Meeting Date: October 21, 1996 Time: 10:30 a.m. - 1:00 p.m. Location: PKLN-14B56

NDA 20-632 Meridia (sibutramine hydrochloride monohydrate) Capsules

Type of Meeting: General

Meeting Chair: Dr. Bruce Stadel

External Participant lead: Dr. Mel Spigelman

Meeting Recorder: Ms. Maureen Hess

FDA attendees and titles:

Dr. Solomon Sobel, Division Director DMEDP
Dr. Gloria Troendle, Deputy Division Director DMEDP
Dr. Bruce Stadel, Medical Reviewer DMEDP
Dr. Eric Colman, Medical Reviewer DMEDP
Dr. Edward Nevius, Division Director DOBII
Dr. Lee Pian, Statistical Reviewer DOBII
Ms. Maureen Hess, CSO DMEDP

External participant attendees and titles:

Dr. Gerald Faich	President
Dr. Donald Smith	Mount Sinai Medical Center, Weight Management Program
Dr. Ernst Schaefer	Tufts University School of Medicine
Dr. Harold Lebovitz	SUNY Health Science Center at Brooklyn
Vaseem Iftekhar	Knoll, Associate Director, Project Management
Dr. Bob Patel	Knoll
Dr. Abraham Varghese	Knoll, Associate Director, Regulatory Affairs
Dr. Mel Spigelman	Knoll, Vice President, Research and Development
Dr. Tim Seaton	Knoll, Senior Director, Endocrine and Metabolism
Dr. Carl Mendel	Knoll, Director of Endocrine and Metabolism

Meeting Objectives:

Requested by Knoll Pharmaceutical Company to discuss October 9, 1996 meta-analysis submission.

Discussion Points:

- The firm began the meeting by stating that they felt it necessary to have a discussion of the data regarding safety management of sibutramine which had not

been formally submitted to the NDA at the time of the 9/26/96 Advisory Committee meeting. The firm stated it has submitted eight individual reports including, efficacy, mean blood pressure, lipids, outliers, glycemia, uric acid and safety. The firm stated it would like the Division to review the data as quickly as possible, and have brought consultants, familiar with the data, to discuss the issues.

- The firm discussed study 1047 and the four quadrant scatterplot analyses. The firm stated that the focus should be on what happens in the right upper and right lower quadrant together. The firm further stated that 20% of placebo fall into either quadrant. The firm acknowledged that sibutramine does have a potential impact on blood pressure, but the incidence of substantial increases can be controlled by a screening process.

- The Division stated that it is important to look at the data below the line in the scatterplot, because that area contains patients who lost weight and therefore are more inclined to stay on sibutramine.

- The Division stated that the scatterplot was presented to the Advisory Committee because the NDA states there are no clinically significant problems with blood pressure and it is a concern that the firm did not adequately convey to the Advisory Committee. The firm responded that blood pressure concerns can be relayed in labeling. The Division replied that the proposed blood pressure screens should have been presented to the Advisory Committee. The firm responded that there were no discontinuations of sibutramine for blood pressure. The firm further stated that it asked the Division if there was anything else that should be addressed before the Advisory Committee meeting. The Division replied that some of the important issues did not emerge until late July 1996.

- The firm pointed out that there were a percentage of patients that had a 10-mm hg increase in blood pressure on placebo, and stated the need to compare placebo with the drug. The Division responded that a more definitive screen is needed and suggested comparing the right lower quadrant with the left lower quadrant. The Division further stated that the firm's current proposed screen is a good first step toward screening for high blood pressure. The Division further stated that it is willing to work with the firm to develop a more effective and simple screening mechanism. The Division further recommended to devise a number of models, to accomplish this.

- The Division noted that the 30 mg dose has been dropped and recommended that

the firm drop the 20 mg dose. The firm stated that they spoke to Dr. Flack and stated that Dr. Flack feels that the 20 mg dose is a problem. The firm stated that maybe it should look at the 20 mg dose before it is approved and obtain more data. They also stated that they have thought long and hard about dose and safety and perhaps this should be a labeling issue.

- The Division stated that it is difficult to discount the results of the ambulatory blood pressure data. The firm stated that the study is going to be repeated. They further stated that Holter monitoring was performed with doses up to 30 mg, two week's duration per dosage.

- The Division stated that it feels as if it is analyzing the same data as the firm, but reaching different conclusions. The Division further stated that this drug is going to be used by a fairly healthy population. The firm responded that the drug should not be given to those for cosmetic weight loss and is willing to put this in the labeling.

- The Division stated that the immediate problem is timing, as the user fee goal date is 11/9/96. Will a short prospective study with a smaller range of dosing be required for approval? The firm asked for further clarification. The Division replied that it needs to be shown that the screen works. A 12-week study in which the firm applies the screen, designed from the current data set, would provide the needed information. The firm responded that they have already done this. The Division replied that the current data provides a hypothesis. New data need to be generated and the hypothesis tested with that data. In addition, more than one baseline blood pressure measurement may be needed. The firm added that a 4% increase in HDL shows a clear positive effect on lipids with heart disease risk reduction. The Division replied that the people with spiking blood pressure need to be screened out.

- The Division stated that the original NDA did not stratify lipid data and weight loss and that the pooled lipid data with statistical analyses were not submitted until after the Advisory Committee meeting. The firm responded that the lipid data is consistent. The Division asked the firm why is there a decrease in HDL with a pharmacologically induced weight loss of 5%, but not with the placebo? The firm replied that there is no clear answer.

- The Division stated that it is having difficulty reproducing the numbers of the meta-analysis submission and that protocols should be agreed upon ahead of time. The firm responded that it will work with the Division's statisticians.

- The Division cited October 16, 1996 letter submitted by the firm. The Division stated a need for validation of analysis and adequate review time. The firm replied that further analysis may dictate the labeling such as a black box warning and is willing to work with the Division.

Decisions (agreements) reached:

- The Division will review new submissions as expeditiously as possible.

Unresolved issues or issues requiring further discussion:

- None

Action Items:

- None

Signature, minute's preparer _____

Concurrence Chair: _____

APPEARS THIS WAY
ON ORIGINAL

cc: NDA Arch
HFD-510
Attendees
HFD-510/EGalliers/DLawson
HFD-510/MHess/n20632mm.2
drafted: MHess/10.22.96/n20632mm.2

Concurrences:
BStadel/11.4.96/EColman/11.4.96/GTroendle/11.4.96/SSobel/11.4.96/LPian/10.23.96/
ENevius/11.5.96/EGalliers/11.5.96

final type: 11/5/96

APPEARS THIS WAY
ON ORIGINAL

MEMORANDUM OF A MEETING
DIVISION OF METABOLISM AND
ENDOCRINE DRUG PRODUCTS (HFD-510)

MEETING DATE: August 30, 1996 TIME: 11:00 a.m. PLACE: Parklawn Rm 14B-56

DRUG: Meridia (Sibutramine hydrochloride monohydrate)

NDA: 20-632

TYPE OF MEETING Pre-Phase 4 meeting

MEETING CHAIR: Dr. Solomon Sobel, M.D., Division Director

EXTERNAL PARTICIPANTS LEAD: Abraham Varghese, Ph.D., Associate Director, Regulatory Affairs

MEETING RECORDER: Steve McCort, Project Manager
(for Mareen Hess, Project Manager)

PARTICIPANTS:

From FDA:

Solomon Sobel, M.D. Division Director (HFD-510)
Gloria Troendle, M.D., Deputy Director (HFD-510)
Bruce Stadel. M.D., M.P.H., Medical Reviewer (HFD-510)
Eric Colman, M.D., Medical Reviewer (HFD-510)
Leo Lutwak, M.D. Ph.D., Medical Reviewer (HFD-510)
Lee Pian, Ph.D., Statistics Reviewer (HFD-715)
Steve McCort, Project Manager (HFD-510)

From Knoll Laboratories:

Gerald Faich, M.D., M.P.H., President,
Abraham Varaghese, Ph.D., Regulatory Affairs, Knoll Pharmacaceuticals
Tim Seaton, Ph.D., Research and Development, Knoll Pharmaceuticals
Carl Mendel, Ph.D., Research and Development, Knoll Pharmaceuticals
Jeffrey A Staffa, Ph.D., Scientific and Technical Affairs, Knoll Pharmaceuticals
B.J. Patel, Ph.D., Biostatistics, Knoll Pharmaceuticals
James Trammel, Statistical Consultant,
Mel Spielman, Vice President, Research and Development, Knoll Pharamaceuticals

Meeting Objective:

To discuss study issues for a Phase 4
The Phase 4

DISCUSSION POINTS:

1. Discussion of the firm's proposed
   Phase 4 trial. The trial to assess
   Sibutramine.

2. The following were issues discussed:

   a.

   b.

   c.

   d.

   e.

DECISIONS REACHED:

1. The appears reasonable.

2. The Division recommends:

   a

   b.

   c.

   d.

3. The firm will submit phase 4 for review.

4. Additional comments cannot be made at this time regarding their proposed protocol by FDA.

ACTION ITEMS:

1. Firm will : **Phase 4**

2. Copy of the minute meeting notes will be sent by FDA.

Signature of Minutes Preparer: _____ 9-15-96

Concurrence Chair: _____

cc: NDA 20-632
HFD-510/DivFile
HFD-510/SSobel
HFD-510/GTroendle
HFD-510/EColman
HFD-510/LLutwak
HFD-715/LPian
HFD-510/SMcCort/MHess

M. HESS

AUG 30 1996

Meeting Date: July 25, 1996 Time: 10:00 am - 12:00 pm Location: PKLN-L

NDA 20-632 Meridia (sibutramine hydrochloride monohydrate) Capsules

Type of Meeting: General

Meeting Chair: Dr. Eric Colman

External participant lead: Dr. Mel Spigelman

Meeting Recorder: Mr. Randy Hedin

FDA attendees and titles:

Dr. James Bilstad, Office Director ODEII
Dr. Solomon Sobel, Division Director DMEDP
Dr. Gloria Troendle, Deputy Division Director DMEDP
Dr. Edward Nevius, Division Director DOBII
Dr. Leo Lutwak, Medical Reviewer DMEDP
Dr. Eric Colman, Medical Reviewer DMEDP
Dr. David Orloff, Medical Reviewer DMEDP
Dr. Lee Pian, Statistical Reviewer DOBII
Dr. Martin Haber, Chemistry Reviewer DNDCII
Ms. Kathleen Reedy, Advisory Committee Staff
Mr. Randy Hedin, CSO DMEDP
Ms. Maureen Hess, CSO DMEDP

External participant attendees and titles:

Gerald Faich, M.D., M.P.H.	President
Lourdes Frau, M.D.	Knoll, Director Corporate Safety/Epidemiology/Medical Information
Finian Kelly, M.D.	Knoll, Director of International Development (Sibutramine)
Neil Kurtz, M.D.	CEO
JoAnn Manson, M.D., Dr.PH.	Harvard School of Medicine, Associate Professor of Medicine
Carl Mendel, M.D.	Knoll, Director of Endocrine and Metabolism
Tim Seaton, M.D.	Knoll, Senior Director, Endocrine and Metabolism
Sylvia Smoller, Ph.D.	Albert Einstein College of Medicine, Professor, Head of Epidemiology & Biostatics
Mel Spigelman M.D.	Knoll, Vice President, Research and Development
Jeff Staffa, Ph.D	Knoll, Vice President, Scientific and Technical Affairs
Vaseem Iftekhar	Knoll, Associate Director, Project Management
Abraham Varghese, Ph.D.	Associate Director, Regulatory Affairs

Meeting Objectives:

Requested by Knoll Pharmaceutical Company to address FDA concerns raised at April 23, 1996 meeting, obtain feedback regarding approvability of sibutramine and advise on planning for Advisory Committee meeting, September 26, 1996.

Discussion Points:

- Dr. Finian Kelly presented an overview of the efficacy of Meridia and the Division asked if 13 month and 15 month follow-up weight loss data are available. The firm replied negatively but will obtain the data.

- The Division asked if statistics were performed concerning the mean percentage change in plasma lipids in healthy obese patients in placebo-controlled studies. The firm replied negatively.

- The firm stated that the efficacy of sibutramine has been demonstrated over a wide dose range for up to 12 months and the degree of placebo subtracted weight loss is consistent between studies. The firm further stated that favorable trends in lipid profiles and glycemic control have been observed, and it is their opinion that the Division's weight-loss criteria have been satisfied.

- The firm stated that sibutramine causes a mean increase of approximately 2 mm Hg in systolic and diastolic blood pressure. This effect is the same in normotensives and in hypertensives and is the same whether patients are at the low end of the normal range or at the high end of the normal range. In hypertensives, this effect is the same whether patients are on or off antihypertensive medications.

- The Division asked the firm to explain the difference between July 15, 1996 background package (figure 3) submission regarding percent of outliers (systolic or diastolic BP increased by >25 mm hg from baseline) by dose group in placebo-controlled obese studies, and this presentation, as the 7-15-96 submission showed a 23% placebo group and the current slide shows a 12.7% placebo group. The firm stated it must be a different population; however, it will investigate this discrepancy and respond to the Division.

- The Division asked, concerning the information presented on outliers by dose group in the placebo-controlled obesity studies, how many times blood pressure observations were made. The firm responded 12.

- The Division asked if the contributions to percentages are almost entirely on the systolic side or the diastolic. A 5.0 mm Hg increase in diastolic pressure is a much more significant increase than if it is in systolic pressure. The firm stated they will run an analysis that distinguishes between systolic and diastolic pressures.

- The Division asked if the firm investigated how well the NHANES data represents the sibutramine population. The firm replied negatively.

- The Division asked if any of the models presented incorporate changes in systolic and diastolic pressure. The firm replied negatively. The Division then asked if there is any evidence of interaction between changes in blood pressure with changes in lipids or other adverse reactions. The firm replied negatively that blood pressure and cholesterol are independent risk factors and they are unsure of independence of the variables on pharmacologic effect. The Division stated that it is concerned that blood pressure and cholesterol may not be independent risk factors, and may be pharmacologically related. The Division asked if the model took into account if changes are statistically significant. The firm replied that some hypertension findings are significant and some aren't and that

they were grouped together for the model. The Division stated it was difficult to come to a firm conclusion on risk/benefit of sibutramine based on the models presented.

- The Division noted the study that showed an increase in mortality with an increase in BMI and asked the firm if there is data that show a decrease in mortality with a decrease in BMI. The firm replied that weight reduction is difficult to sustain so there is no good epidemiologic data available. However, CDC looked at intentional weight loss over a 1 year period on patients with comorbid conditions and showed a 20% reduction in all cause mortality. The division asked if that was pharmacologic weight loss, because sibutramine is a norepinephrine reuptake inhibitor and may show increases in cholesterol due to sympathetic changes. The firm stated that the increase in risk of CHD with the increase in blood pressure resulting from sibutramine is offset by the beneficial effects of weight loss on lipids, resulting in a net decrease in risk of CHD between 6% and 10%. The Division stated that a positive risk benefit ratio can not be demonstrated, and HDL was significantly increased in only one study. The Division stated that the risk benefit ratio of the safety and efficacy of the drug is the type of issue that is best addressed by an Advisory Committee. The Division stated that there is so much data in the NDA and the data conflict, thereby making it difficult to understand what the effect of the drug is. The positive changes in lipids are not a consistent finding.

Decisions (agreements) reached:

- The Division recommended an analysis of increased blood pressure and lipid changes; due to concerns that it may be a negative interaction. The firm agreed to perform further analysis.

- The Division recommended that the FDA's Cardio-Renal Division assess the blood pressure data to determine if changes are significant. The firm agreed to put the blood pressure data together for submission in one week.

-

- The Division agreed to work with the firm to determine a list of issues that need to be addressed before the advisory committee meeting.

Unresolved issues or issues requiring further discussion:

- None

Action Items:

Post Meeting Action Items:

- Consult sent to Cardio-Renal Division 8/5/96. Requested a completion date of 8/29/96.

Signature, minutes preparer_____

Concurrence Chair:_____

Attachments
Overheads used during presentation

cc: NDA Arch
HFD-510
Attendees
HFD-510/EGalliers
HFD--510/MHess/8.1.96/N20632.mn1

Concurrences:
EColman/8.1.96/LLutwak,DOrloff,GTroendle/8.2.96/MHaber/8.5.96/SSobel/8.6.96/
EGalliers/8.20.96

Goals

- Address FDA concerns raised at April 23, 1996 meeting
- Obtain FDA feedback regarding approvability of sibutramine
- Plan for constructive advisory panel meeting (September 27, 1996)

Agenda

Introduction	M. Spigelman
Overview of efficacy	F. Kelly
Analysis of blood pressure changes	C. Mendel
Epidemiologic benefit-risk	S. Smoller J. Manson G. Faich
FDA assessment of approvability	
Dose escalation schema	M. Spigelman
Preparation for advisory panel meeting	

Placebo-Controlled Obesity Studies with Sibutramine

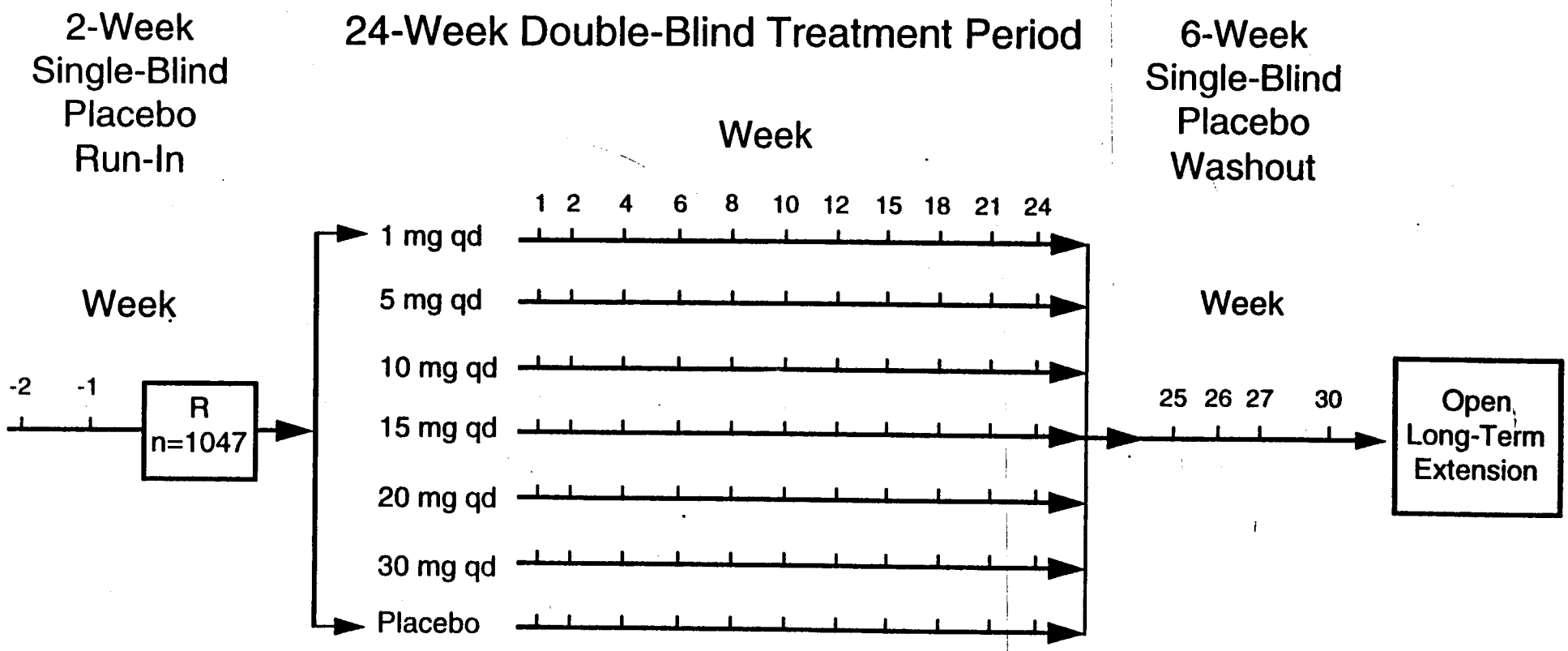
Study No.	n	Dosages (mg)	Obese Population	Duration* (weeks)	Results (p≤0.05 vs. Placebo)
BPI 852	1047	1, 5, 10, 15, 20, 30	Uncomplicated	24	5 - 30 mg
SB 1042	204	1, 10, 20	Uncomplicated	12	10 - 20 mg
SB 1043	236	5, 10, 15	Uncomplicated	12	10 - 15 mg
SB 1047	485	10, 15	Uncomplicated	52	10 - 15 mg
SB 1049	159	10	Uncomplicated	52	10 mg
SB 1052	75	10	Uncomplicated	12	10 mg
SB 2057	127	10	Hypertensive	12	10 mg
SB 3051	91	15	Diabetic	12	15 mg
SB 2059	182	10	Dsylipidemic	16	10 mg

