

# Pharmacologic Interventions: Present and Future

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**Jeanine Albu, M.D.**  
**Associate Professor of Clinical Medicine**  
**New York Obesity Research Center**  
**St. Luke's Roosevelt Hospital Center**  
**Columbia University**

# Case: 50-Year-Old Female with a BMI of 30

Parameter	ATP III Criteria*	Patient Values
Waist Circumference	>35 in (88 cm)	38 in
Blood Pressure	≥130/≥85 mm Hg	130/90 mm Hg
Fasting Glucose	≥110 mg/dL	105 mg/dL
Triglycerides	≥150 mg/dL	165 mg/dL
HDL-C	<50 mg/dL	45 mg/dL

*\*Third Report of the National Cholesterol Education Program Expert Panel. Executive Summary; May 2001. NIH publication No. 01-3670.*

## ICD-9 Codes

- **Dysmetabolic Syndrome X: 277.7**
- **Hypertension: 401.9**
- **Dyslipidemia: 272.0**

# Treatment of Metabolic Syndrome

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According to the guidelines from the ATP III,<sup>1</sup> JNC VI,<sup>2</sup> and ADA<sup>3</sup>:

First-Line Therapy = Weight Reduction With Lifestyle Modifications

1. *Third Report of the National Cholesterol Education Program Panel. Executive Summary*; May 2001. NIH publication No. 01-3670.

2. *The Sixth Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure*. NIH/NHLBL. November 1997; NIH publication No. 98-4080.

3. American Diabetes Association Position Statement. *Diabetes Care*. 2002;25(suppl 1):S50-S60.

# A Guide to Selecting Treatment: NIH Guidelines\*

## BMI Category

Treatment	25–26.9	27–29.9	30–34.9	35–39.9	≥40
Diet, physical activity, behavior therapy	Yes with comorbidities	Yes with comorbidities	Yes	Yes	Yes
Pharmacotherapy		Yes with comorbidities	Yes	Yes	Yes
Weight-loss surgery				Yes with comorbidities	Yes

\*Yes alone indicates that the treatment is indicated regardless of the presence or absence of comorbidities. The solid arrow signifies the point at which therapy is initiated.

# Weight Management: Initial Intervention

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## According to the NIH Guidelines:

- Initial intervention = Therapeutic lifestyle change
  - Low-calorie diet
  - ↑ Physical activity
  - Behavior therapy
- Duration
  - 6-mo trial period

# Goals of Weight Management: A 10% Weight Loss

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“The initial goal of weight loss therapy for the overweight patient is a reduction in body weight of about 10%. Moderate weight loss of this magnitude can significantly decrease the severity of obesity-associated risk factors.”

# Weight Management: Pharmacologic Intervention

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## NIH Guidelines for Pharmacotherapy:

- Initiate when weight goals are difficult to achieve/maintain through diet and physical activity
- Administer for the long term
- Always use in conjunction with diet, physical activity, and behavior therapy

# Drugs Approved by FDA for Treating Obesity

Generic Name	Trade Names	DEA Schedule	Approved Use	Year Approved
Orlistat	Xenical	None	Long-term	1999
Sibutramine	Meridia	IV	Long-term	1997
Diethylpropion	Tenulate	IV	Short-term	1973
Phentermine	Adipex, Ionamin	IV	Short-term	1973
Phendimetrazine	Bontril, Prelu-2	III	Short-term	1961
Benzphetamine	Didrex	III	Short-term	1960

