
Attendees
HFD-510/DLawson

APPEARS THIS WAY
ON ORIGINAL

Meeting Date: September 10, 1997 Time: 2:00 p.m. - 4:00 p.m. Location: PKLN-"L"

NDA 20-632 Meridia (sibutramine hydrochloride monohydrate) Capsules

Type of Meeting: General

Meeting Chair: Dr. Cynthia McCormick

External Participant lead: Dr. Mel Spigelman

Meeting Recorder: Ms. Maureen Hess

FDA attendees and titles:

Dr. Cynthia McCormick, Director, DACCADP
Dr. Curtis Wright, Deputy Director, DACCADP
Dr. Solomon Sobel, Director, DMEDP
Dr. Gloria Troendle, Deputy Director, DMEDP
Dr. Eric Colman, Medical Reviewer, DMEDP
Dr. Michael Klein, Team Leader (Controlled Substances) DAACADP
Dr. Belinda Hayes, Pharmacology Reviewer, DAACADP
Ms. Maureen Hess, CSO, DMEDP
Ms. Corinne Moody, SCSO, DAACADP
Dr. Lee Pian, Statistician, DMEDP
Dr. Silvia Calderon, DAACADP
Dr. Bruce Stadel, Medical Reviewer, DMEDP

External participant attendees and titles:

Dr. Mel Spigelman	Knoll, Vice President, Research and Development
Dr. Carl Mendel	Knoll, Director of Endocrine and Metabolism
Dr. Tim Seaton	Knoll, Senior Director, Endocrine and Metabolism
Dr. Bob Ashworth	Knoll, Director, Regulatory Affairs
Dr. Jeffrey Staffa	Knoll, Vice President, Scientific and Technical Affairs
Dr. Charles Schuster	Knoll, WSU
Dr. Chris-Ellyn Johanson	Knoll, WSU
Mr. Vaseem Iftekhar	Knoll, Associate Director, Project Management
Dr. Steven Weinstein	Knoll, Research and Development
Dr. Donald Jasinski	Knoll, Johns Hopkins Bayview Medical Center
Dr. Lawrence Bassin	Knoll
Dr. Kenneth Kashkin	Knoll

Meeting Objectives:

Meeting requested by Knoll to discuss their plan for post marketing surveillance for Meridia. Project manager advised Knoll on September 5, 1997 that the FDA is changing the meeting objectives to include discussion of dropping the 20 mg dose and scheduling of the drug in Schedule IV under the Controlled Substances Act.

Discussion Points:

- Dr. Colman stated the Division (DMEDP) believes it would be safer for the patient if the sponsor dropped the 20 mg dose from marketing and presented trend test analyses regarding this recommendation. The firm inquired if dropping other groups have the same effect? The Division responded that it is not plausible to drop the middle group. The firm agreed, but inquired if there is a loss of power. The Division responded that they are looking at the portion of people that have a pressor response when going from 15-20 mg. The firm cited other drugs that have a greater pressor response. The Division stated that they are not in a position to comment on drugs in other divisions, but this drug focused on patients with a systolic blood pressure exceeding baseline by 20 mmHg. The firm requested copies of the presentation and stated that they want the opportunity to review the data and will respond to the Division's recommendation of dropping the 20 mg dose within 10 days-two weeks. The Division added that a cautious approach should be taken by the sponsor when Meridia is marketed; patient blood pressure should be measured and recorded as it will most likely be used primarily by women and by those without morbid obesity.

- Dr. Klein presented the rationale for recommendation of scheduling the drug in Schedule IV under the Controlled Substances Act. He stated that there is a large number of adverse reactions that make the drug look like amphetamine and there are individuals who withdrew from study secondary to adverse reactions. The firm inquired if this was compared to placebo? The Division responded that placebo information was not available. The firm replied that they will provide that information. Dr. Hayes stated that the animal self-administration study is also a worrisome finding as well as the binding data of the metabolites. Dr. Wright summarized that all the factors together point to the picture of a drug that is amphetamine-like. The firm replied that the clinical studies showed that the patients did not like sibutramine. Dr. Wright replied that a number of worrisome things are seen in the profile of testing of this drug and it may be that the subjects tested are predictive of the population at large or they may not be. Dr. Wright added that the Division has looked at the data and made their best judgement and

are recommending schedule IV for sibutramine.

- The firm inquired about their options. HFD-170 offered the following:

  1. Submission of a letter by the sponsor stating that they go along with the scheduling recommendation. This would help the scheduling process move much more quickly.

  2. If the sponsor chooses to contest the scheduling, then most likely, the scheduling issue would go before an advisory committee.

  3. The firm was given the option for review before the drug abuse advisory committee.

  The firm inquired about descheduling, if, they agree to scheduling. The Division replied that three years worth of good data would be needed before descheduling can be considered.

Action Items:

- Copy of Dr. Colman's overheads were given to the firm on 9/10/97.

Decisions (agreements) reached:

- The sponsor will provide placebo information to HFD-170.
- The firm will review the data provided by HFD-510 before a decision is made regarding dropping the 20 mg dose.
- The firm will meet internally to discuss the Agency's scheduling recommendation and notify the Agency of its plans.

Post-Meeting Action Items:

- Sponsor submitted a letter September 19, 1997 requesting scheduling of sibutramine.

Signature, minutes preparer:_____

Concurrence chair:_____
0

Concurrences:
Bstadel/10.15.97/EColman/10.15.97/GTroendle/10.20.97/LPian/10.17.97/SSobel/10.21.97/
MKlein/10.17.97/BHayes/10.20.97/CMoody/10.24.97/SCalderon/10.17.97/CMcCormick/10.21.9
7

cc: NDA 20-632
HFD-510/Div. Files
HFD-510/Attendees
HFD-170/Attendees

Attachments

HESS

JUL 8 1997

Meeting Date: May 21, 1997 Time: 1:00 p.m. - 2:30 p.m. Location: PKLN-"O"

NDA 20-632 Meridia (sibutramine hydrochloride monohydrate) Capsules

Type of Meeting: General

Meeting Chair: Dr. Curtis Wright

External Participant lead: Dr. Mel Spigelman

Meeting Recorder: Ms. Maureen Hess

FDA attendees and titles:

Dr. Curtis Wright, Acting Division Director DACADP
Dr. Solomon Sobel, Division Director DMEDP
Dr. Gloria Troendle, Deputy Division Director DMEDP
Dr. Eric Colman, Medical Reviewer DMEDP
Dr. Michael Klein, Acting Team Leader (Controlled Substances) DACADP
Dr. Belinda Hayes, Pharmacology Reviewer DACADP
Ms. Maureen Hess, CSO DMEDP

External participant attendees and titles:

Dr. Mel Spigelman	Knoll, Vice President, Research and Development
Dr. Carl Mendel	Knoll, Director of Endocrine and Metabolism
Dr. Tim Seaton	Knoll, Senior Director, Endocrine and Metabolism
Dr. Bob Ashworth	Knoll, Director, Regulatory Affairs
Dr. William Woolverton	Knoll, University of Mississippi Medical Center
Dr. David Heal	Knoll, CNS Pharmacology
Dr. Jeffrey Staffa	Knoll, Vice President, Scientific and Technical Affairs
Dr. Charles Schuster	Knoll, WSU
Mr. Vaseem Iftekhar	Knoll, Associate Director, Project Management
Dr. Steven Weinstein	Knoll, Research and Development
Dr. Jonathon Cole	Knoll, Harvard University
Dr. Donald Jasinski	Knoll, Johns Hopkins Bayview Medical Center

Meeting Objectives:

Meeting requested by Knoll to discuss the results of the abuse potential studies.

Discussion Points:

- The firm presented the results of sibutramine MDMA drug discrimination study that was conducted in rats. Rats were trained to recognize discriminate racemic

MDMA from saline. Three test substances were tested in the rats to see if they would recognize (discriminate) the substances as MDMA. Results presented: 2 rats/12 showed some partial generalization to MDMA, 1 for each of the 2 metabolites and none to sibutramine itself. The firm will provide complete results to the NDA.

- The firm presented clinical abuse liability studies. The studies were conducted by three different investigators at three different centers. Two studies (Cole's and Schuster's) did not demonstrate sibutramine to be a drug of abuse and therefore concluded as such. The remaining study (Jasinski's) showed clear separation of sibutramine from placebo on the Amphetamine, Benzedrine, and morphine-benzedrine scale (the euphoria-indicating scale). This was especially true of the lower dose of sibutramine tested (25 mg vs 75 mg). The Agency asked the firm how to reconcile the difference between the results at the low dose and high dose. The firm was not able to explain the difference. The Agency responded that the studies are under review to try to assess the basis for the difference in the results. One issue to be reconciled was that different batches of test drug were used in the different studies for the 25 mg sibutramine capsules. In addition, the Agency is examining other possible causes to explain the difference. The Agency requested that the firm provide information on HF01 and JL04 regarding the batches of the test drug. The firm agreed. It was also noted that in both Jasinski's and Schuster's studies there was considerable increase in blood pressure and pulse rate which were comparable with those produced by d-amphetamine.

- The firm asked the Agency's opinion on whether or not sibutramine will be scheduled. The Agency responded that a thorough review of all the data is needed and that sibutramine may need to go to the Drug Abuse Advisory Committee in November.

- The Agency told the firm that a surveillance plan is needed for introduction to the market. The firm replied that they will provide a detailed plan.

- The firm was told that the PDUFA clock would start when the drug discrimination study is submitted, as that would complete all the outstanding issues of the approvable letter. The Agency informed the firm that once the drug discrimination study is submitted, the Agency then has six months to complete the review and issue an action letter.

Unresolved issues or issues requiring further discussion:

- None

Action Items:

- Firm will submit requested information on the batches of drug.

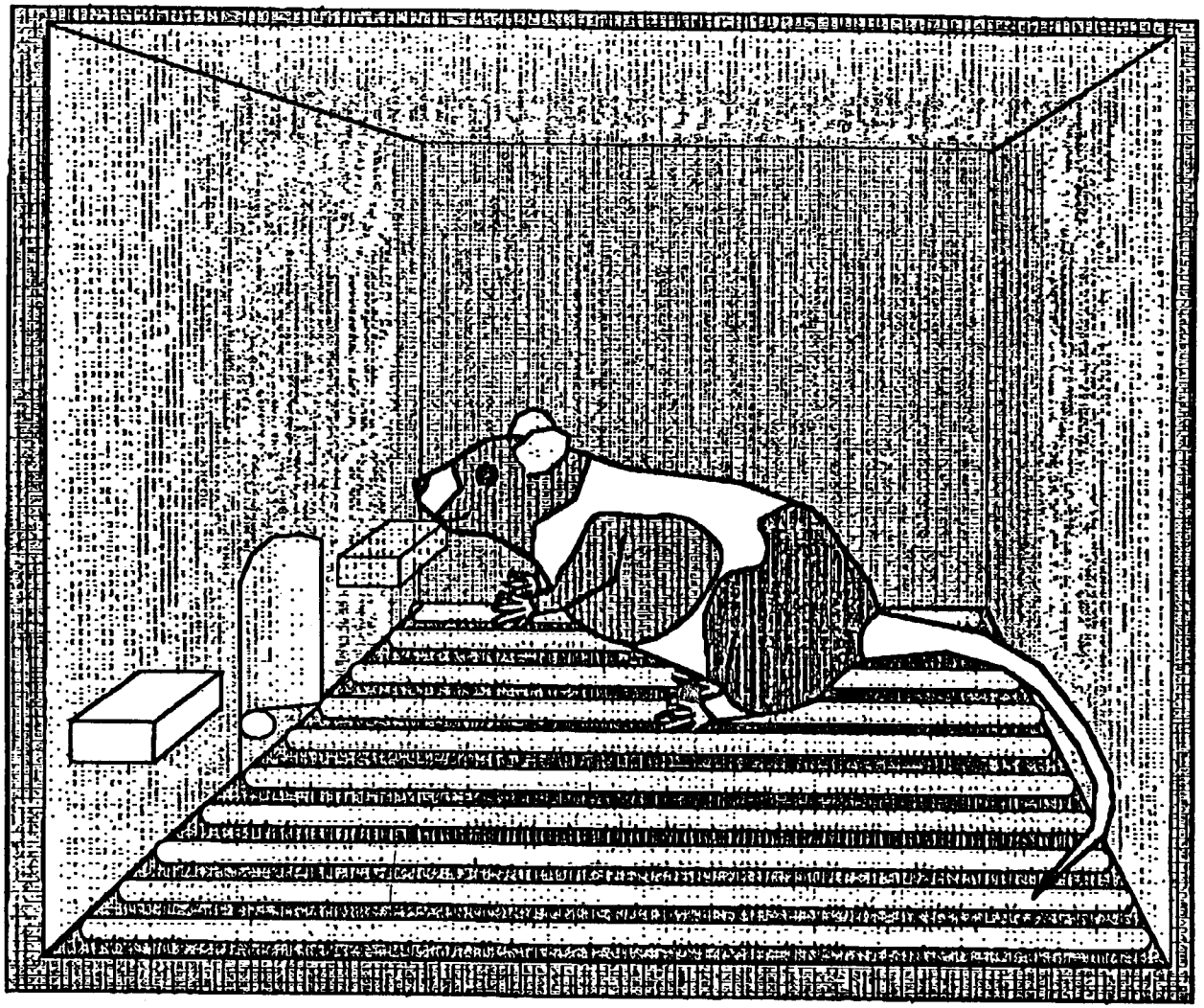
- Firm will provide final study report on the drug discrimination study.

Signature minute's preparer: _____

Concurrence Chair: _____

Concurrence:
Ssobel/6.2.97/GTroendle/5.30.97/EColman/5.30.97/MKlein/5.30.97/BHayes/6.2.97/CWright/6.8.97

cc: NDA 20-632
HFD-510
Attendees
HFD-510/DLawson



Abuse Potential Assessed Using a Discriminative-Cued 2-Choice lever Pressing Model

Female PVG (hooded) rats.

Rats trained to lever press for a sweetened milk reward.

