

# **Medical Need and Clinical Efficacy of Rimonabant**

**Pierre Rosenzweig, MD**

Internal Medicine Clinical Development

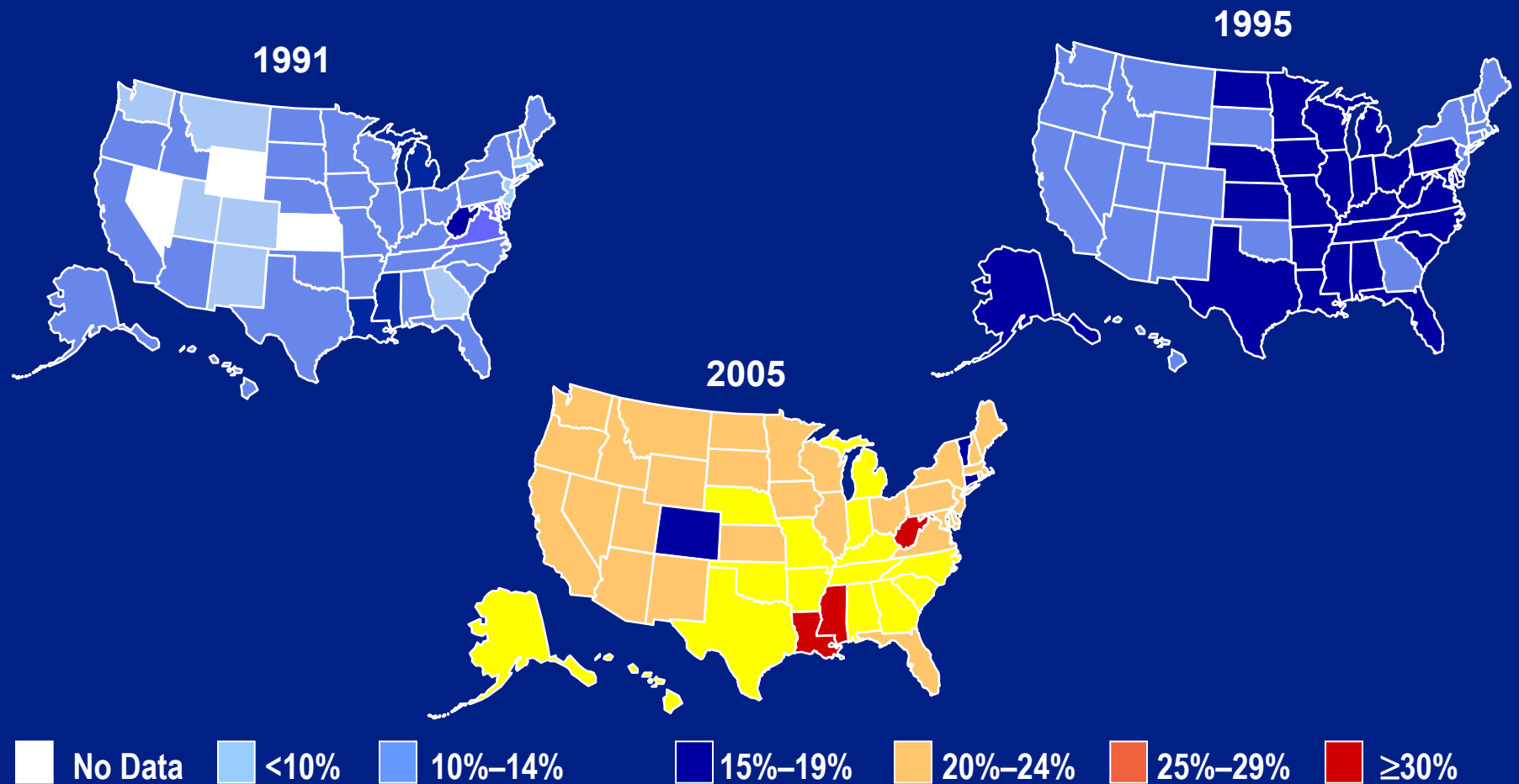
# Presentation Outline

---

- **Medical Need**
- Treatment of obesity
- Glycemic control in type 2 diabetes
- Relationship between metabolic improvements and body weight loss
- Conclusion