# FDA-Approved Obesity Agents: Mechanism of Action

Short Term

Long Term

Centrally Acting

Locally Acting

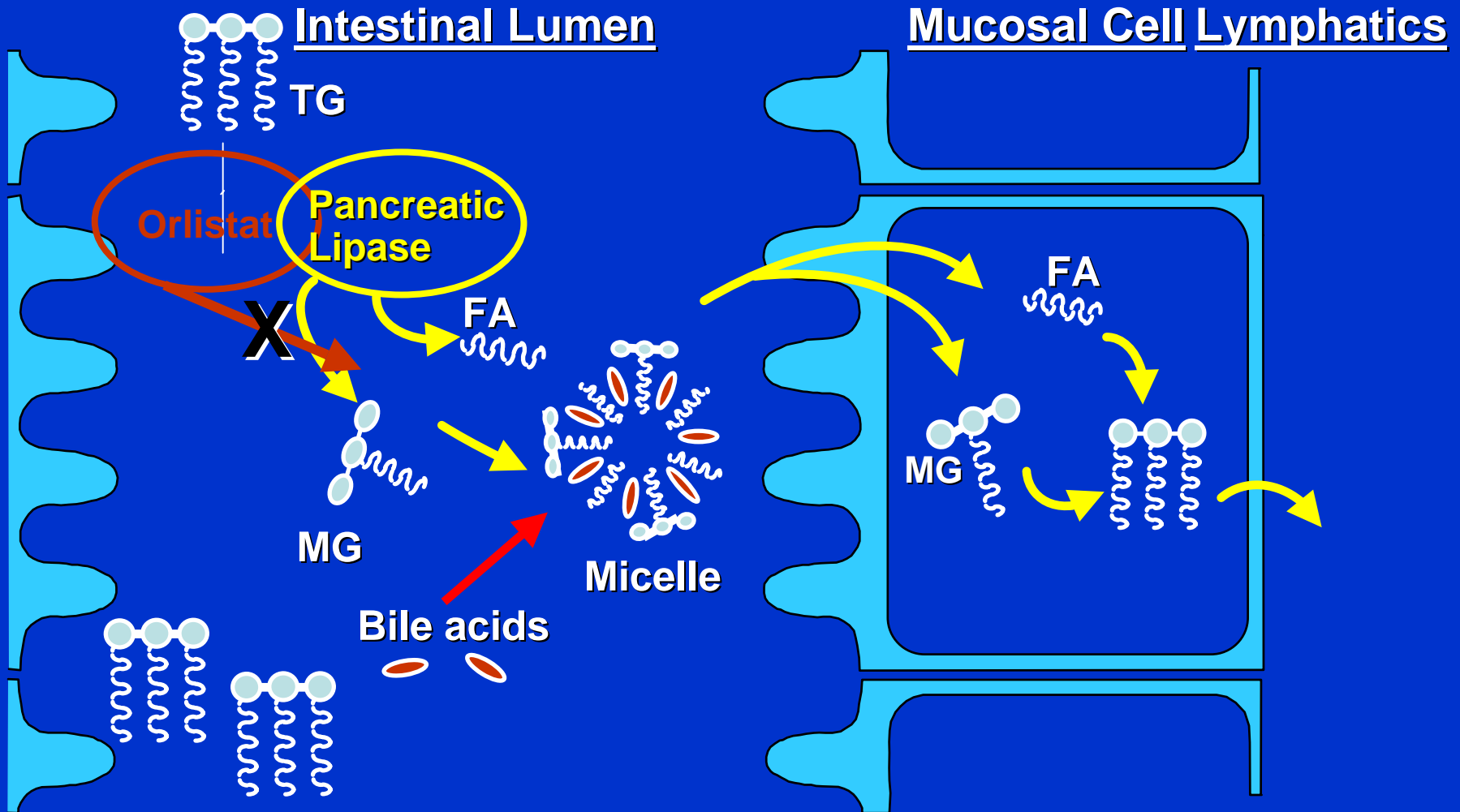
Phentermine

Sibutramine

Orlistat



# Orlistat: Mechanism of Action



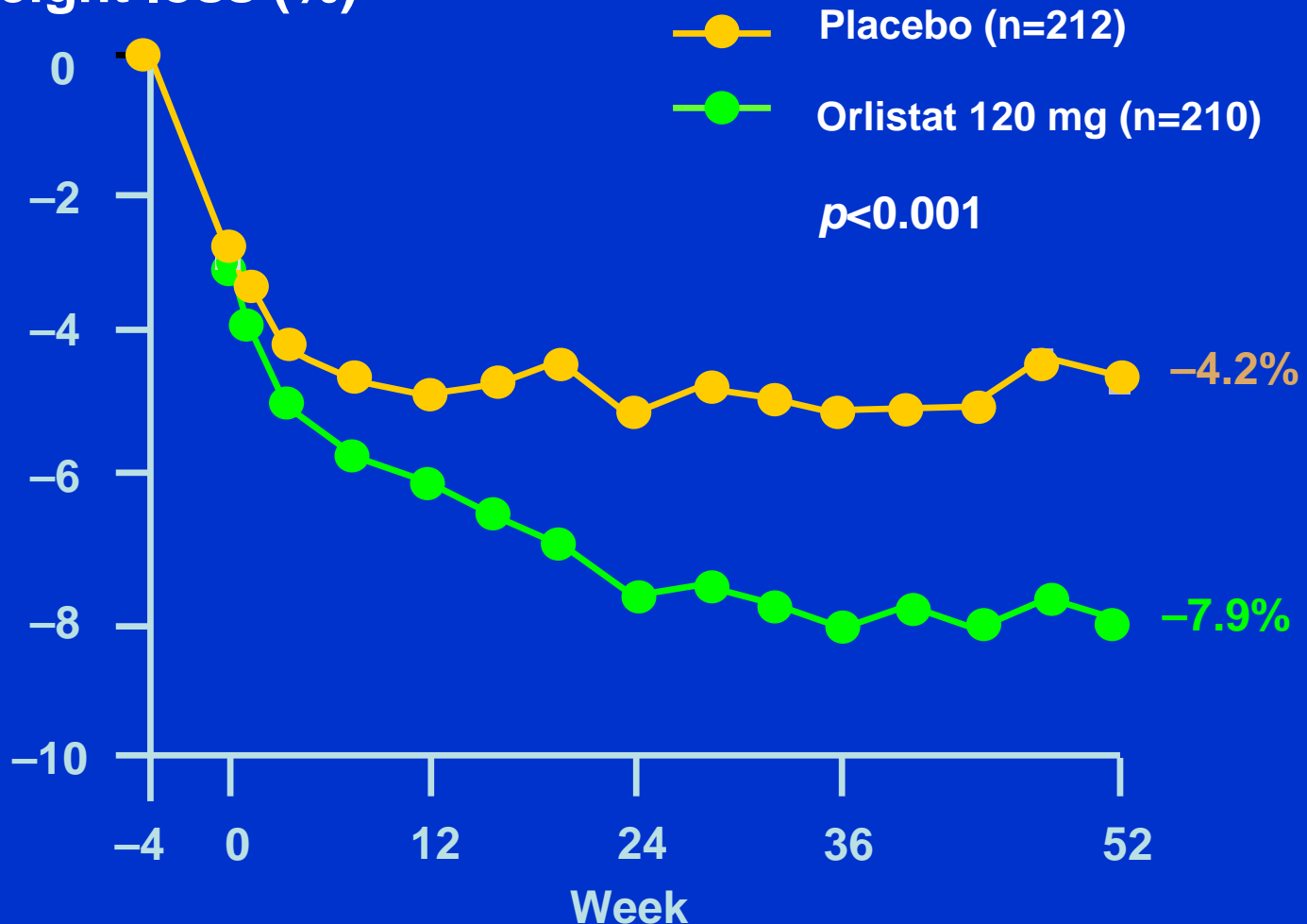
# Orlistat

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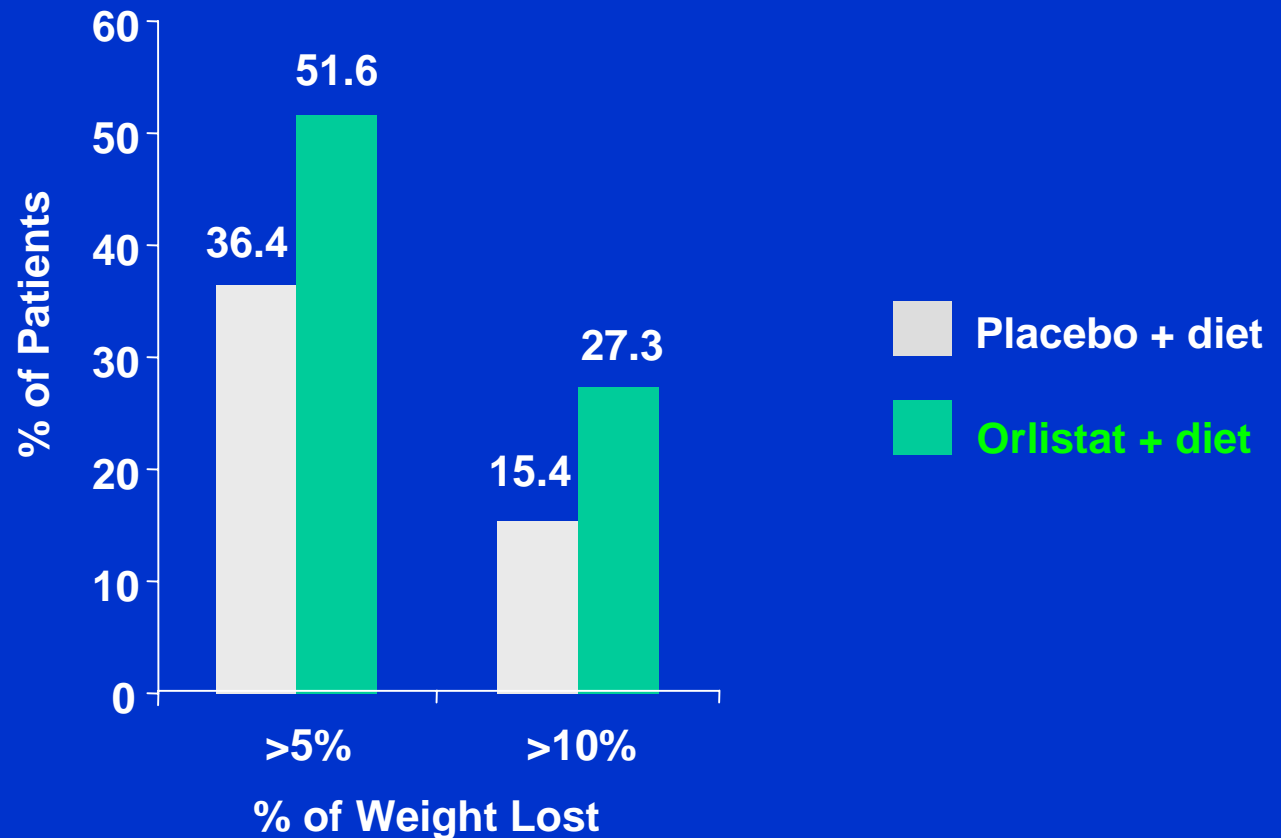
- FDA approved in 1999
- Gastric and pancreatic lipase inhibitor
- Reduces absorption of ~30% of dietary fat
- Up to 4 years efficacy and safety data
  - Weight loss
  - Weight maintenance
  - Risk factors reduction
- TID dosing with meals
  - Vitamin supplement recommended

# Orlistat Use in a Primary Care Setting

Mean weight loss (%)

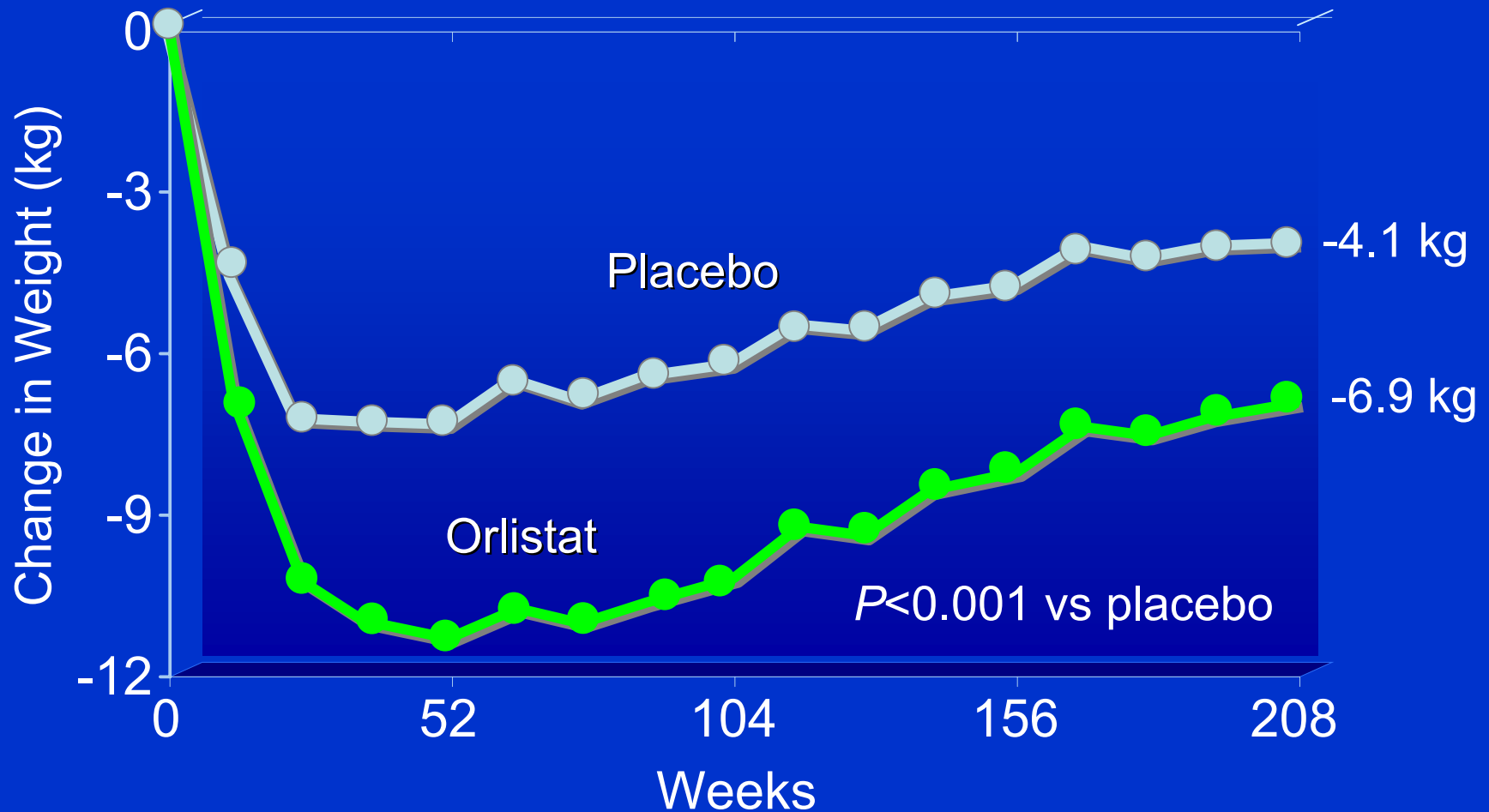


# Orlistat: 2-Year Efficacy

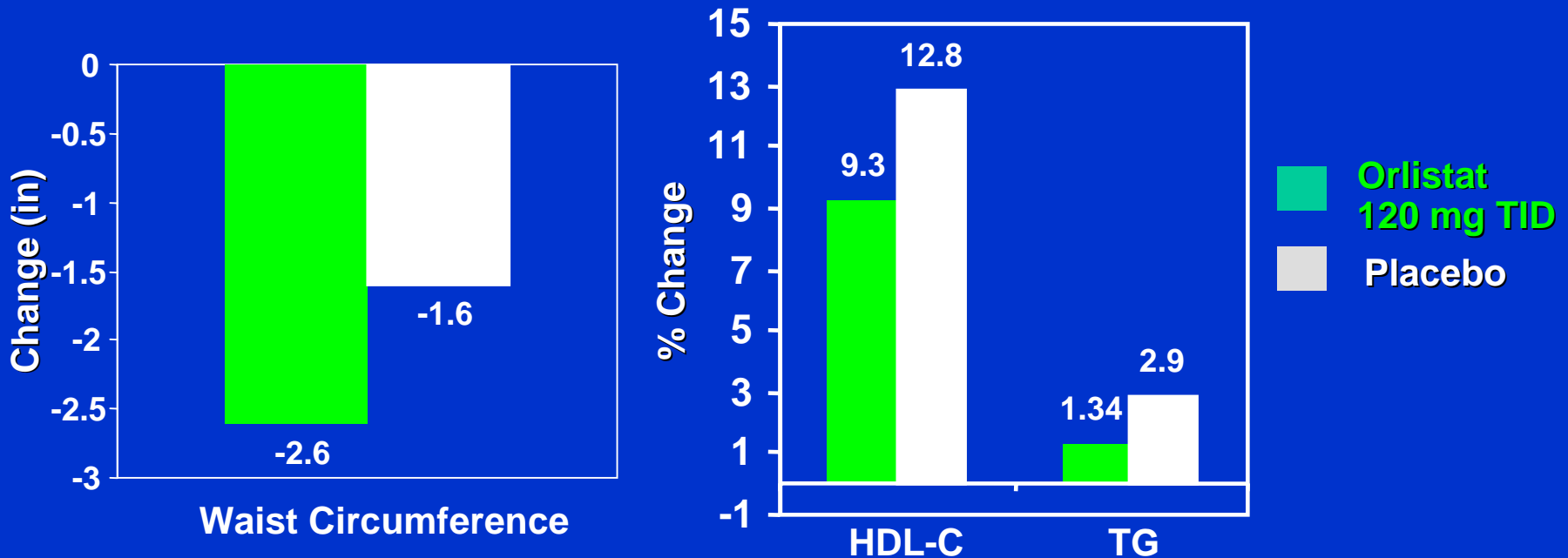


Meta-analysis of data derived from 4 clinical trials

# Effect of Long-term Orlistat Therapy on Body Weight



# Orlistat: Effect on Metabolic Syndrome



# Orlistat Reduces Glucose in Obese Patients With Type 2 DM Treated With Metformin

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516 patients

All on metformin, some on sulfonylurea

HbA1C > 8

Treatment:

Hypocaloric diet

261 randomized to orlistat, 255 to placebo

Results	<u>Orlistat</u>	<u>Placebo</u>
Weight loss $\geq$ 5%	39.0%	15.7%
Weight loss $\geq$ 10%	14.1%	3.9%
HbA1C reduction $\geq$ 1%	46%	29%
Reduction in dose of sulfonylurea	11.5 mg	0.9 mg

Miles J, Leiter L, Hollander P et al. Effect of orlistat in overweight and obese patients with type 2 diabetes treated with metformin.

