CENTER FOR DRUG EVALUATION AND RESEARCH

ADVISORY COMMITTEE: ENDOCRINOLOGIC AND METABOLIC DRUGS ADVISORY COMMITTEE

DATE OF MEETING: 03/13/98

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SLIDES

XENICAL® (orlistat)

Hoffmann-La Roche Inc.

Novel Site of Action and Mode of Activity

Site of Action

- Localized to the gastrointestinal tract

Mode of activity

- Reduces absorption of some ingested fat

Expert Panel's Assessment - May 1997

- Mutagenicity, genotoxicity and carcinogenicity studies in animals with systemic exposures many times that in man showed no evidence of any carcinogenic potential.
- Times to diagnoses of a number of the breast cancer cases were too soon after randomization for the case to be due treatment.
- The direct causative effect of orlistat is unlikely due to negligible systemic absorption.
- No mechanism resulting from a secondary effect of orlistat that could be identified linking orlistat to breast cancer.
- Chance or detection bias were possible explanations for the observed imbalance.

Analysis of Breast Cancer Cases

Data Collected

- Medical Records
- Pre- and post-study mammograms
- Histopathology slides
- Follow-up survey all female patients ≥ 45 years of age

Efficacy and Tolerability

Dr. Aram Chobanian
Dean, Department of Medicine
Boston University School of Medicine - Boston, MA

Dr. Douglas Greene
Professor of Internal Medicine
Department of Endocrinology
University of Michigan - Ann Arbor, MI

Dr. Jonathan Hauptman
Clinical Research Director
Hoffmann-La Roche Inc.

Dr. Eric Colman
Medical Review Officer
Food and Drug Administration

Evaluation of Breast Cancer Cases

Dr. Martin Huber

Clinical Research Director, Oncology
Hoffmann-La Roche Inc.

Dr. Timothy Anderson

Research Director, Toxicology & Pathology
Hoffmann-La Roche Inc.

Dr. James Schlesselman

Professor of Epidemiology
University of Miami School of Medicine - Miami, FL

Dr. James McGee

Chairman, Department of Pathology and Bacteriology
Oxford University - Oxford, England

Overall Benefit/Risk Assessment

Dr. Jonathan Hauptman
Clinical Research Director
Hoffmann-La Roche Inc.

FDA Presentation

Dr. Bruce Stadel
Medical Review Officer, Epidemiology
Food and Drug Administration

Dr. Eric Colman
Medical Review Officer
Food and Drug Administration

Consultants

Dr. Gary Williams

Director, Naylor Dana Inst. & Chief of Pathology & Toxicology
American Health Foundation
Research Professor, Department of Pathology, New York Medical College - Valhalla, NY

Dr. Andrew Seidman

Memorial Sloan Kettering Cancer Center - New York, NY

Dr. Stephen Feig

Chief Division of Mammography, Thomas Jefferson University
Philadelphia, PA

Dr. Bess Dawson-Hughes

USDA Nutrition Center, Tufts University - Boston, MA

Dr. James Olson
Vitamin Research Group, Iowa State University - Ames, IA

Dr. Dennis Ahnen
Professor of Medicine
University of Colorado Health Center - Denver, CO

Dr. Michael Wargovich
Associate Professor of Medicine
University of Texas - Houston, TX

Dr. Michael Jensen

Associate Professor of Medicine
Mayo Clinic, Rochester, MN

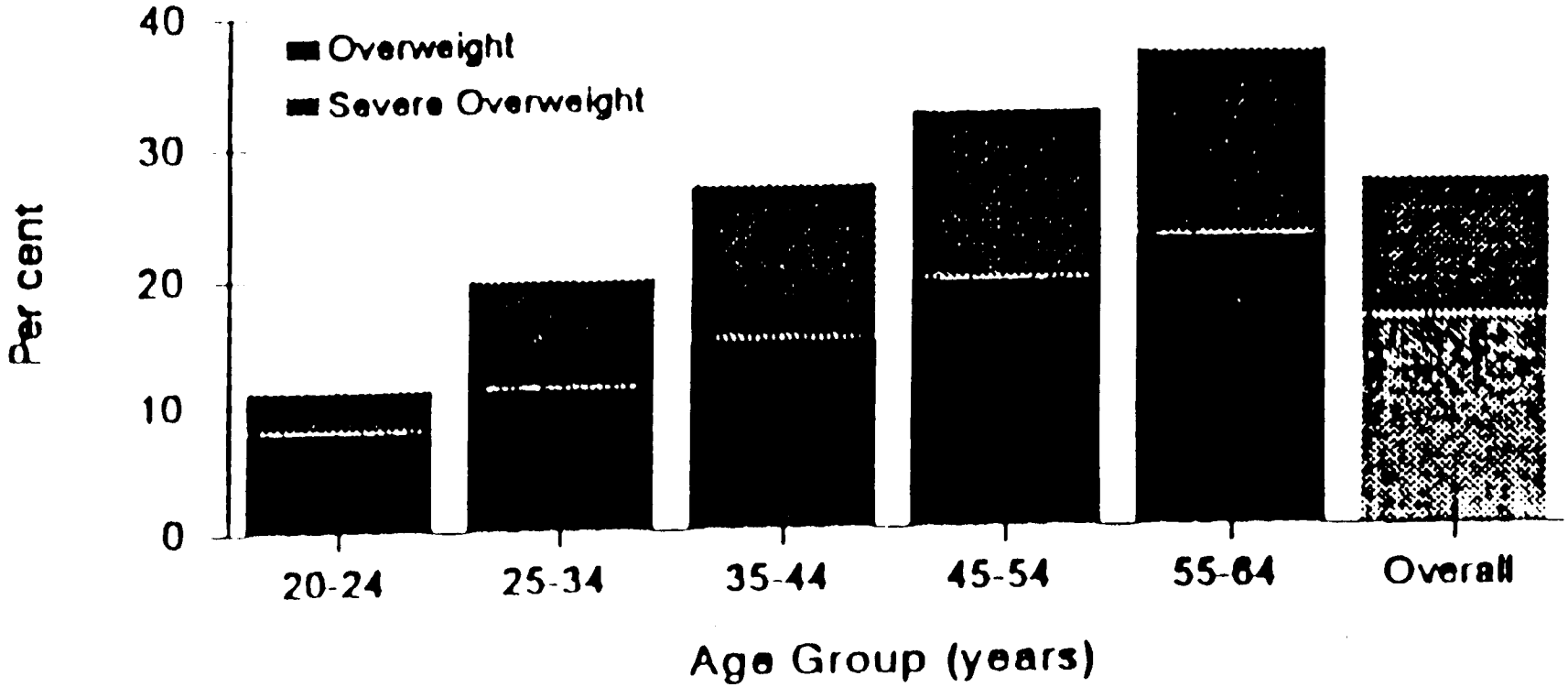
Dr. David Kelley

Associate Professor and Associate Director
Obesity and Nutrition Research Center
University of Pittsburgh School
of Medicine
Pittsburgh, PA

Dr. Aram Chobanian

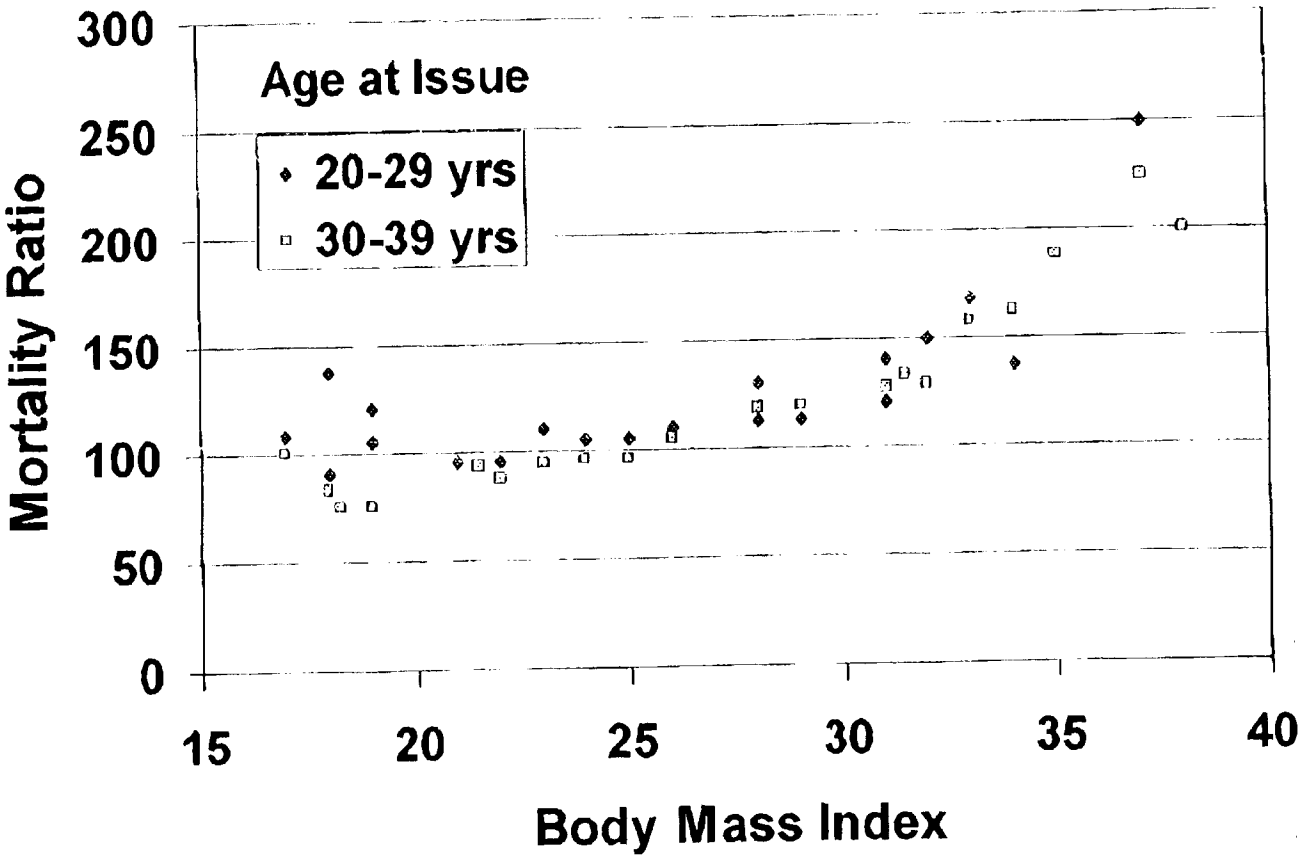
Dean, Department of Medicine
Boston University School of Medicine - Boston, MA

Percentage Overweight and Severely Overweight U.S. Women



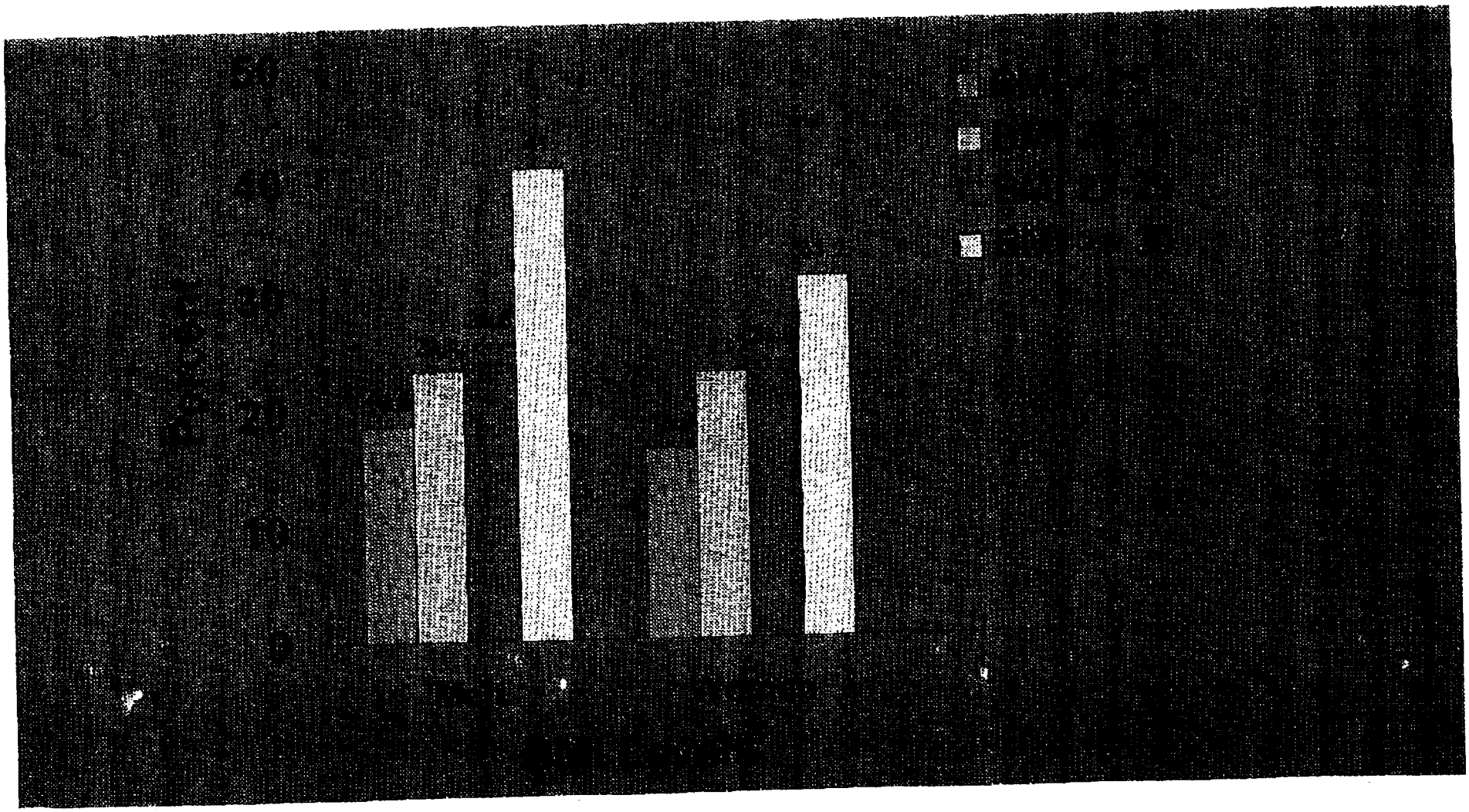
Overweight = BMI 27.8+ (men) 27.3+ (women)
Severe overweight BMI 31.1 (men) and 32.3+ (women)

Relationship of BMI to Excess Mortality



Bray GA. Ann Int Med 103:1052, 1985

NHANES III Age-Adjusted Prevalence of Hypertension According to Body Mass Index



Trials of Hypertension Prevention

Subjects with high normal blood pressure studied 3-5 yr

A 3-4 kg decrease in body wt associated with:

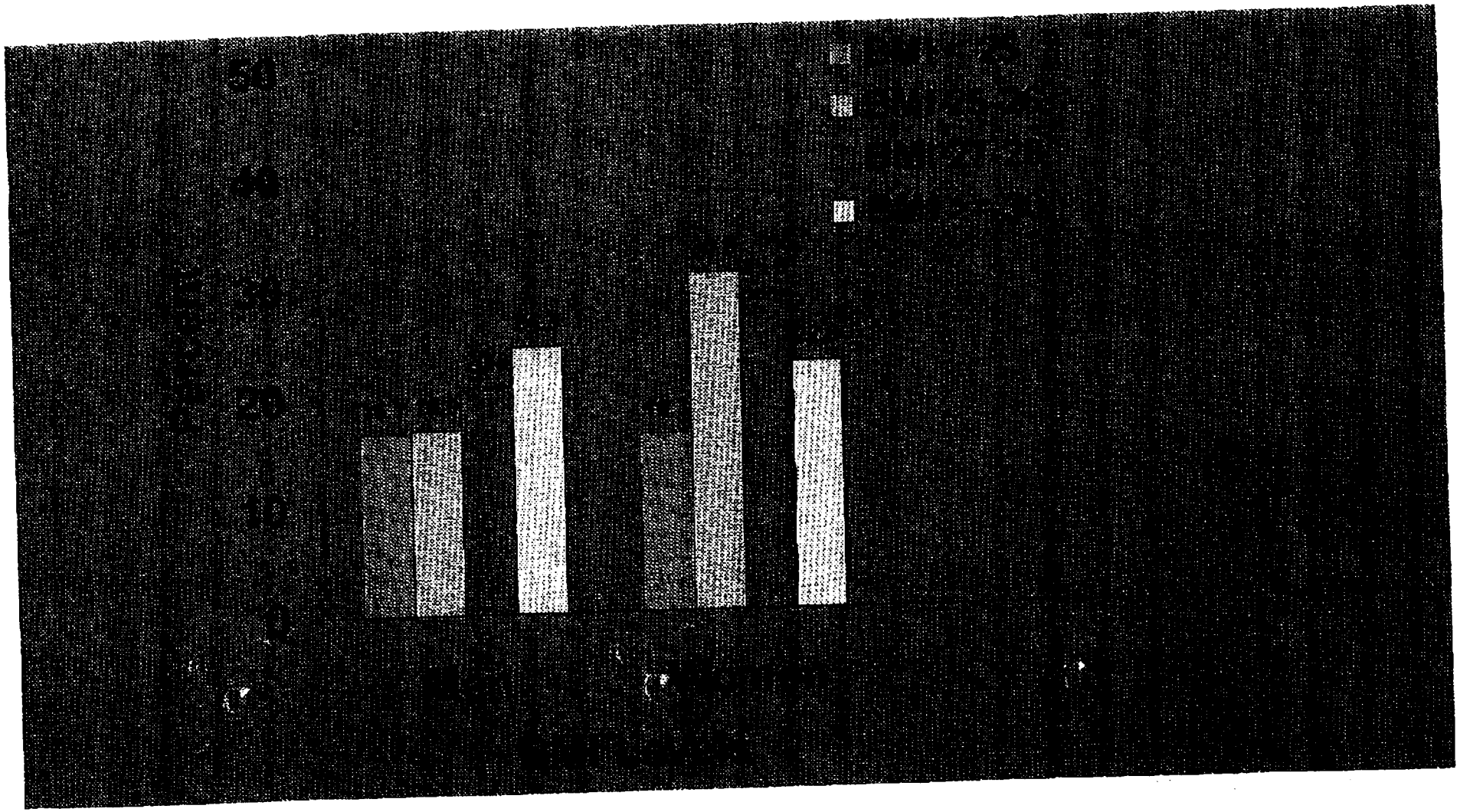
2-3 mmHg decrease in SBP and DBP, and

50% lower incidence of hypertension

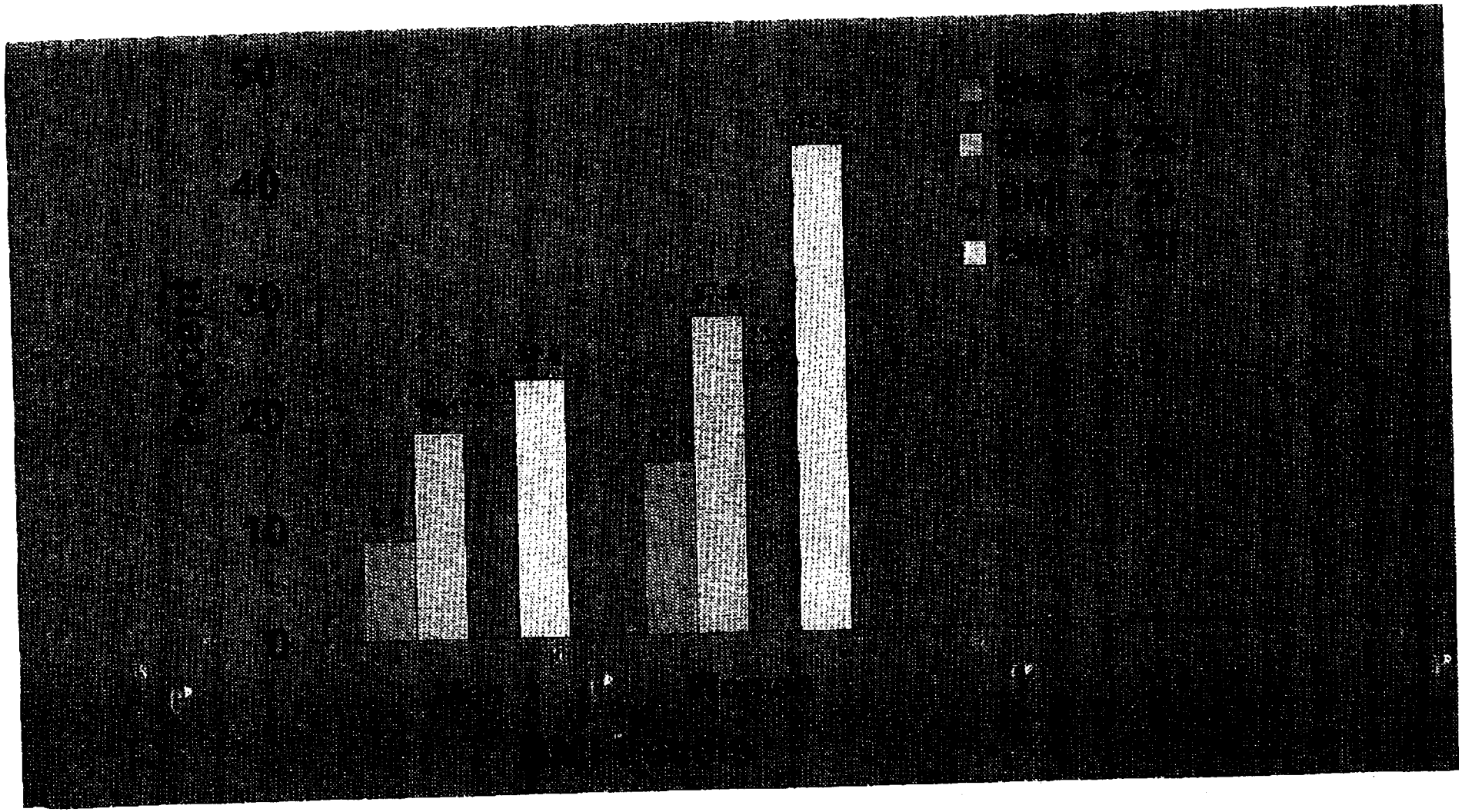
TOHP Study. Arch Int Med 157:657, 1997

HPT Study. Arch Int Med 150:153, 1990

NHANES III Age-Adjusted Prevalence of High Blood Cholesterol According to Body Mass Index



NHANES III Age-Adjusted Prevalence of Low HDL Cholesterol According to Body Mass Index



Lipid Research Clinic

Coronary Primary Prevention Trial

- Every 1% decrease in plasma cholesterol associated with a 2.1% reduction in CHD risk

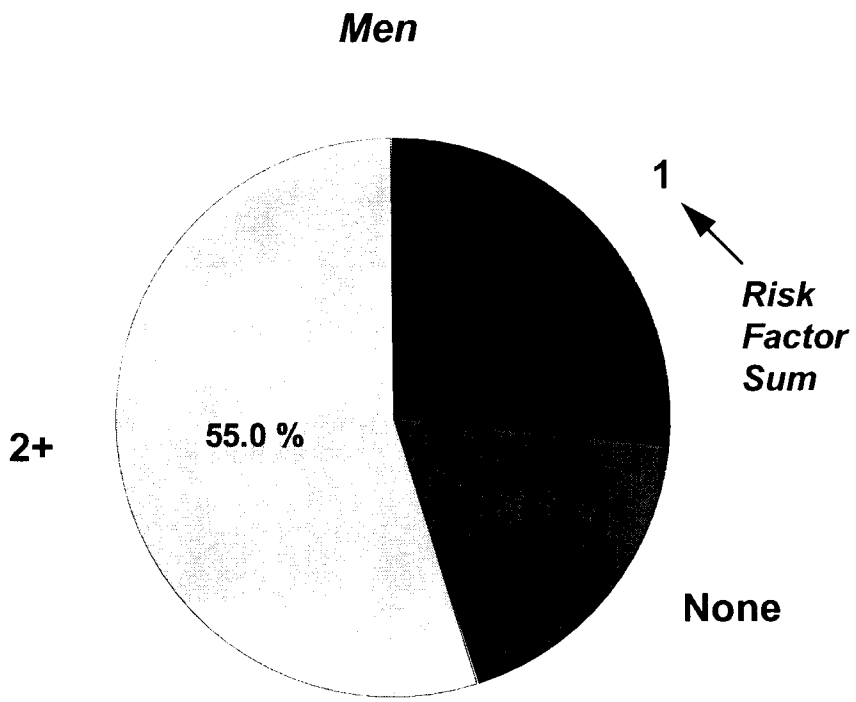
JAMA 1984, 251:351

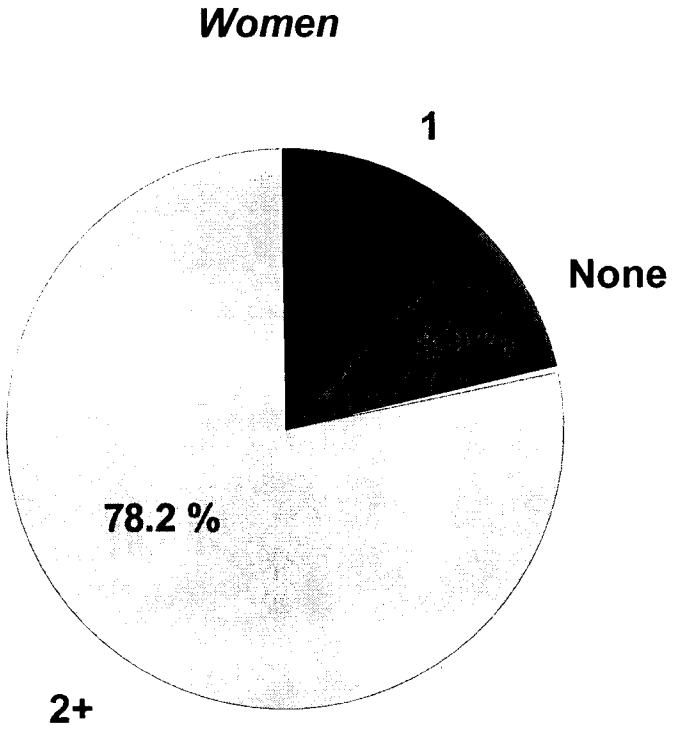
Average Risk Factor Values in Lean vs Obese Persons with Stable Weights over 6 Years