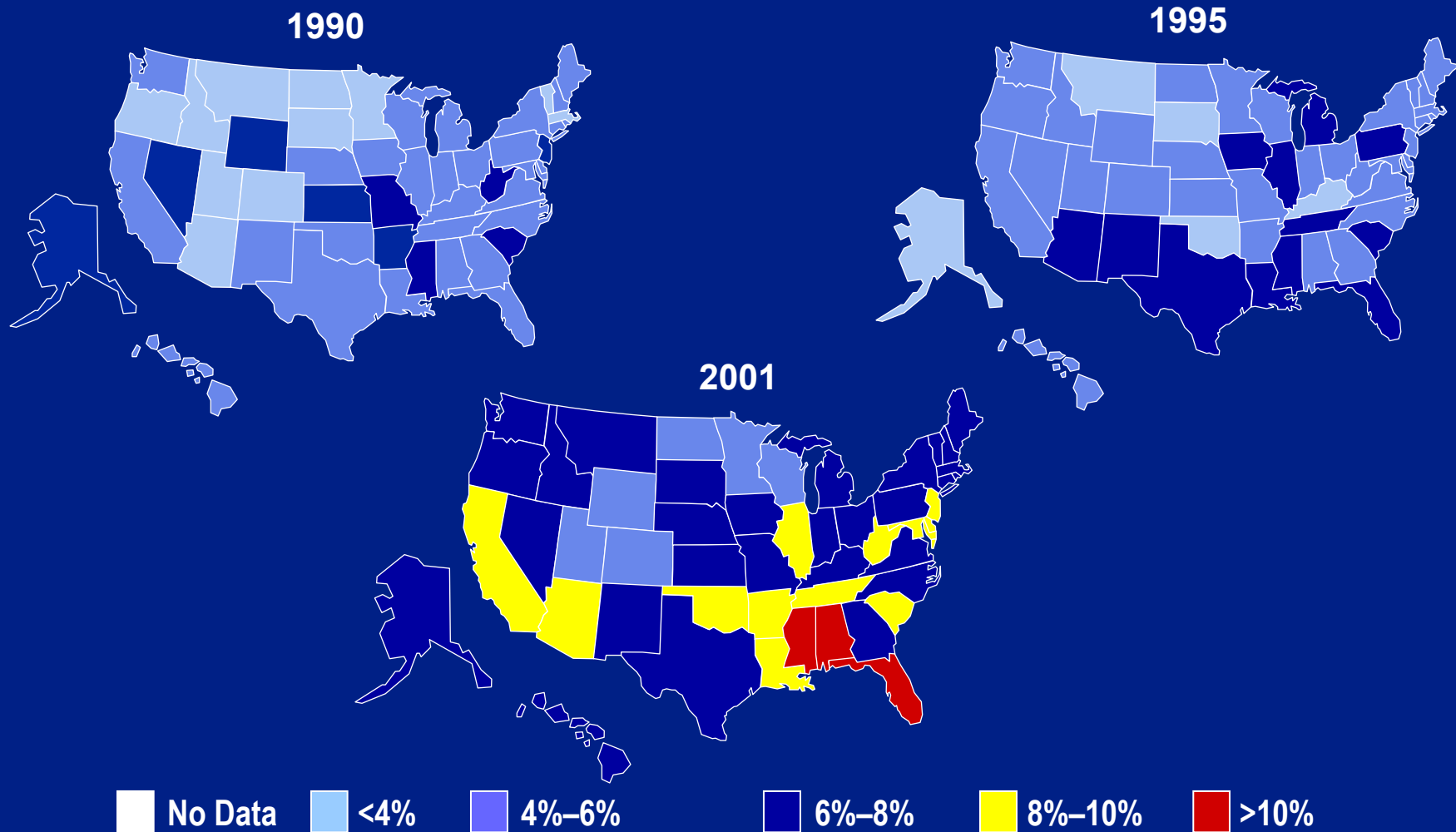
# Obesity\* Trends Among US Adults

(\*BMI  $\geq$  30, or about 30 lb overweight for 5'4" person)



Available at: <http://www.cdc.gov/nccdphp/dnpa/obesity/trend/maps/>

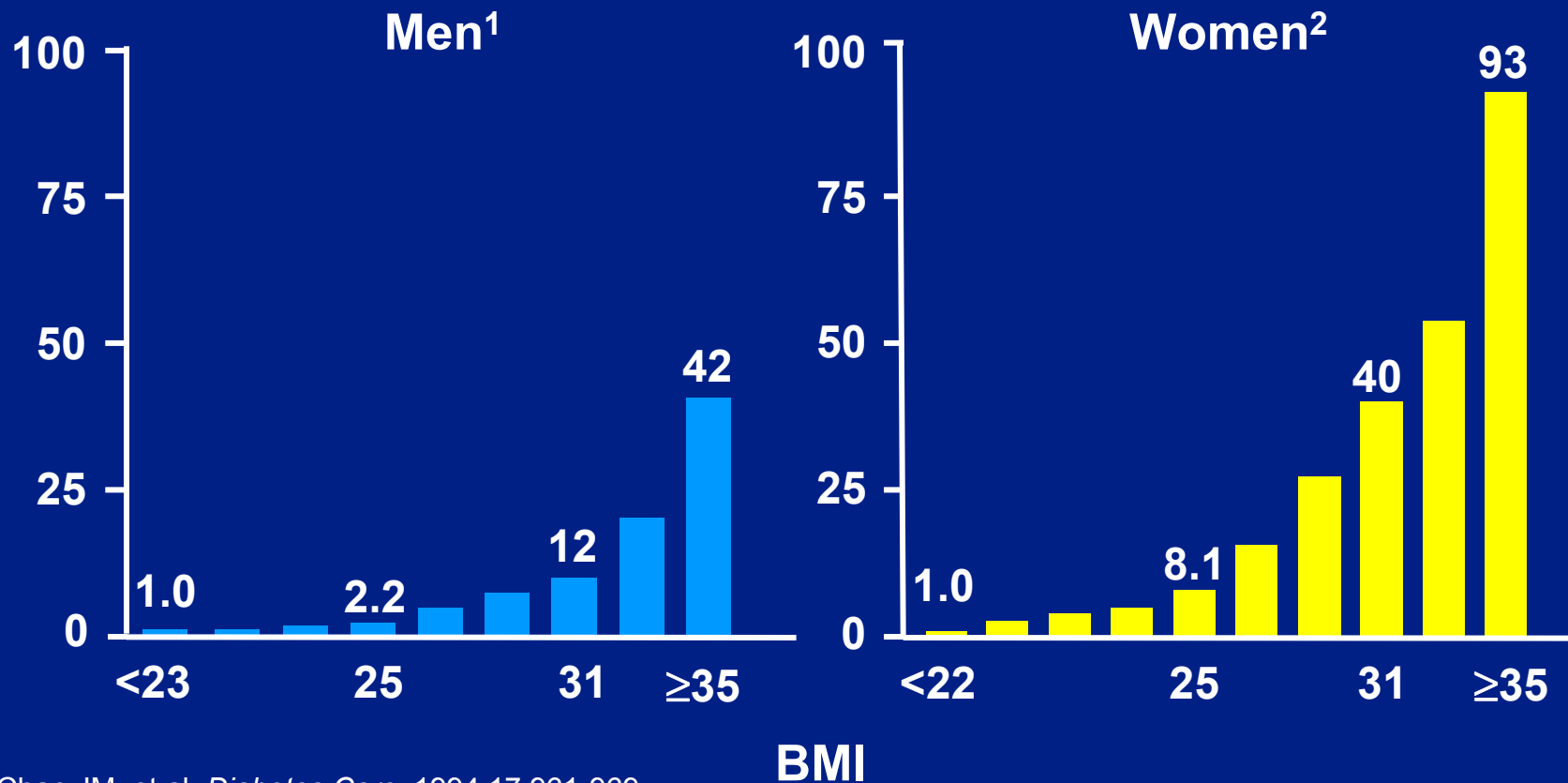
# Diabetes Trends Among Adults in the U.S.



Source: Mokdad et al., *Diabetes Care* 2000;23:1278-83; *J Am Med Assoc* 2001;286:10.

# Obesity and the Risk for Type 2 Diabetes

## Age-adjusted relative risk of type 2 diabetes



1. Chan JM, et al. *Diabetes Care*. 1994;17:961-969.  
2. Colditz G, et al. *Ann Intern Med*. 1995;122:481-486.

# The Obese Patient Perspective (1)

- Impaired Quality of Life including social discrimination, restricted activity, exercise intolerance, low self esteem, and social isolation<sup>1</sup>
- Frequent co-morbidities including sleep apnea, osteoarthritis, back pain, and infertility<sup>2</sup>
- Risk of developing diabetes, dyslipidemia and cardiovascular disease<sup>3</sup>

<sup>1</sup>NIH guideline 1998.

<sup>2</sup>National Task Force on the Prevention and Treatment of obesity. *Arch Intern Med* 2000; 160:898-904.

<sup>3</sup>AGA Technical Review on Obesity. Klein S. *Gastroenterology* 2002; 123:882-932.

# The Obese Patient Perspective (2)

- Obese patients are desperately trying to lose weight but most weight loss interventions fail<sup>1</sup>
- Obese patients have unrealistic weight loss goals<sup>2</sup>
- Frustration and disappointment lead many obese patients to products not approved for weight loss<sup>3</sup>
- Bariatric surgery as the last resort; effective, though with risks and complications

Outcome	Weight (lbs)	% Reduction
Initial	218	0
Dream	135	38
Happy	150	31
Acceptable	163	25
Disappointed	180	17

<sup>1</sup> Williamson DF et al. *Am J Public Health* 1992;82:1251-7.