# Orlistat: Efficacy

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- Reduces amount of absorbed dietary fat by 30%
- Improves lipids (with an independent effect on LDL, down 16%), glucose, blood pressure, insulin, and other comorbid conditions

# Gastrointestinal Events\*

## Orlistat 120 mg TID + Diet

Year One

	Incidence	Withdrawals
	%	%
Oily spotting	26.6	1.7
Flatus with discharge	23.9	0.6
Fecal urgency	22.1	0.3
Fatty/oily stool	20.0	0.1
Oily evacuation	11.9	0.0
Increased defecation	10.8	0.3
Fecal incontinence	7.7	1.1

\*Defined as an incidence of  $\geq 5\%$  and twice the frequency of the placebo group.

Data on file (Ref. 038-002).

Please see complete product Information.

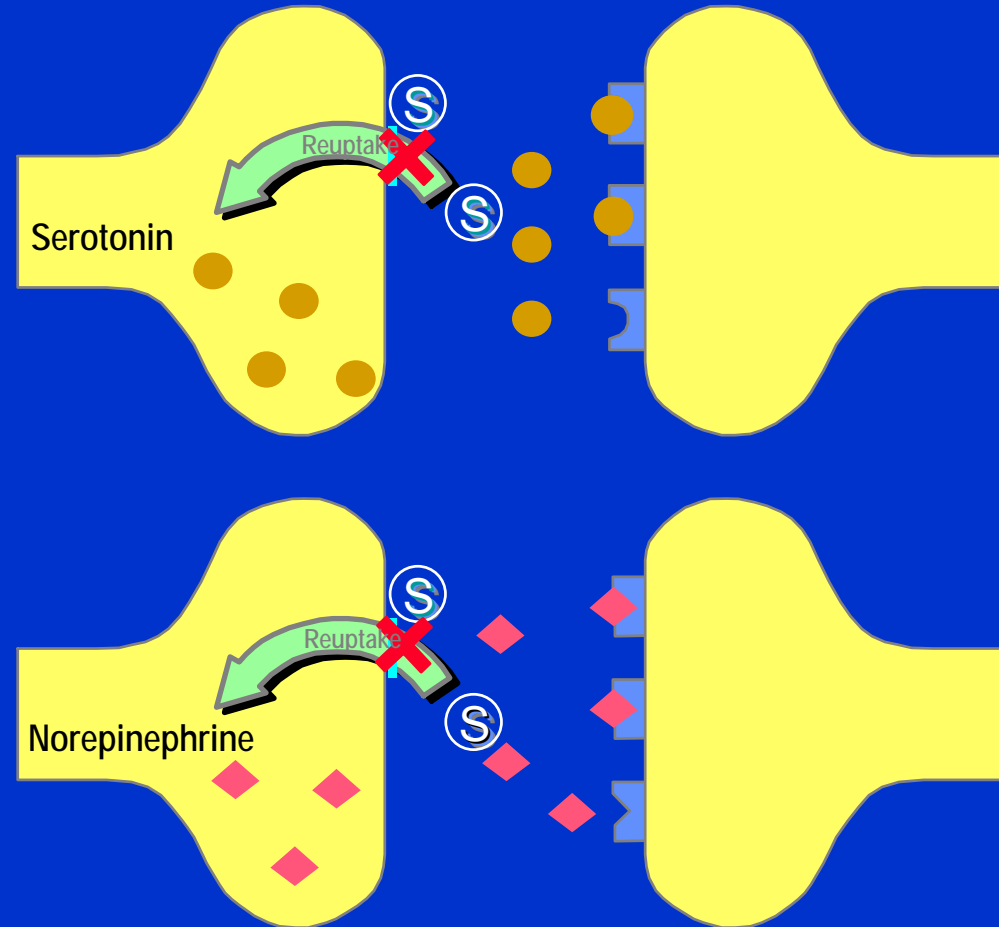
# Orlistat: Safety

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- GI events are related to increased fecal fat excretion and are a predictable consequence of the mode of action of orlistat-they may help compliance-patients test their limits
- GI symptoms may be reduced with psyllium
- In clinical trials more dropouts with placebo
- Reduction in fat soluble vitamins levels (D, E) has been demonstrated, though levels still within normal range
- Vitamin supplementation is recommended in U.S.