Training schedule FR 1 (1 lever press ANY lever = 1 sweetened milk reward; maintenance schedule FR 5 (5 CORRECT lever presses = 1 sweetened milk reward.

Random assignment of one lever to the Saline (1 ml/kg ip) cue; one lever to the Discriminative cue, eg MDMA (1.5 mg/kg ip)

Rats only acceptable for drug testing if they show $\geq$ 75% presses on the correct lever for both Saline and the MDMA Cue.

Test drugs are injected via the intraperitoneal route.

Abuse Potential Assessed Using a Discriminative-Cued 2-Choice lever Pressing Model

Groups of at least 6 rats used for each drug dose.

Doses are **increased in 0.5 log units** (0.1, 0.3, 1 mg/kg etc) until **there is generalisation to the Discriminative Cue** or **marked suppression (≤ 1 SD) of lever pressing (Invalid) responding determined in the previous 4 MDMA trials.**

Testing commences 15min after drug injection (except sibutramine, tested 60 minutes after drug injection; time of peak effect).

Test schedule 2.5min (non-rewarded) + 7.5min (rewarded)

Protocol as described in No. P88019.

Individual Rat

Response Alternatives

- Presses 'SALINE' lever - SAL
- Presses 'MDMA' lever - MDMA
- Presses BOTH levers - NOP
- Lever pressing is suppressed - INVALID
  (≥ 1 SD in previous 4 MDMA tests)

Calculation of % Generalisation to MDMA

For individual rats - R1, R2, R3 etc

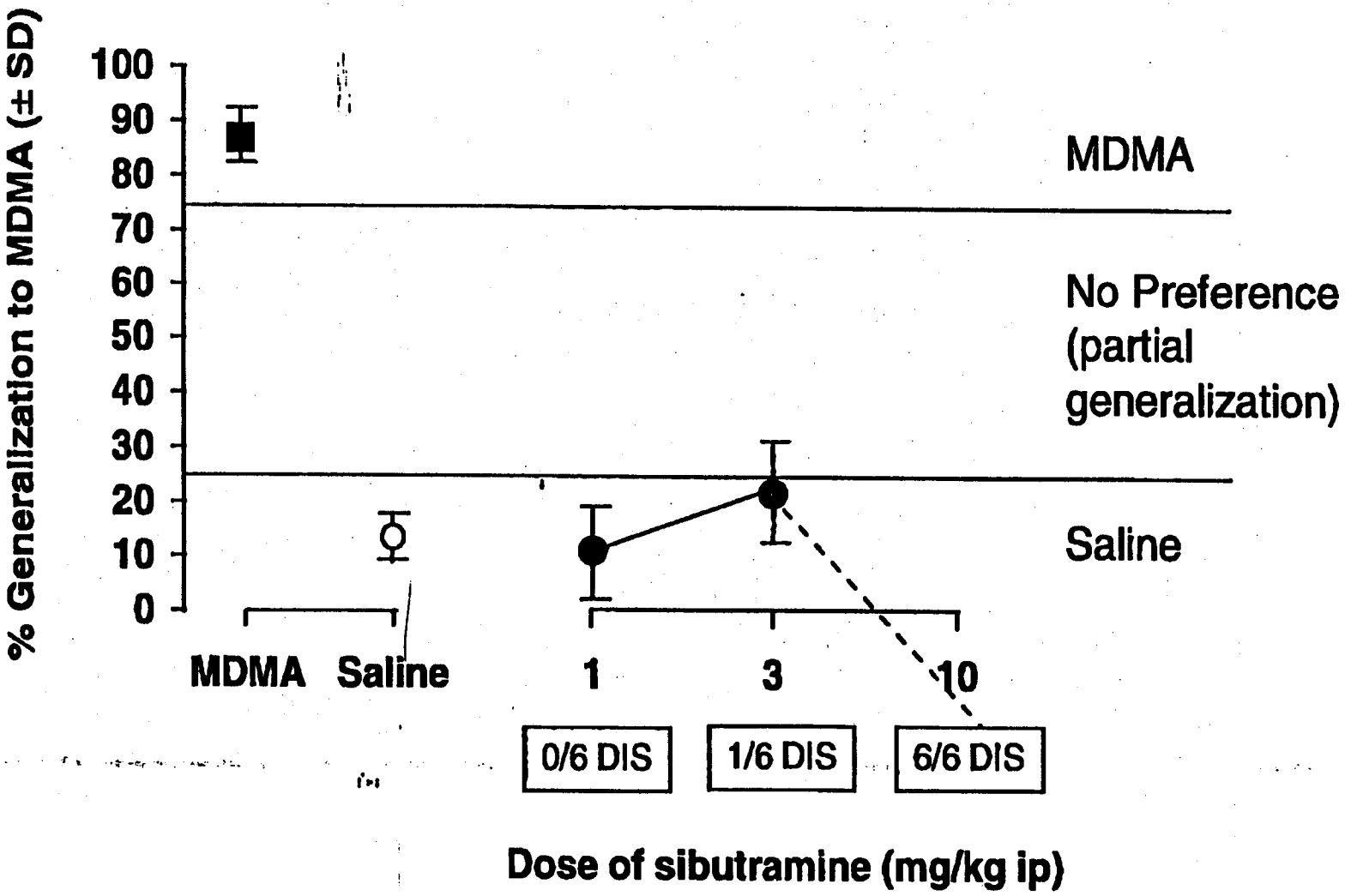
$$\%\ \text{Generalisation to MDMA for Drug X, Dose Y} = \frac{\text{Number of MDMA lever presses in test of Drug X, Dose Y}}{\text{Total lever presses in test of Drug X, Dose Y test session}} \times 100$$

Total lever presses = MDMA lever presses + Saline lever presses

For groups of rats -

Data presented as mean % generalisation to MDMA ± SD.

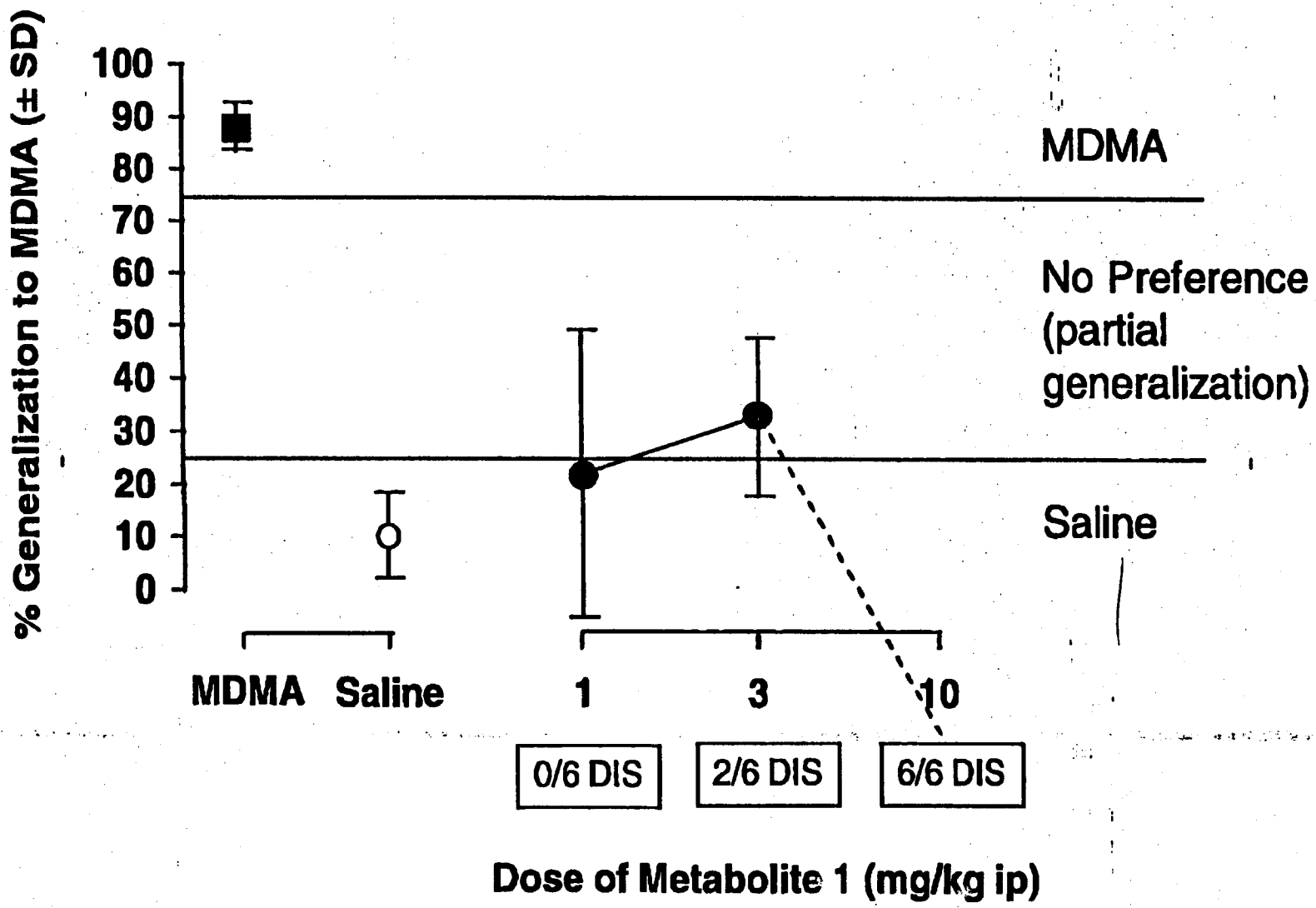
Results for Sibutramine in the MDMA study



Sibutramine - Disrupted Responding

Drug	Dose	Test Lever Presses	Mean Total Presses in 4 previous MDMA Tests (± SD)	% Suppression
Sibutramine	1	-	-	-
Sibutramine	3	11	33.3 ± 3.6	67%
Sibutramine	10	3	29.8 ± 4.2	90%
	10	0	32.0 ± 5.4	100%
	10	0	38.0 ± 3.2	100%
	10	0	31.5 ± 3.5	100%
	10	4	25.8 ± 3.2	84%
	10	0	29.5 ± 2.5	100%

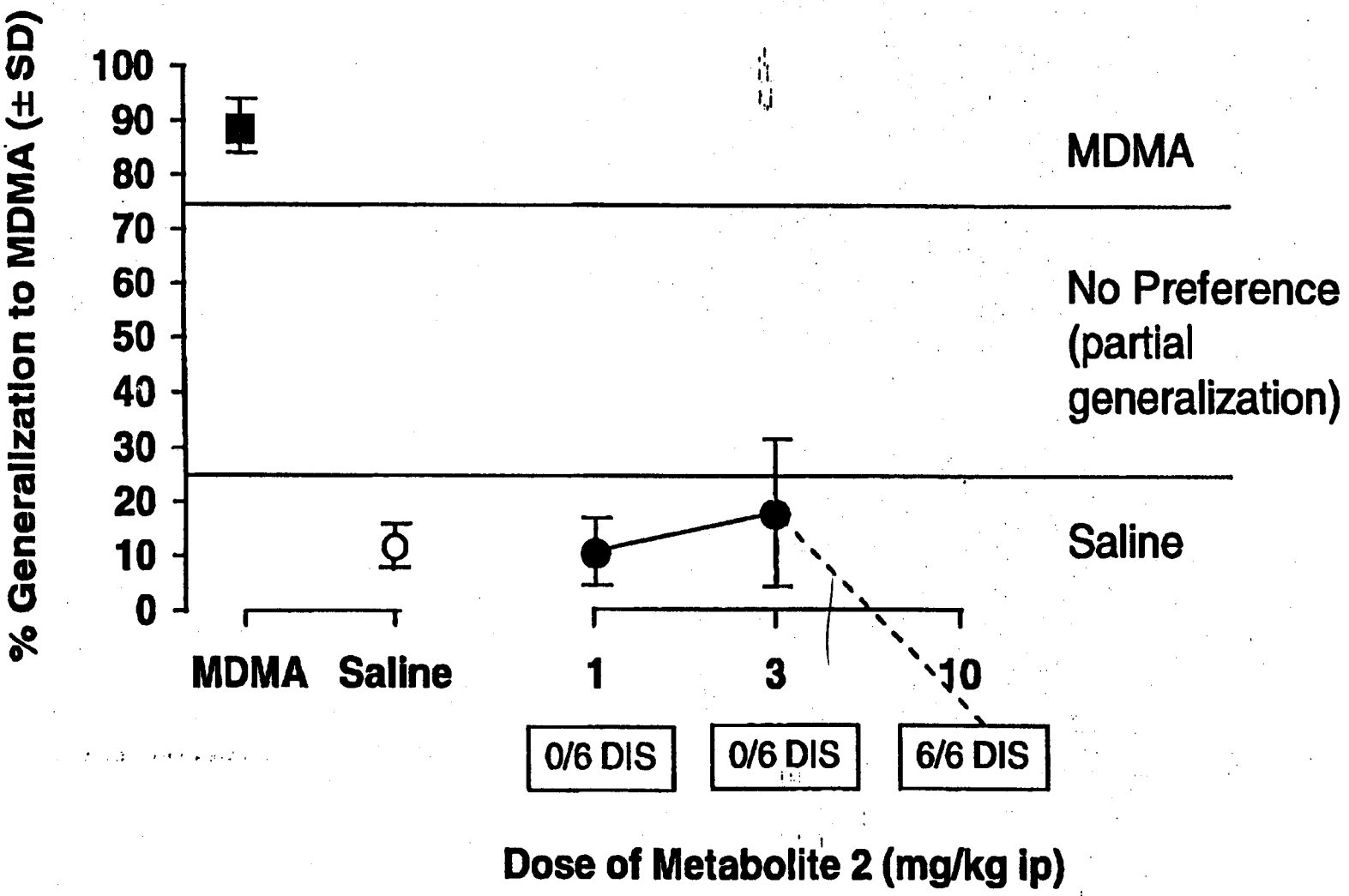
Results for Metabolite 1 in the MDMA study