* duration of sibutramine treatment

4023.07.10

BPI 852—US Dose-Ranging Efficacy Study

Study Design



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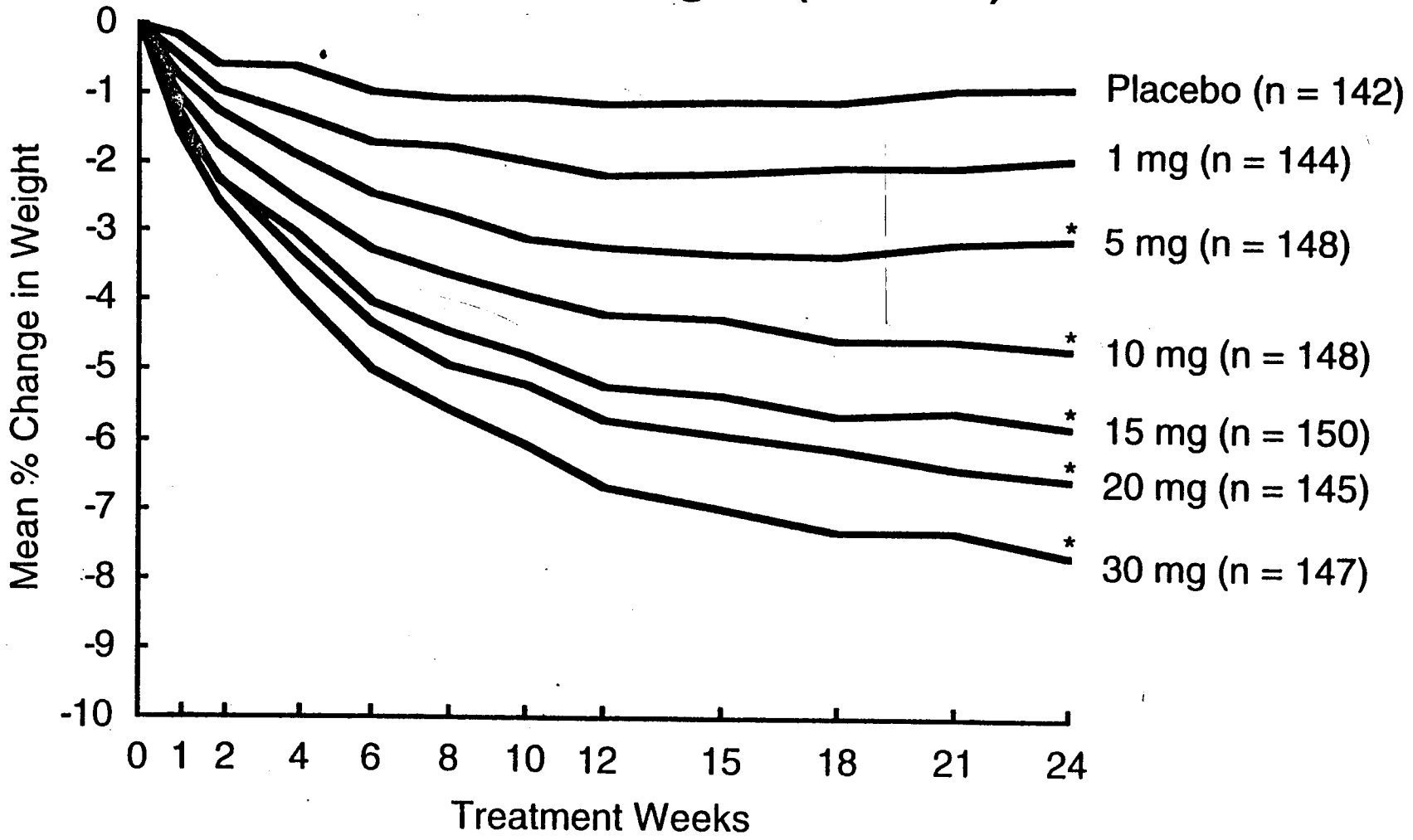
BPI 852—Mean Percent Change from Baseline Weight (LOCF)



* $p \leq 0.05$ vs placebo

4061.07.03

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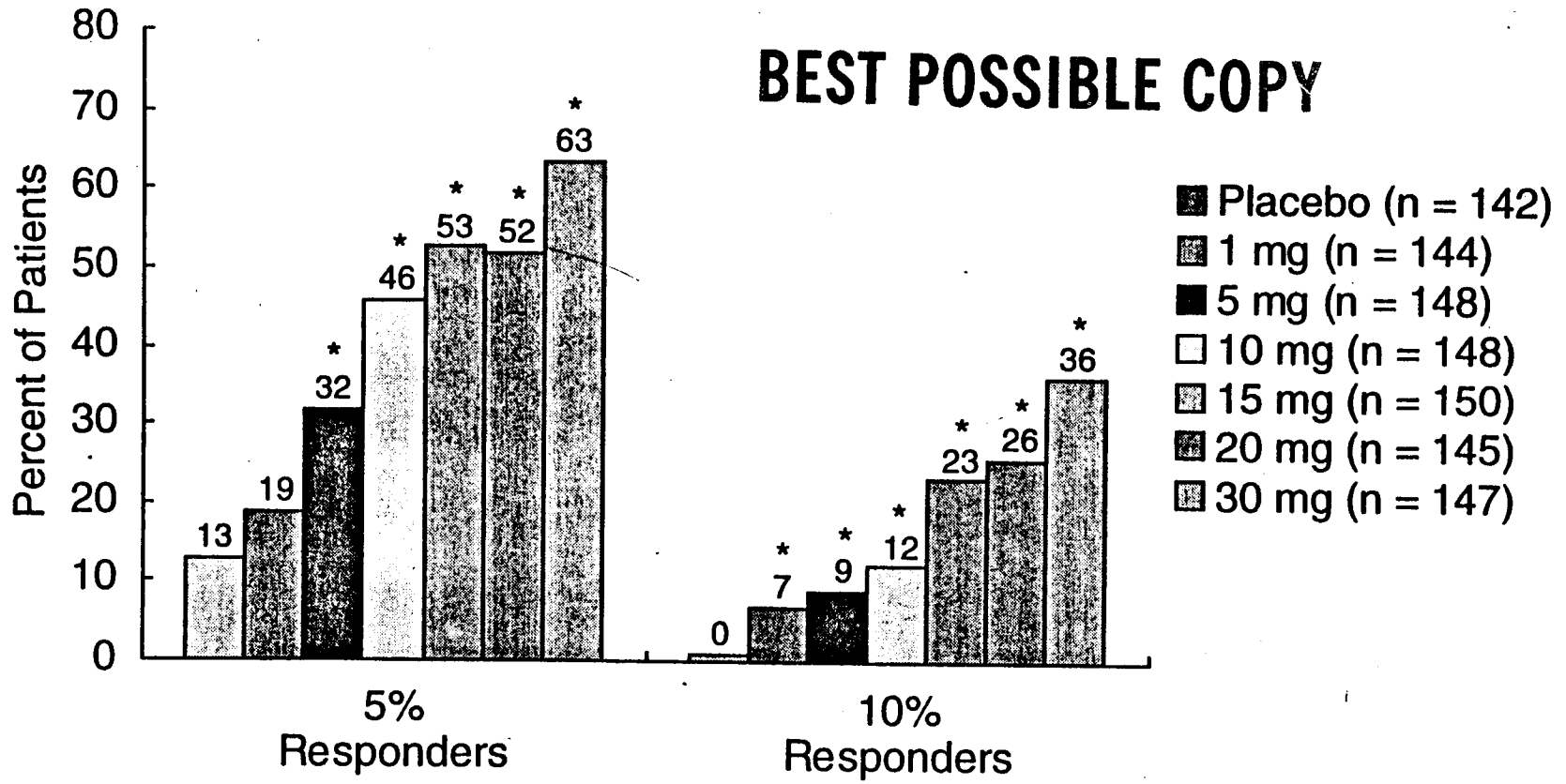
BPI 852—Percentages of Patients Losing at Least 5% or 10% of Baseline Weight by Week 24 (LOCF)



* $p \leq 0.001$ compared to placebo

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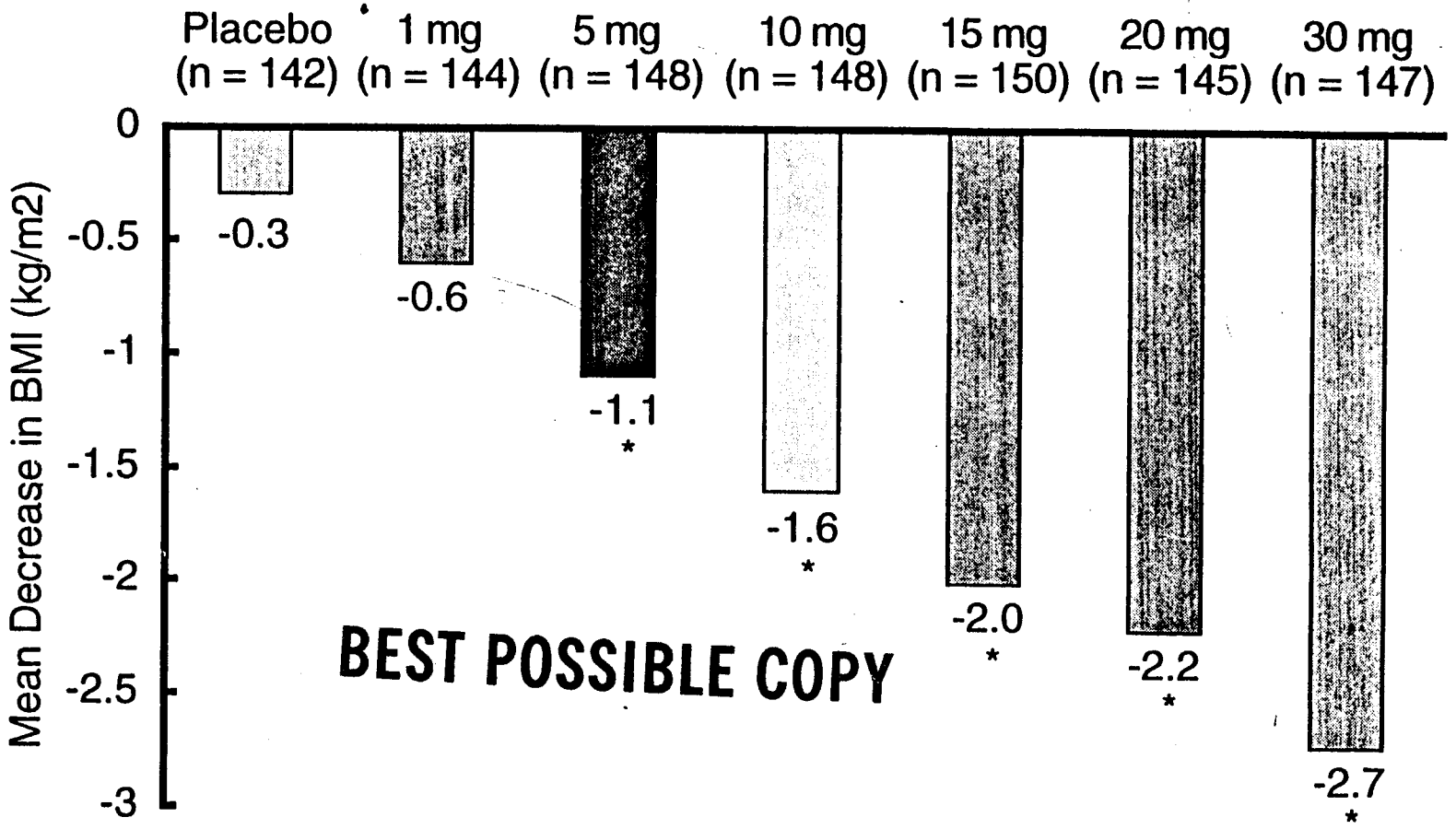
BPI 852—Mean Change from Baseline in BMI at Week 24 (LOCF)

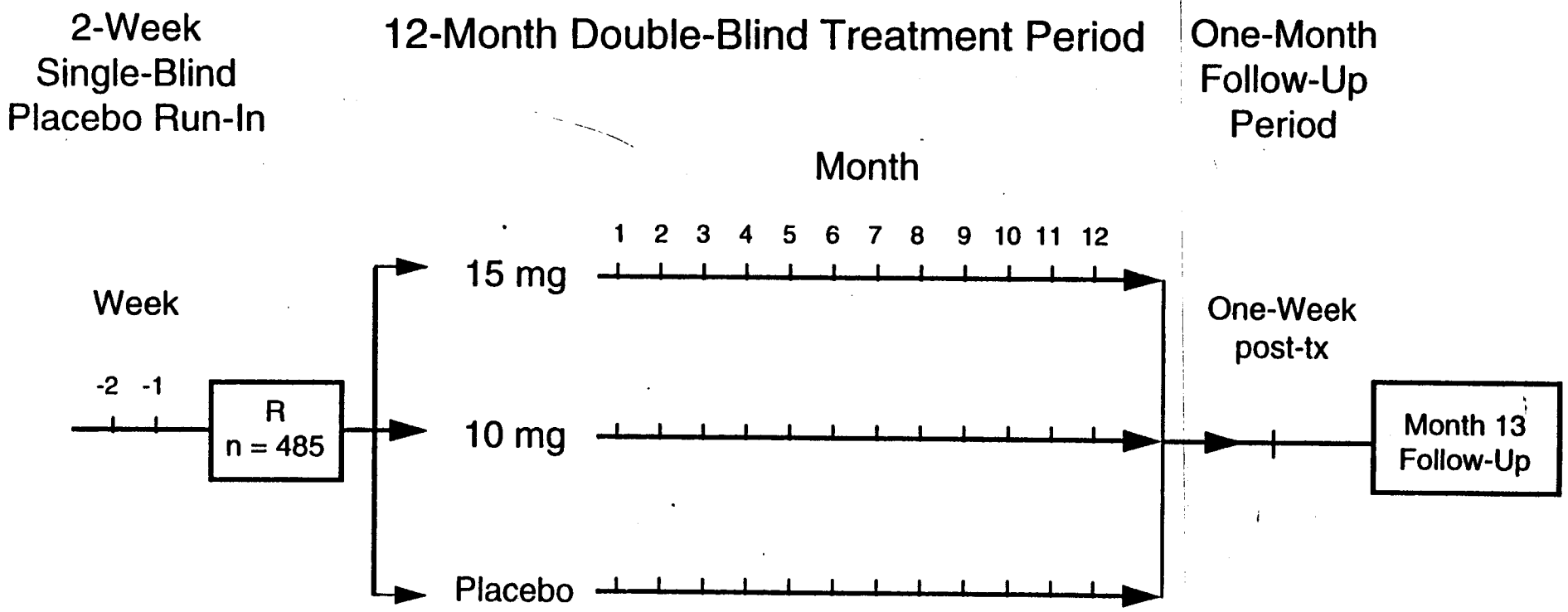


* $p \leq 0.05$ compared to placebo

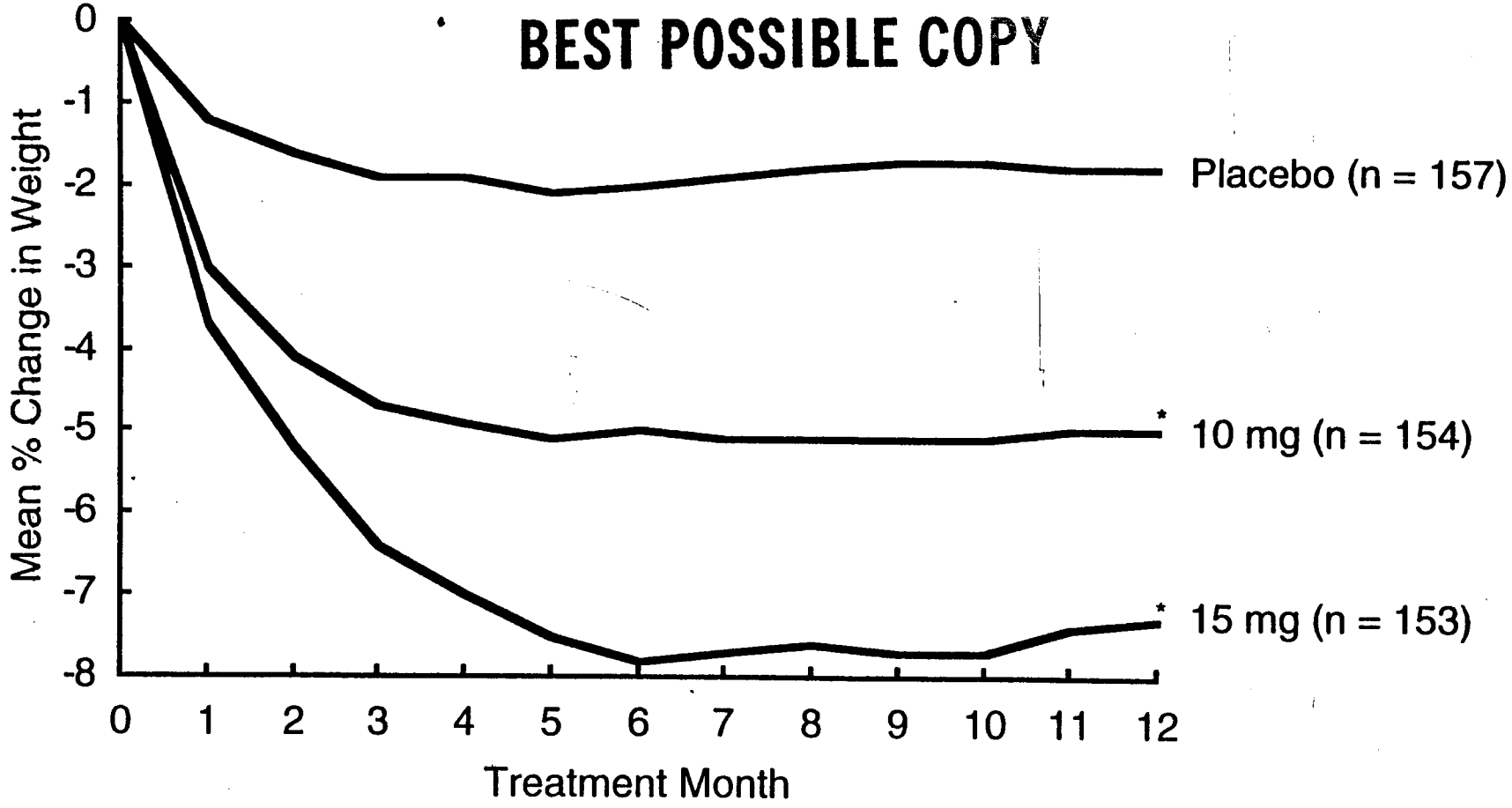
4069.04.25

SB 1047—UK Efficacy Study

Study Design



SB 1047—Mean Percent Change from Baseline Weight (LOCF)



* $p < 0.001$ vs placebo

4072.07.23

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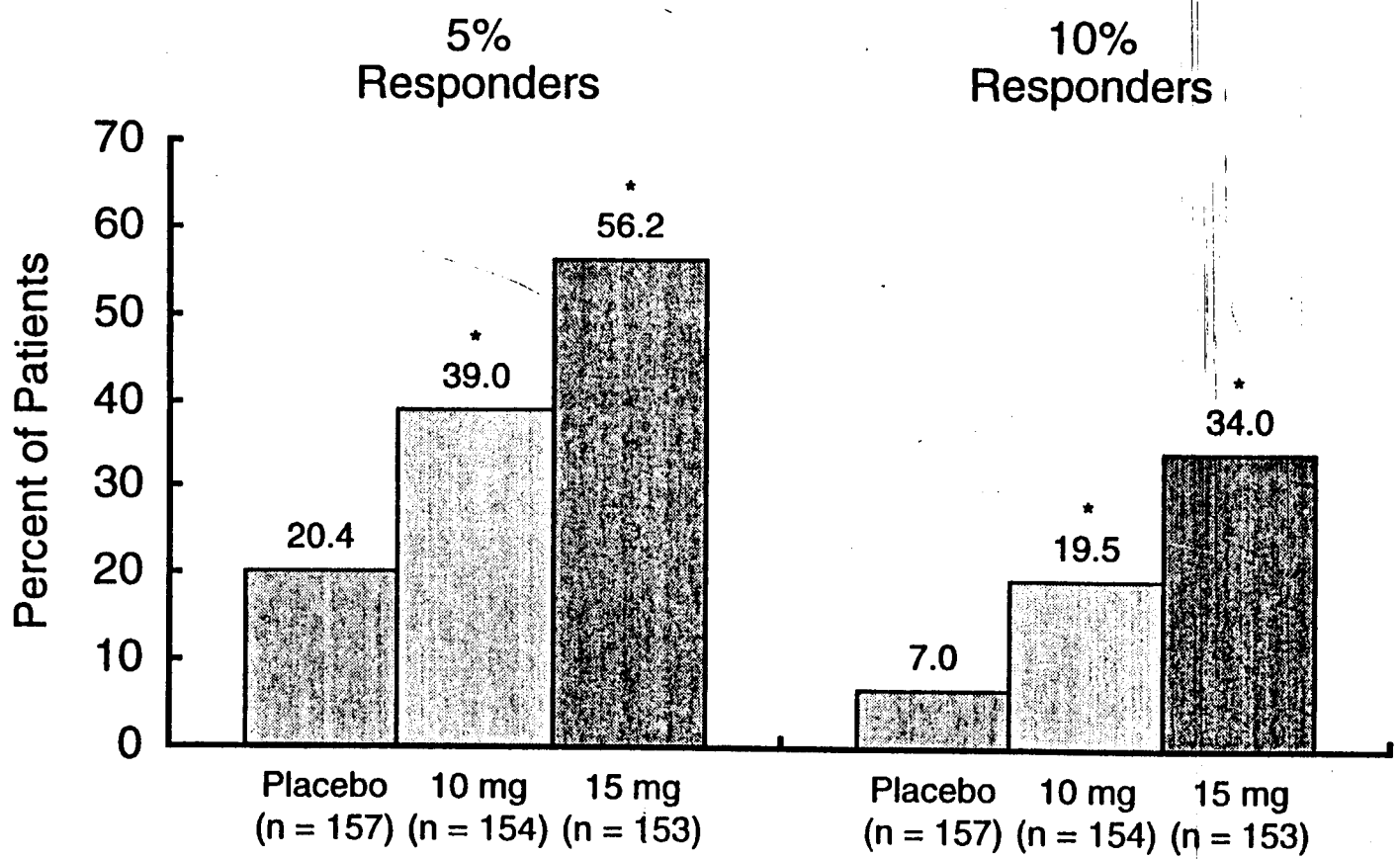
SB 1047—Percentage of Patients Losing At Least 5% or 10% of Baseline Weight by Month 12 (LOCF)



* $p < 0.001$ compared to placebo

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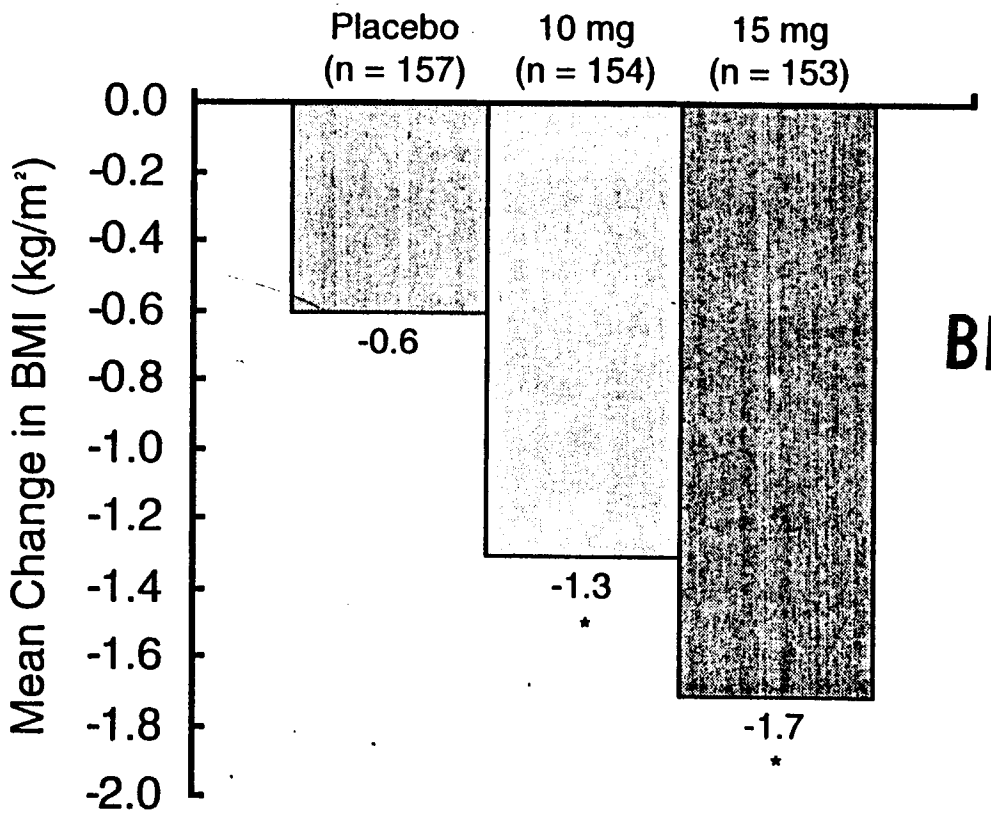
SB 1047—Mean Change in BMI (LOCF)