# Sibutramine: Mechanism of Action

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S = sibutramine

◆ = norepinephrine, ● = serotonin

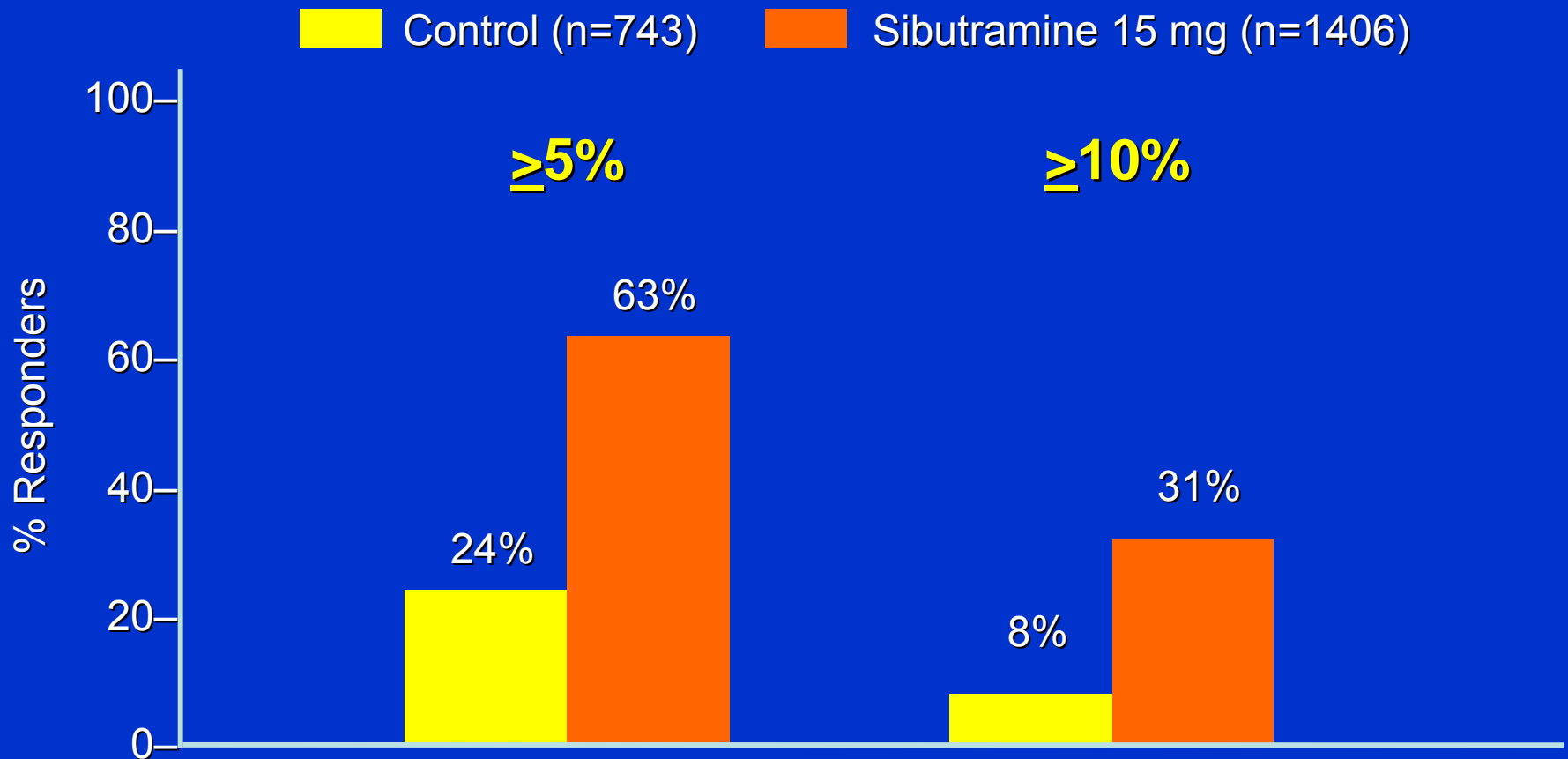
# Sibutramine

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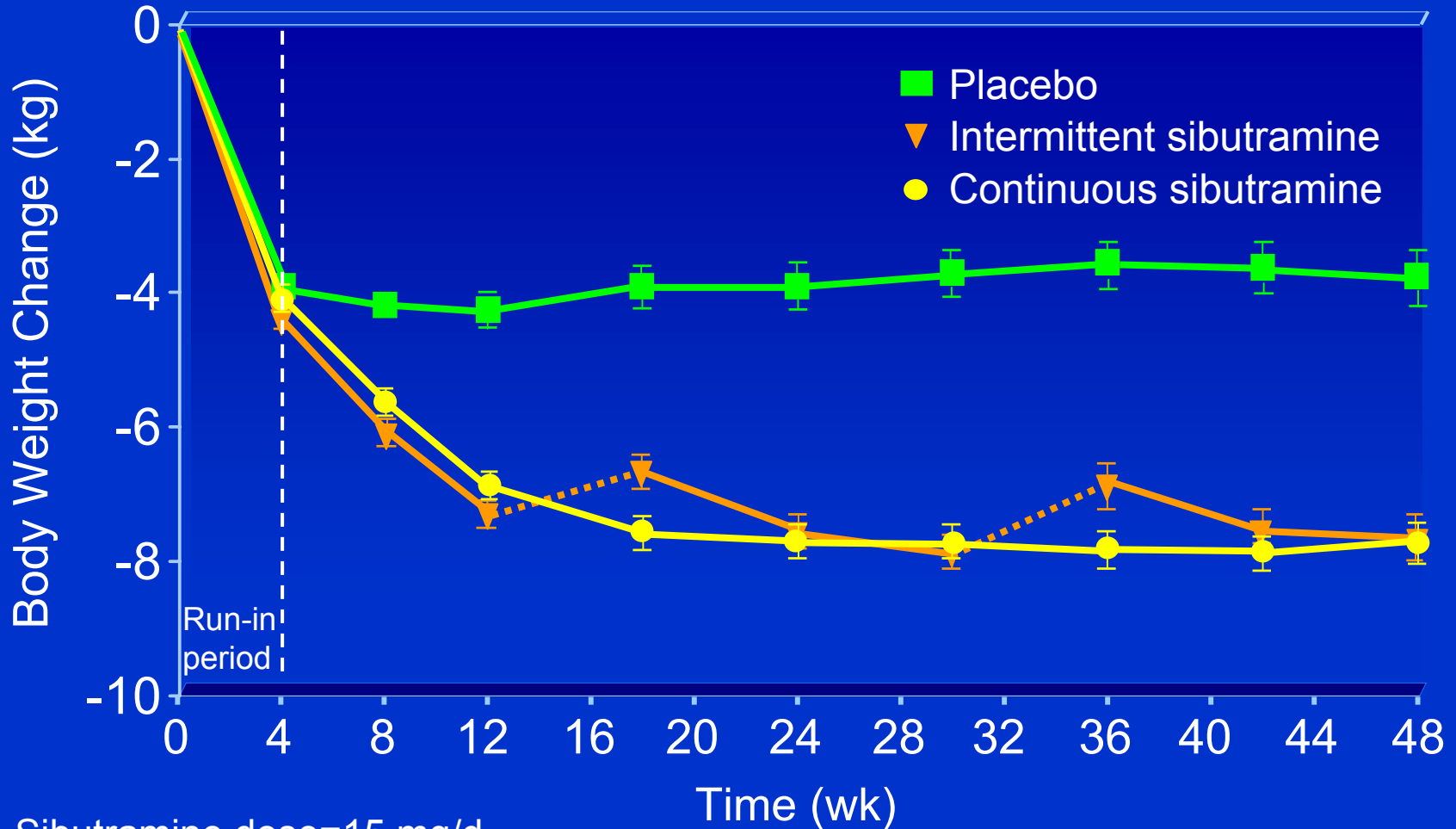
- FDA approved in 1997
- Serotonin and noradrenaline reuptake inhibitor
- Decreases food intake
- 2-year efficacy and safety data
  - Weight loss
  - Weight maintenance
  - Risk factors reduction
- QD dosing with or without food, 10 or 15 mg

# Sibutramine: 1-Year Efficacy

(Six 12-month placebo-controlled studies)

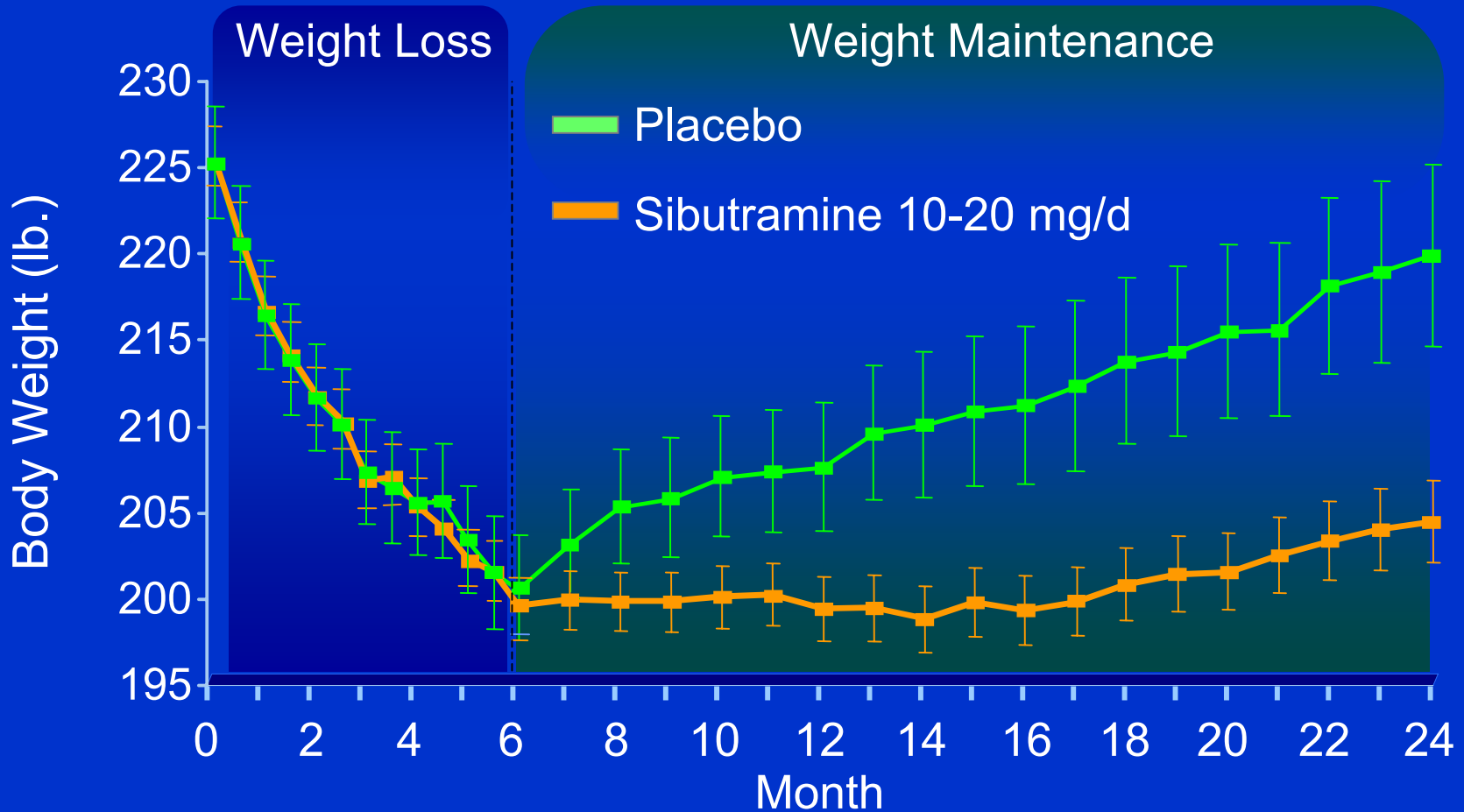


# Effect of Continuous vs Intermittent Sibutramine Therapy on Body Weight



Sibutramine dose=15 mg/d.

# Initial Responders to Sibutramine Can Maintain Long-term Weight Loss

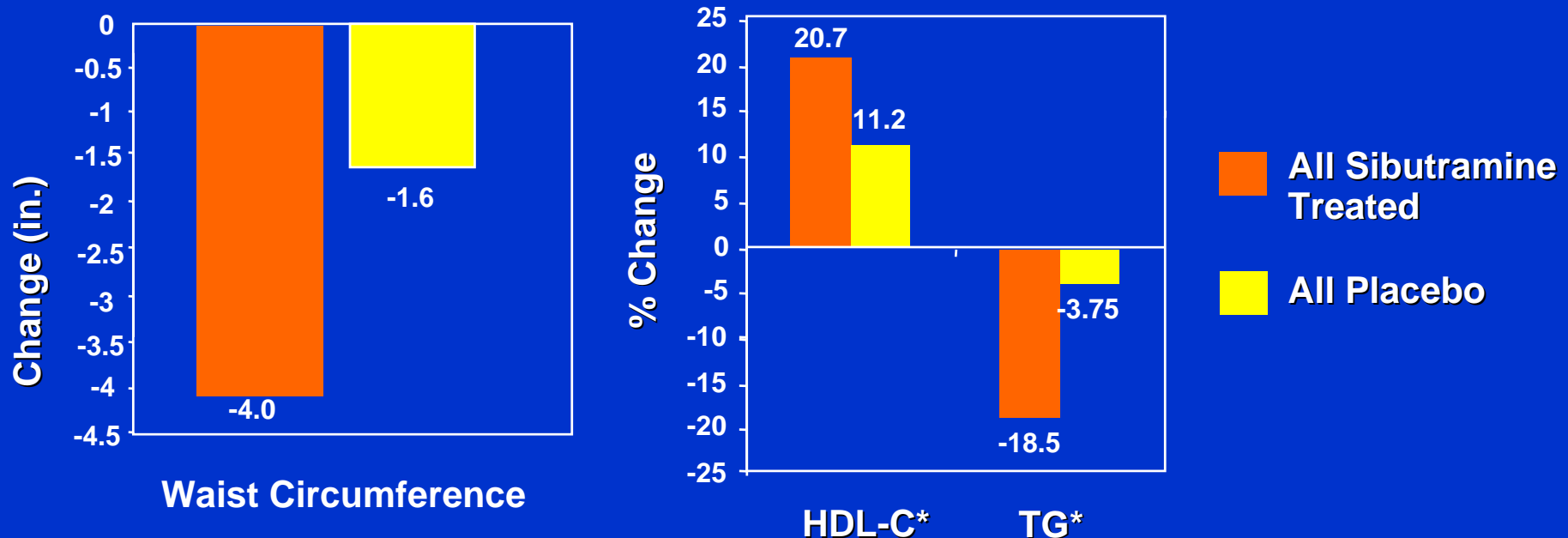


Randomization at 6 months in those with  $\geq 5\%$  weight loss.

**James et al. *Lancet* 2000;356:2119.**

# Sibutramine: Effect on Metabolic Syndrome

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\* $P < 0.001$  for results seen in those patients receiving sibutramine.

James WPT, et al *Lancet*. 2000;356:2119-2125.

# STORM: Change in Vital Signs— Baseline to 24 Months

Mean Change  
Sibutramine                      Placebo

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BP, mm Hg

Systolic

0.1

−4.7

Diastolic

2.3

−1.6

Pulse rate (bpm)

4.1

−1.9

# Sibutramine: Cardiovascular Safety Profile Based on Results From Clinical Trials

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- Mean increases in systolic and diastolic BP of 1 to 4 mm Hg relative to placebo, and mean increase in pulse rate of 4 to 5 bpm relative to placebo
- No evidence of primary pulmonary hypertension or valve dysfunction
- No evidence of serotonin syndrome
- No evidence of increased risk for cardiovascular or cerebrovascular events in short term (2 y) studies
- Longer term studies ongoing  
**(SCOUT)**
- Contraindicated in patients with uncontrolled hypertension, coronary heart disease, other vascular disease.