Metabolite 1 - Disrupted Responding

Drug	Dose	Test Lever Presses	Mean Total Presses in 4 previous MDMA Tests (± SD)	% Suppression
Metabolite 1	1	-	-	-
Metabolite 1	3	15	28.3 ± 4.9	47%
	3	7	26.5 ± 1.7	74%
Metabolite 1	10	0	24.0 ± 1.4	100%
	10	3	25.3 ± 3.1	88%
	10	0	28.5 ± 7.0	100%
	10	6	27.5 ± 5.0	78%
	10	2	27.0 ± 2.4	93%
	10	0	23.0 ± 4.5	100%

Results for Metabolite 2 in the MDMA study



Metabolite 2 - Disrupted Responding

Drug	Dose	Test Lever Presses	Mean Total Presses in 4 previous MDMA Tests (± SD)	% Suppression
Metabolite 2	1	-	-	-
Metabolite 2	3	-	-	-
Metabolite 2	10	0	36.8 ± 6.4	100%
	10	0	25.8 ± 2.6	100%
	10	0	28.3 ± 4.6	100%
	10	0	29.5 ± 5.8	100%
	10	6	36.8 ± 3.3	84%
	10	0	30.0 ± 5.9	100%

Preclinical Summary

Sibutramine

- Is structurally different from dexamphetamine, dexfenfluramine and MDMA
- Is an SNRI
- Is not a monoamine-releasing agent
- Lacks the potential for psychostimulant abuse
- Lacks hallucinogenic properties
- Has minimal reinforcing properties
- Does not produce physical dependence

Abuse Potential Studies—BPI 863, BPI 883, BPI 893 Overview

Psychostimulant Users

- Do not like sibutramine
- Dislike sibutramine
- Are unwilling to pay for sibutramine
- Do not want to take sibutramine again
- Do not identify sibutramine as an hallucinogen at 3-15x the recommended dose

Hallucinogen Users

- Do not like sibutramine
- Dislike sibutramine
- Are unwilling to pay for sibutramine
- Do not want to take sibutramine again
- Do not identify sibutramine as an hallucinogen at 3-15x the recommended dose

MDMA Users

- Do not like sibutramine
- Dislike sibutramine
- Are unwilling to pay for sibutramine
- Do not want to take sibutramine again
- Do not identify sibutramine as an hallucinogen at 3-15x the recommended dose

Abuse Potential Study Findings—Dexamphetamine

	A	BG	MBG	LSD	Liking	Disliking	"High"	Street Value	Want Again?
BPI 863									
20 mg	+	+	+	+	ND	ND	+	+	+
30 mg	+	+	+	+	ND	ND	+	+	+
BPI 883									
10 mg	+	+	+	-	-	*	-	-	ND
30 mg	+	+	+	-	+	*	+	+	ND
BPI 893									
20 mg	+	+	+	-	+	*	+	-	-

ND = Not determined
\- = Registered negatively on scale
\+ = Registered positively on scale
* = Registered negatively on scale, but scale indicates LACK of abuse potential

4802.05.06.97

Abuse Potential Study Findings—Sibutramine

	A	BG	MBG	LSD	Liking	Disliking	"High"	Street Value	Want Again?
BPI 863									
20 mg	-	-	-	-	ND	ND	-	-	-
30 mg	-	-	-	+	ND	ND	-	-	-
BPI 883									
25 mg	+	+	+	-	-	√	-	-	ND
75 mg	+	-	-	-	-	√	-	-	ND
BPI 893									
25 mg	-	-	-	-	-	-	-	-	-
75 mg	-	-	-	+	-	√	-	-	-

ND = Not determined
\- = Registered negatively on scale
\+ = Registered positively on scale
√ = Registered positively on scale, but scale indicates LACK of abuse potential

4803.05.06.97

Clinical Trials Database (n > 4500)

- No euphoria
- No drug seeking behavior
- No withdrawal syndrome
- No evidence of abuse

Abuse Potential—Conclusions

- Differentiated from amphetamine
  - Dexamphetamine as positive control in studies
- Distinct from hallucinogens and MDMA
  - No hallucinations, no euphoria
  - Hallucinogen and MDMA users in studies
- Not liked and even disliked by substance abusers
  - Psychostimulant users, hallucinogen users, MDMA users
- No evidence of abuse in clinical trials (n > 4500)
- Therefore abuse potential low

HESS

Meeting Date: October 28, 1996 Time: 11:30 a.m. - 1:30 p.m. Location: PKLN-"B"

NDA 20-632 Meridia (sibutramine hydrochloride monohydrate) Capsules

Type of Meeting: General

Meeting Chair: Dr. Curtis Wright

External Participant lead: Dr. Mel Spigelman

Meeting Recorder: Ms. Maureen Hess

FDA attendees and titles:

Dr. Solomon Sobel, Division Director DMEDP
Dr. Curtis Wright, Acting Division Director DACADP
Dr. Eric Colman, Medical Reviewer DMEDP
Dr. Michael Klein, Chemistry Reviewer DACADP
Dr. Belinda Hayes, Pharmacology Reviewer DACADP
Dr. Gloria Troendle, Deputy Division Director DMEDP
Ms. Corinne Moody, SCSO DACADP
Ms. Maureen Hess, CSO DMEDP

External participant attendees and titles:

Dr. Mel Spigelman	Knoll, Vice President, Research and Development
Dr. Carl Mendel	Knoll, Director of Endocrine and Metabolism
Dr. Tim Seaton	Knoll, Senior Director, Endocrine and Metabolism
Dr. Abraham Varghese	Knoll, Associate Director, Regulatory Affairs
Dr. William Woolverton	Knoll, University of Mississippi Medical Center
Dr. David Heal	Knoll,
Dr. Jeffrey Staffa	Knoll, Vice President, Scientific and Technical Affairs
Dr. Charles Schuster	Knoll, WSU
Vaseem Iftekhar	Knoll, Associate Director, Project Management

Meeting Objectives:

Requested by the Agency to discuss issues regarding the potential abuse liability of sibutramine that prevent its classification under the Controlled Substances Act.

Discussion Points:

- Dr. Klein stated problems observed with the J. Cole et al. abuse liability study

include an inappropriate comparator and that the majority of the activity of sibutramine resides in its two primary active metabolites. He further stated that these metabolites peak between four and six hours and although the firm conducted hourly subjective testing; it was only up to four hours beyond time of drug administration. The firm replied that the study was in fasting subjects so the metabolite peak was at 2-3 hours.

- Dr. Hayes proposed two detailed preclinical protocols. The first study will assess the pharmacologic similarity of the drug to MDMA which is a Schedule I hallucinogen with combined serotonergic and dopaminergic receptor activity. Dr. Hayes further stated that amphetamine is not the appropriate positive control and recommended a drug discrimination-stimulus generalization study to demonstrate whether the animals recognized sibutramine as MDMA, rather than amphetamine. The second protocol entails the drug to be given chronically and then withdrawn. This would demonstrate whether the drug has dependence producing properties in animals. The firm replied that the drug is not like MDMA and that fenfluramine has some MDMA-like properties. The firm further stated that at least one enantiomer of MDMA was self administered in animals.

- Dr. Wright questioned whether or not the drug has a hallucinogenic component and expressed concern that the drug may have activity like that of other hallucinogens such as LSD and MDMA. He further stated that amphetamine should not be used as a positive control anymore, as the firm has successfully demonstrated that sibutramine is not like amphetamine, but has not shown that sibutramine is not hallucinogenic or similar to other drugs in lower levels of CSA control where all other anorectics are currently scheduled. Dr. Wright also expressed concern about the positive response of sibutramine on the LSD scale. The firm replied that if sibutramine were like other hallucinogens, it would have shown a positive responses on the MBG scale (which measures euphoria), as well as showing positive responses on the LSD scale. Therefore, the firm stated that sibutramine is only a dysphoriant. Dr. Wright replied that the drug needs to be compared to a weak dysphoriant.

- The firm presented an overview of pre-clinical pharmacology data to attempt to demonstrate that sibutramine's effects are solely related to reuptake inhibitor. The overview included the following:

Pharmacological mechanism of action

Effect on food intake
Thermogenesis
Differentiation from various other weight reducing drugs

- Dr. Klein stated that in the J. Cole et al. study, the test doses were done at therapeutic levels and such abuse liability studies should be run at supratherapeutic levels. He further stated that because so much CNS activity resides in the active metabolites, other preclinical study results which compared sibutramine to other drugs in a variety of species did not provide clarity as to time of response after administration and therefore did not indicate the extent of drug metabolism at the time of drug response. Dr. Klein added that this study was conducted only with men.

- Dr. Klein stated that the sponsor had initiated two abuse liability studies (Jasinski et al. and Schuster et al) and one preclinical self administration study (Woolverton, University of Mississippi) after the NDA was submitted. He further stated that the firm submitted the clinical protocols to HFD-170 and the Division reviewed them and provided comments to the sponsor. Dr. Klein added, that data from these clinical protocols has not been submitted for review nor has the new preclinical protocol. The new clinical studies still used amphetamine as a positive control. Dr. Woolverton briefly described the primate study and provided early results demonstrating positive self administration responses greater than from placebo, but less than positive control (cocaine).

- Dr. Wright expressed concern that any new anorectic that is not controlled will be heavily tested by the drug-abusing community and may be associated with overdose cases. He further stated that while sibutramine is not amphetamine-like, it may fit into the niche of PCP, MDMA-like drugs where the population that finds such drugs appealing is not selective. The firm stated that they are committed to public health interest. Dr. Wright stated that the information the firm is currently developing is needed to determine scheduling. In addition, the Agency will provide the firm with comments on their draft protocols.

- The firm asked if the abuse liability issues will affect approvability of sibutramine. Dr. Sobel replied, probably not.

Decisions (agreements) reached:

- The Agency will provide the firm with draft protocols to assess the pharmacologic similarity of the drug to MDMA. The Agency agreed to meet with the firm for further clarification of the protocols.

Unresolved issues or issues requiring further discussion:

- None

Action Items:

- Project manager will provide the firm with the draft protocols.

Post-Meeting Action Items:

- Protocols faxed by HFD-170.

APPEARS THIS WAY ON ORIGINAL

Signature, minutes preparer _____

Concurrence Chair: 11/22/96

cc: NDA Arch
HFD-510
HFD-170
Attendees
HFD-510/EGalliers/DLawson

drafted: MHess/11.6.96/n20632.mm4
final type: 11/20/96

Concurrences:
EColman/11.7.96/GTroendle/11.7.96/SSobel/11.8.96/MKlein/11.7.96/BHayes/11.7.96/CWright/11.8.96

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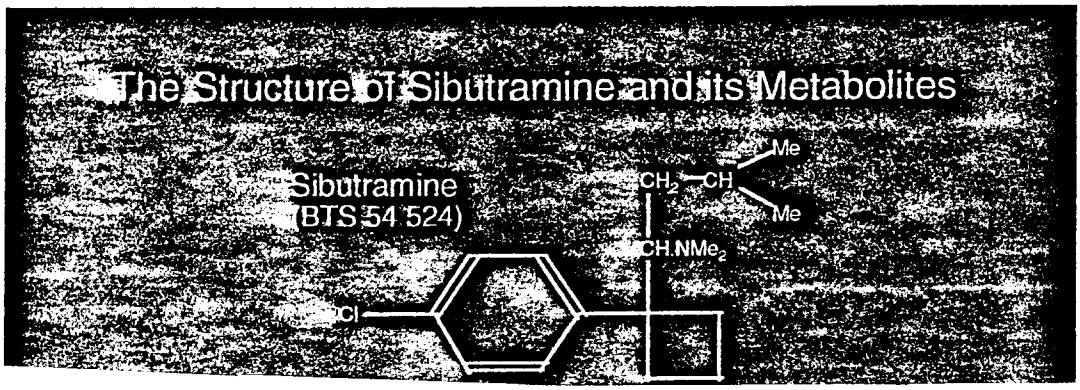
Sibutramine - Mode of Action

- Pharmacological mechanism of action.
  Sibutramine potently inhibits norepinephrine and serotonin (5-HT), but not dopamine, reuptake in vivo.
- Effect on food intake.
  Sibutramine reduces food intake by enhancing satiety, a central effect mediated via norepinephrine and serotonin (5-HT) reuptake inhibition.
- Thermogenesis.
  Sibutramine increases energy expenditure by enhancing central sympathetic drive to brown adipose tissue.
- Differentiation from various other weight reducing drugs.
  Sibutramine's mode of action is different from that of the monoamine releasing agents dexamphetamine and dexfenfluramine.