<sup>2</sup> Foster et al. *J Consult Clin Psychol.* 1997;65:79

<sup>3</sup> Ipsos-Insight PharmTrends Report, 2004

# 5-10% BW Loss: A Realistic Objective with Important Clinical Benefits

- Medical weight loss
  - long-term reduction in weight and fat mass with improvement in physical health in high-risk patients<sup>1</sup>
- 5-10% weight loss
  - positive Impact on CV Risk Factors: type 2 diabetes, blood pressure, dyslipidemia<sup>2-3</sup>
  - improvement in co-morbidities: sleep apnea, osteoarthritis, infertility
  - improvement in QoL<sup>4</sup>

<sup>1</sup> Colman E. Advisory Committee Meeting January 23, 2006.

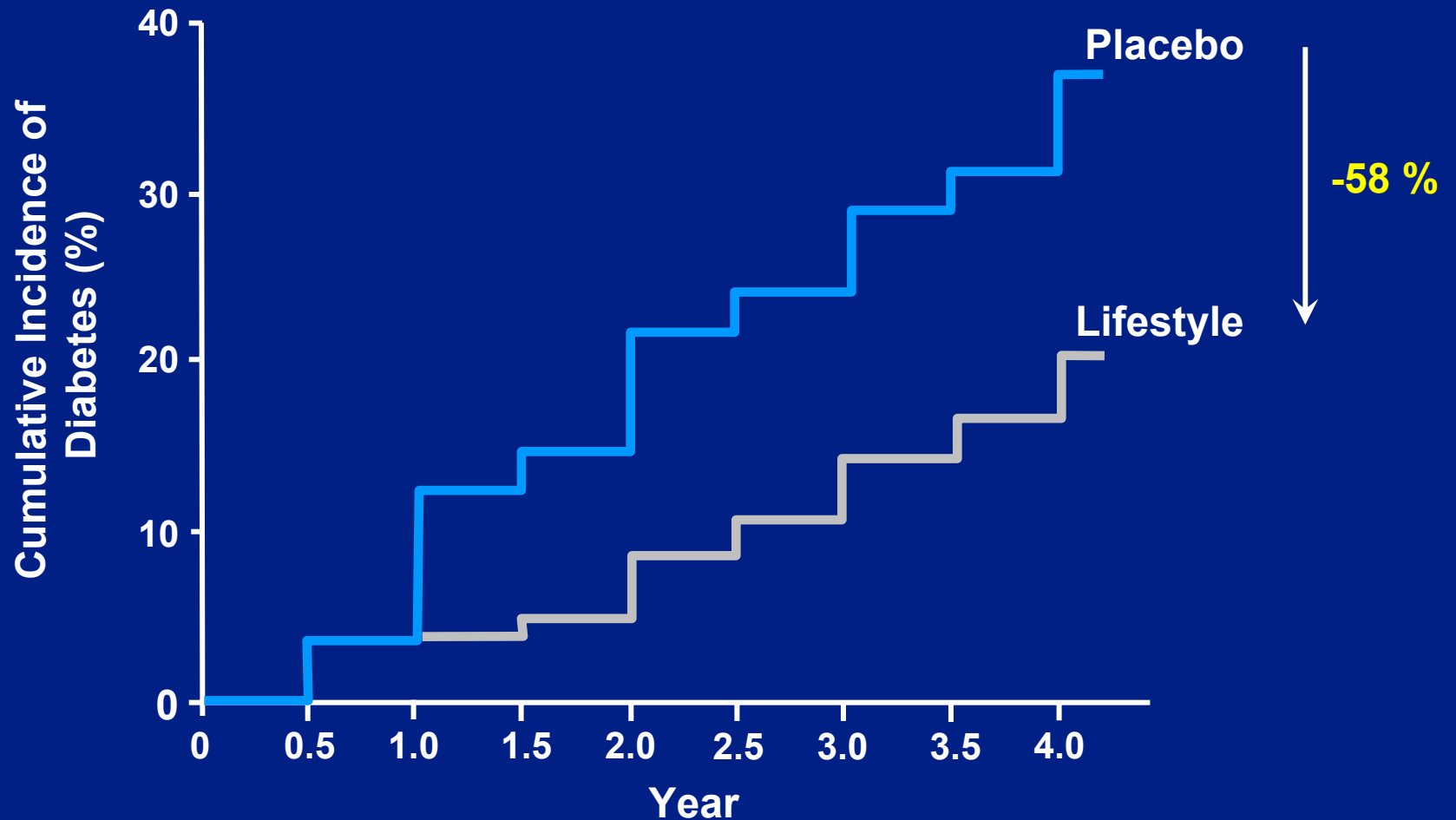
<sup>2</sup> Goldstein KR et al. *Qual Life Res* 1999;8:275-277.

<sup>3</sup> NIH guideline 1998.

<sup>4</sup> Fontaine DJ. *Int J Obes Relat Metab Disord* 1992;16:379-415.



# DPP Study: 5% Weight Loss and Regular Exercise Prevent Diabetes in Overweight/Obese with Impaired Glucose Tolerance



Diabetes Prevention Program Research Group. *N Eng J Med* 2002;346:393.

# A Guide to Selecting Treatment: NIH Guidelines

Treatment	BMI Category (kg/m <sup>2</sup> )				
	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

- Since obesity is a chronic disorder, the short-term use of drugs is not helpful: administer for the long term

*The Practical Guide: Identification, Evaluation, and Treatment of Overweight and Obesity in Adults.* NIH/NHLBI/NAASO; October 2000. NIH publication No. 00-4084.

# FDA Approvals of Anti-obesity Drugs



1959 – phentermine

1973 – fenfluramine

1996 – dexfenfluramine

1997 – sibutramine (Meridia®)      1997 – Withdrawal of fenfluramine  
and dexfenfluramine

1999 – orlistat (Xenical®)

# Summary

- Obesity and type 2 diabetes: a growing epidemic
- Many patients use unapproved weight loss products and resort to bariatric surgery, effective but with risks and complications
- Modest 5-10% weight loss provides important medical benefits
- Pharmacotherapy is a recognized treatment from BMI > 27 with comorbidities and BMI  $\geq$  30