Bray GA et al. *Obes Res.* 1999;7:189-198.

Yanovski SZ, Yanovski JA. *N Engl J Med.* 2002;346:591-602.

# Blood Pressure Management With Sibutramine

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- Regular monitoring of blood pressure and pulse rate is required and specified in the product warning
  - Check the patient's blood pressure *before* prescribing sibutramine
  - Periodically monitor the patient's blood pressure during therapy
  - Follow the JNC VI guidelines for the prevention and treatment of high blood pressure

# Adverse Effects of Sibutramine Therapy

Adverse Effect	Subjects (%)	
	Placebo	Sibutramine
Headache	18.6	30.3
Dry mouth	4.2	17.2
Constipation	6.0	11.5
Insomnia	4.5	10.7
Dizziness	3.4	7.0
Hypertension	0.9	2.1
Tachycardia	0.6	2.6
Palpitation	0.8	2.0

# Combining Therapies Produces Better Outcomes: Sibutramine + Meal Replacements + Lifestyle Group

Percentage of 53 Participants Meeting Different Weight Loss Criteria at Month 12

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Group	No.	5%-9.9%	10%-14.9%	>15%
Drug-alone	19	21.1	5.3	5.3
Drug-plus-lifestyle	17	17.6	11.8	23.5
Combined therapy Drug+lifestyle+partial liquid x16 wks, then slowly to food	17	11	17.6	58.8

Conclusion: More intensive behavioral intervention yields much better results

**Old and new anti-diabetic  
drugs with favorable effects on  
weight**

# Old and new anti-diabetic drugs with favorable effects on weight

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- **Metformin:** insulin-sensitizing, approved for treatment of type 2 DM, monotherapy in the DPP and UKPDS showed favorable effect on weight
- **Pramlintide:** synthetic analog of amylin, a hormone co-secreted with insulin from the beta-cells ; slows gastric emptying, suppresses glucagon and increases satiety in type 1 and type 2 DM patients
- **Exenatide:** a GLP-1 (glucagon-like peptide1) analog has an incretin effect, suppresses glucagon, slows gastric emptying and induces weight loss in type 2 DM patients; approved for treatment of hyperglycemia not for weight loss
- Other: **acarbose, miglitol**

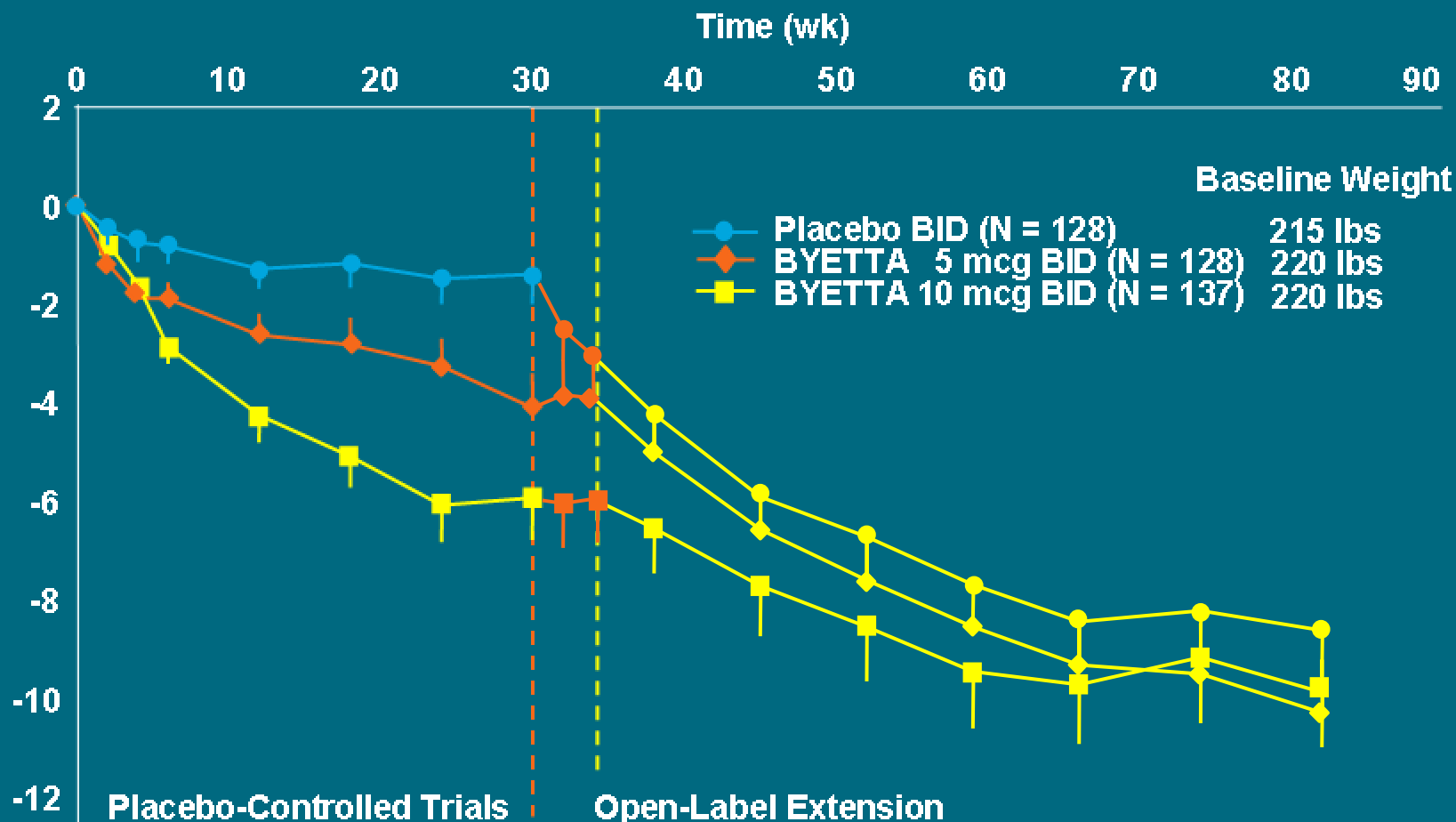
# Old and new anti-diabetic drugs with favorable effects on weight : Safety Information

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- Metformin, pramlintide and exenatide have not been approved for weight loss; rather all have specific indications for patients with diabetes
- All have GI side effects, nausea for pramlintide and exenatide in various degrees, metformin also has been rarely associated with lactic acidosis and pramlintide has a black box warning for hypoglycemia in patients with diabetes treated with insulin

# Open-Label Extension – Combined BYETTA Continued to Reduce Weight

Mean  $\Delta$  Weight From Baseline (lbs)



See Important Safety Information included in this presentation  
82-wk completers; Mean (SE); Weight was a secondary endpoint  
Data on file, Amylin Pharmaceuticals, Inc.

**Byetta™**  
exenatide injection

# Pramlintide

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- **SYMLIN<sup>®</sup> (pramlintide acetate) injection is indicated to be given at mealtimes as an adjunct to mealtime insulin therapy in patients with type 2 or type 1 diabetes who have failed to achieve desired glucose control despite optimal insulin therapy, with or without concurrent sulfonylurea agent and/or metformin.**
- **Pramlintide is under investigation as a weight-loss agent in obese subjects. The dosages and formulations under investigation are different from those of SYMLIN and have not been approved for clinical use by any governmental health agency or authority.**

# Subject Disposition

## Pramlintide Dose-Escalation Study

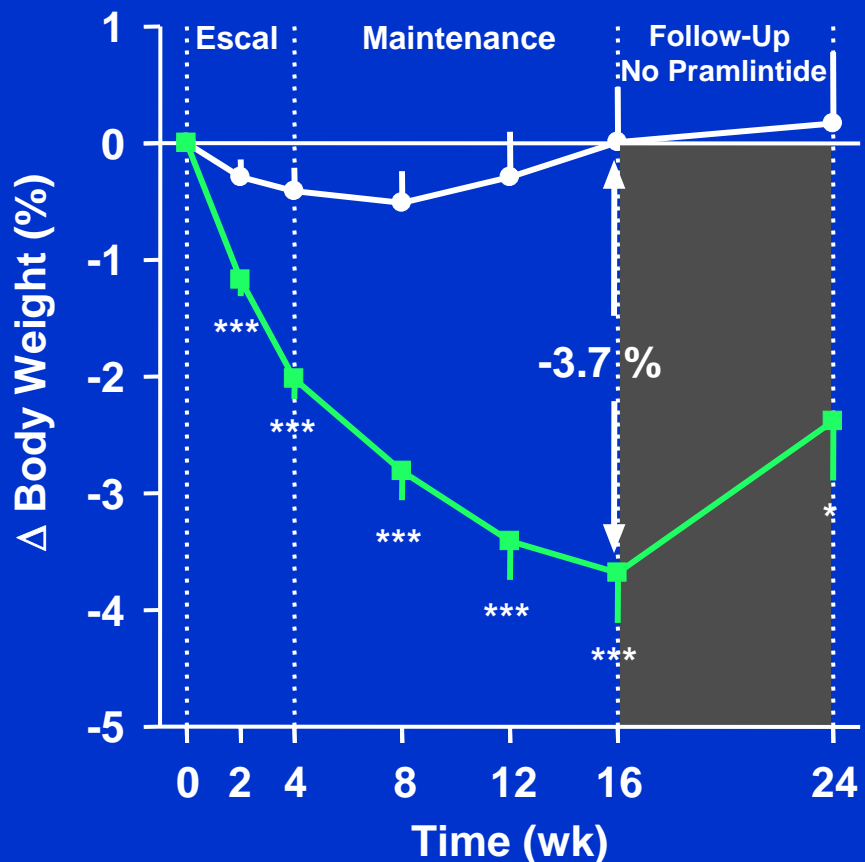
Disposition	Placebo	Pramlintide
Randomized (intent-to-treat, n)	67	137
Withdrew	25%	29%
Withdrawal of consent	15%	15%
Adverse event	3%	4%
Other	7%	11%
Completed maintenance period	75%	71%
Evaluable	72%	71%

