CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020632

STATISTICAL REVIEW(S)

AUG 8 1996

Statistical Review and Evaluation
(Carcinogenicity Review)

NDA: 20-632

APPLICANT: Knoll Pharmaceutical Company

NAME OF DRUG: MERIDIA™ (sibutramine hydrochloride monohydrate) Capsules

DOCUMENTS REVIEWED: Vol. 1.56 - 1.68 dated 31 January 1992.
Data on floppy diskettes supplied by the sponsor.

REVIEWING PHARMACOLOGIST: Mr. David H. Hertig

I. BACKGROUND

In this NDA submission, two animal carcinogenicity studies (MC0031 in mice and RC0078 in rats) were included. These two studies were conducted to investigate whether sibutramine affects tumor incidence in mice and rats when administered in the diet at some selected dose levels for up to 104 weeks.

II. THE MOUSE STUDY MC0031

IIa. Design

Male and female barrier-reared CD-1 mice were obtained from Charles River UK and were aged 28 ± 1 days at supply. Within four days after arrival, the mice were randomly allocated to treatment groups as described below.

Group	Treatment	Nominal Dosage mg/kg Daily	Number and Sex
A	Control 1	0	52 M, 52 F
B	Control 2	0	52 M, 52 F
C	Sibutramine	1.25	52 M, 52 F
D	Sibutramine	5	52 M, 52 F
E	Sibutramine	20	52 M, 52 F

Sibutramine was administered by incorporation in the diet at levels calculated to achieve the nominal dosages; these levels were altered as required to maintain the nominal dosages. Control animals received untreated powdered diet.

The first day of treatment was designated "day 0"; treatment continued for 95 weeks for males, and for 104 weeks for females.

The general condition and behavior of the animals was observed daily throughout the study, detailed findings were recorded weekly. Commencing week 27, the location, appearance and dimensions of all palpable tissue-masses were recorded weekly.

The bodyweight of each mouse was recorded weekly, commencing one week before the start of the treatment.

Food consumption for each cage of mice was recorded weekly, commencing one week before the start of the treatment. Each cage contained four mice of the same sex and dosage group.

Surviving male mice were killed after 95 weeks' treatment, when survival in one control group and in the group at 20 mg/kg approached 25%. Surviving female mice were killed after 104 weeks' treatment. All animals were killed by carbon dioxide inhalation. All animals were dissected and examined macroscopically.

IIb. Sponsor's Analysis and Reviewer's Comments

Sponsor's analyses were performed using the combined data from the control groups, except for terminal myelograms where only one control group was examined. In addition, for tumor analysis, comparisons were also made against the individual control groups by the sponsor but data were not presented.

Survival Analysis: Survival analysis was carried out using the logrank test procedure of the SAS system (LIFETEST). Body weight and food consumption were analyzed over 26-week periods up to week 78; beyond this point, intercurrent mortality makes interpretation difficult. For each animal, the average bodyweight over the period was calculated and, for each cage of mice, the average food consumption was calculated. Bodyweights were analyzed with week 0 bodyweights as a covariate. Food consumption was analyzed using analysis of variance.

Terminal haematology and myelograms were analyzed using Williams' test or, for nonparametric data, Shirley's test or the Wilcoxon rank sum test, with the probabilities adjusted according to Sidak(1967).

Comparisons of treatment groups against controls were performed at the 5% and 1% levels of significance.

Sponsor's results are contained in Appendix A (see sponsor's Table 3 in vol. 1.57, Figure 1 and Figure 2 in vol. 1.58). The sponsor stated that the analysis of survival throughout the study revealed no statistically significant differences between treated and control groups.

Tumor Analysis: Tumor incidence was analyzed according to the methods of Peto et al.(1980). Where the observed tumor incidence was small, p-values were also calculated for the exact distribution because of the possible inappropriateness of the normal approximation. The test for trend was performed at the one-sided 5% level for an increasing trend, and at the one-sided 5% for a decreasing trend.

Sponsor's results are contained in Tables 14 to 19 in Vol. 1.57 - 1.58, appendix 9 and 10 in vol. 1.59 - 1.61. The sponsor stated that sibutramine administered up to the maximum tolerated dose of 20 mg/kg daily to mice for up to two years was not tumorigenic.

Reviewer's Comments: The sponsor stated that (on page 0011, vol 1.57) analysis of survival throughout the study revealed no statistically significant differences. Though, the survival data (sponsor's Table 3 on pp. 0037 and 0038 in vol. 1.57) and the figures for Kaplan-Meier survival functions (sponsor's Figures 1 through 3 on pp. 0157 through 0159 in vol. 1.58) are provided, none of the test statistics and their p-values are reported.

IIc. Reviewer's Analysis

This reviewer independently performed analyses on the survival and the tumor data provided by the sponsor on a floppy diskette. For survival data analysis, methods described in the paper by Cox(1972) and of Gehan (1965) were used. The tumor data were analyzed using the methods described in the paper of Peto et al. (1980) and the method of exact permutation trend test developed by the Division of Biometrics. Since both of the control groups were treated in a similar way and the survival test did not show any statistically significant difference between them, they were combined to increase the power of the test. These results are included in the Appendix.

Survival Analysis: The purpose of the survival analysis was two-fold: (1) To examine the differences in the survival distributions among different dose groups (referred to as the test of homogeneity), and (2) To determine the significance of positive linear trend in proportions of deaths with respect to dose levels (called the test of linear trend).

For the theoretical background of these analyses, please refer to Lin et al.(1994) and Thomas et al. (1976).

The following results for survival analysis are contained in the Appendix:

- Tables 1a and 1b summarize the intercurrent mortality data for the male and female mice respectively. No trend or pattern is evident for female mice. For male mice, there is an increased mortality in the high dose group when compared to the other doses.

- Figures 1a and 1b depict the Kaplan-Meier survival distributions for males and females respectively. For female mice, the curves for different dose groups intertwine each other suggesting that there is no significant difference between their survival patterns. But for male mice, there is an increased mortality in the high dose group when compared to the other doses.

- Table 2 describes the p-values of the test of homogeneity and of positive linear trends for males and females using the Cox test and the generalized Kruskal-Wallis test. It is well known that the Kruskal-Wallis test gives more weight to early differences in death rates between groups than the Cox test. None of these tests are significant except the trend test for males that shows a marginal significant result which confirms the graphical findings of figures 1a and 1b.

Tumor Analysis: The tumor data analysis was performed to detect, for a selected tumor type in a selected organ/tissue, the significance of positive linear trend in the proportions of discovered tumors with respect to dose levels. The tumor type were classified as fatal and non-fatal.

Following Peto et al. (1980), this reviewer applied the death-rate method and the prevalence method to fatal and non-fatal tumors respectively. For tumors that caused deaths for some, but not all animals, a combined analysis was performed. The exact permutation trend test was used to calculate the p-values of all trend tests, except when the tumor was found in both categories, in which case the continuity corrected normal test was used. The scores used were 0, 1.25, 5.0 and 20.0 for control, low, medium and high dose groups respectively. This was done in order to reflect the actual dose levels of 0, 1.25, 5.0 and 20.0 mg/kg of sibutramine. The time-intervals used were 0-52, 53-78, 79-93, 94 and beyond for males, and 0-52, 53-78, 79-93, 94-103, 104 and beyond for females.

The following results for tumor analysis are contained in the Appendix:

- Tables 3a and 3b describe the p-values for the test of trend based on the tumor data. None of the p-values are significant for males. But, for females, a significant linear dose tumor-trend was indicated for haemangioma [B] for uterus. The statistical information is given below.

Female Mice			Tumor Rate				Trend Test
Organ	Tumor Name	Tumor Type	Control	Low	Medium	High	p-value
UTERUS	HAEMANGIOMA [B]	M	N=104 0	N=52 0	N=52 0	N=52 2	0.0027

A pairwise comparison of High Dose versus Control yielded a significant p-value of 0.0205.

III. THE RAT STUDY RC0078

IIIa. Design

Male and female barrier-reared Sprague-Dawley CD rats were obtained from Charles River Portage, Portage, Michigan, USA and were aged 28 ± 1 days old at supply. Within six days after arrival, the rats were randomly allocated to treatment groups as described below, such that the mean bodyweight values for each group were comparable within each sex.

Group	Treatment	Nominal Dosage mg/kg Daily	Number and Sex
A	Control 1	0	52 M, 52 F
B	Control 2	0	52 M, 52 F
C	Sibutramine	1	52 M, 52 F
D	Sibutramine	3	52 M, 52 F
E	Sibutramine	9	52 M, 52 F

Sibutramine was administered by incorporation in the diet at levels calculated to achieve the nominal dosages; these levels were altered as required to maintain the nominal dosages. Control animals received untreated diet.

The first day of treatment was designated "day 0"; treatment continued for 104 weeks.

The general condition and behavior of the animals was observed daily throughout the study, detailed findings were recorded weekly. Commencing week 27, the location, appearance and dimensions of all palpable tissue-masses were recorded weekly.

The bodyweight of each rat was recorded weekly, commencing one week before the start of the treatment.

Food consumption for each cage of rats was recorded weekly, commencing one week before the start of the treatment. Each cage contained four rats of the same sex and dosage group.

IIIb. Sponsor's Analysis and Reviewer's Comments

Sponsor's analyses were performed, where appropriate, using the combined data from the control groups.

Survival Analysis: Survival analysis was carried out using the logrank test procedure of the SAS system (LIFETEST). Body weight and food consumption were analyzed over 26-week periods up to week 78; beyond this point, intercurrent mortality makes interpretation difficult. For each animal, the average bodyweight over the

period was calculated and, for each cage of rats, the average food consumption was calculated. Bodyweights were analyzed with week 0 bodyweights as covariate. Food consumption was analyzed using analysis of variance.

Terminal hematology and myelograms were analyzed using Williams' test or, for nonparametric data, Shirley's test or the Wilcoxon rank sum test, with the probabilities adjusted according to Sidak(1967).

Comparisons of treatment groups against controls were performed at the 5% and 1% levels of significance.

Sponsor's results are contained in Appendix B (see sponsor's Table 3 in vol. 1.63, Figure 1 and Figure 2 in vol. 1.64). The sponsor stated that the analysis of survival throughout the study revealed no statistically significant differences between treated and control groups.

Tumor Analysis: Tumor incidence was analyzed according to the methods of Peto et al.(1980). Where the observed tumor incidence was small, p-values were also calculated for the exact distribution because of the possible inappropriateness of the normal approximation. The test for trend was performed at the one-sided 5% level for an increasing trend, and at the one-sided 5% for a decreasing trend.

Sponsor's results are contained in Tables 14 to 19 in Vol. 1.63 - 1.64, appendix 9 and 10 in vol. 1.65 - 1.67. The sponsor stated that the administration of sibutramine in the diet at 1, 3 or 9 mg/kg to rats for two years resulted in a small increase in the incidence of benign interstitial-cell tumors of the testes and a decrease in the incidence of mammary fibroadenomas in males. The highest dose used in the study, 9 mg/kg daily, was a maximum tolerated dose by virtue of the reduced bodyweight in both sexes.

Reviewer's Comments: The sponsor stated that (on page 0012, vol 1.63) statistical analysis of survival throughout the study revealed no statistically significant differences between treated and control groups. Though, the survival data (sponsor's Table 3 on pp. 0037 and 0038 in vol. 1.63) and the figures for Kaplan-Meier survival functions (sponsor's Figures 1 through 3 on pp. 0001 through 0003 in vol. 1.64) are provided, none of the test statistics and their p-values are reported.

IIIc. Reviewer's Analysis

This reviewer independently performed analyses on the survival and the tumor data provided by the sponsor on a floppy diskette. For survival data analysis, methods described in the paper by Cox(1972) and of Gehan (1965) were used. The tumor data were analyzed using the methods described in the paper of Peto et al. (1980) and the method of exact permutation trend test developed by the Division of Biometrics. Since both of the control groups were treated in a similar way and the survival test did not

show any statistically significant difference between them, they were combined to increase the power of the test. These results are included in the Appendix.

Survival Analysis: The purpose of the survival analysis was two-fold: (1) To examine the differences in the survival distributions among different dose groups (referred to as the test of homogeneity), and (2) To determine the significance of positive linear trend in proportions of deaths with respect to dose levels (called the test of linear trend).

For the theoretical background of these analyses, please refer to Lin et al.(1994) and Thomas et al. (1976).

The following results for survival analysis are contained in the Appendix:

- Tables 4a and 4b summarize the intercurrent mortality data for the male and female rats respectively. No trend or pattern is evident.

- Figures 2a and 2b depict the Kaplan-Meier survival distributions for males and females respectively. The curves for different dose groups intertwine each other suggesting that there is no significant difference between their survival patterns.

- Table 5 describes the p-values of the test of homogeneity and of positive linear trends for males and females using the Cox test and the generalized Kruskal-Wallis test. It is well known that the Kruskal-Wallis test gives more weight to early differences in death rates between groups than the Cox test. None of these tests are significant, which confirms the graphical findings of figures 2a and 2b.

Tumor Analysis: The tumor data analysis was performed to detect, for a selected tumor type in a selected organ/tissue, the significance of positive linear trend in the proportions of discovered tumors with respect to dose levels. The tumor type were classified as fatal and non-fatal.

According to Peto et al[3], this reviewer applied the death-rate method and the prevalence method to fatal and non-fatal tumors respectively. For tumors that caused deaths for some, but not all animals, a combined analysis was performed. The exact permutation trend test was used to calculate the p-values of all trend tests, except when the tumor was found in both categories, in which case the continuity corrected normal test was used. The scores used were 0, 1, 3 and 9 for control, low, medium and high dose groups respectively. This was done in order to reflect the actual dose levels of 0, 1, 3 and 9 mg/kg of sibutramine. The time-intervals used were 0-52, 53-78, 79-93, 94-103, 104 and beyond.

The following results for tumor analysis are contained in the Appendix:

- Tables 6a and 6b describe the p-values for the test of trend based on the tumor data. None of the p-values are significant for females. But, for males, a significant linear dose tumor-trend was indicated for interstitial-cell tumor[B] for testis. The statistical information is given below.

Male Rat			Tumor Rate				Trend Test
Organ	Tumor Name	Tumor Type	Control	Low	Medium	High	p-value
TESTIS	INTERSTITIAL-CELL TUMOR [B]	S	N=104 1	N=52 5	N=52 6	N=52 6	0.0153

Pairwise comparisons yielded the following significant p-values:
High Dose versus Control= 0.0045, Medium Dose versus Control=0.0070, Low Dose versus Control=0.0180.

IV. SUMMARY

Mouse Study (MC0031): The results of the statistical tests did not show any statistically significant (at 0.05 level) positive linear trend or increment in mortality in the treated groups in either sex except for males. For males, the trend test shows a marginally significant result indicating that there is an increased mortality in the high dose group when compared to the other doses.

The positive linear trend in benign haemangioma in uterus in female mice is considered to be statistically significant.

Rat Study (RC0078): The results of the statistical tests did not show any statistically significant (at 0.05 level) positive linear trend or increment in mortality in the treated groups in either sex.

The positive linear trend in benign interstitial-cell tumor in testis in male rats is considered to be statistically significant.

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Mathematical Statistician (Biomed)

Concur: Mr. Marticello

Dr. Lin

cc: Archival NDA 20-632
HFD-510/Hertig, CSO, Division File
HFD-715/Taneja, Marticello, Lin, Nevius, Division File, Chron.

APPENDIX

(Combined Controls)

Table 1a

Intercurrent Mortality Rates

Animal Type: MOUSE

Sex: MALE

	Dose											
	Ctrl			Low			Med			High		
	No. Died	No. Risk	Cumu Pct. Died	No. Died	No. Risk	Cumu Pct. Died	No. Died	No. Risk	Cumu Pct. Died	No. Died	No. Risk	Cumu Pct. Died
Time(wks)												
0-52									13.5			
53-78									26.9			
79-93									65.4			
FNL KILL									34.6			

Source: Knoll Pharmaceutical Company (Combined Controls)

Table 1b

Intercurrent Mortality Rates

Animal Type: MOUSE

Sex: FEMALE

	Dose											
	Ctrl			Low			Med			High		
	No. Died	No. Risk	Cumu Pct. Died	No. Died	No. Risk	Cumu Pct. Died	No. Died	No. Risk	Cumu Pct. Died	No. Died	No. Risk	Cumu Pct. Died
Time(wks)												
0-52									1.9			
53-78									25.0			
79-93									40.4			
94-103									51.9			
FNL KILL									48.1			

Source: Knoll Pharmaceutical Company (Combined Controls)

Table 3a

Test of Trend Based on the Tumor Data

Animal Type: MOUSE

Sex: MALE

Organ Name	Tumor Name	Tumor Type	Exact p	Asymp p	#Incid /Ctrls	Dose 1.25	Dose 5.0	Dose 20.0
ADRENAL	Cortical ADENOMA [B]	S-	0.8739	(0.8557)				
ADRENAL	Cortical CARCINOMA [M]	S-	1.0000	(0.7637)				
ADRENAL	Uni-lateral PHAEOCHROMOCY	S-	0.3214	(0.0868)				
LUNG	ADENOCARCINOMA [M]	M-	(0.7536)	0.7628				
LUNG	ADENOMA [B]	M-	(0.2203)	0.2215				
LUNG	ADENOMATA [B]	M-	(0.7347)	0.7301				
LUNG	Multifocal ADENOCARCINOMA	M-	(0.4405)	0.6383				
LYMPH NODE	HAEMANGIOMA [B]	S-	0.3561	(0.1934)				
PANCREAS	Small islet-cell ADENOMA	S-	1.0000	(0.7637)				
SEMINAL VESICLE	Large SQUAMOUS-CELL CARCI	S-	0.1684	(0.0187)				
SEMINAL VESICLE	Papillary ADENOMA [B]	S-	1.0000	(0.7637)				
SKIN	FIBROMA [B]	S-	1.0000	(0.8343)				
SKIN	Multifocal SARCOMA/FIBROS	S-	0.0815	(0.0563)				
SKIN	SARCOMA/FIBROSARCOMA/MYXO	M-	(0.9087)	0.9028				
SKIN	SQUAMOUS-CELL CARCINOMA [	S-	1.0000	(0.7715)				
SKIN	SQUAMOUS-CELL PAPILLOMA [	S-	0.6105	(0.7065)				
SKIN	Well differentiated sebac	S-	0.4390	(0.5444)				

Note: Tumor Type=M indicates that the tumor is fatal to some but not all animals. Tumor Type=S indicates that the tumor is either fatal or non-fatal to all animals.

An '+' indicates a significant linear dose-tumor trend.
A '-' indicates a non-significant linear dose-tumor trend.

Source: Knoll Pharmaceutical Company (Combined Controls)

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Table 3a (Continued)

Test of Trend Based on the Tumor Data

Animal Type: MOUSE

Sex: MALE

SPLEEN	HAEMANGIOSARCOMA [M]	M-	(0.2158)	0.1813
GALLBLADDER	PAPILLOMA [B]	S-	0.3307	(0.1783)
STOMACH	Forestomach- PAPILLOMA [B	S-	0.4187	(0.4749)
STOMACH	Metastasizing SQUAMOUS-CE	S-	0.6000	(0.7168)
STOMACH	Secretory- ADENOCARCINOMA	S-	1.0000 –	(0.9928)
TESTIS	Interstitial-cell ADENOMA	S-	0.2420	(0.2147)
TESTIS	Metastasizing SEMINOMA/DY	S-	0.6105	(0.7065)
TESTIS	Stromal SARCOMA [M]	S-	0.3347	(0.1707)
TESTIS	Uni-lateral HAEMANGIOMA [	S-	0.6105	(0.7065)
THYMUS	LYMPHOSARCOMA [M]	M-	(0.7369)	0.7812
THYROID	Small follicular ADENOMA	S-	1.0000	(0.7637)
URINARY BLADDER	Submucosal HAEMANGIOSARCO	S-	1.0000	(0.7823)
URINARY BLADDER	Transitional-cell PAPILLO	S-	1.0000	(0.7823)
INTESTINE- DUODENUM	Well differentiated ADENO	S-	0.1870	(0.0253)
HAEMOPOIETIC TISSUE	Metastasizing LYMPHOSARCO	M-	(0.8287)	0.8328
HAEMOPOIETIC TISSUE	Metastasizing histiocytic	S-	0.8249	(0.7975)
HAEMOPOIETIC TISSUE	Myeloid LEUKAEMIA [M]	M-	(0.2088)	0.2138
HAEMOPOIETIC TISSUE	Myelomonocytic LEUKAEMIA	M-	(0.1238)	0.0923
INTESTINE- ILEUM	ADENOCARCINOMA [M]	M-	(0.4300)	0.6282
INTESTINE- CAECUM	Plasmacytic LYMPHOSARCOMA	S-	0.1684	(0.0187)

Note: Tumor Type=M indicates that the tumor is fatal to some but not all animals. Tumor Type=S indicates that the tumor is either fatal or non-fatal to all animals.

An '+' indicates a significant linear dose-tumor trend.
A '-' indicates a non-significant linear dose-tumor trend.

Source: Knoll Pharmaceutical Company (Combined Controls)

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Table 3a (Continued)

Test of Trend Based on the Tumor Data

Animal Type: MOUSE

Sex: MALE

KIDNEY	ADENOCARCINOMA [M]	S-	1.0000	(0.8343)
LACRIMAL (HARDERIAN)	ADENOCARCINOMA [M]	S-	0.6105	(0.7065)
LACRIMAL (HARDERIAN)	ADENOMA [B]	S-	0.9686	(0.9350)
LACRIMAL (HARDERIAN)	ADENOMATA [B]	S-	1.0000	(0.7637)
LIVER	HAEMANGIOSARCOMA [M]	M-	(1.0000)	0.8858
LIVER	Hepatocellular ADENOMA [B	M-	(0.3288)	0.3383
LIVER	Hepatocellular CARCINOMA	M-	(0.3073)	0.3136
LIVER	Multifocal hepatocellular	M-	(0.9910)	0.9562
LIVER	Two hepatocellular ADENOM	S-	0.6201	(0.7227)

Note: Tumor Type=M indicates that the tumor is fatal to some but not all animals. Tumor Type=S indicates that the tumor is either fatal or non-fatal to all animals.

An '+' indicates a significant linear dose-tumor trend.
A '-' indicates a non-significant linear dose-tumor trend.

Source: Knoll Pharmaceutical Company (Combined Controls)

Table 3b

Test of Trend Based on the Tumor Data

Animal Type: MOUSE

Sex: FEMALE

Organ Name	Tumor Name	Tumor Type	Exact p	Asymp p	#Incid /Ctrls	Dose 1.25	Dose 5.0	Dose 20.0
ADRENAL	Cortical ADENOMA [B]	S-	0.0722	(0.0369)				
LUNG	ADENOCARCINOMA [M]	M-	(0.1986)	0.1938				
LUNG	ADENOMA [B]	M-	(0.2607)	0.2632				
LUNG	ADENOMATA [B]	S-	0.1285	(0.1059)				
LYMPH NODE	FIBROSARCOMA [M]	S-	1.0000	(0.7601)				
LYMPH NODE	HAEMANGIOMA [B]	S-	1.0000	(0.7601)				
LYMPH NODE	LYMPHOSARCOMA [M]	S-	0.1676	(0.1376)				
MAMMARY GLAND	ADENOCARCINOMA [M]	M-	(0.3204)	0.3558				
MAMMARY GLAND	Metastasizing ADENOCARCIN	M-	(1.0000)	0.8537				
MAMMARY GLAND	Multifocal ADENOCARCINOMA	S-	0.6075	(0.7234)				
OVARY	HAEMANGIOMA [B]	S-	0.4603	(0.5883)				
OVARY	LUTEOMA [B]	S-	0.2824	(0.3288)				
OVARY	Metastasizing stromal SAR	S-	0.4049	(0.5394)				
OVARY	THECOMA [B]	S-	0.6160	(0.6300)				
OVARY	Uni-lateral CYSTADENOMA [	S-	0.1720	(0.1608)				
PANCREAS	Small islet-cell ADENOMA	S-	0.0523	(0.0068)				
PITUITARY	ADENOMA [B]	M-	(0.2793)	0.3034				

Note: Tumor Type=M indicates that the tumor is fatal to some but not all animals. Tumor Type=S indicates that the tumor is either fatal or non-fatal to all animals.

An '+' indicates a significant linear dose-tumor trend.
A '-' indicates a non-significant linear dose-tumor trend.

Source: Knoll Pharmaceutical Company (Combined Controls)

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Table 3b (Continued)

Test of Trend Based on the Tumor Data

Animal Type: MOUSE

Sex: FEMALE

SKIN	HIBERNOMA [B]	S-	0.4553	(0.5747)
SKIN	Metastasizing SARCOMA [M]	S-	0.6079	(0.7224)
SKIN	SARCOMA/FIBROSARCOMA/MYXO	M-	(0.8434)	0.8412
SKIN	SQUAMOUS-CELL PAPILLOMA [	S-	0.5588	(0.7039)
SPINAL CORD	MENINGIOMA [M]	S-	1.0000 –	(0.7747)
SPLEEN	HAEMANGIOSARCOMA [M]	M-	(0.4891)	0.3849
SPLEEN	LYMPHOSARCOMA [M]	S-	0.4120	(0.2505)
STOMACH	Forestomach- PAPILLOMA [B	S-	0.2941	(0.1363)
STOMACH	Poorly differentiated SAR	S-	0.2000	(0.0304)
STOMACH	Secretory- ADENOCARCINOMA	S-	0.1127	(0.0873)
STOMACH	Secretory- ADENOMA [B]	S-	0.7056	(0.7489)
THYMUS	LYMPHOSARCOMA [M]	M-	(0.8636)	0.8863
THYROID	Follicular CARCINOMA [M]	S-	0.3529	(0.5092)
TONGUE	Small SQUAMOUS-CELL CARCI	S-	1.0000	(0.7937)
UTERUS	Endometrial ADENOCARCINOM	S-	1.0000	(0.8401)
UTERUS	Endometrial ADENOMA [B]	S-	0.8128	(0.8384)
UTERUS	Endometrial SARCOMA [M]	M-	(1.0000)	0.8516
UTERUS	FIBROMA [B]	S-	1.0000	(0.7409)
UTERUS	GRANULAR CELL TUMOUR [B]	S-	0.6429	(0.7459)
UTERUS	HAEMANGIOMA [B]	M+	(0.0352)	0.0027

Note: Tumor Type=M indicates that the tumor is fatal to some but not all animals. Tumor Type=S indicates that the tumor is either fatal or non-fatal to all animals.

An '+' indicates a significant linear dose-tumor trend.
A '-' indicates a non-significant linear dose-tumor trend.

Source: Knoll Pharmaceutical Company (Combined Controls)

Table 3b (Continued)

Test of Trend Based on the Tumor Data

Animal Type: MOUSE

Sex: FEMALE

UTERINE CERVIX	FIBROSARCOMA [M]	S-	0.5448	(0.7120)
UTERINE CERVIX	HISTIOCYTIC SARCOMA [M]	S-	1.0000	(0.7409)
UTERINE CERVIX	Stromal SARCOMA [M]	M-	(0.8216)	0.8262
ABDOMINAL CAVITY	Poorly differentiated SAR	S-	0.6400	(0.7458)
THORACIC CAVITY	Metastasizing HISTIOCYTIC	S-	1.0000_	(0.7937)
HAEMOPOIETIC TISSUE	Metastasizing LYMPHOSARCO	M-	(0.5702)	0.5806
HAEMOPOIETIC TISSUE	Metastasizing histiocytic	M-	(0.5169)	0.5365
HAEMOPOIETIC TISSUE	Myeloid LEUKAEMIA [M]	S-	0.6227	(0.6281)
HAEMOPOIETIC TISSUE	Myelomonocytic LEUKAEMIA	S-	0.6019	(0.7207)
TAIL	Metastasizing capillary H	S-	1.0000	(0.7409)
TAIL	Very small capillary HAEM	S-	0.6429	(0.7459)
ADIPOSE TISSUE	Small HAEMANGIOMA [B]	S-	1.0000	(0.7937)
INTESTINE- CAECUM	FIBROSARCOMA [M]	S-	0.7056	(0.7489)
JOINT (KNEE)	HAEMANGIOSARCOMA [M]	S-	0.6041	(0.7246)
LACRIMAL (HARDERIAN)	ADENOCARCINOMA [M]	S-	0.6120	(0.7281)

Note: Tumor Type=M indicates that the tumor is fatal to some but not all animals. Tumor Type=S indicates that the tumor is either fatal or non-fatal to all animals.

An '+' indicates a significant linear dose-tumor trend.
A '-' indicates a non-significant linear dose-tumor trend.

Source: Knoll Pharmaceutical Company (Combined Controls)

Table 3b (Continued)

Test of Trend Based on the Tumor Data

Animal Type: MOUSE

Sex: FEMALE

Organ Name	Tumor Name	Tumor Type	Exact p	Asymp p	#Incid /Ctrls	Dose 1.25	Dose 5.0	Dose 20.0
LACRIMAL (HARDERIAN)	ADENOMA [B]	S-	0.9298	(0.9226)				
LACRIMAL (HARDERIAN)	ADENOMATA [B]	S-	0.2321	(0.0442)				
LIVER	HAEMANGIOSARCOMA [M]	S-	0.5357	(0.6779)				
LIVER	Hepatocellular ADENOMA [B	S-	0.7606	(0.8305)				
LIVER	Hepatocellular CARCINOMA	S-	0.4120	(0.2505)				

Note: Tumor Type=M indicates that the tumor is fatal to some but not all animals. Tumor Type=S indicates that the tumor is either fatal or non-fatal to all animals.

An '+' indicates a significant linear dose-tumor trend.
A '-' indicates a non-significant linear dose-tumor trend.

Source: Knoll Pharmaceutical Company (Combined Controls)

Table 4a

Intercurrent Mortality Rates

Animal Type: RAT

Sex: MALE

	Dose											
	Ctrl			Low			Med			High		
	No. Died	No. Risk	Cumu Pct. Died	No. Died	No. Risk	Cumu Pct. Died	No. Died	No. Risk	Cumu Pct. Died	No. Died	No. Risk	Cumu Pct. Died
Time(wks)												
0-52												
53-78									7.7			
79-93									19.2			
94-103									34.6			
FNL KILL									65.4			

Source: Knoll Pharmaceutical Company (Combined Controls)

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Table 4b

Intercurrent Mortality Rates

Animal Type: RAT

Sex: FEMALE

	Dose											
	Ctrl			Low			Med			High		
Time(wks)	No. Died	No. Risk	Cumu Pct. Died	No. Died	No. Risk	Cumu Pct. Died	No. Died	No. Risk	Cumu Pct. Died	No. Died	No. Risk	Cumu Pct. Died
0-52									1.9	.	.	.
53-78									7.7			
79-93									25.0			
94-103									36.5			
FNL KILL									63.5			

Source: Knoll Pharmaceutical Company (Combined Controls)

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Table 5

ANIMAL: RAT

TEST OF HOMOGENEITY

SEX	METHOD	p-value
Male	Cox	0.2627
	Kruskal-Wallis	0.3054
Female	Cox	0.2986
	Kruskal-Wallis	0.1903

TEST OF LINEAR TREND

SEX	METHOD	p-value
Male	Cox	0.6952
	Kruskal-Wallis	0.8957
Female	Cox	0.1303
	Kruskal-Wallis	0.0708

Table 6a

Test of Trend Based on the Tumor Data

Animal Type: RAT

Sex: MALE

Organ Name	Tumor Name	Tumor Type	Exact p	Asymp p	#Incid /Ctrls	Dose 1.0	Dose 3.0	Dose 9.0
ADRENAL	Cortical ADENOCARCINOMA [	S-	0.6011	(0.7319)				
ADRENAL	Cortical ADENOMA [B]	S-	0.1986	(0.0411)				
ADRENAL	MIXED PHAEOCHROMOCYTOMA/N	S-	0.1986	(0.0411)				
ADRENAL	PHAEOCHROMOCYTOMA [B]	S-	0.7022	(0.7172)				
ADRENAL	PHAEOCHROMOCYTOMA [M]	S-	0.2282	(0.2198)				
LYMPH NODE	LYMPHOSARCOMA [M]	S-	1.0000	(0.7857)				
LYMPH NODE	Mesenteric- HAEMANGIOMA [	S-	0.6878	(0.7354)				
MAMMARY GLAND	ADENOCARCINOMA [M]	S-	1.0000	(0.8242)				
MAMMARY GLAND	ADENOMA [B]	S-	0.1986	(0.0411)				
MAMMARY GLAND	FIBROADENOMA [B]	S-	0.9995	(0.9853)				
PANCREAS	Islet-cell ADENOCARCINOMA	S-	0.4737	(0.4947)				
PANCREAS	Islet-cell ADENOMA(TA) [B	S-	0.8082	(0.8124)				
PANCREAS	Small acinar-cell ADENOMA	S-	1.0000	(0.8339)				
PARATHYROID	Uni-lateral ADENOMA [B]	S-	1.0000	(0.7857)				
PITUITARY	ADENOMA [B]	M-	(0.6369)	0.6404				
SKELETAL MUSCLE	Metastasizing HISTIOCYTIC	S-	1.0000	(0.8209)				
SKIN	BASAL-CELL CARCINOMA [M]	S-	0.5624	(0.5746)				

Note: Tumor Type=M indicates that the tumor is fatal to some but not all animals. Tumor Type=S indicates that the tumor is either fatal or non-fatal to all animals.

An '+' indicates a significant linear dose-tumor trend.
A '-' indicates a non-significant linear dose-tumor trend.

Source: Knoll Pharmaceutical Company (Combined Controls)

Table 6a (Continued)

Test of Trend Based on the Tumor Data

Animal Type: RAT

Sex: MALE

SKIN	FIBROMA [B]	M-	(0.9011)	0.8989
SKIN	KERATOACANTHOMA [B]	M-	(0.5859)	0.6006
SKIN	LIPOMA [B]	M-	(0.6372)	0.6641
SKIN	Large diffuse HAEMANGIOSA	S-	1.0000	(0.8339)
SKIN	Locally invasive SQUAMOUS	S-	0.4384	(0.5254)
SKIN	OSTEOSARCOMA [M]	S-	1.0000	(0.8852)
SKIN	PAPILLOMA [B]	S-	0.3381	(0.3439)
SKIN	SARCOMA/FIBROSARCOMA	M-	(0.4211)	0.4446
SKIN	Sebaceous gland(s) ADENOM	S-	0.6525	(0.7482)
SKIN	Small ADENOMA [B]	S-	0.6525	(0.7482)
SKIN	TRICHOEPITHELIOMA [B]	S-	0.9341	(0.8905)
SPLEEN	HAEMANGIOSARCOMA [M]	S-	1.0000	(0.8339)
BRAIN	ASTROCYTOMA [M]	S-	1.0000	(0.8979)
BRAIN	MENINGIOMA [M]	S-	0.1986	(0.0411)
STOMACH	Forestomach- PAPILLOMA [B	S-	1.0000	(0.8105)
STOMACH	Forestomach- SQUAMOUS-CEL	S-	0.6525	(0.7482)
TESTIS	INTERSTITIAL-CELL TUMOUR	S+	0.0153	(0.0107)
THYMUS	THYMOMA [M]	S-	0.3991	(0.5002)
THYROID	C-cell ADENOMA [B]	S-	0.8744	(0.8823)
THYROID	C-cell CARCINOMA [M]	S-	0.6525	(0.7482)

Note: Tumor Type=M indicates that the tumor is fatal to some but not all animals. Tumor Type=S indicates that the tumor is either fatal or non-fatal to all animals.

An '+' indicates a significant linear dose-tumor trend.
A '-' indicates a non-significant linear dose-tumor trend.

Source: Knoll Pharmaceutical Company (Combined Controls)

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Table 6a (Continued)

Test of Trend Based on the Tumor Data

Animal Type: RAT

Sex: MALE

THYROID	Follicular ADENOMA [B]	S-	0.2168	(0.2180)
THYROID	Follicular CARCINOMA [M]	M-	(0.5537)	0.5615
URINARY BLADDER	Transitional-cell PAPILLO	S-	1.0000	(0.8339)
HAEMOPOIETIC TISSUE	Metastasizing HISTIOCYTIC	M-	(0.7275)	0.7475
HAEMOPOIETIC TISSUE	Metastasizing LYMPHOSARCO	M-	(0.2117)	0.2167
HAEMOPOIETIC TISSUE	Metastasizing monocytic L	S-	0.1909	(0.0367)
LIMB	KERATOACANTHOMA [B]	S-	0.1489	(0.0187)
LIMB	PAPILLOMA [B]	S-	0.4397	(0.5267)
EPIDIDYMIS	Metastasizing ADENOCARCIN	S-	1.0000	(0.8339)
TAIL	KERATOACANTHOMA [B]	S-	0.6525	(0.7482)
TAIL	PAPILLOMA [B]	S-	0.6768	(0.7423)
EYE	SARCOMA [M]	S-	0.4397	(0.5267)
HEART	Pericardial ADENOCARCINOM	S-	0.6884	(0.7813)
INTESTINE- ILEUM	SARCOMA [M]	S-	1.0000	(0.8174)
KIDNEY	Cortical ADENOCARCINOMA [	S-	0.6525	(0.7482)

Note: Tumor Type=M indicates that the tumor is fatal to some but not all animals. Tumor Type=S indicates that the tumor is either fatal or non-fatal to all animals.