	Lean Persons BMI <22		*Obese Persons BMI >27*	
Risk Factor	**Men**	**Women**	**Men**	**Women**
BP Systolic (mm Hg)	129	125	139	145
BP Diastolic (mm Hg)	80	79	89	89
Cholesterol (mg/dl)	231	242	251	256
Glucose (mg/dl)	78	79	81	82
Number	77	255	281	228

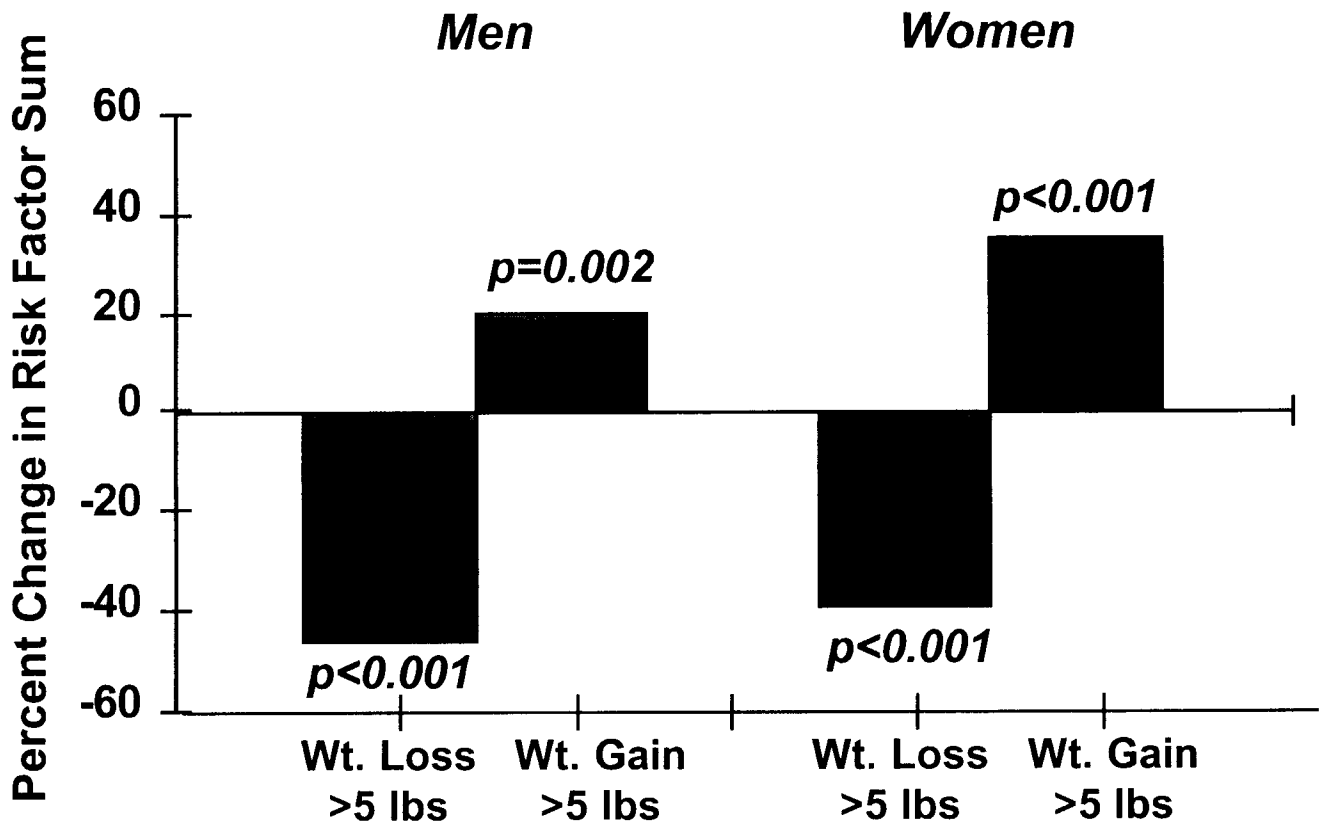
Weight stable within 5 lbs. RFs adjusted for age.

Percentage of CHD Events According to Risk Factor Sum Framingham/Offspring 16 Year Follow up





Impact of Weight Change over 16 Years on Risk Factor Sum



Includes adjustments for age and baseline Body Mass Index
Comparisons relative to persons whose weight remained stable (less than 5 lbs change over 16 years)
Baseline Mean RF Sum = 0.96 (men) and 1.01 (women)

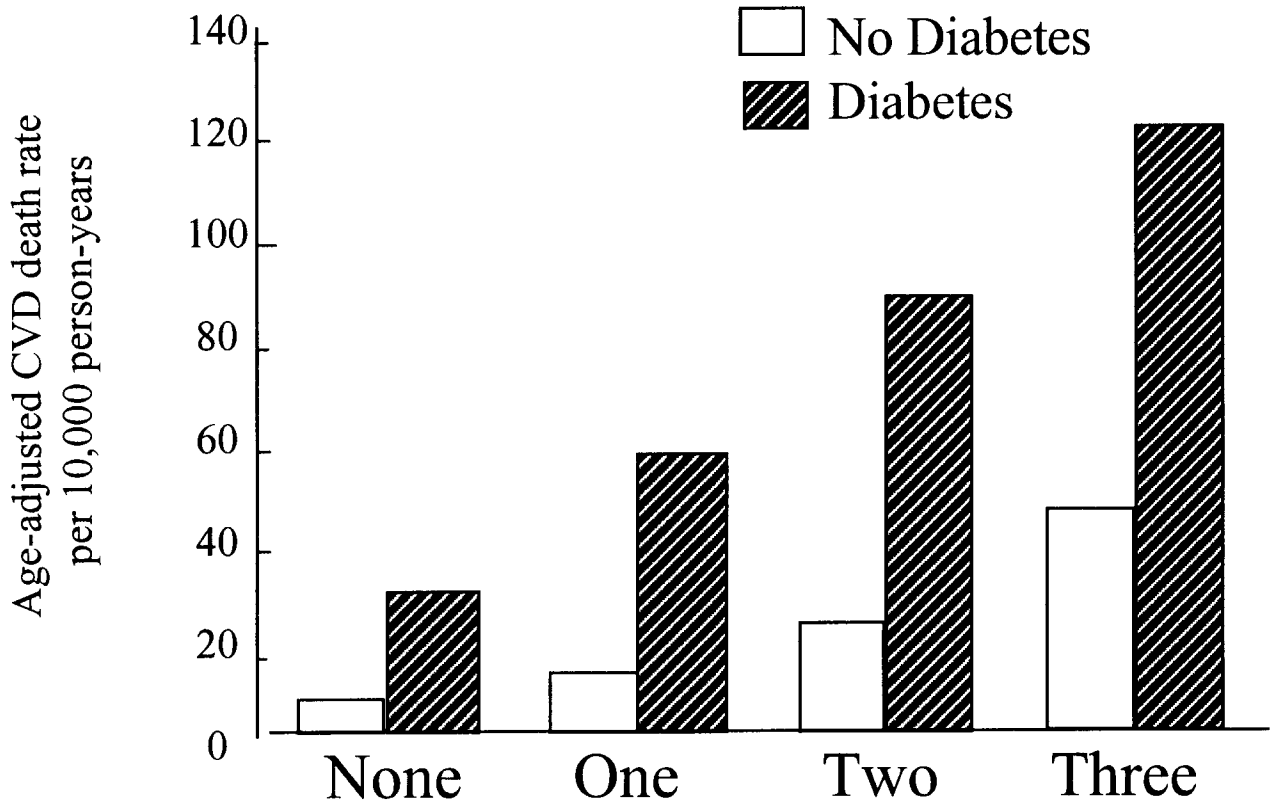
EPI 3

Dr. Douglas Greene

Professor of Internal Medicine
Department of Endocrinology
University of Michigan - Ann Arbor, MI

FDA Advisory Presentation

Age-Adjusted CVD Death Rates by Number of CVD Risk Factors for Diabetic and Nondiabetic Men



Subjects are screenees for the MRFIT study; risk factors are hypercholesterolemia, hypertension, and smoking

Diabetes in America

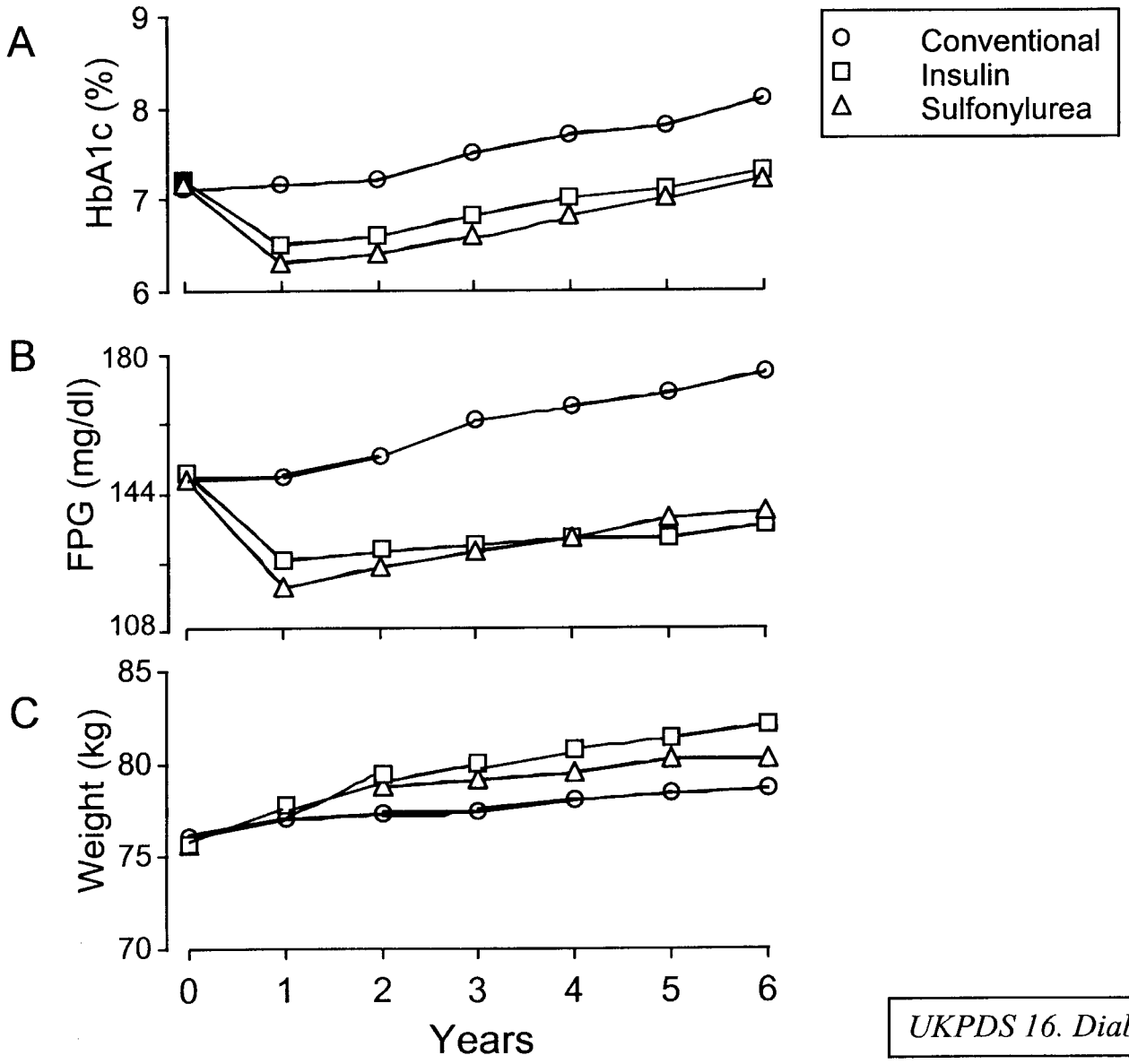
Type 2 Diabetes:
A Problem in Overall Risk Management

- Glycemic control
- Cardiovascular Disease
  - Hypertension
  - Dyslipidemia

Treatment of Type 2 Diabetes

- Diet and exercise
- Pharmacotherapy
  - Sulfonylurea medications
  - Biguanides (Metformin)
  - Alpha-glucosidase inhibitor (Acarbose)
  - Insulin
  - Troglitazone

HbA1c (A), fasting plasma glucose (B), and body weight (C) over 6 y in newly diagnosed Type 2 diabetic patients



UKPDS 16. Diabetes 44:1249, 1995

UKPDS:

Natural History of Progression of Type 2 Diabetes

- Worsening glycemia
- Progressive weight gain
- Exacerbated cardiovascular disease risk

Treatment of Type 2 Diabetes

- Diet and exercise
- Pharmacotherapy
  - Sulfonylurea medications
  - Biguanides (Metformin)
  - alpha-Glucosidase inhibitors (Acarbose)
  - Insulin
  - Insulin-sensitizer (Troglitazone)
- Weight management

Treatment of Type 2 Diabetes:

Desired characteristics of weight management component

- Potentiate initial weight loss
- Prevent weight regain
- Beneficial effect on glycemic control
- Improve comorbidities
- Hypoglycemic agent-sparing

American Diabetes Association: Clinical Practice Recommendations 1998

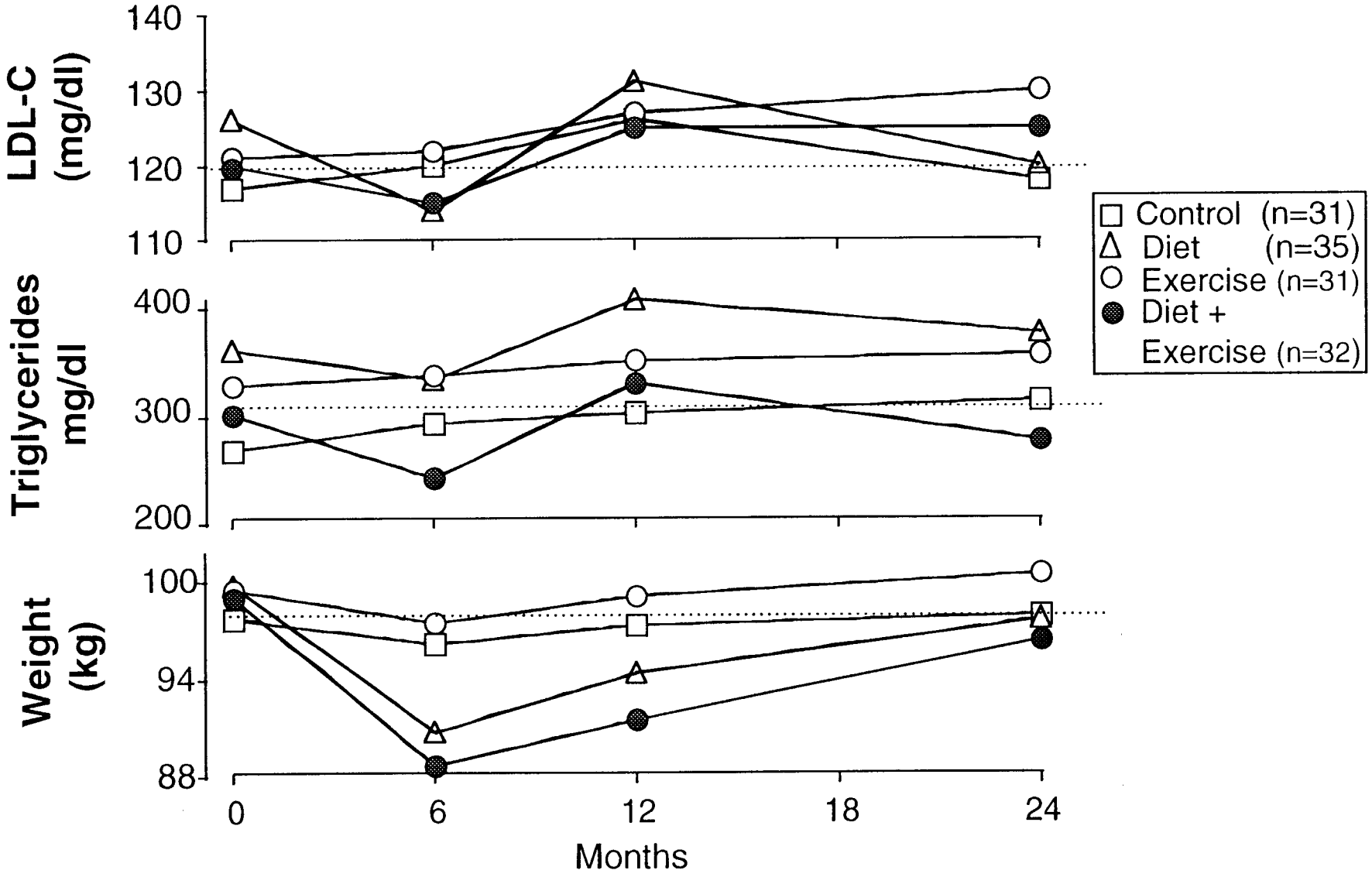
POSITION STATEMENT

Management of Dyslipidemia in Adults With Diabetes

- Weight loss and increased physical activity will lead to decreased triglyceride and increased HDL cholesterol levels and also to modest lowering of LDL levels.
- Treatment of LDL cholesterol is considered as the first priority for pharmacological therapy of dyslipidemia.

Diabetes Care; Suppl 1: S36, 1998

Body weight and Lipid Levels over 2 y of Lifestyle Intervention in Obese Subjects with Parental Diabetes

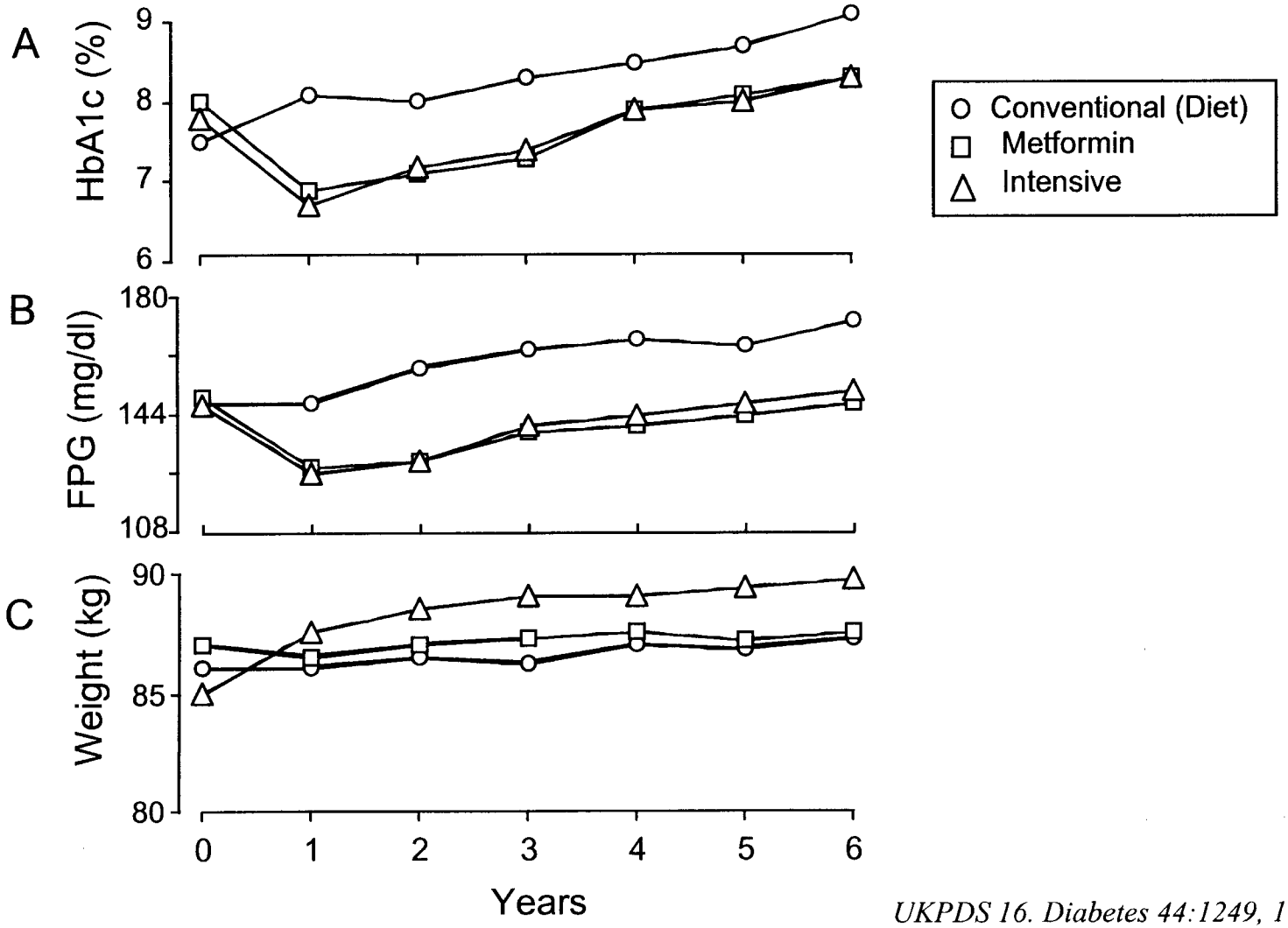


Wing et al. Diabetes 21:350, 1998

Desired Characteristics of Pharmacotherapy

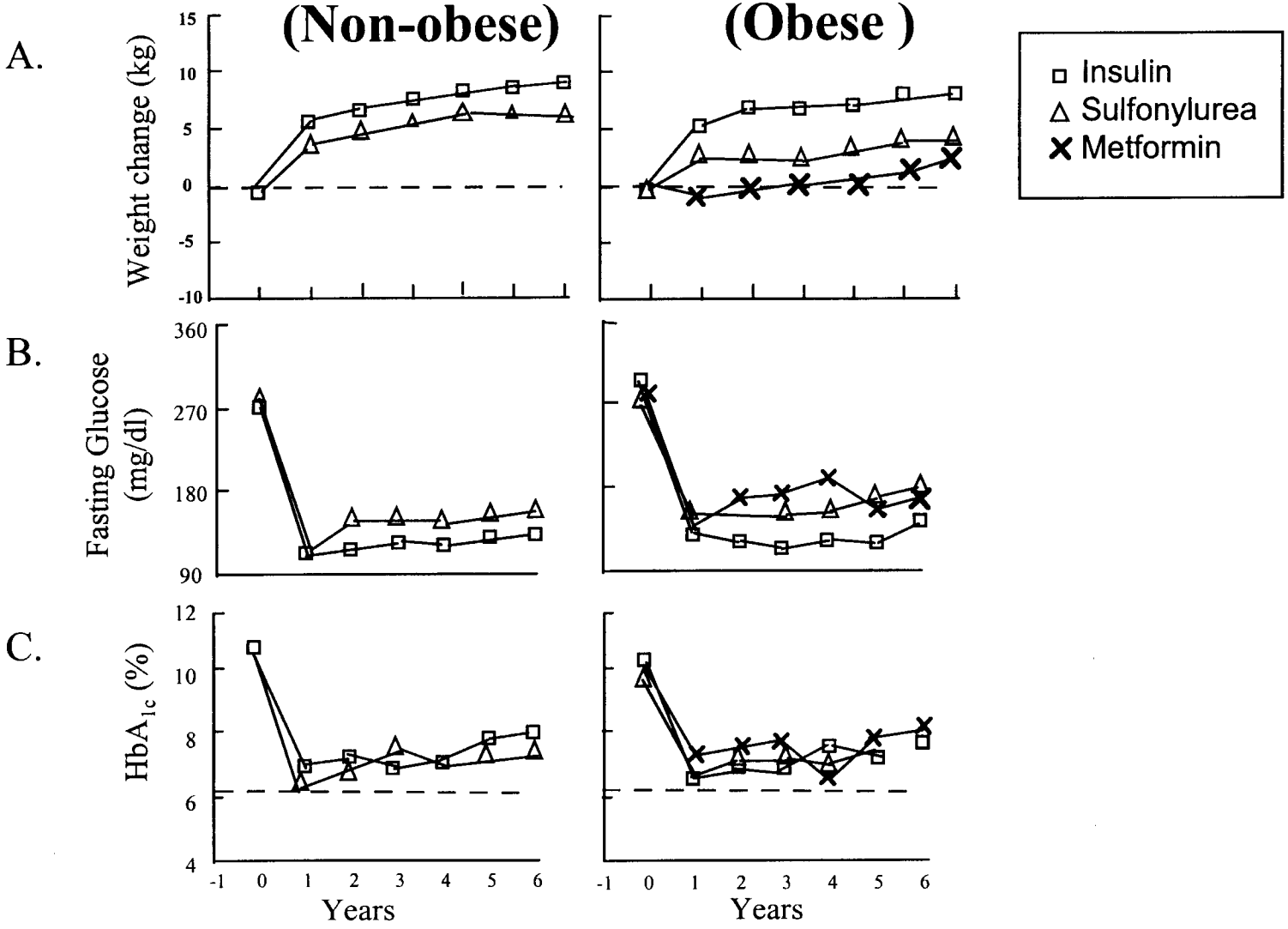
- Potentiates weight loss
- Minimizes or prevents weight regain
- Achieves and sustains weight loss sufficient to achieve and sustain health benefits
- An adjunctive weight management tool to prevent diabetes in obese persons at high risk

HbA1c (A), fasting plasma glucose (B), and body weight (C) over 6 y in obese patients assigned to conventional (diet), metformin, or intensive (insulin or sulfonylurea) therapy



UKPDS 16. Diabetes 44:1249, 1995

Changes in body weight (A), fasting glucose (B), and HbA_{1c} (C) over 6 years in patients in the primary diet failure group allocated to insulin, sulfonylurea, or metformin. The horizontal dashed lines indicate HbA_{1c} of 6.2 % (the upper 97.5th percentile of normal).