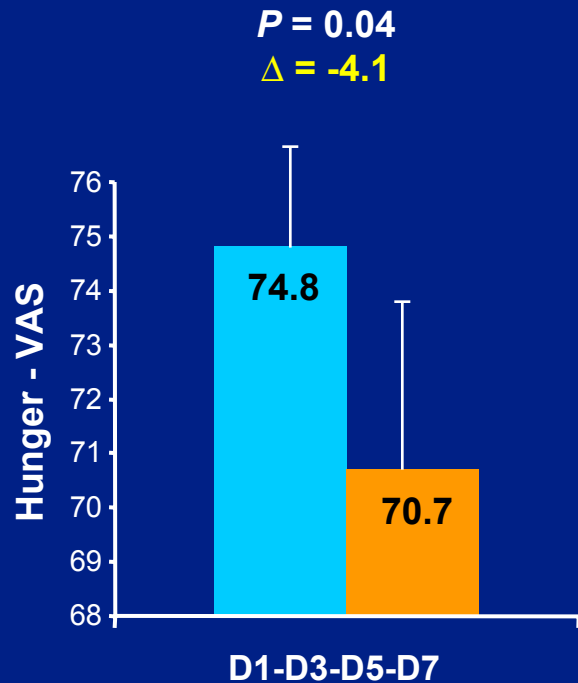
# Presentation Outline

---

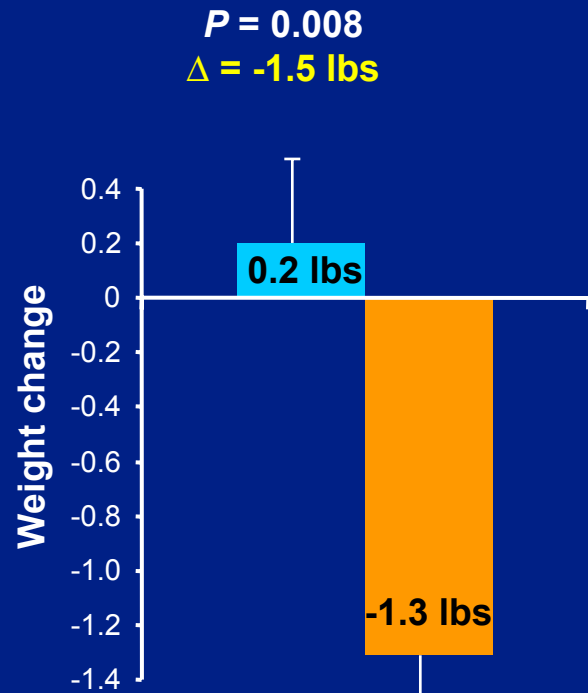
- Medical Need
- **Treatment of obesity**
- Glycemic control in type 2 diabetes
- Relationship between metabolic improvements and body weight loss
- Conclusion