An '+' indicates a significant linear dose-tumor trend.
A '-' indicates a non-significant linear dose-tumor trend.

Source: Knoll Pharmaceutical Company (Combined Controls)

Table 6a (Continued)

Test of Trend Based on the Tumor Data

Animal Type: RAT

Sex: MALE

Organ Name	Tumor Name	Tumor Type	Exact p	Asymp p	#Incid /Ctrls	Dose 1.0	Dose 3.0	Dose 9.0
KIDNEY	Cortical ADENOMA [B]	S-	1.0000	(0.8339)				
KIDNEY	LIPOSARCOMA [M]	S-	0.8591	(0.8387)				
KIDNEY	Well differentiated uni-l	S-	0.4397	(0.5267)				
LIVER	Hepatocellular ADENOMA [B	M-	(0.2325)	0.2233				
LIVER	Hepatocellular CARCINOMA	S-	0.8366	(0.8470)				
LUNG	Anaplastic CARCINOMA [M]	S-	0.4397	(0.5267)				

Note: Tumor Type=M indicates that the tumor is fatal to some but not all animals. Tumor Type=S indicates that the tumor is either fatal or non-fatal to all animals.

An '+' indicates a significant linear dose-tumor trend.
A '-' indicates a non-significant linear dose-tumor trend.

Source: Knoll Pharmaceutical Company (Combined Controls)

Table 6b

Test of Trend Based on the Tumor Data

Animal Type: RAT

Sex: FEMALE

Organ Name	Tumor Name	Tumor Type	Exact p	Asymp p	#Incid /Ctrls	Dose 1.0	Dose 3.0	Dose 9.0
ADRENAL	Arterial medial LEIOMYOMA	S-	0.2143	(0.0485)				
ADRENAL	Cortical ADENOCARCINOMA [	S-	1.0000	(0.8278)				
ADRENAL	PHAEOCHROMOCYTOMA [B]	S-	0.1465	(0.1122)				
LYMPH NODE	LYMPHOSARCOMA [M]	S-	1.0000	(0.8342)				
MAMMARY GLAND	ADENOCARCINOMA [M]	M-	(0.9499)	0.9394				
MAMMARY GLAND	ADENOMA [B]	M-	(0.2221)	0.2285				
MAMMARY GLAND	FIBROADENOMA [B]	M-	(0.8724)	0.8726				
MAMMARY GLAND	Intraductal FIBROMA [B]	S-	0.2143	(0.0485)				
OVARY	Bi-lateral THECOMA [B]	S-	1.0000	(0.8342)				
OVARY	GRANULOSA CELL TUMOUR [B]	S-	0.4325	(0.5648)				
PANCREAS	Islet-cell ADENOCARCINOMA	S-	0.8424	(0.8447)				
PANCREAS	Islet-cell ADENOMA(TA) [B	S-	0.4669	(0.4809)				
PITUITARY	ADENOMA [B]	M-	(0.7386)	0.7406				
SALIVARY GLAND	Metastasizing poorly diff	S-	0.2267	(0.0540)				
SKELETAL MUSCLE	Locally invasive HAEMANGI	S-	1.0000	(0.8342)				
SKIN	Anaplastic subcutaneous C	S-	1.0000	(0.8342)				
SKIN	FIBROMA [B]	S-	0.8075	(0.8093)				

Note: Tumor Type=M indicates that the tumor is fatal to some but not all animals. Tumor Type=S indicates that the tumor is either fatal or non-fatal to all animals.

An '+' indicates a significant linear dose-tumor trend.
A '-' indicates a non-significant linear dose-tumor trend.

Source: Knoll Pharmaceutical Company (Combined Controls)

Table 6b (Continued)

Test of Trend Based on the Tumor Data

Animal Type: RAT

Sex: FEMALE

SKIN	KERATOACANTHOMA [B]	S-	0.8470	(0.8358)
SKIN	LIPOMA [B]	M-	(0.0933)	0.0850
SKIN	PAPILLOMA [B]	S-	1.0000	(0.7874)
SKIN	SARCOMA/FIBROSARCOMA	M-	(0.3414)	0.3819
BRAIN	ASTROCYTOMA [M]	S-	1.0000	(0.8323)
BRAIN	GLIOMA [M]	S-	0.4262	(0.5299)
BRAIN	MENINGIOMA [M]	S-	0.3400	(0.4645)
BRAIN	OLIGODENDROGLIOMA [M]	S-	0.4031	(0.5141)
THYROID	C-cell ADENOMA [B]	S-	0.3853	(0.4072)
THYROID	C-cell CARCINOMA [M]	S-	0.7104	(0.7604)
THYROID	Follicular ADENOMA [B]	S-	0.5300	(0.4976)
THYROID	Follicular CARCINOMA [M]	S-	1.0000	(0.8342)
URINARY BLADDER	Transitional-cell PAPILLO	S-	0.6357	(0.7513)
UTERUS	Endometrial ADENOMA [B]	S-	0.6357	(0.7513)
UTERINE CERVIX	FIBROMA [B]	S-	0.8622	(0.8585)
UTERINE CERVIX	KERATOACANTHOMA [B]	S-	1.0000	(0.8342)
UTERINE CERVIX	LEIOMYOSARCOMA [M]	S-	0.6313	(0.7501)
UTERINE CERVIX	Locally invasive SQUAMOUS	S-	0.8178	(0.8251)
UTERINE CERVIX	SARCOMA [M]	S-	0.2143	(0.0485)
NASAL CAVITY	SQUAMOUS-CELL CARCINOMA [	S-	0.4343	(0.5414)

Note: Tumor Type=M indicates that the tumor is fatal to some but not all animals. Tumor Type=S indicates that the tumor is either fatal or non-fatal to all animals.

An '+' indicates a significant linear dose-tumor trend.
A '-' indicates a non-significant linear dose-tumor trend.

Source: Knoll Pharmaceutical Company (Combined Controls)

Table 6b (Continued)

Test of Trend Based on the Tumor Data

Animal Type: RAT

Sex: FEMALE

HAEMOPOIETIC TISSUE	Metastasizing HISTIOCYTIC	M-	(0.8679)	0.8578
HAEMOPOIETIC TISSUE	Metastasizing LYMPHOSARCO	S-	0.8473	(0.8416)
TAIL	FIBROMA [B]	S-	0.2143	(0.0485)
ADIPOSE TISSUE	HAEMANGIOSARCOMA [M]	S-	0.6357	(0.7513)
KIDNEY	Cortical ADENOMA [B]	S-	1.0000	(0.8336)
KIDNEY	LIPOSARCOMA [M]	S-	0.6357	(0.7513)
LIVER	Hepatocellular ADENOMA [B	S-	0.3466	(0.3638)
LIVER	Hepatocellular CARCINOMA	M-	(0.4486)	0.4463

Note: Tumor Type=M indicates that the tumor is fatal to some but not all animals. Tumor Type=S indicates that the tumor is either fatal or non-fatal to all animals.

An '+' indicates a significant linear dose-tumor trend.
A '-' indicates a non-significant linear dose-tumor trend.

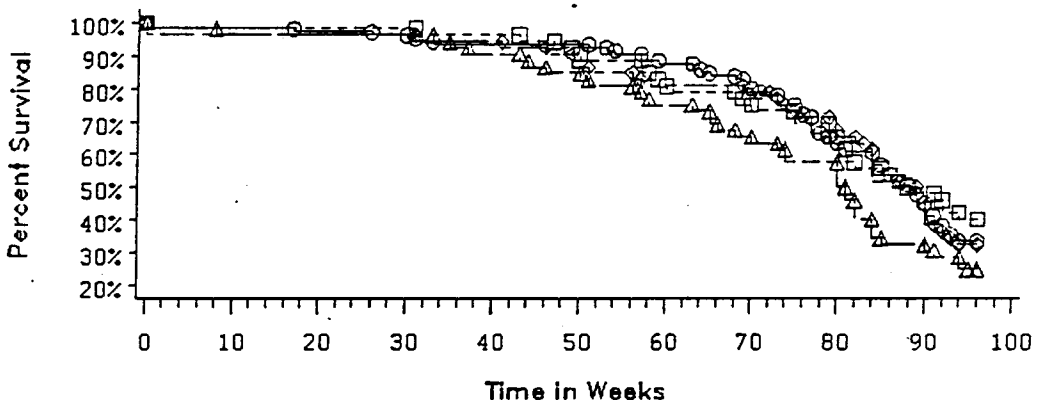
Source: Knoll Pharmaceutical Company (Combined Controls)

Figure 1a

Kaplan–Meier Survival Function

Animal: MOUSE

Sex: MALE



Dose: Ctrl Low Med High

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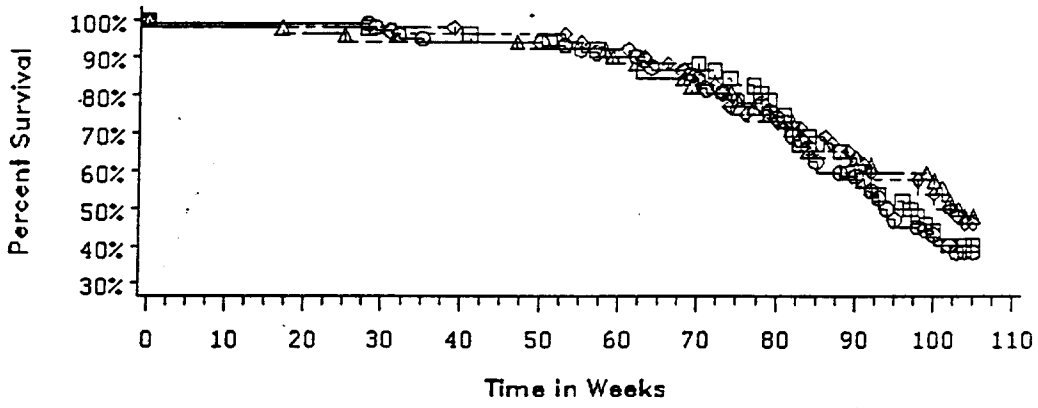
Figure 1b

Kaplan–Meier Survival Function

Animal: MOUSE

Sex: FEMALE



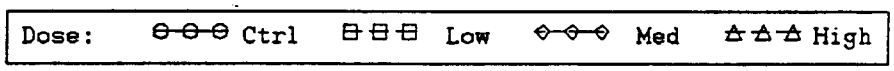


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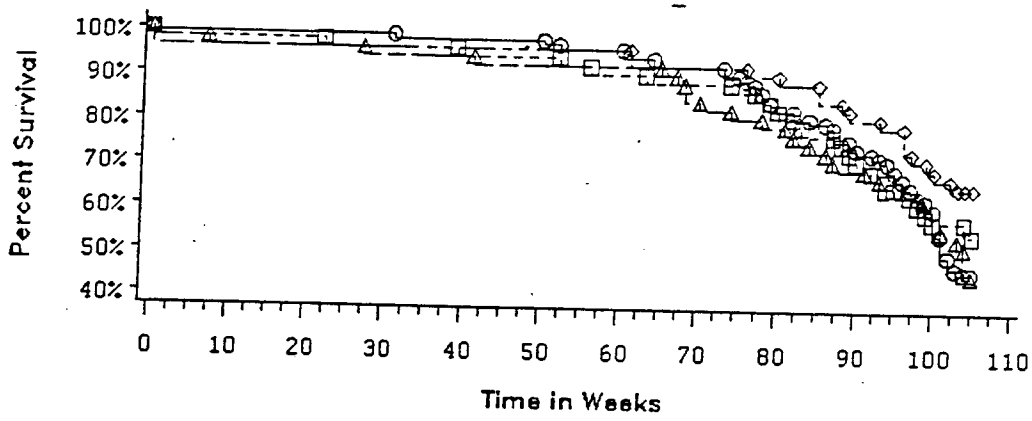
Figure 2a

Kaplan–Meier Survival Function

Animal: RAT

Sex: MALE



Dose: Ctrl Low Med High

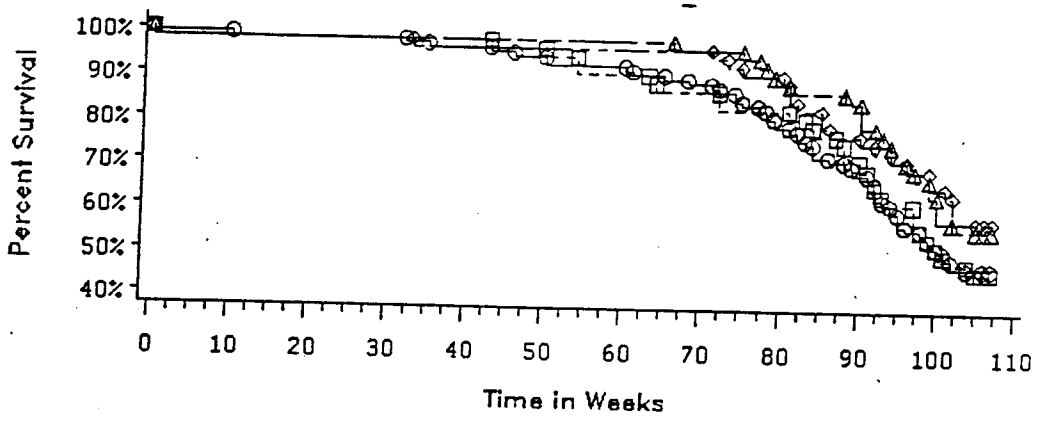
APPEARS THIS WAY
ON ORIGINAL

Figure 2b

Kaplan–Meier Survival Function

Animal: RAT

Sex: FEMALE



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Statistical Review and Evaluation

NDA#: 20-632 NOV 14 1997

Applicant: Knoll Pharmaceutical Company

Name of Drug: Meridia (sibutramine hydrochloride monohydrate) Capsules

Documents Reviewed: Vols. 1-5
Submission dated November 7, 1997

Subject: SB5078 Amendments 7-9
Echocardiographic Screening Final Report

Introduction

The objective of Amendments 7-9 was to determine the incidence of left-sided valvular heart disease in obese patients who had received sibutramine or placebo in the ongoing Study SB5078. Study SB5078 is a multicenter, randomized, placebo-controlled, double-blind 1-year study followed by an 1-year open treatment phase in obese type II diabetic patients who have not previously received antidiabetic medication. During the open treatment phase, all patients are to take sibutramine.

Patient Disposition

The disposition of patients in Amendments 7-9 is as follows:

# of Patients Enrolled in SB5078	236
# of Dropouts (prior to initiation of Amendments 7-9)	24
Adverse Event	18
Other	6
# of Patients Actively Participating in SB5078 at time of Initiation of Amendments 7-9	212
# of Patients Enrolled in Amendments 7-9	211
# of Patients Included in Analysis	210
# of Patients Excluded from Study	1[a]
# of Patients Excluded from Analysis	1[b]

[a] One patient with a long-standing history of mild aortic stenosis which was recorded at the SB5078 baseline visit.
[b] Data for one patient was not received by the cut-off date of November 3, 1997.

Patient Classification in Amendments 7-9

Study SB5078 was initiated in June 1996 and Amendment 7-9 was initiated on October 7, 1997 with a data cut-off date of November 3, 1997. As the study is ongoing for over a year, some of the placebo patients (in double-blind phase) are currently taking sibutramine in the open treatment phase. To account for this, those placebo patients who had echocardiographs performed while receiving sibutramine in the open-treatment phase were classified as sibutramine patients as the following table displays:

Table 1 Treatment Classification, Treatment Duration and Number for ECHO patients

Randomized Treatment	Amendments 7-9			
ECHO Time	Treatment Classification		No. of Patients	
placebo				
ECHO in Double-blind[b]	placebo		77	
ECHO in Open-label[a]	**sibutramine**			
Sibutramine		Open-label	61	133 sibutramine
ECHO in Open-label[b]	sibutramine			
ECHO in Double-blind[b]	sibutramine	Double-blind(DB)	72	

[a]The duration of treatment equals date of echocardiography minus date of first open-label dose (sibutramine).
[b]The duration of treatment equals date of echocardiography minus date of first double-blind dose.

From the above, a sibutramine patient in the Amendments 7-9 can be a randomized sibutramine patient in the double-blind phase (sibutramine DB) or in the open-label phase or a randomized placebo patient in the open-label phase. Only a randomized placebo patient in the double-blind phase can be classified as placebo patient in the amendment.

Of the 210 patients analyzed in Amendments 7-9, 149 were in the double-blind treatment phase and 61 were in the open treatment phase at the time of echocardiography. Of the 149 patients in the double-blind phase, 72 were receiving sibutramine and 77 were receiving placebo.

Patient Demographic and Baseline Characteristics

1. Gender

The number of male and female patients by treatment group is summarized in the following table.

Number (%) of Patients by Gender

Treatment Group	Male	Female	Total
Sibutramine	52 (39.1%)	81 (60.9%)	133
Sibutramine DB*	35 (48.6%)	37 (51.4%)	72
Placebo	34 (44.2%)	43 (55.8%)	77
Overall	86 (41.0%)	124 (59.0%)	210

* Patients in the double-blind treatment phase at the time of echocardiography; this group is a subset of the sibutramine group.

2. Age

The descriptive statistics for age is displayed by treatment group in the following table.

Descriptive Statistics for Age

Treatment Group	n	Mean	S.D.	Median	Range
Sibutramine	133	53.9	9	55	
Sibutramine DB	72	53.1	9	54	
Placebo	77	54.8	8	54	
Overall	210	54.2	9	55	

The number of patients by age category of <50 years or ≥50 years is summarized by treatment group in the following table.

Number (%) of Patients by Age Category

Treatment Group	<50	≥50	Total
Sibutramine	36 (27.1%)	97 (72.9%)	133
Sibutramine DB	21 (29.2%)	51 (70.8%)	72
Placebo	24 (31.2%)	53 (68.8%)	77
Overall	60 (28.6%)	150 (71.4%)	210

3. Duration of Treatment

Descriptive statistics for duration of treatment by treatment group are displayed in the following table.

Descriptive Statistics for Duration of Treatment (days)

Treatment Group	n	Mean	S.D.	Median	Range
Sibutramine	133	229	134	226	
Sibutramine DB	72	227	82	226	
Placebo	77	228	79	217	
Overall	210	229	117	220	

The number of patients by duration of treatment category (<180 days or ≥180 days) is displayed in the following table.

Number (%) of Patients by Duration of Treatment Category

Treatment Group	<180 days	≥180 days	Total
Sibutramine	56 (42.1%)	77 (57.9%)	133
Sibutramine DB	25 (34.7%)	47 (65.3%)	72
Placebo	23 (29.9%)	54 (70.1%)	77
Overall	79 (37.6%)	131 (62.4%)	210

4. History of Hypertension

Ninety-five (45.2%) of the 210 patients had a history of hypertension. Eleven (5.2%) had a history of receiving three antihypertensive medications concomitantly.

Study Outcome

The overall incidences of aortic insufficiency and mitral regurgitation are summarized in the following tables.

Table 2 Number (%) of Patients with Aortic Insufficiency

Treatment Group	n	None	Trace	Mild	Moderate	Severe
Sibutramine	133	123 (92.5%)	6 (4.5%)	**4 (3.0%)**	0	0
sibutramine DB	72	67 (93.1%)	3 (4.2%)	2 (2.8%)	0	0
Placebo	77	73 (94.8%)	2 (2.6%)	**1 (1.3%)**	0	**1 (1.3%)**

Table 3 Number (%) of Patients with Mitral Regurgitation

Treatment Group	n	None	Trace	Mild	Moderate	Severe
Sibutramine	133	115 (86.5%)	17 (12.8%)	1 (0.8%)	0	0
sibutramine DB	72	63 (87.5%)	9 (12.5%)	0	0	0
Placebo	77	73 (94.8%)	3 (3.9%)	1 (1.3%)	0	0

Using FDA case definition for left-sided valvular disease as severity of mild or greater for aortic insufficiency and/or moderate or greater for mitral regurgitation, all cases (6) were from patients with aortic insufficiency and none from mitral regurgitation.

Of the six cases, only one placebo treated patient was under 50 years old. Of the four cases in sibutramine treatment group, two were males and two were females, none occurred in a patient under 50 years old (three of the four cases occurred in hypertensives). The one severe placebo case was a male and the one mild placebo case was a female. Both of the two female sibutramine patients are in the double-blind phase and none of the two male sibutramine patients are from the double-blind phase. The mean duration of treatment in the four cases of sibutramine-treated patients was 7 months which is similar to 7.5 months of the sibutramine-treated patients as a whole. One sibutramine case received sibutramine for only 3 weeks following a 12-month treatment with placebo.

Sponsor's Analysis

The sponsor presented normal approximation 90% confidence intervals for the incidence of left-sided valvular disease for the treatment groups, the difference between them, and Mantel-Haenszel method for the odds ratio (sibutramine vs. placebo) as displayed in the following table.

Table 4 Left-Sided Valvular Disease: 90% Confidence Intervals (CI)

Treatment Group	Incidence of Valvular Disease	90% CI
sibutramine	4/133 (3.0%)	(0.006, 0.054)
placebo	2/ 77 (2.6%)	(0.000, 0.056)
sibutramine - Placebo	0.4%	(-0.034, 0.043)
Odds Ratio	1.16	(0.274, 4.940)

Reviewer's Analysis

The sponsor's confidence intervals are calculated using large-sample methods. Since two of the expected values of the 4 cells are small(<5), the large sample approximation might not be adequate. The exact inference is more appropriate. The exact 90% and 95% confidence intervals are displayed in the following tables.

Table 5 Left-Sided Valvular Disease: Exact 90% Confidence Intervals

Treatment Group	Incidence of Valvular Disease	90% CI
sibutramine	4/133 (3.0%)	(0.010, 0.068)
placebo	2/ 77 (2.6%)	(0.046, 0.080)
sibutramine - Placebo	0.4%	(-0.071, 0.071)
Odds Ratio	1.16	(0.211, 8.848)
Relative Risk	1.16	(0.216, 8.633)

Table 6 Left-Sided Valvular Disease: Exact 95% Confidence Intervals (CI)

Treatment Group	Incidence of Valvular Disease	95% CI
sibutramine	4/133 (3.0%)	(0.008, 0.075)
placebo	2/ 77 (2.6%)	(0.003, 0.091)
sibutramine - Placebo	0.4%=0.004	(-0.083, 0.080)
Odds Ratio	1.16	(0.162, 13.130)
Relative Risk	1.16	(0.166, 12.800)

Conclusion

From the data of Amendments 7-9 and using the confidence interval approach of the exact inference, the relative risk (or odds ratio) of sibutramine relative to placebo is 1.16 with a wide upper confidence limit which indicates that odds ratio as large as 9 at 90% confidence level and as large as 13 at 95% confidence level can not be ruled out.

Lee-Ping Pian, Ph.D.
Mathematical Statistician

Concur: Dr. Nevius

cc:

Archival NDA 20-632
HFD-510
HFD-510/SSobel
HFD-510/GTroendle
HFD-510/BStadel
HFD-510/EColman
HFD-510/MHess
HFD-715/division file, Chron., LPian
Pian/word/meridia/11/10/97

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MEMORANDUM OF CONSULTATION

Date: NOV 4 1997

Between: Eric Colman, M.D. (HFD-510)

And: Lee-Ping Pian, Ph.D. (HFD-715)

Subject: Meridia NDA 20-632
Protocol for the Collection of Echocardiographic Data

Knoll Pharmaceutical Co., submitted Echocardiography Amendment (dated October 20, 1997) and Statistical Analysis Plan for Echocardiography Amendment to Protocol SB 5078 on October 21, 1997 and October 23, 1997. Dr. Colman requested a calculation of statistical power for the Echo Amendment.

The purpose of the Echo amendment is to collect and analyze on the incidence of valvular heart disease in sibutramine-treated patients versus placebo-treated patients. This safety endpoint was not in the original protocol.

Approximately 200 patients in the study will be screened for the presence of pathologic left-sided cardiac valvular regurgitation. The case definition of incidence is chosen according to the FDA developed thresholds for valvopathy of aortic insufficiency (AI) and mitral regurgitation (MR).

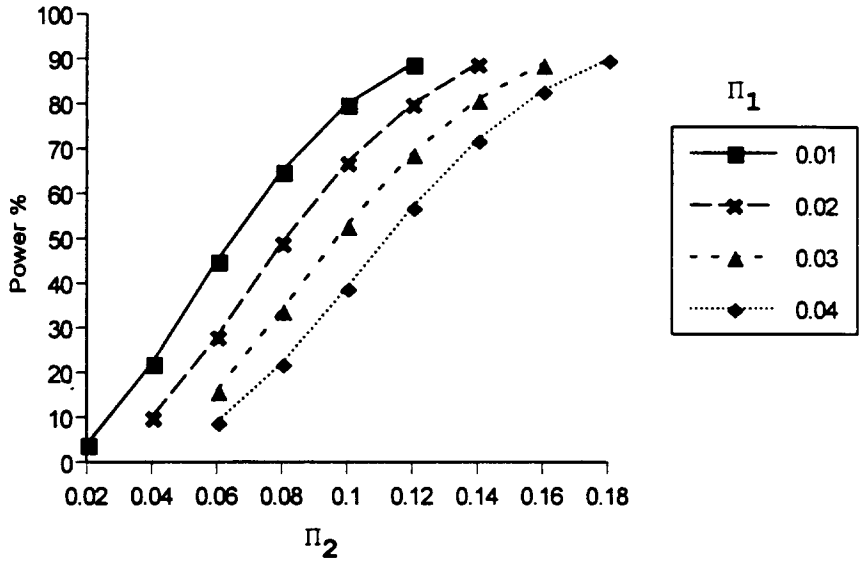
The primary analysis objective is to construct 90% confidence intervals for the incidence of left sided valvular heart disease for two treatment groups (placebo and sibutramine) and the difference in incidence rates of left sided valvular heart disease between sibutramine and placebo groups.

The following table displays the power of the continuity corrected Chi-square test with 2-sided α=0.1 and various hypothetical incidence rates of placebo and sibutramine.

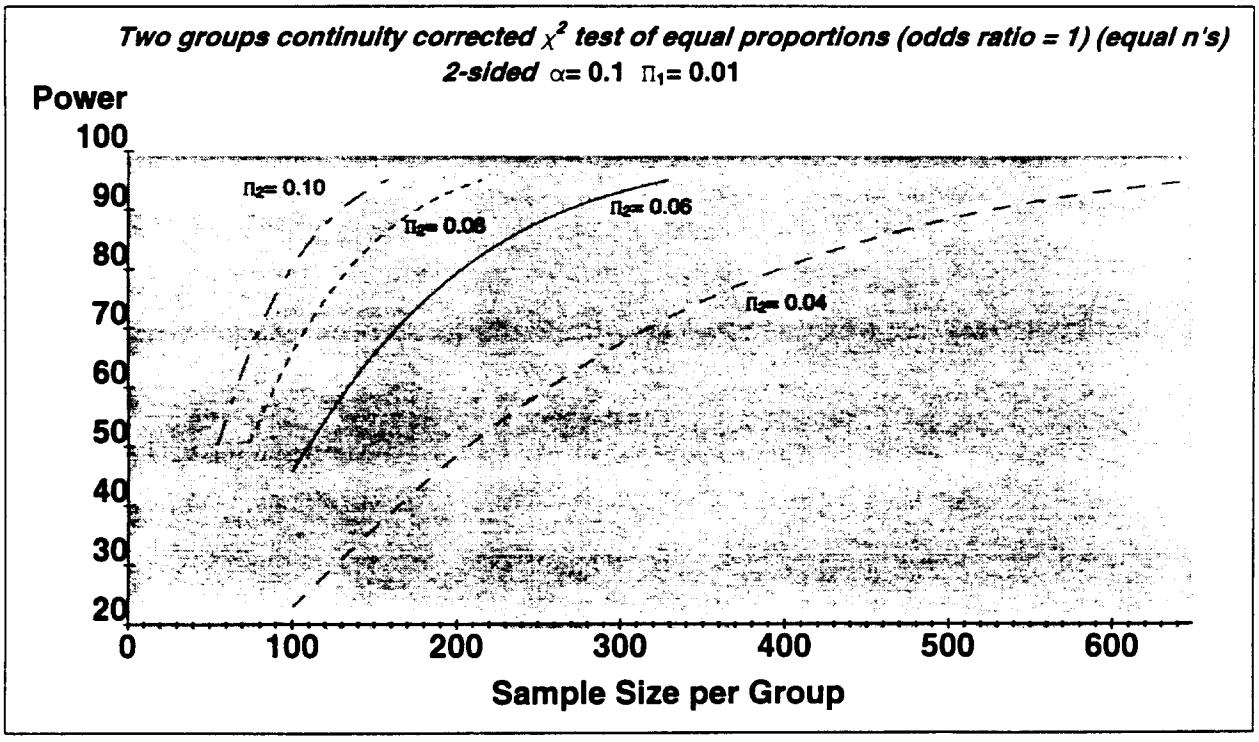
Table 1 Power from continuity corrected chi-square test with α=0.1 and n=100 per group

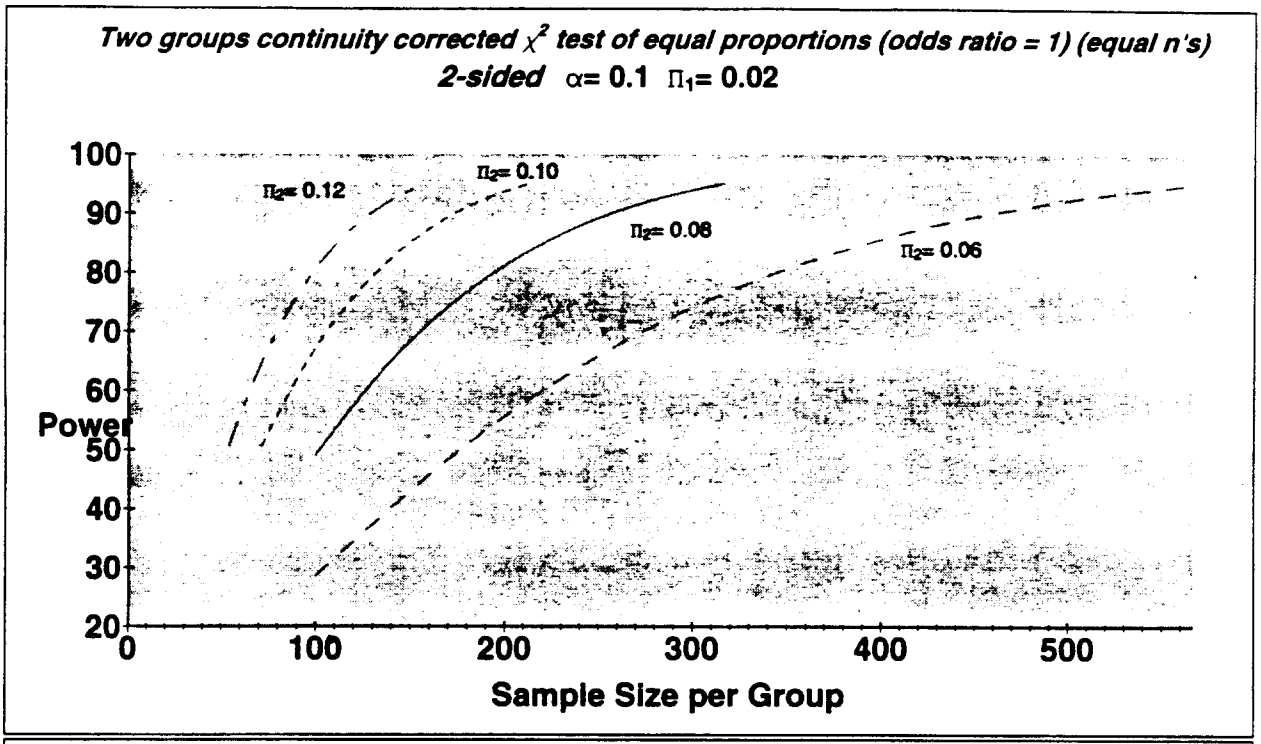
Π_1 \ Π_2		0.02	0.04	0.06	0.08	0.10	0.12	0.14	0.16	0.18
0.01	OR	2.0	4.1	6.3	8.6	11	13.5			
	power %	**4**	**22**	**45**	**65**	**80**	**89**			
0.02	OR		2.0	3.1	4.3	5.4	6.7	8.0		
	power %		**10**	**28**	**49**	**67**	**80**	**89**		
0.03	OR			2.1	2.8	3.6	4.4	5.3	6.2	
	power %			**16**	**34**	**53**	**69**	**81**	**89**	
0.04	OR			1.5	2.1	2.7	3.3	3.9	4.6	5.3
	power %			**9**	**22**	**39**	**57**	**72**	**83**	**90**

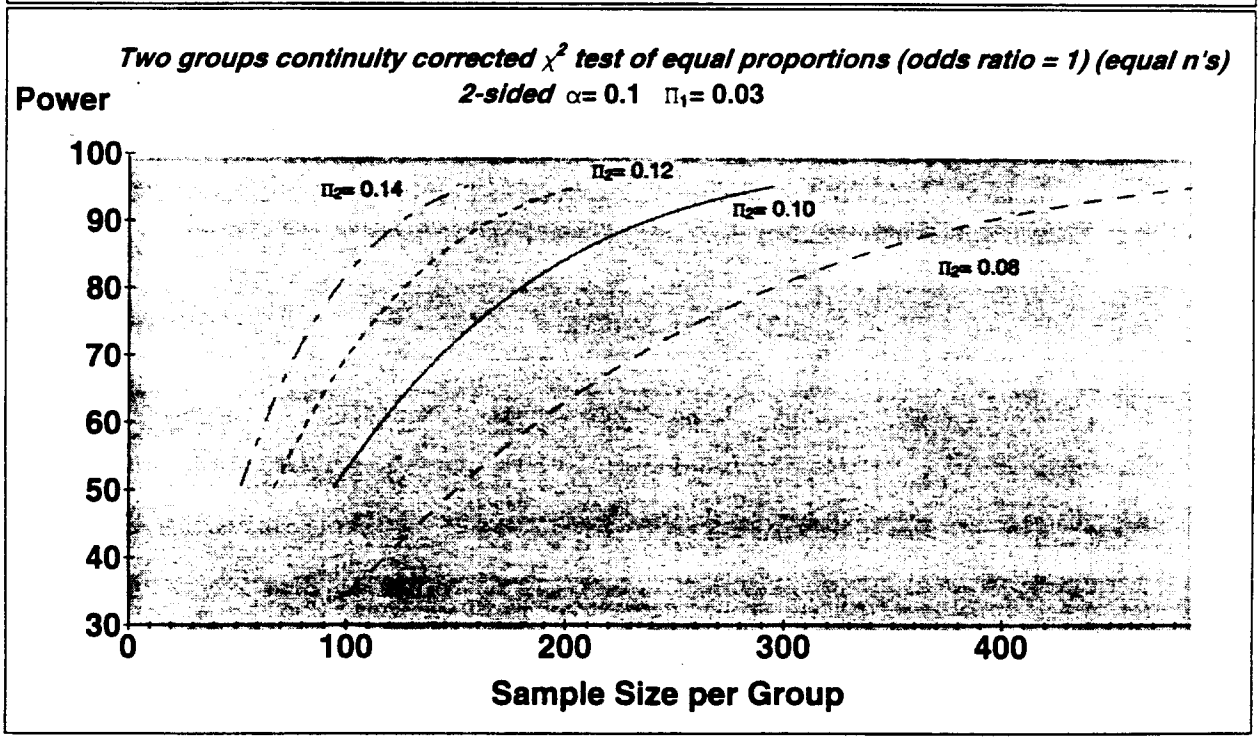
The following graph displays the power with α=0.1, n=100 per group and various Π_1 and Π_2.