DJH/C18



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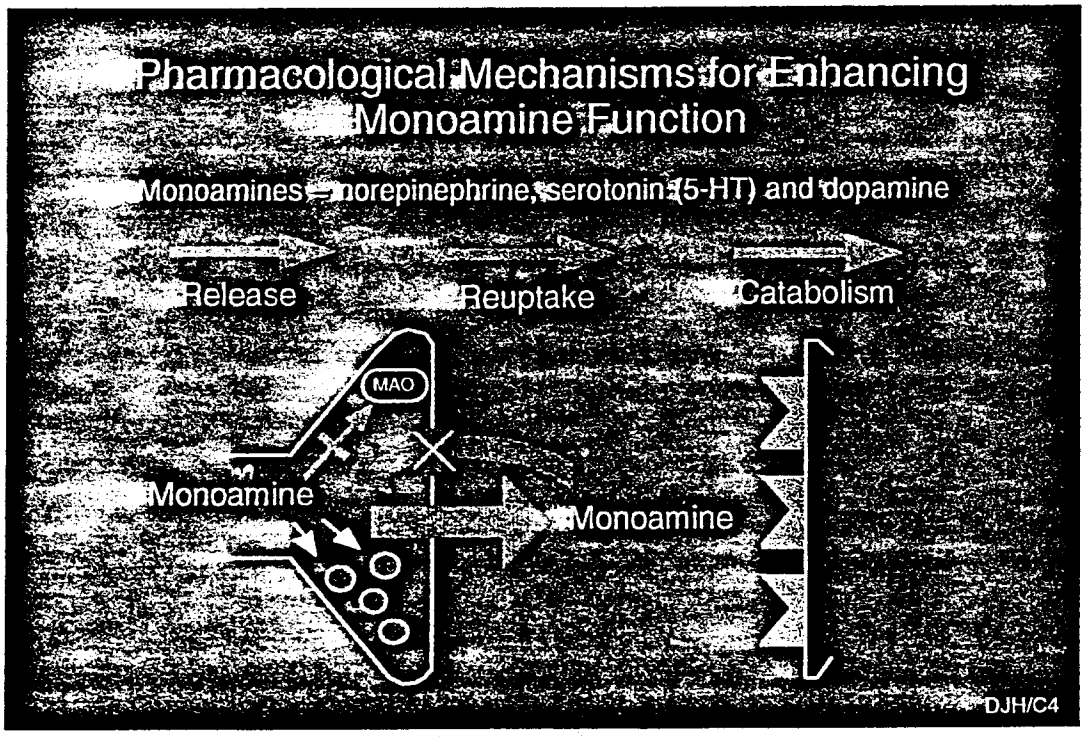

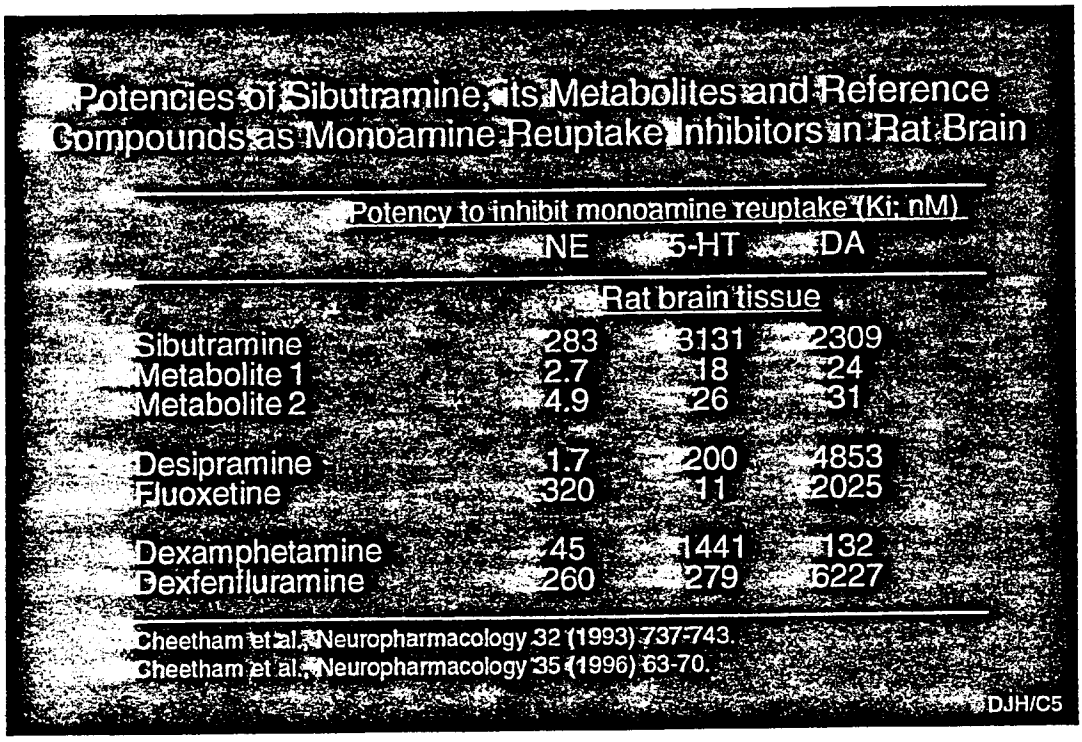

Potencies of Sibutramine, its Metabolites and Reference Compounds as Monoamine Reuptake Inhibitors in Rat Brain

	Potency to inhibit monoamine reuptake (Ki; nM)		
	NE	5-HT	DA
	Rat brain tissue		
Sibutramine	283	3131	2309
Metabolite 1	2.7	18	24
Metabolite 2	4.9	26	31
Desipramine	1.7	200	4853
Fluoxetine	320	11	2025
Dexamphetamine	45	1441	132
Dexfenfluramine	260	279	6227

Cheetham et al., Neuropharmacology 32 (1993) 737-743.
Cheetham et al., Neuropharmacology 35 (1996) 63-70.

DJH/C5

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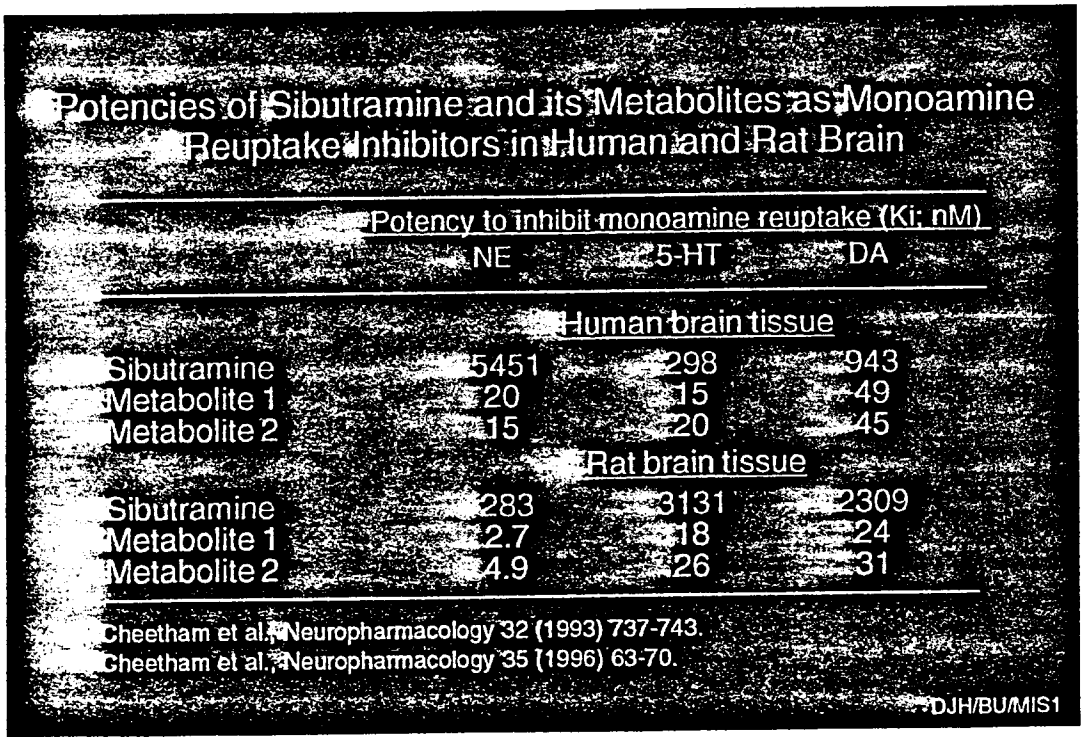


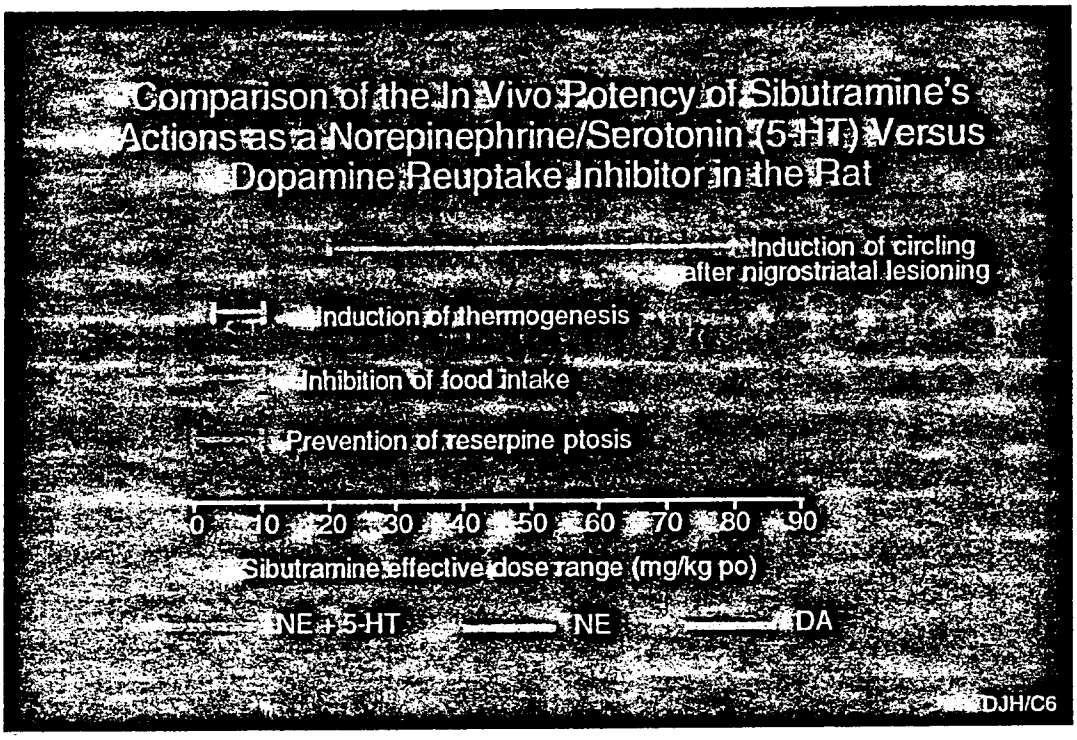
Potencies of Sibutramine and its Metabolites as Monoamine Reuptake Inhibitors in Human and Rat Brain

	Potency to inhibit monoamine reuptake (Ki; nM)		
	NE	5-HT	DA
	Human brain tissue		
Sibutramine	5451	298	943
Metabolite 1	20	15	49
Metabolite 2	15	20	45
	Rat brain tissue		
Sibutramine	283	3131	2309
Metabolite 1	2.7	18	24
Metabolite 2	4.9	26	31

Cheetham et al., Neuropharmacology 32 (1993) 737-743.
Cheetham et al., Neuropharmacology 35 (1996) 63-70.

DJH/BU/MIS1

Comparison of the In Vivo Potency of Sibutramine's Actions as a Norepinephrine/Serotonin (5-HT) Versus Dopamine Reuptake Inhibitor in the Rat



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Effect of Sibutramine and its Metabolites on [^{3}H]NE, [^{3}H]5-HT and [^{3}H]DA Release from Rat Brain Slices In Vitro

	Uptake Ki (nM)	% Release at 100nM	% Release at 1,000nM	% Release at 10,000nM
NE				
Sibutramine	283	–	–	–
Metabolite 1	2.7	–	–	–
Metabolite 2	4.9	–	–	–
Dexamphetamine	45	57	135	162
Dexfenfluramine	260	–	–	82
5-HT				
Sibutramine	3131	–	–	–
Metabolite 1	18	–	–	–
Metabolite 2	26	–	–	–
Dexamphetamine	1441	–	–	136
Dexfenfluramine	279	–	64	282
DA				
Sibutramine	2309	–	–	–
Metabolite 1	24	–	–	–
Metabolite 2	31	–	–	–
Dexamphetamine	132	56	122	138
Dexfenfluramine	6227	ND	ND	ND

– = no statistically significant effect, ND = not determined.

Heal et al., Psychopharmacology 107 (1992) 303-309. Heal et al., Br. J. Pharmac. 117 (1996) 325P.

DJH/BU/MIS3

Sibutramine and its Metabolites Lack Monoamine Oxidase Activity and Affinity for a Range of Neurotransmitter Receptors

- Sibutramine and its metabolites (10,000nM) do not inhibit monoamine oxidase activity in vitro in rat brain or liver.
- Sibutramine and its metabolites (1000nM) exhibit no significant affinity for a wide range of central and peripheral neurotransmitter receptors (α_1, α_2, β_1, β_2, β_3, 5-HT_1, 5-HT_{1A}, 5-HT_{1D}, 5-HT_{2A}, 5-HT_{2C}; D_1, D_2, muscarinic, H_1, benzodiazepine).