Ann Intern Med. 1998. 128:165-175.

XENICAL® (orlistat) in the Treatment of Obesity

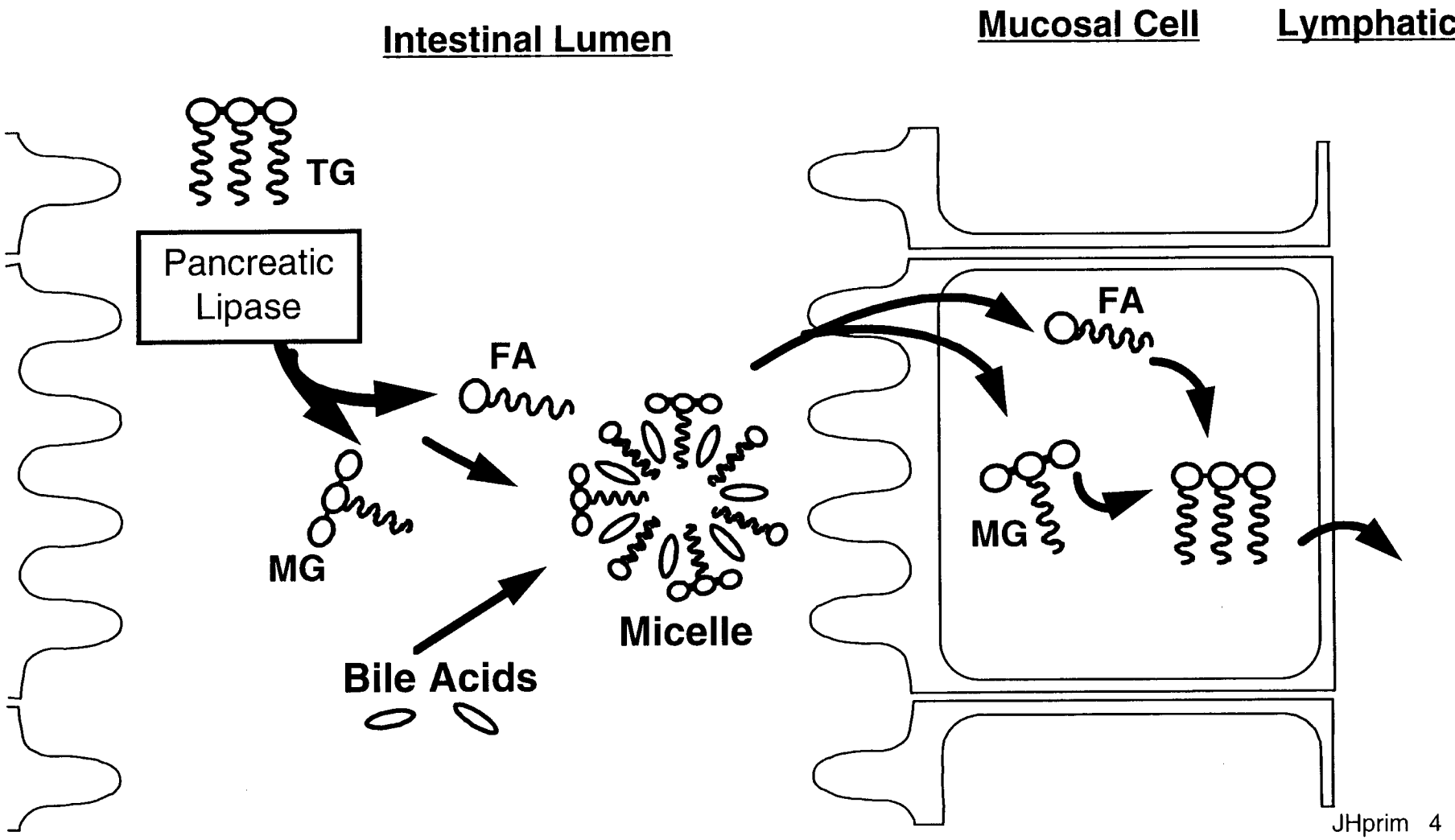
Jonathan Hauptman, MD
Hoffmann-La Roche
Nutley, New Jersey

Medically Significant Obesity

- BMI $\geq$ 30
- BMI $\geq$ 27 with risk factors
  - Type 2 Diabetes
  - Impaired Glucose Tolerance
  - Hyperlipidemia
  - Hypertension

Orlistat Selectively Inhibits Fat Absorption to Produce a Caloric Deficit

Physiology of Fat Absorption



Phase III Clinical Program

7 Double-Blind, Randomized, Placebo-Controlled Trials (N = 4188)

- 5 studies evaluated weight loss and maintenance for one year
  - 4 studies had a second year of treatment
- 1 study evaluated patients with Type 2 Diabetes on oral hypoglycemic agents
- 1 study evaluated prevention of weight regain after weight loss with diet alone

As Part of an Overall Weight Management Program, Orlistat

- Helps to produce and maintain a clinically meaningful weight loss
- Demonstrates favorable effects on obesity-related risk factors

Overall Weight Management Program

Year One Goal: Weight Loss and Maintenance

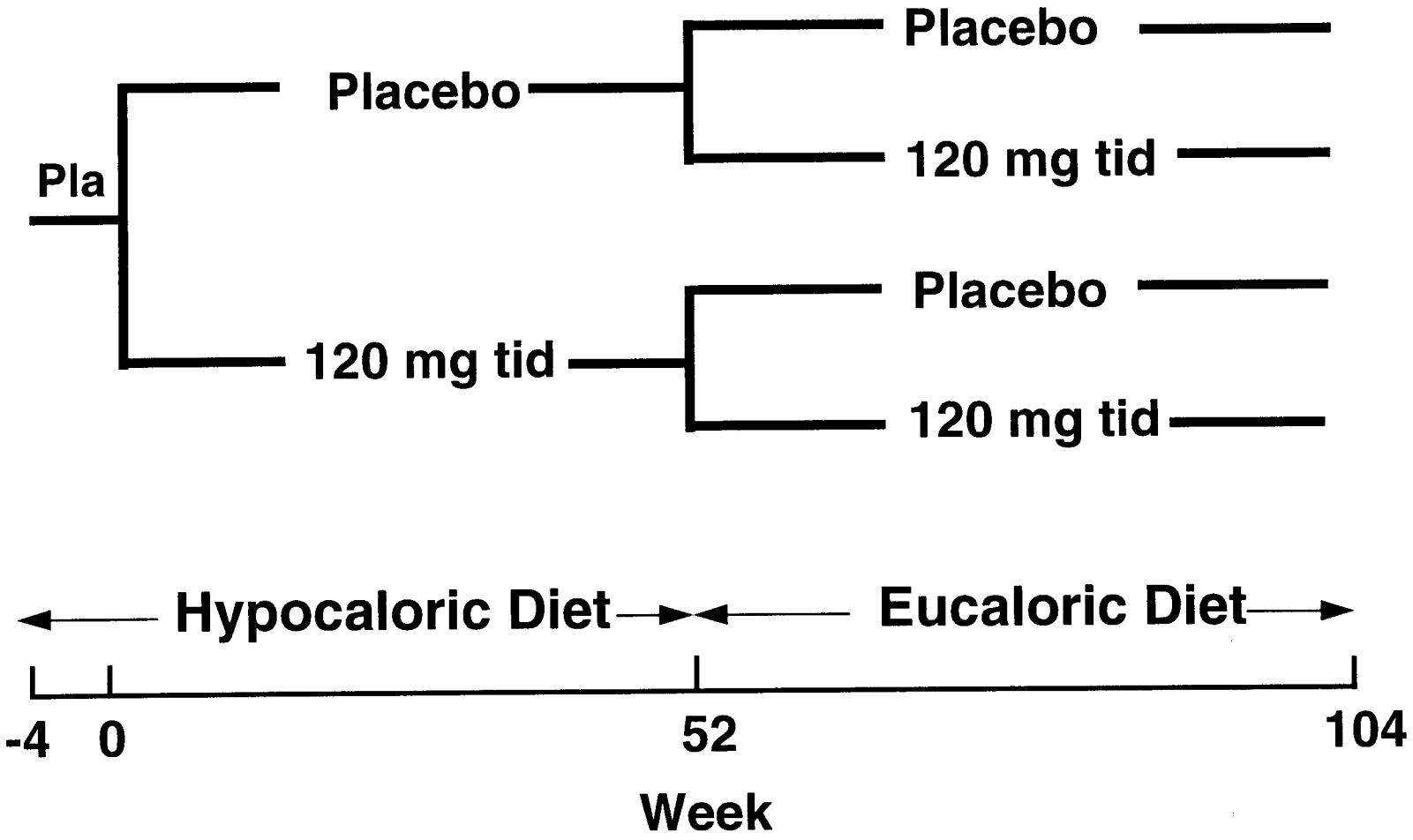
- Balanced hypocaloric diet
- Dietary counseling
- Behavior modification
- Frequent clinic visits

Overall Weight Management Program

Year Two Goal: Help Prevent Weight Regain

- Balanced eucaloric diet
- Counseling to diminish weight regain
- Longer intervals between clinic visits

Study BM14119C

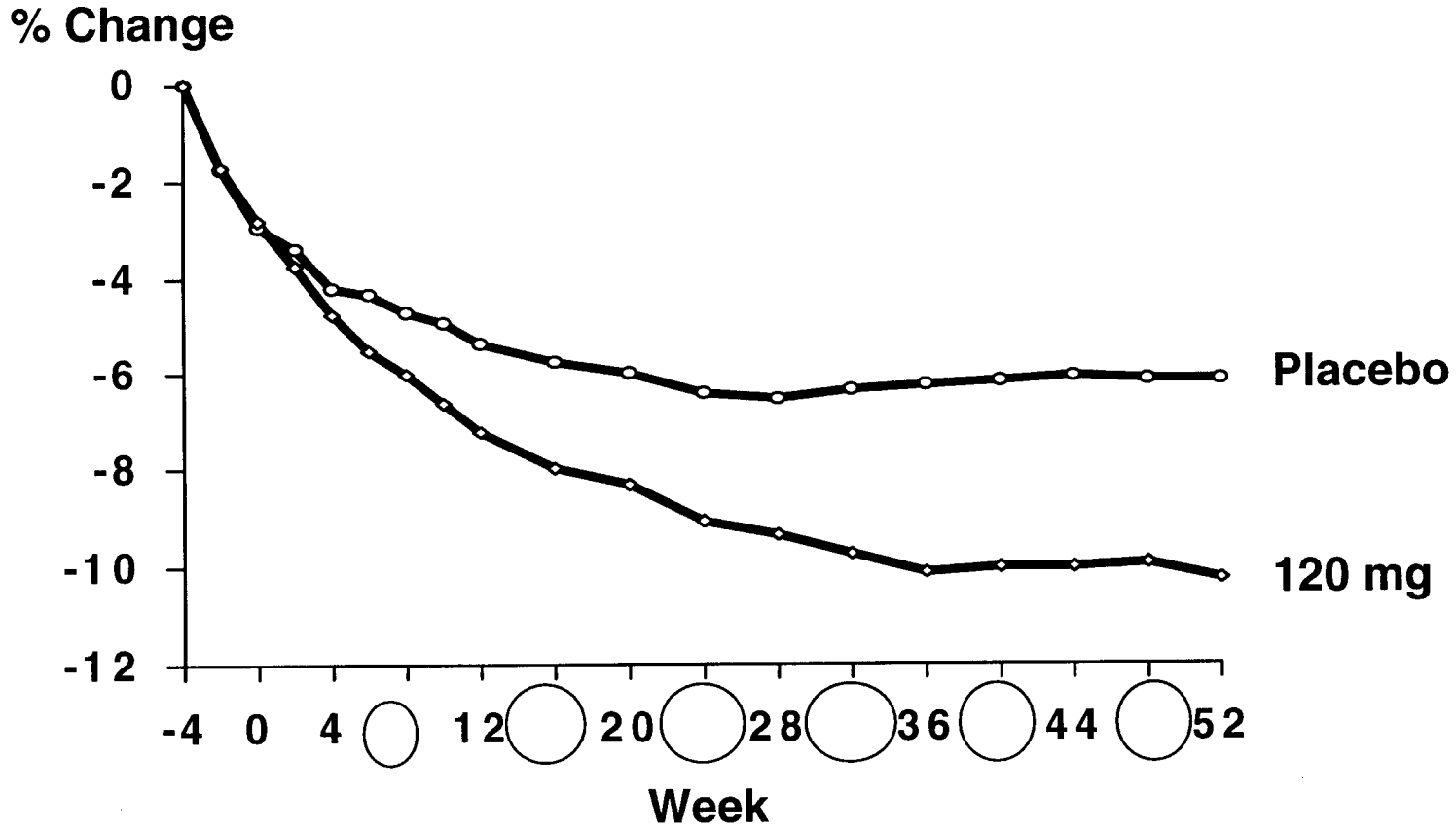


Demography

		Placebo n=340	120 mg n=343
Sex	Male	16.8%	17.2%
	Female	83.2%	82.8%
Age (y)	Mean	44.3	45.2
Race	White	99.4%	99.1%
	Black	0.6%	0.3%
Weight (kg)	Mean	99.8	99.1
BMI (kg/m^2)	Mean	36.1	36.0

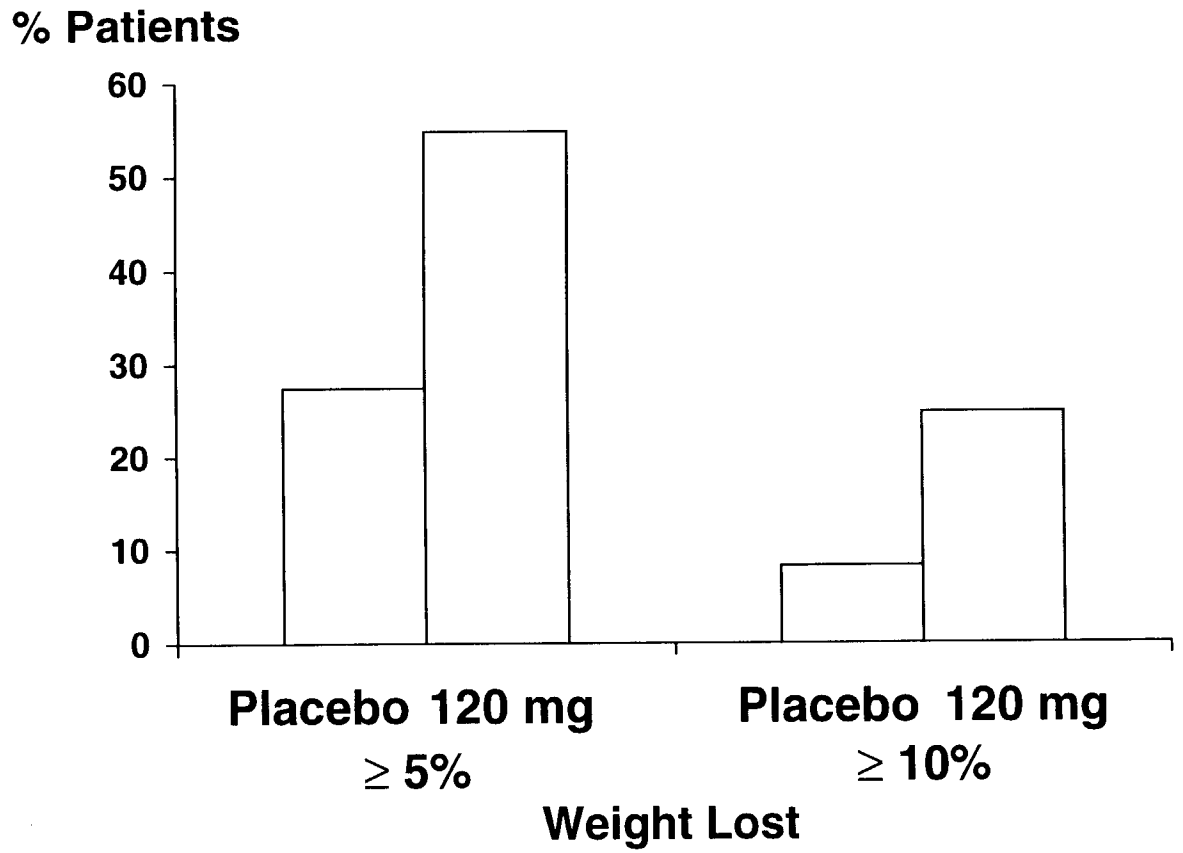
Year One Weight Loss and Maintenance

Mean Percent Change from Initial Body Weight (Intent-to-Treat Population)

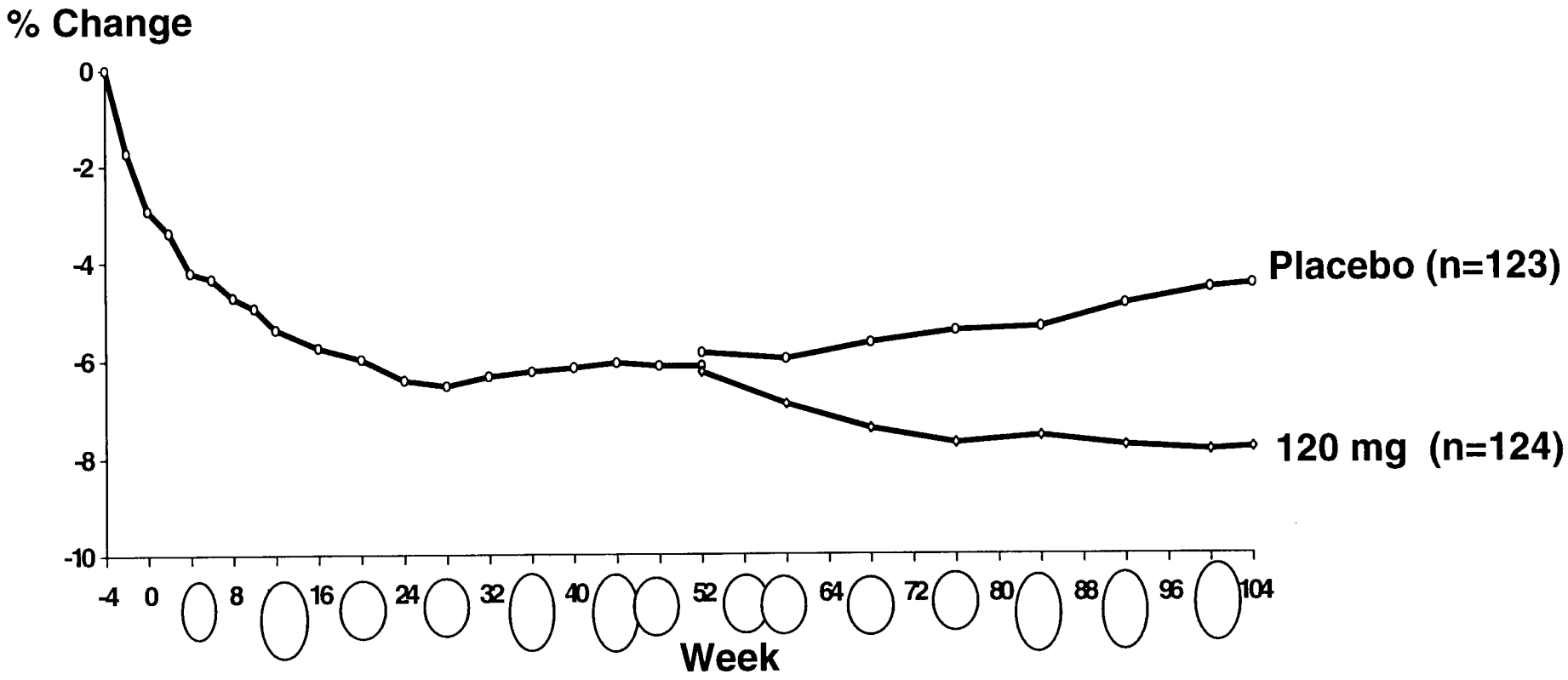


Year One Weight Loss and Maintenance

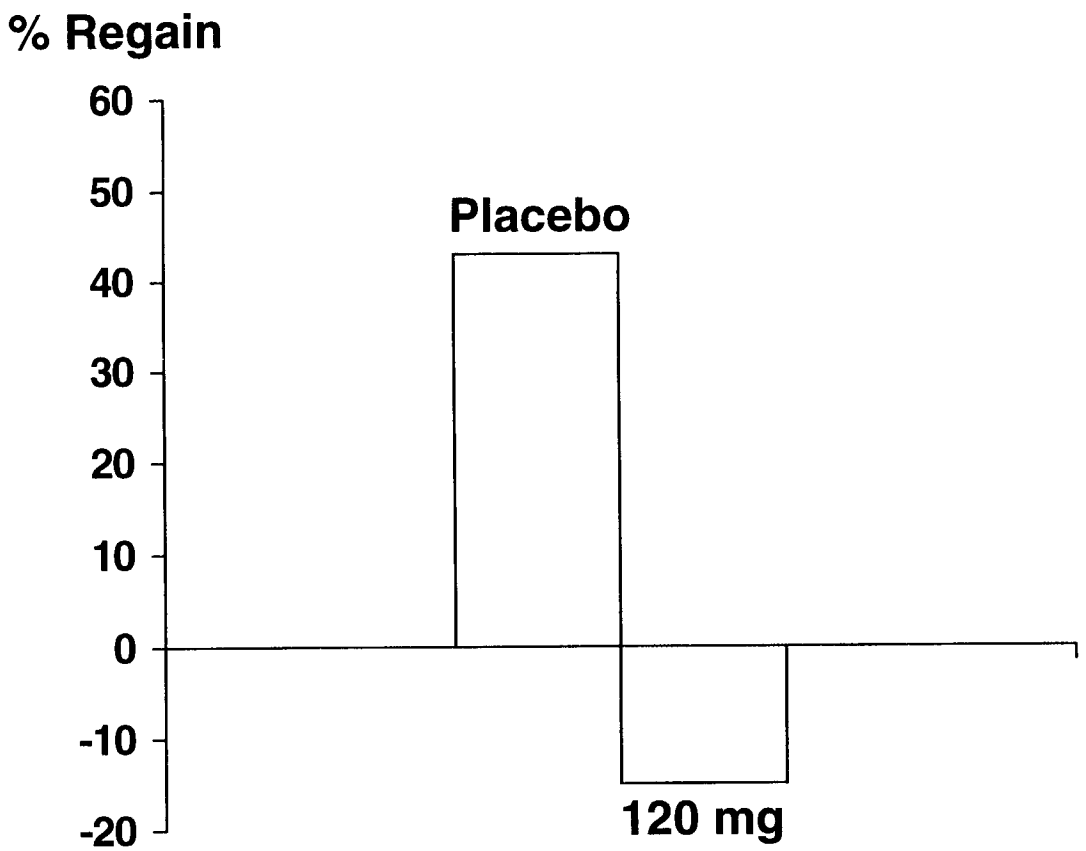
Responder Analysis
(Change from Baseline)



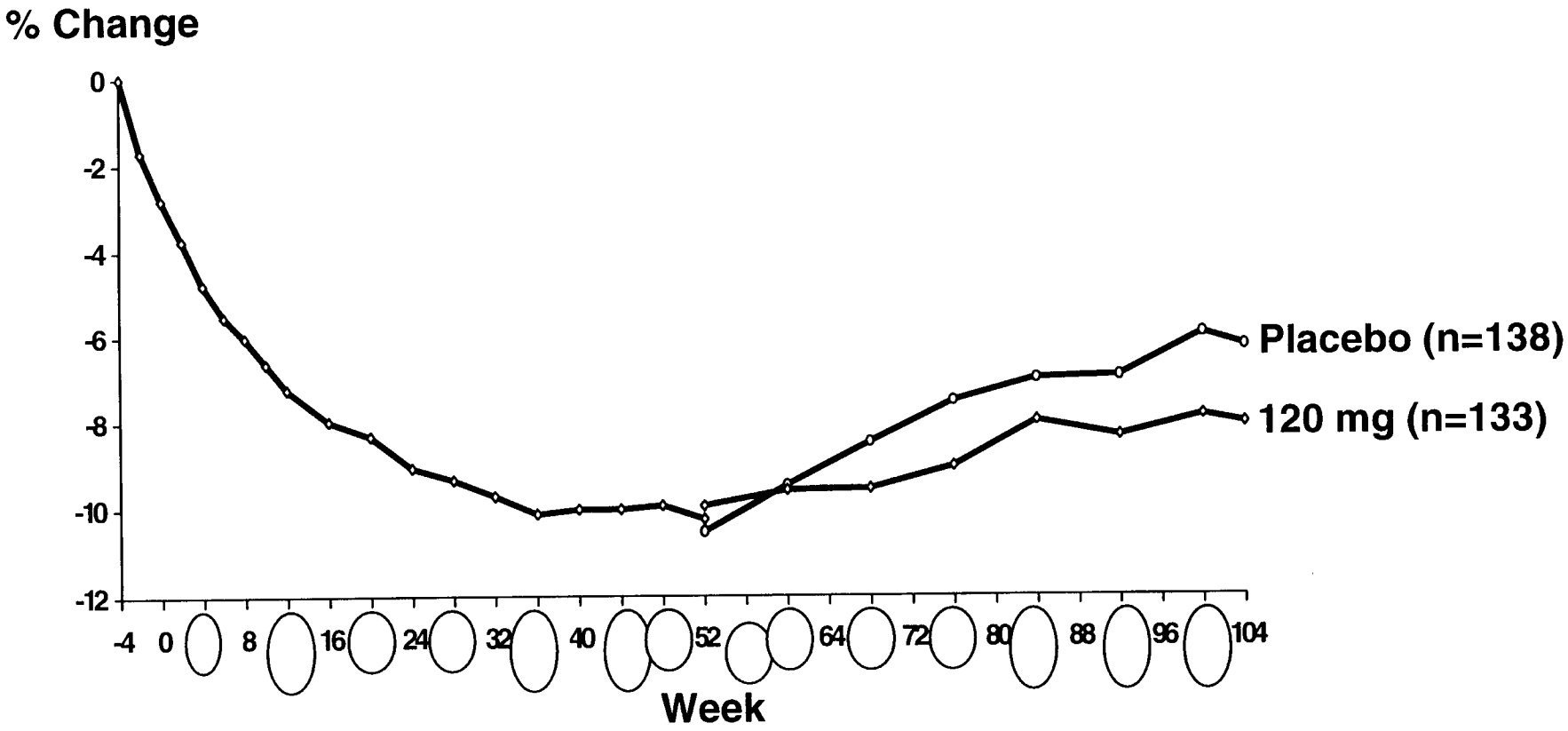
Prevention of Weight Regain in Year Two in Patients who Received Placebo in Year One