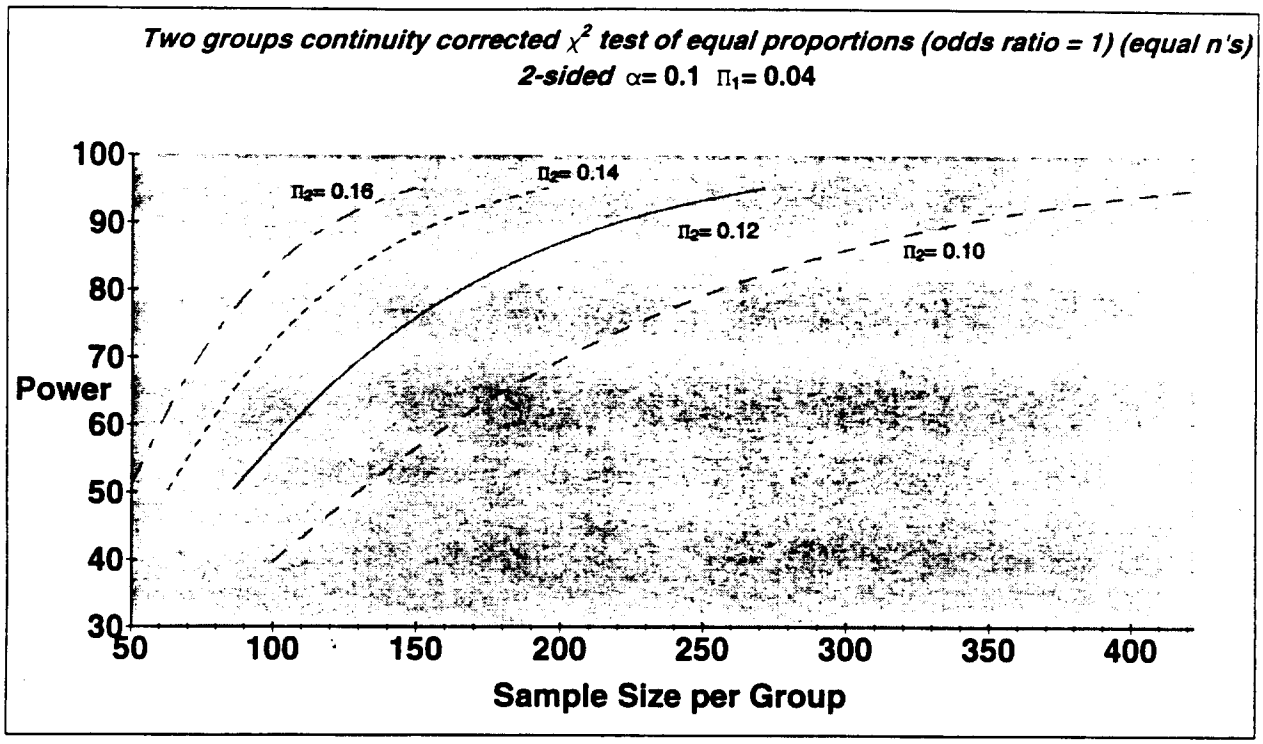


The following graphs display power versus sample size per group for different combinations of Π_1 and Π_2 with 2-sided α=0.1.









In summary, the incidence rates which have at least 80% power with 2-sided α=0.1 and 100 patients per group are (Π_1=0.01, Π_2=0.10, OR=11), (Π_1=0.02, Π_2=0.12, OR=6.7), (Π_1=0.03, Π_2=0.14, OR=5.3), and (Π_1=0.04, Π_2=0.16, OR=4.6).

Lee-Ping Pian, Ph.D.
Mathematical Statistician

cc:

Archival NDA 20-632
HFD-510
HFD-510/SSobel
HFD-510/GTroendle
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HFD-510/EColman
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HFD-715/division file, Chron., LPian
Pian/word/meridia/11/3/97

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MEMORANDUM OF CONSULTATION

Date: MAR 13 1997

Between: Bruce Stadel, M.D. (HFD-510)

And: Lee-Ping Pian, Ph.D. (HFD-715)

Subject: Meridia Capsules Amendment to Pending NDA 20-632 Dated January 3, 1997

To follow up on the memorandum of consultation dated March 11, 1997 the proportion of patients with two consecutive blood pressure elevations over baseline of ≥10, ≥15 and ≥20 mm Hg were compared between sibutramine and placebo for the systolic blood pressure and ≥5, ≥10, and ≥15 mm Hg for the diastolic blood pressure. The doses of sibutramine 5 mg, 10 mg, and 15 mg were combined in Study BP852 and the 10 mg and 15 mg sibutramine groups were combined in Study SB1047. The comparison between sibutramine and placebo was made for each study separately and the two studies were combined using the Mantel-Haenszel method. For completeness, the 20 mg sibutramine group is also compared to the placebo group in Study BP852.

Systolic blood pressure

The proportions by treatment group and the p-values of the chi-square test are displayed in Table 1 and Table 2 for Studies BP 852 and SB 1047, respectively.

Table 1. Study BP 852 - Proportion of Patients with 2 Consecutive Elevations over Baseline on Systolic BP, ITT Population

Treatment Group	n	2 Consecutive Elevations over Baseline SBP		
		≥10mmHg	≥15mmHg	≥20mmHg
Placebo	148	43 (29%)	18 (12%)	10 (7%)
Sibutramine 5 mg, 10 mg, & 15 mg	453	182 (40%)	80 (18%)	47 (10%)
p-value		0.02	0.12	0.19
Sibutramine 20 mg	146	71 (49%)	39 (27%)	24 (16%)
p-value, 20mg vs. Placebo		0.0006	0.0016	0.0094

Table 2. Study SB 1047 - Proportion of Patients with 2 Consecutive Elevations over Baseline on Systolic BP, ITT Population

Treatment Group	n	2 Consecutive Elevations over Baseline SBP		
		≥10mmHg	≥15mmHg	≥20mmHg
Placebo	163	56 (34%)	29 (18%)	21 (13%)
Sibutramine 10 mg, & 15 mg	322	131 (41%)	75 (23%)	58 (18%)
p-value, Chi-Square		0.18	0.16	0.15

The Cochran-Mantel-Haenszel test and the estimated common odds ratio with the 95% confidence interval for the two studies combined (with no sibutramine 20 mg group in Study BP852) are as follows:

Table 3. Meta-analysis of the SBP Combining BP852 & SB1047

	2 Consecutive Elevations over Baseline SBP		
	≥10mmHg	≥15mmHg	≥20mmHg
Common Odds Ratio (C.I.)	1.465 (1.107, 1.937)	1.466 (1.024, 2.099)	1.547 (0.996, 2.342)
p-value, CMH Chi-Square	0.008	0.037	0.052

Diastolic Blood Pressure

The same tests were performed on the diastolic blood pressure for the two studies.

Table 4. Study BP 852 - Proportion of Patients with 2 Consecutive Elevations over Baseline on DBP, ITT Population

Treatment Group	n	2 Consecutive Elevations over Baseline DBP		
		≥5mmHg	≥10mmHg	≥15mmHg
Placebo	148	55 (37%)	29 (20%)	6 (4%)
Sibutramine 5 mg, 10 mg , & 15 mg	453	205 (45%)	122 (27%)	31 (7%)
p-value, Chi-Square		0.09	0.07	0.22
Sibutramine 20 mg	146	86 (59%)	52 (36%)	15 (10%)
p-value, 20 mg vs. Placebo		0.0002	0.0021	0.0395

Table 5. Study SB 1047 - Proportion of Patients with 2 Consecutive Elevations over Baseline on DBP, ITT Population

Treatment Group	n	2 Consecutive Elevations over Baseline DBP		
		≥5mmHg	≥10mmHg	≥15mmHg
Placebo	163	47 (29%)	26 (16%)	9 (6%)
Sibutramine 10 mg , & 15 mg	322	136 (42%)	90 (28%)	28 (9%)
p-value, Chi-Square		0.004	0.003	0.214

The Cochran-Mantel-Haenszel test and the estimated common odds ratio with the 95% confidence interval for the two studies combined (without the 20 mg group in Study BP852) is as follows:

Table 6. Meta-analysis of the DBP Combining BP852 & SB1047

	2 Consecutive Elevations over Baseline DBP		
	≥5mmHg	≥10mmHg	≥15mmHg
Common Odds Ratio (C.I.)	1.578 (1.197, 2.080)	1.745 (1.256, 2.425)	1.677 (0.938, 2.999)
p-value, CMH Chi-Square	0.001	0.001	0.081

Lee-Ping Pian, Ph.D.
Mathematical Statistician

Figure 1

Mean Placebo Subtracted Change from Baseline in Resting SBP in Outliers

Sibutramine 5 – 20 mg – Observed Data

Study BPI 852

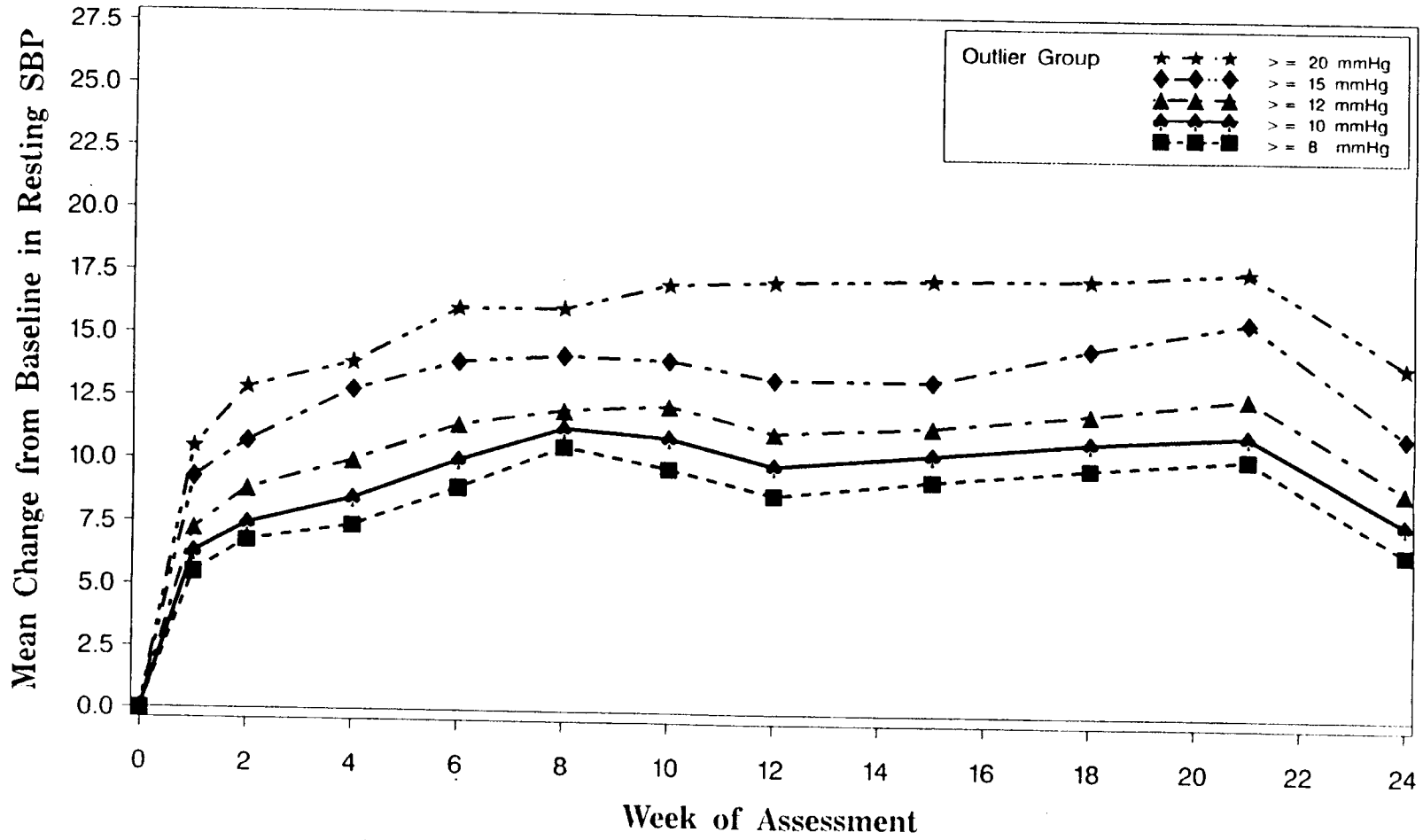


Figure 2

Mean Placebo Subtracted Change from Baseline in Resting DBP in Outliers

Sibutramine 5 – 20 mg – Observed Data

Study BPI 852

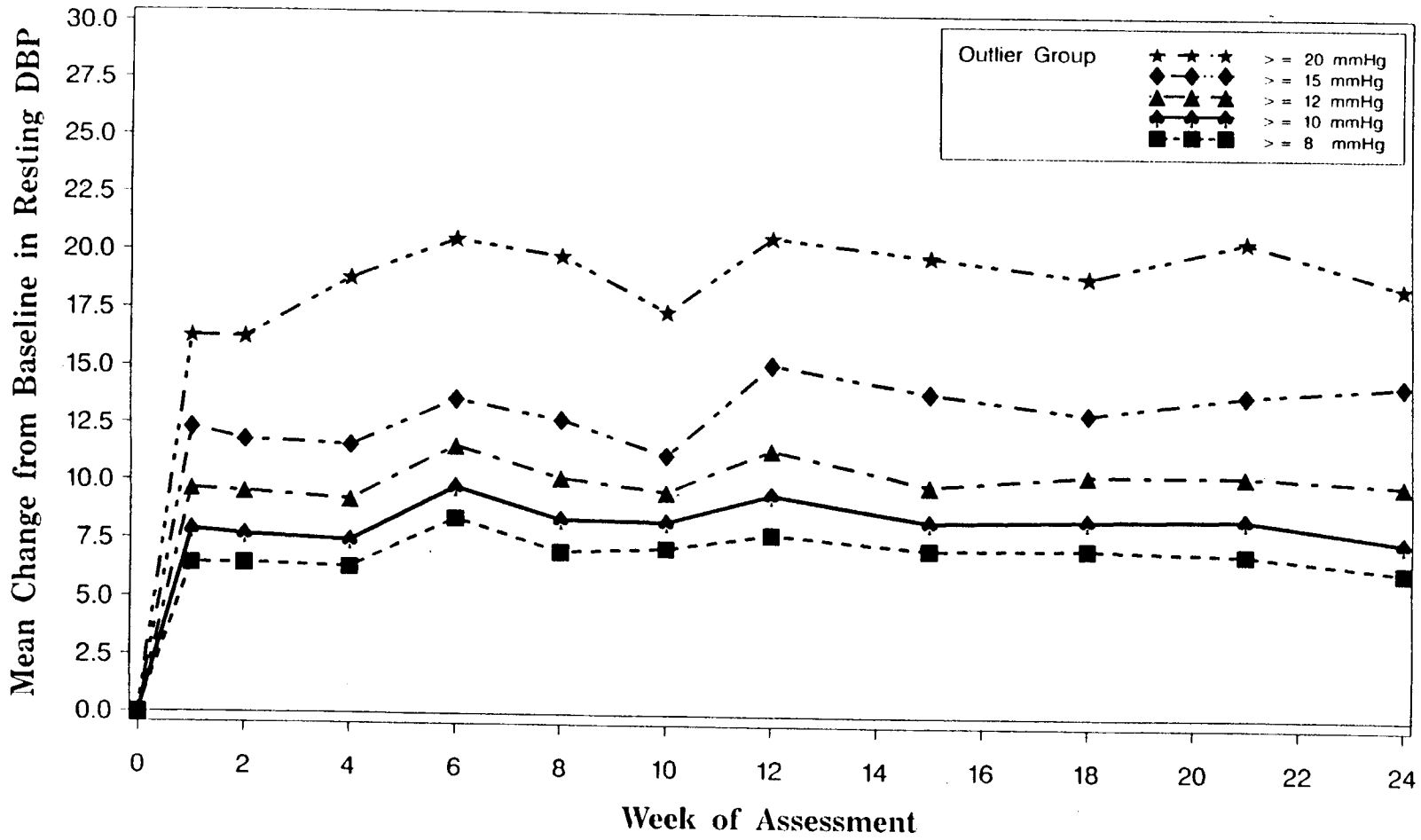


Figure 3

Mean Placebo Subtracted Change from Baseline in Resting SBP in Outliers

Sibutramine 10 – 15 mg – Observed Data

Study SB 1047

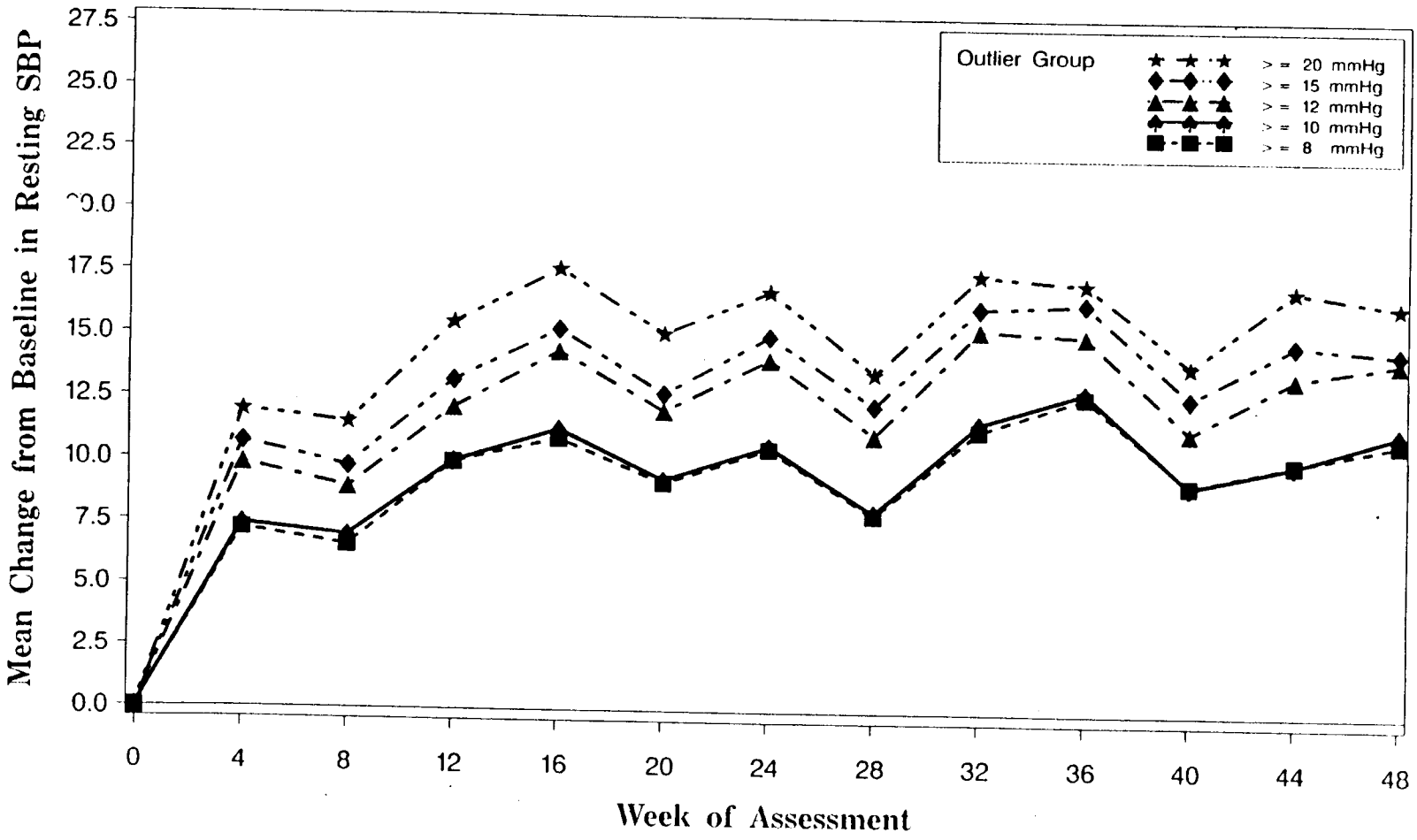
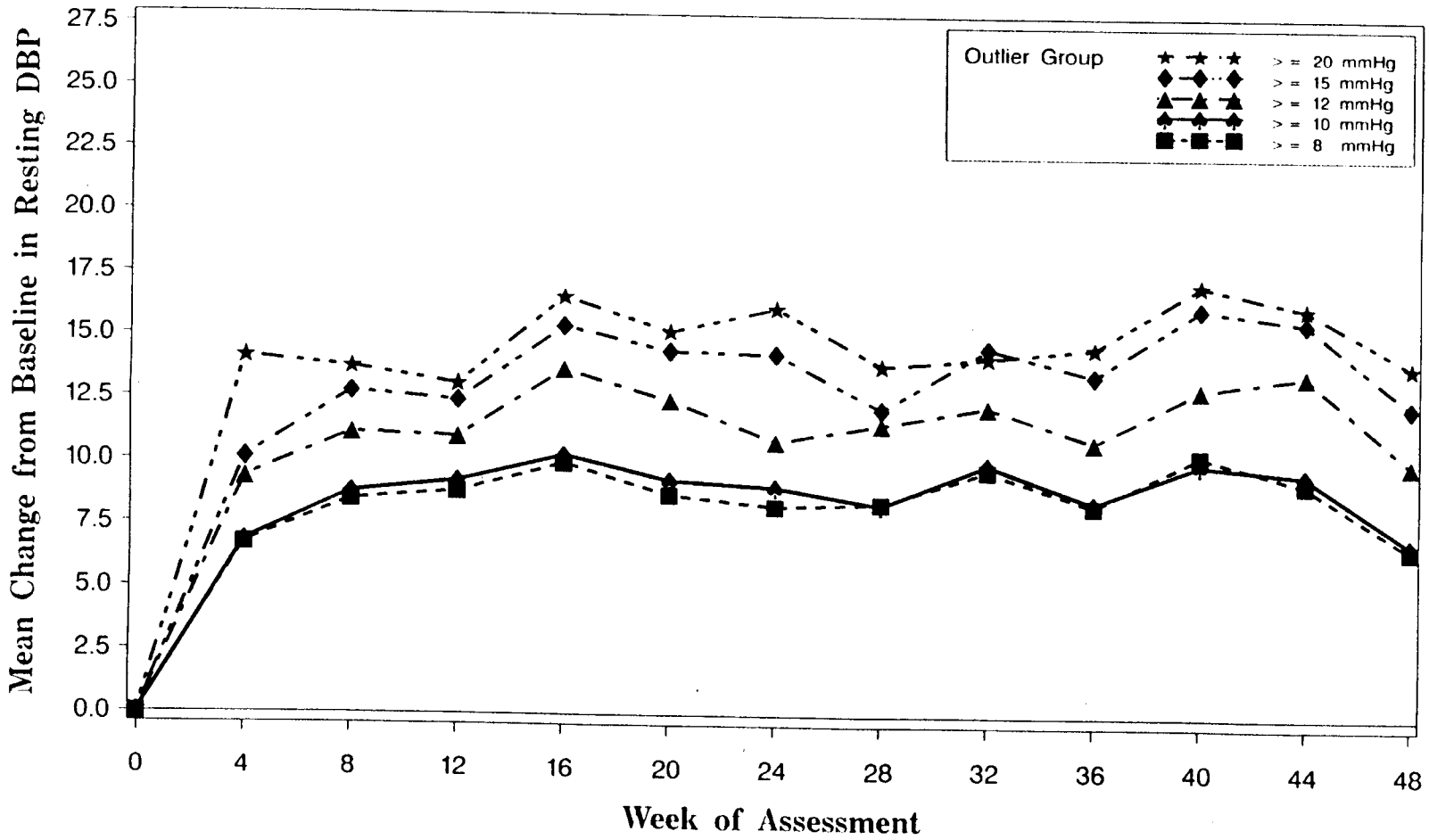


Figure 4

Mean Placebo Subtracted Change from Baseline in Resting DBP in Outliers

Sibutramine 10 – 15 mg – Observed Data

Study SB 1047



MEMORANDUM OF CONSULTATION

Date: MAR 11 1997

Between: Bruce Stadel, M.D. (HFD-510)

And: Lee-Ping Pian, Ph.D. (HFD-715)

Subject: Meridia Capsules Amendment to Pending NDA 20-632 Dated January 3, 1997

Background

In responding to the approvable letter of November 8, 1996, the sponsor filed amendments to the NDA to address issues raised in the approvable letter. One item included in this amendment was additional analyses of the blood pressure data from the clinical trials BP 852 and SB 1047.

The proportion of patients with two consecutive blood pressure measurements exceeding baseline by at least 8, 10, 12, 15, and 20mm Hg was looked at for the systolic blood pressure and also for diastolic blood pressure with an additional outcome of 5mm Hg or more. The sponsor defined patients with those two consecutive increase as outliers. Therefore, there are five different definitions of outliers for the systolic blood pressure and 6 different definitions of outliers for the diastolic blood pressure.

Systolic blood pressure

In study BP 852 with the ITT population the Cochran-Armitage trend test is performed on each of the binary responses (e.g., ≥8mmHg or <8mmHg) to test for the dose response relationship. The results are displayed in Table 1.

Table 1. Study BP 852 - Proportion of Patients with 2 Consecutive Elevations over Baseline on Systolic BP, ITT Population

Treatment Group	n	2 Consecutive Elevations over Baseline SBP				
		≥8mmHg	≥10mmHg	≥12mmHg	≥15mmHg	≥20mmHg
Placebo	148	52 (35%)	43 (29%)	29 (20%)	18 (12%)	10 (7%)
Sibutramine						
5 mg	151	73 (48%)	62 (41%)	43 (28%)	21 (14%)	13 (9%)
10 mg	150	80 (53%)	69 (46%)	53 (35%)	33 (22%)	16 (11%)
15 mg	152	67 (44%)	51 (34%)	42 (28%)	26 (17%)	18 (12%)
20 mg	146	81 (55%)	71 (49%)	59 (40%)	39 (27%)	24 (16%)
p-value, trend test		0.0054	0.0141	0.0007	0.0014	0.0054
p-value without 20 mg in the trend test		0.0849	0.3110	0.0614	0.0912	0.1061

The test results showed that there was a significant increasing trend for each binary response of ≥8mmHg, ≥10mmHg, ≥12mmHg,

≥15mmHg, and ≥20mmHg. When the same test is repeated without the 20 mg group, the trend is weakened substantially. In the SB 1047 study, there were only three treatment groups of placebo, 10 mg and 15 mg and the Cochran-Armitage test results were similar to that of study BP 852 without the 20 mg group as displayed in Table 2.

Table 2 Study SB 1047 - Proportion of Patients with 2 Consecutive Elevations over Baseline on Systolic BP, ITT Population

Treatment Group	n	Two Consecutive Elevations over Baseline SBP				
		≥8mmHg	≥10mmHg	≥12mmHg	≥15mmHg	≥20mmHg
Placebo	163	58(36%)	56 (34%)	35 (21%)	29 (18%)	21 (13%)
Sibutramine						
10 mg	161	68(42%)	63 (39%)	40 (25%)	36 (22%)	27 (17%)
15 mg	161	71(44%)	68 (42%)	45 (28%)	39 (24%)	31 (19%)
p-value, trend test		0.1186	0.1453	0.1771	0.1585	0.1207

Diastolic Blood Pressure

The same procedure was applied to the diastolic blood pressure and the results are displayed in tables 3 and 4 for studies BP852 and SB1047, respectively.

Table 3. Study BP 852 - Proportion of Patients with 2 Consecutive Elevations over Baseline on Diastolic BP, ITT Population

Treatment Group (n)	2 Consecutive Elevations over Baseline DBP					
	≥5mmHg	≥8mmHg	≥10mmHg	≥12mmHg	≥15mmHg	≥20mmHg
Placebo (n=148)	55 (37%)	35 (24%)	29 (20%)	16 (11%)	6 (4%)	2 (1%)
Sibutramine 5 mg (n=151)	66 (44%)	54 (36%)	44 (29%)	30 (20%)	11 (7%)	4 (3%)
10 mg (n=150)	67 (45%)	53 (35%)	44 (29%)	25 (17%)	11 (7%)	1 (1%)
15 mg (n=152)	72 (48%)	60 (39%)	34 (22%)	19 (13%)	9 (6%)	2 (1%)
20 mg (n=146)	86 (59%)	70 (48%)	52 (36%)	32 (22%)	15 (10%)	4 (3%)
p-value, trend test	0.0003	0.0000	0.0315	0.1436	0.1403	0.7710
p-value without the 20 mg group	0.0820	0.0066	0.6068	0.9043	0.5277	0.7484

Table 4. Study SB 1047 - Proportion of Patients with 2 Consecutive Elevations over Baseline on Diastolic BP, ITT Population

Treatment Group (n)	2 Consecutive Elevations over Baseline DBP					
	≥5mmHg	≥8mmHg	≥10mmHg	≥12mmHg	≥15mmHg	≥20mmHg
Placebo (n=163)	47 (29%)	36 (22%)	26 (16%)	10 (6%)	9 (6%)	3(2%)
Sibutramine 10 mg (n=161)	69 (43%)	53 (33%)	48 (30%)	21 (13%)	16 (10%)	9 (6%)
15 mg (n=161)	67 (42%)	48 (30%)	42(26%)	20 (12%)	12 (7%)	7 (4%)
p-value, trend test	0.1525	0.1214	0.0320	0.0647	0.4275	0.2434

Conclusion:

From the trend analysis, the sibutramine 20 mg causes a significant increase in the proportion of "outliers". When the 20 mg patients were not in the analysis in study BP852 or in study SB1047 which had 3 treatment groups of placebo, 10 mg and 15 mg of sibutramine most trend analyses are not significant.

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Lee-Ping Pian
Mathematical Statistician

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Archival NDA 20-632
HFD-510
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HFD-510/EColman
HFD-715/division file, DMarticello, LPian
Chron.
Pian/word/meridia/3/8/97

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MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

Date: OCT 2 3 1996

From: Mathematical Statistician (HFD-715)

Through: Director, Division of Biometrics II (HFD-715)

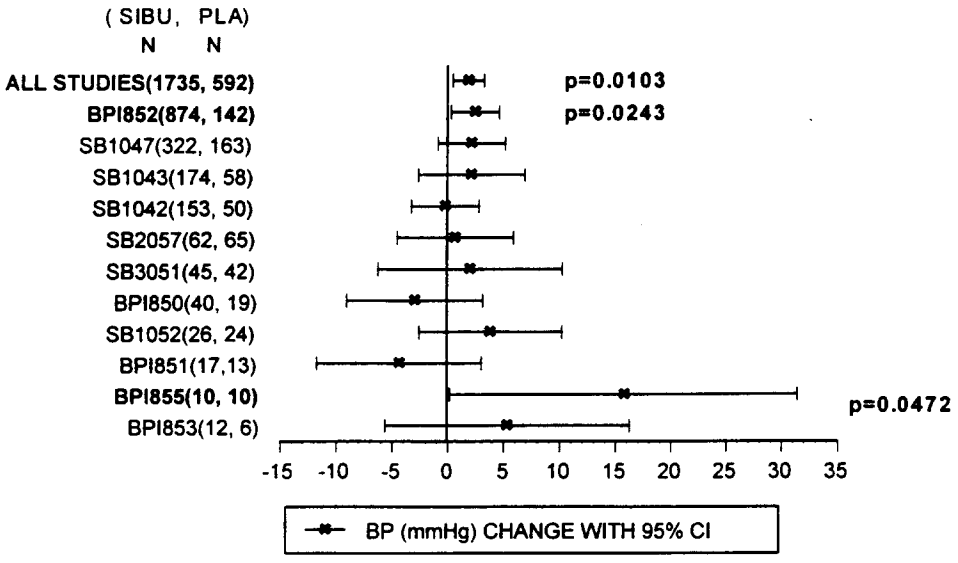
Subject: Meta-Analysis of Placebo-Controlled Obesity Studies Submitted on October 9, 1996

To: File (NDA 20-632)

The sponsor submitted meta-analysis on the risk (vital signs) and benefit (lipid profile, serum glucose, serum uric acid) outcomes (Attachments 1 to 5) and "outlier analyses" on time to first occurrence of clinically significant elevations in blood pressure.

In the sponsor's meta-analysis the weight assigned to each study is proportional to the inverse of the variance, therefore, the two larger studies BPI852 and SB1047 greatly influenced the overall results of the meta-analysis as the following graph of the analysis on blood pressure shows.

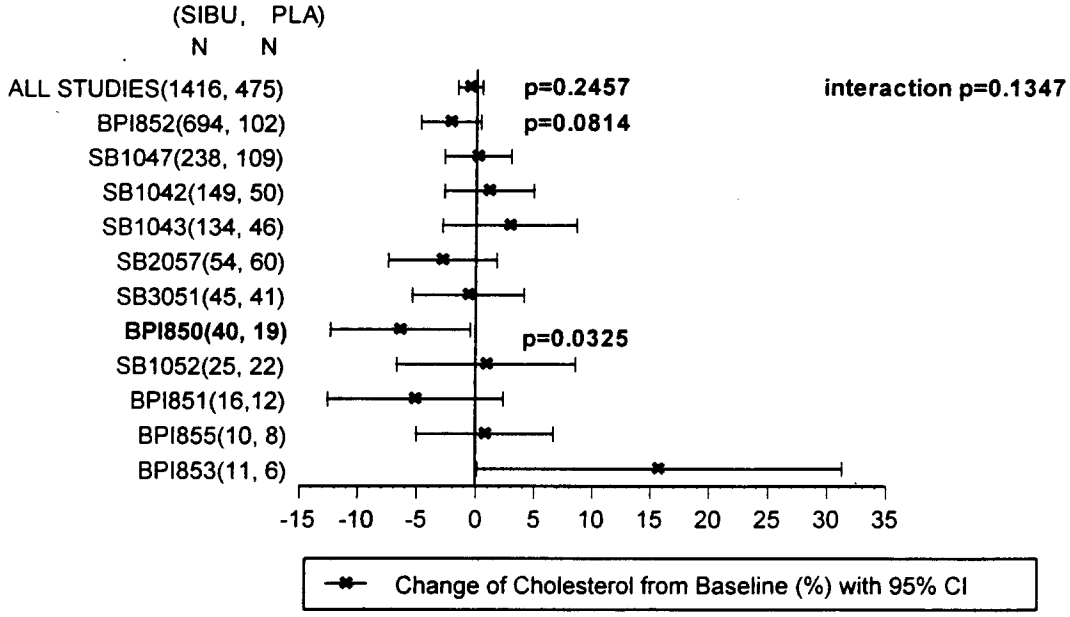
Fig 1 Resting Systolic Blood Pressure
Sibutramine versus All Placebo Patients



In the lipid analysis, the different doses of sibutramine in each study were combined into one sibutramine group. The percent change from baseline was the outcome variable. In the original NDA, lipid data were displayed as descriptive statistics of means for each treatment group. The sponsor indicated in Study BPI 852 that although the protocol specified that patients should have fasted for eight hours before a blood draw, compliance with this instruction was variable. Our analysis were performed on the pairwise comparisons of each treatment group versus placebo.