**Note: 88% of subjects randomized to pramlintide treatment escalated to 240 µg TID.**

# Weight Decreased Regardless of Presence or Absence of Diabetes

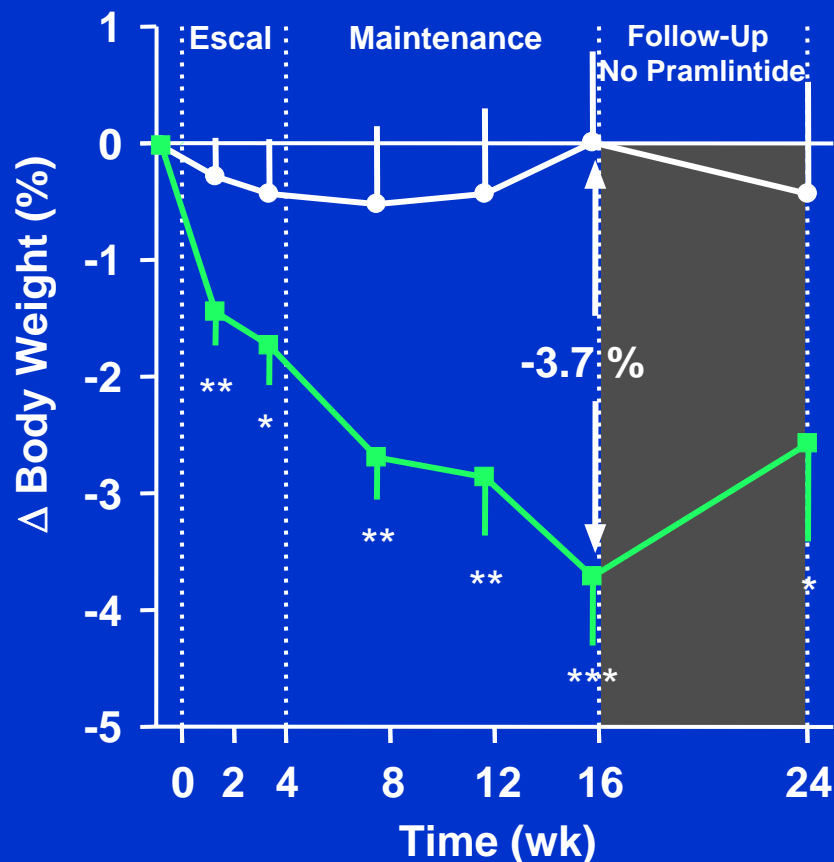
● Placebo (n = 35)  
■ Pramlintide (n = 78)

Subjects Without Type 2 Diabetes



● Placebo (n = 13)  
■ Pramlintide (n = 19)

Subjects With Type 2 Diabetes



Evaluable; N = 145; Mean (SE); \* P<0.05; \*\* P<0.01; \*\*\* P<0.001

Baseline body weight = 106 kg (placebo), 104 kg (pramlintide)

Data from Weyer C, 67th Annual Meeting of the Endocrine Society, 2005; 344 (Abstract P1-701).

# **New anti-obesity drugs**

# **The Endocannabinoid System: A New Target For Multiple Risk Factor Management**

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- **The endocannabinoid system is a physiologic neurocrine-paracrine-autocrine system which is overactivated in animal models of obesity leading to excessive food intake and fat accumulation.**
- **Multiple endogenous membrane-phospholipid-derived, locally-acting, short-lived, rapidly metabolized agonists act thru  $G_{i/o}$ -protein-coupled  $CB_1$  and  $CB_2$  receptors down-stream signaling via membrane ion channels, adenylate cyclase, and MAP-kinase.**

# Effects of Endocannabinoid System Overactivity on Obesity and Metabolic Abnormalities

Excess food intake  
Highly palatable food  
-> Obesity

**Overactivity of EC System**

**BRAIN**

Hypothalamus:  
↑ appetite

Nucleus accumbens:  
↑ motivation to eat

**PERIPHERAL TISSUE**

Adipose tissue:  
↑ fat accumulation

**Increased food intake**

↑ Glucose intolerance

↓ Adiponectin

↓ HDL-C

↑ Triglycerides

↑ Insulin resistance

# **The Endocannabinoid System: A New Target For Multiple Risk Factor Management**

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- **CB<sub>1</sub>-knock-out mice have a lean phenotype and resistance to diet-induced obesity.**
- **In rodents, CB<sub>1</sub> receptor antagonism:**
  - **Suppresses hypothalamic and limbic endocannabinoids;**
  - **Reduces food consumption, adiposity, insulin resistance and body weight;**
  - **Protects against diet-induced obesity**
  - **increases adiponectin gene expression in adipocytes.**
- **Rimonabant selectively blocks CB<sub>1</sub> receptors centrally and peripherally, reducing the increased activation of the endocannabinoid system**

# Rimonabant Phase III program

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- **RIO Program in Obesity / Overweight**  
(>6,600 patients enrolled)

**RIO~North America – 2-year treatment**

**RIO~Europe – 2-year treatment**

**RIO~Lipids – 1-year treatment**

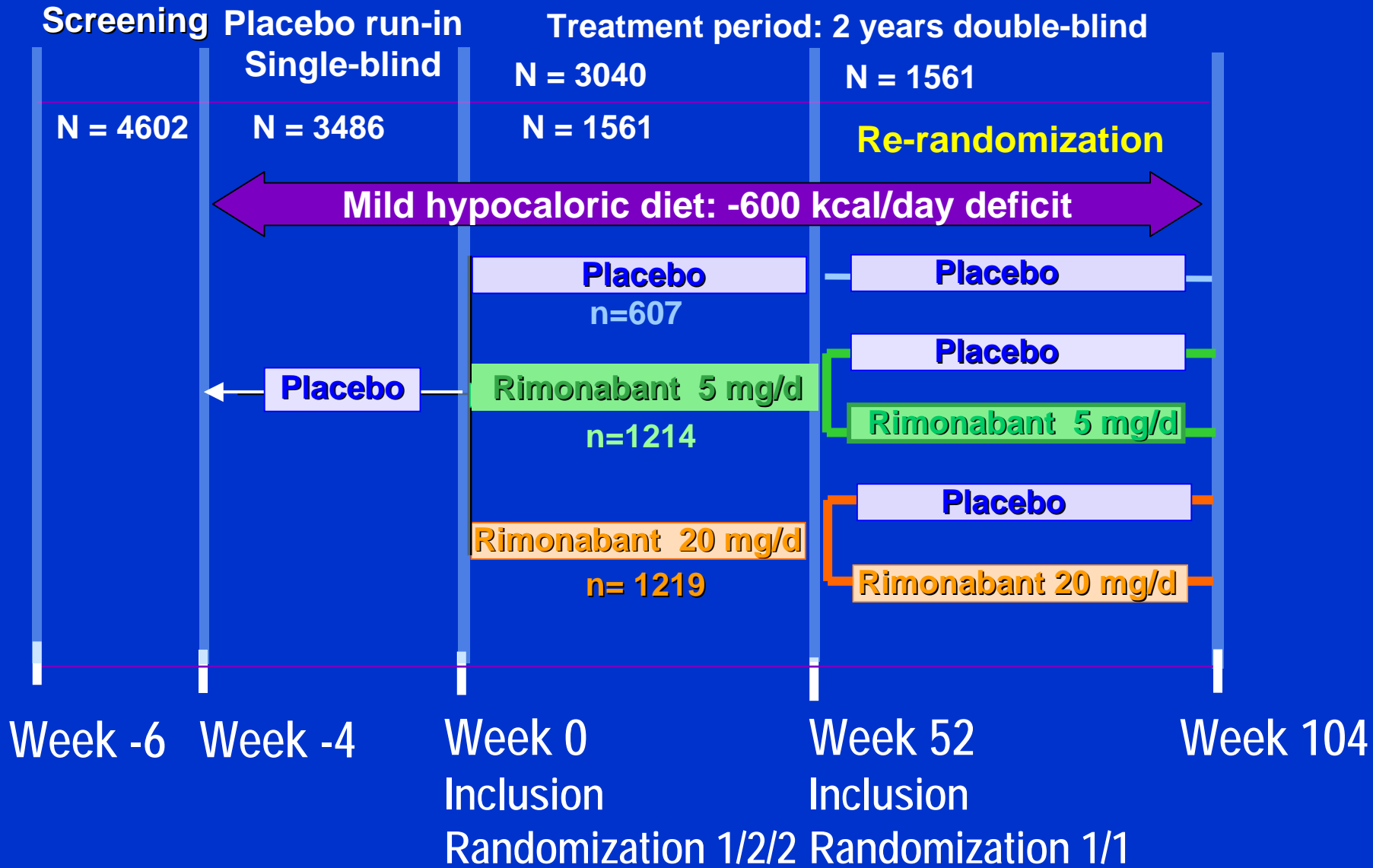
**RIO~Diabetes – 1-year treatment**

**F. Xavier Pi-Sunier, MD et al, JAMA, 2006 ; 295: 761-776**

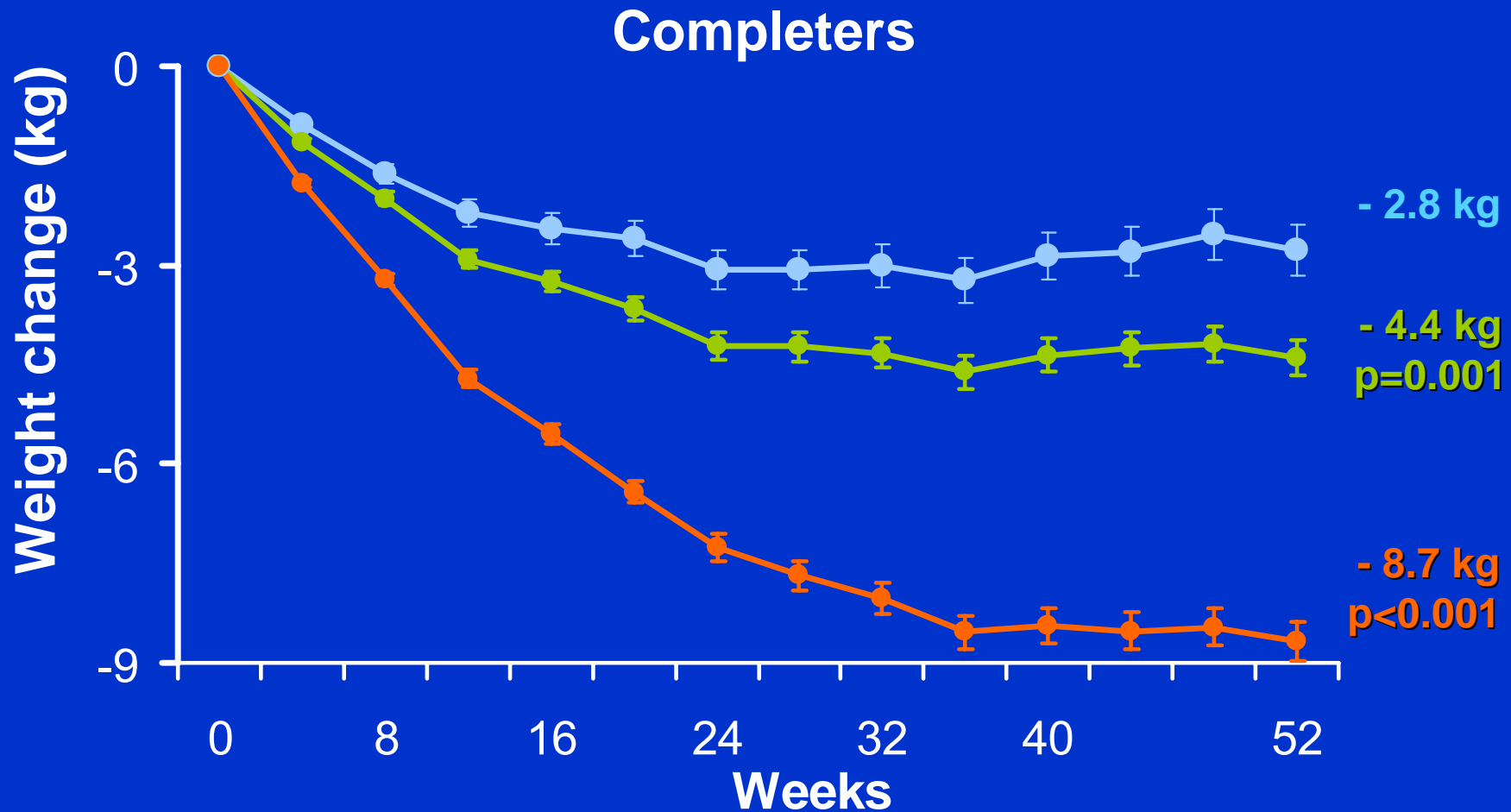
**Van Gaal LF. et al, from the RIO-Europe study. Lancet 2005; 365:1389-1397**