* $p < 0.001$ compared to placebo

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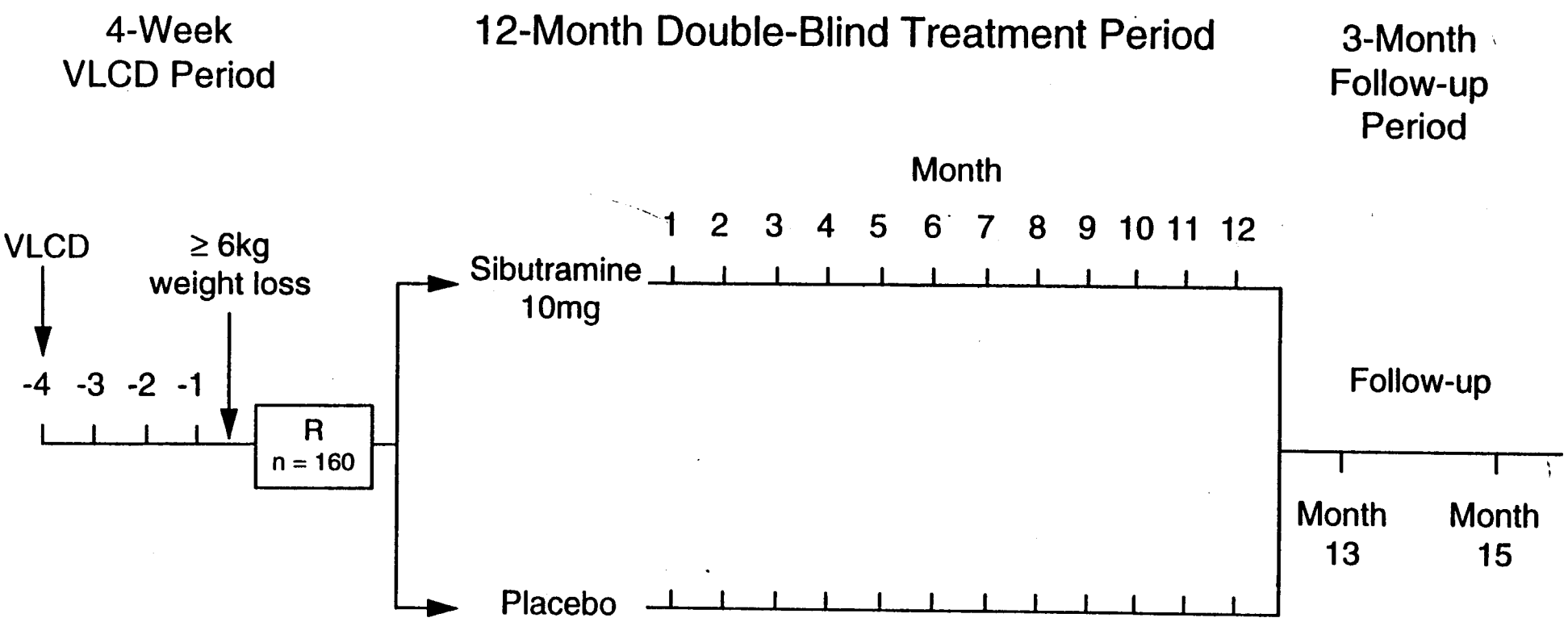
SB 1049–Maintenance Post-VLCD



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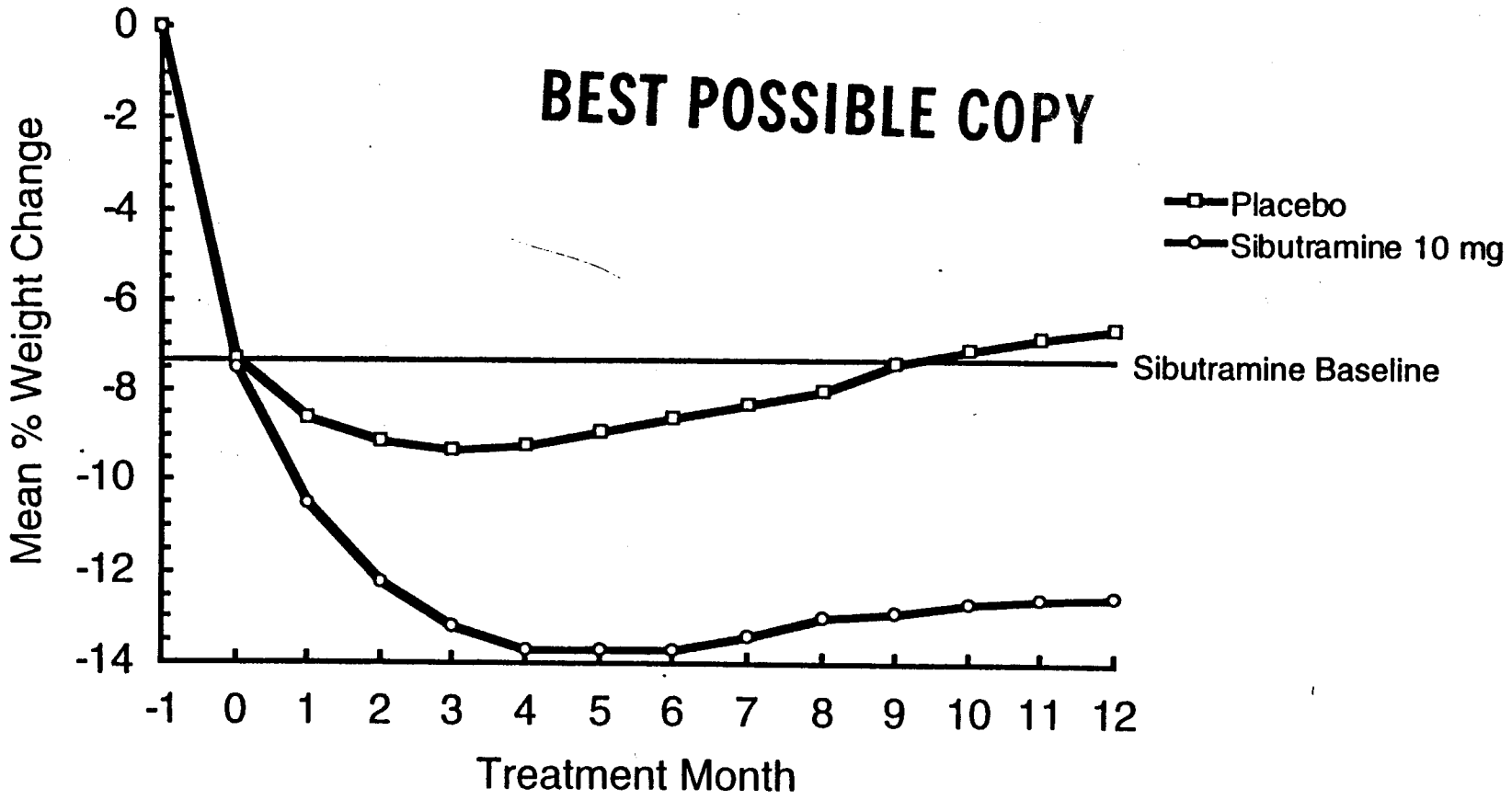
SB 1049–Maintenance Post-VLCD

Demographics Prior to VLCD

	Sibutramine 10mg (n = 82)	Placebo (n = 78)
Mean age (yr)	36	39
Gender		
Female	82%	77%
Male	18%	23%
Mean weight (kg)	103	105
Mean BMI (kg/m^2)	38	39

SB 1049—Maintenance Post-VLCD

Mean Percentage Change from Screening Weight (LOCF)



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SB 1049—VLCD - France

	Sibutramine 10 mg	Placebo	Treatment Effect
VLCD mean weight change (kgs)	-7.7	-7.4	—
On-treatment weight change (kgs)	-5.5	0.1	-5.6
On-treatment percentage change	-5.3%	0.6%	-5.9%

Sibutramine

Pivotal Efficacy Studies - Percentage Weight Change (LOCF)

	Sibutramine 10 mg	Placebo	Treatment Effect
BPI 852	-4.7	-0.9	-3.8
SB 1047	-3.9	-1.0	-2.9

	Sibutramine 15 mg	Placebo	Treatment Effect
BPI 852	-5.8	-0.9	-4.9
SB 1047	-6.3	-1.0	-5.3

SB 1049—Maintenance Post-VLCD

Mean Percentage Lipid Changes from Baseline (LOCF)

	Sibutramine 10 mg	Placebo	Treatment Effect	p-value
Triglycerides	-4.9	9.2	-14.1	< 0.05
Total cholesterol	16.6	18.9	-2.3	ns
HDL cholesterol	32.0	23.6	8.4	< 0.05
LDL cholesterol	14.5	19.5	-5.0	ns
LDL/HDL ratio	-11.9	-4.2	-7.7	< 0.05

ns = not significant

4499.07.23

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BPI 852—U.S. Dose-Ranging Study Mean Percent Change from Baseline in Patients with Abnormal Lipid Values

	Triglycerides ≥ 250		HDL < 45		LDL ≥ 160		Cholesterol ≥ 200	
Dose	n	Mean	n	Mean	n	Mean	n	Mean
Placebo	10	-27	29	5	25	-9	52	-6
1 mg	16	-9	45	3	27	-7	61	-5
5 mg	9	-33	49	5	36	-6	70	-4
10 mg	16	-41	41	11	22	-12	55	-9
15 mg	11	-53	45	14	27	-9	68	-5
20 mg	13	-28	43	12	29	-13	58	-9
30 mg	11	-40	41	16	30	-17	61	-10

BPI 852—U.S. Dose-Ranging Study
Mean Percent Change in Lipids for Completed Patients with ≥ 10% Reduction in Weight at Week 24

Mean Percent Change from Baseline (%)

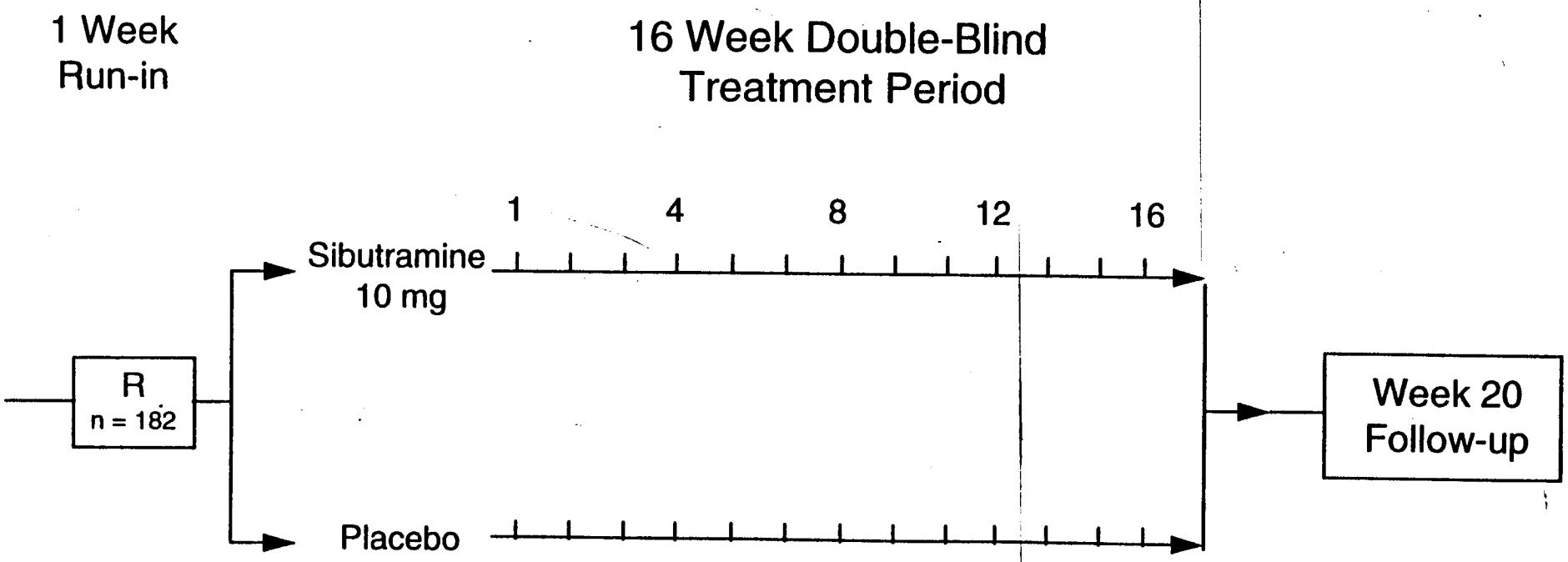
n	Triglycerides	HDL	LDL	Cholesterol
156	-28.1	+5.6	-10.6	-10.2

SB 3051—UK NIDDM Study

Mean Percentage Changes in Lipid Profile from Baseline (LOCF)

	Sibutramine 15 mg	Placebo	Treatment Effect
Triglycerides	-8.0	9.0	-17.0
Cholesterol	-0.5	3.0	-3.5
HDL cholesterol	5.0	-0.3	5.3
LDL cholesterol	2.0	3.0	-1.0
VLDL cholesterol	-3.0	8.0	-11.0

SB 2059–Dyslipidemia - Spain



Dyslipidemia inclusion criterion:

either
- total cholesterol 200 - 300 mg/dl or
- total triglycerides 200 - 400 mg/dl

4465.07.19

SB 2059—Dyslipidemia - Spain
Mean Weight and Percentage Lipid Changes (LOCF)

	Sibutramine 10 mg (n = 89)	Placebo (n = 90)	Treatment Effect
Weight loss (kgs)	7.8	5.6	-2.2*
Triglycerides	-20.4	-14.5	-5.9
Cholesterol	-2.9	-1.5	-1.4
HDL cholesterol	-2.5	-1.2	-1.3
LDL cholesterol	-4.1	-2.2	-1.9
VLDL cholesterol	-23.6	-15.0	-8.6
LDL/HDL ratio	-2.7	-0.4	-2.3

* $p < 0.05$

4501.07.24

Mean Percentage Change in Plasma Lipids in Healthy Obese Patients in Placebo-Controlled Studies

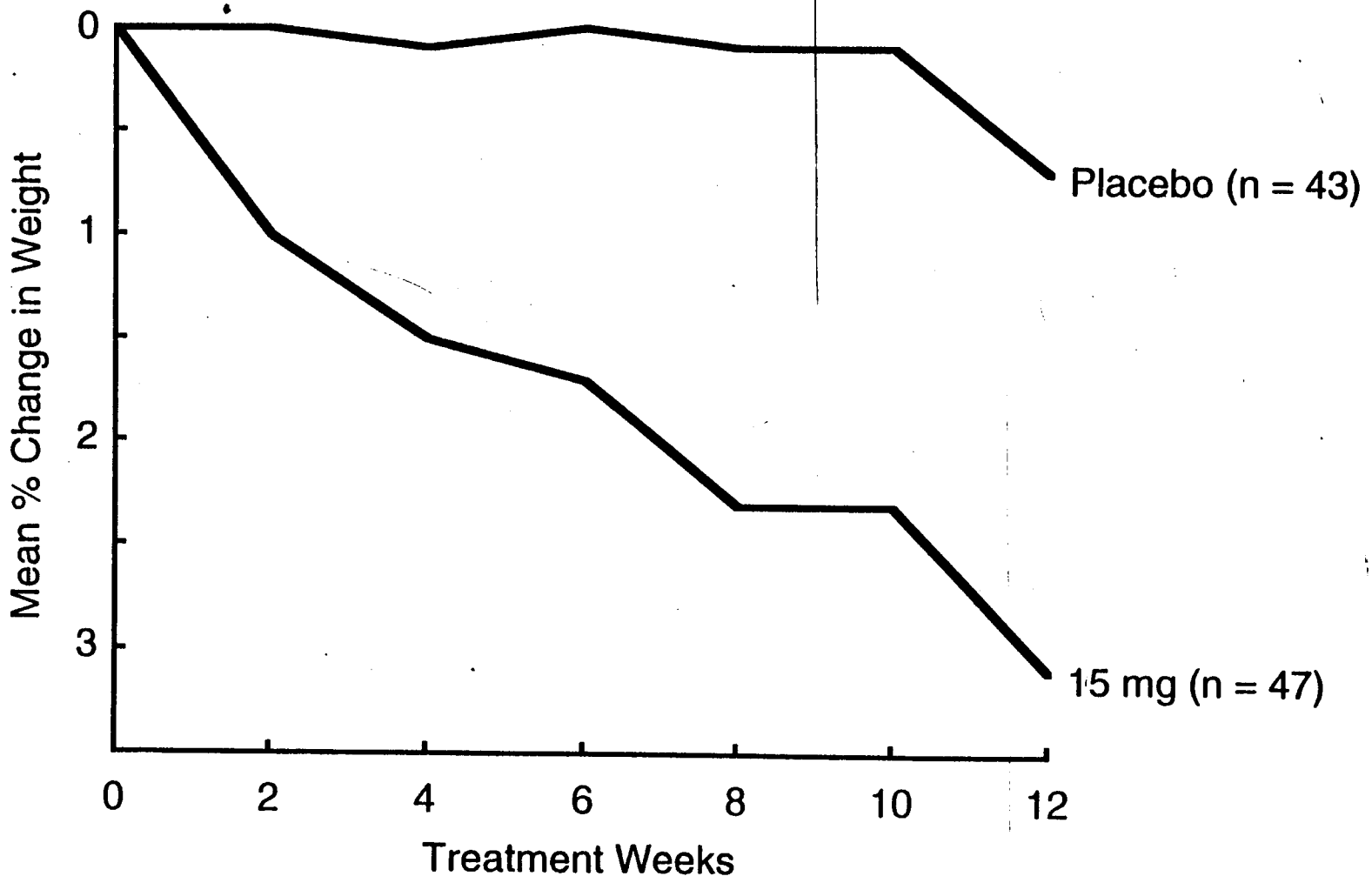
	Mean percent change from baseline			
	Placebo		Sibutramine[a]	
Triglycerides	0.2	(360)	-8.9	(1296)
Total cholesterol	-1.7	(360)	-3.4	(1297)
HDL cholesterol	-0.2	(133)	3.1	(749)
LDL cholesterol	-1.0	(121)	-4.2	(729)

a = all doses of sibutramine combined

() number of patients

5254.07.12

SB 3051—Mean Percent Change from Baseline Weight (LOCF)



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SB 3051—NIDDM - UK

Mean Changes in Fasting Blood Glucose and HbA_1 (LOCF)

	Mean Change in Fasting Blood Glucose (mg/dl)		
	n	Mean	Treatment Effect
Placebo	42	25	
Sibutramine	47	-5	-30

	Mean Change in HbA_1 (%)		
	n	Mean	Treatment Effect
Placebo	41	0.0	
Sibutramine	45	-0.4	-0.4

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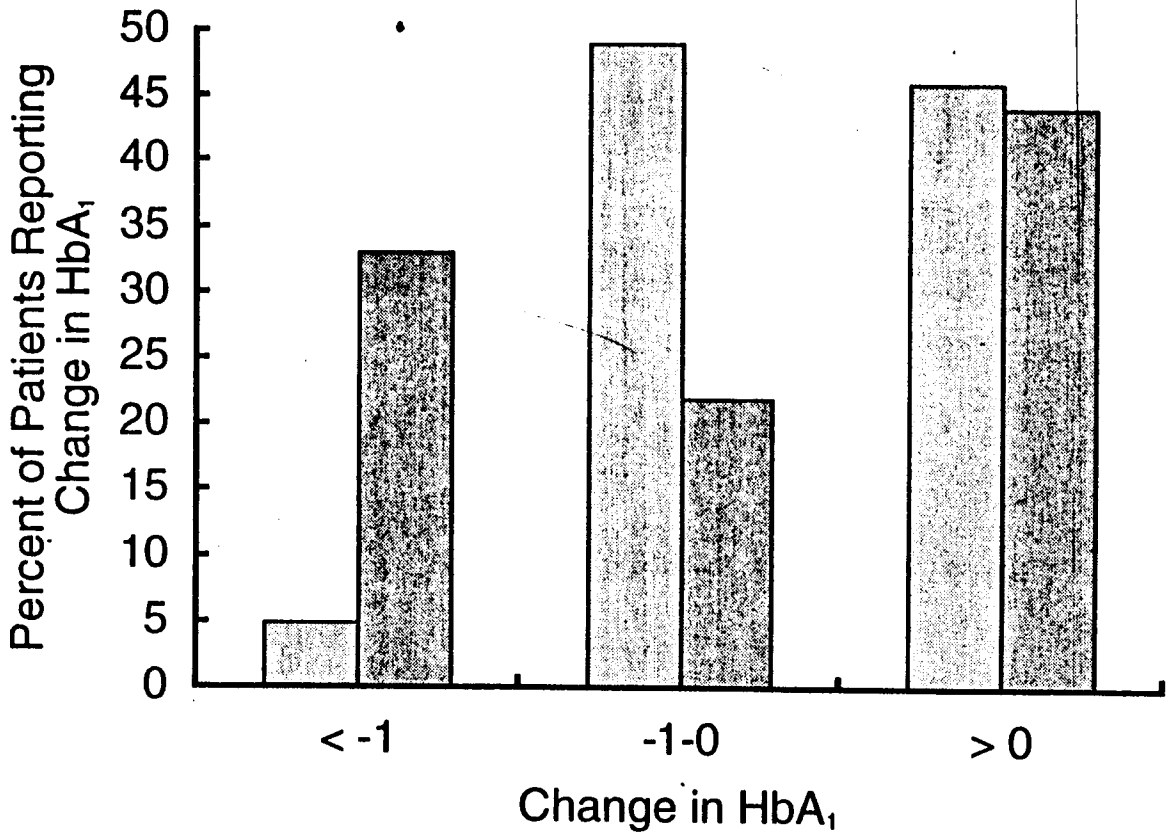
SB 3051—Change in Hemoglobin A_1 (LOCF)