# First Pharmacodynamic Results in Overweight Humans (PDY3255)

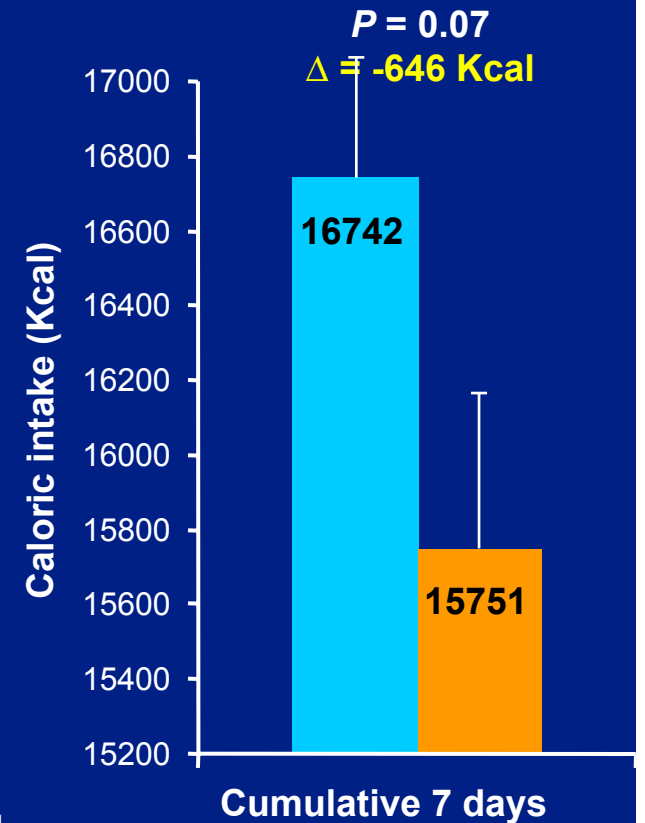
### Hunger Visual Analog Scale



### Weight



### Caloric intake

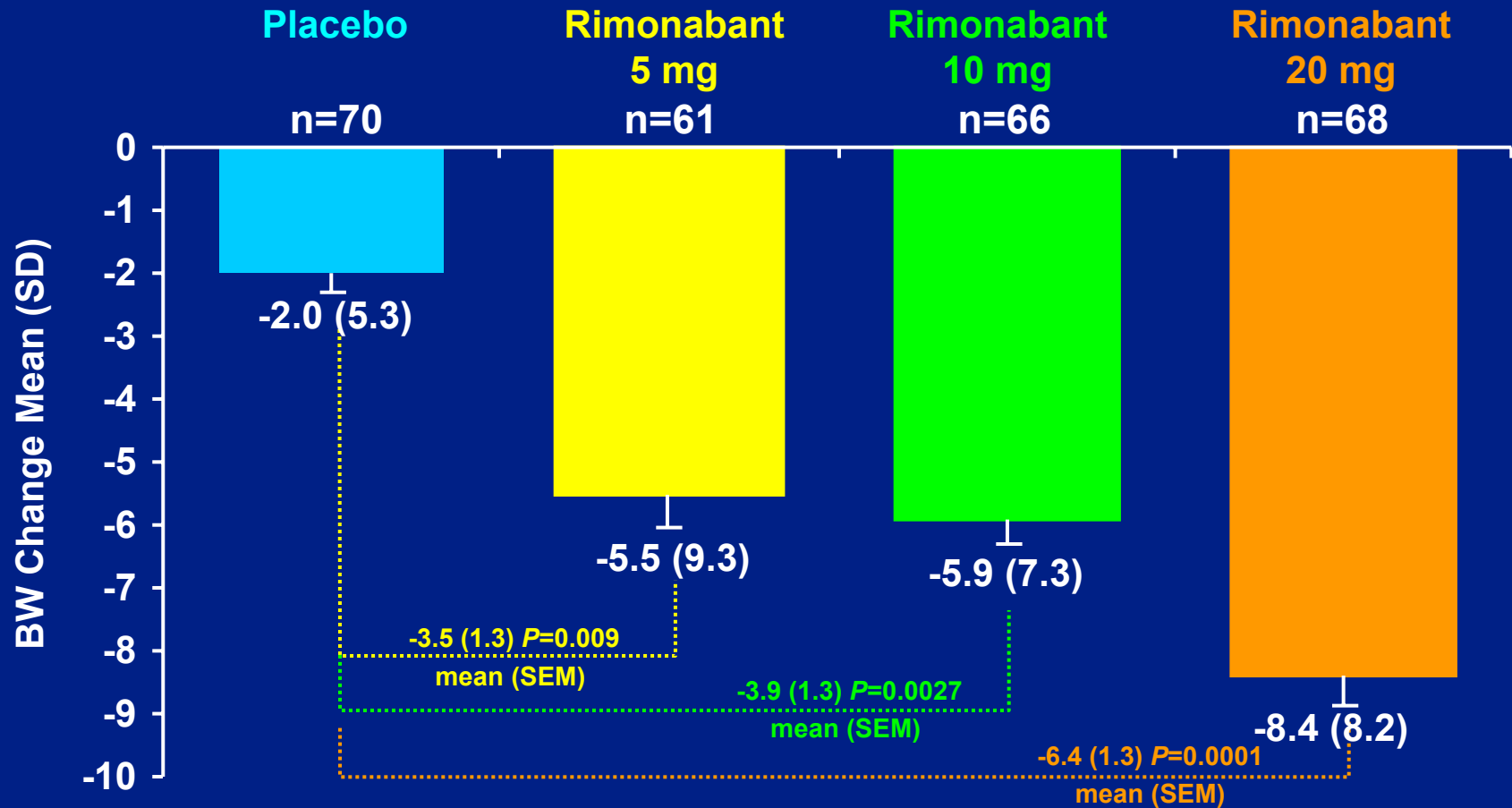


■ Placebo    ■ Rimonabant 20mg

MM-49

# Phase 2 Study (DRI3388)

Weight loss (lbs) at 16 Weeks: ITT - LOCF



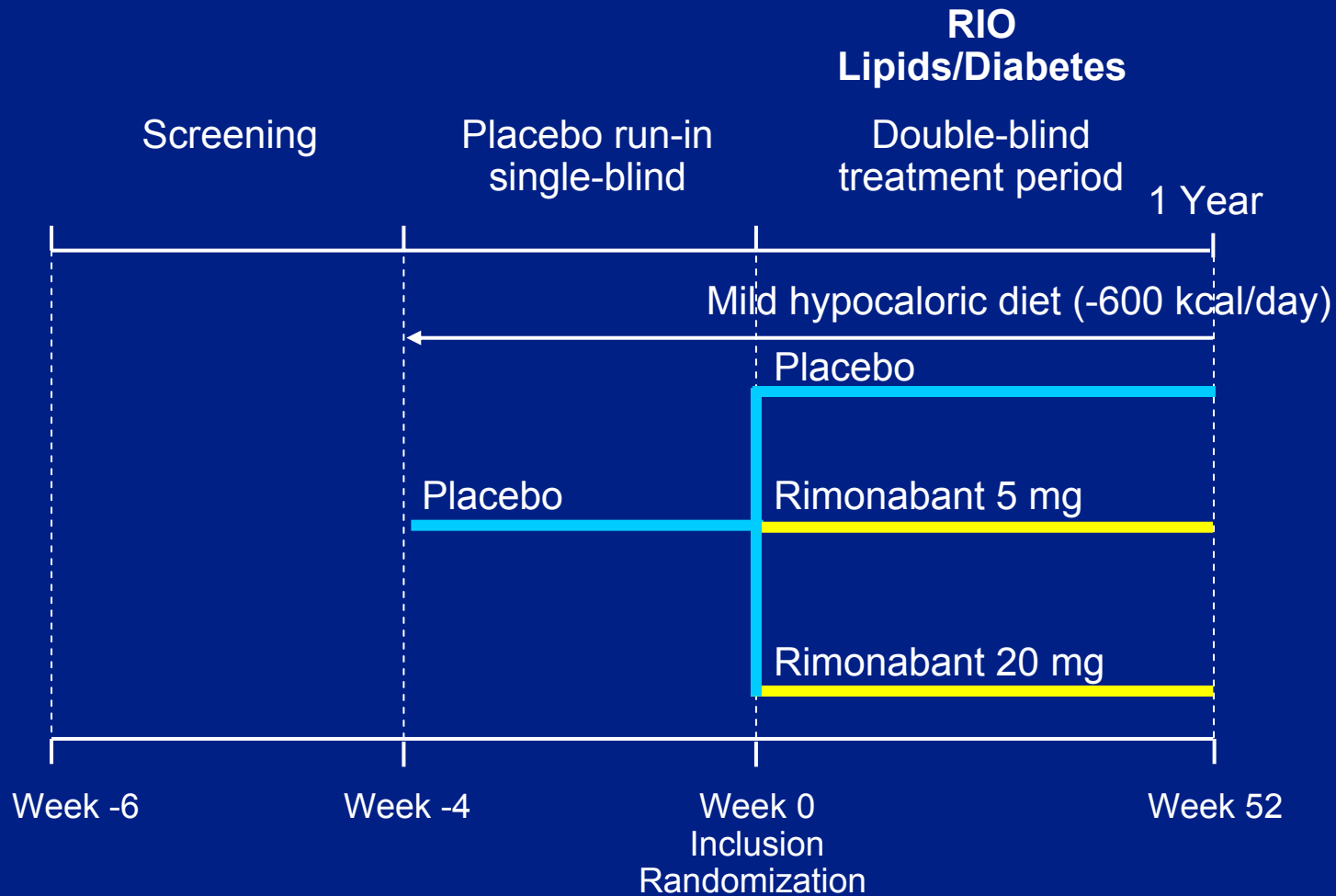
# Rimonabant in Obesity (RIO) Global Clinical Development

Study	Population	6625 Patients*	Duration
RIO- North America	Obese or overweight with comorbidities (non-diabetic)	3040	1 yr + 1 yr
RIO- Europe	Obese or overweight with comorbidities (non-diabetic)	1507	2 yrs
RIO- Lipids	Obese or overweight with untreated dyslipidemia (non-diabetic)	1033	1 yr
RIO- Diabetes	Obese or overweight type 2 diabetes receiving metformin or sulfonylurea	1045	1 yr