Figures 2 to 5 are graphs of the meta-analysis with a corresponding table of all studies and studies BPI852 and/or SB1047 on lipid profiles:

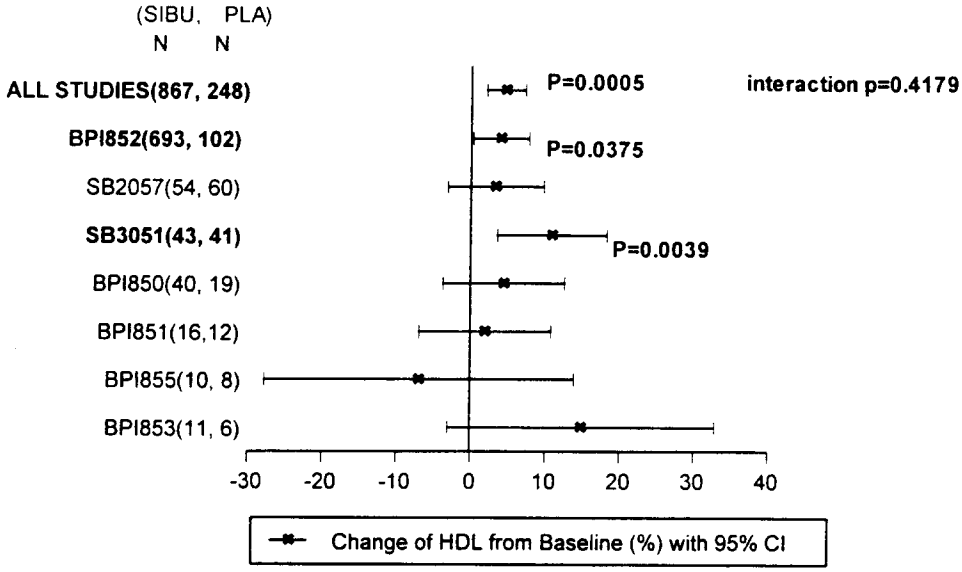
Fig 2. Treatment Difference of Cholesterol Sibutramine versus All Placebo Patients



Cholesterol

Study(Weight,%)	Sibutramine N	Sibutramine Mean	Placebo N	Placebo Mean	Difference (Sib-Pla)	p-value
All	1416	-2.22	475	-1.60	-0.62	0.246
BPI852(27.45)	694	-5.09	102	-2.84	-2.25	0.081
SB1047(23.12)	238	1.89	109	1.82	0.07	0.961

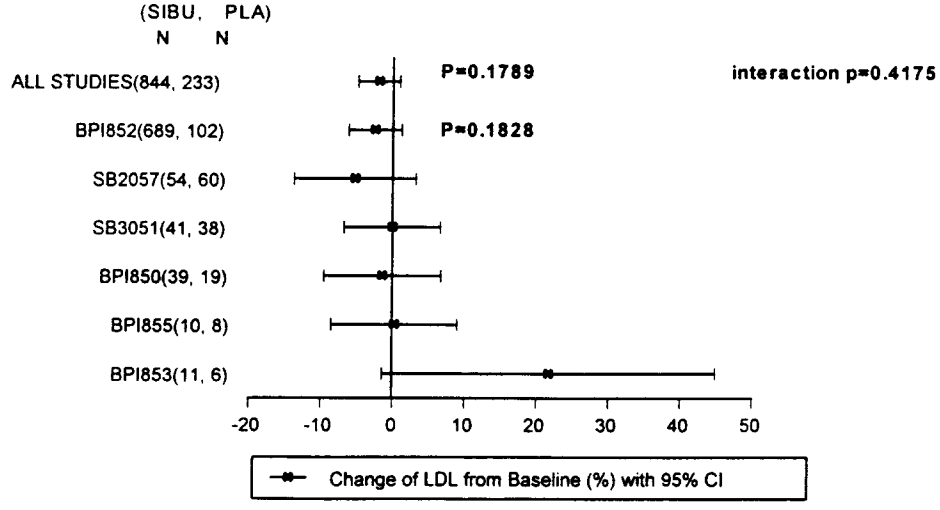
Fig 3. Treatment Difference of HDL Sibutramine versus All Placebo Patients



HDL

Study(Weight%)	Sibutramine N	Sibutramine Mean	Placebo N	Placebo Mean	Difference (Sib-Pla)	p-value
All	867	3.98	248	-0.58	4.56	0.0005
BPI852(53.91)	693	2.61	102	-1.33	3.94	0.0375

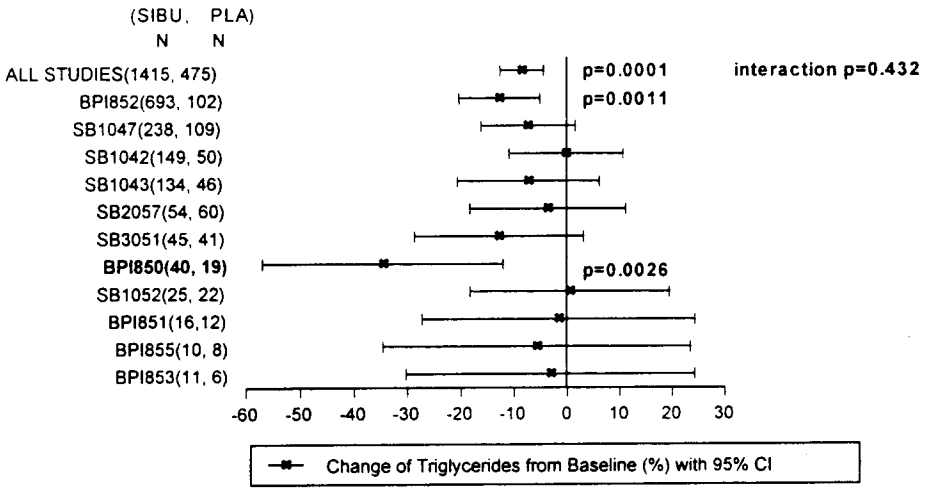
Fig 4. Treatment Difference of LDL Sibutramine versus All Placebo Patients



LDL

Study(Weight%)	Sibutramine N	Sibutramine Mean	Placebo N	Placebo Mean	Difference (Sib-Pla)	p-value
All	844	-2.14	233	-0.15	-1.99	0.1789
BPI852(56.38)	689	-4.73	102	-2.24	-2.49	0.1828

Fig 5. Treatment Difference of Triglycerides Sibutramine versus All Placebo Patients



Triglycerides

Study(Weight%)	Sibutramine N	Sibutramine Mean	Placebo N	Placebo Mean	Difference (Sib-Pla)	p-value
All	1415	-8.03	475	0.48	-8.52	0.0001
BPI852(27.37)	693	-10.29	102	2.43	-12.72	0.0011
SB1047(23.08)	238	-9.75	109	-2.39	-7.36	0.1049

The sponsor also made comparisons of sibutramine patients who lost ≥5% from initial weight to all placebo patients and concluded that "there were statistically significant differences between sibutramine and the all-placebo group for all parameters. When those patients who lost at least 5% of their body weight on sibutramine and on placebo were compared, there were no significant differences for any of the lipid parameters. " The comparison between the ≥5% sibutramine patients and all placebo patients is not made by comparing patients with "similar" outcomes which means it is confounded (more weight loss in the sibutramine group) and overestimates the treatment differences.

Reviewer's Comments

As the sponsor indicated these analyses are retrospective in nature which is the main difficulty with meta-analyses. To minimize bias, we need to plan ahead with a meta-analysis protocol to determine in advance whether to pool all the sibutramine groups into one or to look at individual doses or to pool the common doses used in the study.

The effect size is assumed constant for studies in the sponsor's method for meta-analysis. The studies have different sibutramine dose regimens (e.g. BP852, 1, 5, 10, 15, 20, 30 mg and SB1047, 10 & 15 mg). When sibutramine groups are combined into one group

for each study, the drug effect is not constant over studies.

Lee-Ping Pian, Ph.D.
Mathematical Statistician

Concur: Mr. Marticello

cc:Archi. NDA 20-632
HFD-510
HFD-510/SSobel, GTroendle, EGalliers, RHedin
HFD-510/EColman
HFD-715/Division file, DMarticello, LPian, Chron.

Pian/74257/wpfiles/meridia

This memorandum consists of 5 pages of text

APPEARS THIS WAY
ON ORIGINAL

SEP 23 1996

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

Date: SEP 23 1996

From: Mathematical Statistician (HFD-715)

Through: Director, Division of Biometrics II (HFD-715) BEN 9-23-96

Subject: Data analysis on blood pressure of study BPI852

To: File (NDA 20-632)

The results of repeated measure analyses using a mixed effect model on treatment groups 5 mg, 10 mg and 15 mg combined (low dose) versus 20 mg and 30 mg combined (high dose) from Week 1 to Week 24 on the change from baseline in blood pressure are as follows:

1. Change in standing diastolic BP

Treatment Dose	LSMean (C.I.)	p-value
Low		0.0566
High		

Difference (High-Low) of LSMeans (C.I.)
0.96(-.03, 1.95)

2. Change in supine diastolic BP

Treatment Dose	LSMean (C.I.)	p-value
Low		0.0151
High		

Difference (High-Low) of LSMeans (C.I.)
1.18(0.23, 2.13)

3. Change in standing systolic BP

Treatment Dose	LSMean (C.I.)	p-value
Low		0.4717
High		

Difference (High-Low) of LSMeans (C.I.)
0.50(-.85, 1.85)

4. Change in supine systolic BP

Treatment Dose	LSMean (C.I.)	p-value
Low		0.0150
High		

Difference (High-Low) of LSMeans (C.I.)
1.58(0.31, 2.85)

Note that these analyses are based on a post-hoc grouping of doses and therefore, should be taken as exploratory in nature.

Lee-Ping Pian, Ph.D.
Mathematical Statistician

Concur: Mr. Marticello

cc:Archi. NDA 20-632
HFD-510
HFD-510/SSobel, GTroendle, EGalliers, RHedin
HFD-510/EColman
HFD-344/ALisook
HFD-715/Division file, DMarticello, LPian, Chron.

Pian/74257/wpfiles/meridia

This memorandum consists of 2 pages of text

Statistical Review and Evaluation

SE

NDA#: 20-632/Class 1S

Applicant: Knoll Pharmaceutical Co.

Name of Drug: MERIDIA™ (Sibutramine hydrochloride monohydrate) capsules

Indication: Antiobesity

Documents Reviewed: Vols. 1.1, 326-540
Submission dated August 9, 1995

Background:

MERIDIA is a new class of serotonin (5-HT) and norepinephrine (NE) reuptake inhibitors that was studied for the long-term treatment of obesity.

The NDA includes two large multicenter, placebo-controlled studies conducted in the United States and the United Kingdom with 1047 and 485 patients respectively. Nine other placebo-controlled studies and one active-controlled (dexfenfluramine) study were also included in the submission.

The dose ranging study, BPI 852-USA, was conducted at 7 sites over a 24-week therapy period with treatment groups 1 mg, 5 mg, 10 mg, 15 mg, 20 mg and 30 mg/day sibutramine versus placebo. The number of patients were 149, 151, 150, 152, 146, 151 vs. 148, respectively. Male to Female ratio was 20/80. Black/Caucasian/Oriental ratio was 15/77/8. Age ranged from 19-65 with a mean of 43.6. The average baseline body mass index (BMI) (30-40 kg/m^2, inclusive) was 35 kg/m^2.

Study SB 1047-UK was conducted at 12 sites with a duration of 12-months of therapy in the treatment of mild-to-moderate obesity patients The treatment groups were sibutramine 10 mg or 15 mg/day and placebo with 161, 161 and 163 patients, respectively. The male to female ratio was 20/80 and 99% of the patients were Caucasian.

SB 1049-France is a ongoing study with 12-months duration of therapy.

Study Protocol - BPI 852

The primary objectives are

1. To compare the effects of the above mentioned doses of sibutramine and placebo on weight loss in obese patients when given in conjunction with modest caloric restriction, exercise, and behavior modification for up to 12 weeks.

2. To assess the effects of sibutramine and placebo on supine and standing heart rate in obese patients after 2 and 12 weeks.

3. 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.

The secondary objective is to assess the efficacy, safety, and tolerability of sibutramine for up to 24 weeks in obese patients.

Study Design

This was a multicenter, double-blind, repeated-dose, placebo-controlled, parallel-group, dose-ranging study. After screening and a 2-week placebo run-in period, patients were randomized to one of 7 treatment groups for a **12-week double-blind** treatment period, followed by a second 12-week modified double-blind extension. All patients had the option of entering a long-term extension study BPI 852X. Patients not entering BPI 852X completed a mandatory 6-week placebo washout period before returning for a final study visit. Patients who had ongoing adverse events at either premature termination or the final study visit had follow-up visits scheduled until the adverse events had resolved or stabilized. Throughout the study, including the placebo run-in and washout period, patients received ancillary therapy comprising of an individualized caloric restriction plan, a standard exercise regimen and modest behavior modification program.

Dose Reduction

In the event of an intolerable adverse event, or two mean supine pulse rates greater than 100 bpm, or a blood pressure greater than 160 mmHg (systolic) or 95 mmHg (diastolic), the patient's dose was reduced (fall back) or the patient was discontinued from medication, as appropriate.

Protocol Amendments

Four amendments were made to the original study protocol (approved on 4/16/92). Amendment 1 (approved on 6/8/92) included altering the BMI range for patient inclusion from to 30-40 kg/m^2, renaming the exercise program to an activity

Attachment 1

MAR 13 1997

CONSULT RETURN

DATE: March 11, 1997

FROM: Division of Biometrics 2 (HFD-715)

THRU: Project Manager

TO: Document Room, HFD-510

SUBJECT: Original statistical review attached

Please log-in attached statistical review consult and copy all HFD-510 recipients.

Contact person in case of questions: Dan Marticello, 443-3510, ext 78

Thank you.

APPEARS THIS WAY
ON ORIGINAL

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ON ORIGINAL

MEMORANDUM OF CONSULTATION

Date: MAR 1 1 1997

Between: Bruce Stadel, M.D. (HFD-510)

And: Lee-Ping Pian, Ph.D. (HFD-715)

Subject: Meridia Capsules Amendment to Pending NDA 20-632 Dated January 3, 1997

Background

In responding to the approvable letter of November 8, 1996, the sponsor filed amendments to the NDA to address issues raised in the approvable letter. One item included in this amendment was additional analyses of the blood pressure data from the clinical trials BP 852 and SB 1047.

The proportion of patients with two consecutive blood pressure measurements exceeding baseline by at least 8, 10, 12, 15, and 20mm Hg was looked at for the systolic blood pressure and also for diastolic blood pressure with an additional outcome of 5mm Hg or more. The sponsor defined patients with those two consecutive increase as outliers. Therefore, there are five different definitions of outliers for the systolic blood pressure and 6 different definitions of outliers for the diastolic blood pressure.

Systolic blood pressure

In study BP 852 with the ITT population the Cochran-Armitage trend test is performed on each of the binary responses (e.g., ≥8mmHg or <8mmHg) to test for the dose response relationship. The results are displayed in Table 1.

Table 1. Study BP 852 - Proportion of Patients with 2 Consecutive Elevations over Baseline on Systolic BP, ITT Population

Treatment Group	n	2 Consecutive Elevations over Baseline SBP				
		≥8mmHg	≥10mmHg	≥12mmHg	≥15mmHg	≥20mmHg
Placebo	148	52 (35%)	43 (29%)	29 (20%)	18 (12%)	10 (7%)
Sibutramine						
5 mg	151	73 (48%)	62 (41%)	43 (28%)	21 (14%)	13 (9%)
10 mg	150	80 (53%)	69 (46%)	53 (35%)	33 (22%)	16 (11%)
15 mg	152	67 (44%)	51 (34%)	42 (28%)	26 (17%)	18 (12%)
20 mg	146	81 (55%)	71 (49%)	59 (40%)	39 (27%)	24 (16%)
p-value, trend test		0.0054	0.0141	0.0007	0.0014	0.0054
p-value without 20 mg in the trend test		0.0849	0.3110	0.0614	0.0912	0.1061

The test results showed that there was a significant increasing trend for each binary response of ≥8mmHg, ≥10mmHg, ≥12mmHg,

≥15mmHg, and ≥20mmHg. When the same test is repeated without the 20 mg group, the trend is weakened substantially. In the SB 1047 study, there were only three treatment groups of placebo, 10 mg and 15 mg and the Cochran-Armitage test results were similar to that of study BP 852 without the 20 mg group as displayed in Table 2.

Table 2 Study SB 1047 - Proportion of Patients with 2 Consecutive Elevations over Baseline on Systolic BP, ITT Population

Treatment Group	n	Two Consecutive Elevations over Baseline SBP				
		≥8mmHg	≥10mmHg	≥12mmHg	≥15mmHg	≥20mmHg
Placebo	163	58(36%)	56 (34%)	35 (21%)	29 (18%)	21 (13%)
Sibutramine						
10 mg	161	68(42%)	63 (39%)	40 (25%)	36 (22%)	27 (17%)
15 mg	161	71(44%)	68 (42%)	45 (28%)	39 (24%)	31 (19%)
p-value, trend test		0.1186	0.1453	0.1771	0.1585	0.1207

Diastolic Blood Pressure

The same procedure was applied to the diastolic blood pressure and the results are displayed in tables 3 and 4 for studies BP852 and SB1047, respectively.

Table 3. Study BP 852 - Proportion of Patients with 2 Consecutive Elevations over Baseline on Diastolic BP, ITT Population

Treatment Group (n)	2 Consecutive Elevations over Baseline DBP					
	≥5mmHg	≥8mmHg	≥10mmHg	≥12mmHg	≥15mmHg	≥20mmHg
Placebo (n=148)	55 (37%)	35 (24%)	29 (20%)	16 (11%)	6 (4%)	2 (1%)
Sibutramine 5 mg (n=151)	66 (44%)	54 (36%)	44 (29%)	30 (20%)	11 (7%)	4 (3%)
10 mg (n=150)	67 (45%)	53 (35%)	44 (29%)	25 (17%)	11 (7%)	1 (1%)
15 mg (n=152)	72 (48%)	60 (39%)	34 (22%)	19 (13%)	9 (6%)	2 (1%)
20 mg (n=146)	86 (59%)	70 (48%)	52 (36%)	32 (22%)	15 (10%)	4 (3%)
p-value, trend test	0.0003	0.0000	0.0315	0.1436	0.1403	0.7710
p-value without the 20 mg group	0.0820	0.0066	0.6068	0.9043	0.5277	0.7484

Table 4. Study SB 1047 - Proportion of Patients with 2 Consecutive Elevations over Baseline on Diastolic BP, ITT Population

Treatment Group (n)	2 Consecutive Elevations over Baseline DBP					
	≥5mmHg	≥8mmHg	≥10mmHg	≥12mmHg	≥15mmHg	≥20mmHg
Placebo (n=163)	47 (29%)	36 (22%)	26 (16%)	10 (6%)	9 (6%)	3(2%)
Sibutramine 10 mg (n=161)	69 (43%)	53 (33%)	48 (30%)	21 (13%)	16 (10%)	9 (6%)
15 mg (n=161)	67 (42%)	48 (30%)	42(26%)	20 (12%)	12 (7%)	7 (4%)
p-value, trend test	0.1525	0.1214	0.0320	0.0647	0.4275	0.2434

Conclusion:

From the trend analysis, the sibutramine 20 mg causes a significant increase in the proportion of "outliers". When the 20 mg patients were not in the analysis in study BP852 or in study SB1047 which had 3 treatment groups of placebo, 10 mg and 15 mg of sibutramine most trend analyses are not significant.

Lee-Pin Pian
Mathematical Statistician

cc:

Archival NDA 20-632
HFD-510
HFD-510/SSobel
HFD-510/GTroendle
HFD-510/BStadel
HFD-510/EColman
HFD-715/division file, DMarticello, LPian
Chron.
Pian/word/meridia/3/8/97

Attachment 2

MAR 13 1997

CONSULT RETURN

DATE: March 13, 1997

FROM: Division of Biometrics 2 (HFD-715)

THRU: Project Manager

TO: Document Room, HFD-510

SUBJECT: Original statistical review attached

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Please log-in attached statistical review consult and copy all HFD-510 recipients.

Contact person in case of questions: Dan Marticello, 443-3510, ext 78

Thank you.

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MEMORANDUM OF CONSULTATION

Date: MAR 13 1997

Between: Bruce Stadel, M.D. (HFD-510)

And: Lee-Ping Pian, Ph.D. (HFD-715)

Subject: Meridia Capsules Amendment to Pending NDA 20-632 Dated January 3, 1997

To follow up on the memorandum of consultation dated March 11, 1997 the proportion of patients with two consecutive blood pressure elevations over baseline of ≥10, ≥15 and ≥20 mm Hg were compared between sibutramine and placebo for the systolic blood pressure and ≥5, ≥10, and ≥15 mm Hg for the diastolic blood pressure. The doses of sibutramine 5 mg, 10 mg, and 15 mg were combined in Study BP852 and the 10 mg and 15 mg sibutramine groups were combined in Study SB1047. The comparison between sibutramine and placebo was made for each study separately and the two studies were combined using the Mantel-Haenszel method. For completeness, the 20 mg sibutramine group is also compared to the placebo group in Study BP852.

Systolic blood pressure

The proportions by treatment group and the p-values of the chi-square test are displayed in Table 1 and Table 2 for Studies BP 852 and SB 1047, respectively.

Table 1. Study BP 852 - Proportion of Patients with 2 Consecutive Elevations over Baseline on Systolic BP, ITT Population

Treatment Group	n	2 Consecutive Elevations over Baseline SBP		
		≥10mmHg	≥15mmHg	≥20mmHg
Placebo	148	43 (29%)	18 (12%)	10 (7%)
Sibutramine 5 mg, 10 mg, & 15 mg	453	182 (40%)	80 (18%)	47 (10%)
p-value		0.02	0.12	0.19
Sibutramine 20 mg	146	71 (49%)	39 (27%)	24 (16%)
p-value, 20mg vs. Placebo		0.0006	0.0016	0.0094

Table 2. Study SB 1047 - Proportion of Patients with 2 Consecutive Elevations over Baseline on Systolic BP, ITT Population

Treatment Group	n	2 Consecutive Elevations over Baseline SBP		
		≥10mmHg	≥15mmHg	≥20mmHg
Placebo	163	56 (34%)	29 (18%)	21 (13%)
Sibutramine 10 mg, & 15 mg	322	131 (41%)	75 (23%)	58 (18%)
p-value, Chi-Square		0.18	0.16	0.15

The Cochran-Mantel-Haenszel test and the estimated common odds ratio with the 95% confidence interval for the two studies combined (with no sibutramine 20 mg group in Study BP852) are as follows:

Table 3. Meta-analysis of the SBP Combining BP852 & SB1047

	2 Consecutive Elevations over Baseline SBP		
	≥10mmHg	≥15mmHg	≥20mmHg
Common Odds Ratio (C.I.)	1.465 (1.107, 1.937)	1.466 (1.024, 2.099)	1.547 (0.996, 2.342)
p-value, CMH Chi-Square	0.008	0.037	0.052

Diastolic Blood Pressure

The same tests were performed on the diastolic blood pressure for the two studies.

Table 4. Study BP 852 - Proportion of Patients with 2 Consecutive Elevations over Baseline on DBP, ITT Population

Treatment Group	n	2 Consecutive Elevations over Baseline DBP		
		≥5mmHg	≥10mmHg	≥15mmHg
Placebo	148	55 (37%)	29 (20%)	6 (4%)
Sibutramine 5 mg, 10 mg , & 15 mg	453	205 (45%)	122 (27%)	31 (7%)
p-value, Chi-Square		0.09	0.07	0.22
Sibutramine 20 mg	146	86 (59%)	52 (36%)	15 (10%)
p-value, 20 mg vs. Placebo		0.0002	0.0021	0.0395

Table 5. Study SB 1047 - Proportion of Patients with 2 Consecutive Elevations over Baseline on DBP, ITT Population

Treatment Group	n	2 Consecutive Elevations over Baseline DBP		
		≥5mmHg	≥10mmHg	≥15mmHg
Placebo	163	47 (29%)	26 (16%)	9 (6%)
Sibutramine 10 mg , & 15 mg	322	136 (42%)	90 (28%)	28 (9%)
p-value, Chi-Square		0.004	0.003	0.214

The Cochran-Mantel-Haenszel test and the estimated common odds ratio with the 95% confidence interval for the two studies combined (without the 20 mg group in Study BP852) is as follows:

Table 6. Meta-analysis of the DBP Combining BP852 & SB1047

	2 Consecutive Elevations over Baseline DBP		
	≥5mmHg	≥10mmHg	≥15mmHg
Common Odds Ratio (C.I.)	1.578 (1.197, 2.080)	1.745 (1.256, 2.425)	1.677 (0.938, 2.999)
p-value, CMH Chi-Square	0.001	0.001	0.081

Lee-Ping Wang, Ph.D.
Mathematical Statistician

cc:

Archival NDA 20-632
HFD-510
HFD-510/SSobel
HFD-510/GTroendle
HFD-510/BStadel
HFD-510/EColman
HFD-510/MHess
HFD-715/division file, DMarticello, LPian
Chron.
Pian/word/meridia/3/12/97

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Figure 1

Mean Placebo Subtracted Change from Baseline in Resting SBP in Outliers

Sibutramine 5 – 20 mg – Observed Data

Study BPI 852

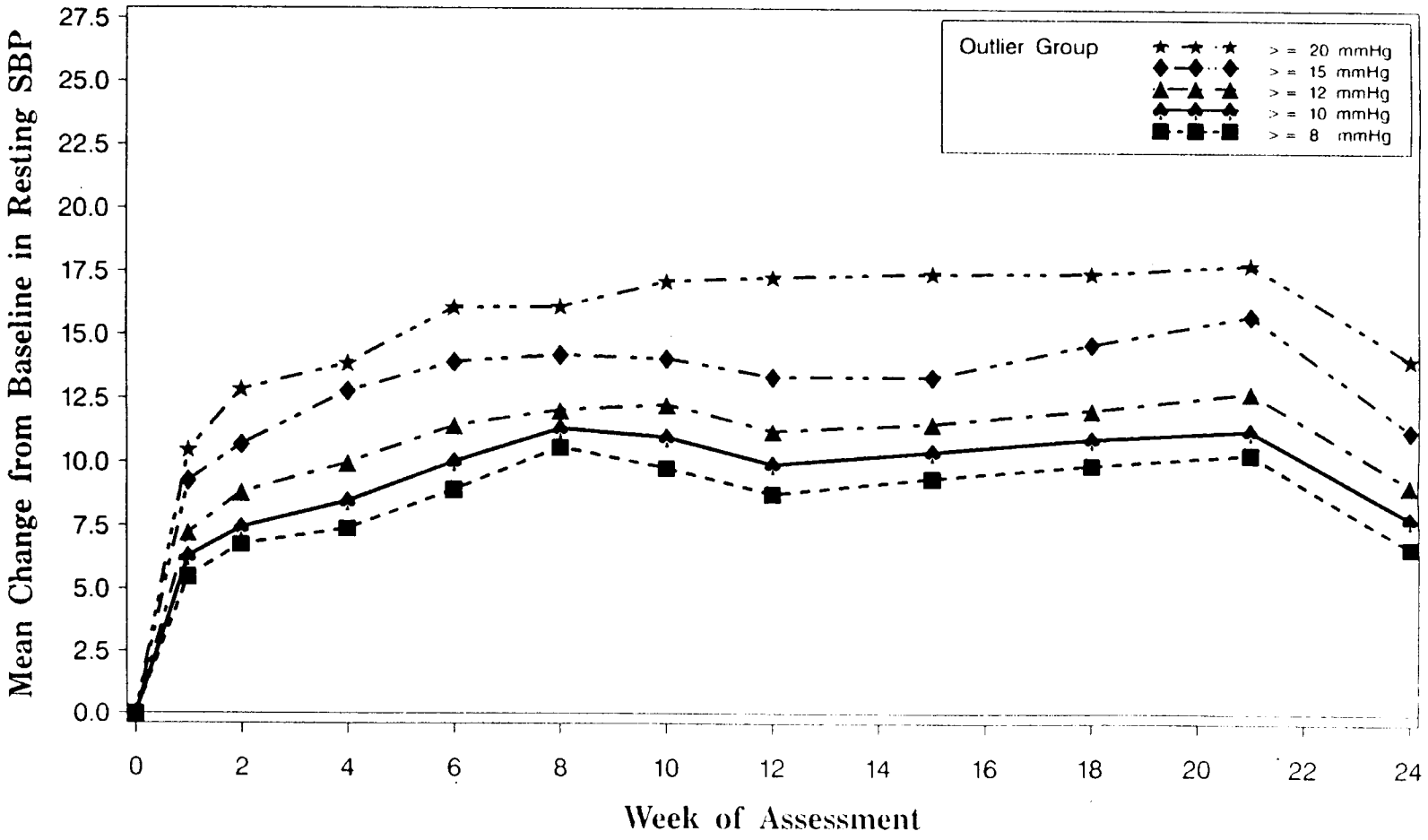


Figure 2

Mean Placebo Subtracted Change from Baseline in Resting DBP in Outliers

Sibutramine 5 – 20 mg – Observed Data

Study BPI 852

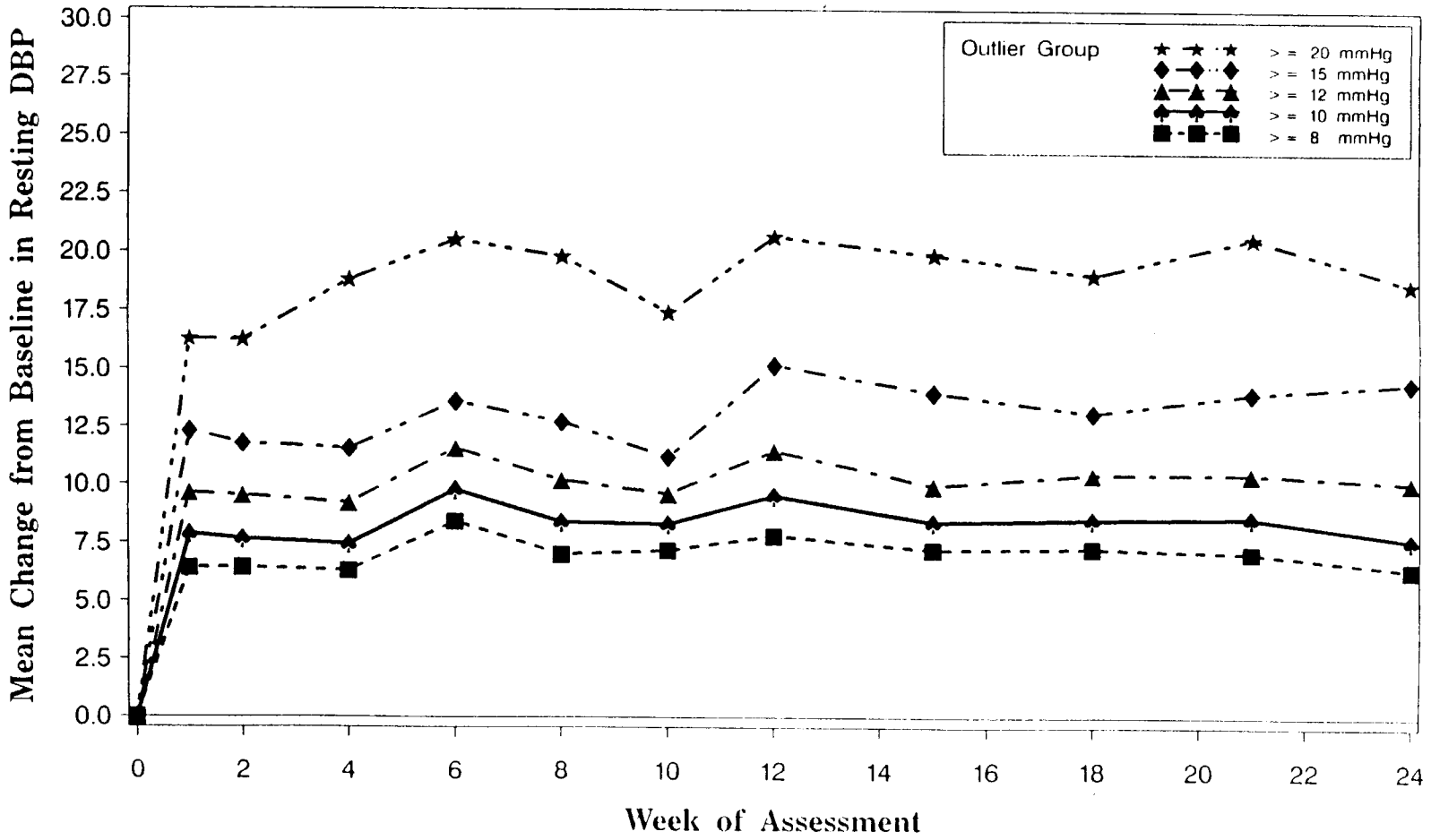


Figure 3

Mean Placebo Subtracted Change from Baseline in Resting SBP in Outliers

Sibutramine 10 – 15 mg – Observed Data

Study SB 1047

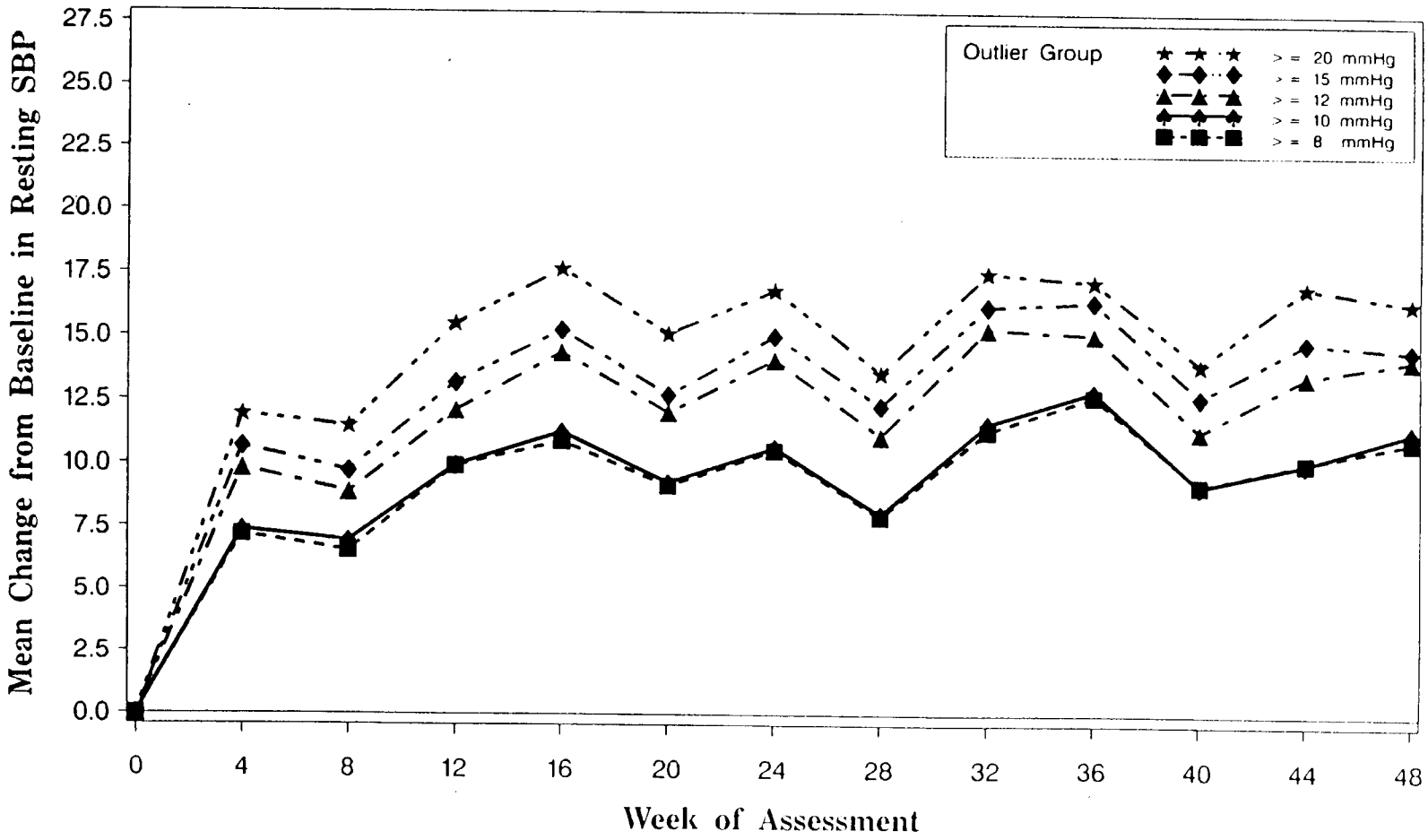
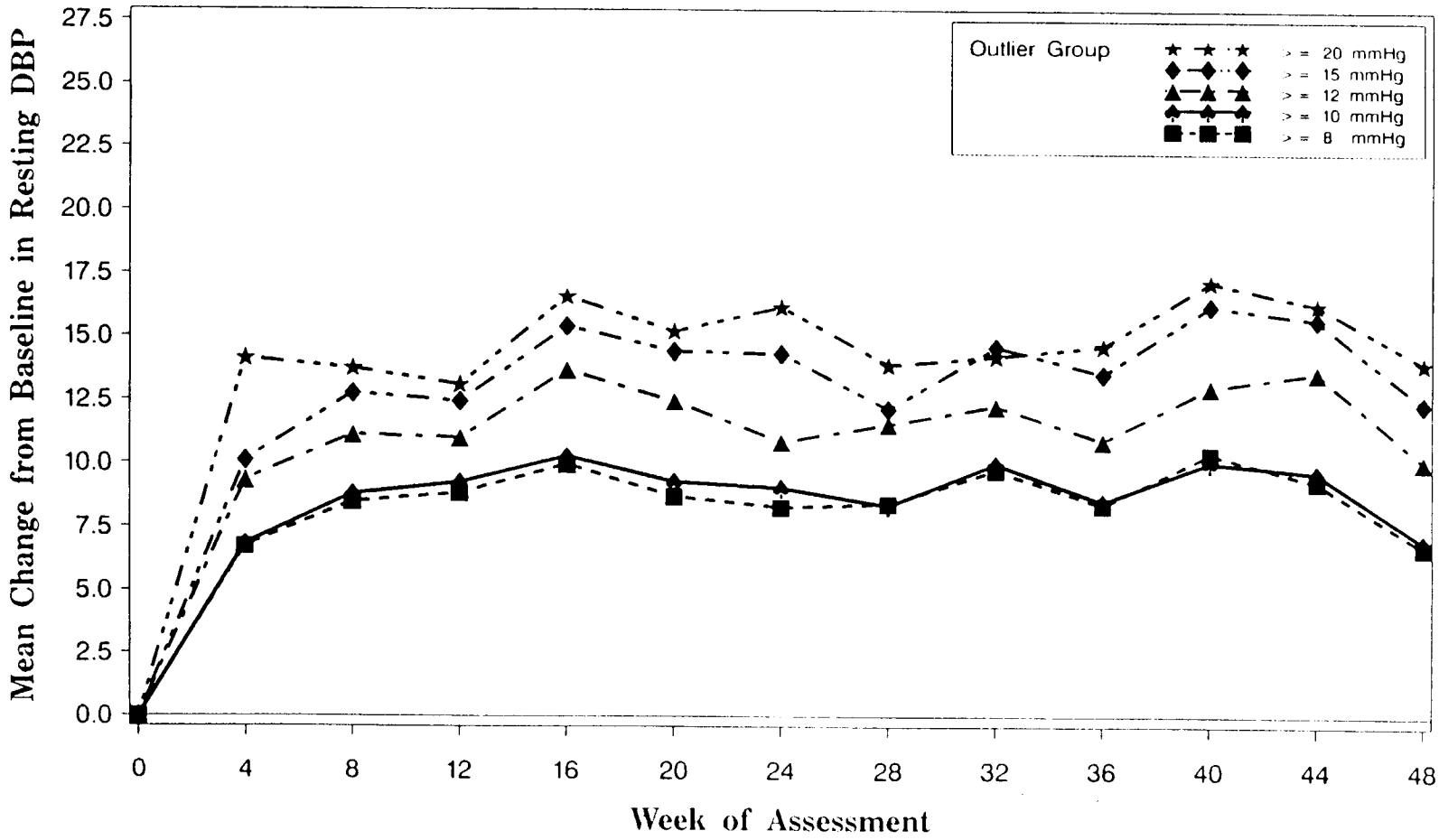


Figure 4

Mean Placebo Subtracted Change from Baseline in Resting DBP in Outliers

Sibutramine 10 – 15 mg – Observed Data

Study SB 1047



MEMORANDUM

DATE: October 16, 1996

APPEARS THIS WAY
ON ORIGINAL

FROM: Eric Colman, M.D.
TO: NDA 20-632

SUBJECT: Abuse Potential of Sibutramine Hydrochloride

A memorandum dated 10/16/1996 from Michael Klein, Ph.D. and Belinda Hayes, Ph.D., reviewers from HFD-170, indicates that there are 2 ongoing preclinical studies examining the abuse potential of Sibutramine. The reviewers conclude: "....there is currently insufficient data to make a recommendation on the appropriateness of scheduling or not scheduling Sibutramine."