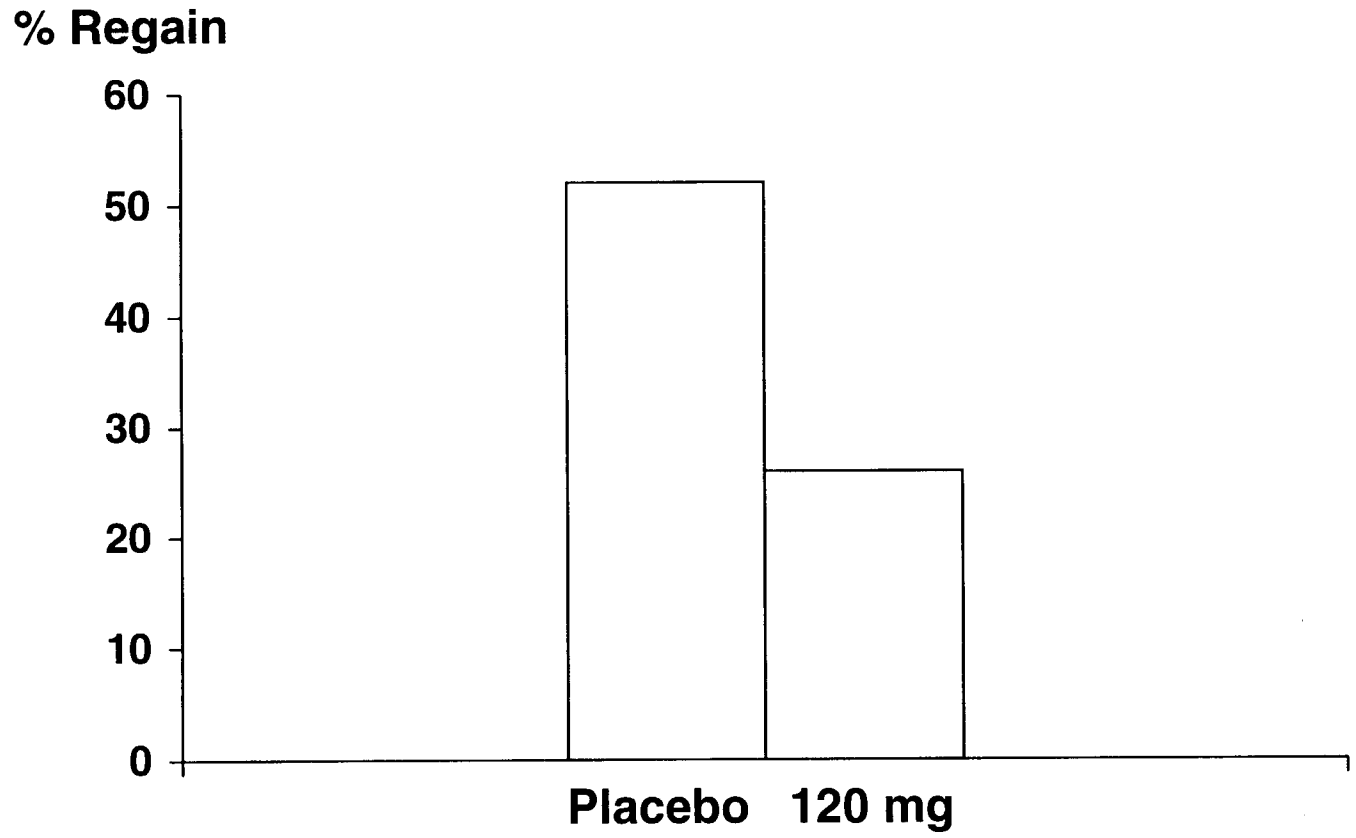
Mean Percent Regain of Lost Weight in Patients Who Received Placebo in Year One



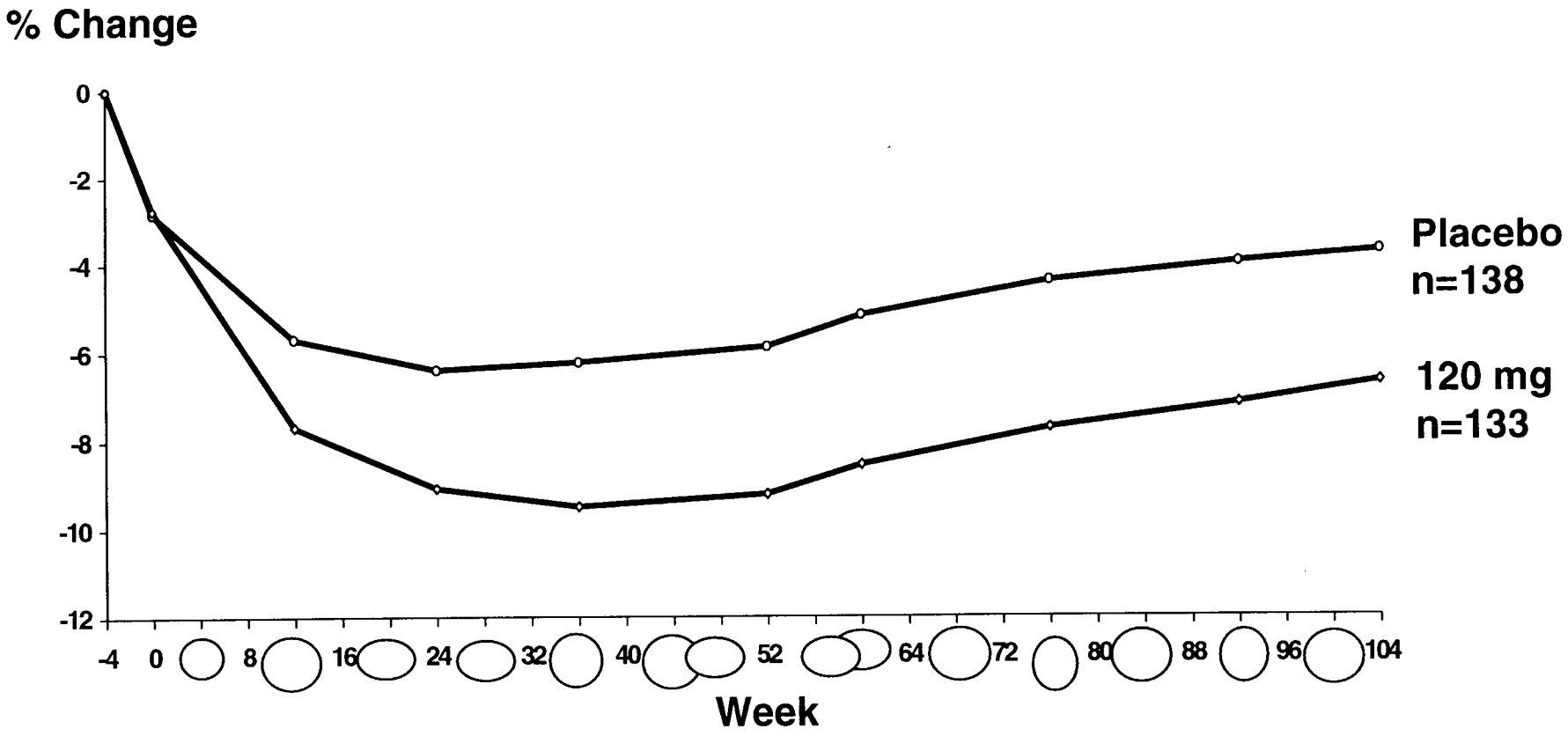
Prevention of Weight Regain in Year Two in Patients Who Received Orlistat in Year One



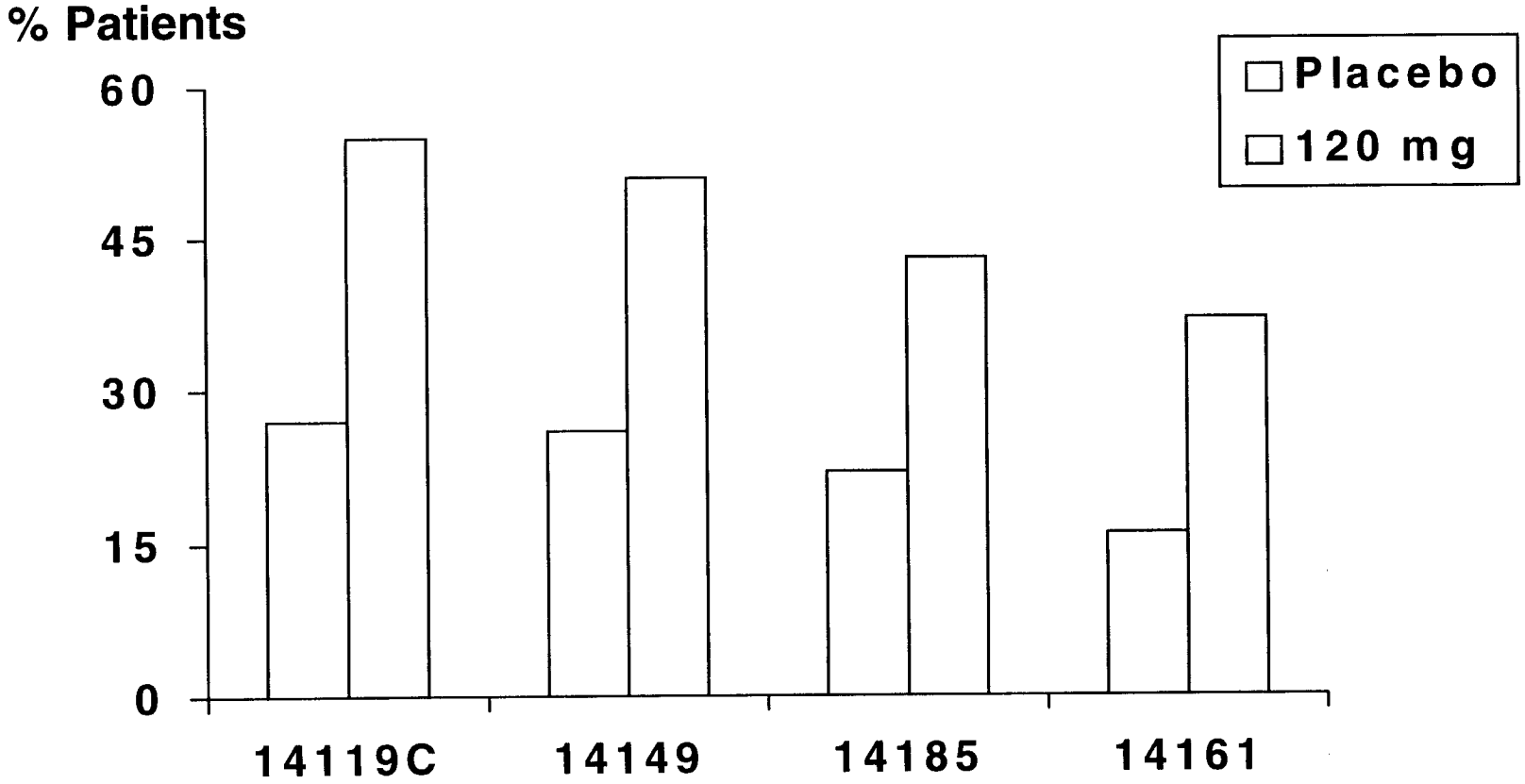
Mean Percent Regain of Lost Weight in Patients Who Received Orlistat in Year One



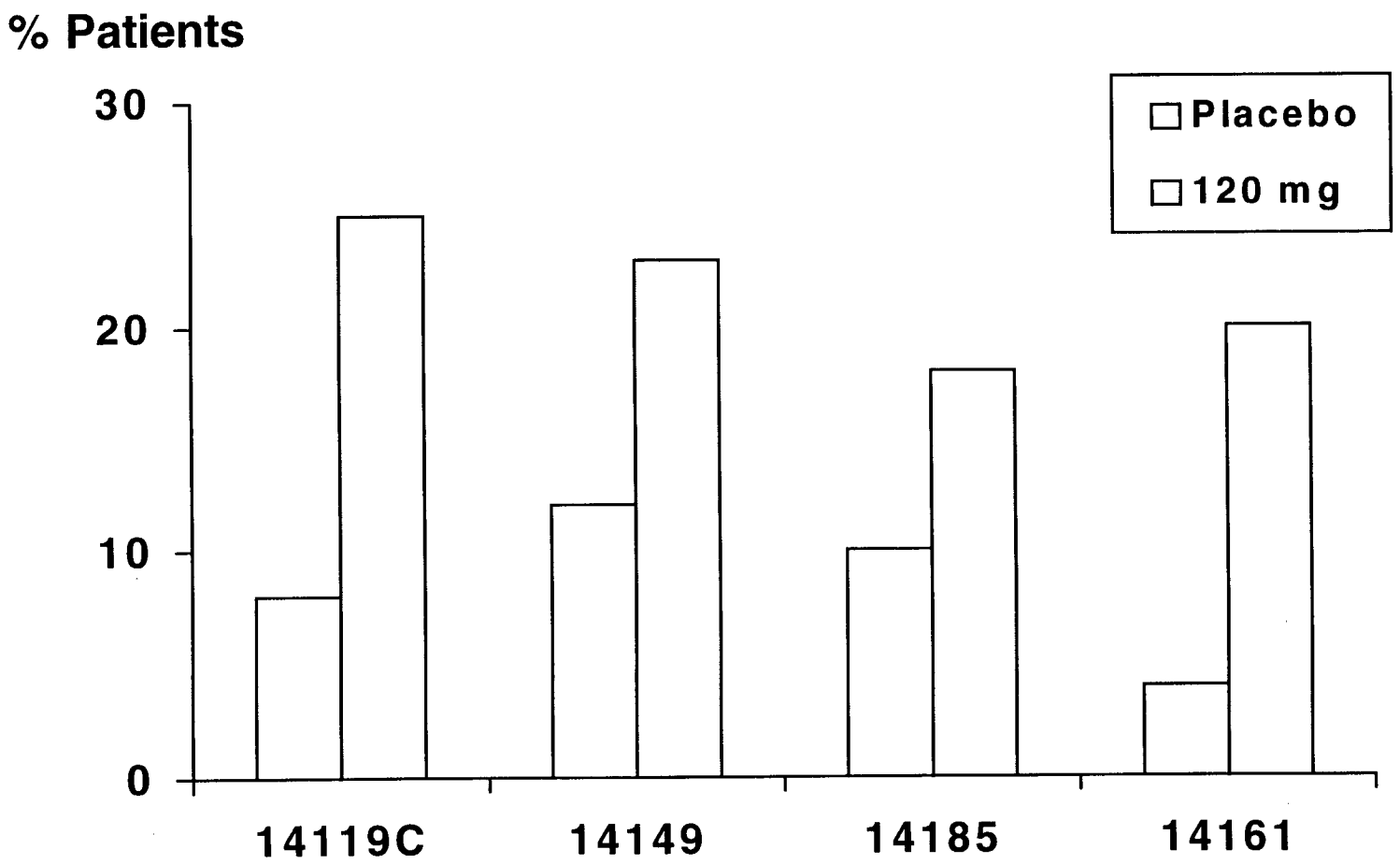
Long-Term Weight Control Over Two Years



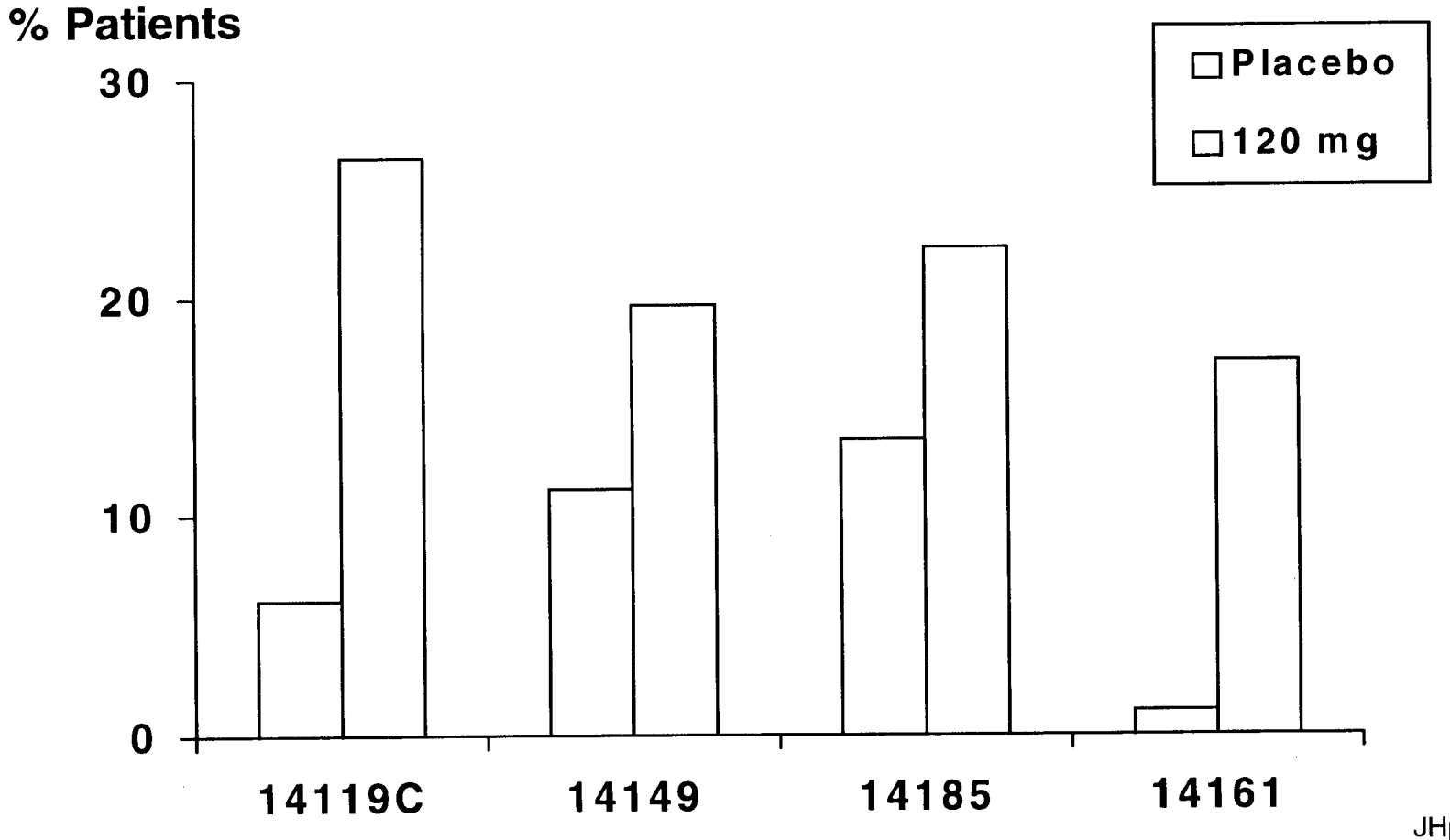
Responder Analysis One Year ≥ 5% Weight Loss from Baseline



Responders Analysis One Year
≥ 10% Weight Loss from Baseline



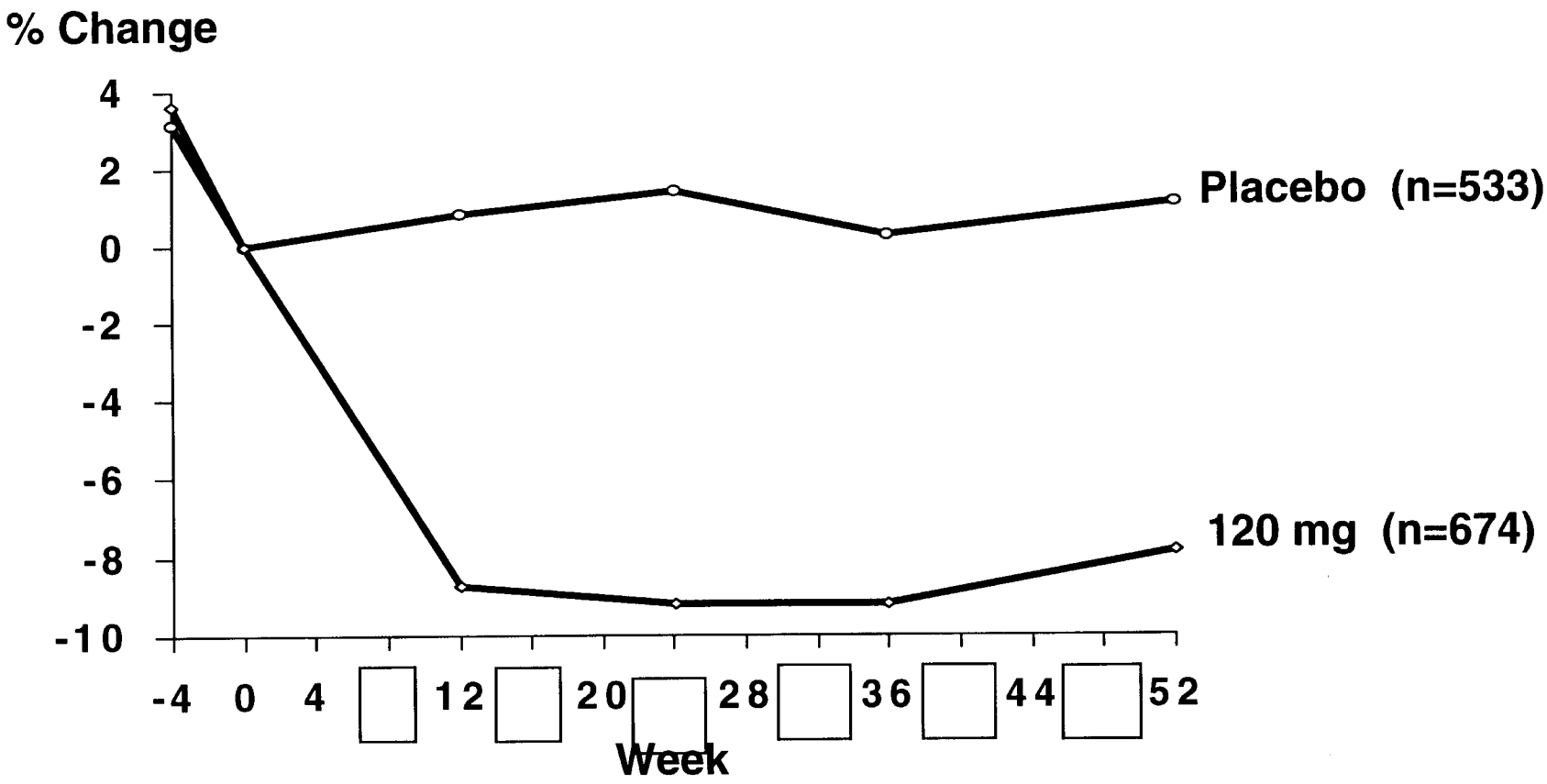
Responders Analysis Two Years
≥ 10% Weight Loss from Baseline



Orlistat Produces Positive Effects on Obesity-Related Risk Factors

- Cardiovascular
- Hyperinsulinemia
- Impaired Glucose Tolerance
- Type 2 Diabetes