DJH/BU/MIS4

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Differentiation of the Pharmacological Profiles of Sibutramine and Dexfenfluramine

	Sibutramine (Metabolites 1+2)	Dexfenfluramine
Monoamine uptake inhibition (Ki < 100 nM)		
NE	✓	X
5-HT	✓	X
DA	✓	X
Monoamine release (≥ 10,000 nM)		
NE	X	✓
5-HT	X	✓
DA	X	NT
Reduces food intake	✓	✓
Enhancement of satiety	✓	✓
Neurotransmitters involved		
NE	✓	X
5-HT	✓	✓
DA	X	X
Induction of thermogenesis	✓	NT
Neurotoxicity	X	✓

DJH/BU3

Differentiation of Sibutramine, Fluoxetine and Dexfenfluramine/Fenfluramine - Reuptake vs Release

	Sibutramine (Metabolites 1 and 2)	Fluoxetine	Dexfenfluramine/ Fenfluramine
Monoamine Uptake Inhibition (Ki < 100nM)			
NE	✓	X	X[a]
5-HT	✓	✓	X[a]
DA	✓	X	X[a]
Monoamine Release (≥10,000nM)			
NE	X	NT	✓[a]
5-HT	X	X	✓[a]
DA	X	NT	NT
In Vivo Microdialysis			
Increases hypothalamic [5-HT] at 10mg/kg ip	↑214%	↑406%	↑2293%[a]
Attenuated by 8-OH-DPAT	✓	✓	X[b]
Attenuated by fluoxetine	N/A	N/A	✓[b]
Attenuated by sibutramine	N/A	N/A	✓[b]

a = dexfenfluramine, b = fenfluramine, NT = not tested, N/A = not applicable

DJH/BU4

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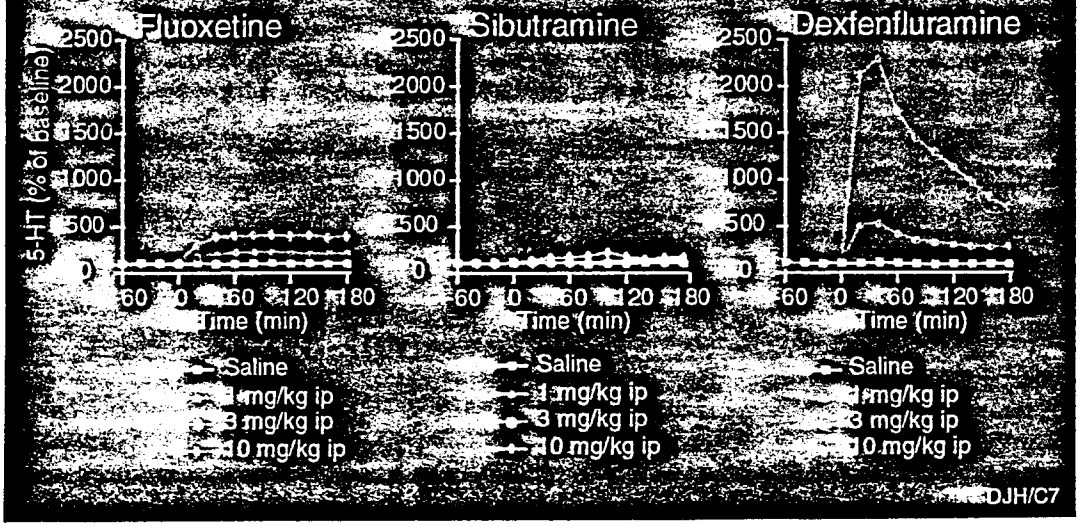
In Vivo Effects of Fluoxetine, Sibutramine and Dexfenfluramine on Extracellular 5-HT Levels in Rat Hypothalamus



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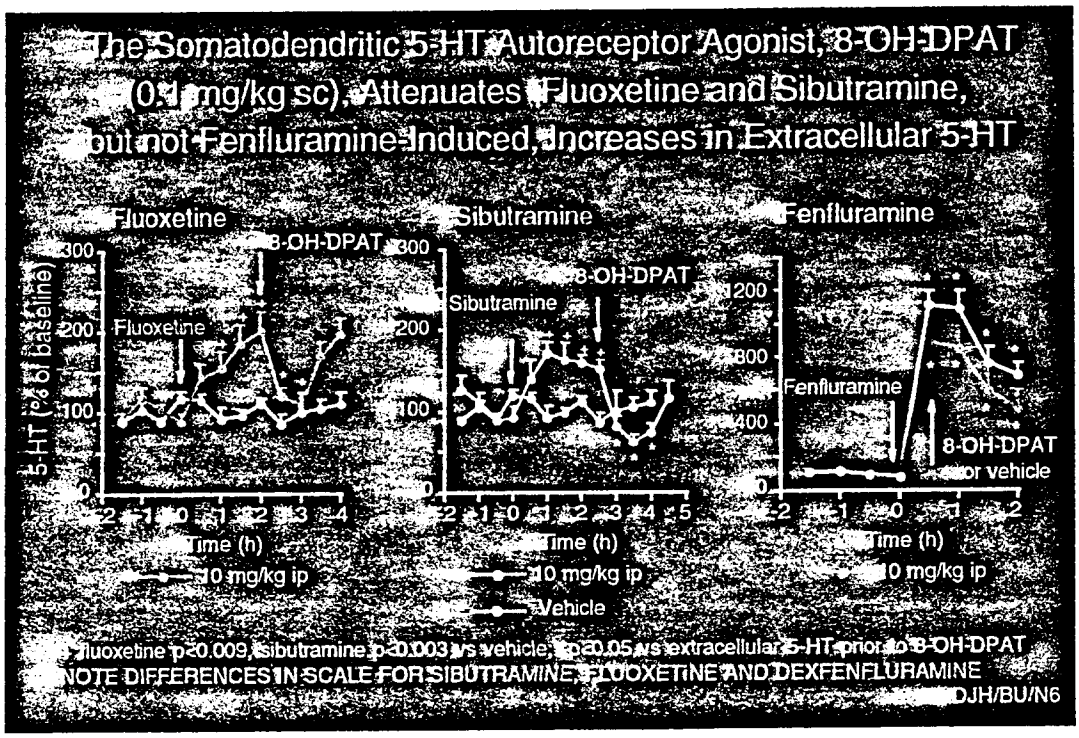
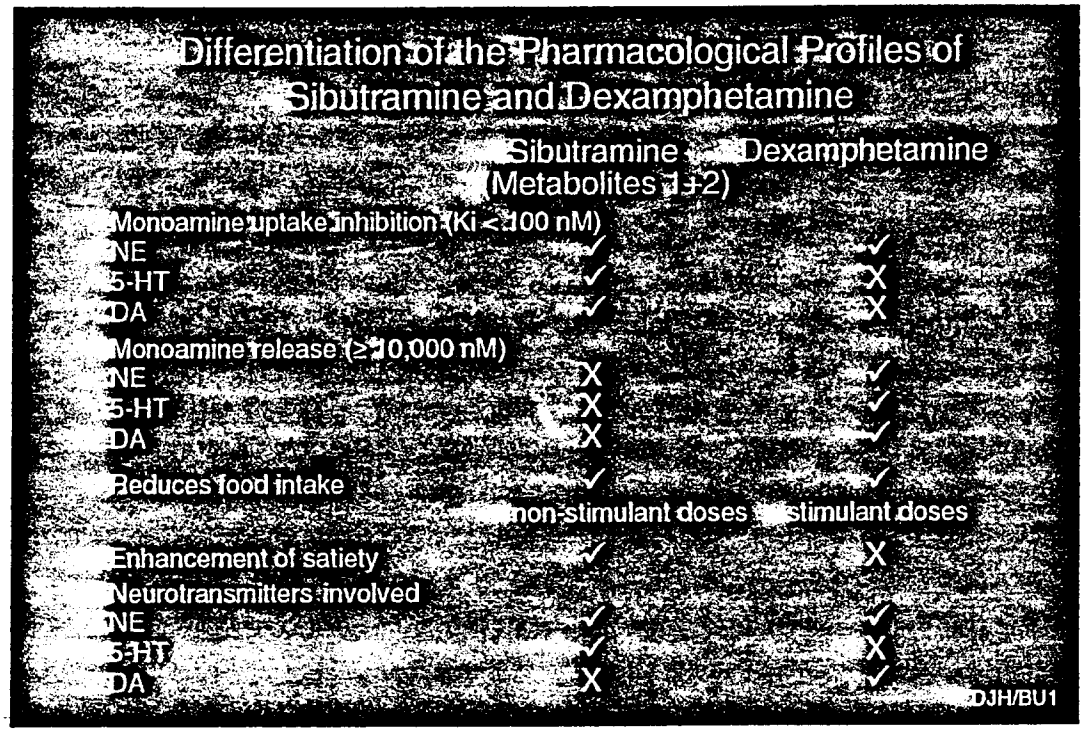
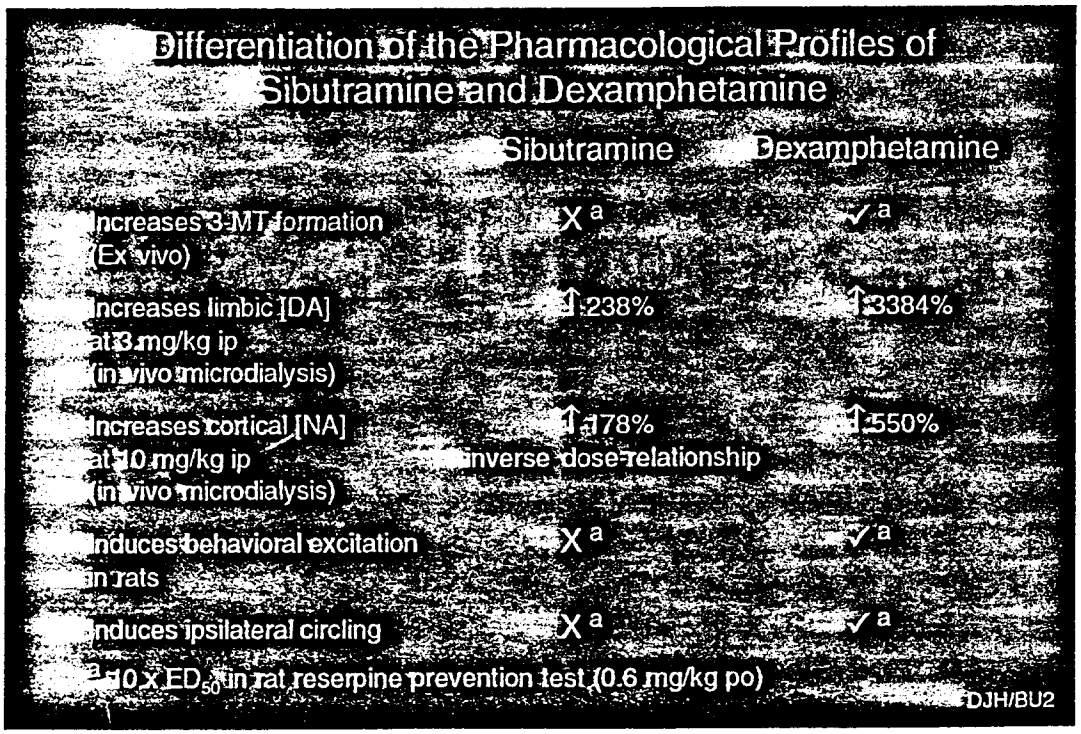
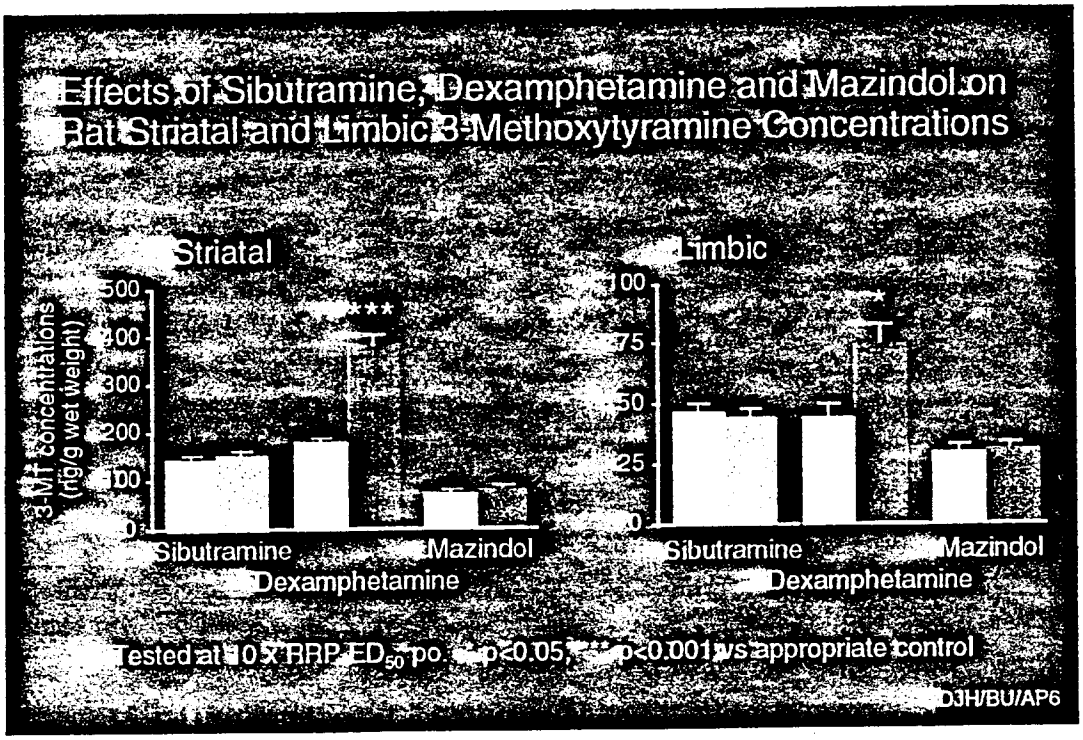
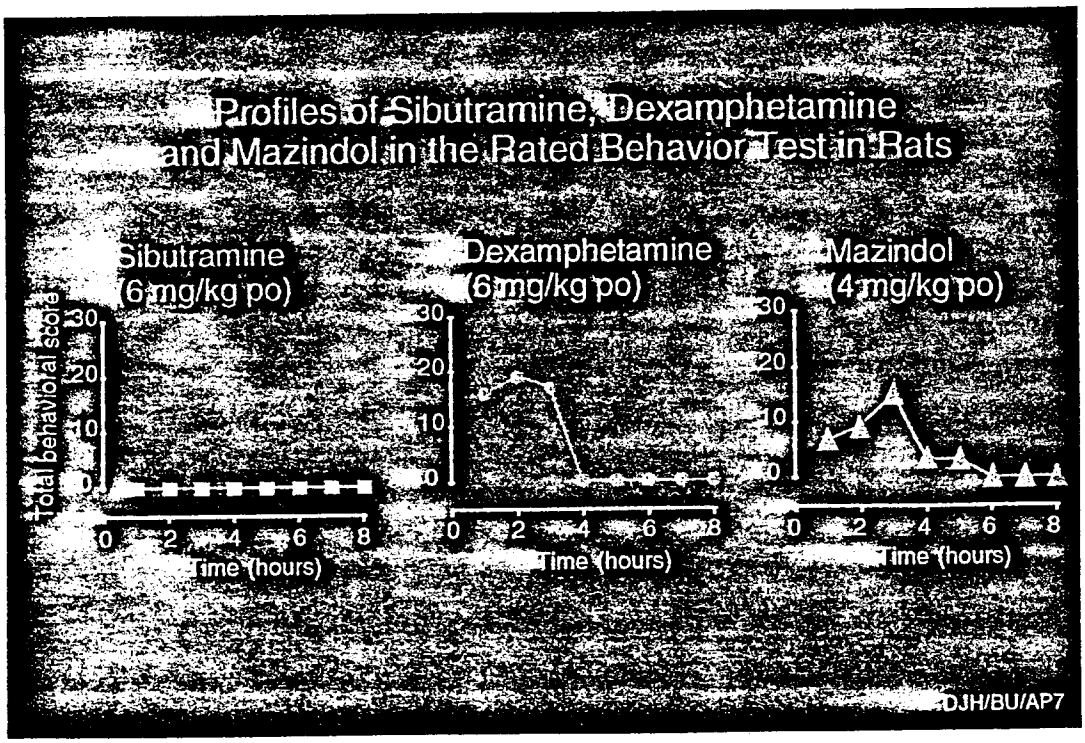