This Reviewer concurs with the conclusion from Drs. Klein and Hayes.

Eric Colman, M.D. 10/16/96

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ON ORIGINAL

SEP - 4 1996

CONSULT RETURN

DATE: September 4, 1996

FROM: Division of Biometrics 2 (HFD-715)

TO: Document Room, HFD-510

SUBJECT: Original statistical review attached

Please log-in attached statistical review consult and copy all HFD-510 recipients.

"PLEASE DO NOT COPY HFD-715 RECIPIENTS"

Contact person in case of questions: Dan Marticello, 443-3510, ext. 78.

Thank you.

Statistical Review and Evaluation

SEP

NDA#: 20-632/Class 1S

Applicant: Knoll Pharmaceutical Co.

Name of Drug: MERIDIA™ (Sibutramine hydrochloride monohydrate) capsules

Indication: Antiobesity

Documents Reviewed: Vols. 1.1, 326-540
Submission dated August 9, 1995

Background:

MERIDIA is a new class of serotonin (5-HT) and norepinephrine (NE) reuptake inhibitors that was studied for the long-term treatment of obesity.

The NDA includes two large multicenter, placebo-controlled studies conducted in the United States and the United Kingdom with 1047 and 485 patients respectively. Nine other placebo-controlled studies and one active-controlled (dexfenfluramine) study were also included in the submission.

The dose ranging study, BPI 852-USA, was conducted at 7 sites over a 24-week therapy period with treatment groups 1 mg, 5 mg, 10 mg, 15 mg, 20 mg and 30 mg/day sibutramine versus placebo. The number of patients were 149, 151, 150, 152, 146, 151 vs. 148, respectively. Male to Female ratio was 20/80. Black/Caucasian/Oriental ratio was 15/77/8. Age ranged from 19-65 with a mean of 43.6. The average baseline body mass index (BMI) (30-40 kg/m^2, inclusive) was 35 kg/m^2.

Study SB 1047-UK was conducted at 12 sites with a duration of 12-months of therapy in the treatment of mild-to-moderate obesity patients (27-40 kg/m^2). The treatment groups were sibutramine 10 mg or 15 mg/day and placebo with 161, 161 and 163 patients, respectively. The male to female ratio was 20/80 and 99% of the patients were Caucasian.

SB 1049-France is a ongoing study with 12-months duration of therapy.

Study Protocol - BPI 852

The primary objectives are

1. To compare the effects of the above mentioned doses of sibutramine and placebo on weight loss in obese patients when given in conjunction with modest caloric restriction, exercise, and behavior modification for up to 12 weeks.

2. To assess the effects of sibutramine and placebo on supine and standing heart rate in obese patients after 2 and 12 weeks.

3. 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.

The secondary objective is to assess the efficacy, safety, and tolerability of sibutramine for up to 24 weeks in obese patients.

Study Design

This was a multicenter, double-blind, repeated-dose, placebo-controlled, parallel-group, dose-ranging study. After screening and a 2-week placebo run-in period, patients were randomized to one of 7 treatment groups for a **12-week double-blind** treatment period, followed by a second 12-week modified double-blind extension. All patients had the option of entering a long-term extension study BPI 852X. Patients not entering BPI 852X completed a mandatory 6-week placebo washout period before returning for a final study visit. Patients who had ongoing adverse events at either premature termination or the final study visit had follow-up visits scheduled until the adverse events had resolved or stabilized. Throughout the study, including the placebo run-in and washout period, patients received ancillary therapy comprising of an individualized caloric restriction plan, a standard exercise regimen and modest behavior modification program.

Dose Reduction

In the event of an intolerable adverse event, or two mean supine pulse rates greater than 100 bpm, or a blood pressure greater than 160 mmHg (systolic) or 95 mmHg (diastolic), the patient's dose was reduced (fall back) or the patient was discontinued from medication, as appropriate.

Protocol Amendments

Four amendments were made to the original study protocol (approved on 4/16/92). Amendment 1 (approved on 6/8/92) included altering the BMI range for patient inclusion from 27-40 kg/m^2 to 30-40 kg/m^2, renaming the exercise program to an activity

program, and limiting activities solely to walking, and renaming the 'behavior modification program' to read 'lifestyle changes.'

Amendment II included accommodation of formal statistics relating to dose-ranging, efficacy, and safety for sibutramine over the entire 24-week period of study. All references to a 'modified double-blind period' (referring to the last 12 weeks of the study) were removed.

Amendment III (approved on 10/15/92) permitted women of childbearing potential who used adequate contraception to participate in the study.

Amendment 4 (approved 10/15/92) allowed an additional enrollment of 25 patients at each of 3 of the 7 study sites, bringing the total target enrollment at those 3 sites up to 175 patients.

Statistical Methodology

Two sets of statistical analyses were performed. The first analysis includes only the data recorded before any dose reductions which were permitted by the protocol. The second analysis includes all data recorded for a patient.

Primary Efficacy Analysis

The primary efficacy variable is the change from baseline in body weight (kg). Analysis of variance with treatment, center, and treatment by center interaction in the models was used for the primary efficacy variable at each time point to evaluate treatment differences. Fisher's Least Significant Difference (LSD) method was used for pairwise treatment comparisons. A repeated measures analysis is used to compare the overall treatment effects across time.

Regression analysis was used to assess the dose-response relationship. Williams test was used to determine the minimum effective dose if the assumptions for the test are valid. If the assumptions of normality or homogeneity of variance are violated, distribution free trend tests were performed. If there are no treatment by center interactions, Page's trend tests for a two-way layout is used. If significant interactions are present, Jonckheere's test for each center is performed.

Missing data were handled by two approaches. The first approach used the last observation carried forward (LOCF) technique. The second approach used an observed cases analysis.

Analysis of Safety

The primary safety parameter is the change from baseline in heart rate. The ANOVA technique was used. Regression analysis was used to characterize the dose-response relationship. Other safety parameters such as electrocardiograms and vital signs were evaluated using descriptive statistics.

BPI 852-USA Results

A total of 1463 patients were screened , and of these, 1047 eligible patients were randomized at 7 sites to one of the 7 treatment groups for 24 weeks of therapy: placebo, 148; 1mg, 149; 5 mg, 151; 10 mg, 150; 15 mg, 152; 20 mg, 146; 30 mg, 151. The dose retained efficacy analyses approach included 1024 patients in the evaluable population (placebo, 142; 1 mg, 144; 5 mg, 148; 10 mg, 148; 15mg, 150; 20 mg, 145; 30 mg, 147).

The 23 excluded patients had no weight evaluation (16 patients) after baseline or only a 'phone-in' weight (6 at Week 24 and 1 not at Week 24). The dose reduction data retained **intent-to-treat (ITT) LOCF** analysis at Week 24 included the 6 patients with Week 24 'phone-in' weight which resulted in a total of 1030 patients.

Eighty percent of the study population are female (842 subjects) and 20% were male (205 subjects) with 77% Caucasians, 15% Blacks and 8% Mexican American. The mean age was 43.6 years, with a range of 19 to 65 years. The mean BMI was 35 kg/m^2. Baseline vital signs were considered low for an obese population with treatment group mean ranges of 67-69 bpm; 114-117 mmHg; 74-76 mmHg for pulse rate, supine systolic blood pressure, and diastolic blood pressure, respectively.

Disposition of Patients

Of the 1047 randomized patients, 824 (78%) patients completed 12 weeks therapy and 684(65%) patients completed 24 weeks therapy. Site 4 had 10-12 patients in each treatment group and the rest of sites had 20-26 patients in each treatment group. Table I. displays the number of patients by site and treatment group at randomization and at Week 24.

Table I. Number of Patients at Randomization and (Week 24) by Treatment and Site

Site	Placebo	1 mg	5 mg	10 mg	15 mg	20 mg	30 mg	Total
1. Blackburn	26(16)	25(17)	25(16)	25(21)	25(16)	24(14)	25(17)	175(117)
2. Bray	24(19)	24(21)	25(21)	25(19)	25(20)	24(22)	26(21)	173(143)
3. Ferguson	22(10)	22(15)	21(18)	20(12)	22(15)	21(14)	22(16)	150(100)
4. Greenway	10(8)	11(7)	12(9)	10(4)	12(5)	10(4)	10(5)	75(42)
5. McMahon	24(12)	25(13)	25(20)	26(16)	25(16)	25(19)	25(15)	175(111)
6. Mendels	22(12)	21(14)	21(13)	22(15)	21(14)	21(11)	22(13)	150(92)
7. Schwartz	20(11)	21(10)	22(12)	22(12)	22(11)	21(10)	21(14)	149(80)
Totals	148(88)	149(97)	151(109)	150(99)	152(97)	146(94)	151(100)	1047(684)

Table II and Figure 1 display numbers and percentages of randomized subjects by visit and treatment.

Table II. Number & % of Randomized Patients by Visit & Treatment

Trt	0	1	2	4	6	8	10	12	15	18	21	24	27*	30*
Placebo	148	142 96%	135 91%	129 87%	122 82%	114 77%	110 74%	106 72%	101 68%	96 65%	90 61%	88 59%	66 45%	53 36%
1 mg	149	144 97%	138 93%	134 90%	129 87%	127 85%	124 83%	118 79%	113 76%	106 71%	103 69%	97 65%	68 46%	61 41%
5 mg	151	148 98%	144 95%	139 92%	138 91%	133 88%	132 87%	127 84%	121 80%	117 77%	116 77%	109 72%	74 49%	58 38%
10 mg	150	148 99%	145 97%	141 94%	132 88%	128 85%	124 83%	120 80%	115 77%	110 73%	106 71%	99 66%	69 46%	61 41%
15 mg	152	150 99%	146 96%	137 90%	132 88%	124 82%	118 78%	114 75%	110 72%	108 71%	104 68%	97 64%	69 45%	51 33%
20 mg	146	145 99%	142 97%	135 92%	123 84%	120 82%	118 81%	116 79%	115 79%	110 75%	105 72%	94 64%	72 49%	57 39%
30 mg	151	148 98%	144 95%	140 93%	133 88%	131 87%	128 85%	123 81%	119 79%	112 74%	108 72%	100 66%	71 47%	56 37%

*6-week single-blind placebo washout after Week 24

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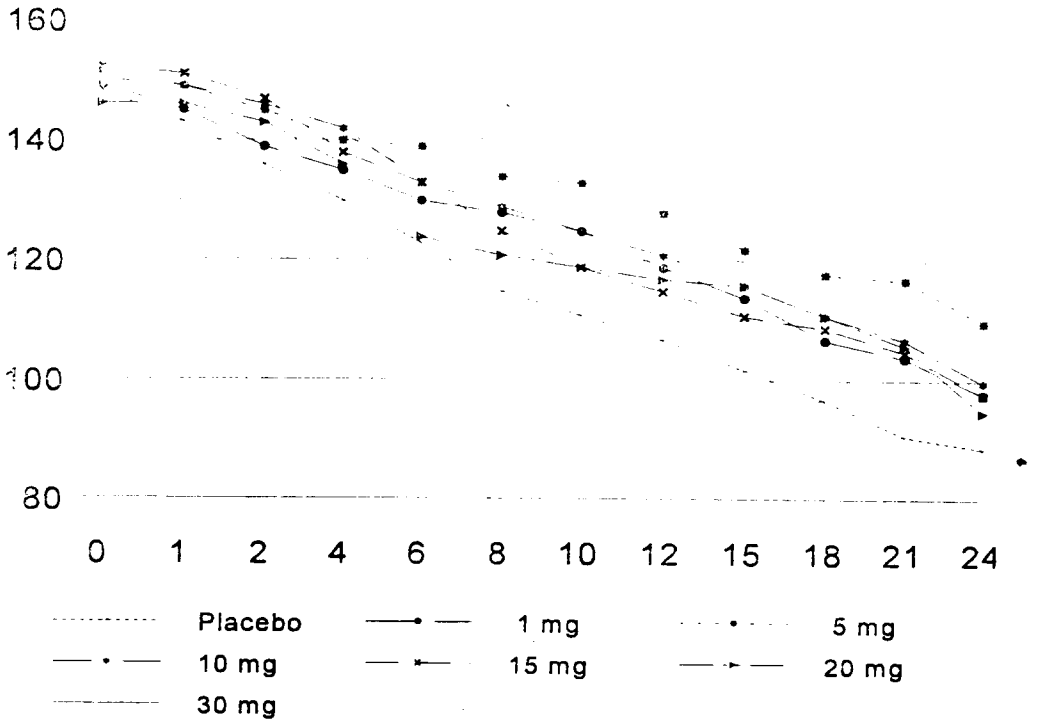
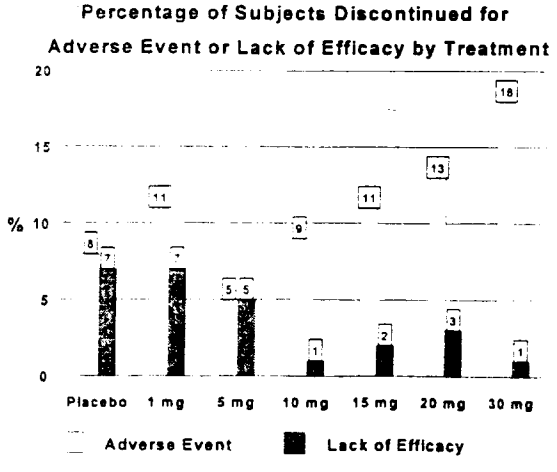
Fig 1. # of Randomized Subjects by Visit & Treatmen

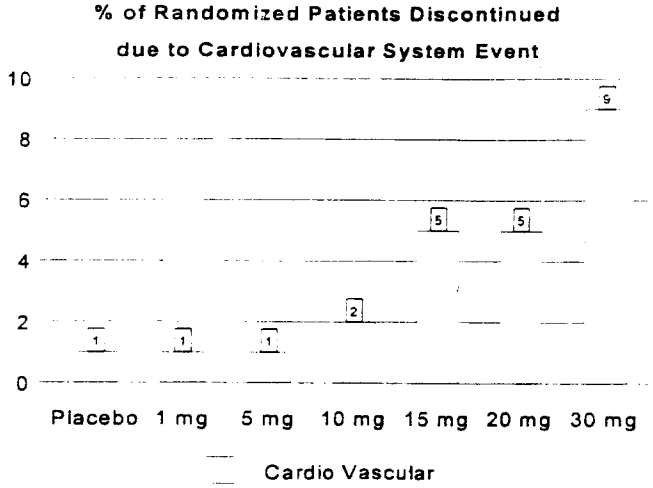


The final status of patients by treatment group is displayed in Table III and figures that follow:

Table III. Status of Patients by Treatment Group

Final Status	Placebo 148	1 mg 149	5 mg 151	10 mg 150	15 mg 152	20 mg 146	30 mg 151	Total 1047
Adverse Event	12 8%	17 11%	8 5%	13 9%	17 11%	19 13%	27 18%	113 11%
Lack of Efficacy	11 7%	11 7%	8 5%	2 1%	3 2%	4 3%	2 1%	41 4%
Lost to Follow-up	2 1%	2 1%	2 1%	4 3%	5 3%	4 3%	3 2%	22 2%
Protocol Violation	26 18%	17 11%	20 13%	27 18%	22 14%	20 14%	14 9%	146 14%
Other	10 7%	7 5%	6 4%	5 3%	7 5%	3 2%	4 3%	42 4%
Completed Study	87 59%	95 64%	107 71%	99 66%	98 64%	96 66%	101 67%	683 65%





Of the 113 discontinued patients due to an adverse event, 31 (31%) discontinued due to a cardiovascular system event.

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

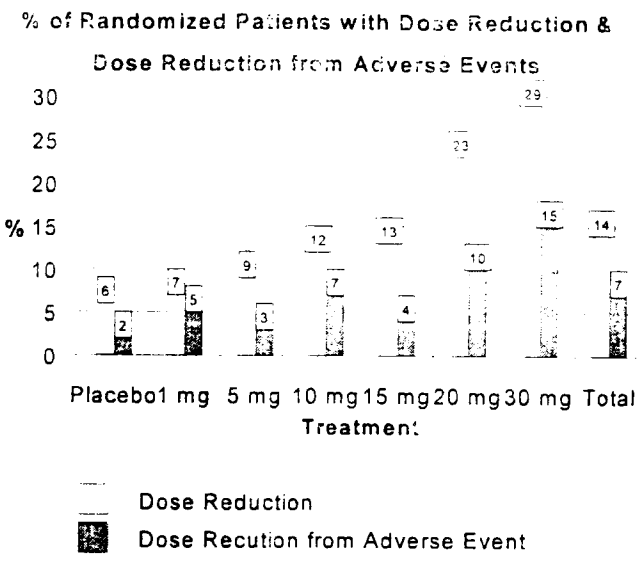
Trt	Placebo (148)	1 mg (149)	5 mg (151)	10 mg (150)	15 mg (152)	20 mg (146)	30 mg (151)	Total (1047)
Cardio Vascular Hypertension	2(1%) 1	1(1%) 0	1(1%) 1	3(2%) 0	8(5%) 2	7(5%) 3	13(9%) 7	35(3.3%) 14

Efficacy analyses were performed in evaluable (1024) and completed patients for LOCF and observed (evaluable patients only). For analysis of dose response, data after a reduction in dose were excluded, only data from randomized dose were included (dose reduction data eliminated data set). For overall efficacy, all data were analyzed (dose reduction data retained data set.)

The number and percent of patients with dose reductions were 9(6%), 10(7%), 14(9%), 18(12%), 20(13%), 33(23%) and 44(29%) for the placebo, 1 mg, 5 mg, 10 mg, 15 mg, 20 mg and 30 mg dosage groups, respectively, as displayed in Table IV.

Table IV. Dose reduction and adverse event related reduction by treatment group

Treatment # Randomized Patients	Placebo 148	1 mg 149	5 mg 151	10 mg 150	15 mg 152	20 mg 146	30 mg 151	Total 1047
#(%)with dose reduction	9 (6%)	10 (7%)	14 (9%)	18 (12%)	20 (13%)	33 (23%)	44 (29%)	148 (14%)
Permanent dose reduction due to Adverse Event	3 (2%)	7 (5%)	4 (3%)	10 (7%)	6 (4%)	15 (10%)	23 (15%)	68 (7%)



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A total of 7 analyses were performed on change from baseline weight loss at Week 24. The names and sample sizes of the analyses are as follows:

	Dose Reduction Retained	Dose Reduction Eliminated
ITT LOCF	n=1030	------
Evaluable LOCF	n=1024	n=1022*
Evaluable OC	n= 653	n= 572
Completers LOCF	n= 683	n= 681

*primary analysis

A "visit window" analysis was employed because of the large number of discrepancies between the scheduled and actual visit dates. The number of days between baseline visit and the actual visit was calculated and the data was assigned to a study week according to the defined "windows", e.g. week 1 (day 1-10), week 2(day 11-21),..., week 24(day 159-179).

Baseline

Baseline blood pressure and pulse rate were not significantly different between treatment groups but mean baseline vital signs were relatively low for this population. The baseline mean vital signs are as follows:

	Supine	Standing
Systolic BP(mmHg)	115.5	114.8
Diastolic BP(mmHg)	75.1	78.4
Pulse (bpm)	67.6	74.5

The baseline mean weight was not significantly different between treatment groups . Although there were

statistically significant differences in BMI (34.0-34.9 kg/m , P=0.14 and percent over ideal body weight (58.8-63.1 , P=0.103, the differences are not clinically significant.

Efficacy Analysis

The last observation carried forward analyses on the dose reduction retained data set with least square mean changes from baseline with treatment, center and treatment by center interaction in the model of BMI, percent change of weight from baseline, and weight change from baseline in kilogram by treatment and visit are displayed in Table V and figures which follow.

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Table 1. Baseline and change from baseline by treatment & Week

Week	Variable							
Baseline	n BMI Weight	142 34.91 96.53	144 34.10 94.73	148 34.33 96.34	[illegible]	144 34.33 93.71	148 34.54 96.08	147 34.98 [illegible]
1	n BMI % Weight Weight	134 -0.04 -0.13 -0.13	135 -0.15 -0.44 -0.40	142 -0.25 -0.78 -0.69	[illegible]	[illegible]	137 -0.46 -1.34 -1.27	[illegible]
2	n' BMI % Weight Weight	142 -0.20 -0.58 -0.54	143 -0.29 -0.98 -0.81	148 -0.41 -1.71 -1.59	147 -0.58 -1.71 -1.59	149 -0.76 -2.21 -2.06	144 -0.74 -2.16 -2.07	147 -0.88 -2.54 -2.40
4	BMI % Weight Weight	-0.20 -0.59 -0.55	-0.42 -1.24 -1.14	-0.62 -1.80 -1.73	-0.85 -2.50 -2.33	-1.03 -2.99 -2.79	-1.11 -3.24 -3.10	-1.32 -3.81 -3.61
6	BMI % Weight Weight	-0.33 -0.97 -0.92	-0.53 -1.58 -1.45	-0.81 -2.34 -2.24	-1.09 -3.21 -2.98	-1.37 -3.97 -3.72	-1.42 -4.14 -3.95	-1.72 -4.95 -4.68
8	BMI % Weight Weight	-0.38 -1.12 -1.07	-0.56 -1.66 -1.52	-0.90 -2.62 -2.52	-1.21 -3.57 -3.32	-1.51 -4.38 -4.11	-1.60 -4.67 -4.44	-1.93 -5.55 -5.27
10	BMI % Weight Weight	-0.37 -1.10 -1.05	-0.62 -1.83 -1.68	-1.02 -2.97 -2.86	-1.31 -3.87 -3.60	-1.62 -4.69 -4.41	-1.69 -4.94 -4.69	-2.10 -6.04 -5.74
12	BMI % Weight Weight	-0.40 -1.18 -1.13	-0.69 -2.06 -1.88	-1.07 -3.11 -2.99	-1.40 -4.12 -3.87	-1.78 -5.16 -4.84	-1.85 -5.41 -5.12	-2.32 -6.67 -6.34
15	BMI % Weight Weight	-0.39 -1.16 -1.10	-0.67 -2.00 -1.82	-1.11 -3.20 -3.08	-1.43 -4.20 -3.93	-1.81 -5.22 -4.92	-1.91 -5.59 -5.29	-2.41 -6.92 -6.56
18	BMI % Weight Weight	-0.42 -1.21 -1.15	-0.64 -1.92 -1.74	-1.11 -3.23 -3.12	-1.54 -4.54 -4.26	-1.90 -5.51 -5.19	-1.95 -5.73 -5.39	-2.53 -7.25 -6.87
21	BMI % Weight Weight	-0.33 -0.97 -0.92	-0.67 -1.98 -1.82	-1.05 -3.06 -2.97	-1.54 -4.54 -4.28	-1.88 -5.44 -5.12	-2.05 -6.03 -5.66	-2.53 -7.27 -6.88
24	BMI % Weight Weight	-0.31 -0.91 -0.87	-0.62 -1.85 -1.67	-1.04 -3.01 -2.92	-1.59 -4.67 -4.39	-1.97 -5.70 -5.36	-2.10 -6.15 -5.78	-2.66 -7.64 -7.22
27	n BMI % Weight Weight	68 -0.26 -0.73 -0.71	63 -0.95 -2.81 -2.54	70 -0.96 -2.80 -2.62	68 -1.78 -5.29 -4.99	68 -2.14 -6.21 -5.73	67 -2.51 -7.25 -6.88	68 -2.90 -8.20 -7.81
30	n BMI % Weight Weight	53 -0.17 -0.46 -0.49	61 -0.90 -2.63 -2.40	59 -0.83 -2.44 -2.28	60 -1.23 -3.71 -3.52	50 -1.69 -4.90 -4.52	60 -1.95 -5.88 -5.20	56 -2.67 -7.58 -7.16

n' unchanged from week 2 to week 24

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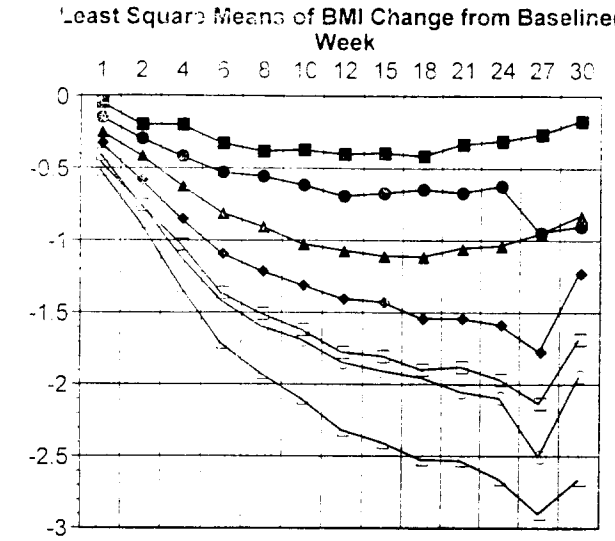
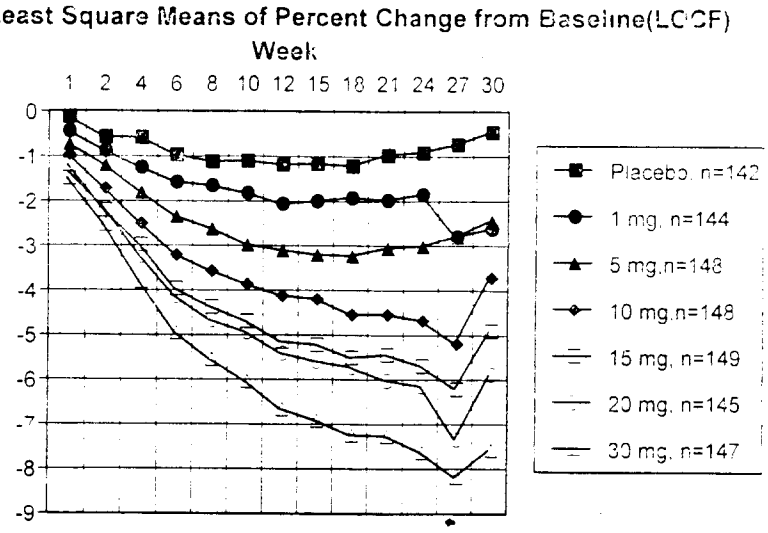
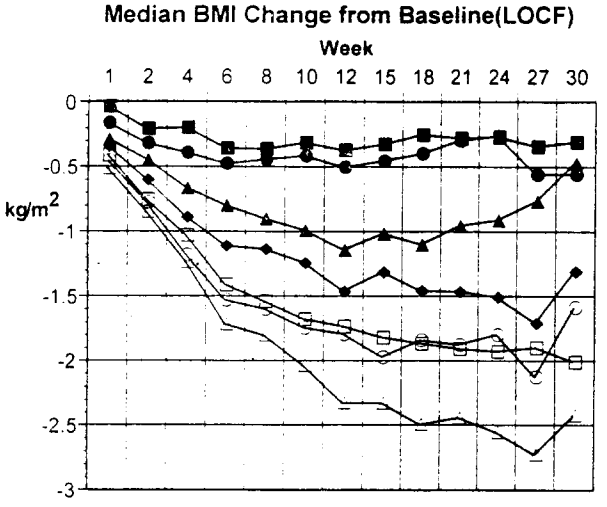
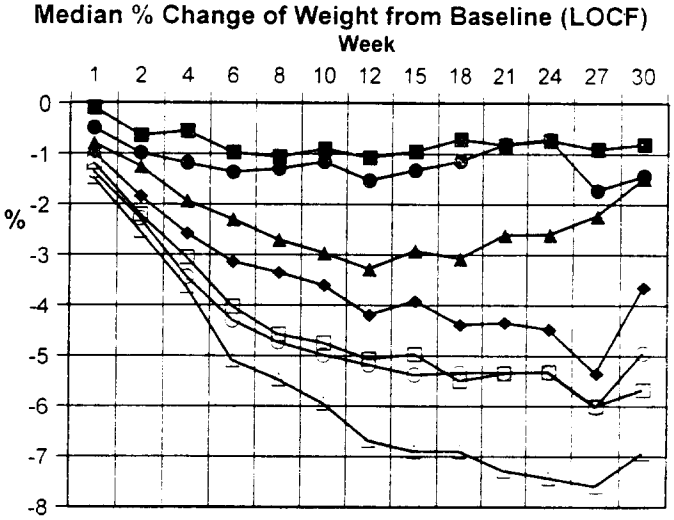








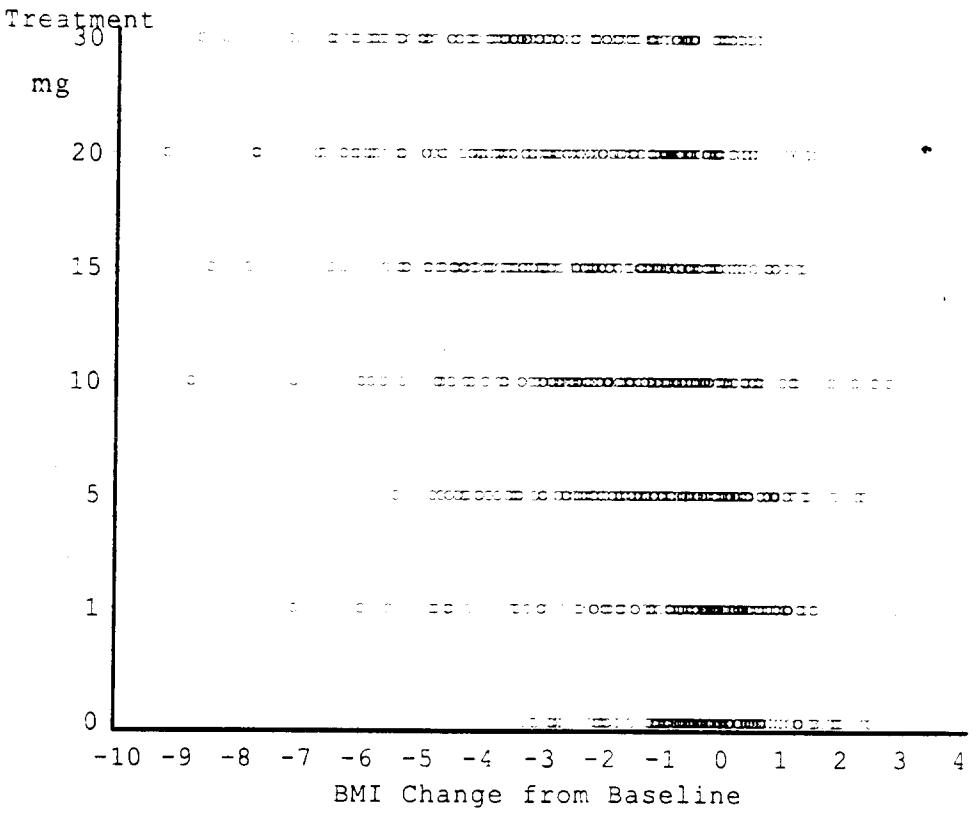
It is noted that the double-blind treatment phase ended at week 24. Those patients who entered a six-week washout phase were assessed at weeks 27 and 30 (patients could enter a two-year, open-label extension study BPI 852X).

The median change in BMI, percent of Weight, and Weight from baseline to Week 24 is as follows:

	0	1 mg	5 mg	10 mg	15 mg	20 mg	30 mg
BMI Change	-0.27	-0.26	-0.91	-1.51	-1.93	-1.80	-2.56
% Wt Change	-0.74	-0.72	-2.61	-4.48	-5.33	-5.35	-7.44
Wt Change	-0.75	-0.70	-2.40	-3.90	-5.10	-5.10	-7.00

The change from baseline in BMI at week 24 by treatment group is displayed in Fig 2.

Figure 2. Change from baseline of BMI at Week 24 by Treatment group

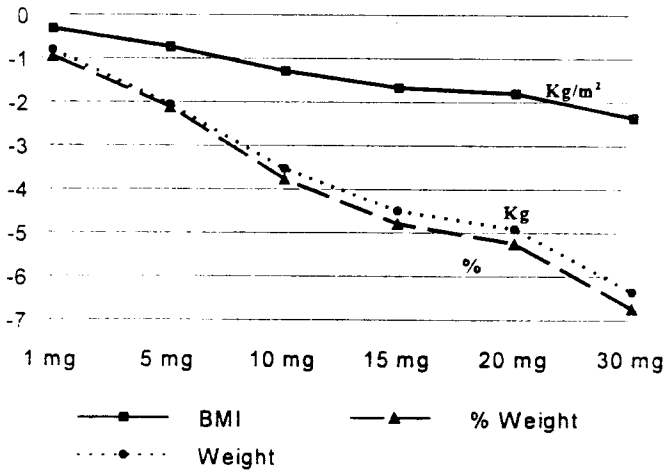


The difference from placebo in least square mean change from baseline at Week 24 by treatment group is displayed in Table VI and Fig. 3.