\*randomized and exposed

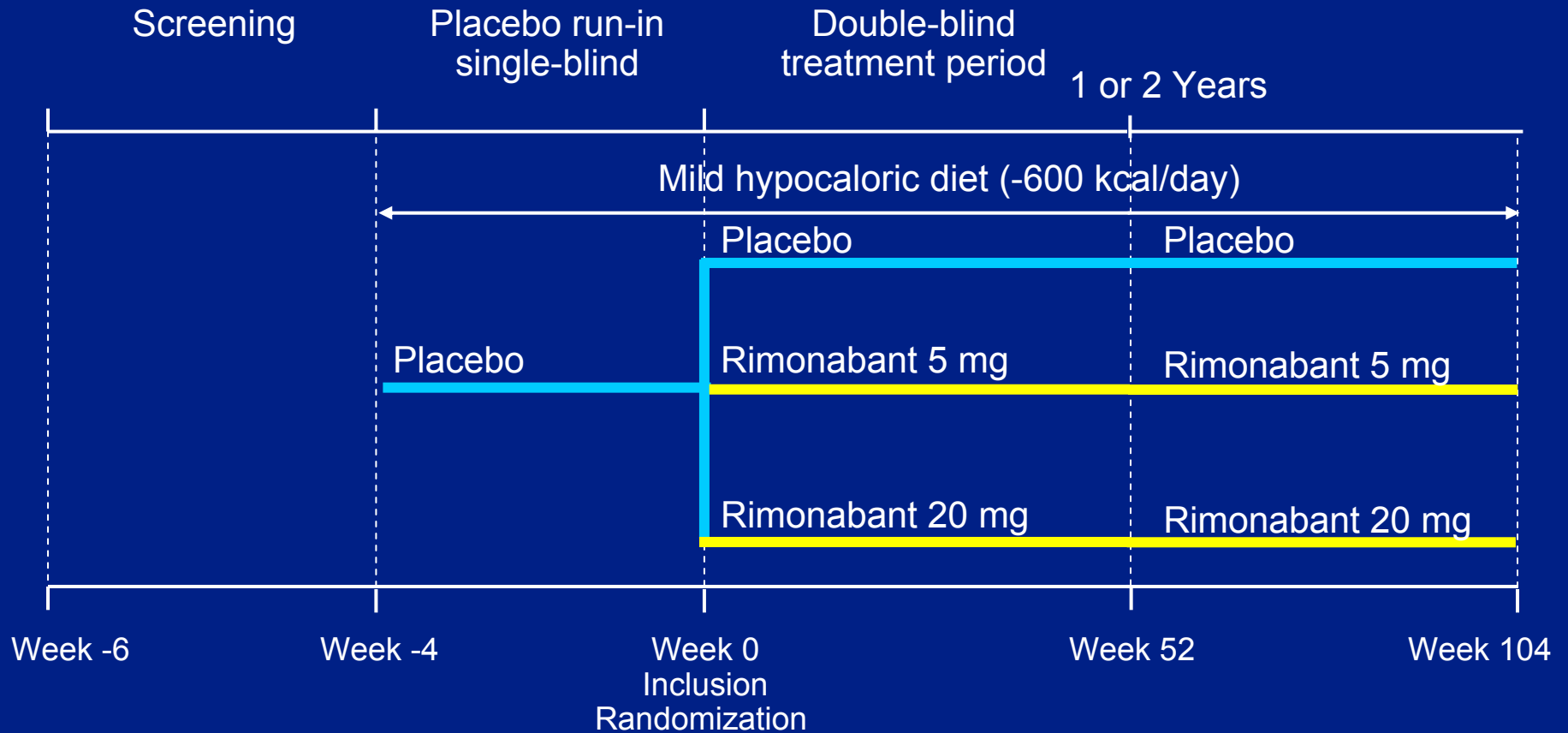


# RIO Studies Design



# RIO Studies Design

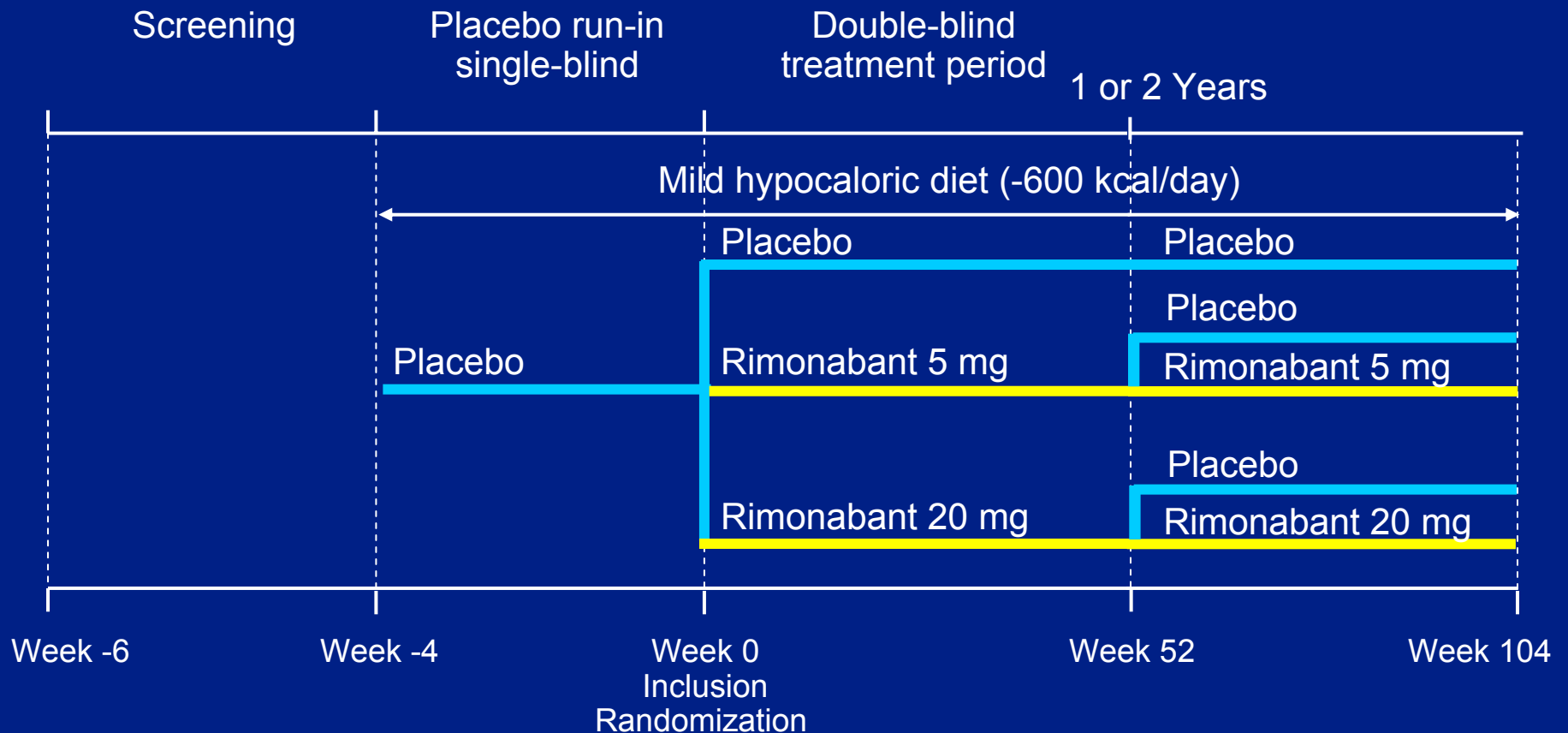
RIO  
Europe



MM-53

# RIO Studies Design

RIO  
NA



MM-54

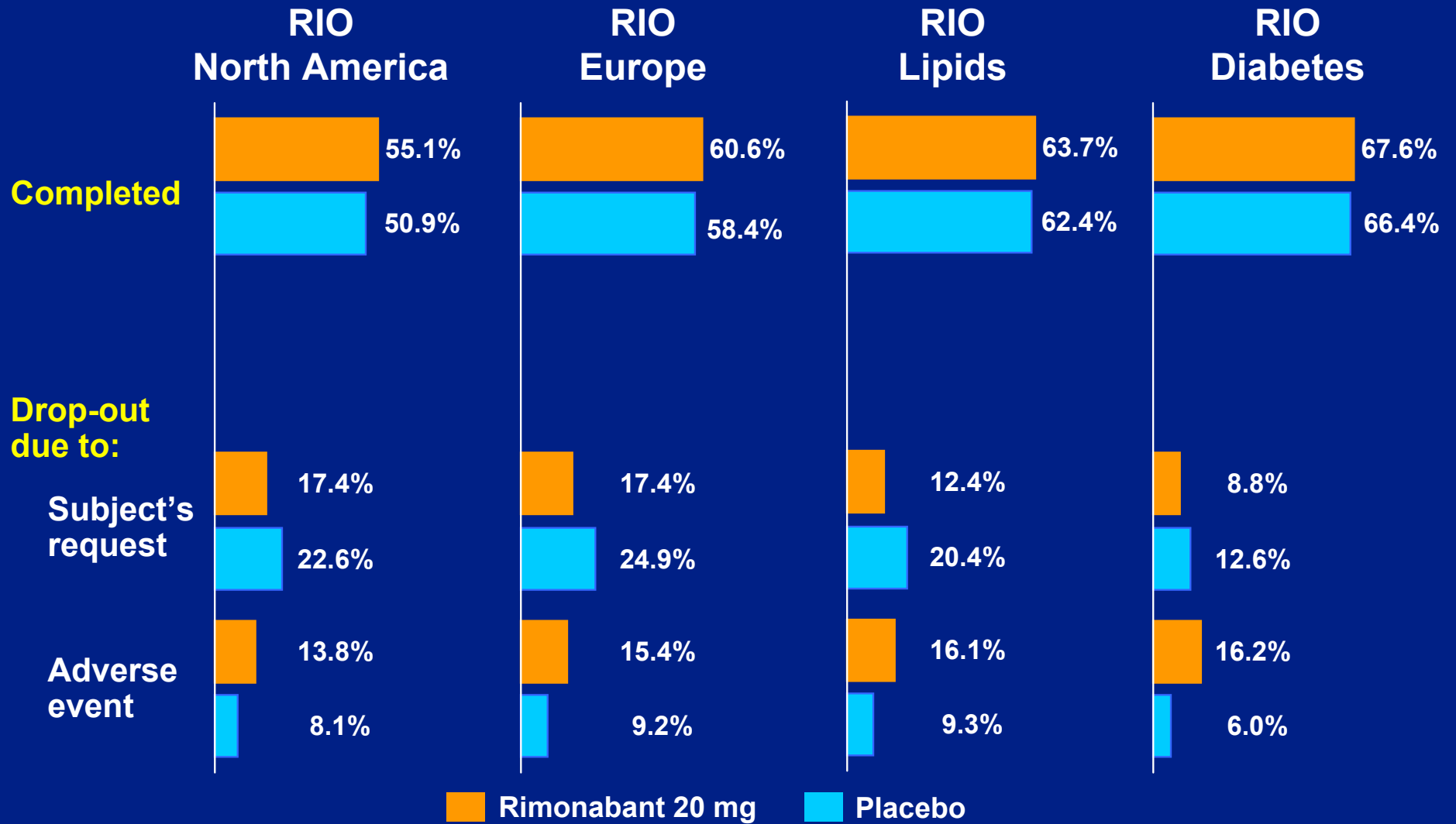
# Baseline Demographics

		RIO-North America (N=3040)	RIO Europe (N=1507)	RIO Lipids (N=1033)	RIO Diabetes (N=1045)
<b>Age (yr)</b>	Mean	45.0	45.0	47.8	55.6
<b>Race (%)</b>	Caucasian	84.0	93.6	96.8	88.5
	Black	11.2	4.8	0.6	5.5
	Other	4.8	1.6	2.6	6.0
<b>Gender (%)</b>	Females	81.7	79.5	60.6	50.9
<b>Weight (lbs)</b>	Mean	230.2	222.8	207.6	212.4
<b>BMI (kg/m<sup>2</sup>)</b>	Mean	37.6	36.0	33.3	33.7
<b>Waist (cm)</b>	Mean	105.8	108.4	105.0	109.0