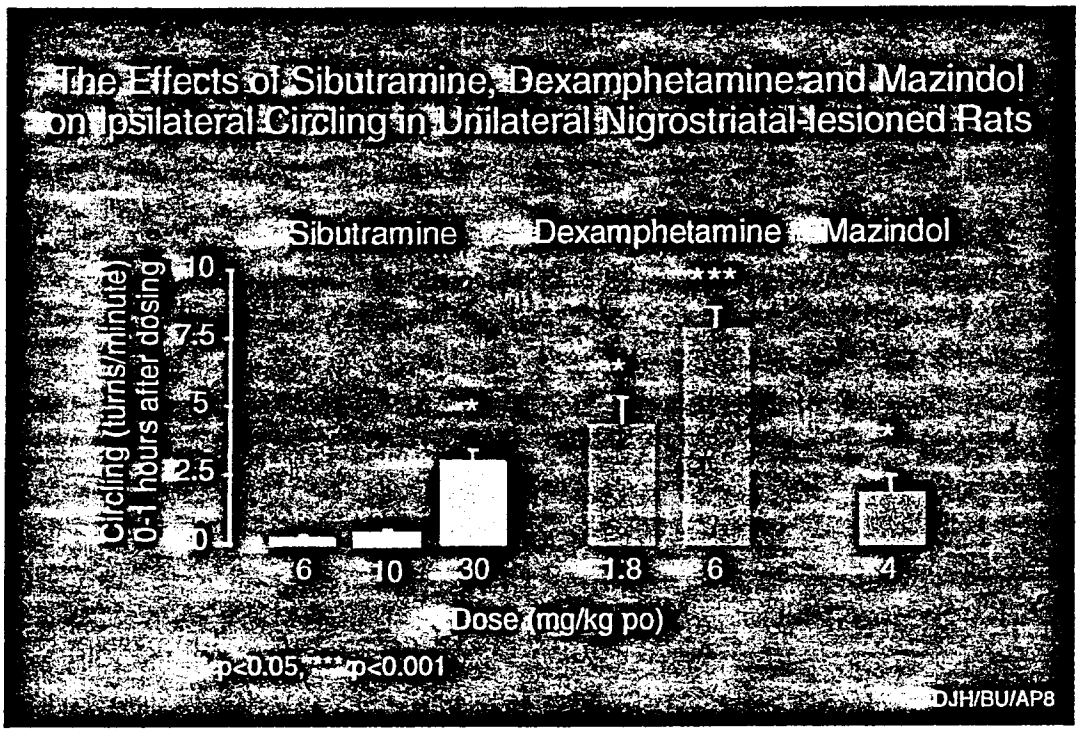








The Effects of Sibutramine, Dexamphetamine and Mazindol on Ipsilateral Circling in Unilateral Nigrostriatal-lesioned Rats



DJH/BU/AP8

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Profiles of Sibutramine and Various Reference Drugs on Rats Trained to Recognise Dexamphetamine

Drug	Dose(mg/kg ip)	Summary	Number of rats responding in each category: Amphetamine	Saline	No Preference	Invalid
Sibutramine.HCl	3.0	SAL	0/16	9/16	4/16	3/16
	5.0	DIS	0/6	0/6	0/6	6/6
Weight-modifiers with abuse potential						
Dexamphetamine	0.3	AMP	6/6	0/6	0/6	0/6
Methamphetamine	0.5	AMP	6/6	0/6	0/6	0/6
Mazindol	3.0	AMP	4/5	0/5	1/5	0/5
Stimulant drugs of abuse						
Amfonelic acid	10.0	AMP	4/4	0/4	0/4	0/4
Cocaine	10.0	AMP	6/9	1/9	1/9	1/9
Fencamfamine	3.0	AMP	5/5	0/5	0/5	0/5
Methylphenidate	3.0	AMP	6/6	0/6	0/6	0/6
Antidepressants without abuse potential						
Bupropion	30.0	AMP	5/7	0/7	0/7	2/7
Nomifensine	3.0	AMP	5/6	0/6	1/6	0/6
Desipramine	5.0	SAL	0/8	5/8	0/8	3/8
	10.0	DIS	0/5	0/5	0/5	5/5
Venlafaxine	10.0	SAL	0/5	5/5	0/5	0/5
	30.0	DIS	0/17	5/17	3/17	9/17

DJH/BU/AP10

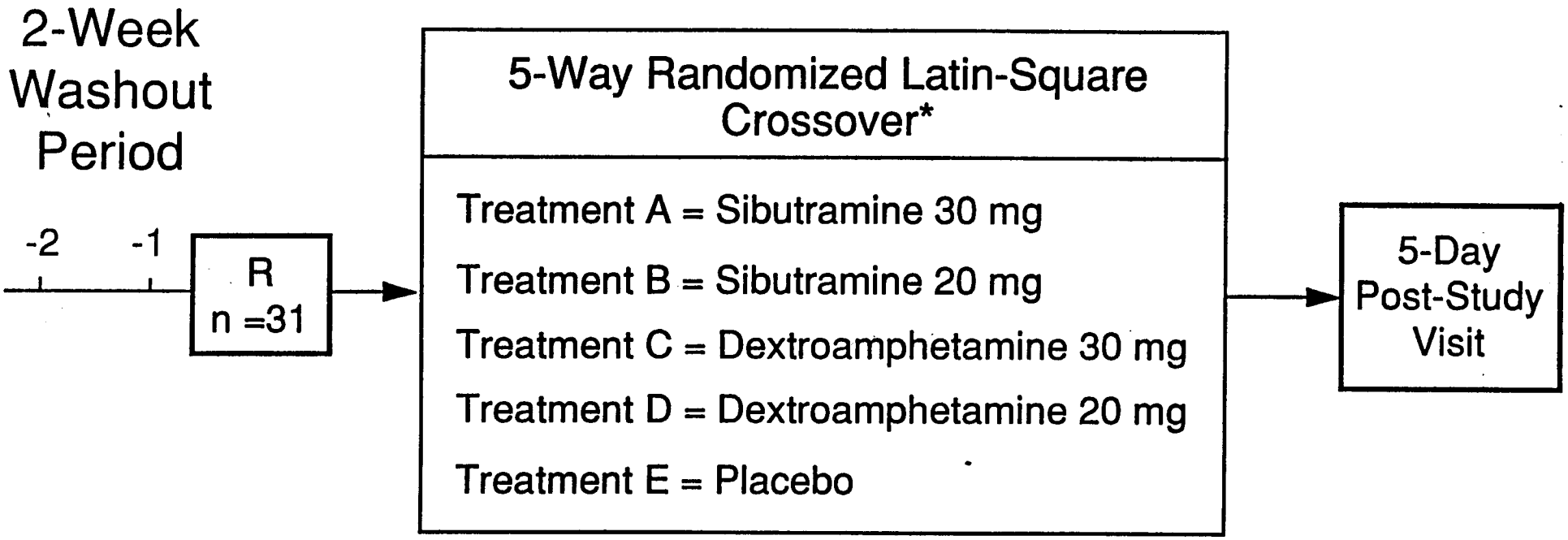
BPI 863—Abuse Comparison to Dextroamphetamine

Study Objective

To assess the potential abuse liability of sibutramine when compared to dextroamphetamine and placebo in recreational stimulant users

BPI 863—Abuse Comparison Dextroamphetamine

Study Design



* Each patient received each of the five treatments in random order with a minimum of 5 days washout between treatments

4237.09.06

BPI 863 - Abuse Comparison to Dextroamphetamine

Inclusion Criteria

- Males
- History of recreational stimulant use (at least 6 occasions)

Exclusion Criteria

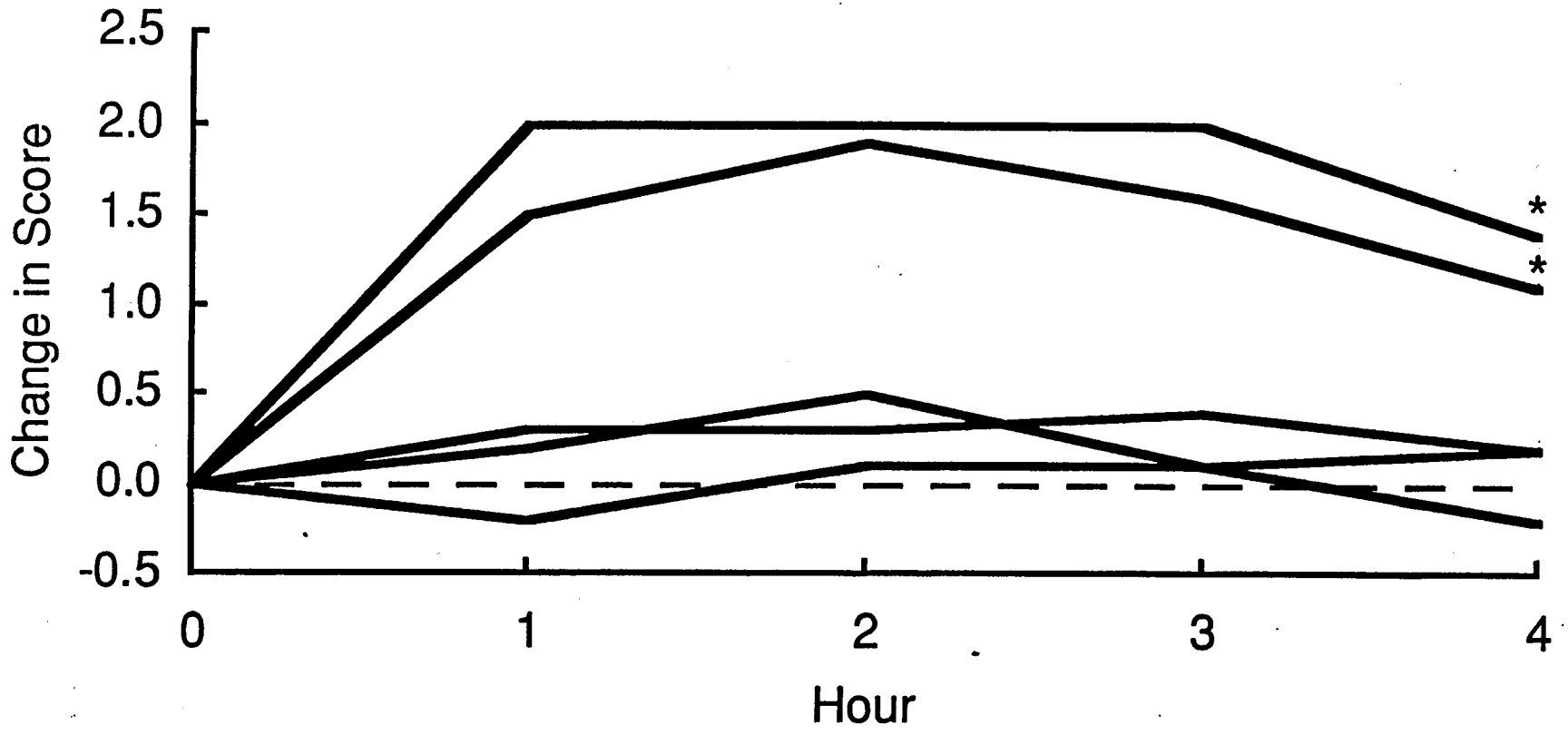
- Drug dependence within the previous year
- Use of psychoactive drugs within the previous 2 days

BPI 863—Major Outcomes Variables

- Addiction Research Center Inventory (ARCI)
  - Phenobarbital - Chlorpromazine - Alcohol group (Sedation)
  - Amphetamine group (Stimulation)
  - Morphine - Benzedrine group (Euphoria)
  - Benzedine group (Stimulation)
  - Lysergic Acid Diethylamine group (Hallucination)
- Enjoyment assessment
- Treatment identification
- Assessment of mental and physical "highs"
- Estimation of street value

BPI 863—Amphetamine Scale

Change from Baseline Score by Hour



—Placebo
—Sibutramine 20 mg
—Sibutramine 30 mg
—Amphetamine 20 mg
—Amphetamine 30 mg