Table VI. Difference from placebo of mean* change from baseline at Week 24

Difference from (Placebo)	1 mg	5 mg	10 mg	15 mg	20 mg	30 mg
BMI (-0.31kg/m²)	-0.31	-0.73	-1.28	-1.66	-1.79	-2.35
% Weight (-1.91%)	-0.94	-2.10	-3.76	-4.79	-5.24	-6.73
Weight (-0.87kg)	-0.80	-2.05	-3.52	-4.49	-4.91	-6.35

Fig 3. Difference from Placebo in Mean* Change from Baseline at Week 24 (LOCF)



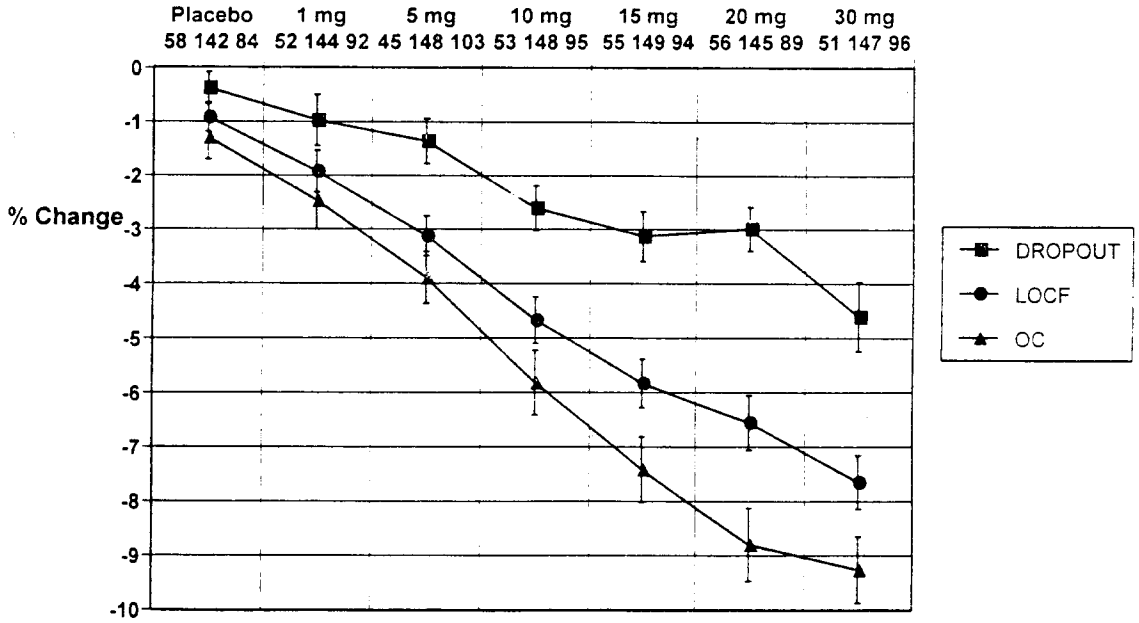
* least squared mean (LSM)

At week 24, treatment groups 20 mg, and 30 mg had a 5% or more reduction in percent change of weight from baseline.

In the overall analysis of efficacy LOCF, dose retained , on percent change from baseline with treatment, site, and treatment-by-site interaction in the model, there were dose-related decreases. The overall analysis at Weeks 1, 2, ...,24 were all significant with p=0.001. The Dunnett's test of all treatments against a placebo showed that for the 1 mg treatment group, only at Week 4 was it statistically significantly better than placebo (-1.24% vs -0.69%) the rest of the weeks it was not significantly different from the placebo. All treatment groups other than 1 mg (5mg, 10mg, 15mg, 20 mg, 30 mg), at all time points, showed a significantly greater percent weight loss than placebo with p=0.001. The treatment-by-center interactions were not significant (p≥0.9).

The observed cases analysis results were similar to those of the LOCF analysis. Fig. 4 displays the percent weight changes for the three datasets of patients (dropout, LOCF, & OC) at Week 24. Numbers under the treatment groups are sample sizes for the three populations. The "Dropout" includes patients who had carried forward data which has a sample size of the difference between LOCF and OC.

Fig. 4 **BPI 852-Week 24 Mean % Change of Body Weight from Baseline**



Percentage of Patients Losing 5 and 10 % Baseline Weight

The Medical Officer requested an intent-to-treat analysis to compare to the observed cases analysis for those responders with greater than 5% and 10% weight loss from baseline weight. The number of 5 and 10% responders at Week 12 and Week 24 is summarized in the following table:

Treatment	Week	Total n		Percentages of Responders			
				5% Responders		10% Responders	
		LOCF	OC	LOCF # (%)	OC # (%)	LOCF # (%)	OC # (%)
Placebo	12	148	98	17(11.5%)	16(16.3%)	0(0.0%)	0(0.0%)
	24	"	84	**18(12.2%)**	**16(19.1%)**	**0(0.0%)**	**0(0.0%)**
1 mg	12	149	114	25(16.8%)	24(21.1%)	8(5.4%)	8(7.0%)
	24	"	92	**27(18.1%)**	**22(23.9%)**	**10(6.7%)**	**9(9.8%)**
5 mg	12	151	125	50(33.1%)	50(40.0%)	3(2.0%)	3(2.4%)
	24	"	103	**47(31.1%)**	**40(38.8%)**	**13(8.6%)**	**13(12.6%)**
10 mg	12	150	115	59(39.3%)	56(48.7%)	6(4.0%)	6(5.2%)
	24	"	95	**68(45.3%)**	**57(60.0%)**	**18(12.0%)**	**17(17.9%)**
15 mg	12	151	108	76(50.0%)	69(63.9%)	15(9.9%)	15(13.9%)
	24	"	94	**79(52.0%)**	**63(67.0%)**	**35(23.0%)**	**34(36.2%)**
20 mg	12	146	111	74(50.7%)	72(64.9%)	25(17.1%)	25(22.5)
	24	"	89	**75(51.4%)**	**65(73.0%)**	**37(25.3%)**	**36(40.4%)**
30 mg	12	151	117	96(63.6%)	86(73.5%)	35(23.2%)	30(25.6%)
	24	"	96	**93(61.6%)**	**72(75.0%)**	**53(35.1%)**	**43(44.8%)**

When compared to placebo for 5% responders, only 1 mg is not significantly different from placebo (p=0.15, week 24), the rest of the sibutramine groups are significantly better than placebo at p≤0.001. For the 10% responders analysis, all sibutramine groups are better than placebo (no responder) with p≤0.001.

Weight Gain

Number of patients gaining weight relative to baseline for evaluable patients, using an LOCF analysis with dose reduction data retained is in the following table:

Week	Treatment, n						
	0mg	1mg	5mg	10mg	15mg	20mg	30mg
	142	144	148	148	150	145	147
12	45(31.7%)	34(23.6%)	27(18.2%)	12(8.1%)	8(5.3%)	8(5.5%)	4(2.7%)
24	**53(37.3%)**	**51(35.4%)**	**40(27.0%)**	**20(13.5%)**	**15(10.0%)**	**13(9.0%)**	**12(8.2%)**

More patients gained weight at week 24 than at week 12 for all doses. An increase in dose is associated with a smaller percentage of patients gaining weight.

Vital Signs

The two-way analysis of variance was applied to the change from baseline for standing pulse rate, supine pulse rate, standing diastolic blood pressure and standing systolic blood pressure for weeks 12 and 24. At week 12, ~25% data were missing and at week 24, ~38% data were missing.

At week 12, the overall test showed that p=0.026 for change from baseline for standing systolic blood pressure. The p-values for standing pulse rate, supine pulse rate, and standing diastolic blood pressure are all 0.0001. The change for standing pulse rate of 20 mg and 30 mg was significant compared to placebo at the week 1 visit. At week 12, the change for standing pulse rate in the sibutramine 5 mg to 30 mg groups was significantly higher when compared to placebo (a difference of 3 to 8 beats more than placebo).

At week 24, the overall test of treatment effect is not significant for change from baseline for standing systolic blood pressure. Other outcomes all are statistically significant at p≤0.001.

On the change for standing diastolic blood pressure, the repeated measure analysis using all available data from week 1 to week 24 showed that Meridia 15 mg and 20 mg are significantly different from placebo and a trend for 30 mg vs. placebo after multiple comparison adjustment (Dunnett, p=0.026, 0.0064 and 0.059, respectively). The same analysis on the change for standing systolic pressure is not significant (p=0.17). Mean changes from baseline for weight, standing pulse rate, standing diastolic blood pressure, and standing systolic blood pressure by treatment at week 24 are summarized in the following table:

Table VII. Mean Change in Vital Signs from Baseline to Week 24(OC)

Treatment	n	Weight	Pulse rate	Diastolic	Systolic
0	84	-1.26	-0.35	0.46	0.52
1	92	-2.24	-0.60	-1.64	0.85
5	103	-3.74*	2.78	0.18	0.76
10	95	-5.50*	4.40*	2.43	4.09
15	94	-7.01*	5.81*	4.10*	4.53
20	88	-8.36*	7.63*	2.64	3.52
30	96	-8.82*	5.25*	2.25	3.31

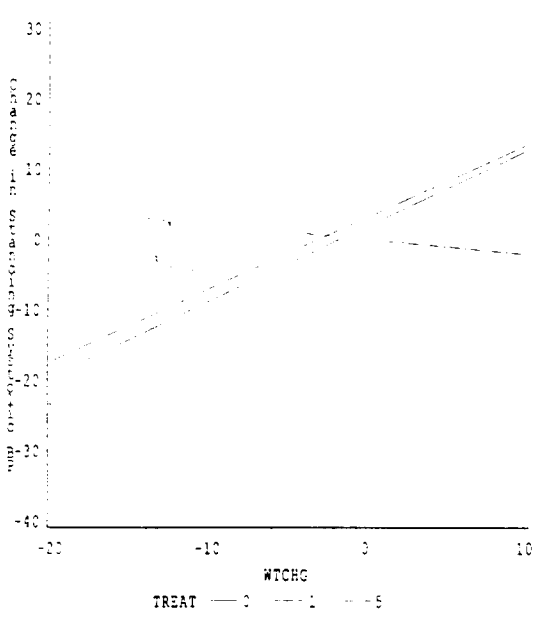
* Significant compared to placebo (Dunnett's test)

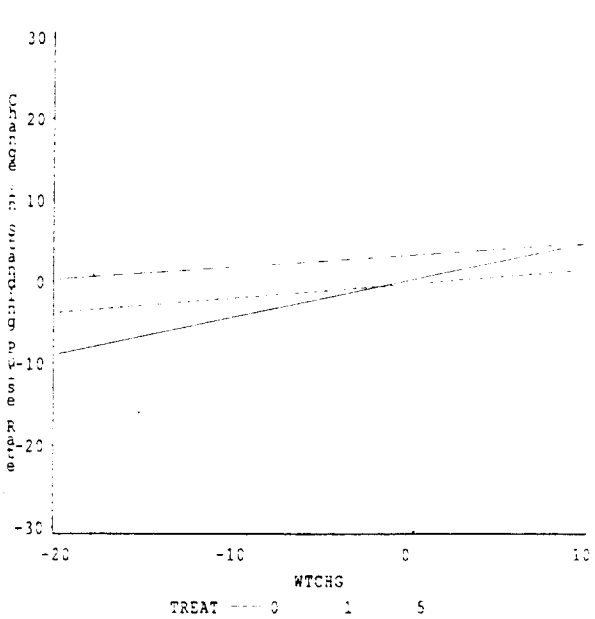
The correlation between change from baseline weight and change from baseline blood pressure or pulse rate showed that in the sibutramine treated groups there is poor correlation between weight change and vital sign change. However, in the placebo group the Pearson correlation is statistically significant as the following table shows:

Table VIII. Correlation of Weight Change and Vital Signs

Treatment	Weight	SBP(corr)	p	Pulse(corr)	p
0	**-1.3**	**0.52(0.30)**	**<0.01**	**-0.35(0.25)**	**0.02**
1	-2.2	0.85(0.29)	<0.01	0.34(0.10)	0.34
5	-3.7	0.76(-.08)	0.40	2.78(0.08)	0.42
10	-5.5	0.41(0.01)	0.90	4.40(-.08)	0.43
15	-7.0	4.53(0.22)	0.03	5.81(0.07)	0.49
20	-8.4	3.52(0.11)	0.30	7.81(0.14)	0.20
30	-8.8	3.31(0.12)	0.23	5.25(0.04)	0.70

The following figures shows the linear regression relationship between weight change from baseline and the vital sign change from baseline for placebo, 1 mg and 5 mg.





The sponsor concluded that the poor correlation suggests that although a patient may have had a large loss in body weight this was not necessarily correlated with a large positive change in vital signs.

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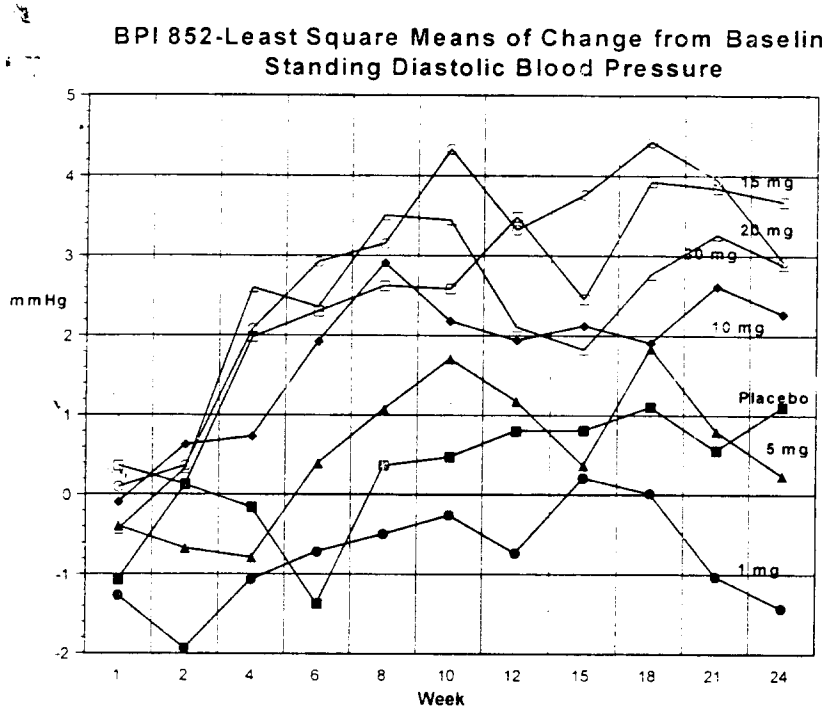
The least square mean change from baseline in standing diastolic blood pressure over the treatment period is displayed in the following graph:



Heart Rate

At each time point the overall treatment effect is statistically significant ($p<0.001$). The dose-related increases in heart rate were evident. Changes in heart rate at week 24 were as follows: placebo, 1 bpm; 1 mg, 3 bpm; 5 mg, 5 bpm; 10 mg, 5 bpm; 15 mg, 5 bpm; 20 mg, 6 bpm; 30 mg, 10 bpm.

Conclusion:

This study of 24 weeks duration demonstrated the efficacy of sibutramine starting from 5 mg of weight loss for obese patients. The weight loss (kg) from baseline on last observation carried forward data analysis at week 24 was 0.9, 1.7, 2.9, 4.4, 5.4, 5.8, and 7.2 for placebo, 1 mg, 5 mg, 10 mg, 15 mg, 20 mg and 30 mg, respectively. For patients who lost 5% or more from baseline weight, the percentages were 12%, 18%, 31%, 45% 52%, 51% and 62%, respectively, from the placebo to 30 mg sibutramine groups. The mean vital signs were relatively low for the population under investigation. The standing pulse rate change and standing diastolic blood pressure change were significantly increased

compared to placebo. At week 24, the difference between sibutramine groups and the placebo group ranged from 3-5 bpm for change of pulse rate and the greatest difference from placebo mean change in standing diastolic blood pressure was 3 mmHg in the sibutramine 15 mg group.

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Study SB1047-UK

This was a double-blind, parallel-group, multicenter study to assess efficacy and safety of sibutramine 10 and 15 mg treatment compared with placebo for a year in mild to moderately obese patients (BMI, 27-40 kg/m^2).

Study objectives were 1). To assess the long-term efficacy and tolerability of sibutramine in the treatment of mild to moderate obesity and 2). To assess the long-term safety of sibutramine in mild to moderate obesity.

Eligible patients were patients in General Practice of either sex with a age of 18 to 65 years, and a BMI within the range of 27-40 kg/m^2. Patients who had lost more than 3 kg in the previous 3 months were to be excluded from the study. Patients with a seated pulse rate of over 100 beats/minute (bpm) or a seated diastolic blood pressure of greater than 100 mmHg on repeated measurements were to be excluded, as were patients being treated for hypertension, except where the condition had been stabilized by medication for 6 months or more.

Patients who fulfilled the entry criteria at screening (week -2) were allocated a **study number** and entered a washout period of 14 days, during which time patients received a dietary advice sheet for them to follow throughout the study. Patients' bodyweight was recorded at the beginning and end of a 2-week washout period to determine weight change during this period. At baseline (week 0) and monthly follow-up, the investigator recorded the patient's weight, blood pressure, pulse rate, and dietary compliance. Patient's self-assessments were recorded using visual analogue scales. At months 0, 6 and 12, the patients' waist and hip circumferences were recorded. Patients entered the 12-month, double blind treatment phase of the study and received either sibutramine 10 mg, 15 mg or placebo, once-daily in the morning. The treatment allocation was determined by the patient **study number** received at screening. Patients were assessed each month throughout the treatment period.

The assessments were summarized as follows:

Week	Month[1]	Assessments
-2	0,1,2,...,12,E[2],13	
-2		Eligibility & consent, Demographics, Medical history, Medication history, History of obesity, Hamilton depression scale, Alcohol usage
-2	12	Physical examination
-2	6, 12	Laboratory, ECG
-2,	0,1,2,...,12, 13	Weight Blood pressure and heart rate Patient self assessment of hunger, satiety and appetite
	0, 6, 12	Waist & hip circumferences
	0,1,2,...,12, 13	Dietary compliance, Concomitant therapy changes
	1,2,...,12, 13	Adverse events
	12,E[2]	Beck Depression Inventory State Anxiety Inventory
-2	3,6,9,12	Pregnancy test(if appropriate) tobacco usage

[1]Double-blind treatment phase from baseline (Month 0) to Month 12 with monthly visit, Month 13 is a no treatment follow-up visit
[2]Extra assessment one week after the month 12 assessment(added by a protocol amendment.

Physical examination was performed at screening and at month 12, and any clinically significant changes from "baseline" were recorded on an adverse event form. A protocol amendment, approved May 28, 1993, added two patient self-assessments at month 12: a 20-point State Anxiety Inventory and a 21-point Beck Depression Inventory. It was intended that approximately 100 patients would fill in these inventories at the month 12 assessment and again one week later to assess whether patients experienced changes in depression or anxiety symptoms after stopping treatment.

If a patient withdrew from the study, withdrawal assessments were completed. These included all the assessments performed at month 12. The patient also returned at the planned month 12 visit for assessment.

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A follow-up assessment was carried out at month 13 or one month after withdrawal.

Reviewer's Comment on the Randomization

Eligible patients should be randomized at baseline visit not at the screening visit (week -2). The randomization should occur after washout and just prior to the double-blind phase to ensure patients are not "lost" (25 withdrew during washout) after randomization because drop-outs prior to the baseline visit might lead to an imbalance in the treatment groups. Also, patients who are eligible at the screening visit might not be so at the baseline visit. For the entry criteria of not losing >3kg in 3 months prior to study commencement, there were 16 patients who lost >3kg during washout who were classified as protocol violators.

Patients Disposition

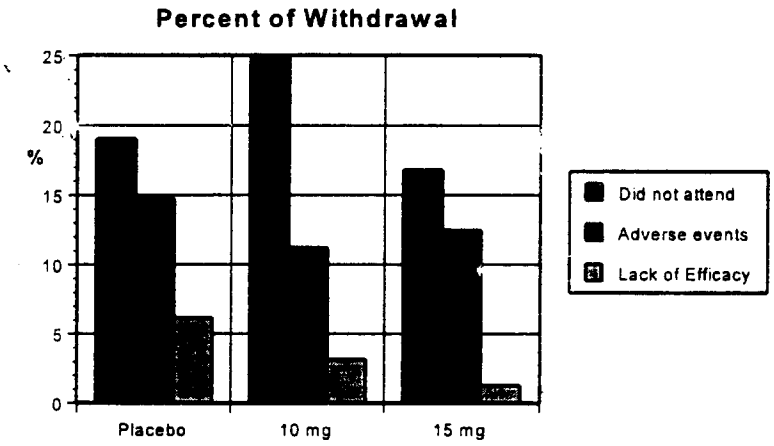
A total of 510 patients were "entered" between May 21 and October 23, 1992. Four hundred and eighty-five (485) patients entered the double-blind phase and 256 patients (53%) completed the 12-month study. The following table displays the number of patients who entered the double-blind phase by center and treatment group:

Table IX. Study SB-1047 - Number of patients by center and treatment group

Site	Placebo		10 mg		15 mg		Total	
	Entered	Completed	Entered	Completed	Entered	Completed	Entered	Completed
1	31	13	28	11	32	17	**91**	**41**
2	35	7	35	10	34	14	**104**	**31**
3	4	2	3	1	4	2	**11**	**5**
4	6	6	8	6	8	4	**22**	**16**
5	9	5	10	[illegible]	12	9	**31**	**21**
6	11	3	11	6	11	5	**33**	**14**
7	16	12	16	13	15	13	**47**	**40**
8	14	5	13	6	13	6	**40**	**17**
9	12	11	12	6	11	11	**35**	**28**
10	8	5	8	5	7	4	**23**	**14**
11	7	6	7	3	4	2	**18**	**11**
12	10	5	10	8	10	7	**30**	**20**
Total	**163**	**80**	**161**	**82**	**161**	**94**	**485**	**256**

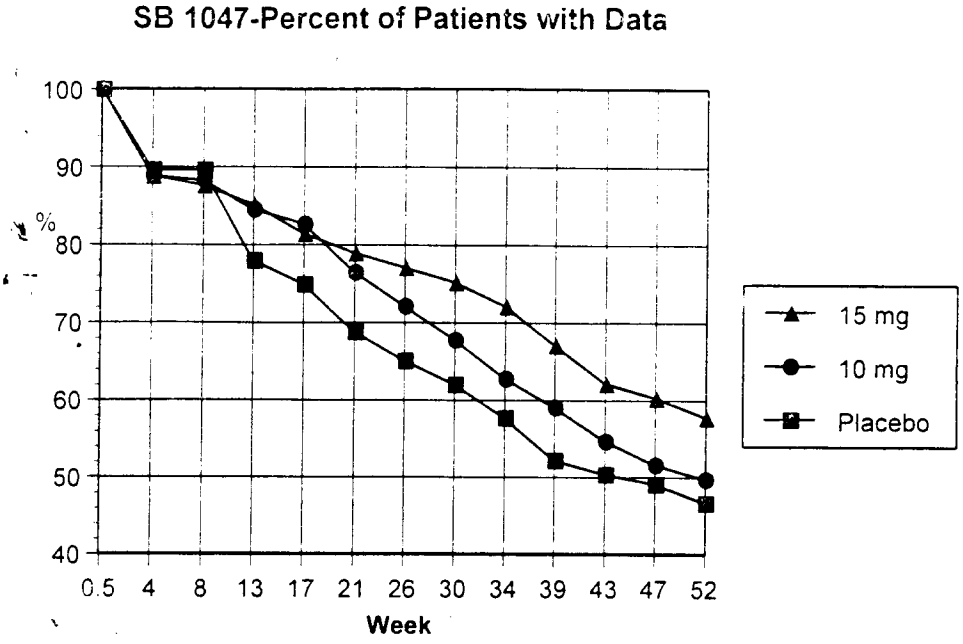
Reasons for withdrawal are summarized in the following table:

Reasons for Withdrawal	Treatment Group		
	Placebo	10 mg	15 mg
	163	161	161
Adverse events	24	18	20
Lack of Efficacy	10	5	2
Did not attend	31	40	27
Protocol violation	6	7	8
Withdrew consent	9	4	2
Others	3	5	8
Total	83	79	67



Number and percent of patients with data by treatment group and visit week is in the following table and figure:

Week	Placebo		10 mg		15 mg		Overall
0.5	163		161		161		485
4	146	(89.6)	143	(88.8)	143	(88.8)	432
8	146	(89.6)	142	(88.2)	141	(88.2)	429
13	127	(77.9)	136	(84.5)	137	(84.5)	400
17	122	(74.8)	133	(82.6)	131	(82.6)	386
21	112	(68.7)	123	(76.4)	127	(76.4)	362
26	106	(65.0)	116	(72.0)	124	(72.0)	346
30	101	(62.0)	109	(67.7)	121	(67.7)	331
34	94	(57.7)	101	(62.7)	116	(62.7)	309
39	85	(52.1)	95	(59.0)	108	(59.0)	286
43	82	(50.3)	88	(54.7)	100	(54.7)	268
47	80	(49.1)	83	(51.6)	97	(51.6)	258
52	76	(46.6)	80	(49.7)	93	(49.7)	249
Endpoint	157	(96.3)	154	(95.7)	153	(95.7)	464



There were 21 patients, 6, 7, 8, in the placebo, 10 mg, and 15 mg treatment groups, respectively, who did not provide a post-baseline weight assessment. The endpoint (n=464) and carry forward repeated measures analyses excluded these 21 patients. Four hundred and thirty-two patients (432) provided an assessment of bodyweight after month 1 and were included in the repeated measures efficacy analyses, other than the carry forward analysis (n=464).

Protocol Violation

The following table displays the number of patients with some form of violation:

Violation	Placebo	10 mg	15 mg	Overall
<24 days between visits	47	43	39	129
>38 days between visits	55	44	43	142
BMI<27 kg/m^2	1	1	0	2
BMI>40 kg/m^2	1	4	0	5
Lost >3kg during washout	5	8	3	16
Taking prohibited medication	6	4	7	17
Compliance <70%	20	5	7	32
# of patients with at least 1 report	88(54%)	79(49%)	72(45%)	239(49%)

Definitions of evaluable assessments

For efficacy analyses, any assessment >14 days after the pre-determined date of final dosing was ignored.

Sponsor's Efficacy Analysis

Testing of Assumptions:

Baseline imbalances of demographic and obesity history variables were examined with treatment allocations represented by A, B, and C. If imbalance is found, the variable will be included as a covariate in the analysis.

Normality assumption was tested by D'Agostino-Pearson statistic (The American Statistician 1990:44;316-321). Equality of variances was tested by Levene's test (Brown & Forsyth, JASA 1974:69:364-7). If the assumptions were not valid, data were transformed and the tests repeated on the transformed data. The protocol indicated that the rank transformation was the most likely one to be employed if required; but the sponsor found that the logarithmic transformation with constant (Berry, Biometrics 1987;43:439-56) was suitable.

Validating of Assumptions:

The results of tests on homogeneity of variance and normality of residuals were performed on change to endpoint, averaged over time and change to month 12 for completers. The least significant results on change to month 12 for completers raw data and log transformed data are displayed in the following table

Change to month 12 for completers	Levene's test		D'Agostino-Pearson	
	Statistic	p-value	Statistic	p-value
original data	4.22	0.016	21.66	<0.001
log transformed Constant=38	2.94	0.055	7.79	0.02

The sponsor indicated that a constant close to the maximum weight gain was used as the log transformation creates a small number of large outliers; these cause the D'Agostino-Pearson test to reject

the normality assumption at the 5% significance level. After the transformation the p-value for homogeneity of variance (Levene's test) is close to 0.05. The robustness of the F-distribution was appealed and no further transformation is required for the lack of normality.

The datasets that correspond to the analyses are summarized in the following table:

Analysis	Patient Population	Patient #
Outcome analyses	Entered double-blind phase	485
Change to endpoint	with post-baseline bodyweight	464
Repeated measures		
1. Carried forward		464
2. All available data	(with month 1 data), unbalanced	432
3. Completers	256-7(>14 days)	=249
4. As for 2 with missing values replaced by predicted values, balanced		432

Outcome Analysis

This was the sponsor's primary analysis on all patients entering the double-blind phase of the study. The outcome analyses included categorical analyses and ranked analyses. The datasets of outcome analyses were 1). Patients who entered the double-blind phase, 2). Patients who withdrew for reasons unrelated to drug were excluded (defined before unblinding). Also, a further outcome analysis ranked the endpoint change in actual bodyweight. Patients who completed the study were given ranks next to the lowest rank (best outcome) of "treatment success" and the highest rank (worst outcome) was given to patients with adverse events or who had a lack of efficacy. The 2-way analysis on the ranked data included treatment group and center as factors after first determining that the treatment group-by-center interaction was not significant by means of the Boos-Brownie test. The Boos-Brownie test is for use with two treatment groups, the test was performed in a pairwise fashion. In the categorical outcome analysis, patients were divided into categories of least to most favorable outcomes. The completers were divided by their percent weight loss from baseline over the course of the study of 20% or more to weight gain. The withdrawals were classified according to the reasons for withdrawal. Patients who withdrew because of "treatment success" were assigned to the best possible outcome, while those who withdrew because of adverse events or lack of efficacy were assigned to the worst possible category and all other withdrawals to the second worst possible category.

Reviewer's Comment on Sponsor's Analysis

The sponsor proposed assumption tests for normality and homogeneity of variance and the transformation scheme if the assumptions were not met. In Box's 1953 Biometrika paper it was stated that "It has been shown that in the commonly occurring case in which the group sizes are equal or not very different, the analysis of variance test is affected surprisingly little by variance inequalities." The p-values of Levene's test on log transformed dataset (change to endpoint, averaged over time, change to month 12 for completers) were 0.02, 0.06 and 0.055, respectively. For handling dropouts, the sponsor cited Gould (Biometrics 36, 721-727) as the basis of outcome analysis. In that paper only treatment-related withdrawals were accommodated in the analyses while withdrawals for reasons unrelated to treatment were ignored. The sponsor classified treatment unrelated withdrawals into the second worst possible category next to the worst category of adverse events or lack of efficacy. Gould's approach to incorporating withdrawals in the analysis of data is to reflect the possible outcomes for a patient. The treatment unrelated dropout is independent of the factors under study, therefore, to classify them as worse than weight gain is inappropriate.

A correspondence from G. Pledger & D. Hall (Biometrics, March 1982, 0. 276), in reply to the Gould article suggested that no single analysis can be taken alone as a valid comparison of efficacy. Rather, consistency of results among statistical methods based on different ways of handling withdrawals is required. The sponsor's analyses were consistent in showing that sibutramine was effective in the reduction of weight.

Sponsor's categorical outcome analysis for all patients in double-blind phase is displayed in Table X.

Table X. All patients categorical outcome analysis

	Placebo	S10	S15
Total Number of Patients	163	161	161
Outcome category			
1. Treatment successes	1	0	1
2. >20% weight loss	1	3	6
3. 15.1%-20.0% weight loss	1	11	8
4. 10.1%-15.0% weight loss	4	11	23
5. 5.1%-10.0% weight loss	16	21	18
6. 0.1%-5.0% weight loss	29	21	18
7. No change	1	0	2
8. Weight gain	28	15	13
9. Withdrew - other reasons	48	56	44
10 Withdrew - lack of efficacy	34	23	22

and/or adverse event

The treatment comparisons with respective statistics and p-values are displayed in the following table:

Comparison	Statistics	p-value
All treatment groups	χ^2=14.18	0.001
Placebo vs sibutramine 10mg	z=4.21	0.04
Placebo vs sibutramine 15mg	z=14.33	<0.001
Sibutramine 10mg vs 15mg	z=2.66	0.10

The outcome analysis excluding administrative withdrawals was similar to the all patients outcome analysis.

There was no treatment-by-center interaction in the outcome analysis of ranked weight loss and there were statistically significantly better changes in rank in the sibutramine 10 mg and 15 mg groups than in the placebo group (for all patients p=0.03 and p<0.001, respectively).

Analysis of Weight Loss

The repeated measures analyses were performed on 4 datasets for both the actual and percentage bodyweight loss. The sponsor stated that results of all 4 analyses were broadly similar, therefore, only the balanced (predicted values replacing missing values) and completers analyses are described. The log transformation for actual change from baseline is log(13.1-change from baseline). The constant 13.1 was chosen to make the residuals close to a sample from a normal distribution.

The factors in the repeated measures analysis of variance are treatment group, center, the treatment-by-center interaction, time(month), and the treatment-by-time interaction. Where appropriate, the degrees of freedom of between-patient comparisons were adjusted by Satterthwaite's approximation, and for within-patient comparisons by the Greehouse-Geisser adjustment. If, there is a significant treatment-by-time interaction(p<0.1), then differences between the treatment groups at each month were analyzed separately.

In the sponsor's repeated measures analyses on actual bodyweight loss, there was a significant treatment-by-time interaction (p≤0.01) and a treatment effect (p<0.001) for the balanced dataset and completers. The subsequent monthly analysis of variance over the 12-month treatment period all showed significant difference between treatment groups for balanced dataset (p<0.001) and completers (p=0.001).

The mean weight loss from baseline for months 3, 6, 9 and 12 is

displayed in the following table:

Treatment group	n	Adjusted mean weight loss from baseline kg[1] Month 3	Month 6	Month 9	Month 12
Balanced					
Placebo	146	1.6	1.4	1.1	1.2
SB 10 mg	143	**3.8**	**4.0**	**4.1**	**3.7**
SB 15 mg	143	**5.6**	**6.9**	**6.8**	**5.6**
Completers					
Placebo	76	1.8	1.7	1.4	1.8
SB 10 mg	80	**4.7**	**5.4**	**5.2**	4.8
SB 15 mg	93	**6.0**	**7.4**	**7.2**	**6.1**

[1]Mean changes are back-transformed from values used in analysis adjusted for the model
p<0.001 (bold), p<0.01 (underline)

Comparisons between the two sibutramine groups showed that, in the balanced dataset, sibutramine 15 mg lost statistically significantly more weight than sibutramine 10 mg at every month for the balanced dataset (p<0.001). In the completers dataset, it was significant at months 2, 3, 4, 5, 6, 9 and 10 (p<0.05). The mean percent weight loss from baseline were consistent with those for actual weight loss.

The analysis of change in BMI at months 6, and 12 and endpoint showed a statistically significant greater reduction for sibutramine than placebo (p<0.001). Compared to sibutramine 10mg, sibutramine 15mg was better in BMI reduction at those time points (p<0.05).

Proportions of patients with > 5%, 10% and 15% weight loss

Percents of patients who lost more than 5%, 10% and 15% of baseline body weight are displayed in Table IX below:

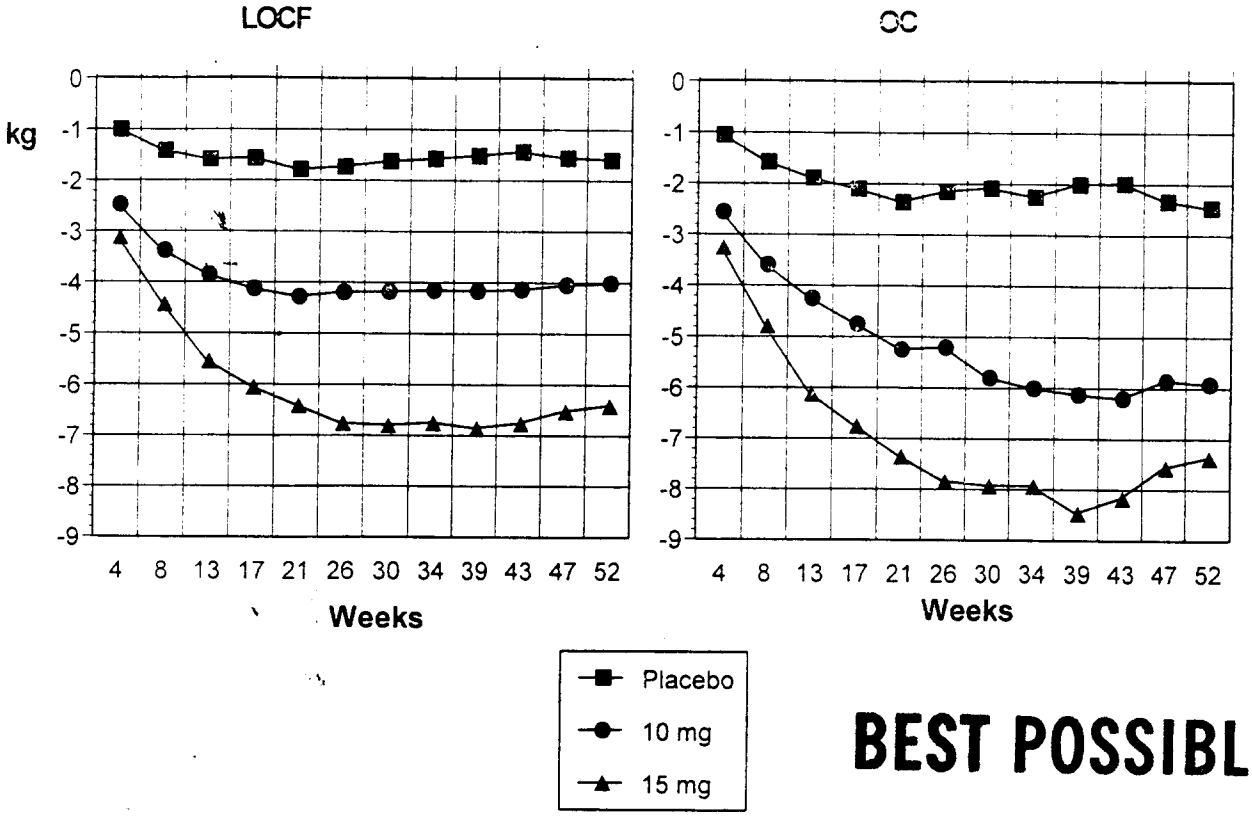
Table IX Percent of patients with change from baseline weight of 5%, 10% and 15%

Treatment	Month 6				Month 12				Endpoint			
	n	5%	10%	15%	n	5%	10%	15%[a]	n	5%	10%	15%
Placebo	106	26	7	4	76	29	8	3	157	20	7	2
S 10 mg	116	**57**	**24**	6	80	**56**	**30**	16	154	**39**	**19**	**10**
S 15 mg	124	**69**	**37**	**18**	93	**65**	**39**	15	153	**57**	**34**	**13**

[a] not analyzed because too few patients
p<.01 compared to placebo

The endpoint analysis showed that 20% of placebo patients, 39% of sibutramine 10 mg patients and 57% of the sibutramine 15 mg patients achieved more than 5% weight loss. The results are statistically significant with p<0.001.