## Baseline Cardiovascular and Metabolic Risk Factors (%)

	RIO-North America (N=3040)	RIO Europe (N=1507)	RIO Lipids (N=1033)	RIO Diabetes (N=1045)
<b>Dyslipidemia</b>	<b>62.6</b>	<b>60.7</b>	<b>100</b>	<b>55.6</b>
TG ≥ 150mg/dL (1.69mmol/L)	33.4	27.4	57.4	53.0
HDL-C (men) < 40mg/dL (1.03mmol/L)	50.3	50.0	62.6	45.1
HDL-C (women) < 50 mg/dL (1.3 mmol/L)	52.8	54.3	70.7	58.3
LDL-C ≥ 130 mg/dL (3.36mmol/L)	34.9	40.6	58.2	32.7
Drug treatment if dyslipidemic	15.1	13.7	0	64.9
<b>Diabetes</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>100</b>
Pre-diabetes				
Fasting glucose ≥ 100 mg/dL (5.55mmol/L)	20.8	29.2	28.8	
2h post glucose load ≥120 mg/dL (7.77mmol/L)		15.4	22.6	
<b>Hypertension</b>	<b>30.4</b>	<b>40.9</b>	<b>27.2</b>	<b>61.2</b>
Drug treatment if hypertensive	68.1	55.1	68.7	93.0