* $p \leq 0.05$ vs placebo

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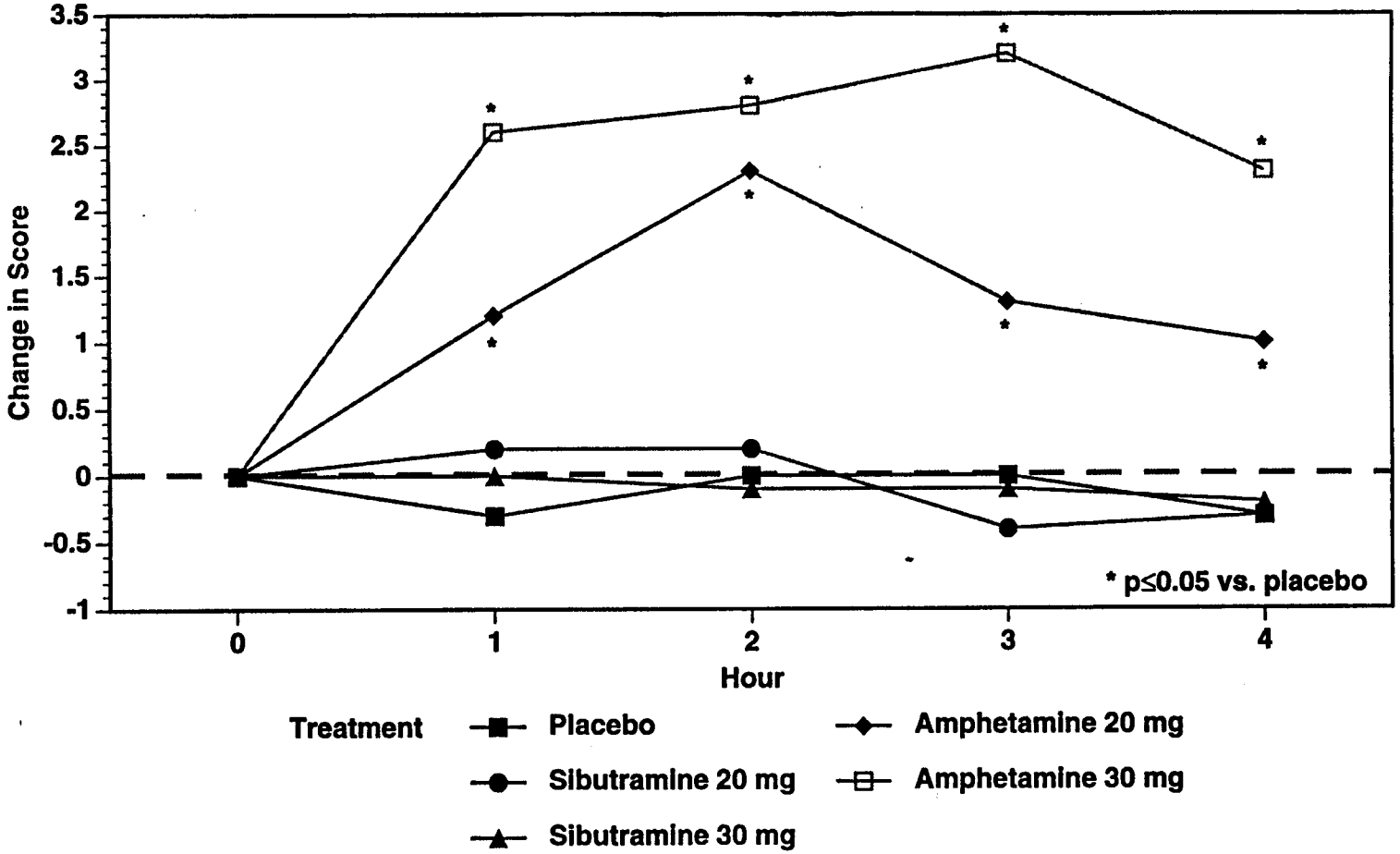
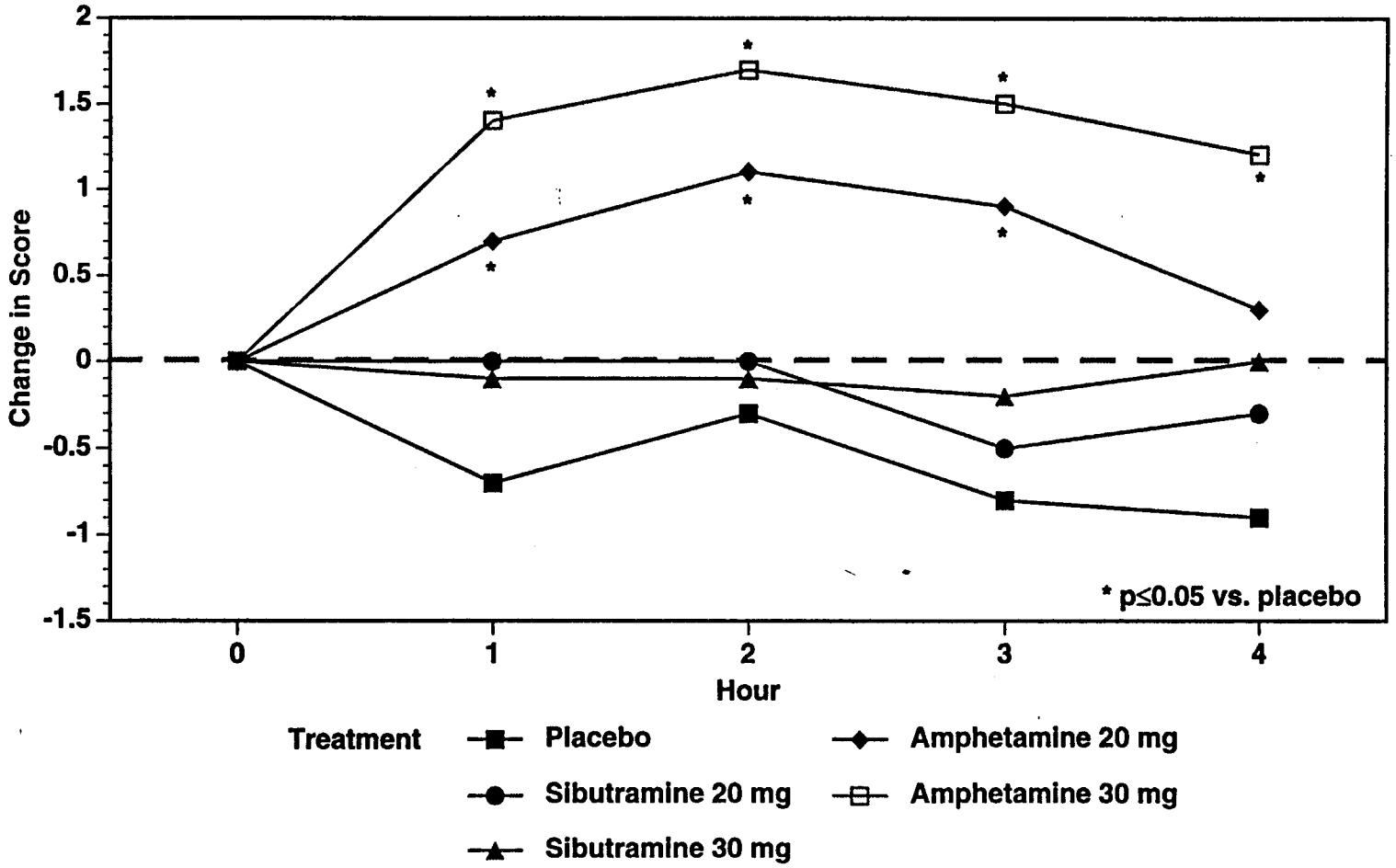
Sibutramine – Study BPI 863