Study SB 1047 - Weight Change from Baseline



Weight change after stopping treatment

The increase in weight of the sibutramine groups from endpoint to the one month follow-up after stopping treatment was statistically significant compared to placebo ($p<0.001$). The adjusted means are 1.1 kg, 1.3 kg, and 0.4 kg, respectively, for 10 mg, 15 mg and placebo.

Reviewer's Analysis

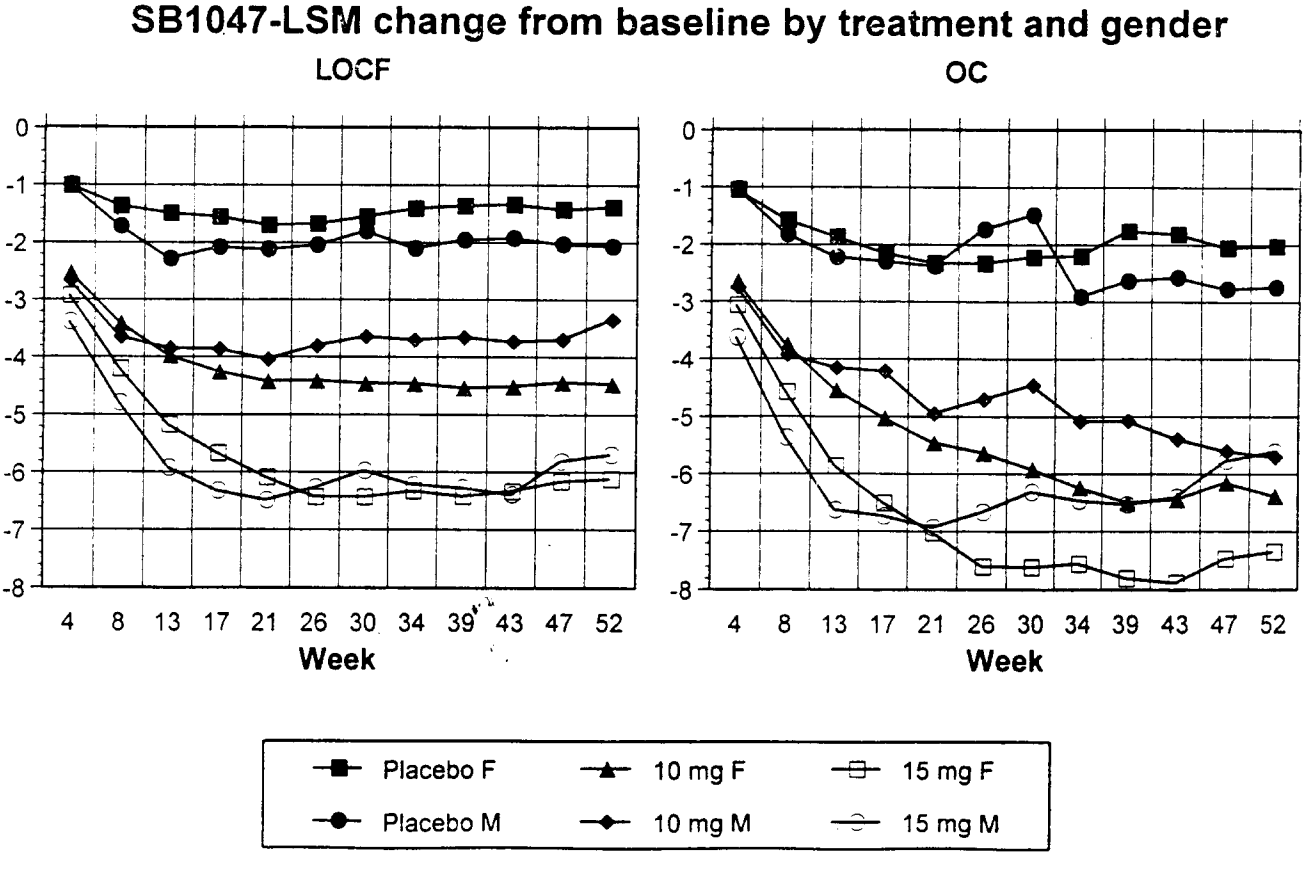
As indicated before, the analysis of variance test can be used safely under most practical conditions. The following graph shows the least square means of weight change from baseline over time for the last observation carried forward and observed cases datasets. The model included treatment, site, and treatment-by-site interaction. The summary of weight change at months 3, 6, 9, and 12 is displayed in Table X.

Table X Summary of least square mean change of weight from baseline

Week	Placebo	Sibutramine 10 mg	Sibutramine 15 mg
LOCF	n=163 LSM(se)	n=161 LSM(se)	n=161 LSM(se)
13	-1.59(0.34)	-3.86(0.35)	-5.55(0.35)
26	-1.74(0.48)	-4.20(0.48)	-6.76(0.49)
39	-1.52(0.52)	-4.18(0.53)	-6.86(0.53)
52	-2.60(0.54)	-4.02(0.55)	-6.42(0.56)
OC	n LSM(se)	n LSM(se)	n LSM(se)
13	127 -1.89(0.41)	136 -4.26(0.37)	137 -6.12(0.37)
26	106 -2.16(0.62)	116 -5.21(0.57)	124 -7.85(0.57)
39	85 -2.01(0.72)	95 -6.14(0.78)	108 -8.48(0.68)
52	76 -2.47(0.83)	80 -5.93(0.88)	93 -7.38(0.82)

The analysis of variance showed statistically significant differences between sibutramine 10 mg and 15 mg compared to placebo at both datasets and all time points and for sibutramine 10 mg compared to sibutramine 15 mg from week 4 on to week 52 on the LOCF dataset. For the OC dataset, the difference between sibutramine 15 mg and sibutramine 10 mg is significant from week 4 to week 30 and it is not significant at week 34 and on to week 52.

The following is a graph for weight change from baseline by



treatment and gender. There is no treatment-by-gender interaction. The ratio of female to male patients is about 3 to 1.

Adverse Events

A total of 1167 adverse events were reported by 364(75%) patients. The number of patients reporting an event and the number of events reported for each treatment group are summarized in the following table:

	Placebo	Sibutramine 10 mg	Sibutramine 15 mg
n	163	161	161
n reporting an event	110(67%)	122(76%)	132(82%)
n of events reported	289	385	493

The number of patients reporting an adverse event was statistically significantly higher in the sibutramine 15 mg treatment group compared with the placebo group ($p<0.001$).

Blood pressure, pulse rate, and ECG

The patient's heart rate, and systolic and diastolic blood pressure (diastolic when Korotkoff sounds have disappeared), were measured, after the patient has been seated for 5 minutes. The change from baseline in systolic blood pressure was not statistically significantly different between treatment groups. There was, a statistically significant difference in change in diastolic blood pressure averaged over all time points. Change from baseline to month 6 pulse rate is significantly different between the sibutramine 15 mg and placebo groups (6.1 bpm vs. 1 bpm) but the change from baseline to month 12 pulse rate is not different for the two groups (1.5 bpm vs -0.2). The increase in heart rate measure from the ECG recording is significant for both 10 mg and 15 mg at month 6 with -1.3 bpm, 4.5 bpm, and 5.8 bmp for the placebo, 10 mg and 15 mg groups, respectively. The change from baseline to month 12 is not significant with 0.6 bpm, 3.1 bpm, and 4.7 bpm for the three treatment groups, respectively.

Conclusion:

The study showed patients on sibutramine lost significantly more weight than placebo. The percent of patients with 5% or more loss of baseline weight was highest in the sibutramine 15 mg group (57%) compared to 39% in the sibutramine 10 mg group and 20% in the placebo group (endpoint analysis, n=464). Weight loss at 12 months were 1.6 kg, 4.0 kg and 6.4 kg for placebo, 10 mg and 15 mg, respectively, on the last observation carried forward dataset. It is consistent with the sponsor's log-transformed 'balanced dataset' analysis which had 1.4 kg, 4.3 kg, and 6.7 kg, respectively, for the three treatment groups. The sibutramine treatment reached maximum

mean weight loss at ~ month 6 and the month 12 results are similar to the month 3 results. The pulse rate and ECG results showed statistically significant increases for the sibutramine groups. The blood pressure was increased in the sibutramine 15 mg group compared to placebo when averaged over all time points. It is concluded that sibutramine 10 mg and sibutramine 15 mg are efficacious in weight loss in mildly obese patients.

Study SB2053

This was a multicenter, double-blind, parallel-group study to compare the effects of sibutramine 10 mg once-daily with dexfenfluramine 15 mg twice-daily, in body weight change in obese patients($BMI \geq 27 kg/m^2$). The study consisted of a 1- to 2-week washout period, a 12-week treatment period and a 4-week follow-up period. A total of 38 centers participated in the study and screened patients between September 15, 1993 and December 30, 1993.

The randomization occurred at the screening visit. A total of 237 patients who fulfilled the entry criteria at screening were allocated a study number and entered a washout period of one to two weeks. Eleven patients withdrew before the baseline visit and, therefore, 226 (112, sibutramine, & 114, dexfenfluramine) patients entered the double-blind treatment phase. A total of 197 patients completed the double-blind phase (102, sibutramine, & 95, dexfenfluramine).

The number and reasons for withdrawal by treatment group is summarized in the table below:

Reason	Treatment Group	
	Sibutramine n=112	Dexfenfluramine n=114
Adverse events	6	11
Lack of efficacy	2	3
Other:withdrew consent	2	4
unable to attend	0	1
Total	10	19

Sponsor's Analysis

Efficacy analyses were performed on intent-to-treat and eligible patient populations. The sponsor considered the analysis of eligible data to be important in addition to the analysis of intent-to-treat data because the trial was designed to establish equivalence and inclusion of patients who were non-compliant and those who violated the protocol in the intent-to-treat analysis would diminish the overall treatment effect and thus make the conclusion of equivalence more likely.

Two patients without a post-baseline assessment of bodyweight were

excluded from the 'intent-to-treat' analysis.

Data from 28 patients were excluded from the eligible analyses because of protocol violations, compliance violations or discrepancies in assessment time relative to study medication. The following table is a summary of these violations:

Violation	Treatment	
	Sibutramine n=112	Dexfenfluramine n=114
Lost>1.5kg during washout	4	5
Assessment>14 days after last study medication	4	5
Baseline assessment >3 days after first medication	0	1
Compliance <75% or >125%	1	4
Taking prohibited medication	1	0
Commenced prohibited medication	3	1
Changed dose of thyroxine/diuretic	2	2
Started thyroxine therapy <6 months before start of study	2	2
# patients with at least 1 report	14	14

Two patients who completed the study but had missing values for weight at week 12 had their week 12 values estimated by interpolation for the repeated measures analysis.

The repeated measures analysis of variance on change in bodyweight included factors for treatment, time and the treatment-by-time interaction. The factor for center was not included in the analyses as the median number of patients recruited at each center was less than 8 patients. The repeated measures analysis was performed on 4 datasets for both patient populations (eligible and intent-to-treat):

1. All available data (unbalanced analysis)
2. All available data with the addition that, for the within group tests, the missing values are replaced by predicted values calculated from the model fitted to the data (balanced analysis). The between group test for treatment effect was not affected
3. All available data, but with missing values replaced by carry forward for both the between and within group tests
4. Patients who completed the 12-week double-blind treatment phase of the study (completers)

The analysis of data set 2 was considered the primary analysis for investigation of equivalence; the other datasets are regarded as sensitivity analyses.

The number of patients who provided bodyweight data at each week for the repeated measures analyses are summarized below:

Data set	Treatment	Week 4	Week 8	Week 12
Intent-to-treat	Sibutramine	112	109	104
	Dexfenfluramine	112	101	96
Total		224	210	200
Eligible	Sibutramine	104	99	91
	Dexfenfluramine	100	91	86
Total		204	190	117

Demographics

The treatment groups were comparable for age, sex, race and height. Ninety-two percent (207/226) were female and 98% (222) were Caucasian. The treatment groups were comparable for bodyweight and BMI for all patients at entry to the study. The median weight was 85.0 kg and the overall mean BMI was 33.5 kg/m^2. However, male patients in the sibutramine group had a higher median weight (126.0kg) and mean BMI ($40.2 kg/m^2$) than those in the dexfenfluramine group (weight 103.2 kg and BMI $34.2 kg/m^2$). The sponsor considered unlikely that these imbalances would affect the study results.

Data set analyzed

A total of 224 patients provided an assessment of bodyweight after baseline and were included in the repeated measures analyses of weight loss.

The assumption of normality was tested as well as the assumption of homogeneity of variance. There were 2 exceptionally large weight losses of 23.2 kg and 21.4 kg in the sibutramine group. The two 'outliers' were replaced by the weight loss corresponding to the next highest residual. This allowed the use of analysis of variance.

The analyses of raw data, in general, had the same conclusion of equivalence as 'winsorized' analyses.

Analysis of actual bodyweight loss

In all analyses of actual weight loss, the treatments were considered equivalent if the difference between treatments was less than 2 kg. The equivalence value of 2 kg was based on advice from French endocrinologists and was used in the study sample size calculations.

For the repeated measure analysis, the test for treatment-by-time

interaction was not significant, the testing of the differences between the treatments was performed for the average value over the three assessment visits.

All four repeated measures analyses are similar, therefore, only the balanced and completers analyses are summarized in the table below:

Data set / Treatment	n	Mean weight loss from baseline(kg) Week 4	Week 8	Week 12	Overall
Balanced					
Sibutramine	112	2.8	4.0	4.6	3.8
Dexfenfluramine	112	2.0	2.9	3.4	2.8
Difference(90% CI)					1.0(0.4,1.6)
Completers					
Sibutramine	102	2.8	4.1	4.7	3.9
Dexfenfluramine	95	2.0	3.0	3.6	2.9
Difference(90% CI)					1.0(0.4-1.6)

Weight loss was greater for sibutramine at each assessment. The 90% confidence intervals were within the pre-determined range for equivalence (-2 kg to +2 kg), therefore, the treatments were considered equivalent.

Reviewer's Analysis

The repeated measurement analysis was carried out using a random effect model of the patient with an unstructured covariance matrix. The 95% confidence interval for the difference between weight loss of sibutramine and dexfenfluramine is 1.1 kg(0.38 kg to 1.77 kg).

Adverse events

Overall, 84 patients in the sibutramine group reported 233 adverse events and 90 patients in the dexfenfluramine group reported 250 adverse events. The most commonly reported events by patients who received sibutramine were flu syndrome, constipation, dry mouth and headache. The most commonly reported events for patients who received dexfenfluramine were asthenia, headache, diarrhea, dry mouth, flu syndrome and infection.

There were small increases in systolic blood pressure for both groups and increase in diastolic blood pressure for the sibutramine group. Dexfenfluramine had a small decrease in diastolic blood pressure; the difference of 4.3 mmHg between the treatment groups for standing diastolic blood pressure at Week 12 was statistically significant (95% C.I. 1.3-7.3). The increases in pulse rate seen in the sibutramine group (3.4 beats/min) were also statistically significant compared to the decreases noted in the dexfenfluramine group (-1.3 beats/min; 95% CI for the difference 2.4-7.0).

Conclusion:

Sibutramine 10 mg and dexfenfluramine 15 mg twice daily were equivalent in weight loss in obese patients according to the prespecified range of -2 to 2 kilograms. At week 12, the sibutramine patients lost one kilogram more than the dexfenfluramine patients (4.6 vs. 3.4 with 90% CI 0.4-1.6). The diastolic blood pressure and heart rate were statistically significantly higher with sibutramine compared to dexfenfluramine.

Overall Conclusion

The 24-week US study and one year UK study showed statistically significant differences in favor of sibutramine 5 mg, 10 mg, 15 mg, 20 mg, and 30 mg over placebo in weight loss in obese patients. Patients in the sibutramine groups lost ~2 to 6 more kilograms over and above placebo and it is dose related. When compared to placebo, about 40% more patients in the 15 mg sibutramine group lost 5% or more weight from baseline weight in the two placebo controlled studies at month 6. The heart rate increase is also dose-related with 5-10 bpm with sibutramine doses of 5 mg to 30 mg. The blood pressure also increases in the sibutramine groups but the dose relationship is not clear. In the dexfenfluramine-controlled study the 10 mg sibutramine patients lost 1 (C.I. 0.4-1.6) more kilogram than the 15 mg twice-daily dexfenfluramine patients at week 12 but it is within the pre-specified equivalence range of -2 kg to 2 kg and it is, therefore, concluded that the two treatments are equivalent. The sibutramine group had significantly greater increases in diastolic blood pressure and pulse rate than dexfenfluramine. The differences were 4.3 mmHg and 4.7 bpm in diastolic blood pressure and pulse rate, respectively.

Lee-Ping Pian, Ph.D.
Mathematical Statistician

Concur: Mr. Marticello

Dr. Nevius

cc: Arch NDA 20-632
HFD-510
HFD-510/SSobel
HFD-510/EColman
HFD-510/Gaillers
HFD-510/RHedin
HFD-715/Division file, DMarticello, LPian
HFD-344/ALisook
Chron.
Pian/73201/wpfiles/miridia
This review contains 37 pages

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020632

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Clinical Pharmacology and Biopharmaceutics Review

NDA:	20-632
Sibutramine Hcl 5 , 10, 15, 20 mg Capsules	MAR 1 0 1997
(Meridia ®)	
Submission Date:	1/29/97
Sponsor:	Knoll Pharmaceuticals
Type of Submission:	Labeling Review
Reviewer:	Michael J. Fossler, Pharm. D., Ph. D.

Submission

The submission to NDA 20-632 is for sibutramine, a serotonin and norepinephrine uptake inhibitor proposed for the long-term treatment of obesity. Sibutramine was given "approvable" status on 11/8/96 pending the resolution of several clinical issues. At that time OCPB asked the firm to re-format the Pharmacokinetics portion of the labeling. The present submission is in response to that request.

Recommendations

The Office of Clinical Pharmacology and Biopharmaceutics/ Division of Pharmaceutical Evaluation II (HFD-870) has reviewed the submission dated 1/29/97 thoroughly. Based on that review, OCPB has a number of changes to the labeling which are detailed in the Comments below. The changes have also been incorporated in the attached labeling, with deletions denoted by ~~strikeout~~ and additions denoted by **bold underline**. The revised labeling should be forwarded to the firm.

Comments (Do not send to firm)

1) Under ***Absorption***, the third sentence was revised to reflect 77% absorption of a dose (this is the amount of radioactivity excreted in the urine). The 85% figure used in the firm's original labeling reflects both fecal and urinary recovery, and as such does not take into account drug which was not absorbed.

The second paragraph was edited for clarity.

2) Under ***Metabolism***, the second paragraph was combined with the section on ***Repeated Dosing and Accumulation***. The last sentence was moved to the end of the first paragraph for clarity.

3) The data on normal volunteers in the summary of pharmacokinetic parameters was deleted, as target population data are available. The data on healthy elderly were also deleted, as these data are adequately described in the ***Special Populations*** section.

4) This section was deleted (see #2 above).

5) The section ***Effect of Food*** was moved and combined with ***Absorption***.

6) Under ***Special Populations***, the text under Obesity was removed, as the comparison of obese patients with normal-weight individuals (who will never receive the drug) is not clinically relevant.

3/10/97

Michael J. Fossler, Pharm. D., Ph. D.

Division of Pharmaceutical Evaluation II
Office of Clinical Pharmacology and Biopharmaceutics

FT initialed by Hae-Young Ahn, Ph. D., Team Leader 3/10/97

CC: NDA 20-632 (orig., 1 copy), HFD-510(E. Colman, Hess), HFD-850(Lesko), HFD-870(M. Chen, Fossler, Ahn), Central Document Room (Barbara Murphy)
1/6/97

"CM"

FINAL PRINTED LABELING HAS NOT BEEN SUBMITTED TO THE FDA.

DRAFT LABELING IS NO LONGER BEING SUPPLIED SO AS TO ENSURE ONLY CORRECT AND CURRENT INFORMATION IS DISSEMINATED TO THE PUBLIC.

26 pages

Clinical Pharmacology & Biopharmaceutics Review

NDA:	20-632
Sibutramine HCl 5, 10, 15 mg Capsules (Meridia®)	MAY 7 1996
Submission Date:	8/7/95 12/6/95 12/19/95
Sponsor:	Knoll Pharmaceuticals
Type of Submission:	New Drug Application (1S)
Reviewers:	Carolyn Jones, Ph. D. Michael J. Fossler, Pharm. D., Ph. D.

Synopsis

Sibutramine is an inhibitor of serotonin (5-HT) and norepinephrine (NE) uptake which is proposed for the long-term treatment of obesity . The pharmacologic actions of sibutramine are primarily through the actions of its primary (M1) and secondary (M2) metabolites, both of which have equal pharmacologic activity. The compound is to be marketed as the racemate as 5, 10, and 15 mg capsules. The proposed starting dose is 5 mg once daily with or without food.

Sibutramine is subjected to extensive first-pass metabolism resulting in the formation of the active metabolites M1 and M2. Both metabolites are bound (> 90%) to albumin. Dosing with food delays the rate but not the extent of absorption of sibutramine as measured by the appearance of the active metabolites. This food effect is not felt to be clinically significant. The capsule formulations (5 and 15 mg) to be marketed in the U.S. are bioequivalent to the clinical trials formulations.

A single-dose study in normal volunteers show that the kinetics of M1 and M2 are in this study, the mean t½ of M1 was 12.6 hrs, and that of M2 was 13.3 hrs. A study was performed examining the single and multiple dose pharmacokinetics of M1 and M2 in normal volunteers and

obese volunteers. In both groups, steady state was achieved in 4 days, with an approximately two-fold accumulation at steady state for both metabolites. After a single 15 mg dose, increased levels of M1 were observed in the obese subjects as compared to the normal controls, with a corresponding decrease in the M2 metabolite. At steady state, these differences persisted, although the magnitude of the differences decreased. The combined M1 and M2 profiles for the two groups are superimposable. Studies examining the effect of age and gender showed that these factors do not have a significant effect on the pharmacokinetics of either metabolite. Patients with moderate hepatic dysfunction showed moderately increased levels (24%) of M1 and M2 with a corresponding increase in the t½ of M2 (16 hrs (normals) vs. 22.7 hrs (impaired)).

Some data are available on the disposition of the stereoisomers of the two active metabolites. Studies in rats show that the (+) stereoisomers of M1 and M2 are about 10 times more potent at reducing food intake than the corresponding (-) stereoisomers. In 28 volunteers given a single 30 mg dose of sibutramine, the levels of the (+) isomer of M2 were about 8 times higher than the (-) isomer. For M1, the differences were less drastic, with levels of the (+) isomer of M1 about 1.8 times higher than the (-) isomer. No difference in t½ was seen between the stereoisomers of M1 or M2.

In vitro studies indicate that CYP3A4 is the major isozyme responsible for the metabolism of sibutramine. An *in vitro* drug interaction study showed that ketoconazole is capable of inhibiting the metabolism of sibutramine at therapeutic concentrations. None of the in vitro studies performed examined the metabolism of the M2 metabolite. Two clinical studies were performed using ketoconazole and erythromycin, which are specific 3A4 inhibitors. Erythromycin did not change the disposition of M1; however ketoconazole increased the AUC(0-24 hrs) and Cmax of M1 by 58% and 36% respectively. For M2, the AUC(0-24) of M2 given with erythromycin was unchanged, but Cmax was increased by about 10%. A drop in the time to peak of M2 was also observed (from 4.3 hrs to 3.5 hrs) after sibutramine/erythromycin. Plasma concentrations of M2 (as measured by AUC(0-24) and Cav, ss) were increased by about 20% when ketoconazole was co-administered, which is not considered to be clinically significant. In a study in 12 normal volunteers given single doses of sibutramine (15 mg) at baseline and again after 7 days of cimetidine 400 mg BID, a 26% increase in Cmax and 35% increase in AUC(0-24 hrs) was seen for the M1 metabolite after dosing with cimetidine. A significantly smaller (by 18%) M2 peak concentration after cimetidine dosing was also noted; however, there was no changes seen in AUC or half-life. The combined measure (M1 + M2) showed no significant differences after cimetidine administration.

In a clinical study (BPI 852) evaluating the safety and efficacy of different doses of sibutramine weight loss appears to be dose- and concentration-dependent, with doses above 20 mg providing little additional weight loss.

The proposed dissolution method is

The proposed specification Additional dissolution studies using the 5 and 15 mg lots that were used in the pivotal bioequivalence study and a 10 mg TBM stability lot were performed and

Recommendation

The clinical pharmacology/biopharmaceutics portion of NDA 20-632 is approved. The recommended dissolution specification is

The text under **XI. General Comments** should be forwarded to the sponsor as appropriate .

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APPEARS THIS WAY
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Appendix I: *Study Summaries (available from DPE-II upon request)*

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Background

Knoll Pharmaceuticals has submitted NDA 20-632 for sibutramine HCl capsules. Sibutramine is to be indicated for the long-term treatment of obesity in patients with a BMI ≥27 kg/m2 in conjunction with diet and exercise. Sibutramine will be marketed as 5, 10 , and 15 mg capsules. The proposed starting dose is 5 mg daily, adjusting the dose upward as needed

Sibutramine is a pro-drug. The parent compound is a potent inhibitor of serotonin (5-HT) and norepinephrine (NE) uptake *in vivo*, but not *in vitro*. The two desmethyl metabolites M1 and M2 (see Figure 1), are potent inhibitors of both 5-HT and NE uptake *in vitro* and *in vivo*. Both metabolites are equally active. Because M1 and M2 are the active forms, and sibutramine is only sporadically detected in human plasma after administration of clinically relevant doses, most of the clinical pharmacology studies submitted to the NDA measure the two active metabolites. The (+) stereoisomers of M1 and M2 are about 10 times more potent (in rats) at reducing food intake than the (-) stereoisomer. The parent compound and relevant metabolites are shown in the Appendix as Figure A1.

Sibutramine ($C_{17}H_{29}Cl_2NO$) has a molecular weight of 334.33 and exists as a racemic mixture. It is soluble in water at a pH≤ 5, but practically insoluble at pH ≥ 7. Its octanol:water partition coefficient is 30.9 at pH 5.0.

Summary of Bioavailability/Pharmacokinetics/Pharmacodynamics

I. Bioavailability/Bioequivalence

A. Absolute Bioavailability

with a bioavailability of approximately 77%. Very little sibutramine exists systemically, as it is extensively converted to the M1 metabolite which then is converted to M2.

B. Effect of Food

In a study designed to determine the effect of a standard breakfast on the rate and extent of absorption of sibutramine, food was found to delay the formation of both M1 and M2. The extent of formation of M1 was not affected by administration with food. For M2, the results are somewhat equivocal in that the AUC(0-t) is increased by 23% when the compound is given in the fasted state. This effect decreases to about 15% when the AUC(0-∞) is examined. However, since plasma samples were only taken up to 24 hours post-dose, a large portion of the AUC(0-∞) values for both M1 and M2 are estimated, and may not be as reliable as the AUC(0-t) values. Looking at the overall results (Table 1), the results suggest that if food affects the extent of absorption, the effect is not large.

Table 1: Results of the food effect study. Food affects the rate but probably not the extent of absorption of sibutramine. Values in the table are mean ratios (fasted/fed) and their 90% confidence intervals.(n = 20) (Study SB 3816)

	AUC(0-t)	AUC(0-∞)	Cmax
*Metabolite 1	90.5 (80.0, 102.3)	97.6 (84.5, 112.7)	126.5 (111.5, 143.5)
**Metabolite 2	123.1 (116.6, 130.0)	114.9 (106.2, 124.2)	148.9 (137.8, 160.9)

*median tmax 3.5 hrs fasted, 5 hrs fed
**median tmax 3.5 hrs fasted, 6 hrs fed

C. Bioequivalence

Two bioequivalence studies were performed comparing the clinical trials formulation to the to-be-marketed (TBM) formulation. Although the formulations do not differ substantially, the blending process was changed in the TBM formulation to avoid adherence of drug substance to equipment surfaces. The bioequivalence of the TBM 5 and 15 mg formulations were compared to the clinical trials formulations in a randomized crossover study in 28 volunteers (26 completed). The results show that the two types of capsules are bioequivalent. The US 10 mg TBM capsule was not used in this study.

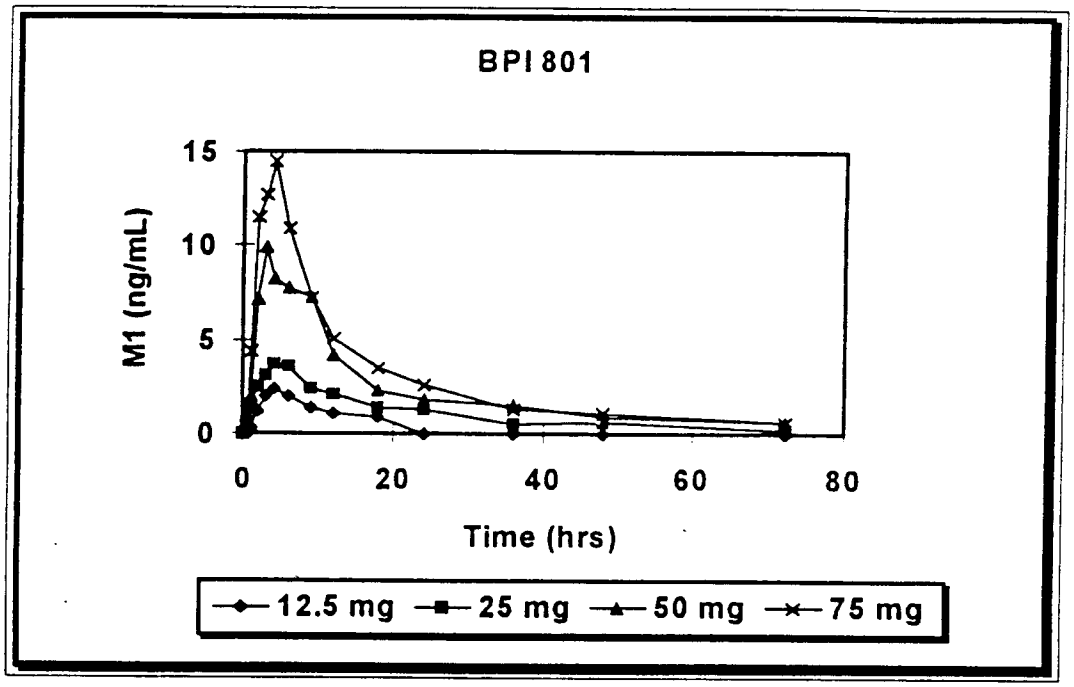
II. Pharmacokinetics

A. Normal Volunteers

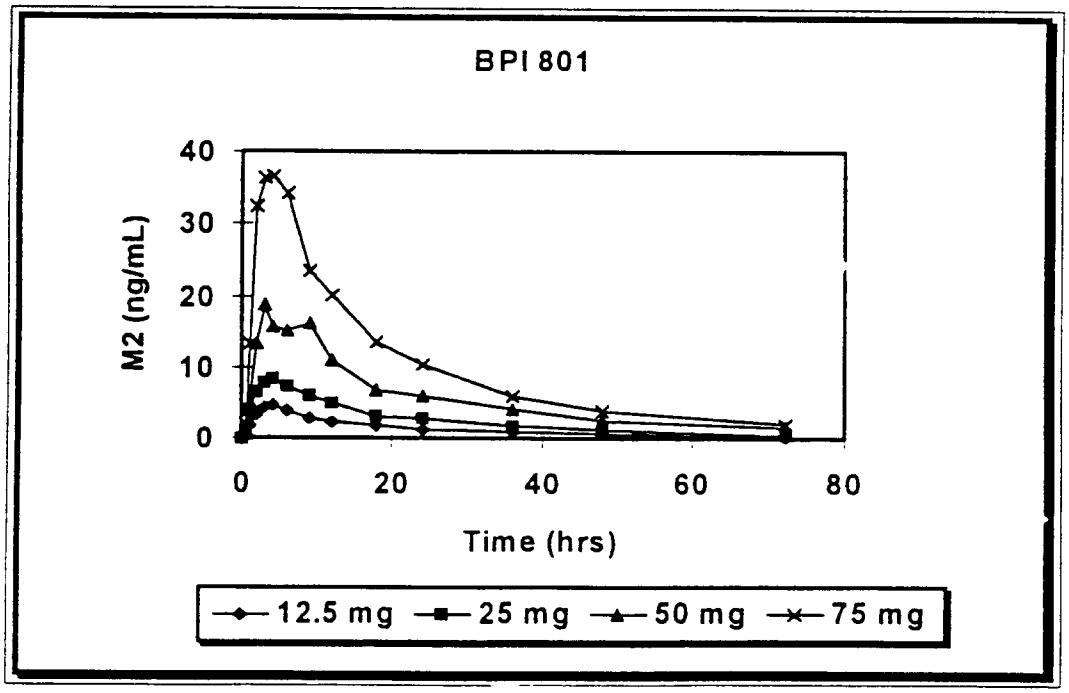
A single-dose study using a parallel group design (one dose /group of 4) was performed using doses In this study, samples were taken up to 72 hours post-dose. Overall plasma concentrations of M2 were 2-3 times higher than M1 concentrations. Peak concentrations were reached for both M1 and M2 around 4-6 hours post-dose.The mean t½ values obtained for all doses for M1 ranged Half-life values for M2 were similar, ranging Secondary peaks were seen in some of the profiles (Figure 1) 6-9 hours post-dose, suggesting enterohepatic recycling.

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).

(A)



(B)



B. Obese vs. Normal Volunteers

A study was performed examining the single and multiple dose pharmacokinetics of M1 and M2 in normal volunteers (n = 18, BMI and obese volunteers (n = 18, BMI The results are shown in Table 2. In both groups, steady state was achieved in 4 days, with an approximately two-fold accumulation at steady state for both metabolites. After a single 15 mg dose, increased levels of M1 were observed in the obese subjects as compared to the normal controls, with a corresponding decrease in the M2 metabolite. Metabolites 5 and 6 tended to be somewhat decreased in the obese subjects, which is expected since these metabolites are oxidative products of M2. This difference between obese and non-obese subjects is probably not clinically significant, as the combined M1 and M2 profiles for the two groups are superimposable (Figure 2), and both metabolites are equally active.