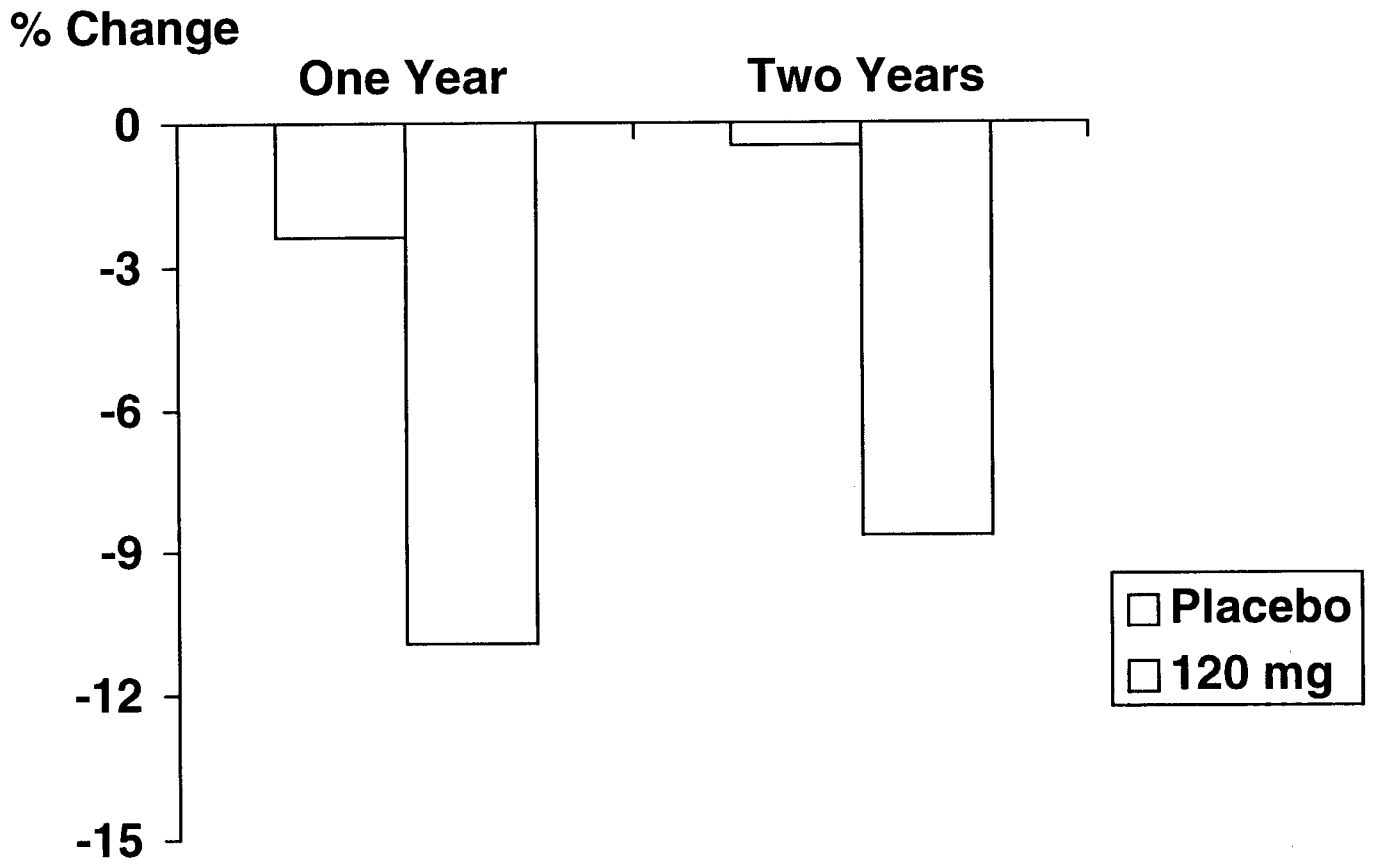
LDL-Cholesterol (≥ 3.36 mmol/L)
Mean Percent Change Over Time



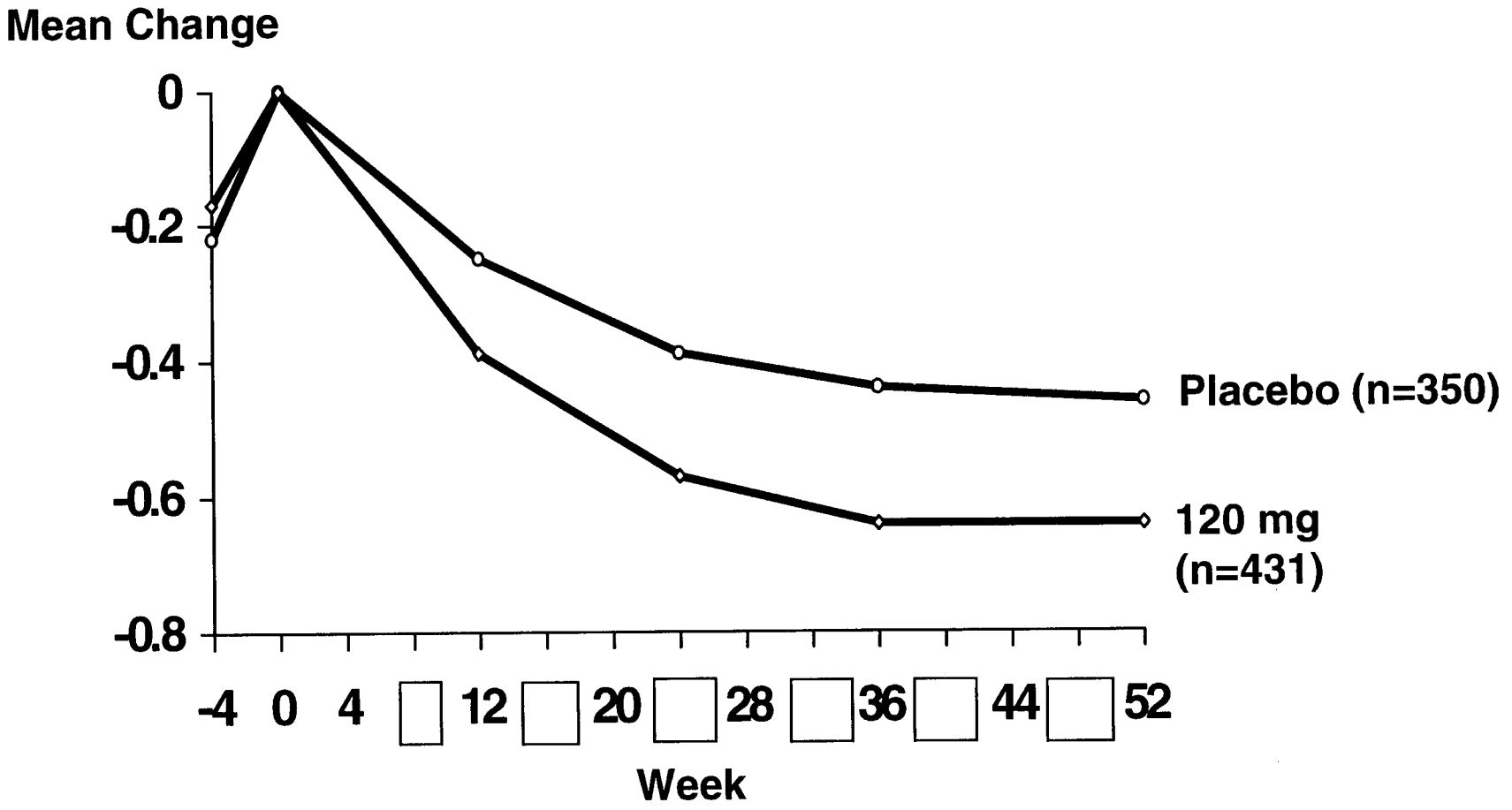
Change of LDL- Cholesterol Status Patients Elevated at Baseline

Elevated	N	% Normal
Placebo	516	14.1
120 mg	660	31.8

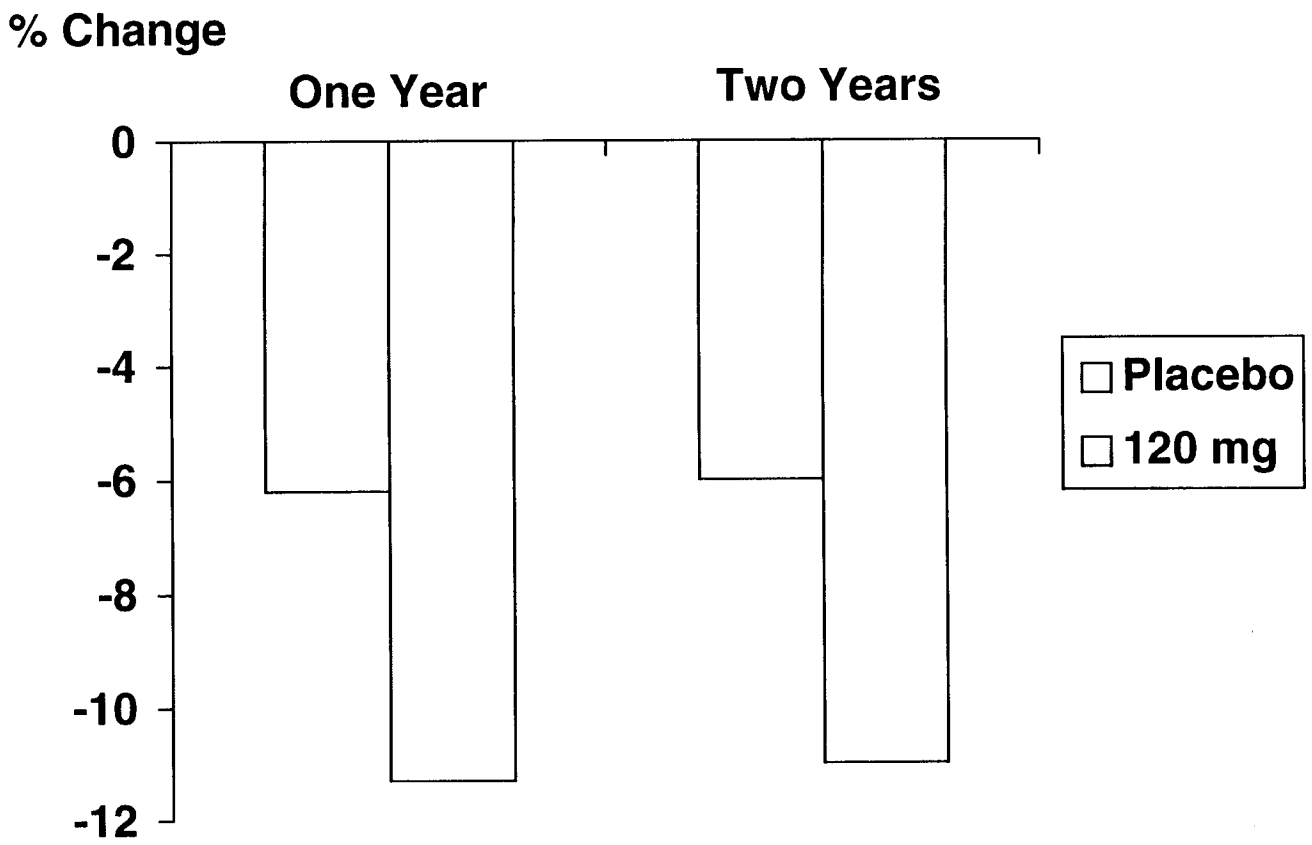
LDL-Cholesterol (≥ 3.36 mmol/L)
Mean Percent Change from Initial



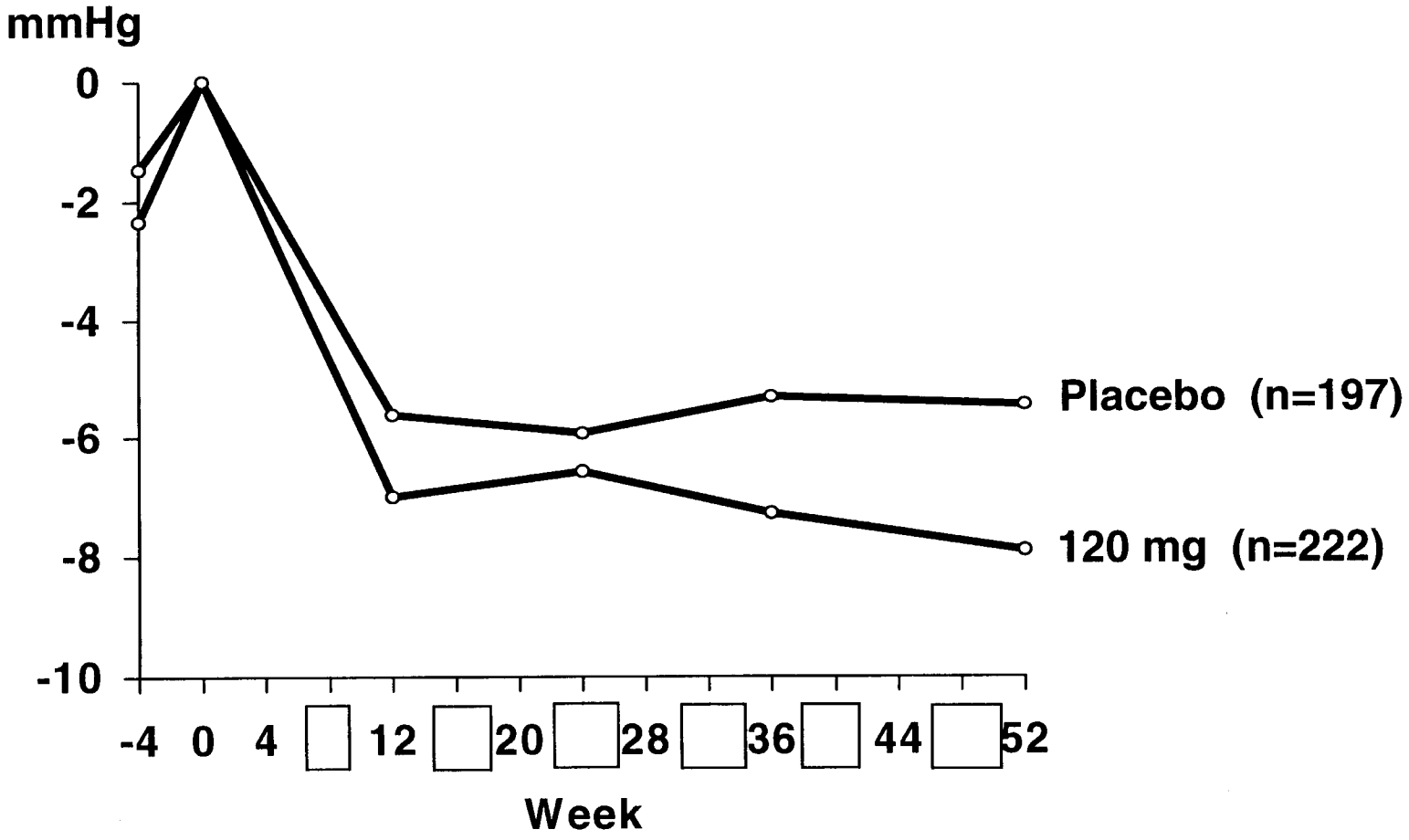
LDL/HDL Ratio (≥ 3.5)
Mean Change Over Time



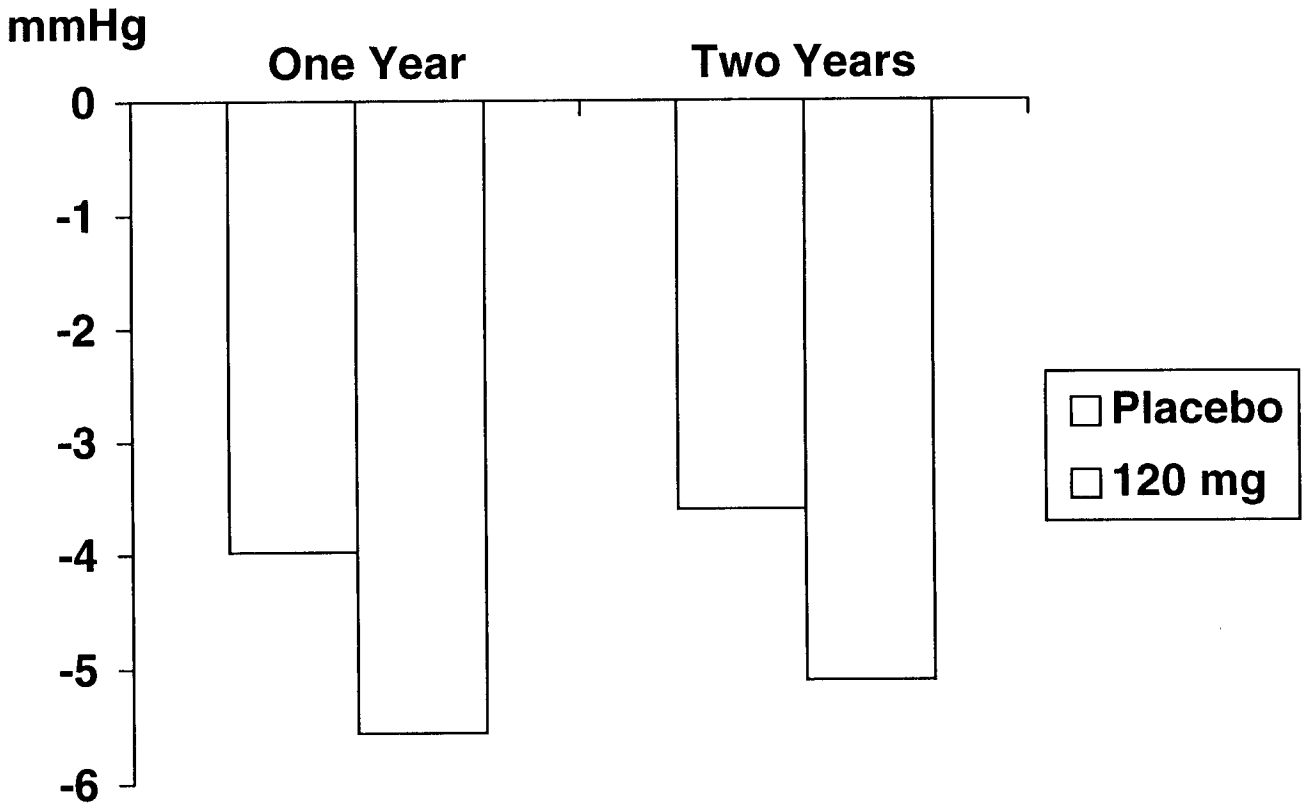
LDL/HDL Ratio (≥ 3.5)
Mean Percent Change from Initial



Diastolic Blood Pressure (≥ 90 mm Hg)
Mean Change Over Time



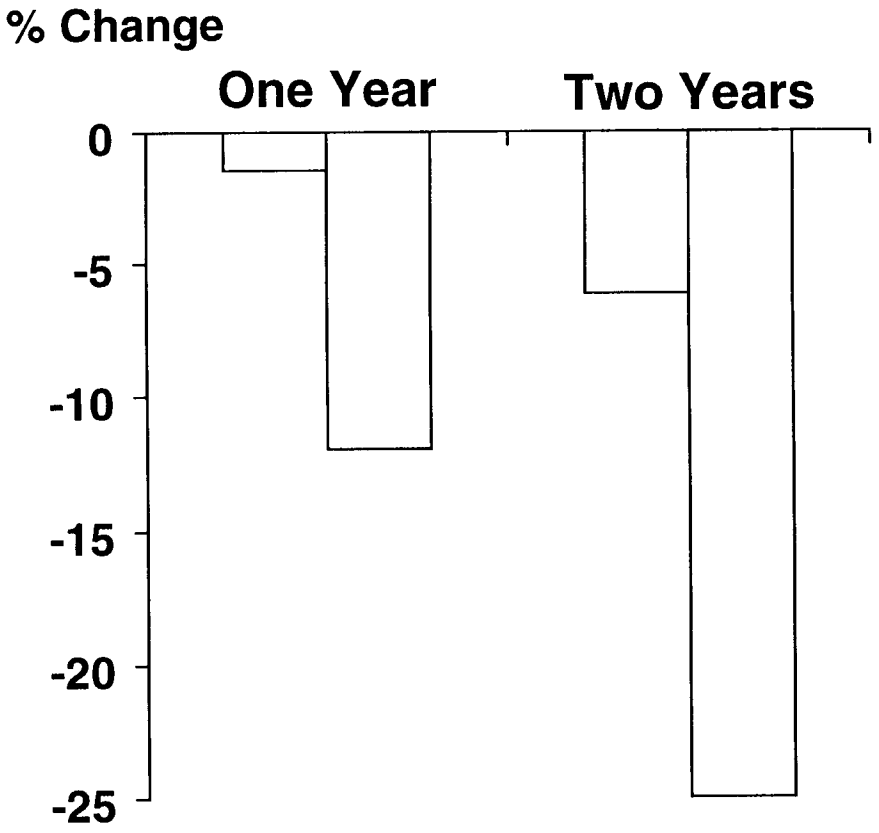
Diastolic Blood Pressure (≥ 90 mmHg) Change From Initial



Orlistat Improves Carbohydrate Metabolism

- Fasting insulin
- Impaired Glucose Tolerance
- Diabetic control

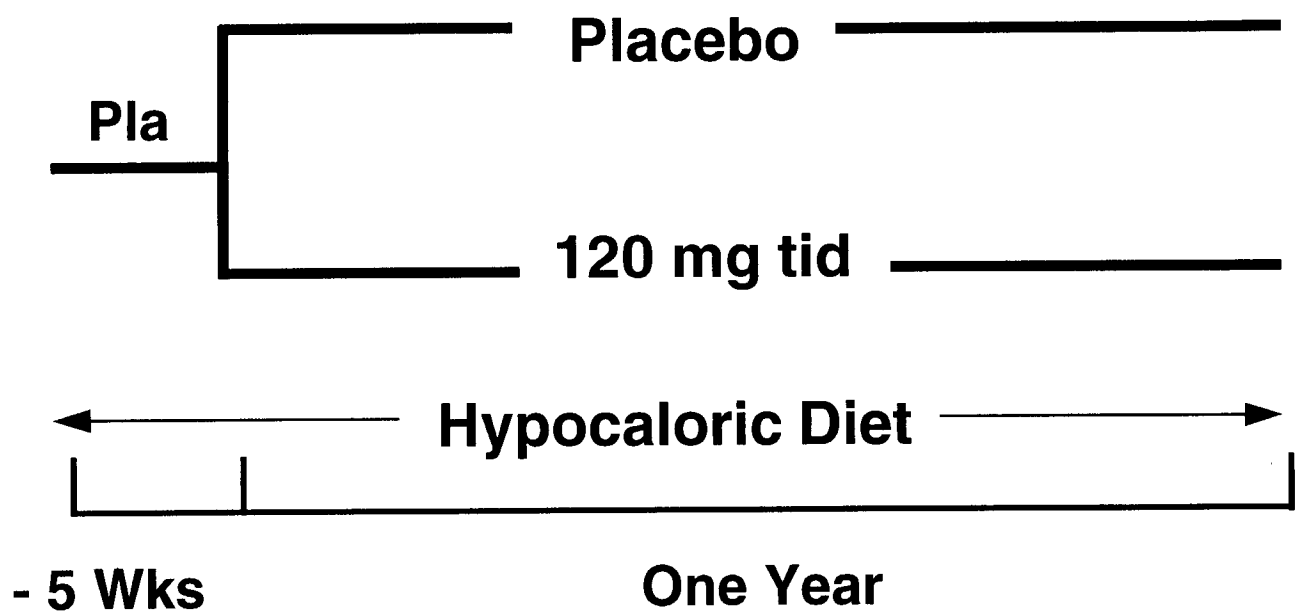
Fasting Insulin (≥ 90 pmol/L)
Mean Percent Change from Baseline



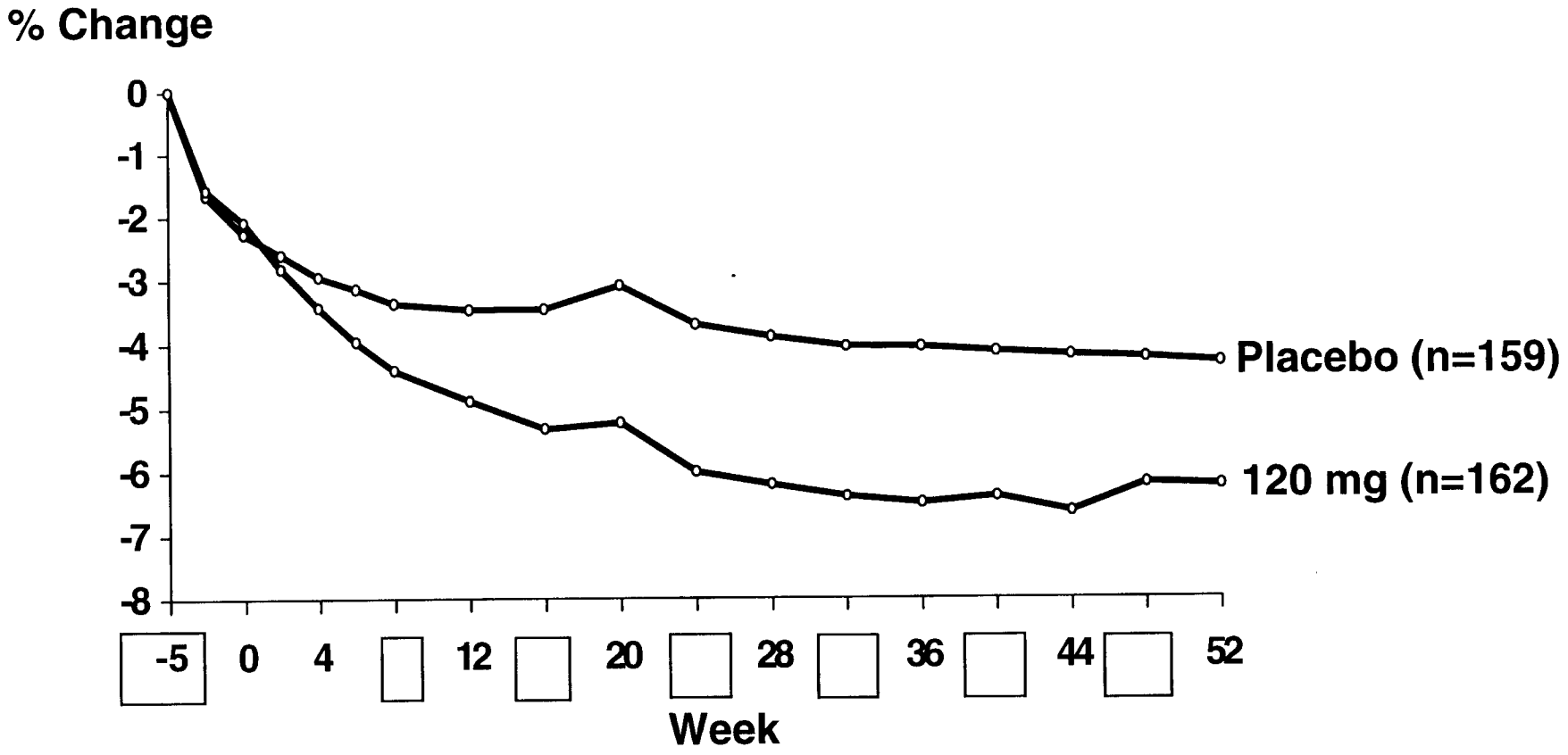
Change of OGTT Status
Patients Impaired at Baseline