Morphine-Benzedrine Scale
Change from Baseline Score by Hour



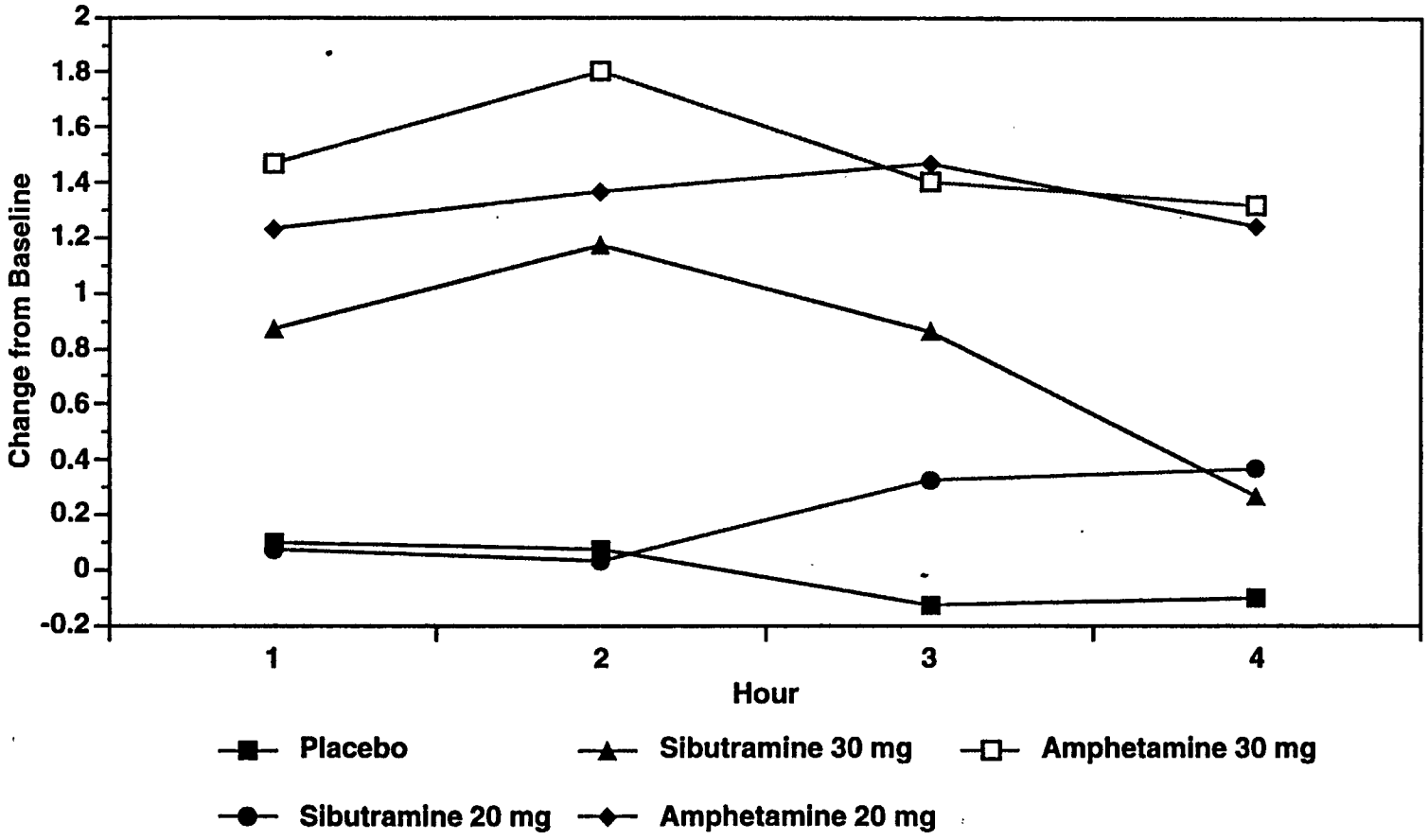
Sibutramine – Study BPI 863

Benzedrine Scale
Change from Baseline Score by Hour



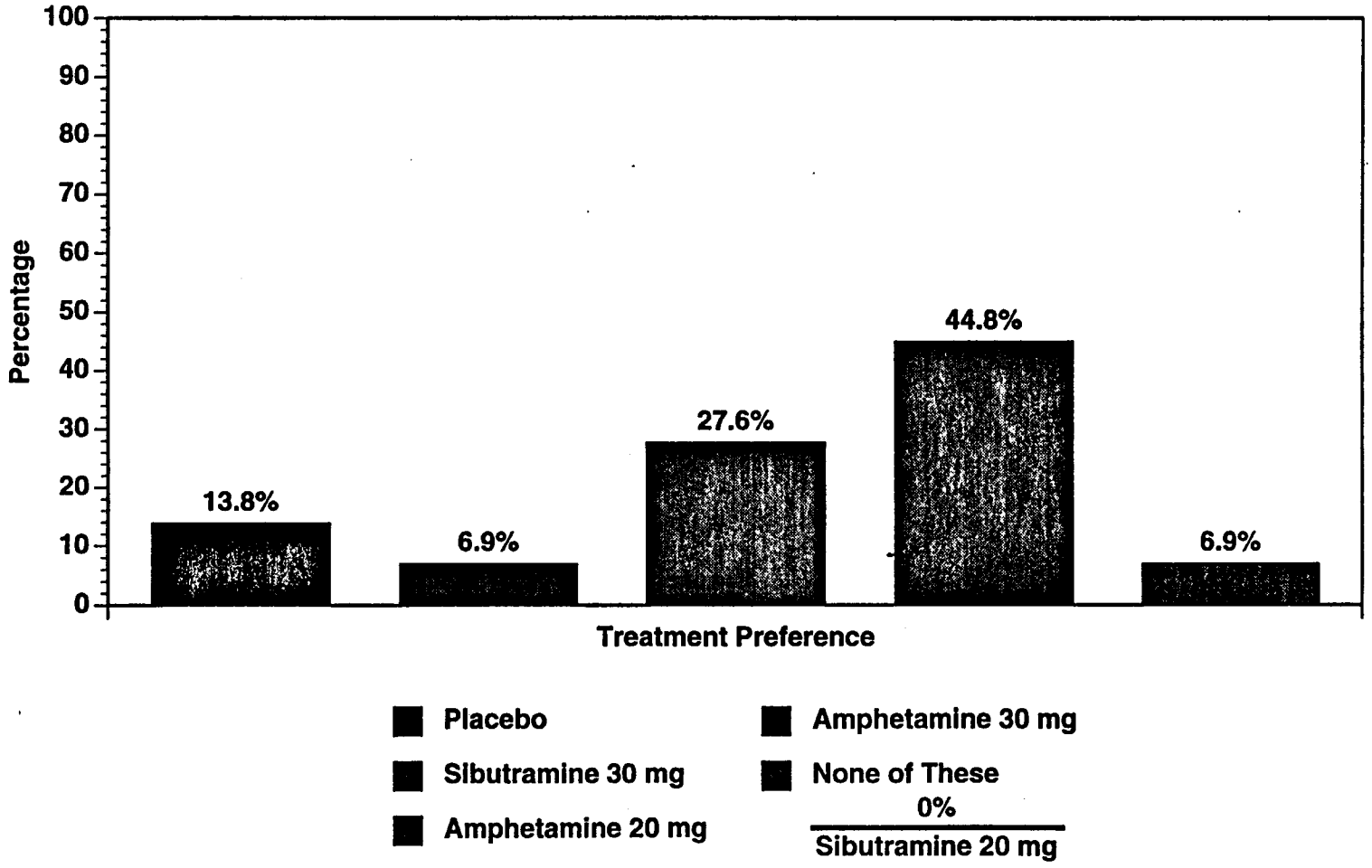
Sibutramine – Study BPI 863

Analysis of Change from Baseline for ARCI – Lysergic Acid Diethylamide Scale

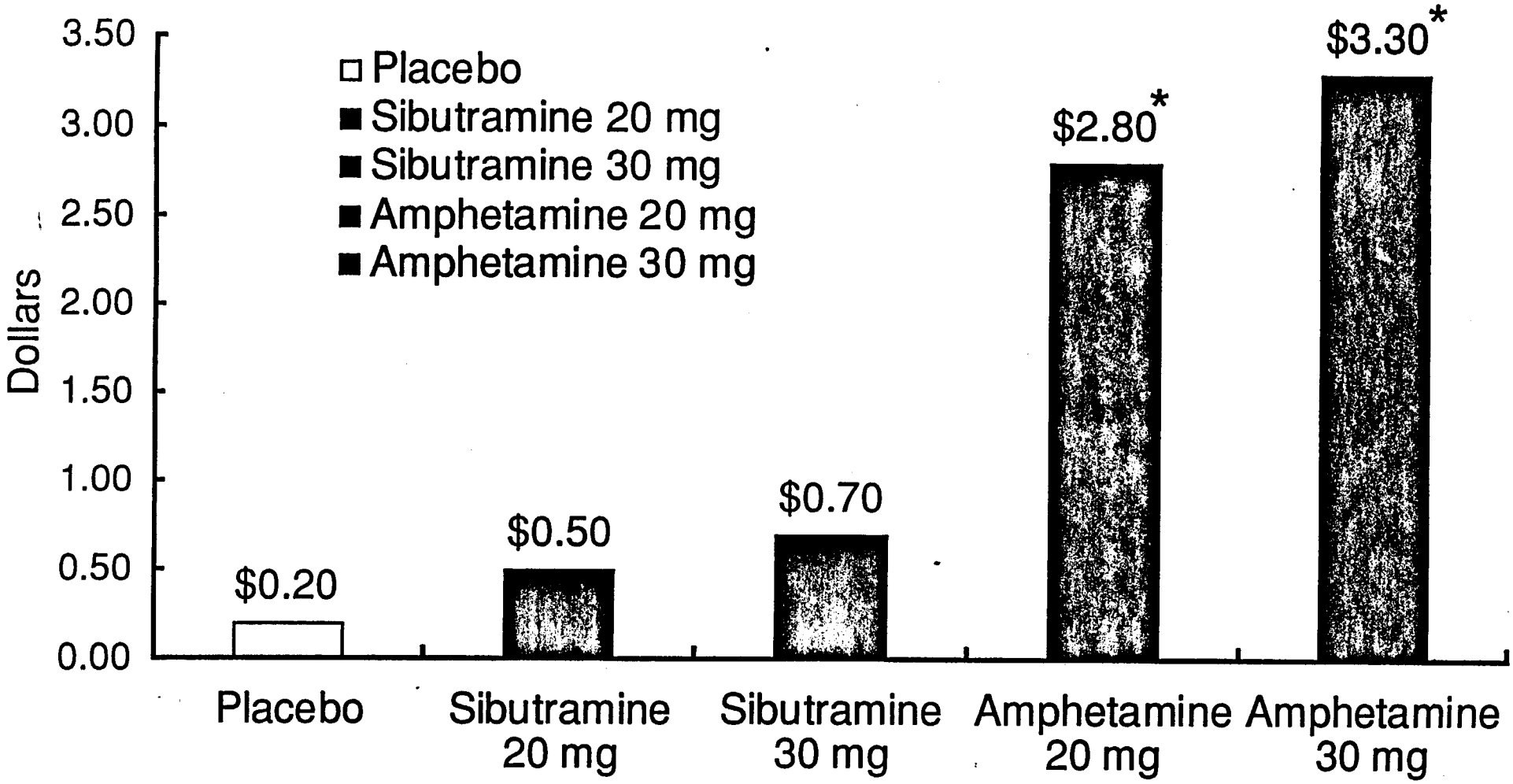


Sibutramine – Study BPI 863

Enjoyment Preference for a Given Treatment



BPI 863—Mean Street Value



* $p < 0.05$ vs placebo

4745.09.24

Sibutramine
Abuse Potential

- No withdrawal/abstinence symptoms
- No mood effects on withdrawal
- No drug seeking behavior
- Not euphoriant
- Not recognized as amphetamine-like

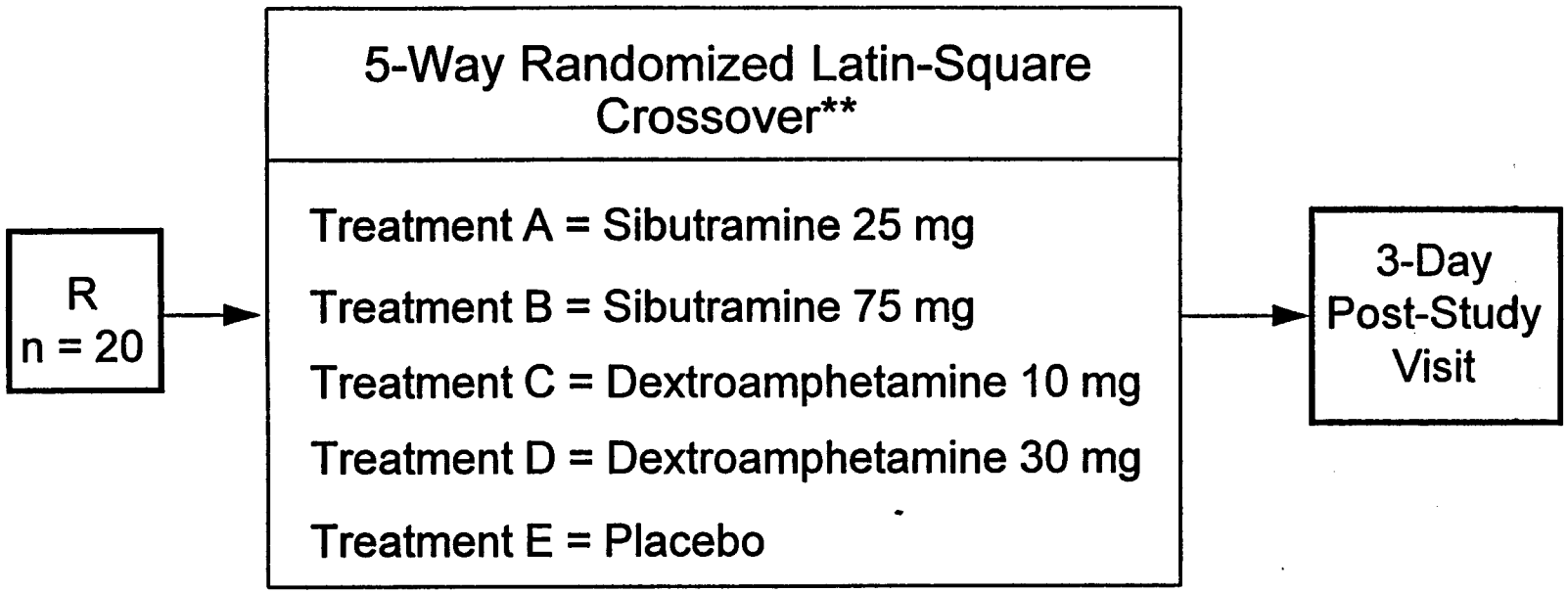
BPI 883—Abuse Comparison to Dextroamphetamine

Study Objective

To assess the potential abuse liability of sibutramine when compared to dextroamphetamine and placebo in diagnosed substance abusers

BPI 883—Abuse Comparison to Dextroamphetamine

Study Design *



* Inpatient study

** Each patient will receive each of the five treatments in random order with a minimum of 3 days washout between treatments

BPI 883 - Abuse Comparison to Dextroamphetamine

Inclusion Criteria

- Male or female

- History of psychoactive substance abuse, including stimulants
- Use of cocaine within the previous 30 days

Exclusion Criteria

- Use of psychoactive drugs within the previous 7 days
- Positive urine drug screen

BPI 883—Major Outcomes Variables

- Addiction Research Center Inventory (ARCI)
  - Pentobarbital - Chlorpromazine - Alcohol group (Sedation)
  - Amphetamine group (Stimulation)
  - Morphine - Benzedrine group (Euphoria)
  - Benzedine group (Stimulation)
  - Lysergic Acid Diethylamine group (Hallucination/Dysphoria)
- Enjoyment assessment
- Treatment identification
- Assessment of mental and physical "highs"
- Estimation of street value

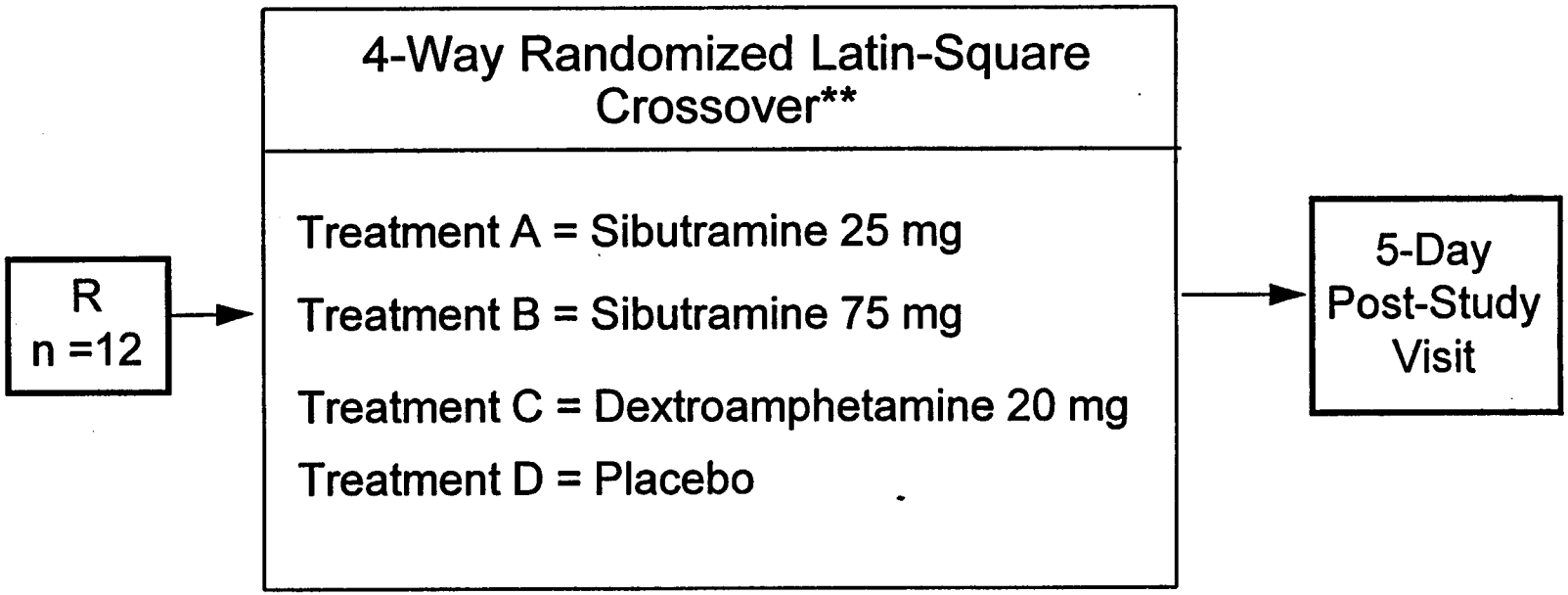
BPI 893—Abuse Comparison to Dextroamphetamine

Study Objective

To assess the potential abuse liability of sibutramine when compared to dextroamphetamine and placebo in recreational stimulant users

BPI 893—Abuse Comparison to Dextroamphetamine

Study Design*



* Inpatient/outpatient study

** Each patient will receive each of the four treatments in random order with a minimum of 5 days washout between treatments

4237.09

BPI 893 - Abuse Comparison to Dextroamphetamine

Inclusion Criteria

- Male or female
- History of recreational stimulant use (at least 6 occasions)

Exclusion Criteria

- Current or past drug dependence
- Use of psychoactive drugs within the previous 7 days
- Positive urine drug screen

BPI 893—Major Outcomes Variables

- Addiction Research Center Inventory (ARCI)
  - Pentobarbital - Chlorpromazine - Alcohol group (Sedation)
  - Amphetamine group (Stimulation)
  - Morphine - Benzedrine group (Euphoria)
  - Benzedine group (Stimulation)
  - Lysergic Acid Diethylamine group (Hallucination/Dysphoria)
- Profile of Mood States
- Assessment of mental and physical "highs" (VAS)
- Treatment identification
- Estimation of street value (reinforcing efficacy)

Table I. Drug-induced increases (+) and decreases (-) on ARCI scales.
Investigators' Estimates: — - -0 0 0+ + ++

Drug Condition	Ef	MBG	PCAG	LSD	SOW
Stimulants—amphetamine, cocaine	+	++	0	0*	0
Opiates—heroin, morphine, methadone	0	++	0*	0	0
Partial opiate agonists—pentazocine, nalbuphine	-	+	+	+	0
Marijuana	-0	++	0*	+	0
Barbiturates—pentobarbital, secobarbital	-0	+	++	0	0
Minor tranquilizers—diazepam	-0	-0	++	0	0
Alcohol	-	+	++	0	0
Major tranquilizers—chlorpromazine	-	0	++	0	0
Narcotic antagonists—nalorphine, cyclazocine	-	0	++	+	+
Hallucinogens—LSD	-	+	0	++	+
Others—scopolamine	—	0	++	+	+
Inactive—zomepirac, loperamide, bupropion		0	0	0	
Opiate withdrawal—morphine, heroin, methadone	-	-	++	+	+++
Alcohol withdrawal	—	-	++	+	++
[1]Simulated barbiturate withdrawal	—	-	++	++	+++
Simulated alcohol withdrawal	—	—	++	++	+++
Simulated opiate withdrawal	—	-	++	++	+++
Simulated pep pill come down	—	-	++	++	++
Simulated cocaine come down	—	-	++	++	++

Note: from Haertzen and Hicky 1987.
[1]Test results based upon retrospective reporting of subjective effects.
EF = Efficiency or BG (Benzedrine group variability)
MBG = Morphine-Benzedrine group
PCAG = Pentobarbital, chlorpromazine, and alcohol group
LSD = LSD group or drug correction
SOW = Strong opiate withdrawal