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Sibutramine

Mean Changes from Baseline in Uric Acid (mg/dl) (LOCF)

Study	Placebo	Sibutramine 10 mg	Sibutramine 15 mg
BPI 852	-0.06	-0.31	-0.30
SB 1047	-0.15	-0.35	-0.45*
SB 1049	-0.72	-1.23*	—

* $p < 0.01$ compared to placebo

Sibutramine Efficacy Conclusions

- Efficacy of sibutramine has been demonstrated over a wide dose range for up to 12 months
- Degree of placebo-subtracted weight loss is consistent between studies
- Favorable trends in lipid profiles and glycemic control have been observed
- FDA weight-loss criteria have been satisfied

EFFECTS OF SIBUTRAMINE ON BLOOD PRESSURE—INTRODUCTION

- Mean changes in systolic and diastolic blood pressure
  - Normotensives
  - Hypertensives
- Clinically significant changes in blood pressure
  - Distribution curves/variability
  - Outliers
  - Discontinuations/Dose Reductions
- Clinically significant events related to blood pressure

Mean Change from Baseline in Resting Diastolic Blood Pressure in Uncomplicated Obese Patients in Placebo-Controlled Studies*

Baseline Stratification	Placebo	Sibutramine (mg) 1	5	10	15	20	30
Overall	-0.6	-0.6	1.5	1.4	1.8	2.2	3.1
≤ 80 mm Hg	1.2	1.9	2.8	3.1	3.7	3.5	4.7
> 80 mm Hg	-4.7	-5.2	-4.0	-2.2	-2.7	-2.8	-2.8

* Last on-treatment measurement ; n = 1606 active/469 placebo

5209.07.16

Mean Change from Baseline in Resting Systolic Blood Pressure in Uncomplicated Obese Patients in Placebo-Controlled Studies*

Baseline Stratification	Placebo	Sibutramine (mg) 1	5	10	15	20	30
Overall	-0.7	0.1	2.0	1.0	2.7	1.7	4.0
≤ 120 mm Hg	4.0	2.3	6.3	6.4	7.6	6.1	6.5
> 120 mm Hg	-5.8	-4.0	-5.5	-5.2	-2.4	-5.6	-2.6

* Last on-treatment measurement; n = 1606 active/469 placebo

5208.07.22

SB 2057[a] —Mean Change in Blood Pressure in Hypertensive Obese Patients

	Mean Change from Baseline (mm Hg)[b]	
Measurement	Placebo (n = 59)	Sibutramine 10 mg (n = 54)
Supine systolic BP	-7.2	-6.1
Supine diastolic BP	-6.8	-5.6

a = 12 week double-blind study
b = last on-treatment visit

5206.07.19

SB 2057[a] —Mean Change in Blood Pressure in Hypertensive Obese Patients On/Off Antihypertensive Medications

	Mean Change from Baseline (mm Hg)[b]	
Measurement	Placebo (n = 59)	Sibutramine 10 mg (n = 54)
Supine systolic BP	-7.2	-6.1
On Antihypertensives	-13.4 (n = 22)	-8.9 (n = 15)
Off Antihypertensives	-3.5 (n = 37)	-5.1 (n = 39)
Supine diastolic BP	-6.8	-5.6
On Antihypertensives	-7.3 (n = 22)	-5.9 (n = 15)
Off Antihypertensives	-6.5 (n = 37)	-5.5 (n = 39)

a = 12 week double-blind study
b = last on-treatment visit

5262.07.22

Mean Change From Baseline in Blood Pressure in Hypertensive Obese Patients[a] On/Off Antihypertensive Medications in Nonhypertension Placebo-Controlled Studies[b]

Measurement	Mean Change from Baseline (mm Hg)		
		Sibutramine	
	Placebo (n = 97)	10 mg (n = 65)	15 mg (n = 77)
Supine systolic BP	-7.6	-4.5	-4.7
On Antihypertensives	(n = 42) -5.2	(n = 14) 0.4	(n = 33) -2.3
Off Antihypertensives	(n = 55) -9.5	(n = 51) -5.9	(n = 44) -6.5
Supine diastolic BP	-2.6	-1.4	0.1
On Antihypertensives	(n = 42) -0.8	(n = 14) -4.9	(n = 33) -0.4
Off Antihypertensives	(n = 55) -4.0	(n = 51) -0.4	(n = 44) 0.4

a = Hypertensive defined as patient with baseline SBP > 140 or DBP > 90 mm Hg, taking antihypertensive medication for hypertension, or with hypertension listed as a concurrent illness

b = Last on-treatment measurement

5378.07.22

Effects of Sibutramine on Mean Blood Pressure—Summary

- Sibutramine causes mean increases of approximately 2 mm Hg in systolic and diastolic blood pressure
  - This effect is the same in normotensives and in hypertensives
  - In normotensives, this effect is the same whether patients are at the low end of the normal range or at the high end of the normal range
  - In hypertensives, this effect is the same whether patients are on or off antihypertensive medications

Percent of Patients Who Had Increases/Decreases/ No Change* in Diastolic Blood Pressure by Dose in Placebo-Controlled Obesity Studies

	Percent of Patients**		
Treatment Group	Increases	Decreases	No Change
Placebo	37	45	18
Sibutramine			
1 mg	41	40	18
5 mg	50	34	17
10 mg	40	39	20
15 mg	44	34	22
20 mg	53	28	19
30 mg	63	25	12
All sibutramine	46	35	19

**Change from baseline to last on-treatment measurement

* n = 1735 active/592 placebo

5253.07.22

Percent of Patients Who Had Increases/Decreases/ No Change* in Systolic Blood Pressure by Dose in Placebo-Controlled Obesity Studies

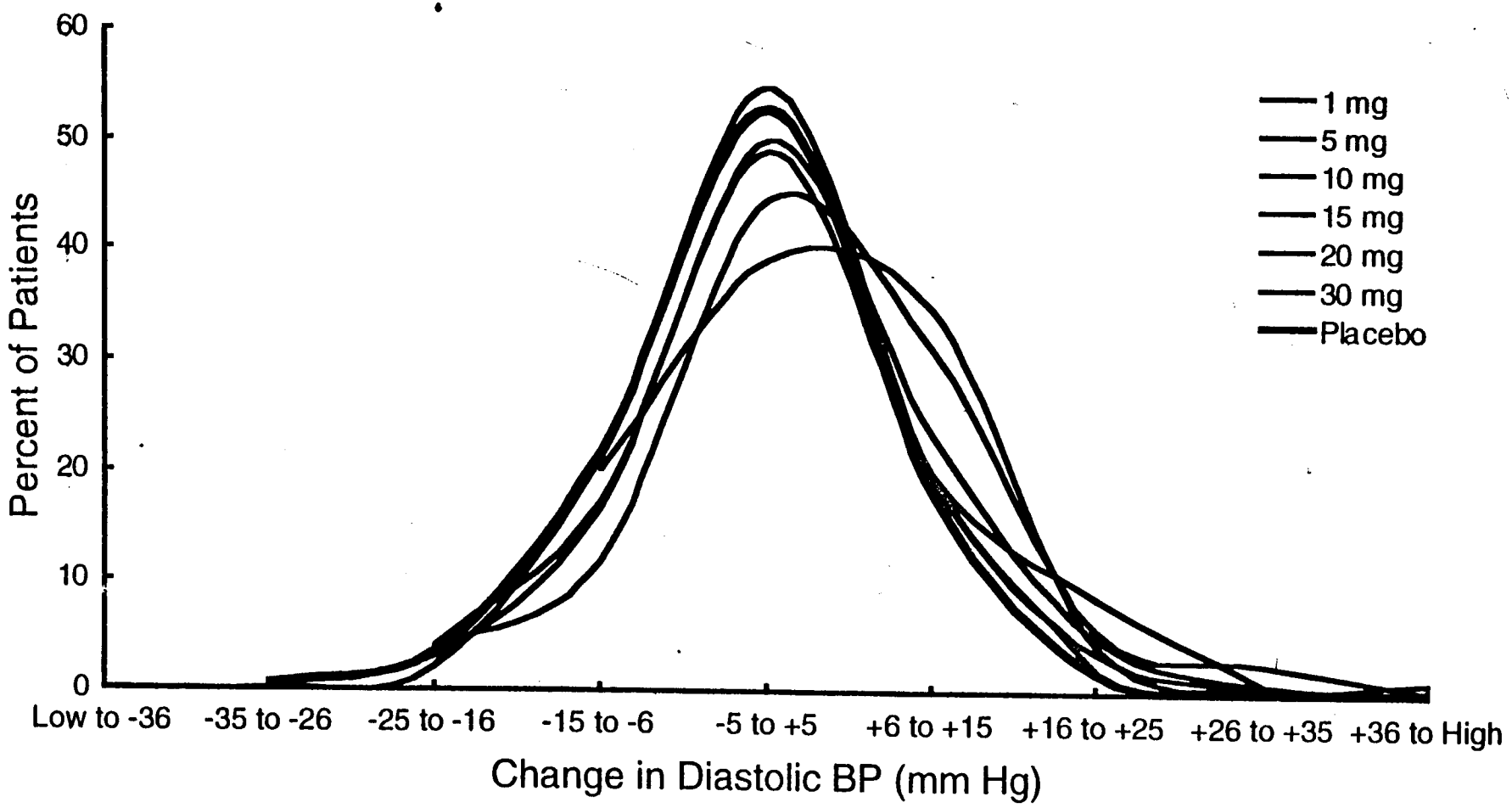
	Percent of Patients**		
Treatment Group	Increases	Decreases	No Change
Placebo	39	47	15
Sibutramine			
1 mg	40	44	16
5 mg	51	39	10
10 mg	44	44	13
15 mg	48	40	13
20 mg	54	38	9
30 mg	57	32	11
All sibutramine	48	40	12

* Change from baseline to last on-treatment measurement

** n = 1735 active/592 placebo

5251.07.22

Frequency Distribution of Change in Diastolic BP by Dose in All Placebo-Controlled Obesity Studies—Baseline to Last On-Treatment Visit



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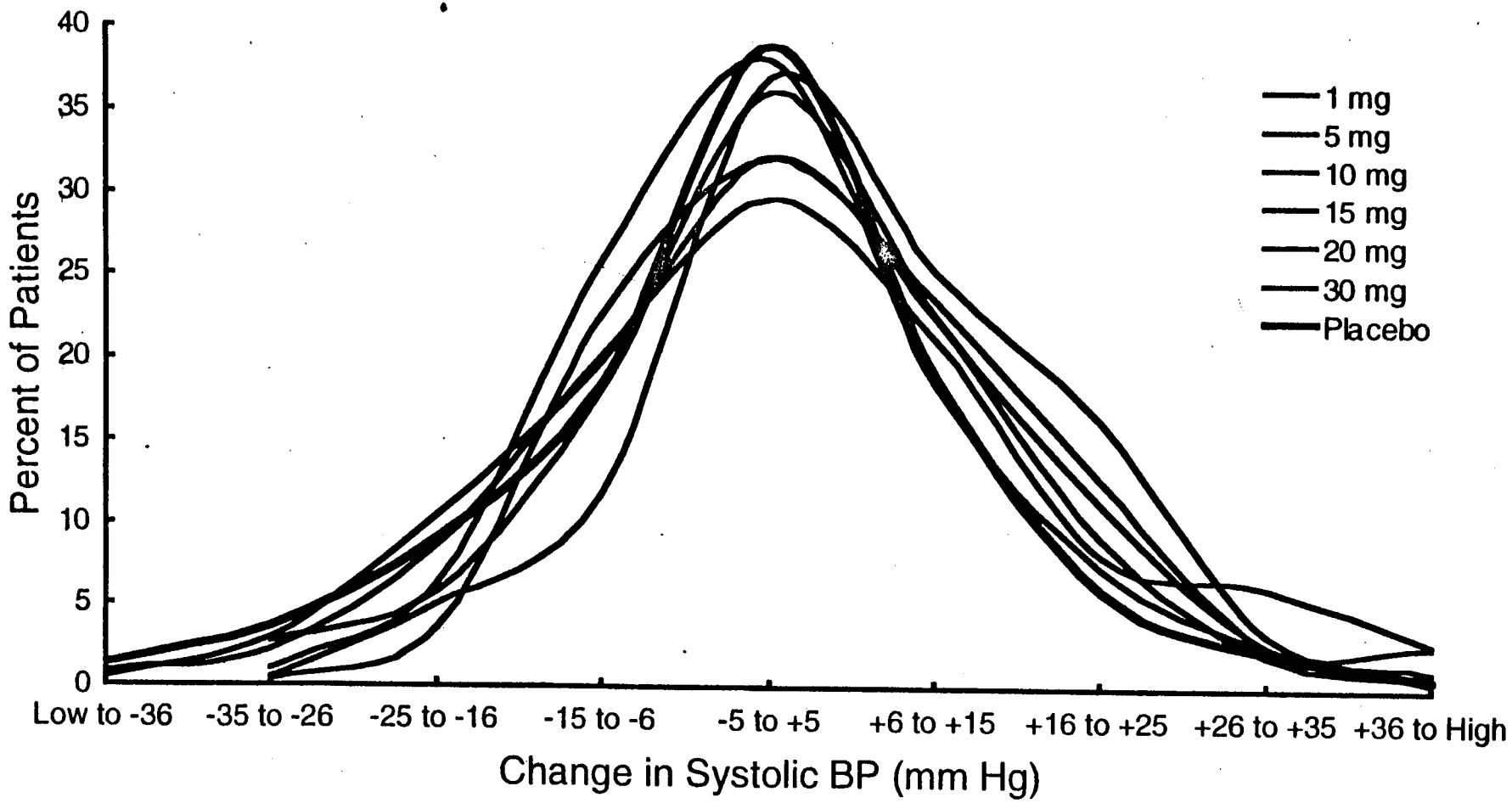
Frequency Distribution of Change in Systolic BP by Dose in All Placebo-Controlled Obesity Studies



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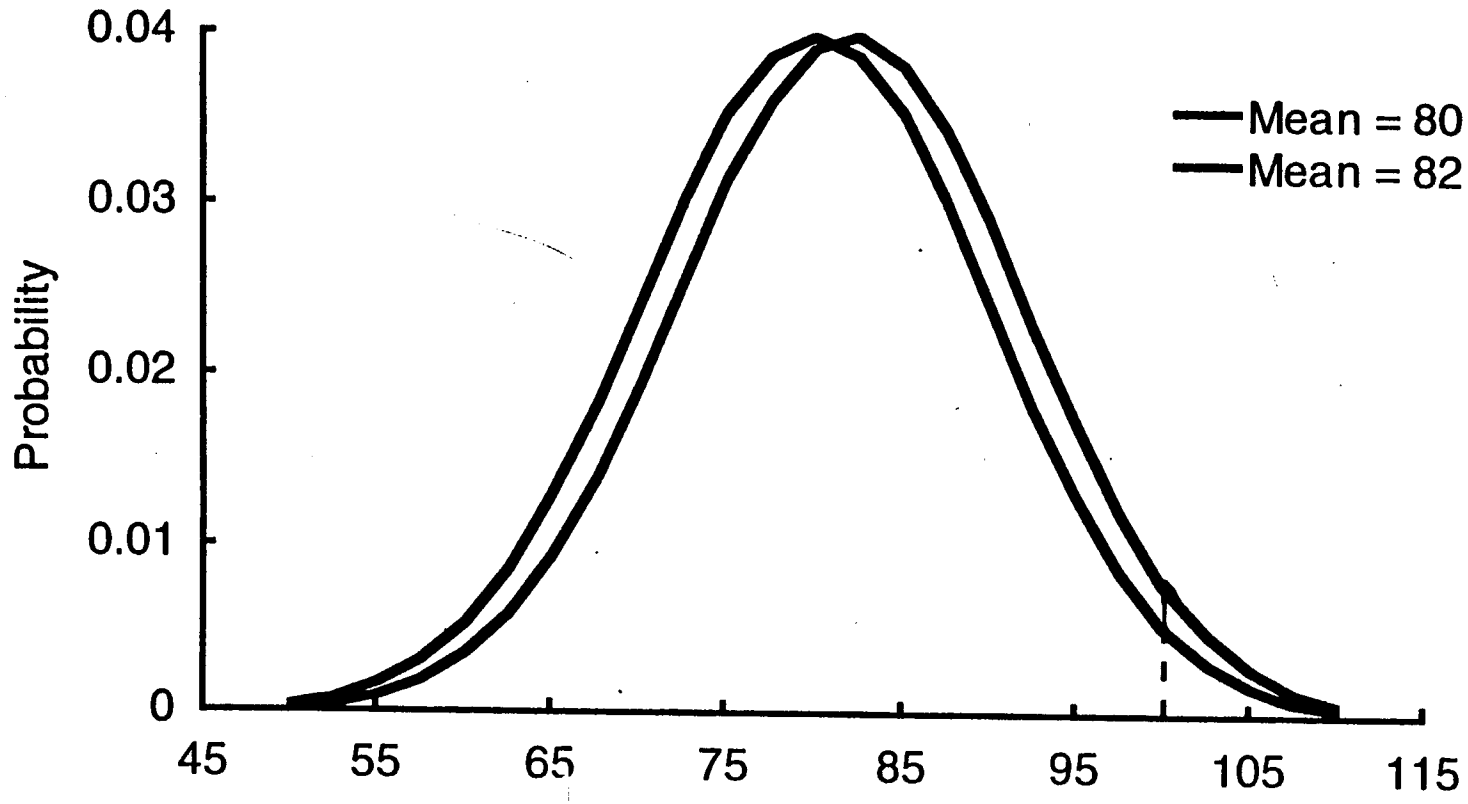
Probability Density Function of Two Normal Random Variables with Means 80 and 82 and the Same Standard Deviation (SD = 10)



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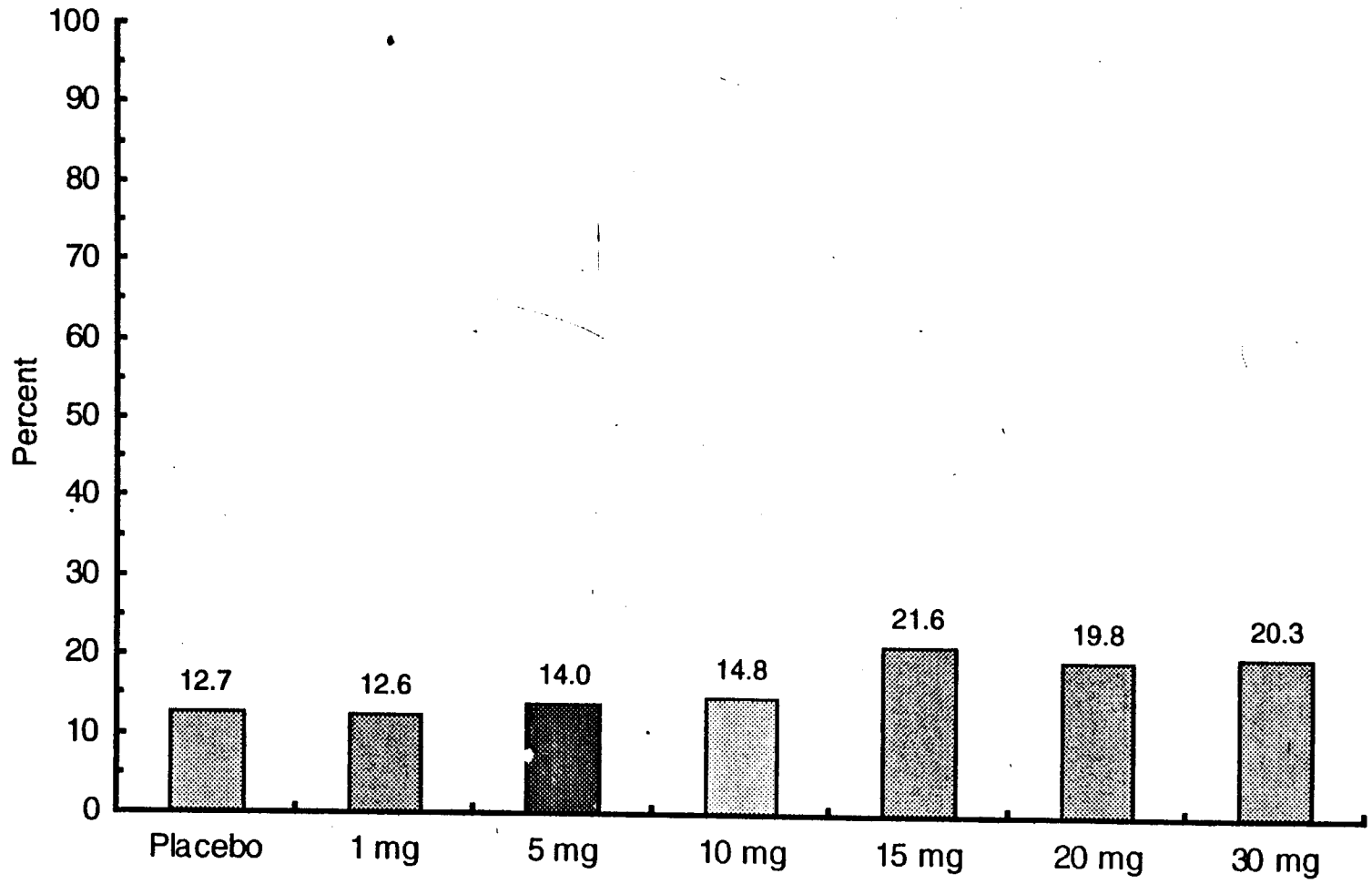
Outliers (Systolic or Diastolic BP Increased by ≥ 25 mm Hg from Baseline) by Dose Group in Placebo-Controlled Obesity Studies (n = 1735 active/592 placebo)