Impaired	N	Normal %	Diabetic %
	Year One		
Placebo	48	45.8	10.4
120 mg	115	72.2	2.6
	Two Years		
Placebo	40	47.5	7.5
120 mg	60	71.7	1.7

Study NM14336
Obese NIDDM Patients Maintained on Oral Hypoglycemic Agents



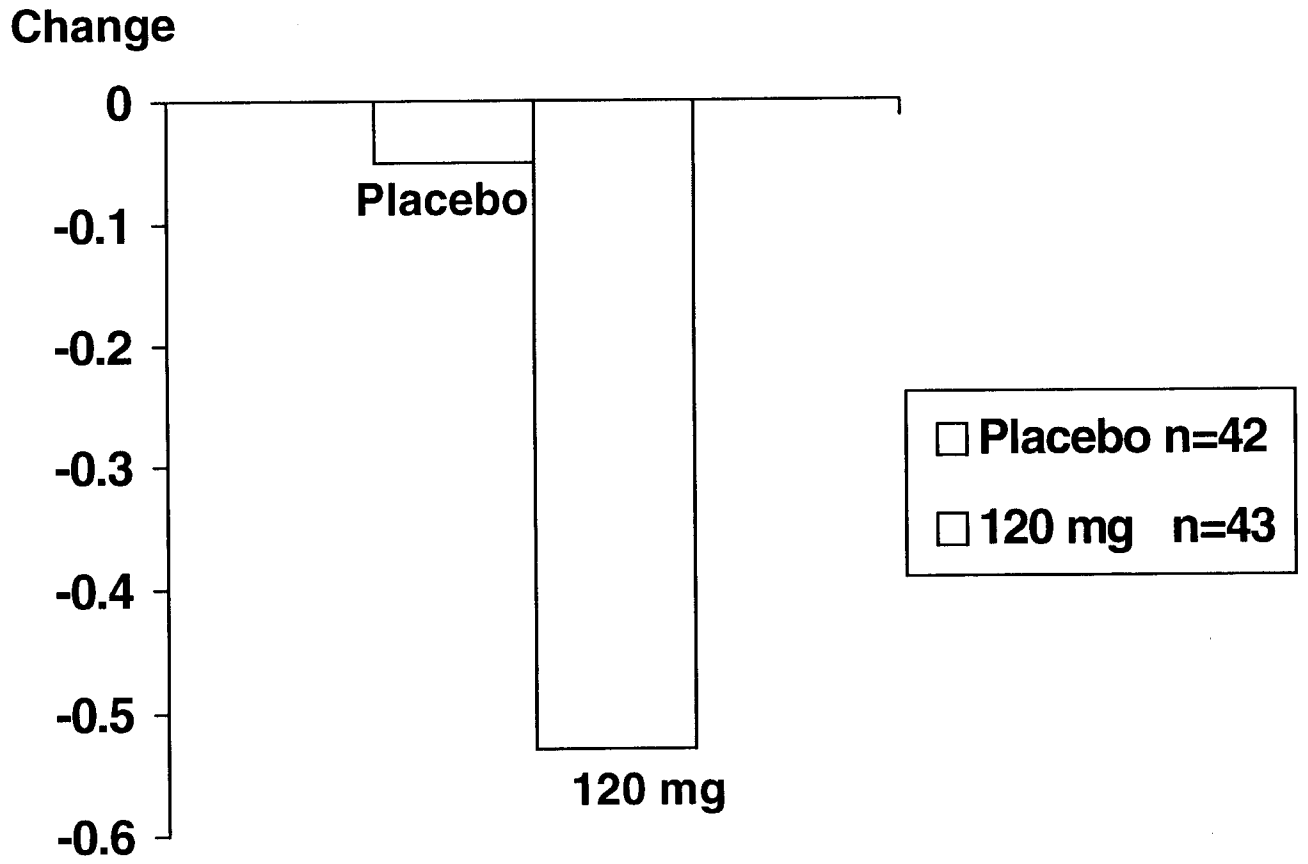
Mean Percent Change from Initial Body Weight



Sulfonylurea Treatment

	Placebo (N = 159) %	120 mg (N = 162) %
Medication Withdrawn	7.5	11.7
Dose Decreased	21.4	31.5
Dose Increased	15.7	7.4
Patient Withdrawn	8.8	2.5

HbA1c (>8%)
Change from Baseline



LSM Percent Difference from Placebo

Total Cholesterol	-9.1%
LDL-Cholesterol	-12.8%
Triglycerides	-10.6%

Orlistat Safety and Tolerability Profile Established During Two Years of Treatment

Extent of Exposure in Phase III Studies

- 2187 patients received one full year of orlistat treatment
  - 1530 receiving 120mg tid
- 777 patients received two full years of orlistat treatment
  - 510 receiving 120mg tid

Orlistat Pharmacokinetics

- Minimal systemic absorption (less than 1%)
- No evidence of accumulation over two years of monitoring

Withdrawal Rate

	Year One		Year Two	
	Placebo n=1466 %	120 mg n=1913 %	Placebo n=524 %	120 mg n=613 %
Total Patients	35.3	29.1	18.7	18.6
Adverse Event	4.9	8.8	2.5	3.6
Death	0	0.1	0.2	0.2
Treatment Failure	2.6	1.0	2.1	1.0
Lost to follow-up	9.8	7.7	3.6	5.2
Other	17.9	11.5	10.3	8.6

Serious Adverse Events

- Approximately 6% reported in year one and in year two in both treatment groups
- Most were sporadic and isolated occurrences

Most Common Adverse Events

≥ 5% in the orlistat group and twice the frequency of the placebo group

Gastrointestinal Events
120 mg

	Year One n=1913		Year Two n=613	
	Incidence %	Withdrawals %	Incidence %	Withdrawals %
Oily Spotting	26.6	1.7	4.4	0.2
Flatus with Discharge	23.9	0.6	2.1	0.2
Fecal Urgency	22.1	0.3	2.8	0.0
Fatty/Oily Stool	20.0	0.1	5.5	0.3
Oily Evacuation	11.9	0.0	2.3	0.0
Increased Defecation	10.8	0.3	2.6	0.0
Fecal Incontinence	7.7	1.1	1.8	0.2

Other Gastrointestinal Adverse Events
At least 5% Frequency

	Year One		Year Two	
	Placebo n=1466	120 mg n=1913	Placebo n=524	120 mg n=613
Adverse Event	%	%	%	%
Abdominal Pain	15.8	20.5	8.4	7.8
Flatulence	13.1	16.0	3.2	4.4
Liquid Stools	11.4	15.8	6.7	5.9
Stools Soft	6.8	8.8	2.5	2.9
Nausea	7.3	8.1	2.7	3.6
Decreased Defecation	10.8	6.7	2.5	2.9
Infectious Diarrhea	4.4	5.3	1.7	1.6
Dyspepsia	5.3	4.5	3.2	2.0
Any GI Event	56.8	79.8	35.1	41.1

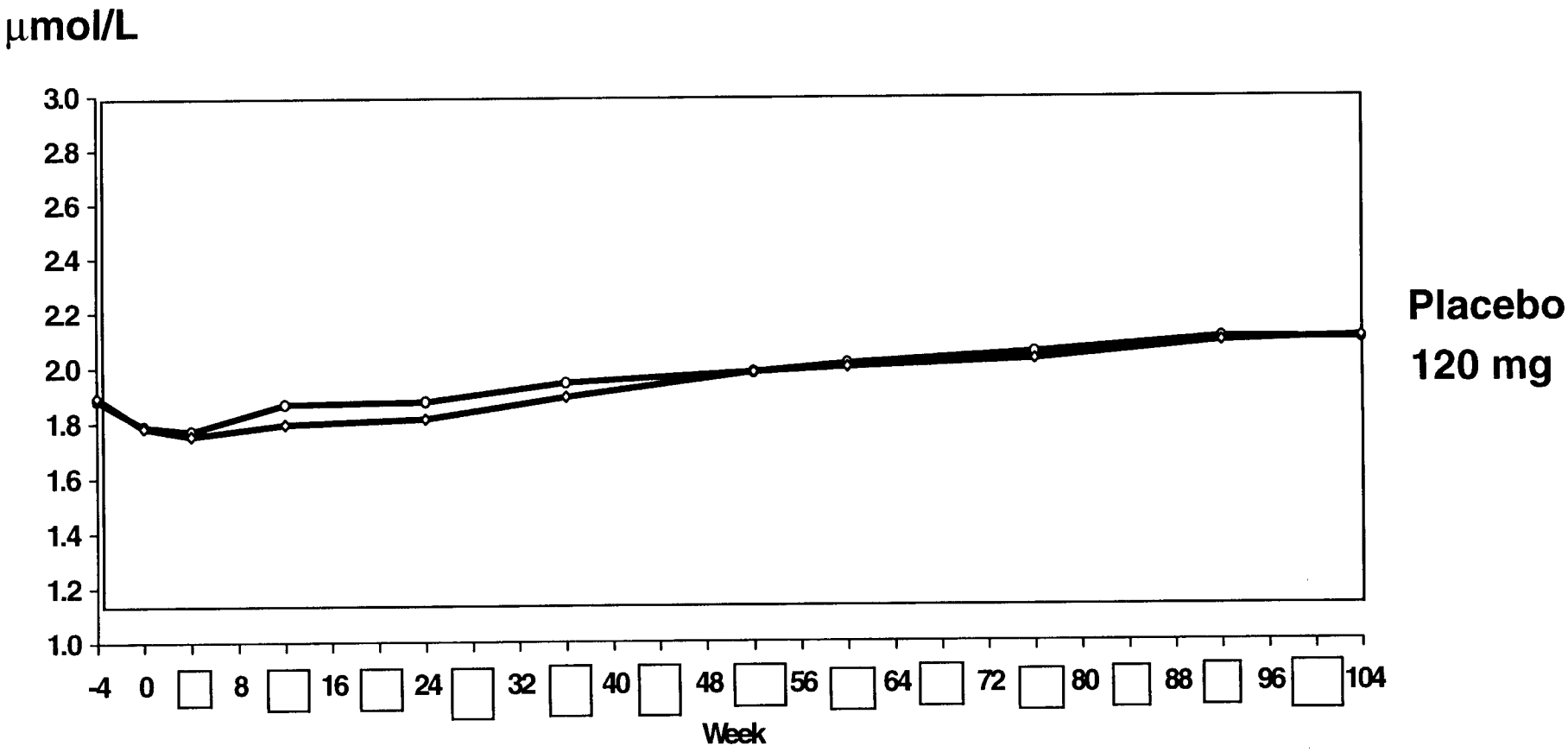
Incidence of Renal Stone Development
Renal Ultrasound

	Year One		Year Two	
	n	%	n	%
Placebo	614	0.2	381	0.8
120 mg	937	0.8	442	0.7

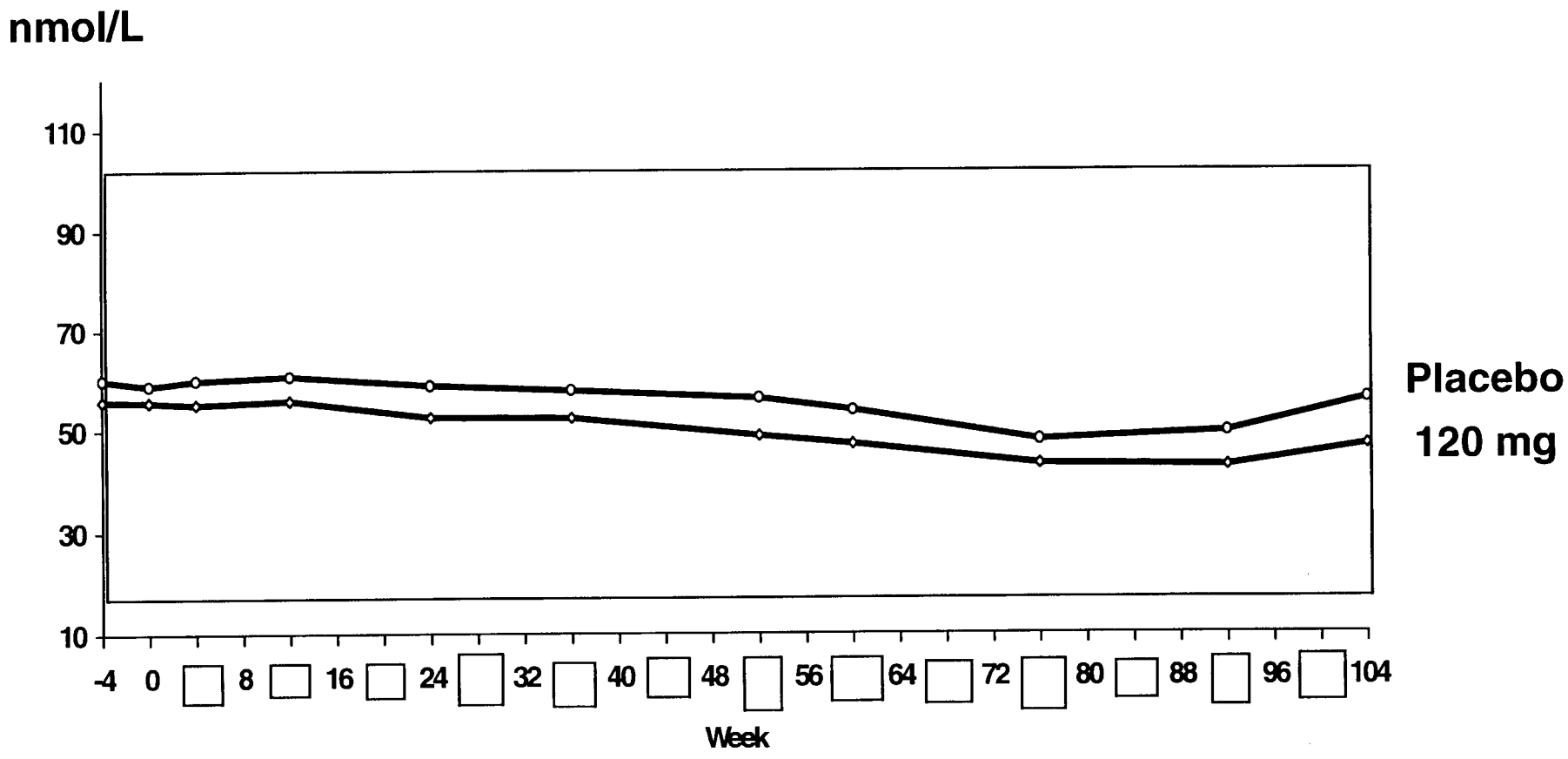
Fat Soluble Vitamins and Carotenoids

- Vitamin A
- Vitamin D
- Vitamin E
- Vitamin K
- Beta-Carotene

Mean Vitamin A Level
(Retinol)



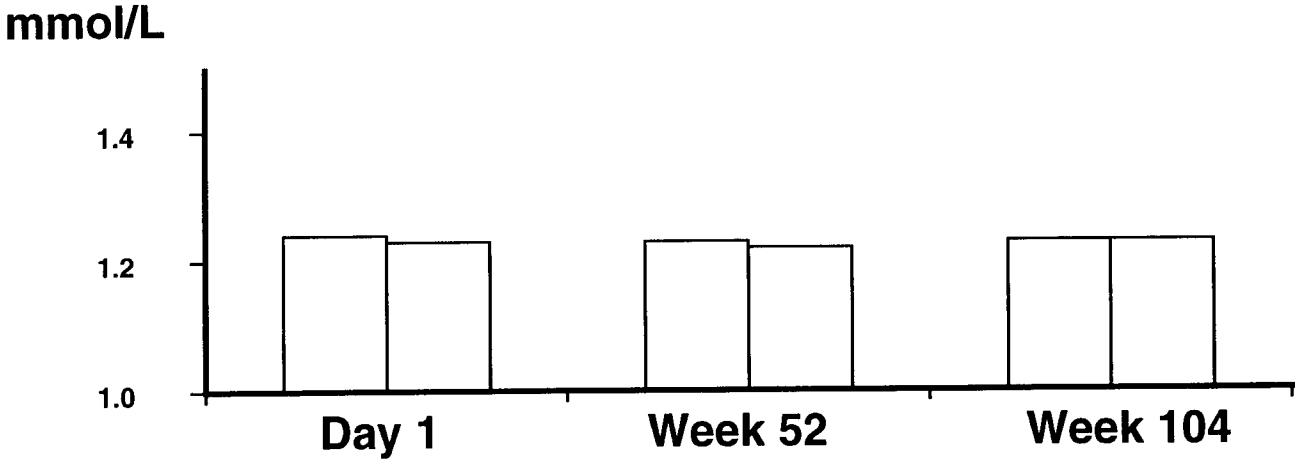
Mean Vitamin D Level
(25-OH-D)



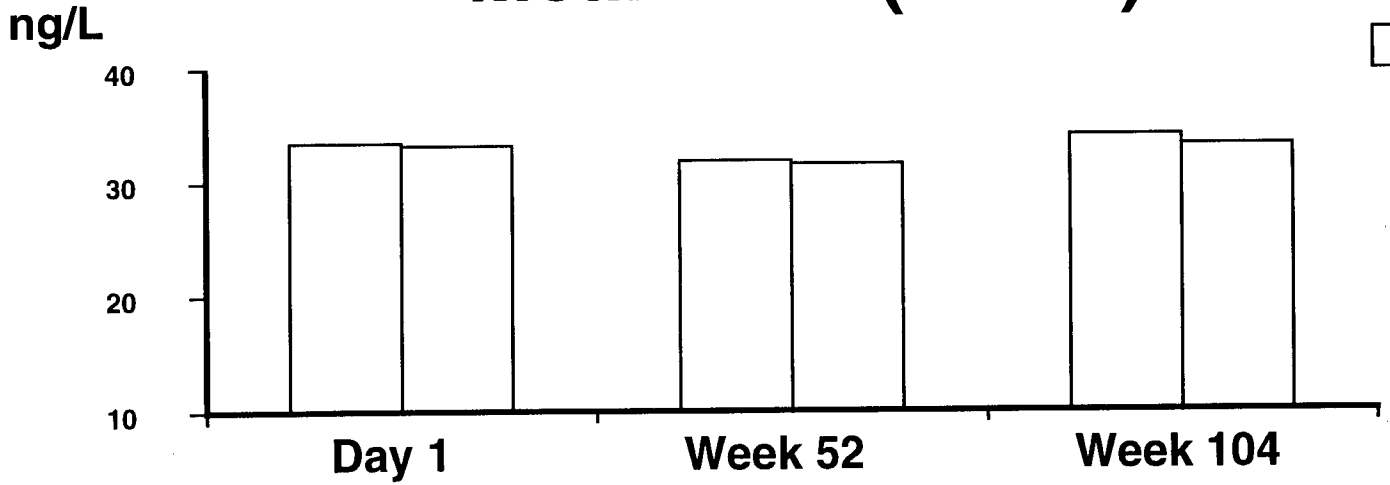
25-OH-D Status Over 2 Years
Patients with Normal Baseline

	Placebo (N=234) %	120 mg (N=285) %
≥ 2 Low Values	13.2	18.2
Received Supplement	8.1	13.0
Last Value Normal	91.9	89.8

Mean Ionized Calcium



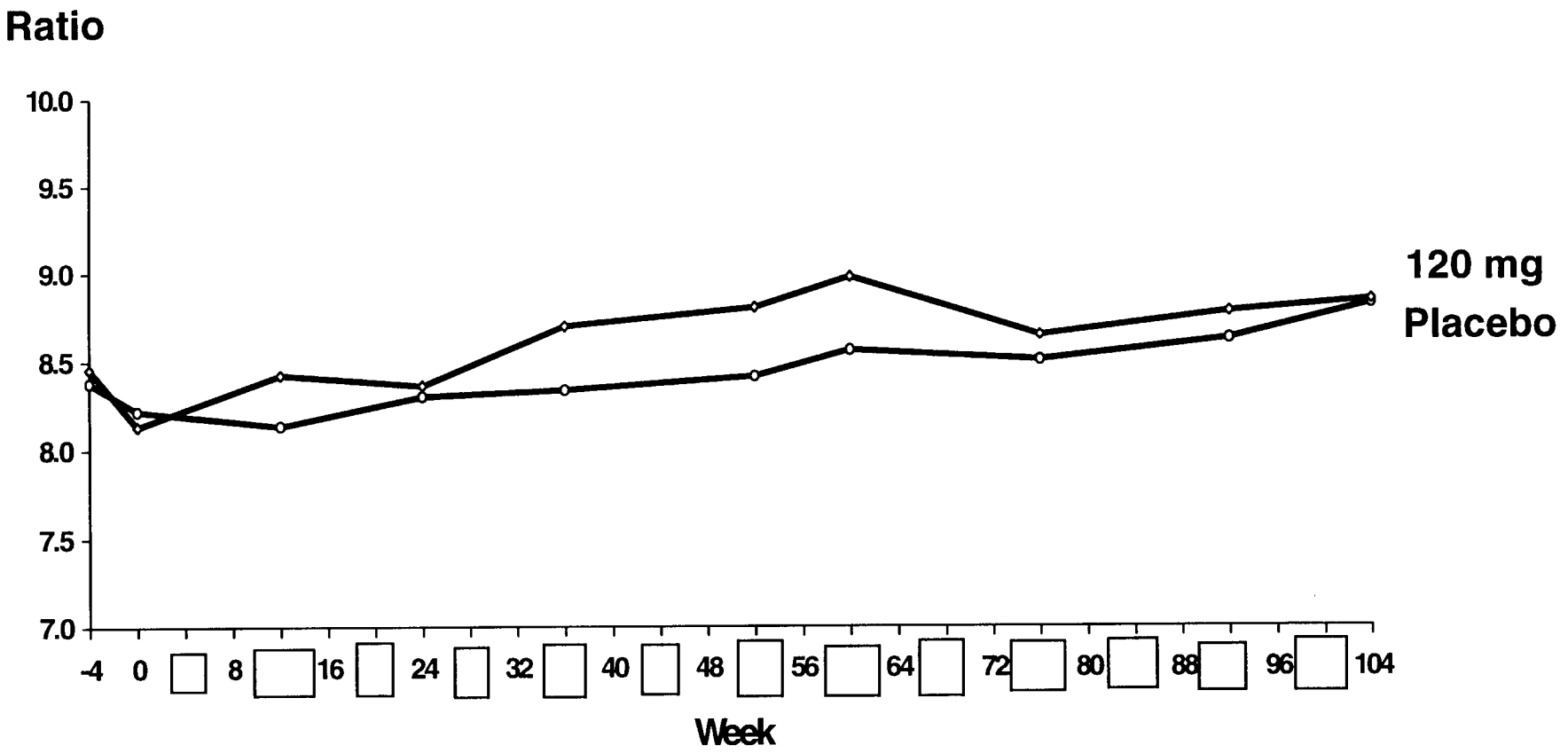
Mean PTH (Intact)



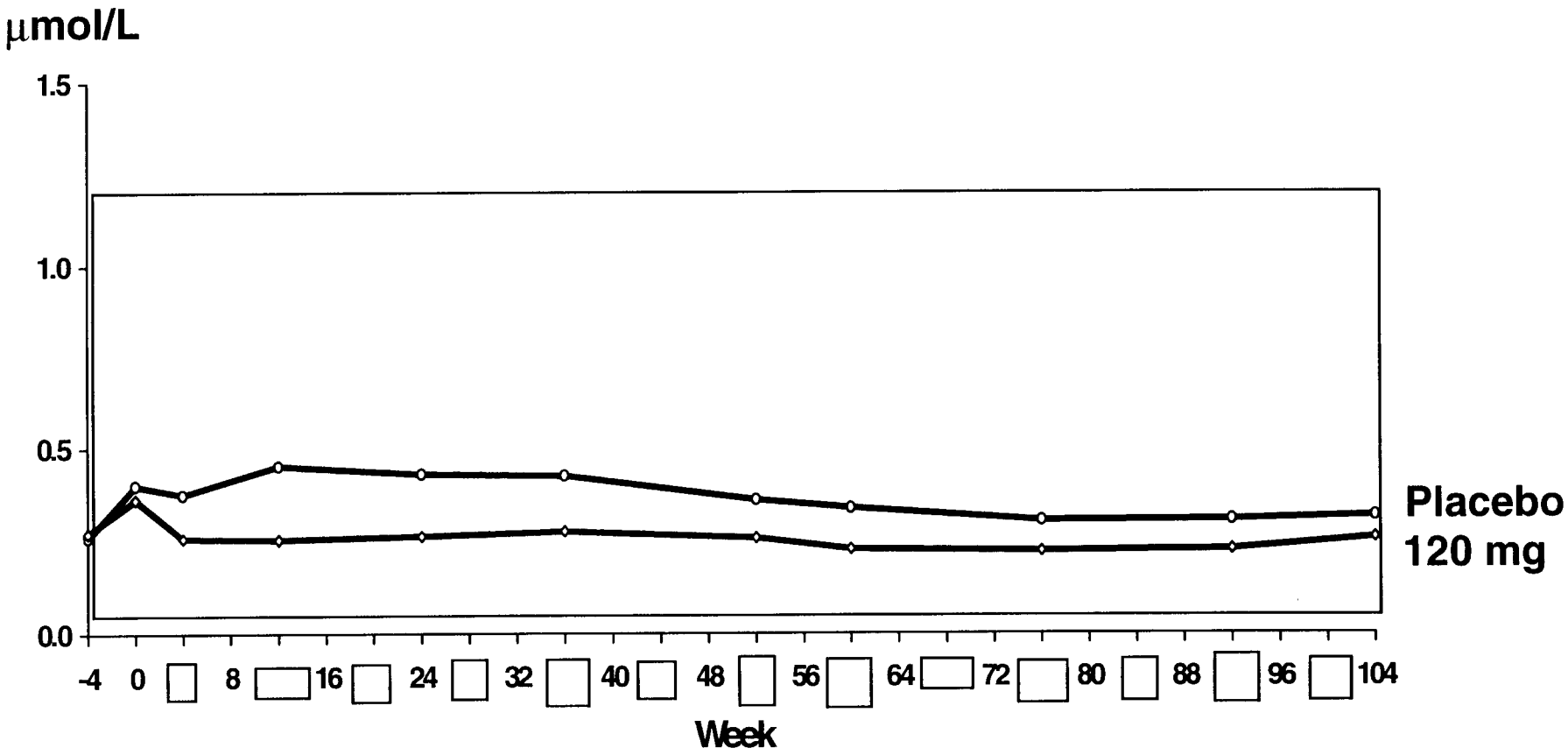
☐ Placebo (n=209)

☐ Orlistat (n=211)

Mean Vitamin E/LDL Cholesterol Ratio



Mean Beta-Carotene Level



Effect of Orlistat on Fat-Soluble Vitamin Levels

- All mean vitamin levels remain within reference range
- Modest decrease in vitamin D and Beta-Carotene levels
- Multivitamin reverses decreased values
- Vitamin supplementation should be given

Safety and Tolerability of Orlistat

- Few clinically significant adverse events
- Well characterized pharmacological effects
  - Limited to gastrointestinal tract
  - Mild to moderate
  - Occurs early
  - Few withdrawals

Orlistat Efficacy on Weight Management

- Produces sustained weight loss
- Diminishes weight regain
- Is effective long-term

Orlistat Efficacy – Risk Factor Improvements

- Improved lipid profiles
- Decreased elevated blood pressure
- Decreased insulin,glucose and c-peptide levels
- Normalized OGTT status
- Improved glycemic control

Martin Huber, M.D.