**Despres JP et al, N Engl J Med 2005; 353: 2121-2134**

# RIO~North America: Study Design



# Changes in Weight at 1 Year



ITT LOCF

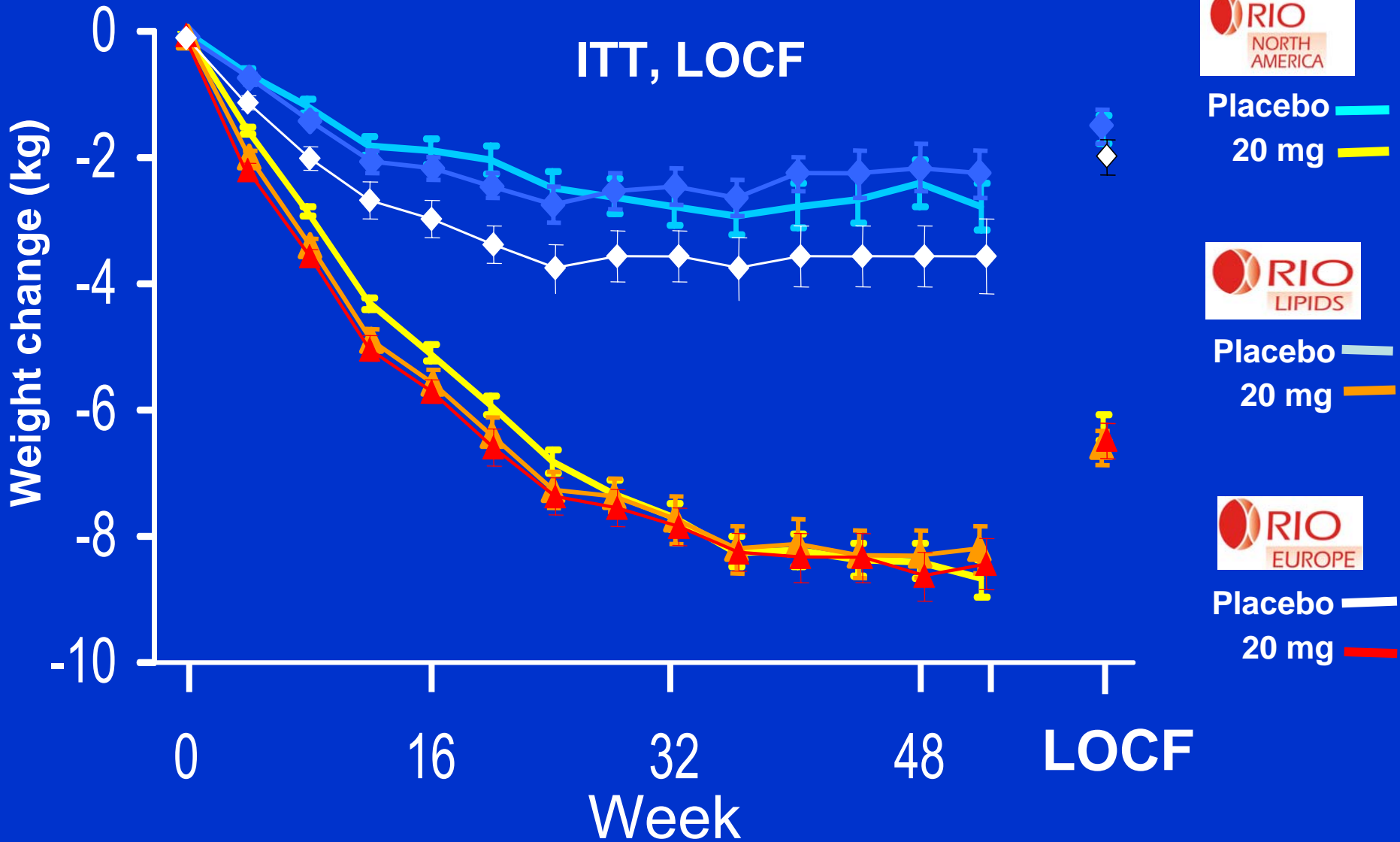
● Placebo ● Rimonabant 5 mg ● Rimonabant 20 mg

Placebo: - 1.6 kg

5 mg: - 2.9 kg ( $p < 0.001$  vs. Placebo)

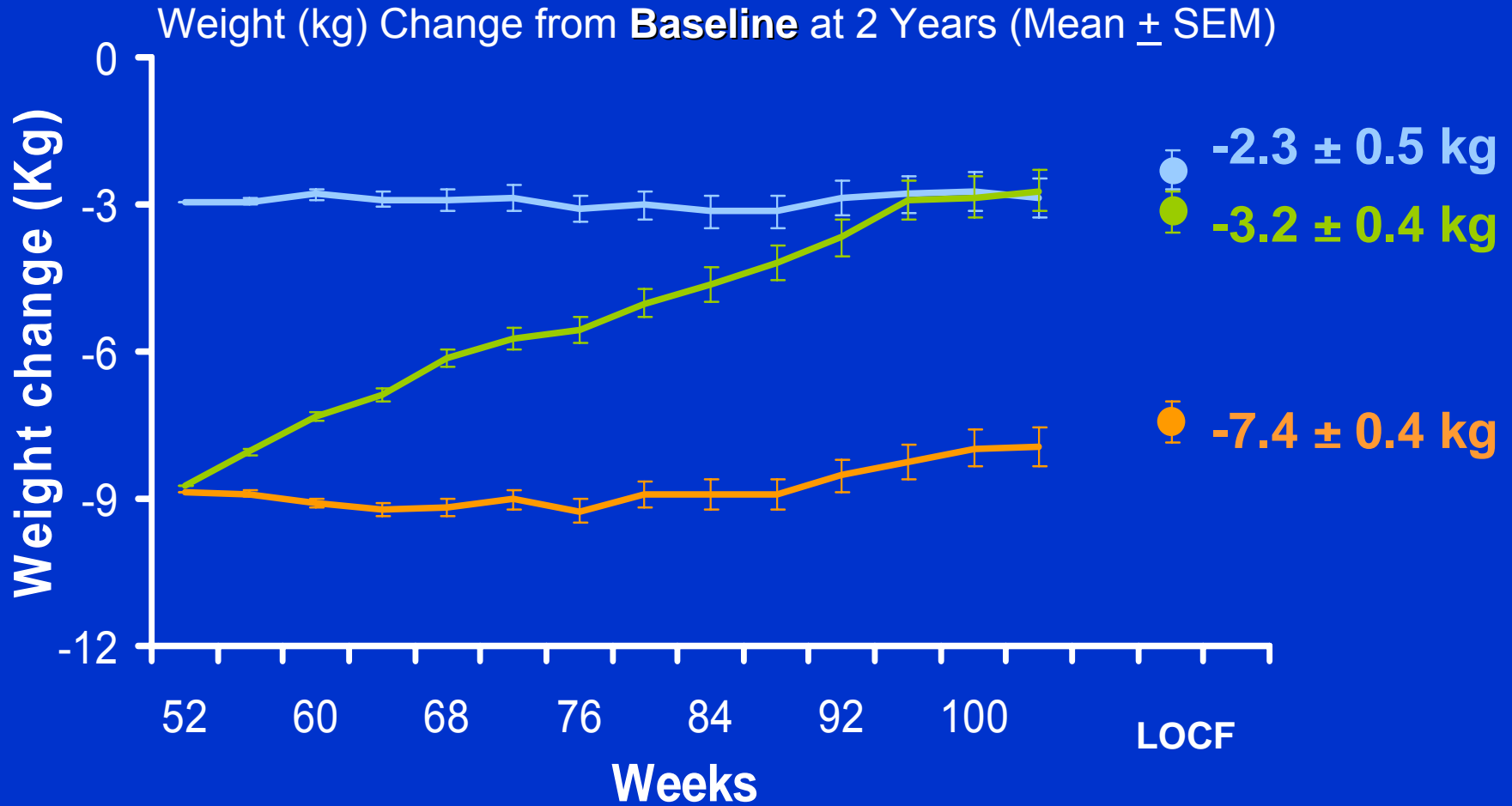
20 mg: - 6.3 kg ( $p < 0.001$  vs. Placebo)