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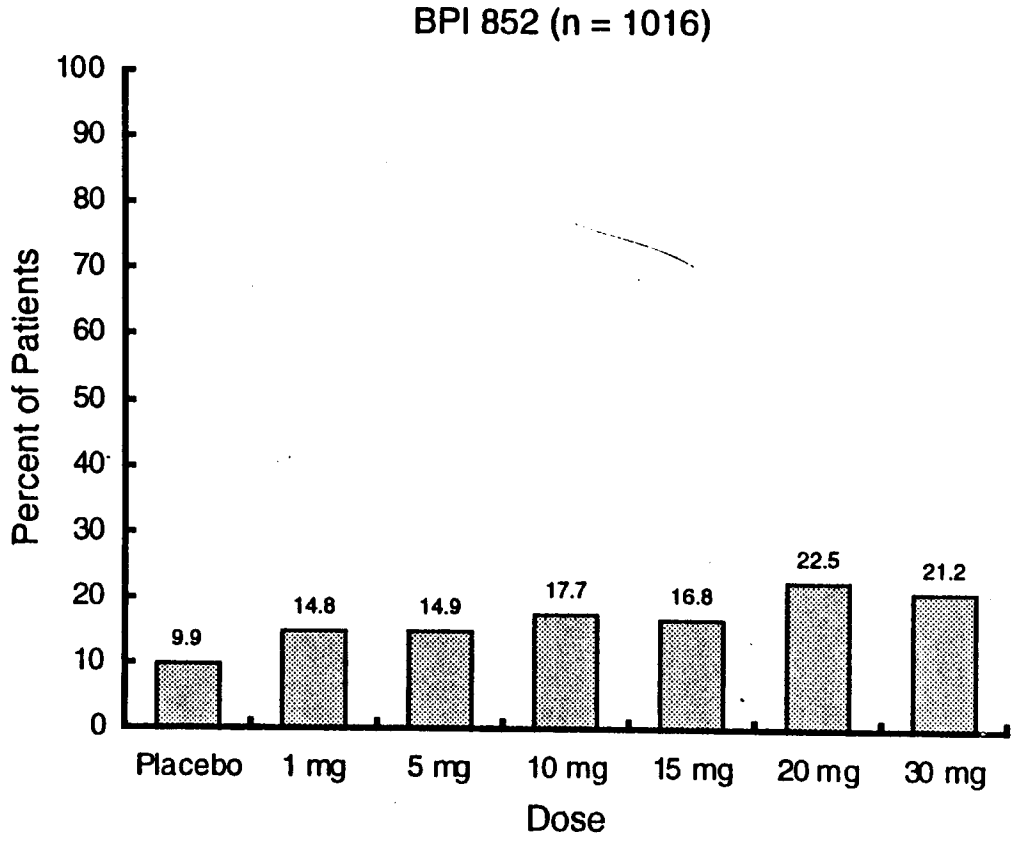
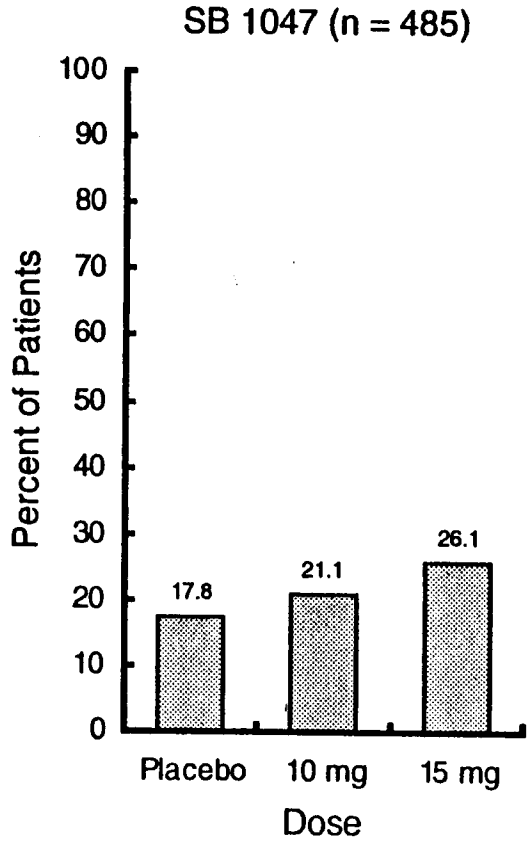
Outliers (Systolic or Diastolic Blood Pressure Increase ≥ 25 mm Hg from Baseline at Any Timepoint) by Dose Group





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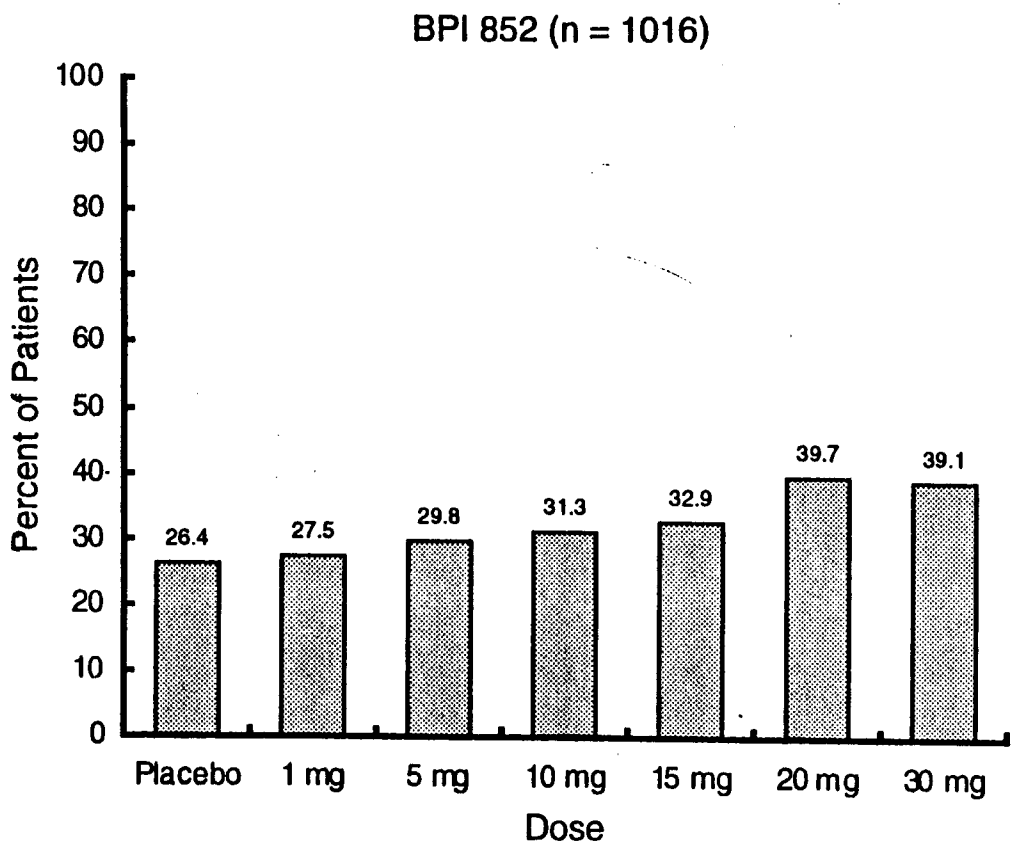
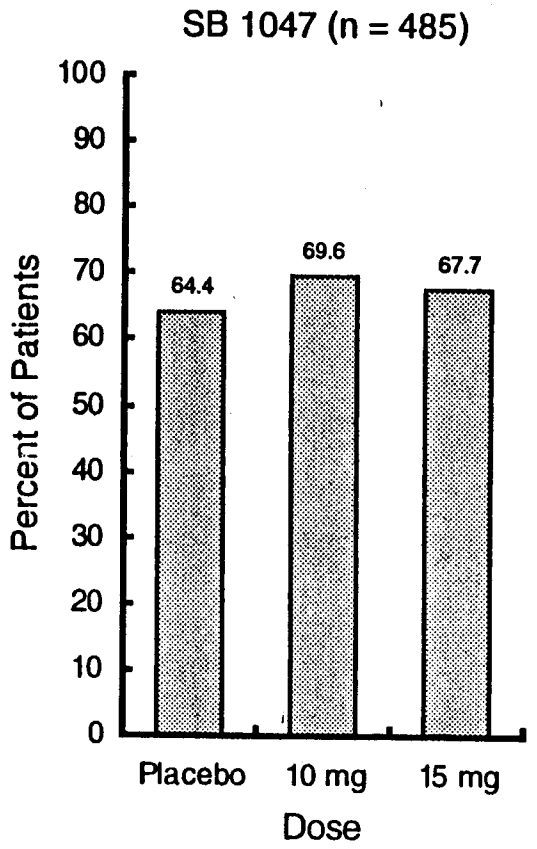
Outliers (Systolic Blood Pressure ≥ 140 mm Hg or Diastolic Blood Pressure ≥ 90 mm Hg at Any Timepoint) by Dose Group





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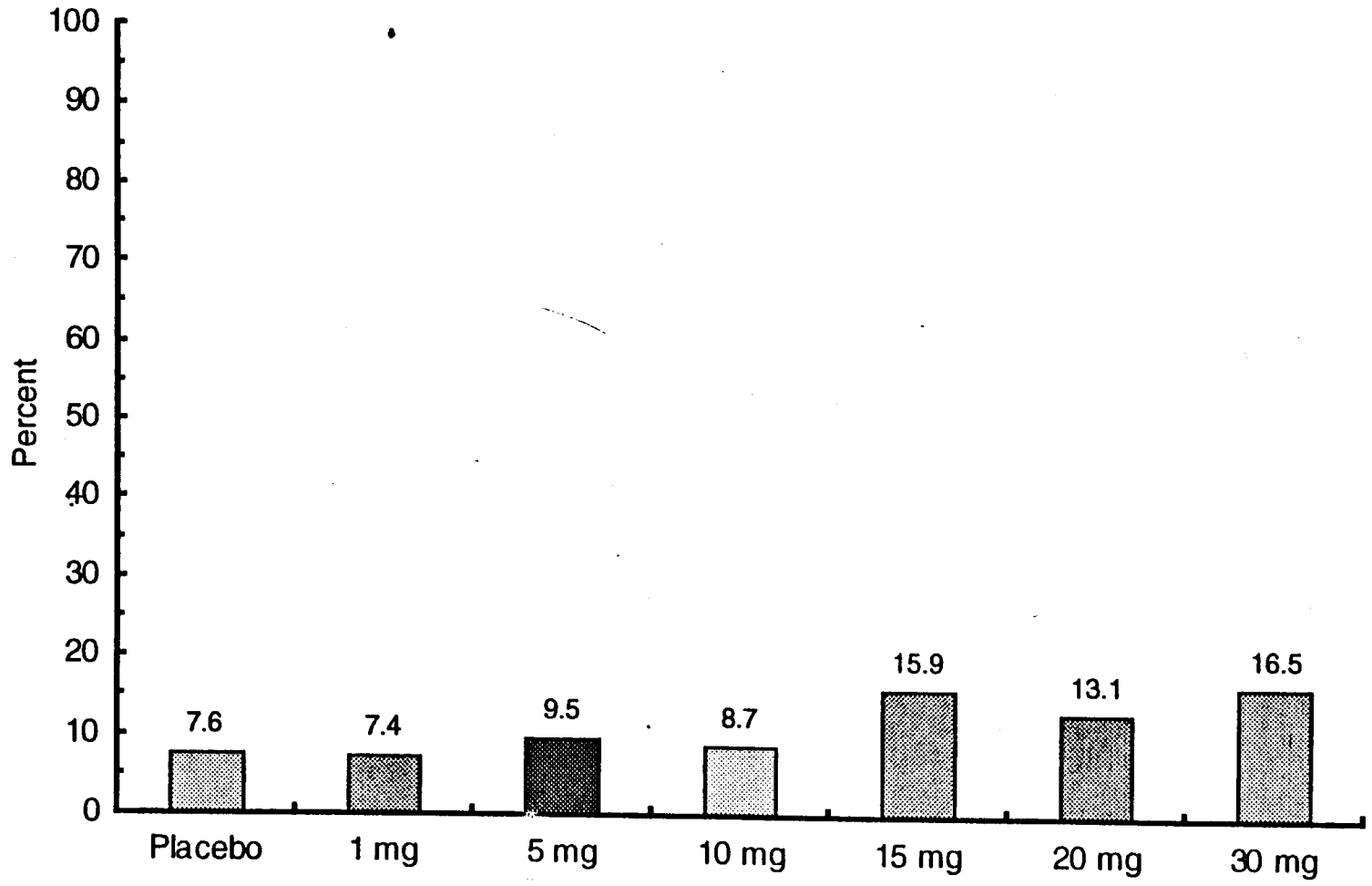
Outliers (Increase from Baseline ≥ 15 mm Hg in Systolic or Diastolic Blood Pressure)* by Dose Group in Placebo-Controlled Obesity Studies



* = for 3 consecutive visits

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Discontinuations or Dose Reductions for Elevated Blood Pressure

- Only 19 discontinuations for elevated blood pressure in placebo-controlled obesity studies (n = 2327)
- All discontinuations occurred in only 3 placebo-controlled studies

	BPI 852* (n = 1047)		SB 1042 (n = 206)		SB 1043 (n = 236)	
	Placebo	Sibutramine	Placebo	Sibutramine	Placebo	Sibutramine
Number discontinued	1 (0.7%)	13 (1.4%)	0 (0.0%)	4 (2.6%)**	1 (0.4%)	0 (0.0%)
Number dose reduced	5 (3.4%)	31 (3.4%)				

* = Discontinuation or dose reduction mandated in BPI 852 for single BP reading of SBP ≥ 160 or DBP ≥ 95 mm Hg
** = Two patients were on sibutramine 1 mg

5371.07.22

Does Sibutramine Cause Clinically Significant Effects on Blood Pressure in Individual Patients?—Summary

- The distribution of observed blood pressure changes in sibutramine-treated patients is similar to that in placebo-treated patients
  - Small, rightward shifts in the curves, consistent with the observed mean changes in blood pressure
  - Absence of prominent leading edges in the curves
  - Curves not biphasic
- Outlier analyses
  - Relatively small increases in the numbers of outliers on sibutramine as compared with placebo, consistent with the observed mean changes in blood pressure
- Discontinuations for hypertension
  - Very small number

    Relative absence of blood pressure changes of clinical concern

5372.07.22

Conclusions

- Sibutramine increases mean systolic and diastolic blood pressure by approximately 2 mm Hg as compared with placebo
  - This effect is the same in normotensives and hypertensives and in hypertensives on and off medicines
- Large, clinically significant increases in blood pressure (beyond those accounted for by intrasubject and measurement variability) have not been seen in sibutramine-treated patients

Introduction

- To explore the interrelationships among changes in blood pressure and lipids and changes in risk of coronary heart disease (CHD) and cardiovascular disease (CVD)
- A small increase in blood pressure is associated with sibutramine treatment

Risk Estimates from Framingham Study

Framingham population

- n = 5209
- Age 30 - 62 years at baseline
- Follow-up: over 18 years for original cohorts and 12 years for offspring of cohorts

Baseline characteristics

	Women	Men
Smokers	39%	41%
Diabetes	5%	7%
Median		
Cholesterol	212	210
HDL	56	43
SBP	123	128
DBP	79	82

Framingham Heart Study - NHANESI

- Framingham heart study has been foundation upon which several national policies regarding risk factors for coronary heart disease mortality are based (N = 5209)
- NHANESI epidemiologic follow-up study is 1st national cohort study based on comprehensive medical examination of a probability sample of US adults (N = 14,407)
- The Framingham model predicts remarkably well for this national sample

REF: Leaverton PE, Sorlie PD, Kleinman JC, Dannenberg AL, Ingster-Moore L, Kannel WB, Cornoni-Huntley JC. **Representatives of the Framingham risk model for coronary heart disease mortality: A comparison with a National Cohort Study.** J Chron Dis Vol 40, No 8, pp 775-784, 1987.

References for Framingham Risk Estimates

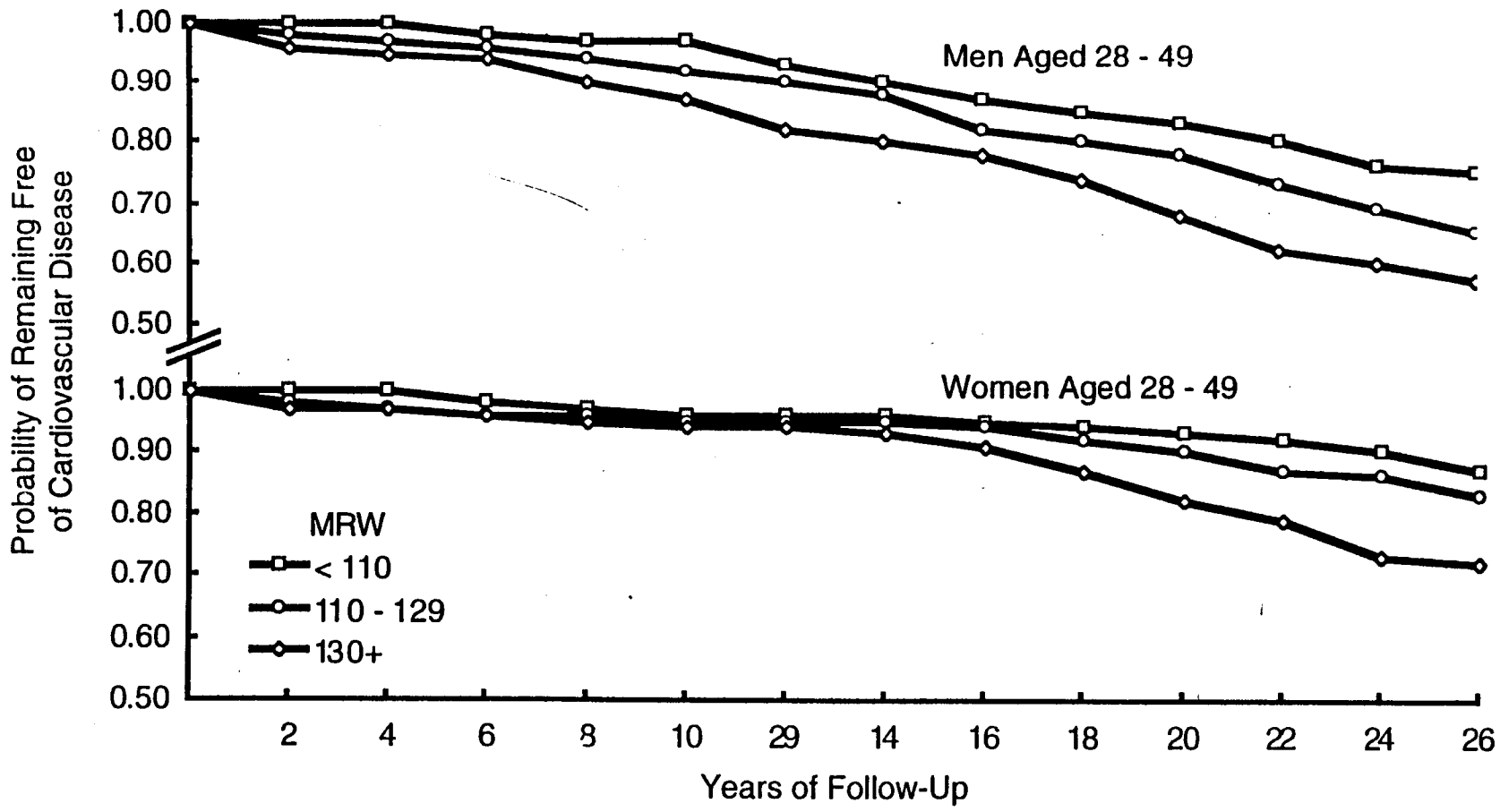
- Kannel WB, McGee D, Gordon T: **A General Cardiovascular Risk Profile: The Framingham Study**. Amer J Cardiology 1976; 38: 46-51
- Hubert HB, Feinleib M, McNamara PM, Castelli WP: **Obesity as an Independent Risk Factor for Cardiovascular Disease: A 26-year Follow-up of Participants in the Framingham Heart Study**. Circulation 1983; 67: 968-974.
- Anderson KM, Wilson PWF, Odell PM, Kannel WB: **An Updated Coronary Risk Profile. A Statement for Health Professionals**. Circulation 1991; 83: 356-362

Framingham

Definitions

- **Coronary Heart Disease (CHD):**
  angina, coronary insufficiency (unstable angina), myocardial infarction, sudden death
- **Cardiovascular Disease (CVD):**
  CHD, congestive heart failure, cerebrovascular disease, intermittent claudication

The Probability of Remaining Free of Cardiovascular Disease at Each Follow-Up Examination By Metropolitan Relative Weight (MRW) at Entry



Framingham

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Effects of Weight Loss on Blood Pressure and Lipid Levels

Weight Loss		
8 - 10 kg	SBP	10 - 18 mm Hg decrease
	DBP	9 - 13 mm Hg decrease
1 kg	Total Cholesterol	1.93 mg/dl decrease
	LDL Cholesterol	0.77 mg/dl decrease
	HDL Cholesterol	0.35 mg/dl increase

J. Manson

Prototype Scenario

A 40 year old woman, nondiabetic, non-smoker, no LVH

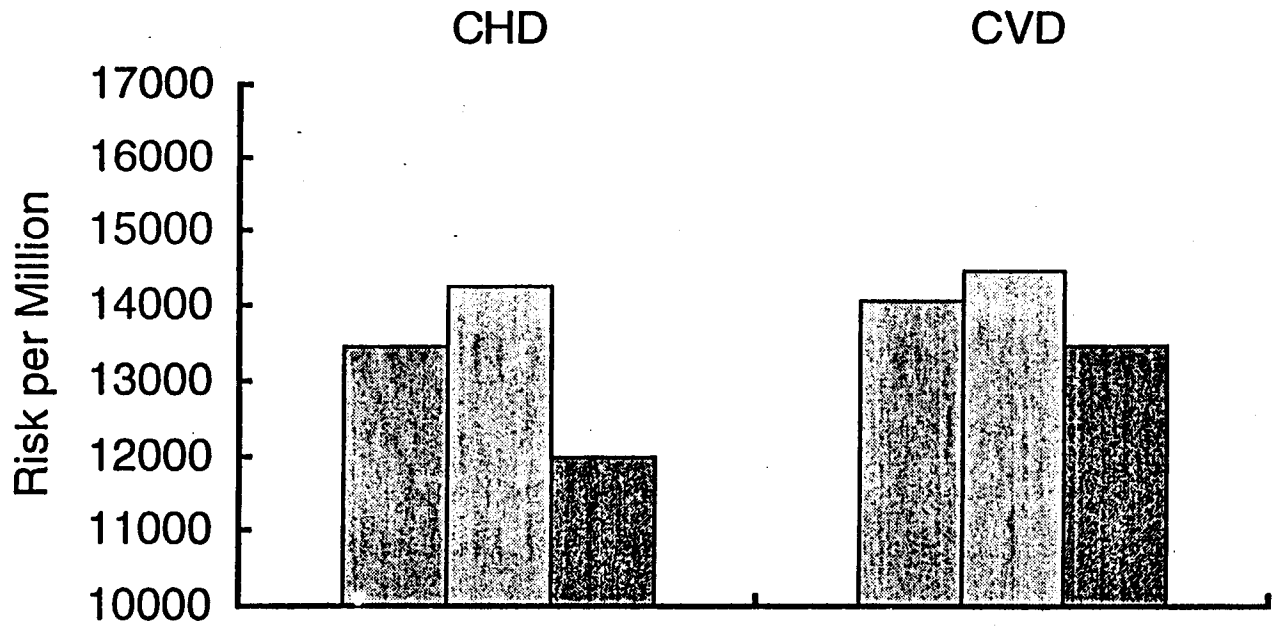
- diastolic blood pressure 80 mm Hg
- cholesterol 220 mg/dl
- HDL 45 mg/dl