Clinical Oncology
Hoffmann-La Roche

Observations in Phase III Programs

- No imbalance in cancers overall
- Imbalance in breast cancer cases
- No breast cancer in women <45

Imbalance in Breast Cancer was Unexpected

- Obesity and breast cancer
- Preclinical Data
- No reports in Phase II
  - 917 women in Phase II
  - 652 on orlistat

Possible Explanations for the Imbalance

- Causality (Initiator)
- Stimulation of pre-existing tumors
- Detection effect
- Chance

Procedures for Assessing Breast Cancer Reports

- Surveys of women ≥45 years of age
- Detailed epidemiologic analyses
- Complete review of preclinical data
- Review of source materials by breast cancer experts

Survey of Women ≥45 in Phase III Trials

- Survey #1 - Assessed the incidence of breast cancer after study
- Survey #2 - Gathered risk factor information

Incidence of Breast Cancer Reported in Orlistat Studies and Follow-Up Period

Treatment Group	Number of reported cases			Number of Women	
	During Trial	During FU Survey	Total	All	≥ 45
Placebo	1	2*	3	1194	579
Orlistat 30/60 mg	1	0	1	648	316
Orlistat 120 mg	9	2	11	1552	747
Total	11	4	15*		

Breast Cancer
Areas of Investigation

Epidemiology	**James Schlesselman, PhD**
Preclinical	**Tim Anderson, DVM, PhD**
Clinical	**Martin Huber, MD**
Histopathology	**James McGee, MD, PhD**

Epidemiology Review

Dr. James Schlesselman

Professor of Epidemiology and
Public Health
Chief, Division of Biostatistics
Sylvester Comprehensive Cancer Center
University of Miami, FL

Biologic effect ... implausible

Breast cancer during clinical trial
Women ≥ 45 years

Treatment Group	No. of Pts	Person-Years of Follow-up	No. of Observed Cases	Relative Risk	95% CI
Placebo	579	713	1	1.0	
Orlistat 30/60 mg	316	395	1	1.8	0.0-142
Orlistat 120 mg	747	1096	9	5.9	0.8-257

Breast cancer during clinical trial and survey Women ≥ 45 years

Treatment Group	No. of Pts	Person-Years of Follow-up	No. of Observed Cases	Relative Risk	95%CI
Placebo	579	1853	2	1.0	
Orlistat 30/60 mg	316	975	1	1.0	0.0-18
Orlistat 120 mg	747	2840	11	3.6	0.8-33

Breast cancer during clinical trial
Women ≥ 45 years

Treatment Group	No. of Pts	Person-Years of Follow-up	No. of Observed Cases	Relative Risk	95% CI
Placebo	579	713	1	1.0	
Orlistat 30/60 mg	316	395	1	1.8	0.0-142
Orlistat 120 mg	747	1096	9	5.9	0.8-257

Relative risk declines with follow-up

- No tumor initiation
- Growth stimulation unlikely

- Women not under continuous surveillance for breast cancer during trial
- No tumor detection method is perfectly sensitive to disease
- Tumors at different stage of growth at time of stimulation

Summary of survey results
Women ≥ 45 years

Treatment Group	Survey Period							
	No. Pts	No. Pts Completed Survey		Person-Years Follow-Up	No. Pts with Mammograms		No. Cases Breast Cancer	No. Cases Breast Cancer in Trial
		N	(%)		N	(%)		
Placebo	579	509	(88)	1140	399	(78)	1	1
Orlistat 30/60 mg	316	280	(89)	580	222	(79)	0	1
Orlistat 120 mg	747	665	(89)	1744	536	(81)	2	9

Breast cancer during clinical trial and survey including third placebo case Women ≥ 45 years

Treatment Group	No. of Pts	Person-Years of Follow-up	No. of Observed Cases	Relative Risk	95%CI
Placebo	579	1853	3	1.0	
Orlistat 30/60 mg	316	975	1	0.6	0.0-8
Orlistat 120 mg	747	2840	11	2.4	0.6-13

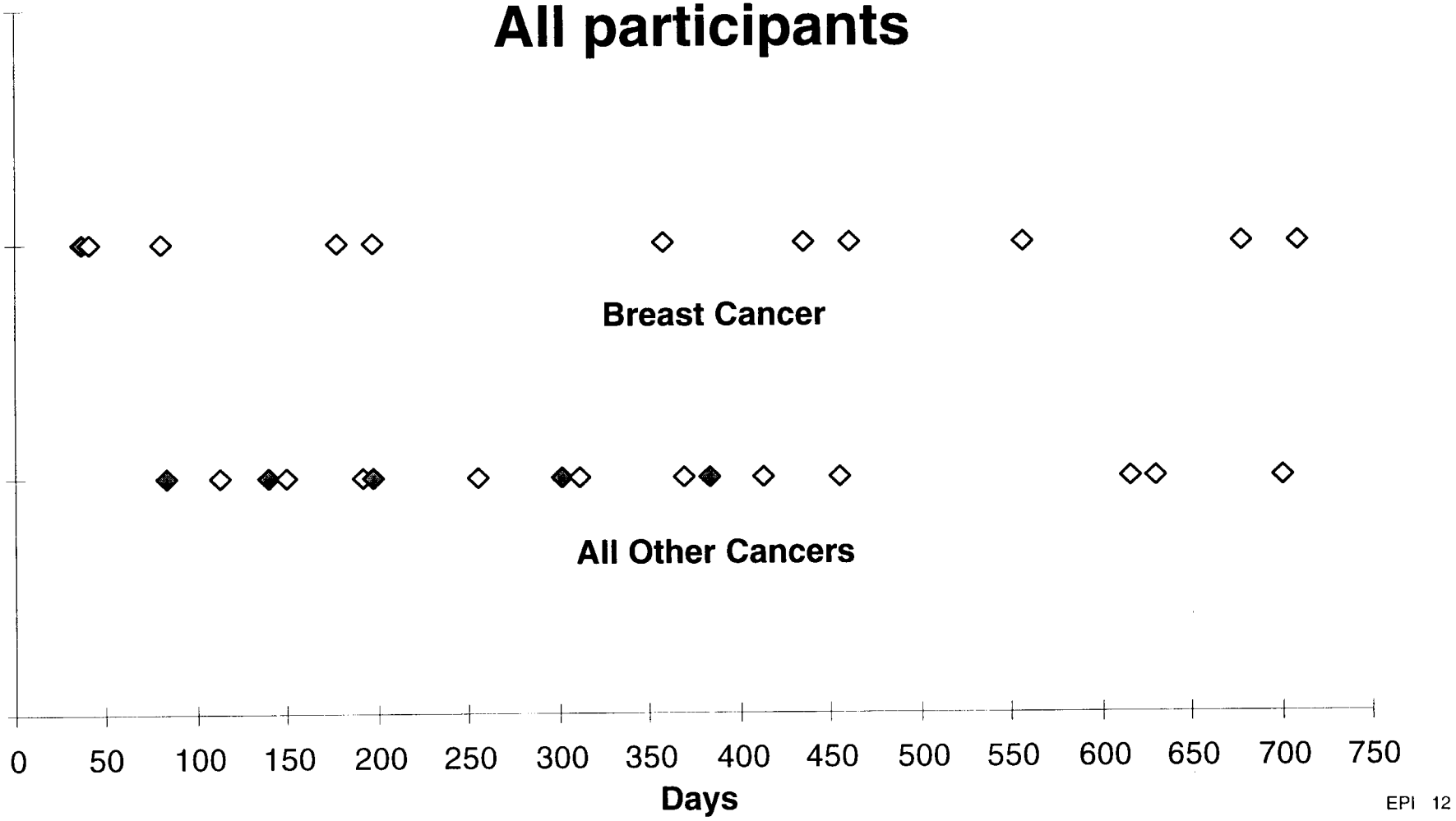
Breast cancer during clinical trial
All cases after first 6 months of treatment
Women ≥ 45 years

Treatment Group	No. of Pts	Person-Years of Follow-up	No. of Observed Cases	Relative Risk	95%CI
Placebo	579	449	1	1.0	
Orlistat 120 mg	747	729	6	3.7	0.4-170

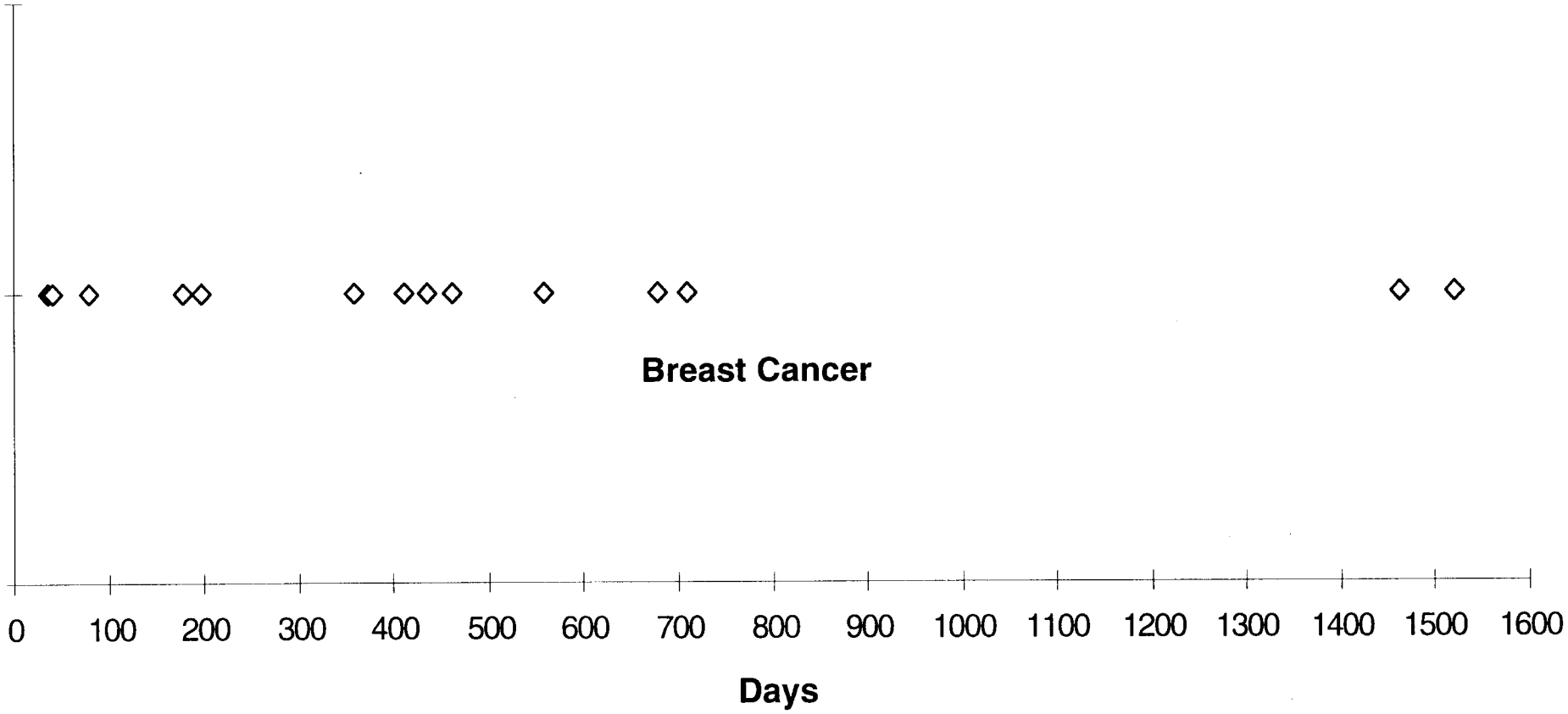
Breast cancer during clinical trial and survey
All cases after first 6 months of treatment
Women ≥ 45 years

Treatment Group	No. of Pts	Person-Years of Follow-up	No. of Observed Cases	Relative Risk	95%CI
Placebo	579	1589	2	1.0	
Orlistat 120 mg	747	2473	8	2.6	0.5-25

Time from randomization to diagnosis
Clinical trial period
All participants



Time from randomization to diagnosis
Clinical trial and survey



Potential explanations

- Confounding
- Bias
- Cause-effect
- Chance

Potential explanations

- Confounding - unlikely
- Bias
- Cause-effect
- Chance

Summary of breast cancer risk factors Women ≥ 45 years

Risk Factor	Placebo	Orlistat 30/60 mg	Orlistat 120 mg
History (Mother)	5%	8%	7%
History (Sister)	7%	5%	5%
Nulliparity	9%	8%	9%
Miscarriage (ever)	32%	27%	29%
Breast Biopsy (ever)	16%	16%	18%
Hormone Replacement	52%	61%	56%
Menarche *	12.6	12.6	12.6
Menopause *	47.6	47.6	46.8
First Live Birth *	23.1	23.2	23.2

* Average age in years

Potential explanations

- Confounding
- Bias - possible
- Cause-effect
- Chance

Potential explanations

- Confounding
- Bias
- Cause-effect - implausible
- Chance

Potential explanations

- Confounding - unlikely
- Bias - possible
- Cause-effect - implausible
- Chance

Conclusion

On the evidence available, chance is the most plausible explanation for the breast cancer findings

Breast Cancer
Areas of Investigation

Epidemiology	**James Schlesselman, PhD**
Preclinical	**Tim Anderson, DVM, PhD**
Clinical	**Martin Huber, MD**
Histopathology	**James McGee, MD, PhD**

No Evidence in Preclinical Studies that Orlistat has any Carcinogenic Potential

- Genotoxicity studies
- Animal carcinogenicity studies
  - 2 year study in rats
  - 2 year study in mice

No Genotoxicity Seen in Orlistat Studies

Orlistat was tested in the following assays:

- Ames test +/- metabolic activation
- V79/HPRT assay in Chinese hamster ovary cells ± metabolic activation
- Unscheduled DNA Synthesis in Rat Hepatocytes
- Human Chromosome Aberrations ± metabolic activation (in vitro assay)
- Mouse Micronucleus Test (in vivo assay)

Animal Studies Are Suitable to Assess Risk - Multiples of Human Exposure*

	Species		
Parameter	Mouse	Rat	Dog
Dose (mg/kg/day)	1500	1000	1000
Duration	2-yrs	2-yrs	1-yr
Orlistat (C_{max}, ng/ml)	12X	730X	130X
M1 Metabolite (C_{max}, ng/ml)	18X	49X	4X
M3 Metabolite (C_{max}, ng/ml)	24X	5X	1X

*120 mg tid to a 70 kg adult
Orlistat = 4ng/ml, M1 = 25 ng/ml, M3 = 92 ng/ml

Carcinogenicity Study in Rats
Incidence of Mammary Neoplasms

Dose (mg/kg/day)	Adenoma	Carcinoma	Fibroadenoma
0	0/50	2/50	14/50
0	1/49	1/49	15/49
150	0/50	2/50	9/50
500	1/47	0/47	9/47
1000	1/49	2/49	3/49*

*$P \leq 0.01$

Carcinogenicity Study in Mice
Incidence of Mammary Neoplasms

Dose (mg/kg/day)	Adenocarcinoma
0	3/49
0	2/50
25	0/49
375	1/49
750	0/49
1500	0/49

Preclinical Evaluation

Orlistat did *not* initiate or promote tumors

No evidence for stimulation of mammary gland or mammary tumors by orlistat.

- Rodent carcinogenicity studies
- Hormonal effects
  - chronic toxicity studies
  - reproductive toxicity studies

No Growth Stimulation or Change in Time to Detection of First Palpable Mammary Masses

Rat Carcinogenicity study

Dose (mg/kg/d)	No. Examined	No. with Palpable Mass	% Incidence	Mean Masses /Rat	Week of First Observation
0	50	17	34	0.44	31
0	50	20	40	0.56	66
150	50	10	20	0.30	55
500	50	8	16	0.18	59
1000	50	5	10	0.12	69

No Histologic Effects of Orlistat on Hormone-Responsive Tissues

No changes observed in mammary tissue, testes, ovaries, vagina, or uterus in:

- **Mice - 2-Years - 1500 mg/kg**
- **Rats - 2-Years - 1000 mg/kg**
- **Dogs - 1-Year - 1000 mg/kg**

No Evidence of Hormonal Activity in Reproductive Studies

- Segment I - Fertility Study in Rats - 400 mg/kg
- Segment II - Teratogenicity in Rats - 800 mg/kg
- Segment II - Teratogenicity in Rabbits - 800 mg/kg
- Segment III - Peri-natal Effects in Rats - 400 mg/kg

"I conclude that the nonclinical studies with Orlistat provide no findings to suggest any human cancer hazard, and in particular, any potential for enhancing or accelerating breast cancer development".

Dr. Gary Williams, MD
Director, Naylor Dana Institute
American Health Foundation

Orlistat Shows No Evidence of Carcinogenic Potential in Animal Studies

- Systemic exposure to orlistat and its metabolites is much higher than in humans
- Not genotoxic
- No increased incidence of mammary adenomas or carcinomas in rats or mice
- Decreased incidence of mammary fibroadenomas
- Not carcinogenic at any other site in rats or mice

Orlistat Did Not Stimulate Mammary Gland or Tumor Growth in Animal Studies

- No hormonal activity in toxicity or reproductive toxicity studies
- No growth stimulation in normal mammary tissue
- No growth enhancement of spontaneous rodent mammary tumors

Breast Cancer
Areas of Investigation

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Preclinical	**Tim Anderson, DVM, PhD**
Clinical	**Martin Huber, MD**
Histopathology	**James McGee, MD, PhD**

Clinical Data

- Natural history
- Mammography
- Vitamin levels
- Estrogen levels

Time from Randomization to Diagnosis

Patient	Day of Diagnosis
BM14149 / 6-60	36
NM14185 / 41-120	41
NM14302 / 68-120	80
NM14302 / 40-120	178
BM14149 / 7-120	198
BM14149 / 65-120	358
NM14185 / 70-PLA	412
NM14185 / 28-120	436

Patient	Day of Diagnosis
BM14149 / 10-120	475
BM14149 / 23-PLA	557
NM14185 / 66-120	678
NM14161 / 18-120	709
BM14119C / 17-120	1462
BM14149 / 22-PLA	1474
NM14185 / 8-120	1520

Radiology Review

- Independent review of available mammograms
  - Post-randomization on 14 of 15 patients
  - Pre-randomization on 9 of 15 patients
- 6 of the 9 patients had evidence of a lesion prior to treatment
  - 1 of 3 patients on placebo
  - 5 of 6 patients on orlistat

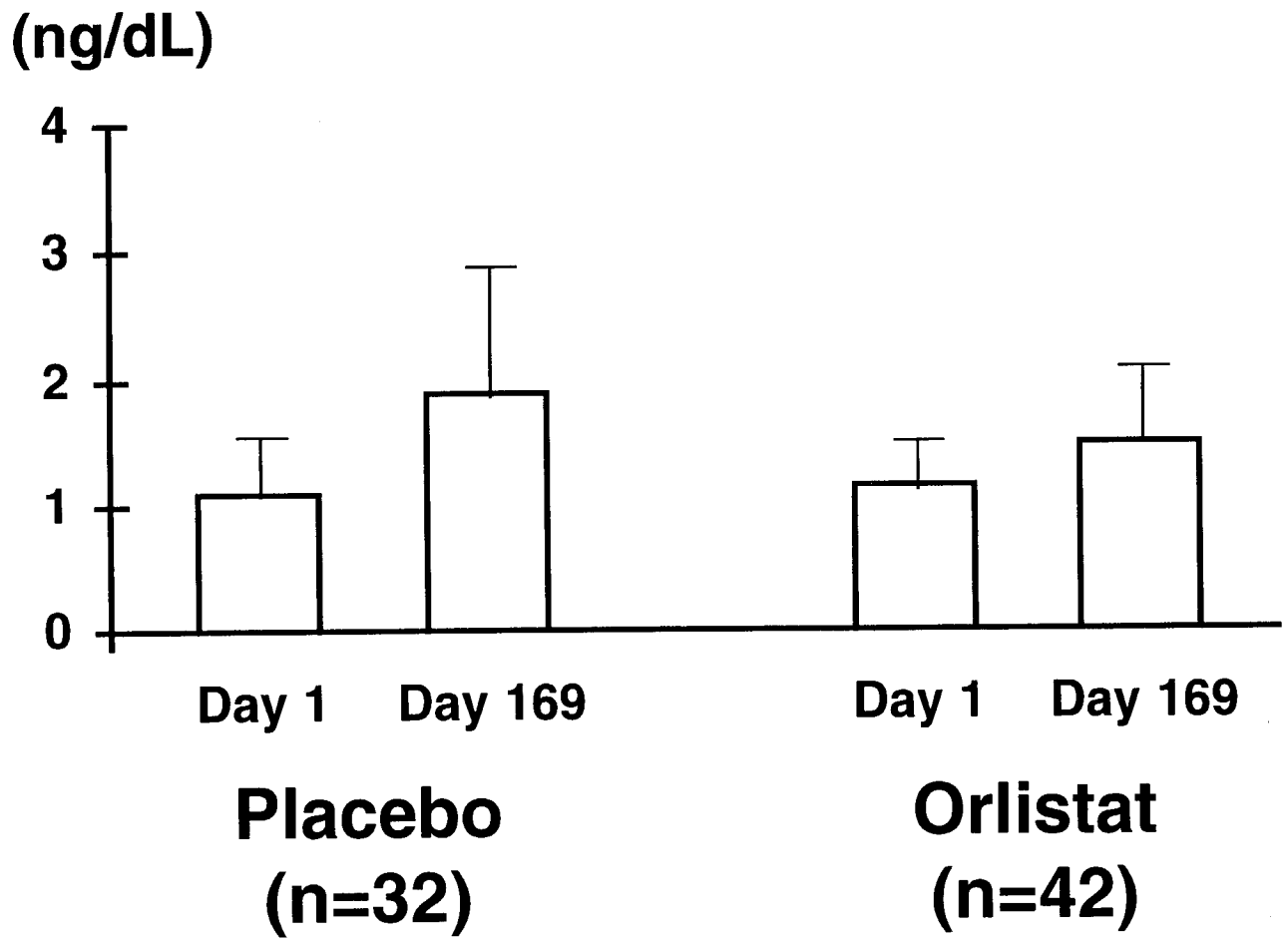
Vitamin Levels in Breast Cancer Patients

- Vitamin E: Almost all measurements within reference range
- Vitamin A: All within reference range
- Vitamin D: Almost all measurements within reference range
- Beta carotene: All within reference range