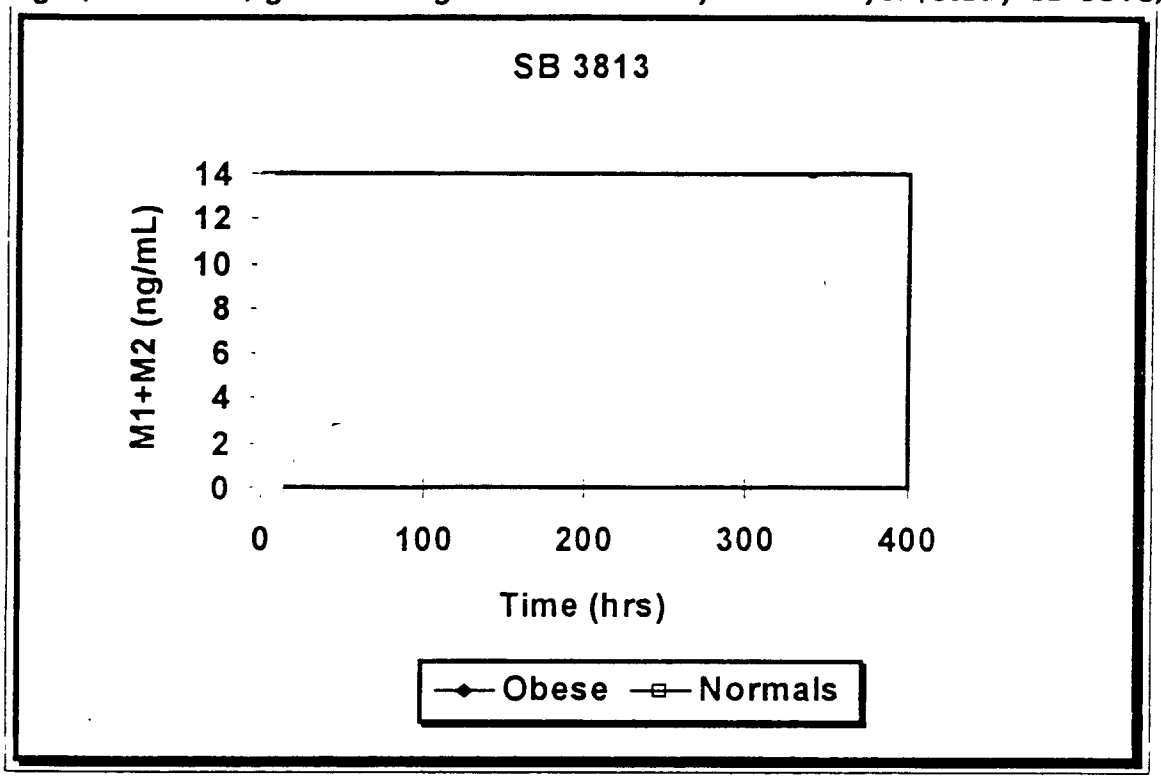
Additionally , there does not seem to be either induction of metabolism or an alteration in the ratio of M1 and M2 with time.

Table 2: Single and multiple -dose pharmacokinetics of the active metabolites (M1, M2) of sibutramine in obese and non-obese subjects given 15 mg sibutramine daily for 14 days. Mean ± SD (Study SB 3813)

		Normal Weight (n = 18)		Obese (n = 18)	
	Metabolite	Single Dose	Steady State	Single Dose	Steady State
Cmax (ng/mL)	M1	2.2 ± 1.1	3.2 ± 1.3	*4.0 ± 1.7	*4.9 ± 2.4
	M2	8.1 ± 2.5	12.2 ± 3.2	*6.4 ± 1.8	12.0 ± 4.2
tmax (hrs)	M1	3.3 ± 1.0	3.4 ± 1.5	3.6 ± 1.0	3.6 ± 1.1
	M2	2.9 ± 1.0	3.0 ± 1.2	3.5 ± 0.6	3.9 ± 1.5
AUC(0-24) (ng·hr/mL)	M1	13.5 ± 10.3	29.0 ± 18.9	*25.5 ± 16.1	*48.1 ± 31.6
	M2	80.0 ± 18.3	149 ± 41.7	*63.2 ± 15.2	142 ± 37.4
AUC(0-∞) (ng·hr/mL)	M1	nc	nc	nc	nc
	M2	111 ± 26.4	-	*92.1 ± 23.6	-
t½ (hrs)	M1	nc	nc	nc	nc
	M2	14.7 ± 5.3	15.5 ± 4.7	17.2 ± 10.0	18.6 ± 8.2
Accumulation Ratio	M1	-	2.3 ± 0.9	-	2.0 ± 0.6
	M2	-	1.9 ± 0.3	-	2.3 ± 0.5

*significantly different from normals, $p < 0.01$ nc = not calculated

Figure 2: Combined M1 and M2 plasma concentration in 36 volunteers (18 normal weight, 18 obese) given 15 mg sibutramine daily for 14 days. (Study SB 3813)



III. Metabolism

Plasma and urine samples taken from healthy male volunteers administered various doses (single dose-10,30 and 60mg and multiple dose--15 mg twice daily)

The unconjugated active metabolites M2 and M1 accounted for 12.5% and 5.6%, respectively, with unchanged parent drug accounting for only 3%

Human hepatic microsomes were studied *in vitro* using probe substrates and

inhibitors specific for various CYP450 isoenzymes. CYP3A4 was found to be the major isoenzyme for the metabolism of sibutramine to M1, and to a much lesser extent, CYP1A2 and CYP2C9. Sibutramine, when metabolized by N-demethylation yields two pharmacologically active metabolites, M1 and M2 which exist as stereoisomers. M2 is further metabolized to glucuronic acid conjugates, M5 and M6 (see Figure A1 in Appendix). The enzyme mediating the metabolism of M2 is not definitively known.

The disposition of the stereoisomers was evaluated in plasma samples obtained from 28 volunteers who were administered a single, oral, 30 mg dose of sibutramine. For M1, plasma levels of the (+) isomer were 1.7 times higher than the (-) isomer and the AUC(0-∞) 1.5 times higher than the (-) isomer. For M2, the plasma concentration of the (+) isomer was 7-fold higher than the (-) isomer and AUC(0-∞) of the (+) isomer 8-fold higher. Similar elimination kinetics were observed for the (+) and (-) isomers of each metabolite.

In vitro data showed that the human plasma protein binding of sibutramine was approximately 97% and the results were similar over a six-fold concentration. For M1 and M2, plasma protein binding was approximately 94%. M1 exhibited similar binding over a five-fold range and M2 over a seven-fold range.

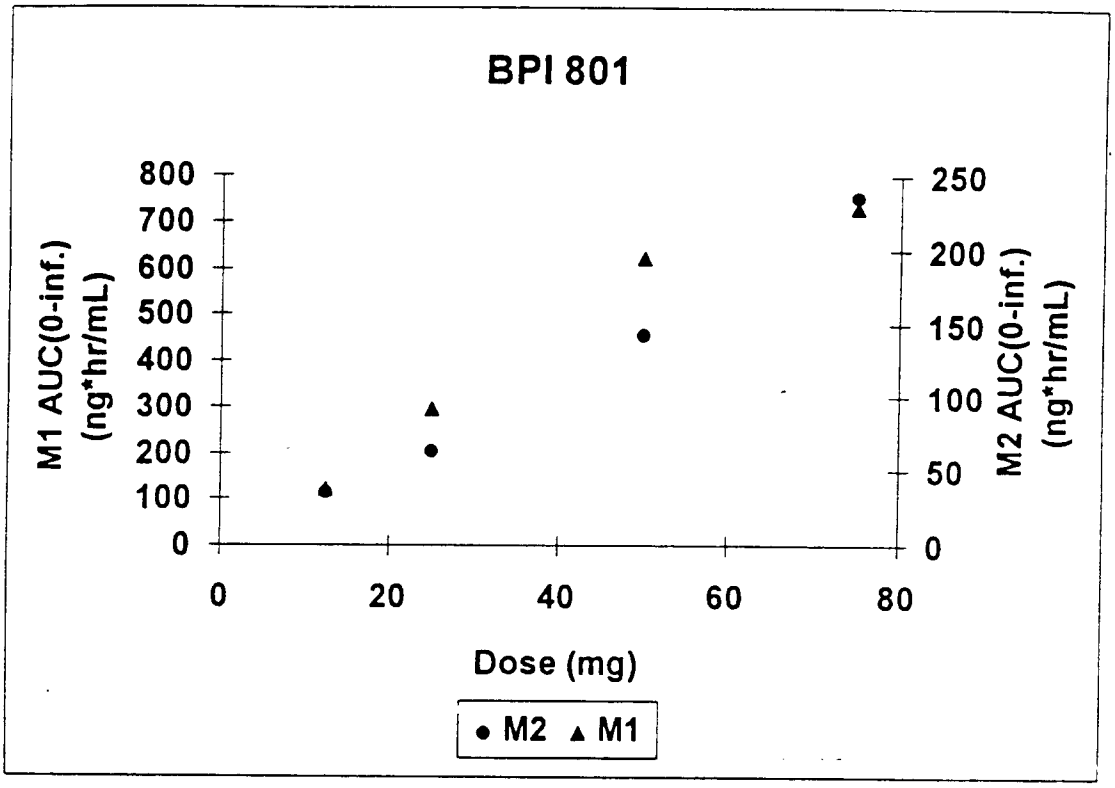
IV. Dose Linearity

A single-dose study using a parallel group design (one dose /group of 4) was performed using doses ranging In this study, samples were taken up to 72 hours post-dose. The results of this study show that the kinetics of M1 and M2 are linear in the range Additionally, in a clinical study evaluating the safety and efficacy of different doses of sibutramine (placebo, 1, 5, 10, 15, 20, 30 mg) trough levels drawn at weeks 12 and 24 confirm dose linearity within the proposed dosing range.

V. Dose Administration

The recommended starting dose of sibutramine is 5 mg daily administered with or without food. The package insert states that if inadequate weight loss is seen, the dose may be titrated up every two weeks in 5 mg increments to a total of 20 mg daily, or up to 30 mg daily if there are no significant increases in heart rate or blood pressure (dbp ≥ 95 mmHg or bpm ≥105). However, in the clinical trials, patients were randomized to a fixed dose, with changes occurring only if patients experienced side effects, so it is unclear how this proposed dosing regimen was determined. The firm has indicated that this portion of the labeling will be revised to more closely reflect what was done in the clinical trials.

Figure 1: Mean AUC(0-∞) for M1 and M2 after doses of sibutramine. n = 4 per data point. (Study BPI 801).



VI. Special Populations

Hepatic

The rate of metabolism of sibutramine and its metabolites was affected by reduced hepatic function. In an open, parallel-group study performed in 12 subjects with moderate impairment and 12 subjects with normal hepatic function, significant differences between the two groups were observed in the pharmacokinetics of the metabolites. C_{max} was 65.3% greater and AUC(0-t) was 95% greater for M1 in the hepatically impaired subjects compared to normals. For M2, AUC(0-∞) was 20.1% greater and K_{el} was 24.1% less in the hepatically impaired group.However, Cmax and AUC(0-t) for M2 were similar between the two patient groups. When M1 and M2 were combined, C_{max} and AUC were 1.7% and 24.4% greater, respectively in the impaired group compared to the normal group. The AUC remained statistically significant.

No significant differences were observed in PK parameters for M5 and M6; although for both metabolites C_{max} was reduced approximately 15% and T_{max}

increased approximately 19% for the impaired group compared to normals. The differences in $AUC_{(0-t)}$ and $AUC_{(0-\infty)}$ were less than 12% for both M5 and M6.

As a result of reduced hepatic function, the bioavailability of the two pharmacologically active metabolites when combined showed a 24.4% increase in the moderately impaired subjects compared to normal subjects. This increase is not expected to be clinically significant and no change in the dosage regimen may be required for moderately impaired hepatic subjects. In the product labeling, cautious use of sibutramine in this population is recommended only if the clinical benefit outweighs the potential risk. Severely impaired subjects have not been evaluated.

Renal

Studies in renally-impaired subjects were not performed. As sibutramine and its active metabolites are hepatically metabolized, no dose adjustment is needed in patients with renal failure.

Age

Twelve young and twelve elderly healthy volunteers were administered orally a single 15 mg dose of sibutramine to determine an age-related effect in its pharmacokinetics. Sibutramine's first-pass metabolism was not impaired in the elderly. No significant differences were observed in M1 and M2 between the two groups; although Kel was reduced for M2, the decrease was not significant. A 50% increase in AUC was observed in the elderly group for both M5 and M6. This difference in AUC for the metabolites was probably related to a lower volume of distribution and reduced renal clearance that is associated with elderly populations.

M5 and M6 are not pharmacologically active, therefore the observed differences are not clinically significant. A similar dosing regimen would be appropriate for the two populations.

Gender, Race, Smoking

In a double-blind randomized parallel group study in 1047 obese patients taking either placebo or 1, 5, 10, 15, 20, or 30 mg sibutramine, no relationship was found between age, gender, smoking status, or race and steady state trough concentrations of M1 and M2.

Pediatric

Sibutramine is not labeled for use in the pediatric population.

VII. Drug Interactions

A. In vitro

A study was performed to investigate drug/drug interactions between [^{14}C] sibutramine hydrochloride and ketoconazole, a specific 3A4 inhibitor using human hepatic microsomes from one subject known to have relatively high CYP3A4 activity. Ketoconazole inhibited the metabolism of sibutramine and had a ki of 0.2 μM. The results indicate a role of CYP3A4 in sibutramine metabolism. The metabolism of M1 and M2 were not investigated.

B. In vivo

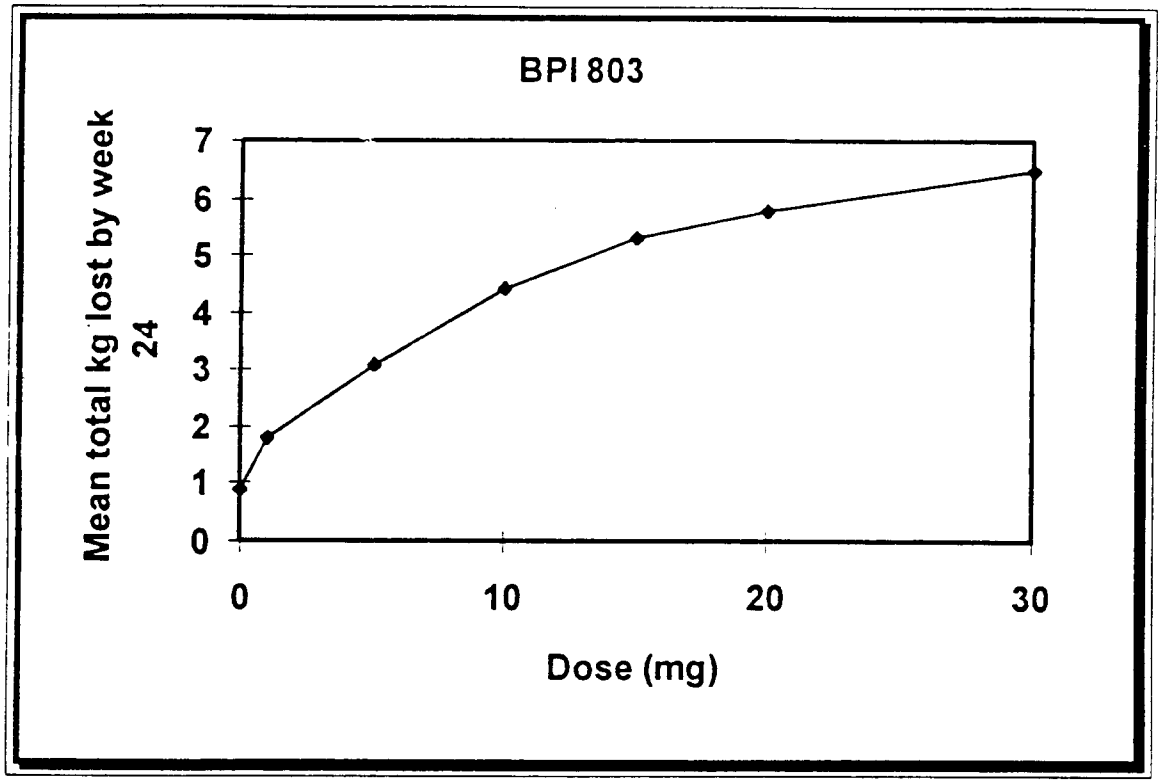
Three studies were performed in volunteers (either normal weight or obese) assessing the effects of commonly-interacting medications on the metabolism of sibutramine. In a study in 12 normal volunteers given single doses of sibutramine (15 mg) at baseline and again after 7 days of cimetidine 400 mg BID, a 26% increase in Cmax and 35% increase in AUC(0-24 hrs) was seen for the M1 metabolite after dosing with cimetidine. A significantly smaller (by 18%) M2 peak concentration after cimetidine dosing was also noted; however, there was no changes seen in AUC or half-life. The combined measure (M1 + M2) showed no significant differences after cimetidine administration.

Two studies were performed using ketoconazole and erythromycin, which are more specific 3A4 inhibitors. Both studies utilized obese patients and the same design: after 7 days of sibutramine 20 mg daily each subject was given the interacting drug (either erythromycin 500 mg TID or 200 mg BID ketoconazole) for an additional seven days. Blood samples and EKG assessments were made at day 7 (sibutramine alone) and at day 14 (sibutramine + interacting agent). Erythromycin did not change the disposition of M1; however ketoconazole increased the AUC(0-24 hrs) and Cmax of M1 by 58% and 36% respectively. For M2, the AUC(0-24) of M2 with erythromycin was unchanged, but Cmax was increased by about 10%. A drop in the time to peak of M2 was also observed (from 4.3 hrs to 3.5 hrs) after sibutramine/erythromycin. Plasma concentrations of M2 (as measured by AUC(0-24) and Cav, ss) were increased by about 20% when ketoconazole was co-administered, which is not considered to be clinically significant. Both these studies are flawed in that the analytical quality control samples for M1 and M2 showed unacceptable variability; however, no clinically significant changes in EKG parameters, blood pressure or heart rate was noted in either study.

VIII. Pharmacokinetic/Pharmacodynamic Relationships

In a clinical study (BPI 852) evaluating the safety and efficacy of different doses of sibutramine (placebo, 1, 5, 10, 15, 20, 30 mg), weight loss appears to be dose-dependent (Figure 4). The graph is much the same when steady-state trough concentrations of the active metabolites of sibutramine are used in place of dose. It appears from Figure 5 that little additional benefit is gained when the dose is increased from 20 to 30 mg daily.

Figure 4: Mean weight loss at week 24 as a function of dose (Study BPI 852) n = 1024.



IX. Formulation

The composition of the to-be-marketed formulation is shown in Table 3.

Table 3: Formulation of the to-be-marketed capsules. Numbers in the table are mg/capsule.

	Capsule Strength		
Ingredient	5 mg	10 mg	15 mg
Sibutramine HCl monohydrate	5.0	10.0	15.0
lactose			
Microcrystalline cellulose			
Colloidal silicon dioxide			
Magnesium stearate			

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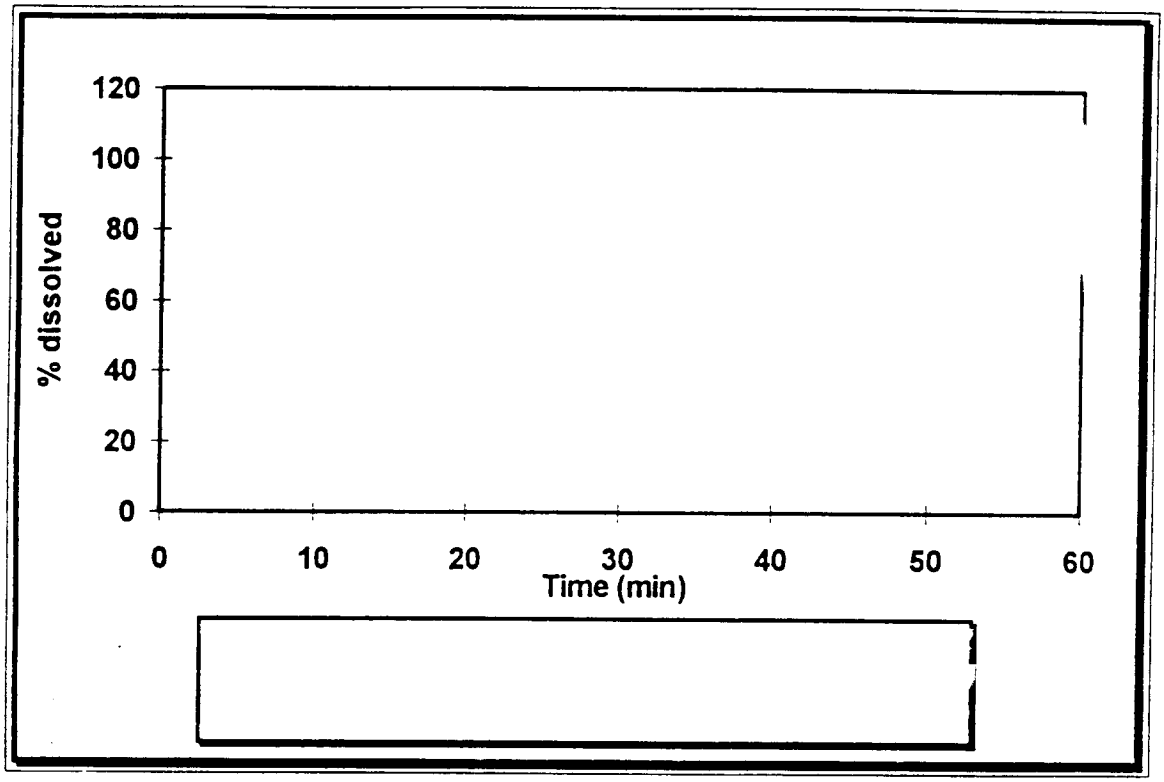
Figure 5: Dissolution profiles



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X. Assay

The assay used to quantitate the active metabolites of sibutramine is an method using a as the detector. Sample clean-up was accomplished using ' Sibutramine itself can not be accurately quantified with this assay. Relevant validation data for the two metabolites are shown below:

	Metabolite 1	Metabolite 2

From the data above, it appears that, although the assay is sufficiently accurate and precise, the current quantitation limit is somewhat optimistic. In the pivotal bioequivalence study (BPI 871) the number of measured concentrations were counted. For M1, 165 samples were found, 125 of which were found . Half-life values for M1 were not computed, so it is unlikely that these measurements will introduce much error. For M2, 125 values between were counted, only two of which were in the elimination phase. It is unlikely that the inclusion of these imprecise measurements will have much of an impact on the conclusions of this study.

XI. General Comments (to be sent to Sponsor)

1. Although the *in vivo* bioequivalence of the 10 mg capsule proposed for marketing has not been demonstrated, and a waiver of the requirement for evidence of *in vivo* bioequivalence has not been formally requested by the firm, based on the similarity of the 10 mg capsule to the 5 and 15 mg strengths in its dissolution characteristics and formulation, a waiver of the requirement for evidence of *in vivo* bioequivalence for the 10 mg capsule is granted.

3. Although the data presented clearly shows that IIIA4 is the P-450 isozyme responsible for the metabolism of sibutramine to M1 and M2, no metabolism studies were performed to determine the isozyme responsible for the metabolism of M2 to M5 and M6. As M2 is the predominant active species, it is the moiety most susceptable to drug-drug interactions. Therefore, we request that, during the next 12 months the metabolism of M2 be further studied in an *in vitro* human microsomal system. The study should be designed to determine what isozyme is responsible for the metabolism of M2, and what commonly-administered drugs could affect the the breakdown of M2 to M5 and M6.

Carolyn D. Jones, Ph. D.

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ON ORIGINAL

Michael J. Fossler, Pharm. D., Ph. D.

Division of Pharmaceutical Evaluation II
Office of Clinical Pharmacology and Biopharmaceutics

FT initialed by Hae-Young Ahn, Ph.D., Team Leader 5/07/96

Biopharm Day held 5/2/96 at 10 AM. Present: Collins, M. Chen, Malinowski, Lazor, Gillespie, C. Jones, Ahn)

cc: NDA 20-632 (orig., 1 copy), HFD-510(Colman, Lutwak, Short), HFD-880(Fleischer), HFD-870(M. Chen, Jones, Fossler, Ahn), HFD-860(Malinowski), HFD-850(Lesko), HFD-870(Drug, Chron., Reviewer), HFD-205(FOI), HFD-340 (Vish)
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Appendix

Outline of sibutramine metabolism

Study Summaries

Proposed Package Insert

Figure A1: Outline of sibutramine metabolism

Clinical Pharmacology and Biopharmaceutics Review

NDA:	20-632
Sibutramine HCl 20 mg Capsules (**Meridia** ®)	MAY - 3 1996
Submission Date:	3/19/96
Sponsor:	Knoll Pharmaceutical Company
Type of Submission:	Request for Waiver of *in vivo* Bioequivalency Requirement
Reviewer:	Michael J. Fossler, Pharm. D., Ph. D.

Submission

The submission dated 3/19/96 is for sibutramine, a monoamine uptake inhbitor presently under review for the long-term treatment of obesity. The original NDA proposes three capsule strengths for marketing: 5, 10, and 15 mg.

The sponsor is basing their request for a waiver on the following:

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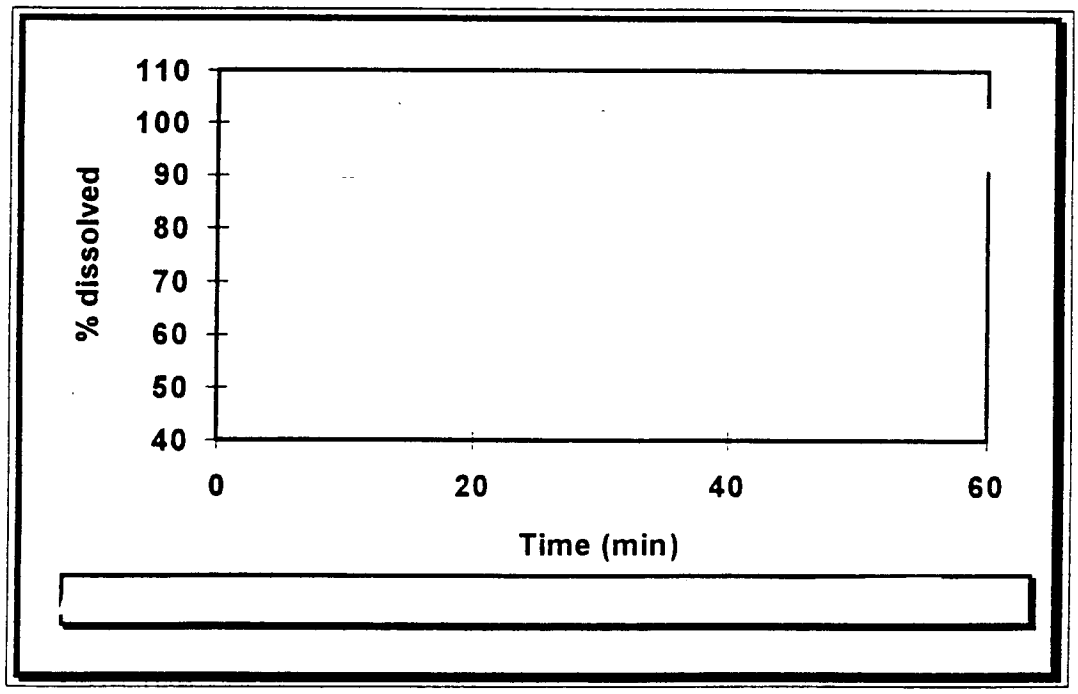
Table 1: Quantitative Composition of sibutramine 5, 10, 15,

Ingredient/capsule (mg)	5 mg	10 mg	15 mg	20 mg
Sibutramine HCl	5.0	10.0	15.0	20.0
Lactose, NF				
Microcrystalline Cellulose, NF				
Colloidal Silicon Dioxide, NF				
Magnesium Stearate, NF				
Total weight				

Figure 2 shows the dissolution of all strengths of capsules in
Although noted between

Figure 1: Mean dissolution profiles *Each point is the mean of 12 capsules.*



[1] In the original NDA submission the 5 and 15 mg clinical trials capsules were found to be bioequivalent to the 5 and 15 mg market capsules.

Figure 2: Mean dissolution profiles of sibutramine capsules
Each point is the mean of 6 capsules.

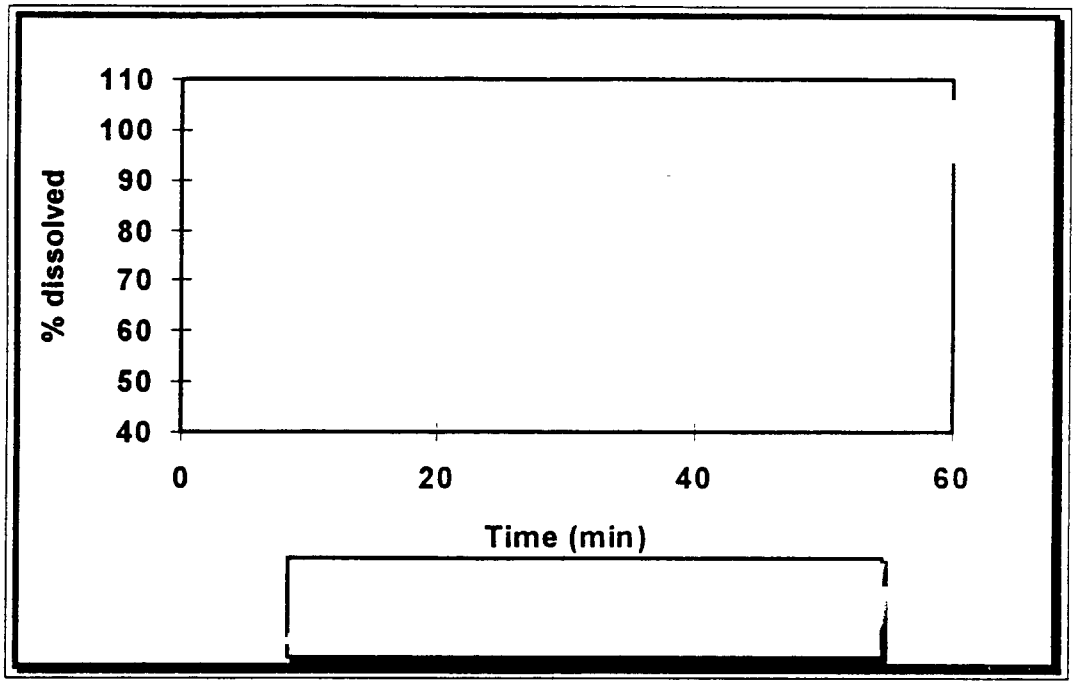


Figure 3 shows the mean AUC(0-inf) values of M1 and M2 (the active metabolites of sibutramine) as a function of dose (10, 20) in normal volunteers. The mean AUC(0-inf) for both active metabolites appear to be linear with dose. Similar results are seen in patients. In study BPI 852, a parallel, randomized, dose-ranging study in obese patients, trough levels of M1 and M2 drawn at 12 and 24 weeks post start of treatment are also linear with dose (Figure 4).

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Figure 3: Mean AUC(0-inf) as a function of dose in xx normal volunteers given 10, 20 , or 30 mg sibutramine as a single dose (clinical trials formulation).

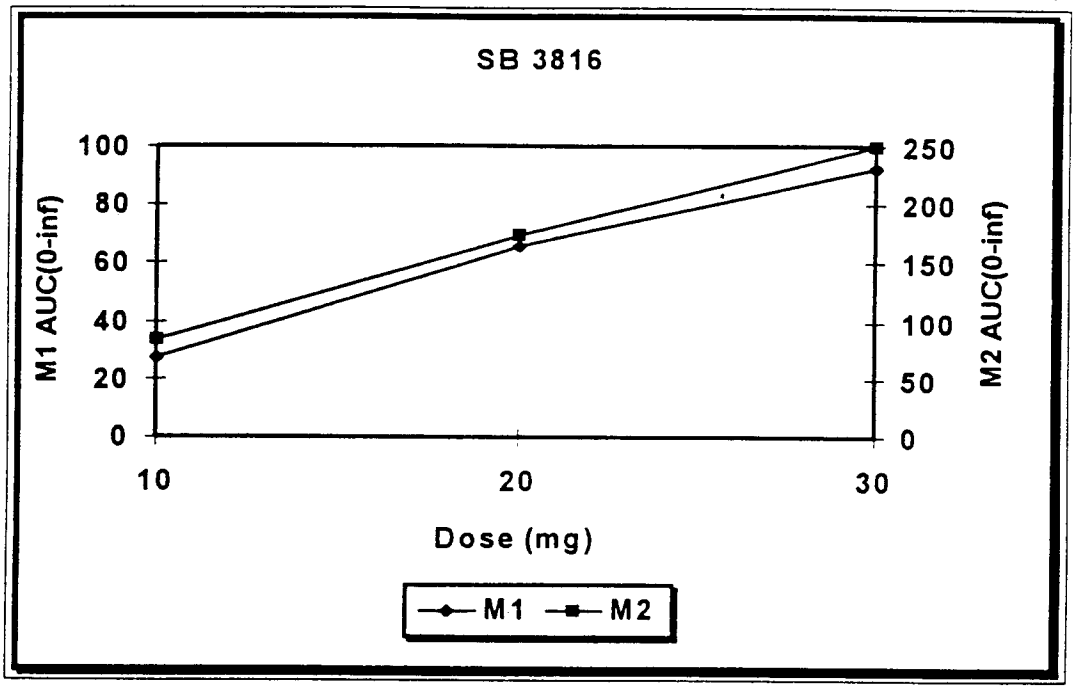
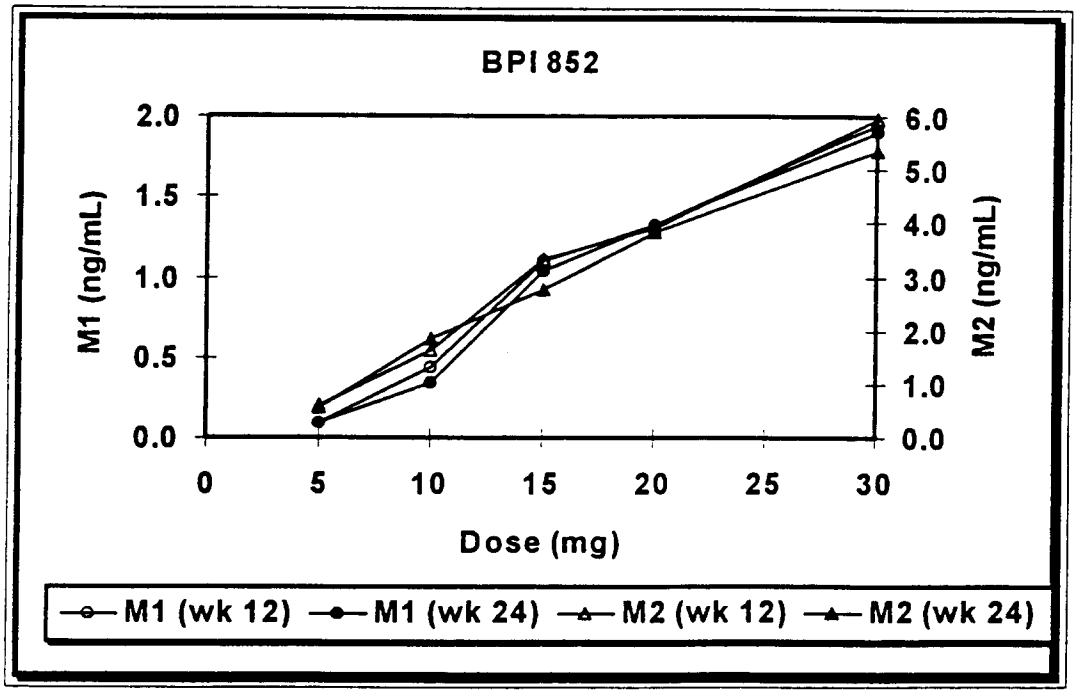


Figure 4: Mean trough levels of M1 and M2 after 5, 10, 15, 20, or 30 mg sibutramine for 12 or 24 weeks in 780 obese patients.



Recommendation

The Office of Clinical Pharmacology and Biopharmaceutics (HFD-870) has reviewed the submission dated 3/19/96 thoroughly.

5/3/96

Michael J. Fossler, Pharm. D., Ph. D.

Division of Pharmaceutical Evaluation II
Office of Clinical Pharmacology and Biopharmaceutics

FT initialed by Hae-Young Ahn, Ph. D., Team Leade _____ 5/03/96

CC: NDA 20-632 (orig., 1 copy), HFD-510(Colman, Lutwak, Short), HFD-860(Malinowski), HFD-870(M. Chen, Fossler) HFD-880(Fleischer), HFD-870(Drug, Chron. File, Reviewer File)
rev 4/9/96

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