Risk of CHD in 8 years, per million	13,450
Risk with increase of 2.0 mm Hg, per million	14,260
Risk with concomitant weight loss of 5 kg resulting in a decrease of 10 mg/dl in cholesterol and an increase of 2 mg/dl in HDL*	11,982
Net events averted in 8 years, per million	-1468
Net events averted per year (assuming linear relationship over time)	-184
Net percent reduction	-10.9%

* Daly, PA, Solomon CG, Manson JE: Preventing myocardial infarction, Oxford U. Press 1996: 203-240

Risk of CHD or CVD in 8 Years for a Woman, Age 40, Non-Smoker, No Diabetes, No LVH

Effect of 2 mm Hg Increase in Blood Pressure



Net Events Averted per Million

-1468 -617

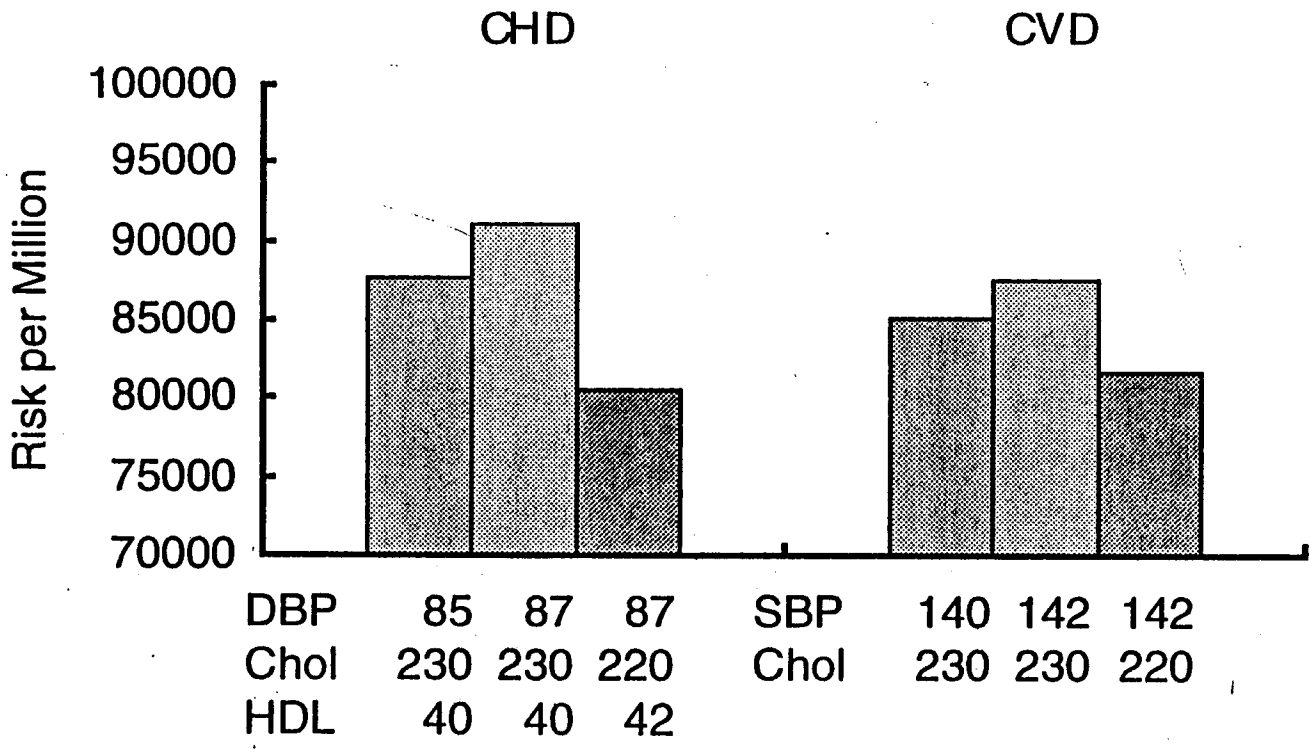
10.9% Reduction in CHD

4.1% Reduction in CVD

Framingham

Risk of CHD or CVD in 8 Years for a Man, Age 50, Non-Smoker, No Diabetes, No LVH

Effect of 2 mm Hg Increase in Blood Pressure



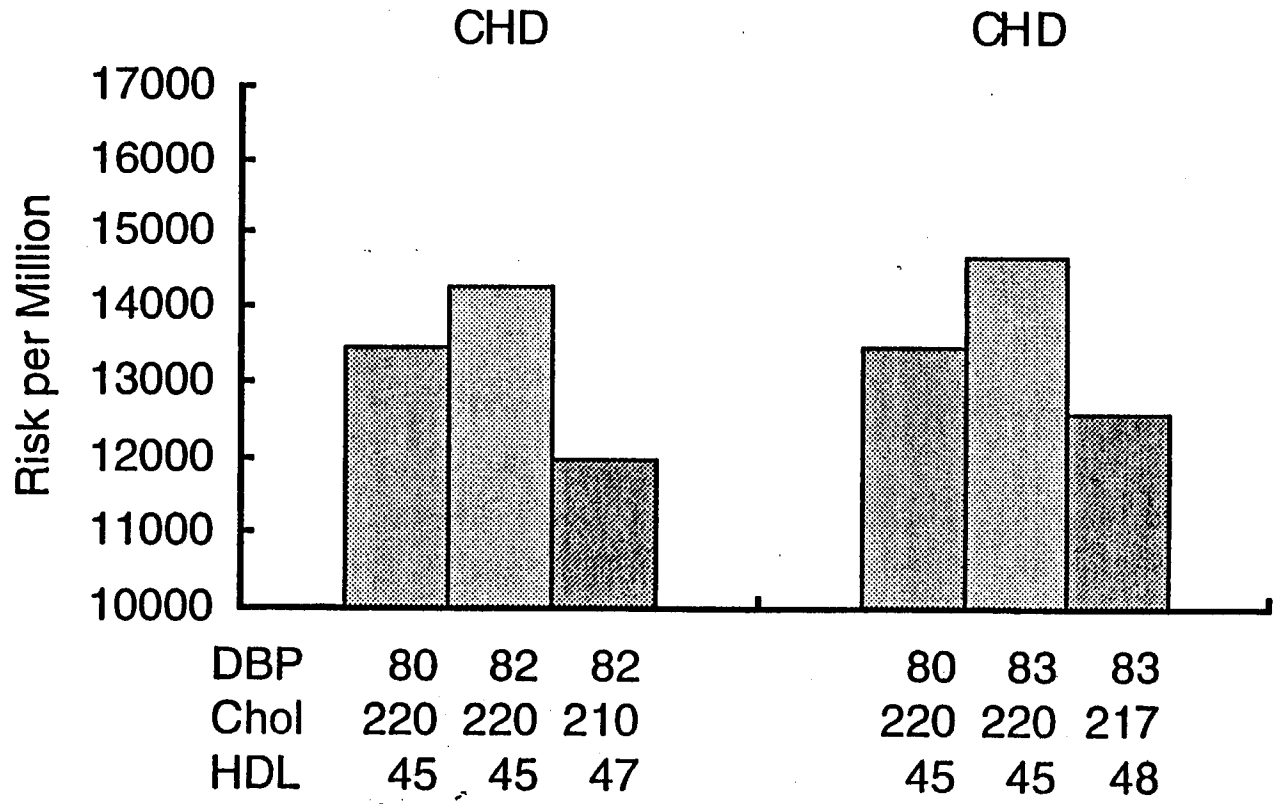
Net Events Averted per Million -7179 -3498

8.2% Reduction in CHD

4.4% Reduction in CVD

Framingham

Risk of CHD in 8 Years for a Woman, Age 40, Non-Smoker, No Diabetes, No LVH



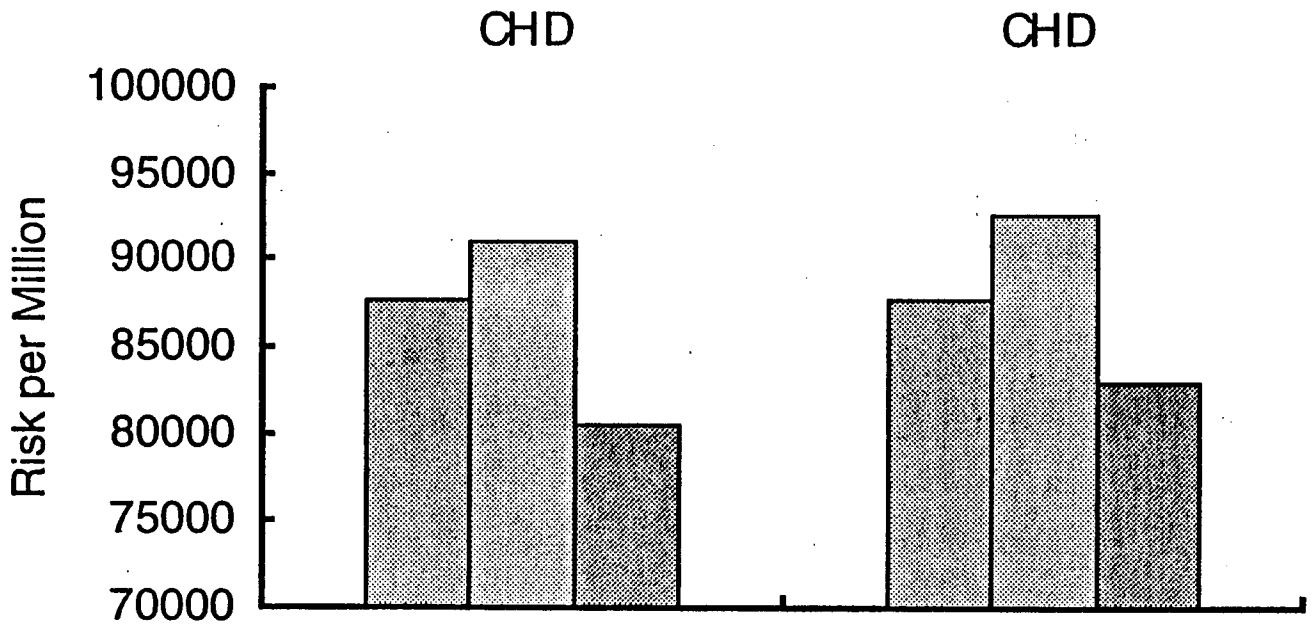
Events Averted per Million -1468 -862

10.9% Reduction in CHD

6.4% Reduction in CHD

Framingham

Risk of CHD in 8 Years for a Man, Age 50, Non-Smoker, No Diabetes, No LVH



DBP	85	87	87	85	88	88
Chol	230	230	220	230	230	227
HDL	40	40	42	40	40	43

Net Events Averted per Million -7179 -4834

8.2% reduction in CHD

5.5% reduction in CHD

Framingham

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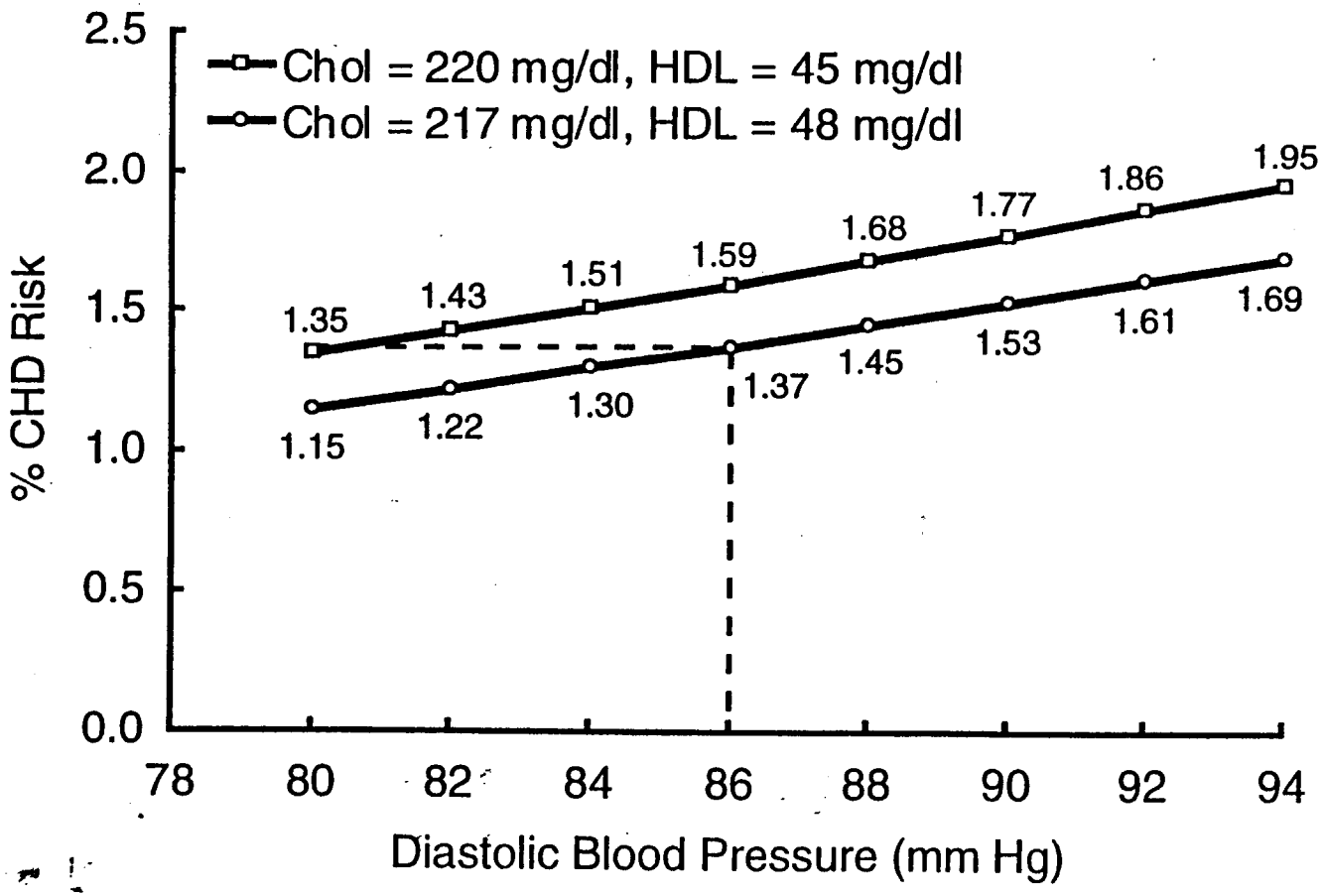
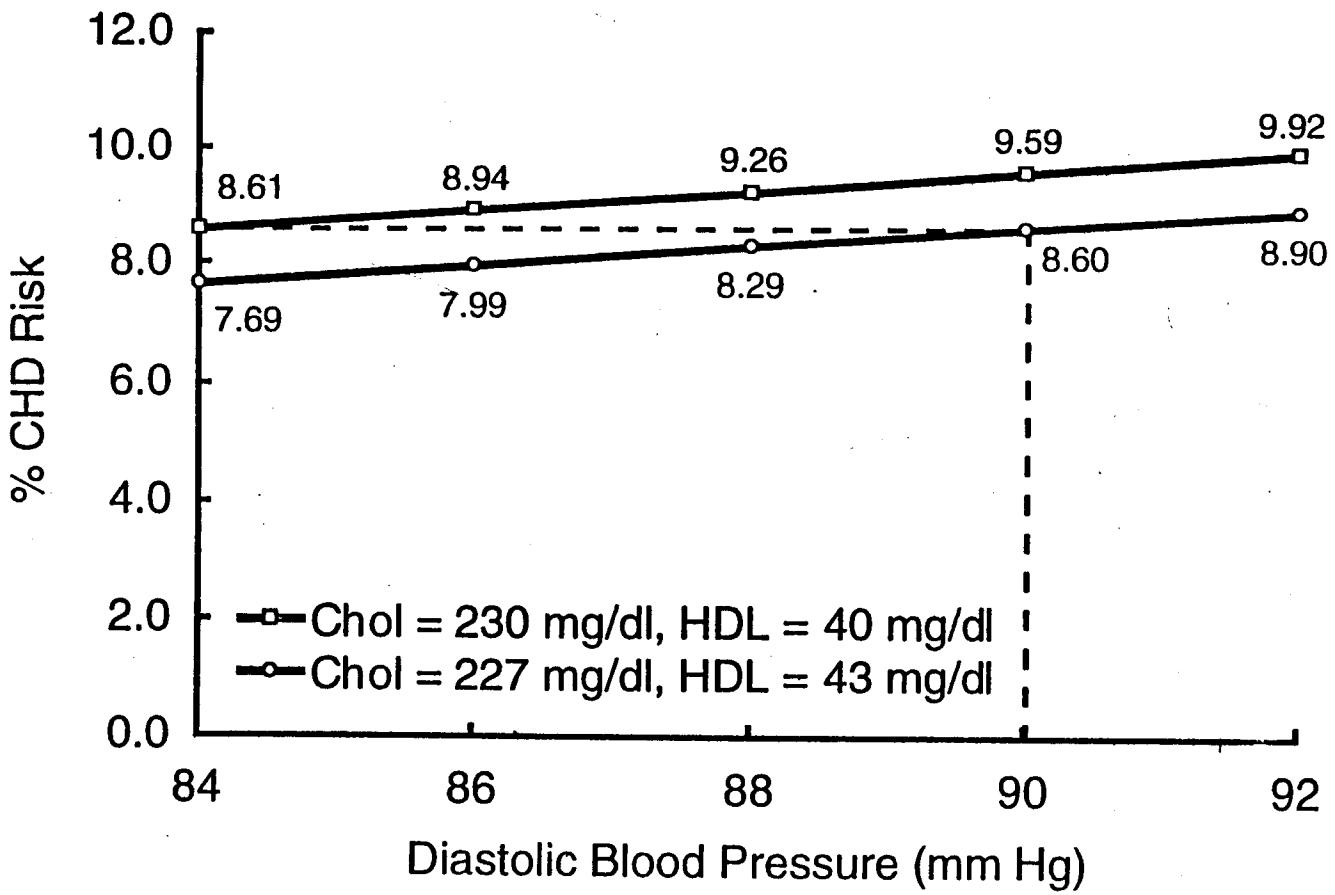
Percent CHD Risk in 8 Years by DBP for a Woman, Age 40, Non-Smoking, No Diabetes, No LVH



Benefit of lipid changes equivalent to risk increase of 5 mm Hg of DBP

Framingham

Percent CHD Risk in 8 Years by DBP for a Man, Age 50, Non-Smoking, No Diabetes, No LVH



Benefit of lipid changes equivalent to risk increase of 6 mm Hg of DBP

Framingham

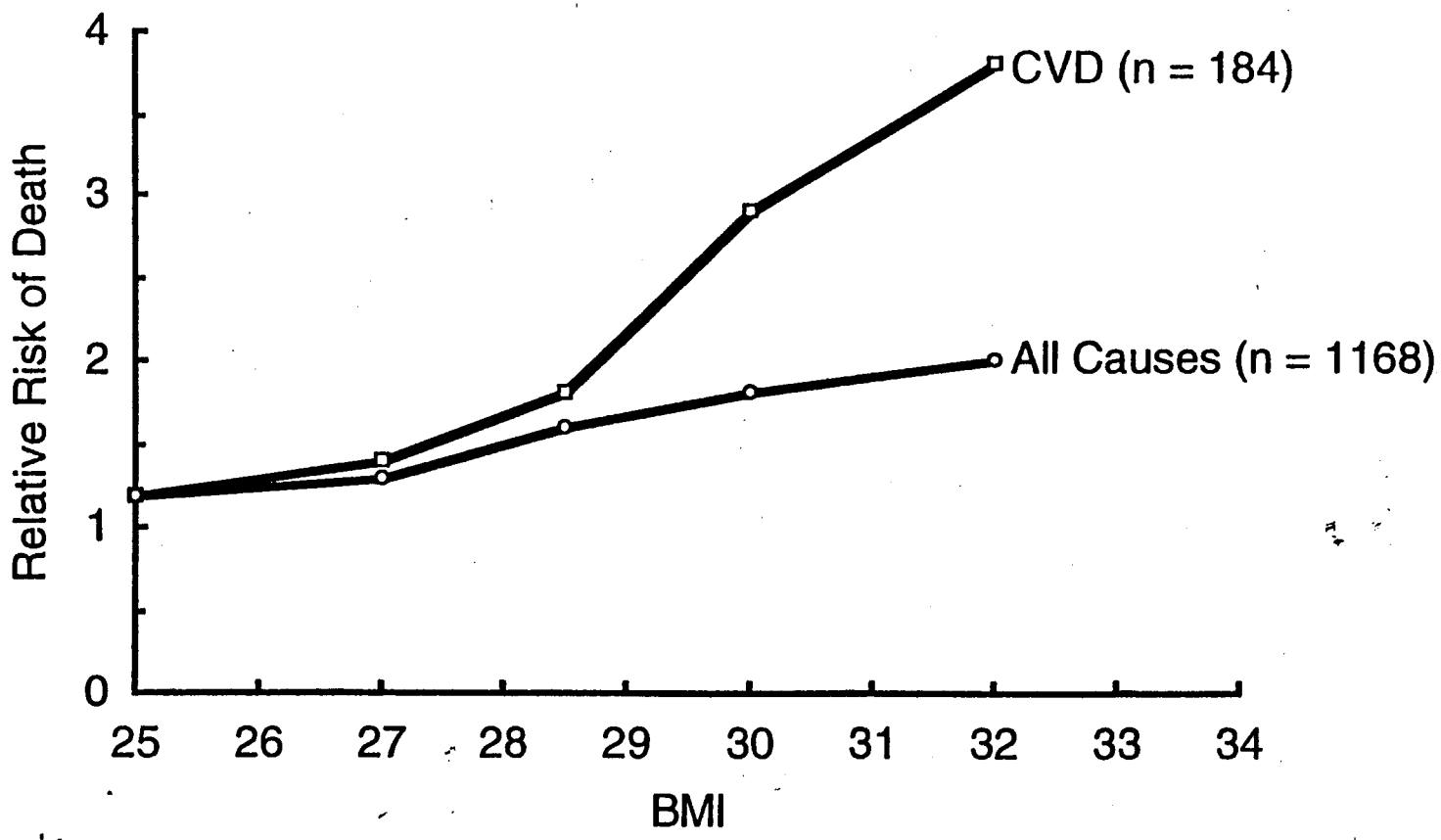
Summary

- The increase in risk of CHD with increase in blood pressure resulting from sibutramine, is offset by the beneficial effects of weight loss on lipids, resulting in a net decrease in risk of CHD between 6% to 10%