# Consistent Weight Change at 1 Year: Rimonabant 20 mg vs Placebo



# Weight Maintenance Over 2 Years in Re-randomized Patients

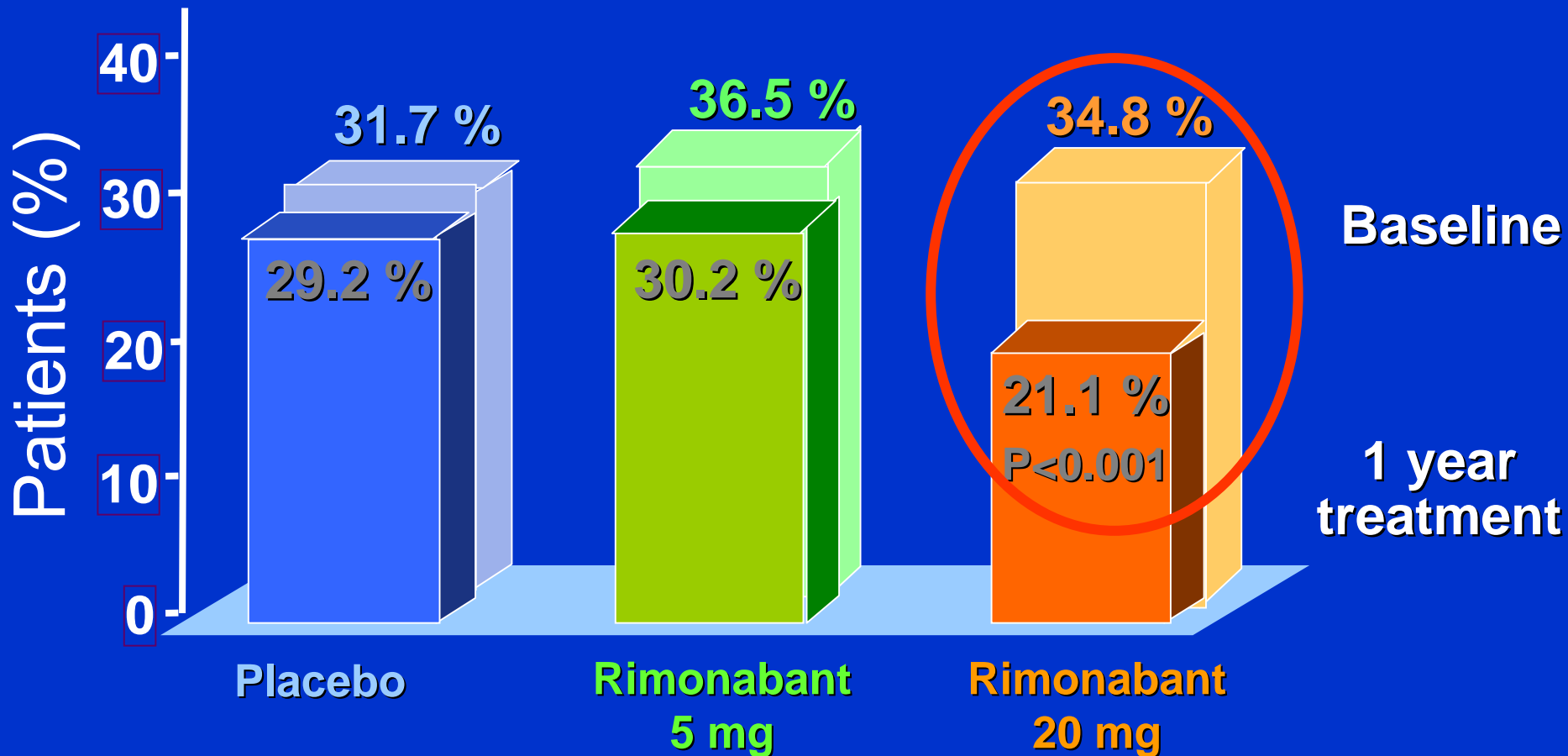
## ITT - LOCF



● Placebo ● Rimonabant 20 mg/Placebo ● Rimonabant 20 mg/20 mg

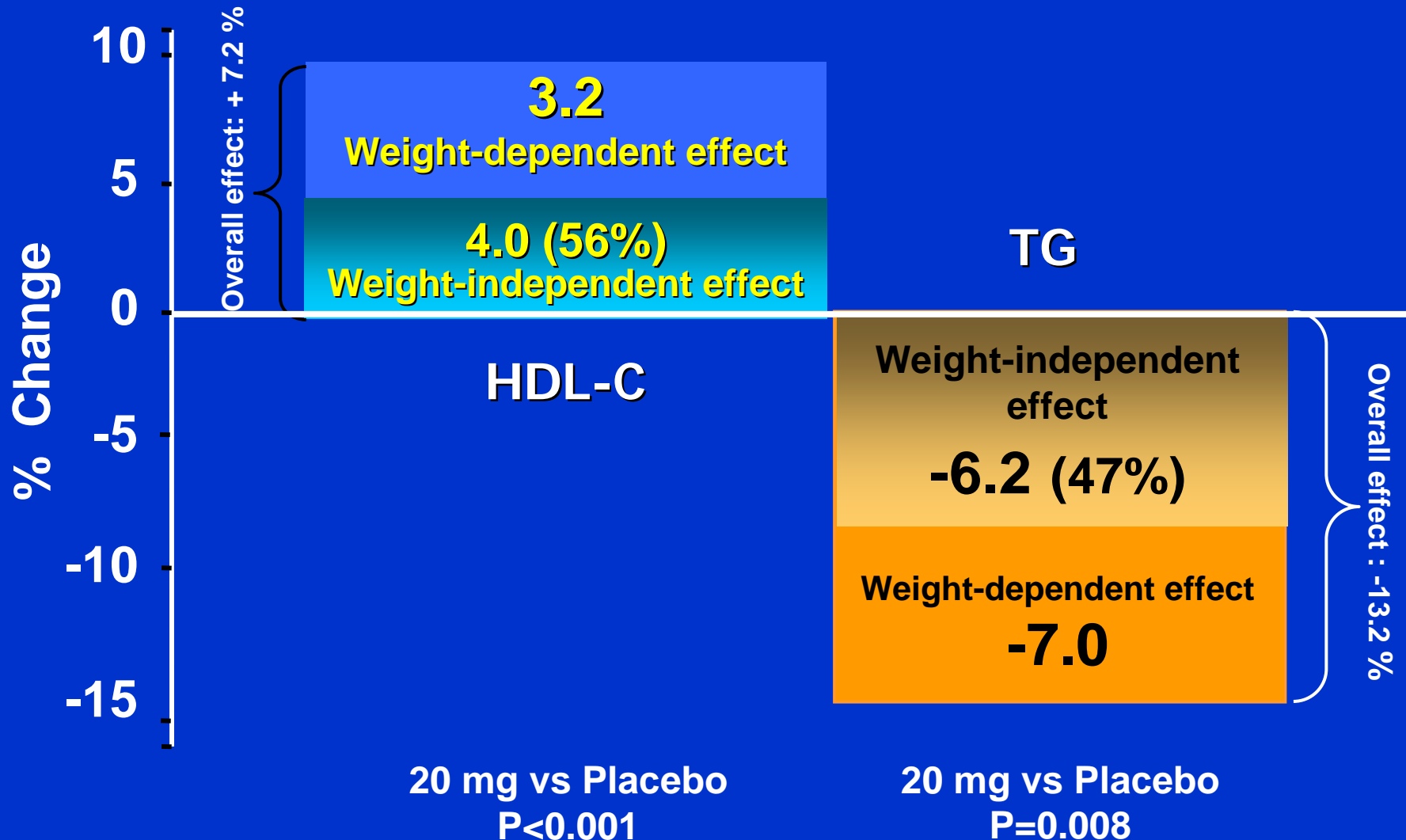
# Change in Metabolic Syndrome at 1 Year

ITT, LOCF



# Improvements in Lipid Parameters Adjusted for Weight Loss

1 Year Analysis



# RIO NA – Overall safety – 1 Year

	Placebo n = 607	Rimonabant 5 mg n = 1214	Rimonabant 20 mg n = 1219
Overall dropout rate	49.1 %	49.0 %	44.9 %
Subjects with any adverse event	82.0 %	83.4 %	85.5 %
Subjects with any serious adverse event	3.5 %	3.8 %	4.5 %
Subjects discontinued due to adverse event	7.2 %	9.4 %	12.8 %

# Pooled RIO Studies 1-Year Overall Safety

	Placebo	Rimonabant 5 mg	Rimonabant 20 mg
	n = 1254	n = 2162	n = 2164
Subjects with any adverse event	82.5 %	83.0 %	86.1 %
Subjects with any serious adverse event	4.1%	5.0 %	5.6 %
Deaths	n = 1	n = 2	n = 1
Subjects discontinued due to adverse event	7.7 %	8.9 %	13.6 %

# Pooled RIO Studies 1-Year: Adverse events leading to drug discontinuation $\geq 0.5\%$

	Placebo	Rimonabant	
	(N=1254) n (%)	5 mg (N=2162) n (%)	20 mg (N=2164) n (%)
<b>Psychiatric disorders</b>	<b>40 (3.2)</b>	<b>79 (3.7)</b>	<b>146 (6.7)</b>
Depressed mood disorders	19 (1.5)	48 (2.2)	63 (2.9)
Anxiety	5 (0.4)	8 (0.4)	24 (1.1)
Irritability	2 (0.2)	4 (0.2)	10 (0.5)
<b>Nervous system disorders</b>	<b>14 (1.1)</b>	<b>25 (1.2)</b>	<b>46 (2.1)</b>
Headache	5 (0.4)	7 (0.3)	10 (0.5)
Dizziness	1 (<0.1)	4 (0.2)	14 (0.6)
<b>Gastrointestinal disorders</b>	<b>5 (0.4)</b>	<b>18 (0.8)</b>	<b>49 (2.3)</b>
Nausea	1 (<0.1)	5 (0.2)	29 (1.3)

According to MedDRA code, 0.5% in any rimonabant group: in the 3 main system organ classes

# RIO~North America: Conclusions

**Rimonabant, the first selective CB<sub>1</sub> blocker**

- Robust data replicated in 3 studies (RIO~NA, RIO~Eu, RIO~Lipids)
  - Significant reductions in weight and waist circumference achieved after 1 year
  - Significant improvement in metabolic profile
- Weight-independent effects on several metabolic variables
- Efficacy achieved at 1 year maintained in the 2nd year
- Good 1 and 2 year safety profile

# Drug Treatment for Obesity

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- Produces clinical benefits, reductions in comorbidity even with little weight loss. Physicians should be encouraged to use pharmacotherapy in appropriate cases with quick identification of non-responders and quick adjustment in therapy.
- Acknowledgment of off-label use of drugs should be done for both unapproved drugs and prolonged use of approved drugs over the current limits; patients' consent should be obtained in such cases.
- Physicians should familiarize themselves with side effects of approved and unapproved drugs being prescribed for weight loss and have extensive informative discussion with their patients regarding the safety and efficacy of such treatment before prescribing it.

# **Drug Treatment for Obesity (cont.)**

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- **Two to four year studies have been done, as long as new drugs for other chronic illnesses, however longer term effects on morbidity and mortality have not been determined.**
- **Behavioral interventions are considered the primary means to promote and maintain weight loss. However more aggressive behavioral interventions will most likely produce better results when combined with effective medication.**
- **In my opinion, effective therapy for obesity is less expensive than treating multiple complications and it should be given to all affected patients.**

**Thank you !**