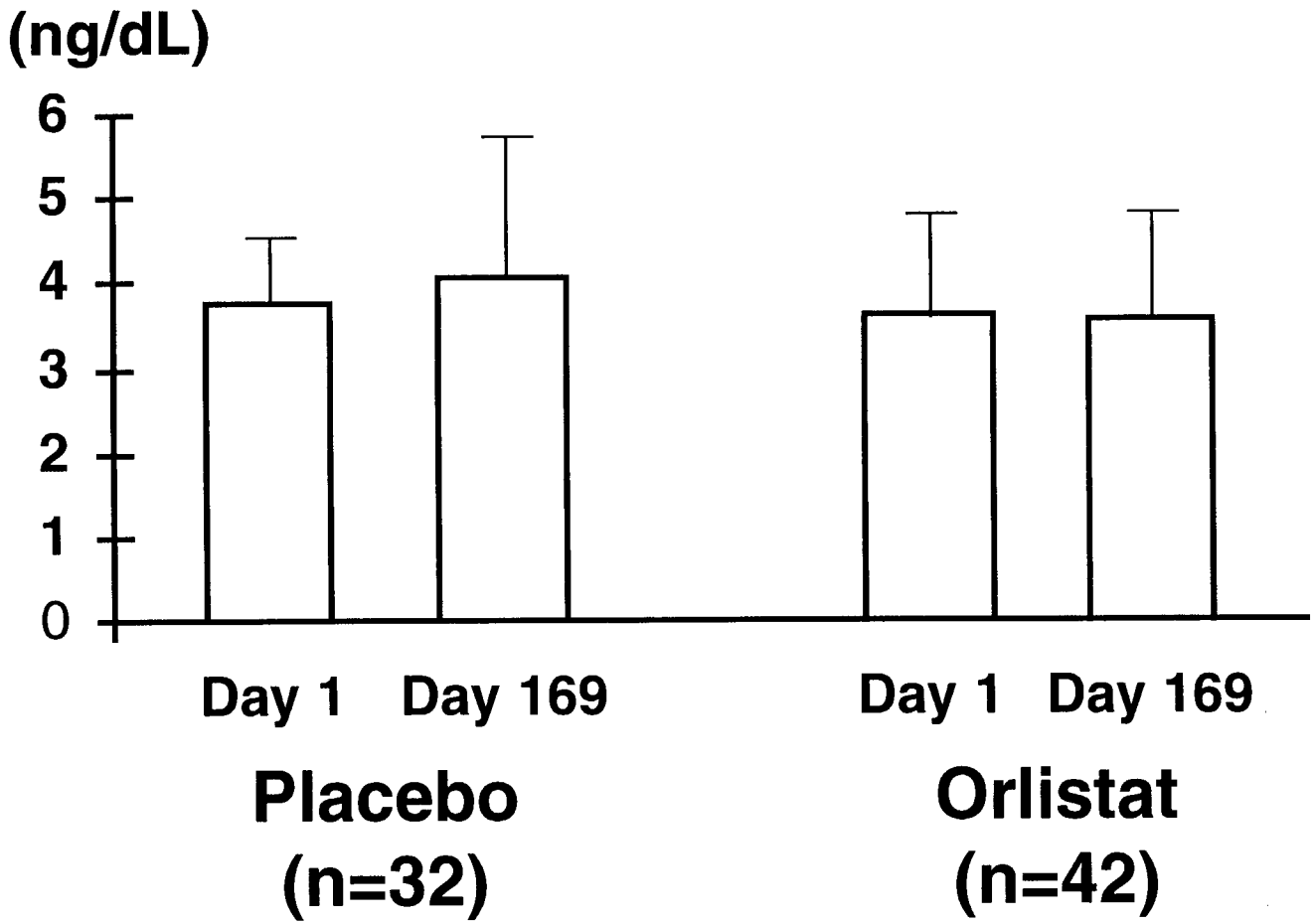
Demographics - Women ≥45 years and FSH >30 IU/ml

	Placebo (32)	120 mg (45)
Age		
median	55	58
range	47-76	45-78
BMI (kg/m^2)		
mean	35.7	35.5
range	29-43	28-43
Weight change (kg)		
mean	-2.0	-6.2
SD	3.5	5.6

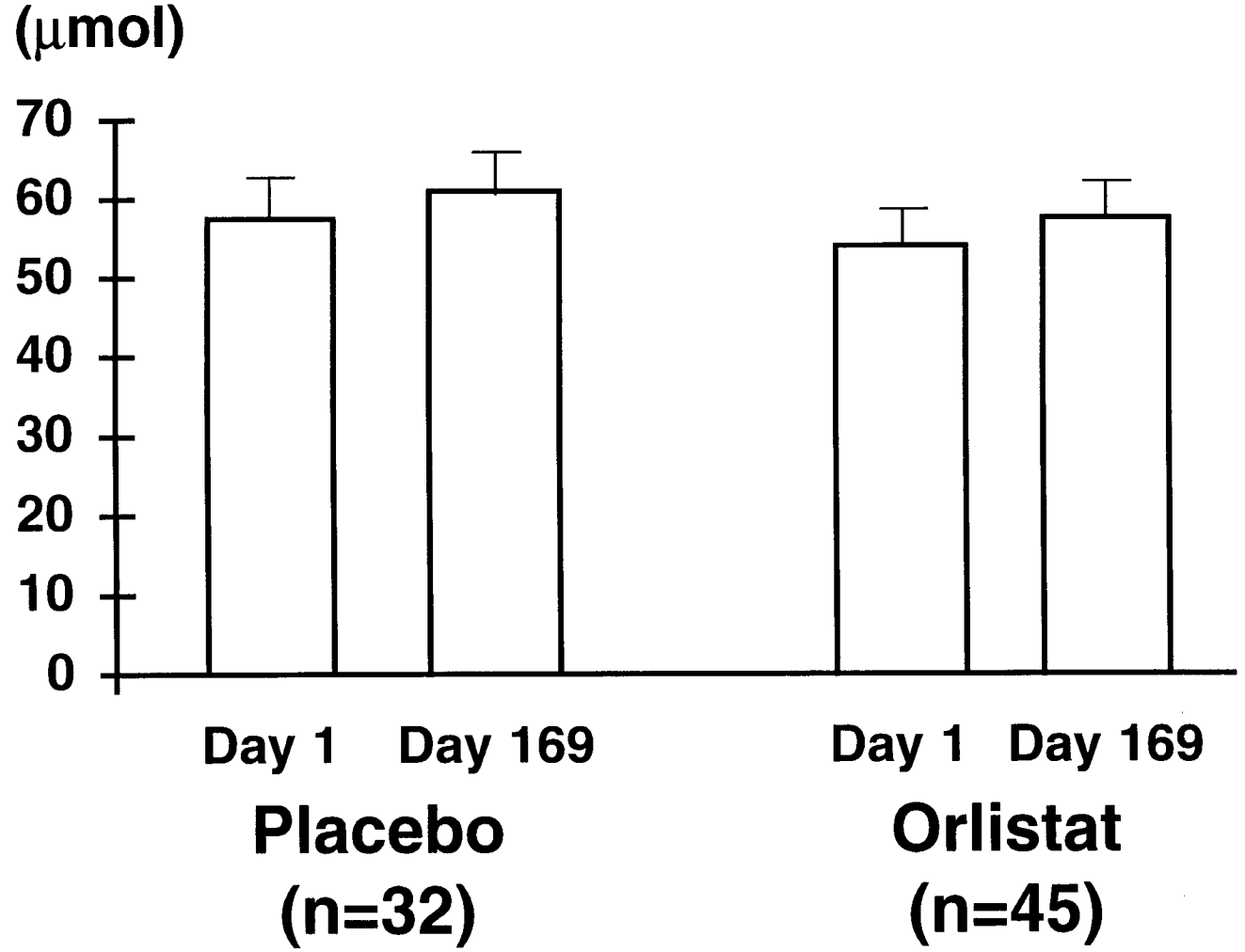
Plasma Estradiol



Plasma Estrone



Serum Sex Hormone Binding Globulin (SHBG)



Clinical Conclusions

- Majority of tumors present at time of randomization
- Vitamin levels normal
- Estrogen levels not increased

Breast Cancer
Areas of Investigation

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Clinical	**Martin Huber, MD**
Histopathology	**James McGee, MD, PhD**

Professor James O'D McGee*, MD, PhD

Chairman Nuffield Department of Pathology and Bacteriology University of Oxford U.K.

*Molecular Pathology of Breast Cancer

*UK National Breast Sceening Pathology Group; Laboratory diagnostic and quality assurance guidelines for breast disease diagnosis. (European Union, Australasia, etc)

Breast Cancer Issues in Orlistat Trials

- Issue One
  - Does orlistat cause breast cancer?
- Issue Two
  - Does orlistat enhance the growth of breast cancer?

Breast Cancers Detected in the Orlistat and Follow-Up Trials: The Issues

NUMBER OF REPORTED CASES

Treatment	During Trial	During FU* Survey	Total	Women (> 44 yrs)
Placebo	1	2	3	579
Orlistat 30/60 mg	1	0	1	316
Orlistat 120 mg	9	2	11	747
Total	11	4	15	1642

* FU = Follow-Up

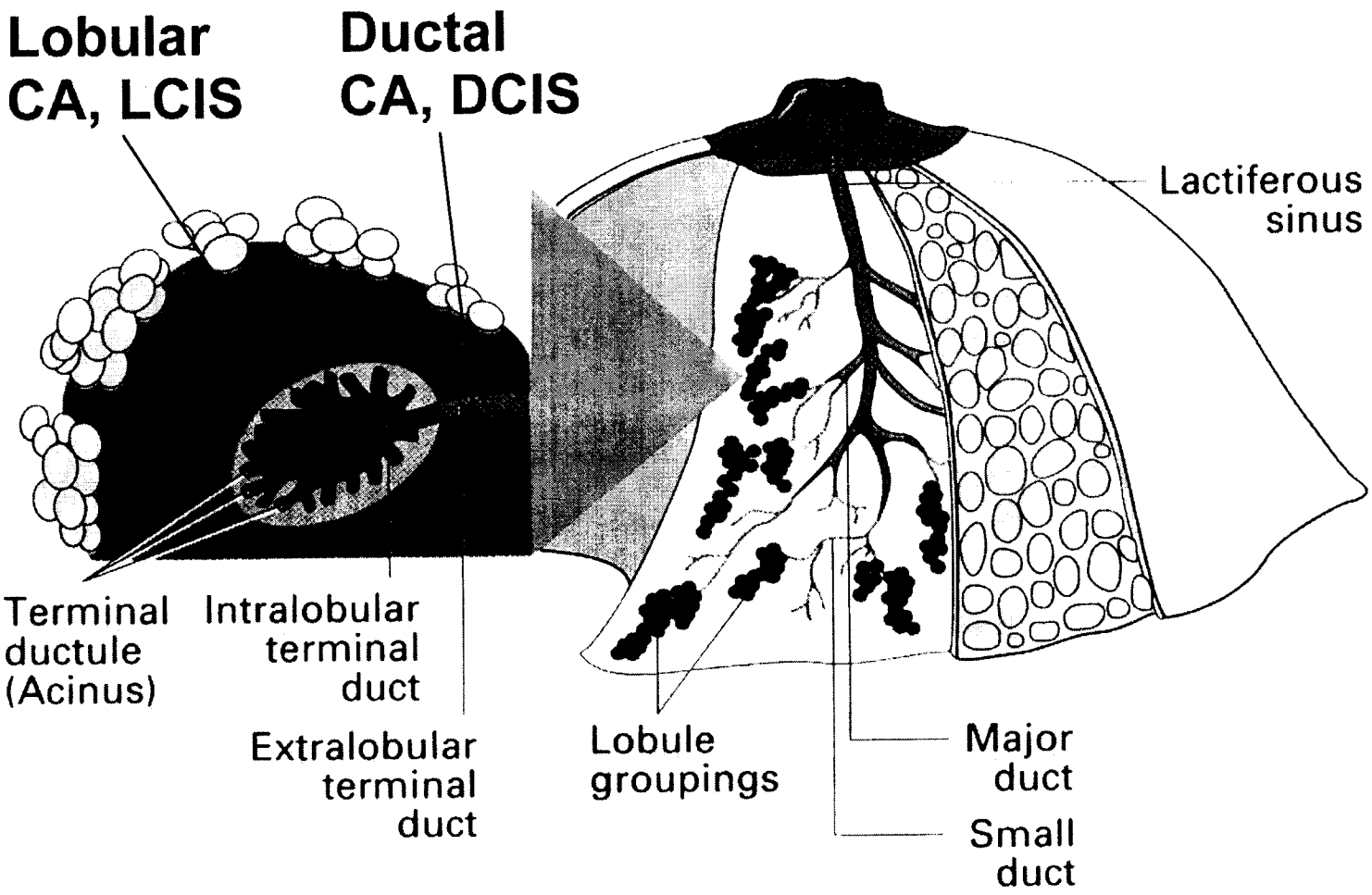
Issue One

Evidence will now be presented indicating that orlistat is not causally related to breast cancer initiation of promotion.

Breast Cancer Causality in Orlistat Trials: Study Design

- "Blinded". To *all* data.
- Analysis of all histologic slides (USA, Finland, Holland, Germany, Sweden, Austria).
- Remarkably all microscopic slides, from all patients, were available for analysis.
- "Unblinded". The report integrates my views and information from other reports.

Histopathologic Terminology



Criteria Used to Determine Causality and Relationship to Treatment

1. Carcinoma in situ (LCIS and DCIS)
   - Increases the risk of breast cancer 10X
   - Over a period of 20-30 years in 25% of women
2. Tumor classification
   - Type
   - Grade
   - Lymph node mets
   - Tumor size

Tumor Size

- Breast cancer requires 9-17 years to grow from a single cell to a clinically detectable mass (~10mm)
- 30 volume doublings required for a 10mm tumor mass (2 x diameter = 8 x volume of a "sphere")

Tumor Size (cont'd)

- Tumor size at time of randomization was calculated
  - Peers et al, 1993; Dutch Breast Screening Clinical Data
  - Tumor volume doubling time occurs on average every 157 days (121-204 days)

Tumor Parameters: Relationship to Treatment

TREATMENT
120 mg
60 mg
Placebo

Tumor Parameters: Relationship to Treatment

TREATMENT	DIAGNOSIS (DAY)
120 mg	41
	80
	178
	198
	358
	436
	475
	678
	709
	1462 (FU)
	1520 (FU)
60 mg	36
Placebo	412
	557
	1474

Tumor Parameters: Relationship to Treatment

TREATMENT	DIAGNOSIS (DAY)	CIS
120 mg	41	-
	80	+
	178	+
	198	+
	358	+
	436	+
	475	+
	678	-
	709	+
	1462 (FU)	+
	1520 (FU)	+
60 mg	36	+
Placebo	412	+
	557	-
	1474	+

Tumor Parameters: Relationship to Treatment

TREATMENT	DIAGNOSIS (DAY)	CIS	TUMOR TYPE*
120 mg	41	-	D
	80	+	L
	178	+	L
	198	+	L
	358	+	L
	436	+	D
	475	+	D
	678	-	L
	709	+	D
	1462 (FU)	+	D
	1520 (FU)	+	D
60 mg	36	+	T
Placebo	412	+	L
	557	-	D
	1474	+	D

* D = Ductal; L = Lobular; T = Tubular

Tumor Parameters: Relationship to Treatment

TREATMENT	DIAGNOSIS (DAY)	CIS	TUMOR TYPE*	GRADE (1 - 3)
120 mg	41	-	D	2
	80	+	L	2
	178	+	L	0
	198	+	L	2
	358	+	L	2
	436	+	D	3
	475	+	D	2
	678	-	L	3
	709	+	D	2
	1462 (FU)	+	D	3
	1520 (FU)	+	D	2
60 mg	36	+	T	1
Placebo	412	+	L	2
	557	-	D	3
	1474	+	D	1

* D = Ductal; L = Lobular; T = Tubular

Tumor Parameters: Relationship to Treatment

TREATMENT	DIAGNOSIS (DAY)	CIS	TUMOR TYPE*	GRADE (1 - 3)	LYMPH NODES
120 mg	41	-	D	2	N/A
	80	+	L	2	+
	178	+	L	0	N/A
	198	+	L	2	N/A
	358	+	L	2	+
	436	+	D	3	+
	475	+	D	2	N/A
	678	-	L	3	-
	709	+	D	2	N/A
	1462 (FU)	+	D	3	+
	1520 (FU)	+	D	2	+
60 mg	36	+	T	1	-
Placebo	412	+	L	2	+
	557	-	D	3	+
	1474	+	D	1	-

* D = Ductal; L = Lobular; T = Tubular

Tumor Parameters: Relationship to Treatment

TREATMENT	DIAGNOSIS (DAY)	CIS	TUMOR TYPE*	GRADE (1 - 3)	LYMPH NODES	SIZE (MM)
120 mg	41	-	D	2	N/A	12
	80	+	L	2	+	>18
	178	+	L	0	N/A	not tumor
	198	+	L	2	N/A	>22
	358	+	L	2	+	>17
	436	+	D	3	+	25
	475	+	D	2	N/A	16
	678	-	L	3	-	>22
	709	+	D	2	N/A	9
	1462 (FU)	+	D	3	+	13
	1520 (FU)	+	D	2	+	7
60 mg	36	+	T	1	-	10
Placebo	412	+	L	2	+	>6**
	557	-	D	3	+	9
	1474	+	D	1	-	12

* D = Ductal; L = Lobular; T = Tubular

Tumor Parameters: Relationship to Treatment

TREATMENT	DIAGNOSIS (DAY)	CIS	TUMOR TYPE*	GRADE (1 - 3)	LYMPH NODES	SIZE (MM)	RELATIONSHIP TO TREATMENT
120 mg	41	-	D	2	N/A	12	Pre-existing (-)**
	80	+	L	2	+	>18	Pre-existing (+)
	178	+	L	0	N/A	not tumor	Pre-existing (+)
	198	+	L	2	N/A	>22	Pre-existing (+)
	358	+	L	2	+	>17	Pre-existing (+)
	436	+	D	3	+	25	Pre-existing
	475	+	D	2	N/A	16	Pre-existing (+)
	678	-	L	3	-	>22	Pre-existing
	709	+	D	2	N/A	9	Possible/Unlikely (-)
	1462 (FU)	+	D	3	+	13	Pre-existing
	1520 (FU)	+	D	2	+	7	Possible/Unlikely
60 mg	36	+	T	1	-	10	Pre-existing
Placebo	412	+	L	2	+	>6**	Pre-existing (+)
	557	-	D	3	+	9	Possible/Unlikely
	1474	+	D	1	-	12	Possible/Unlikely (-)

* D = Ductal; L = Lobular; T = Tubular

** = pretreatment mammography: (+) detectable lesion, (-) not detectable

Patient Tumors Reinterpreted After Full Scientific Evaluation

Treatment	Number of Women (>44 years)	Carcinoma In Situ	Pre-existing Ca: pathology; mammography	Possibly, but unlikely, related to treatment	Total
Orlistat 120 mg	747	9	9	2	11
Orlistat 30/60 mg	316	0	1	0	1
Placebo	579	2	1	2	3

Breast Cancer Causality: Summary of Evidence

- Presence of CIS
- Tumor type heterogeneity
- Tumor grade heterogeneity
- Lymph node metastases
- Tumor size

Conclusion on Causality

In my view there are no data indicating that orlistat is causally related to breast cancer initiation or promotion

Independent Assessment

- Pathologists: Drs, Tavassoli, Wagner and Wright
- Radiologist: Dr. Feig

THERE WAS COMPLETE INDEPENDANT CONCORDANCE ON CAUSALITY ISSUE

Issue Two

Evidence will be presented that there are no cell biologic or pathologic data to support this idea.

Issue Two:
Did orlistat enhance pre-existing breast tumor growth?

- No preclinical evidence for enhancement of growth (Dr. Anderson)
- Human Pathology Evaluation

Growth Enhancement Issue: Predictions

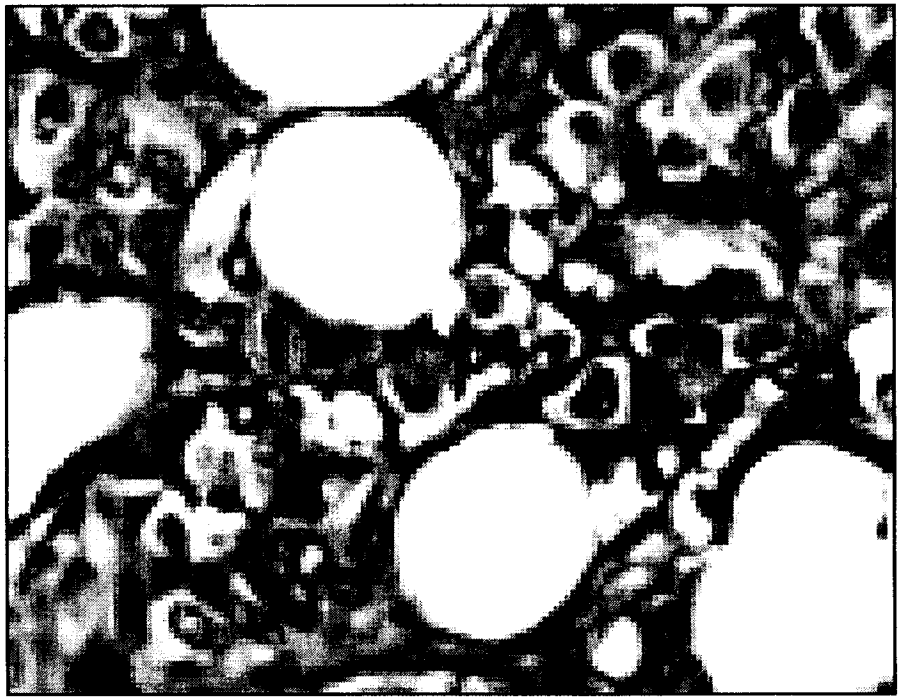
1. INCREASED CELL PROLIFERATION

- Invasive cancers would be high grade (mitoses, etc.)
- CIS lesions would be high nuclear grade (mitoses, etc.)
- Non-tumorous breast tissue may also show evidence of epithelial proliferation

2. DECREASED CELL DEATH

Invasive Cancer Grade

Grade 1



Grade 3

Quantification of Grading

1) Tubule formation

- >75% = 1
- 10-75% = 2
- <10% = 3

2) Nuclear morphology

- Regular = 1
- Large/irregular = 2
- Marked variation = 3

3) Cell mitoses

- 0-9 10/hpf = 1
- 10-19 10/hpf = 2
- >20 10/hpf = 3

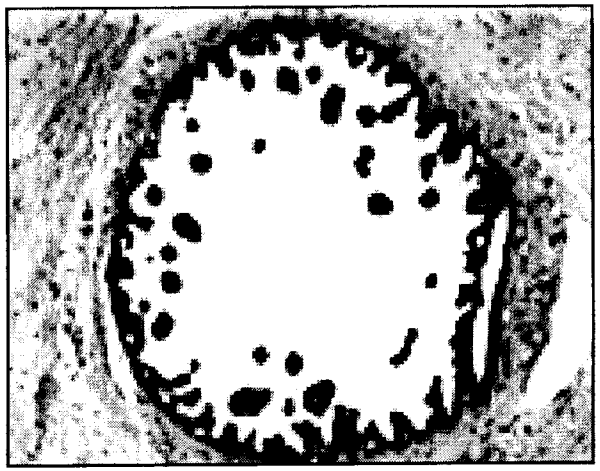
4) TOTAL SCORE

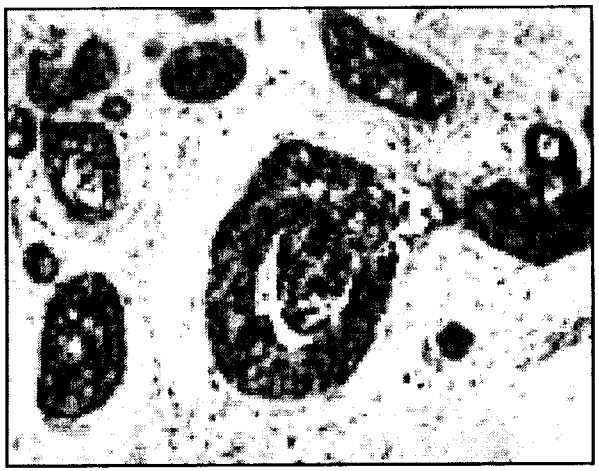
3-5 = grade 1

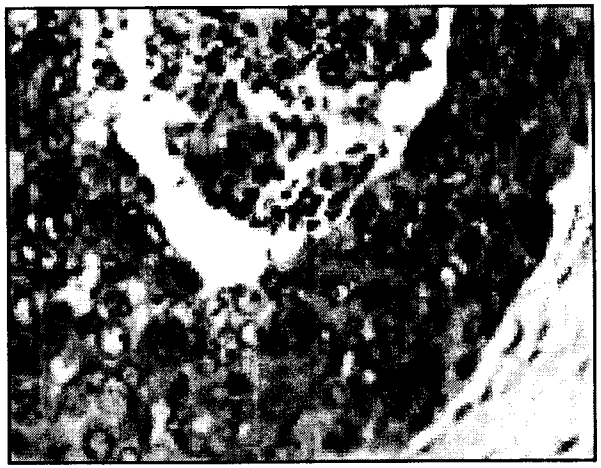
6-7 = grade 2

8-9 = grade 3

Carcinoma in Situ Grades







Low Nuclear Grade

High Nuclear Grade

PLACEHOLDER
Slide to come via Jim

Summary of Evidence on Growth Enhancement in Human Breast Tumors

1. PROLIFERATION
   - Tumors were of heterogeneous grade: 1 = 1; 7 = 2; 2 = 3
   - CIS lesions were also of heterogeneous (low to high) grade: 9 of 11; 2 of 3
   - No evidence of stimulation seen in non-tumorous breast epithelium
2. CELL DEATH
   - No evidence of decreased cell death

Conclusion:
Possible enhancement of tumor growth by orlistat?

From my review there is no cell biological or pathologic evidence indicating that orlistat enhances tumor growth

XENICAL® (orlistat) in the Treatment of Obesity

Jonathan Hauptman, MD

Hoffmann-La Roche

Nutley, New Jersey

3 Key Points to Reconsider

- General safety & tolerability
- Issues related to breast cancer
- Overall efficacy

Safety and Tolerability of Orlistat

- Few clinically significant adverse events
- Well characterized pharmacological effects

Effect of Orlistat on Fat-Soluble Vitamin Levels

- Modest decrease in vitamin D and Beta-Carotene levels
- Multivitamin reverses decreased values
- Vitamin supplementation should be given

Summary of Additional Specialized Safety Evaluation

- **No plausible evidence of a biological association between orlistat & breast cancer**
- **Most plausible explanation is chance**

Taking into consideration the overall benefits and risks of orlistat including the increased incidence of breast cancer in the controlled clinical studies, do you recommend that the drug be approved for the treatment of obesity?

Orlistat Efficacy

- Produces clinically meaningful sustained weight loss
- Diminishes weight regain
- Is effective long-term

Cardiovascular Risk Improvement

- LDL-Cholesterol
- LDL/HDL Ratio
- Blood pressure

Carbohydrate Metabolism Improvement

- Fasting insulin
- Oral Glucose Tolerance Test
- Diabetic control

Benefits of Orlistat

Patients with medically significant obesity will:

- **Lose more weight**
- **Keep weight off long-term**
- **Have lower obesity-related risks**

Conclusion

Administered as part of an overall weight control program, orlistat:

- **is well tolerated**
- **has a good safety profile**
- **is effective in producing and maintaining a clinically meaningful weight loss**
- **improves obesity-related risk factors**