Nurse's Health Study

- 16 year follow-up of 115,000 nurses
- BMI and cause of death
- Age and smoking adjusted
- As BMI goes from 26 to 32
  - All cause mortality increases 90% (968 excess lives lost per million per year)
  - CHD mortality increases 150% (575 excess lives lost per million per year)
  - CVD deaths were 15.75% of all deaths

Relative Risk of Death Due to All Causes, and CVD by BMI (with Baseline Risk at BMI (kg/m2)of 19 to < 22)*



*Manson, NEJM Sept, 1995 Figure 2 and 3
1980 - 92, Non-Smokers

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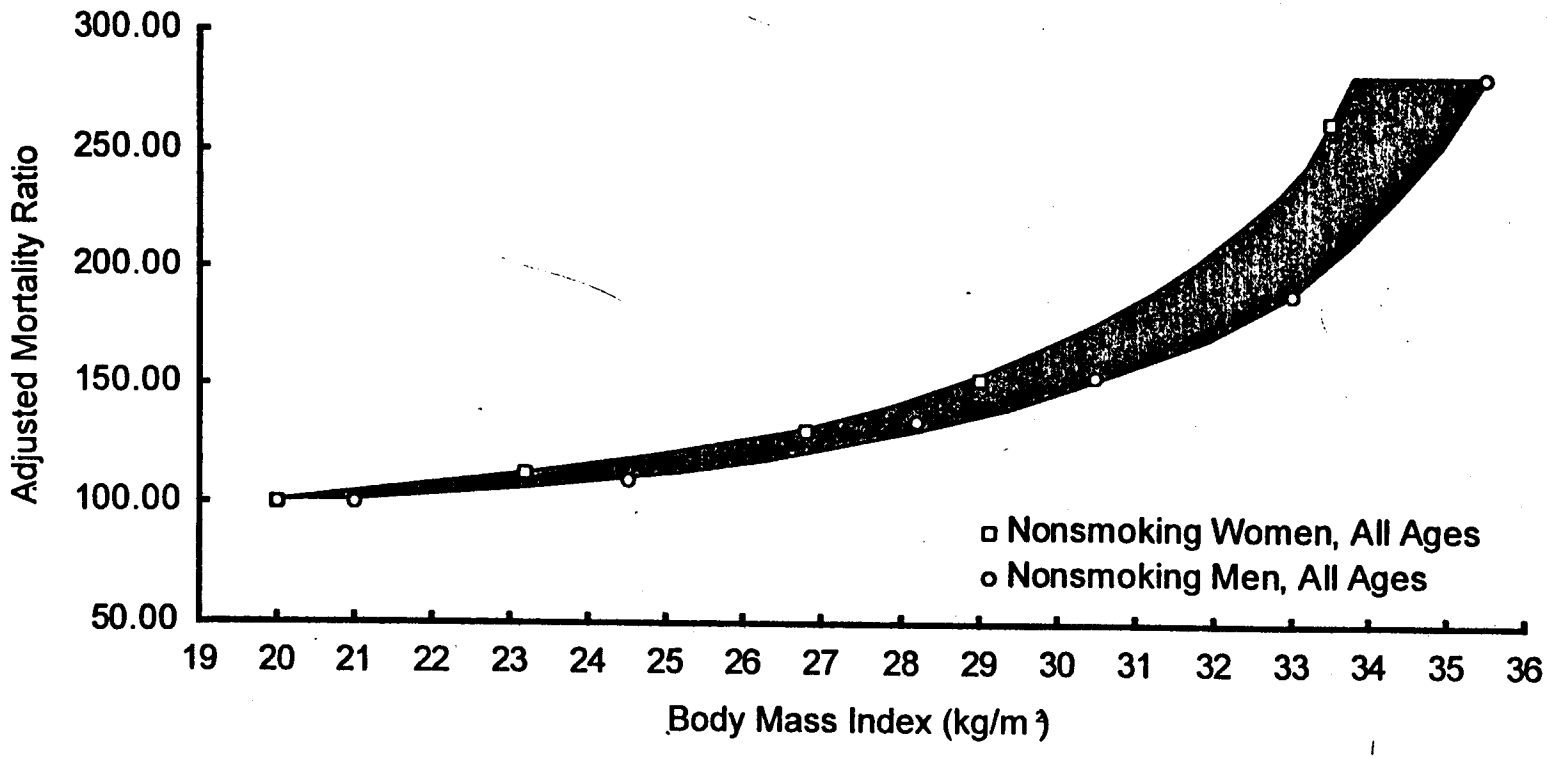
Mortality Ratios by Body Mass Index



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Weight Lost and Resultant BMI After Treatment with Sibutramine 15 mg*

Percent Loss Body Weight	Average Weight Lost (lbs)*	% of Patients Achieving This Weight Loss	Resultant BMI
5% to <10%	15	26	30.0
10% to <15%	25	24	28.5
15% + **	35	15	27.0

* From SB 1047 results applied to a population with a starting BMI of 32 (200 lbs and 5', 6")

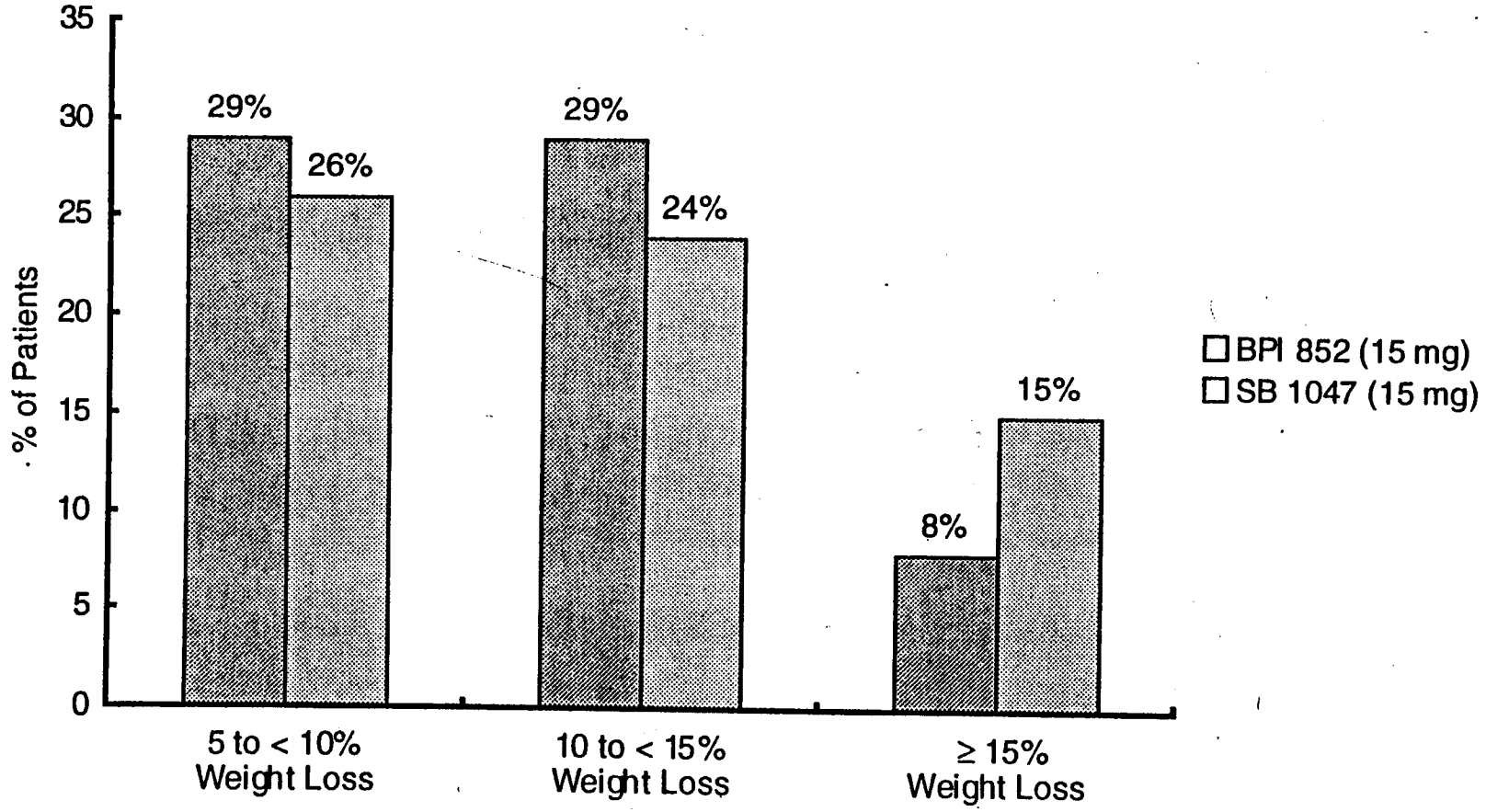
** Using 17.5%

Sibutramine Benefit Risk Model

- Apply trial efficacy data to determine the resultant BMIs of a population
- Apply Nurse's Health Study BMI-specific mortality changes to the population
- Deduct benefits related to BP change associated with weight loss
- Compare to the risk due to BP increase

Risks	Benefits
Mortality due to BP increase (2 mm Hg)	Lives saved due to weight loss
(Framingham Data)	(Nurses Health Study data)

Percent Distribution of Respondents by Proportion of Weight Lost (Completers BPI 852 and SB 1047)



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Weight Lost and Resultant BMI After Treatment with Sibutramine 15 mg*

Percent Loss Body Weight	Average Weight Lost (lbs)*	% of Patients Achieving This Weight Loss	Resultant BMI
5% to <10%	15	26	30.0
10% to <15%	25	24	28.5
15% + **	35	15	27.0

* From SB 1047 results applied to a population with a starting BMI of 32 (200 lbs and 5', 6")

** Using 17.5%

Benefits and Risks of Sibutramine

1. Assume 1 million non-smoking women with an average BMI of 32 kg/m^2 are treated with 15 mg of sibutramine
2. Assume weight loss is that found in sibutramine trials
3. Use NHS data for CVD and all cause mortality rates by BMI to calculate the deaths prevented by reduction of BMI
4. Use Framingham to estimate the risk of a 2 mm Hg blood pressure change

Effect of Sibutramine Weight Loss on All Cause Death Rate Treatment of One Million Women with an Average BMI* of 32 (No Blood Pressure Adjustment)

Percent Weight Loss	Number Achieving This Weight Loss	Resultant BMI	All Cause Deaths Avoided per 10^6	Deaths Avoided
5% to 10%	260,000	30.0	280	73
10% to 15%	240,000	28.5	560	134
**15%+	150,000	27.0	979	147
			Total Lives Saved	354

*Using trial rates 15 mg - SB 1047

**Using 17.5%

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Effect of Sibutramine Weight Loss on CVD Death Rate- Treatment of One Million Women With an Average BMI of 32* (No Blood Pressure Adjustment)

Percent Weight Loss	Number Achieving This Weight Loss	Resultant BMI	CVD Deaths Avoided per 10^6	Deaths Avoided
5% to 10%	260,000	30.0	198	51
10% to 15%	240,000	28.5	440	106
**15%+	150,000	27.0	528	79
			Total Lives Saved	236

*Using trial rates for weight loss (15mg - SB 1047) From Table 5

**Using 17.5%

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Effect of Sibutramine Weight Loss on CVD Deaths - Treatment of One Million Women With an Average BMI of 32* (Adjusted for Lack of Blood Pressure Benefit)

Percent Weight Loss	Number Achieving This Weight Loss	Resultant BMI	CVD Deaths Avoided per 10^6	Deaths Avoided
5% to 10%	260,000	30.0	99	26
10% to 15%	240,000	28.5	220	53
**15%+	150,000	27.0	264	39
			Total Lives Saved	118

*Half of all CVD benefit based on Framingham data

**Using 17.5%

2079.07.23

Weight Loss, Diastolic BP and CVD Risk*

- With diet, a 5 kg weight loss will result in a 5 mm Hg BP decline (Tuck Metanalysis)
- Based on antihypertensive trials, 5 mm of BP decline will result in reductions of 22% in CHD, 38% in CVAs and 25% in CVD (fatalities and events) (Collins Metanalysis)
- Observational studies suggest a 5 mm BP decline will result in up to a 40% reduction in CVD events (Collins)

*Manson; Ridker p. 165

Changes 9 7/24/96 11:30 PM

Potential Effect of Sibutramine Weight Loss on All Cause Death Rate-Treatment of One Million Women with an Average BMI* of 32** (Adjusted for Lack of BP Benefit)

Percent Weight Loss	Number Achieving This Weight Loss	Resultant BMI	All Cause Deaths Avoided per 10^6	Deaths Avoided
5% to 10%	260,000	30.0	181	46
10% to 15%	240,000	28.5	340	82
***15%+	150,000	27.0	715	107
			Total Lives Saved	235

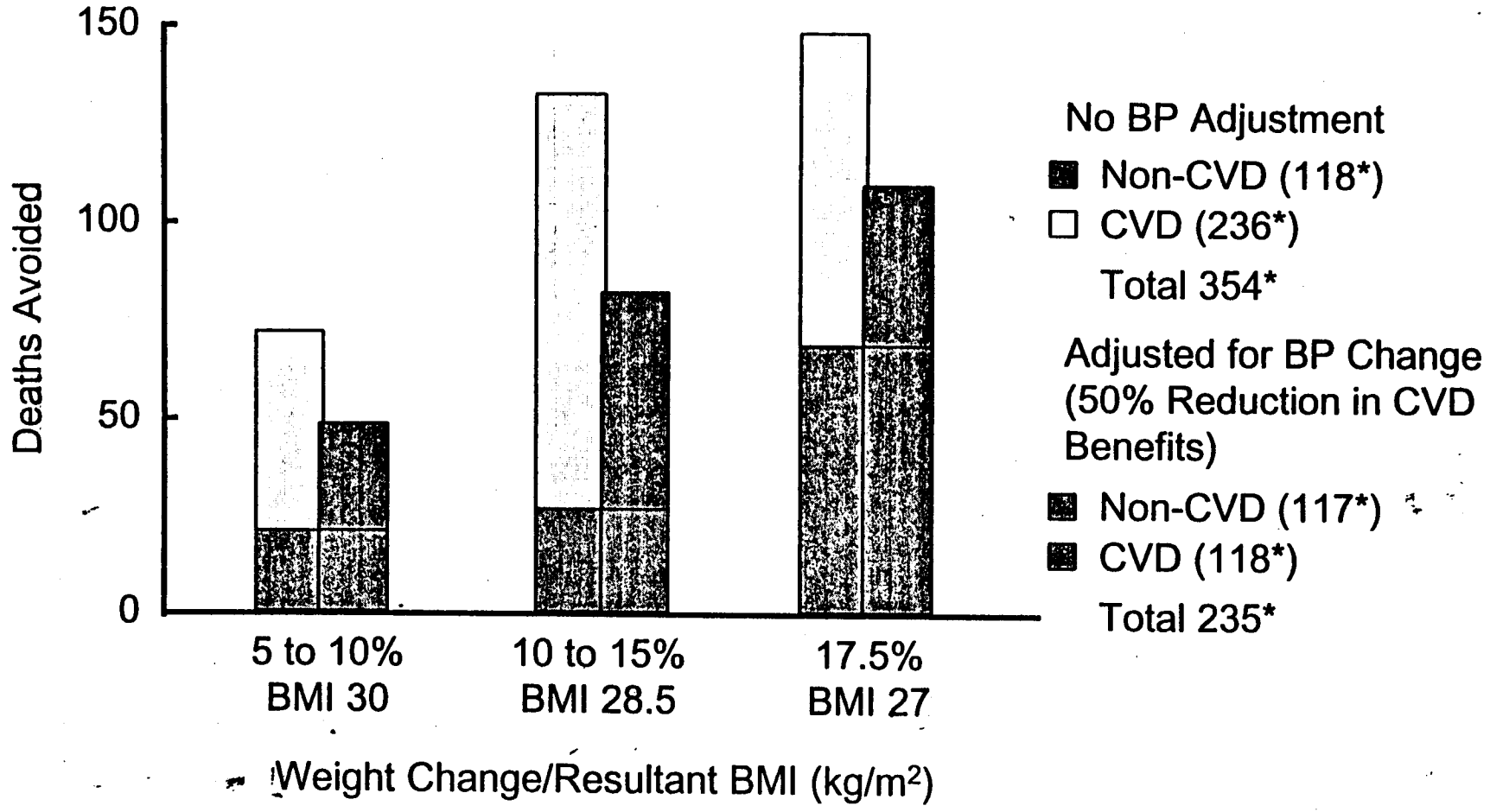
*Using trial rates 15 mg - SB 1047

**CVD benefits reduced by 50%

***Using 17.5%

2077.07.23

Deaths Avoided per Million Obese Patients Treated with Sibutramine



* = number of deaths avoided as a result of a 5 - 17.5% weight loss

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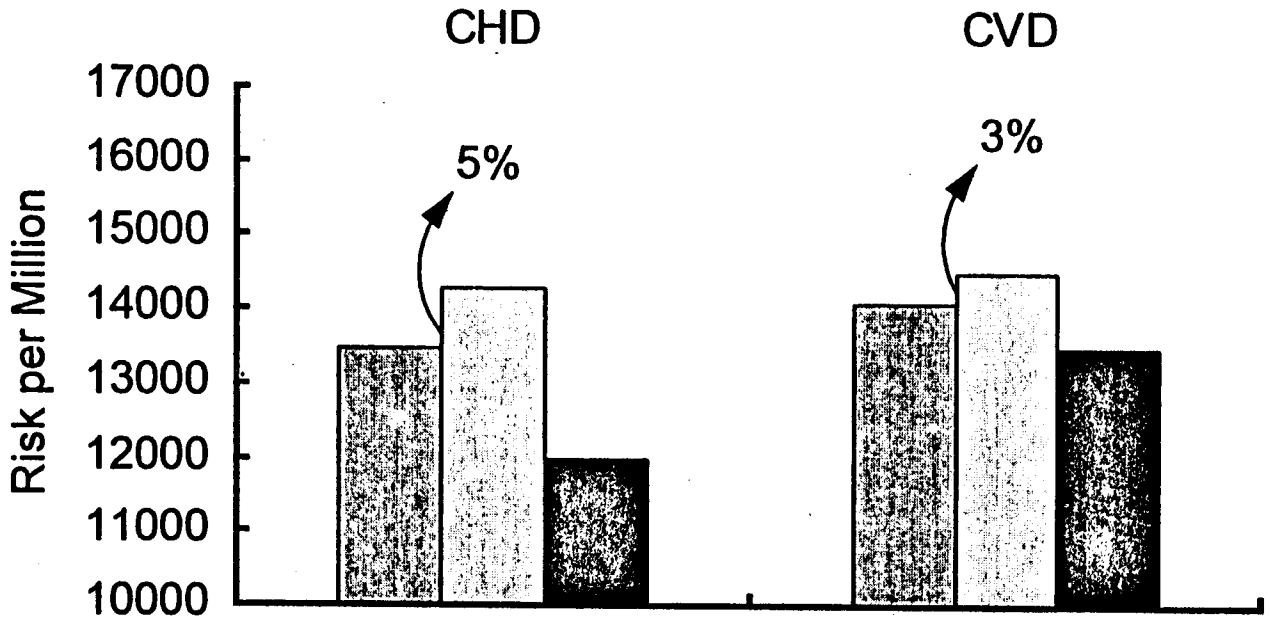
Sibutramine Risk

- Overall there is a 2 mm Hg increase in mean population diastolic blood pressure
- Framingham data show this increases CVD risk by < 5%
- NHS baseline CVD mortality was 220 deaths per million per year with a relative risk of 2.9 for a BMI of 30*, the baseline risk is 638
- Thus, the risk is 32 excess deaths (5% x 638) per million per year

* If BMI of 32 is used, absolute risk is 836 and excess deaths are then 42.

Risk of CHD or CVD in 8 Years for a Woman, Age 40, Non-Smoker, No Diabetes, No LVH

Effect of 2 mm Hg Increase in Blood Pressure



Net Events Averted per Million

-1468 (10.9% Reduction in CHD)

-617 (4.1% Reduction in CVD)

Framingham

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Risks

32 CVD deaths per million P-Y
(due to BP increase of 2 mm Hg)

Benefits

235 lives saved per million P-Y
(due to weight loss)

The net savings of 203 lives represents a 9% reduction in mortality

2061.07.22

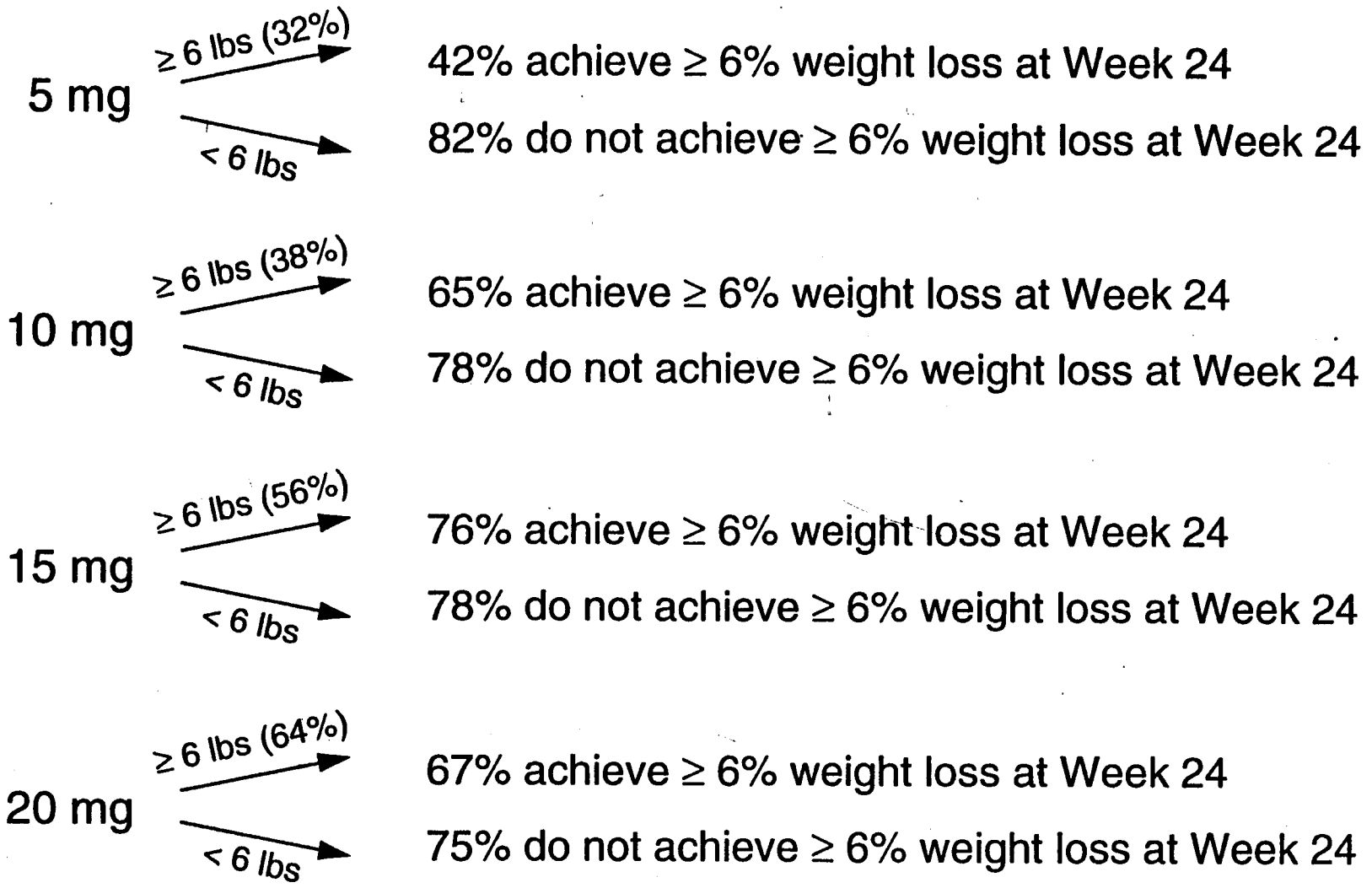
Conclusion

- Obesity has high excess mortality of 1168 per million per year
- Sibutramine treatment, adjusted for the lack of a lowering of blood pressure will save 235 lives per million treated per year
- Sibutramine risk related to an increase in mean blood pressure of 2 mm Hg is estimated to be 32 per million treated per year
- The net benefit of treatment, 203 lives is a 9% reduction in mortality
- Risk may be lowered and benefits enhanced by clinical monitoring and treatment only of responders

Summary

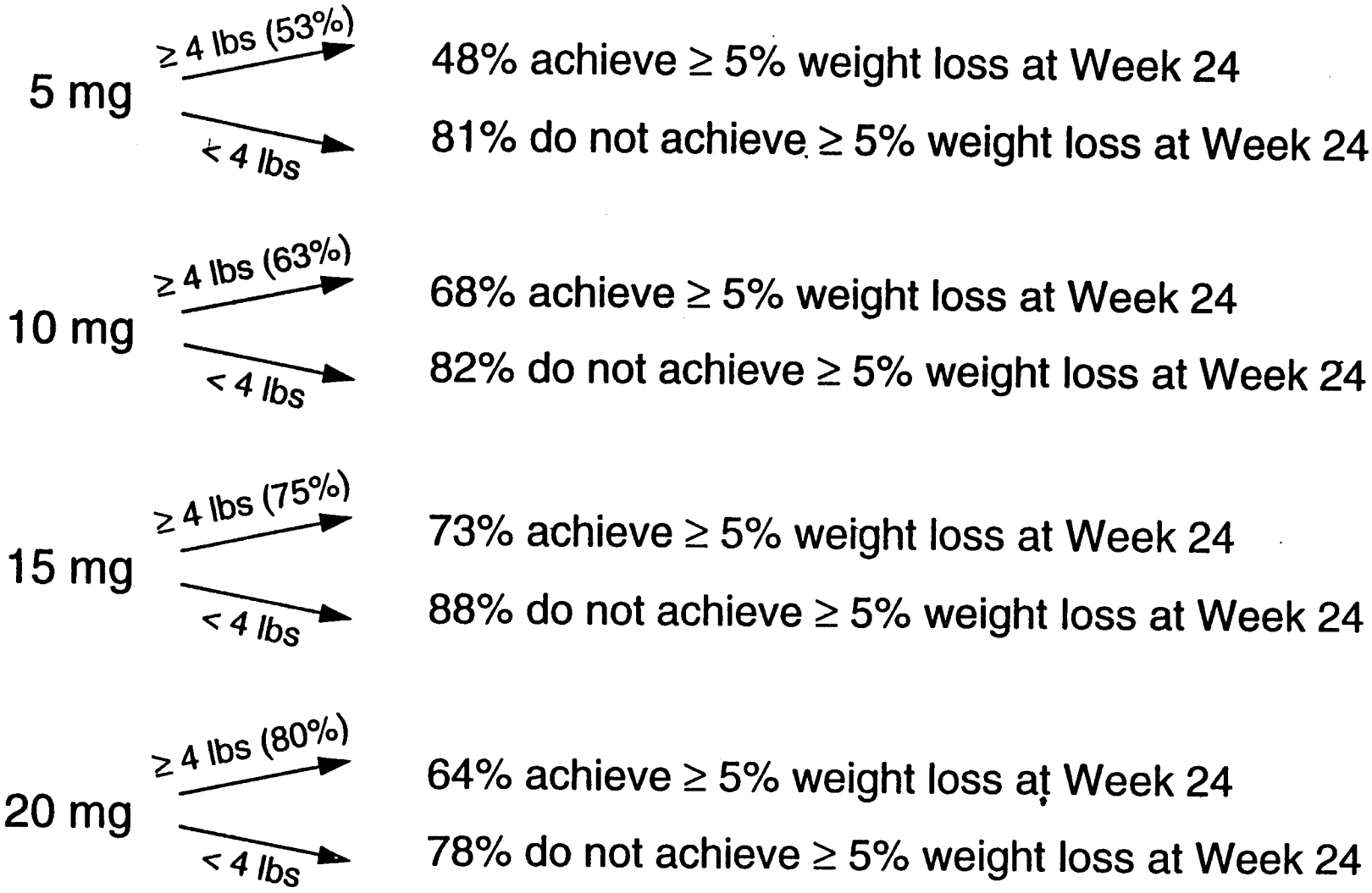
- Clinically meaningful weight loss (satisfying FDA weight loss criteria)
- Favorable trends in lipid, glycemic, and uric acid parameters
- Small increase in mean blood pressure
- Blood pressure changes are not of a clinically significant magnitude over the time period studied
- Epidemiologic evaluations predict that over long periods the benefit/risk will remain favorable

BPI 852–Predictability of Weight Loss in First Four Weeks



4447.07.19

BPI 852–Predictability of Weight Loss in First Four Weeks



4469.07.19

JUN 24 1996

NDA 20-632
Meridia (sibutramine hydrochloride monohydrate) Capsules
Knoll Pharmaceutical Company

April 23, 1996
Parklawn Conf. Room "C"
1:30 pm

MEMORANDUM OF MEETING

Type of Meeting: Pending NDA Status
Meeting Chair: Dr. Colman **Knoll Lead:** Dr. Spigelman
Meeting Recorder: John Short, R.Ph.

FDA Staff:

Solomon Sobel, M.D., Dir., Division of Metabolism and Endocrine Drug Products (DMEDP)(HFD-510)
Gloria Troendle, M.D., Deputy Director, DMEDP
Leo Lutwak, M.D., Medical Officer, DMEDP
Eric Colman, M.D., Medical Officer, DMEDP
David Orloff, M.D., Medical Officer, DMEDP
Alexander Jordan, Ph.D., Pharmacology Team Leader, DMEDP
David Hertig, Pharmacology Reviewer, DMEDP
Martin Haber, Ph.D., Chemistry Reviewer, DMEDP
John Short, R.Ph., Consumer Safety Officer, DMEDP
Kathleen Reedy, Ph.D., Advisors and Consultants Staff (HFD-021)
Joseph F. Contrera, Ph.D., Associate Director for Regulatory Research/OTR (HFD-400)
Lee-Ping Pian, Ph.D., Statistics Reviewer (HFD-715)
Mike Fossler, Ph.D., Biopharmaceutics Reviewer (HFD-870)
Carolyn Jones, Ph.D., Biopharmaceutics Reviewer (HFD-870)

Knoll Representatives:

Grant Bogle, Senior Director, Marketing
Lourdes Frau, M.D., Director, Corporate Drug Safety, Epidemiology and Medical Information
David Heal, Ph.D., Head of CNS Biology (UK)
Vaseem Iftekhar, Associate Director, Project Management
Finian Kelly, M.D., Head of Clinical Development
Hugh Morgan, Ph.D., Head of Toxicology (UK)
Tim Seaton, M.D., Senior Director, Endocrine and Metabolism
Mel Spigelman, M.D., Vice President, Research and Development
Abraham Varghese, Ph.D., Associate Director, Regulatory Affairs
Mike Klepper, M.D., CEO, (Consultant)
Neil Kurtz, M.D., CEO, Consultant)
James Trammel, Senior Statistician, (Consultant)

Purpose: Knoll requested the meeting to help prepare for the upcoming E&M Advisory Committee meeting by presenting 1) new preclinical data re: potential neurotoxicity and abuse potential, 2) minimum dosage to use, 3) their Phase IIIB/IV program, and 4) information on the benefit-to-risk profile in humans.

Meeting Objectives:

1. To determine if the FDA staff had any neurotoxicity concerns, based upon the animal data presented.

2. To determine if FDA staff concur with a 10 or 15 mg minimal dose for starting patients on.

3. To describe to FDA staff what Phase IIIB/IV studies are ongoing in weight loss and co-morbid conditions (primarily outside the U.S.).

4. To demonstrate to FDA staff that the cardiovascular adverse effects of sibutramine are not so bad that the drug should not be approved and that they can be handled with appropriate labeling.

Discussion Points:

1. FDA staff do not believe this is another dexfenfluramine, and, therefore, are not concerned about the neurotoxicity of sibutramine. But, Dr. Contrera noted that it would be useful for the sponsor to include the results of a study in which rats were treated with sibutramine at multiples of the human MRD for 4 days and then sacrificed 14 days later for analysis of the regional brain concentration of 5HT, NE and DA. This would be done to demonstrate directly that sibutramine does not produce prolonged neurotransmitter depletion and this information should be part of the NDA and submitted in advance of the advisory committee meeting. Knoll representative indicated that this type of study is currently nearing completion.

2. FDA staff did not accept Knoll's position that a 10 or 15 mg should be the starting dose. It was generally agree by FDA staff that the lowest dose resulting in weight loss should be used to minimize the adverse effects of the drug. It was suggested that a patient be on a particular dose for at least 2 weeks prior to escalating to higher dose. Dr. Spigelman noted that compliance may become an issue with many patients if they start out at a 5 mg subtherapeutic dose. FDA staff also noted that weight loss seems to plateau at the 20 mg dose, and that there is no need for a 30 mg dose. Knoll representatives indicated they will have to evaluate the highest-dose issue further, because they do not believe they have maxed out at 30 mg.

3. FDA staff had no comment about the Phase IIIB/IV studies.

4. Knoll staff and consultants provided information on cardiovascular events and hypertensive effects, the latter stratified by systolic and diastolic blood pressure (a post hoc evaluation). FDA is very concerned about the cardiovascular effects of the drug. FDA staff raised the issue of how much blood pressure increase should be tolerated while taking a drug for weight loss. Knoll representatives agreed to look into this. Knoll

representatives also were asked to provide 1) extremes in vital sign changes, and 2) additional information about strokes reported in young females (an epidemiological assessment), 3) information addressing whether those patients with increased blood pressure showed an improvement in co-morbid conditions.

5. Because the entire benefit/risk issue was not discussed, Knoll representatives requested another meeting prior to the advisory committee meeting to discuss this issue. FDA staff agreed that such a meeting would be beneficial, but might be accomplished as a teleconference.

Decisions (agreements) Reached:

1. Knoll to submit results (prior to advisory committee meeting) of animal study analyzing the regional brain concentration of 5HT, NE and DA.

2. Knoll to evaluate further the highest-dose issue.

3. Knoll to provide information on how much blood pressure increase should be tolerated while taking a drug for weight loss.

4. Knoll to provide 1) extremes in vital sign changes, and 2) additional information about strokes reported in young females (an epidemiological assessment), 3) information addressing whether those patients with increased blood pressure showed an improvement in co-morbid conditions.

5. Knoll to submit a major amendment after May 9, 1996, which will extend the Goal Date to November 9, 1996, allowing movement of the E & M Advisory Committee meeting from June until September 1996.

6. Mr. Short reminded the Knoll representatives that a safety update would have to be submitted prior to the end of the review period.

Unresolved Issues or Issues Requiring Further Discussion:

None

Action Items:

	Item	Responsible Person	Due Date
1.	See items under "Decisions (agreements) Reached"	Knoll Representative	None

Required Follow-up:

None

Signature _____, John R. Short, CSO, Recorder
Concurrence of Meeting Chair _____, Eric Colman, Medical Reviewer

APPEARS THIS WAY
ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020632

CORRESPONDENCE

NDA 20-632

JUN 12 1997

Knoll Pharmaceutical Company
Attention: Robert W. Ashworth, Ph.D.
Director, Regulatory Affairs
199 Cherry Hill Rd.
Parsippany, NJ 07054

Dear Dr. Ashworth:

We acknowledge receipt on May 23, 1997, of your May 23, 1997, amendment to your new drug application (NDA) for Meridia (sibutramine hydrochloride monohydrate) Capsules.

We also acknowledge receipt of your amendments dated December 17, 1996, January 3 and 23, February 14 and 27, 1997.

These amendments contain the additional information requested in our November 8, 1996, approvable letter.

We consider the May 23 submission to be a major amendment under 21 CFR 314.60 of the regulations and it completes full response to our letter. Therefore, the due date under the Prescription Drug User Fee Act of 1992 (PDUFA) is November 23, 1997.

If you have any questions, please contact Maureen Hess, MPH, RD, Consumer Safety Officer, at (301) 443-3510.

Sincerely yours,

5/29/97

Solomon Sobel, M.D.
Director
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

5-29-97

NDA 20-632

FEB 12 1997

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

Dear Dr. Varghese:

Please refer to your new drug application (NDA) submitted pursuant to section 505(b) of the Federal Food, Drug and Cosmetic Act for Meridia (sibutramine hydrochloride monohydrate) Capsules.

We also refer to the meeting between representatives of your firm and FDA on January 9, 1997. As a result of that meeting, we have the following comments and request for information:

1. The drug discrimination study design that Dr. David Heal routinely uses in rodents is acceptable to further characterize the abuse liability of sibutramine. However, we would like to have the data presented as discussed in the data analysis section described in our November 8, 1996, Approvable letter. Furthermore, we would like the training drug to be MDMA.

2. Based on the information that we presented during the meeting on venlafaxine's adverse drug reaction, we would like sibutramine metabolites and venlafaxine to be tested in the proposed drug discrimination study. In addition, we have no objection to Dr. Heal's proposal to train an additional group of rats to discriminate LSD. Once the rats are trained, sibutramine, venlafaxine and sibutramine metabolites should be tested to determine the rats' ability to generalize to the LSD discriminative stimulus cue.

If you have any questions regarding the study design, please call Dr. Michael Klein or Dr. BeLinda Hayes at (301) 443-3741.

Sincerely,

2/07/97

Solomon Sobel, M.D.
Director
Division of Metabolic and Endocrine Drug Products (HFD-510)
Center for Drug Evaluation and Research

2-11-97

cc: NDA Arch
HFD-510
HFD-510/EColman/MHess
HFD-170/MKlein/BHayes

Concurrence:
MKlein/2.3.97/BHayes/2.3.97/EColman/2.3.97/EGalliers/2.10.97/GTroendle/2.11.97

GENERAL CORRESPONDENCE

**APPEARS THIS WAY
ON ORIGINAL**

NDA 20-632

JUN 25 1996

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

Dear Dr. Varghese:

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

We have completed our review of the environmental assessment (EA) portion of your submission and note the following deficiencies:

1. Regarding Section 4, Description of the proposed action:

   a. Requested approval:

      Requested approval should include a brief description of the product packaging, reference to the NDA identification number (20-632), and indicate the dose/capsule.

   b. Need for action:

      The EA should indicate whether product availability will be limited to a physician's prescription.

   c. Finished dosage form:

      We note that the ZIP code for this address in section 4.c.2. differs from that in EA item 3. Please provide the correct ZIP code at each location of the EA.

2. Regarding Section 6, Introduction of substances into the environment:

   a. A table showing emitted substances from the Shreveport facility is included in Confidential Appendix E. There is no indication as to whether : are used that may be emitted. Please clarify and include CAS numbers if appropriate.

   b. The certification of compliance for the foreign facilities, which is included in Appendix D, should be non-confidential.

c. The information in Appendix E should be summarized to the extent possible and included in the non-confidential EA.

Most of the information in these appendices pertains to endpoint disposal routes of various wastestreams. Other than a reference to scrubbers, no information is provided regarding in-plant controls to minimize, control, or contain wastes within the production process. More information should be provided.

3. In addition to the information noted in deficiency 2. b. and c., the following should be included as public information:

a. Appendix A (it is listed as confidential in format item 15).

b. The MSDS for the drug substance.

General Comment: It is not necessary to submit raw test data. Test reports with appropriate appendices are sufficient.

We would appreciate your prompt written response so we can continue our evaluation of your NDA.

If you have any questions, please contact:

John R. Short, R.Ph.
Consumer Safety Officer
(301) 443-3510

Sincerely yours,

6/24/96

Solomon Sobel, M.D.
Director
Division of Metabolism and Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

cc: Original NDA
HFD-510/Div. Files
HFD-510/CSO/J.R.Short
HFD-510/MHaber, SMoore
HFD-357/NSager, RHassall
drafted: JShort/June 12, 1996/n20632IR.2JS
r/d Initials: MHaber 6/13, SMoore 6/24/96
final: JShort 6/24/96
INFORMATION REQUEST (IR)

V 6/24/96

NDA 20-632

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

JUN 13 1996

Dear Dr. Varghese:

We acknowledge receipt on May 13, 1996, of your May 10, 1996, amendment to your new drug application for Meridia (sibutramine hydrochloride monohydrate) Capsules, 5, 10, and 15 mg.

We consider this a major amendment received by the agency within three months of the user fee due date. Therefore, the user fee clock is extended three months. The new due date is November 9, 1996.

If you have any questions, please contact:

John R. Short, R.Ph.
Consumer Safety Officer
(301) 443-3510

Sincerely yours.

APPEARS THIS WAY ON ORIGINAL

for 6/13/96
Solomon Sobel, M.D.
Director
Division of Metabolism and Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

cc:
Original NDA 20-632
HFD-510/Div. Files
HFD-510/JShort, EColman, GTroendle, MHaber, SMoore, DHertig, AJordan
DISTRICT OFFICE

drafted: JShort/June 11, 1996/n20632EX.JRS
r/d Initials: EGalliers 6/11/96
final: JShort 6/12/96

1/ 6/12/96

REVIEW EXTENSION (New Goal Date 11/9/96)

FAX'd copy to Abraham 6/13/96

NDA 20-632

JUN - 5 1996

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

Dear Dr. Varghese:

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

We have completed our review of the abuse potential section of your submission and conclude that a complete and comprehensive evaluation of the abuse potential cannot be made on the data available. Please address the following issues:

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

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

3. **Clinical Subjective Events Evaluation (Study No. BPI 863)**. The results from this study suggest that sibutramine is not amphetamine-like in healthy male volunteers. At the doses tested in this study, results from the Modified Norris Assessment Questionnaire, sibutramine showed sedative and tranquilizing-like effects. Results from the LSD Group of the Addiction Research Center Inventory (ARCI) suggest that sibutramine may possess hallucinogenic effects at 30 mg. However, these results lack value in contributing to the abuse liability assessment of sibutramine because of the following study deficiencies:

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

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

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

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

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

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

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

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

We would appreciate your prompt written response so we can continue our evaluation of your NDA.

If you have any questions, please contact:

John R. Short, R.Ph.
Consumer Safety Officer
(301) 443-3510

Sincerely yours,

6/5/96

Solomon Sobel, M.D.
Director
Division of Metabolism and Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

cc: Original NDA DDD
HFD-510/Div. Files
HFD-510/CSO/J.R.Short
HFD-510/EColman, GTroendle
HFD-170/BHayes, MKlein

drafted: JShort/June 4, 1996/n20632IR.JRS
r/d Initials: BHayes, MKlein, EColman, GTroendle 6/4/96
final: JShort 6/4/96

INFORMATION REQUEST (IR)

1/ 6/4/96

APPEARS THIS WAY ON ORIGINAL

NDA 20-632

AUG 14 1995

Knoll Pharmaceutical Company
Attention: Abraham Varghese, Ph.D.
3000 Continental Drive North
Mt. Olive, NJ 07828

Dear Dr. Varghese:

We have received your new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product:	Meridia (sibutramine hydrochloride monohydrate) Capsules
Therapeutic Classification:	Standard
Date of Application:	August 7, 1995
Date of Receipt:	August 9, 1995
Our Reference Number:	20-632

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on October 8, 1995, in accordance with 21 CFR 314.101(a).

Should you have any questions, please contact:

Lisa L. Stockbridge, Ph.D.
Consumer Safety Officer
Telephone: (301) 443-3520

Please cite the NDA number listed above at the top of the first page of any communications concerning this application.

Sincerely yours,

8/14/95

Enid Galliers
Chief, Project Management Staff
Division of Metabolism and
Endocrine Drug Products (HFD-510)
Office of Drug Evaluation II
Center for Drug Evaluation and Research