# Completion and Discontinuation Rates at 1-Year



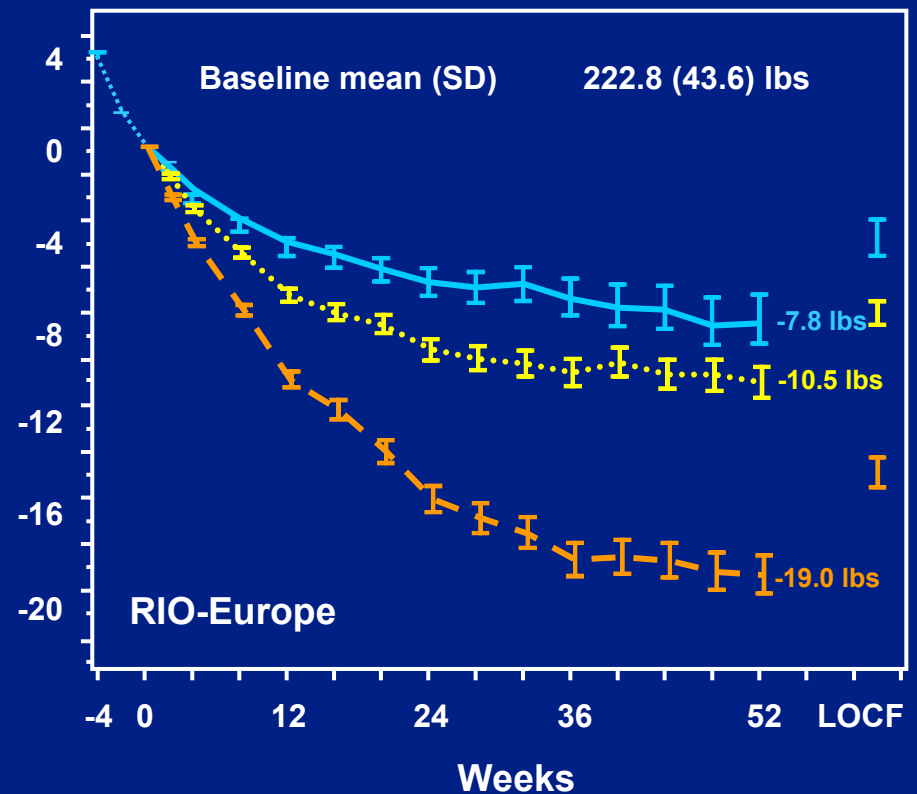
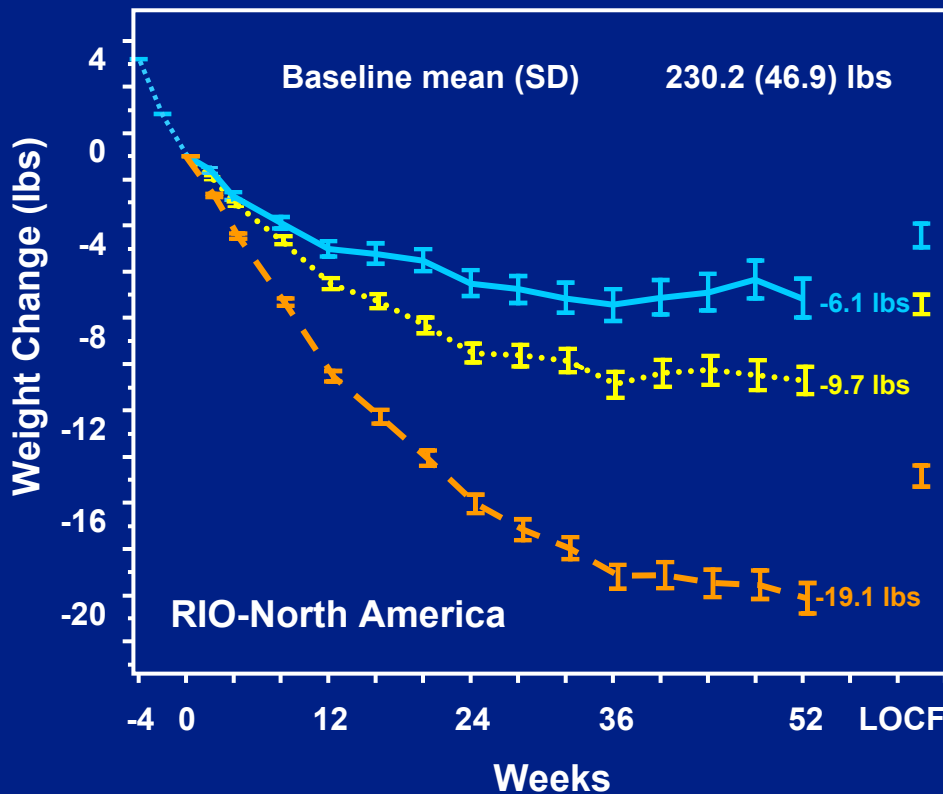
# RIO-North America and RIO-Europe Weight Loss (lbs) at 1-year: ITT-LOCF and Observed Cases

Difference between groups, mean (SEM)

ITT; LOCF 5 mg vs. Pbo -2.9 (0.7) ( $P < 0.001$ )  
 20 mg vs. Pbo -10.5 (0.7) ( $P < 0.001$ )

Difference between groups, mean (SEM)

ITT; LOCF 5 mg vs. Pbo -3.1 (1.0) ( $P = 0.002$ )  
 20 mg vs. Pbo -10.4 (1.0) ( $P < 0.001$ )



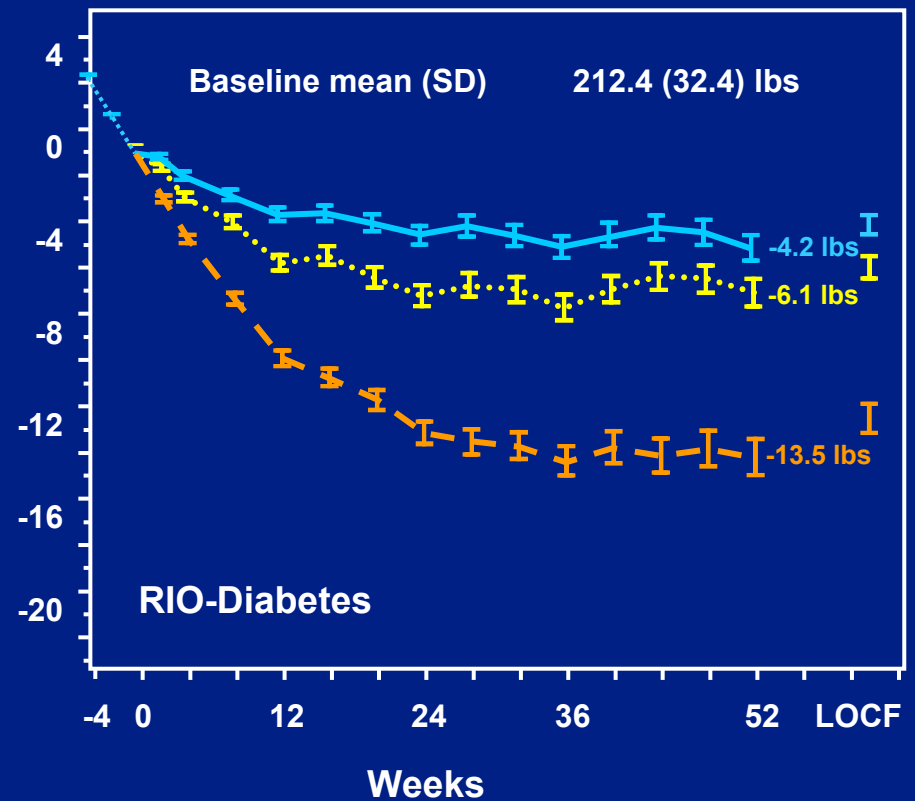
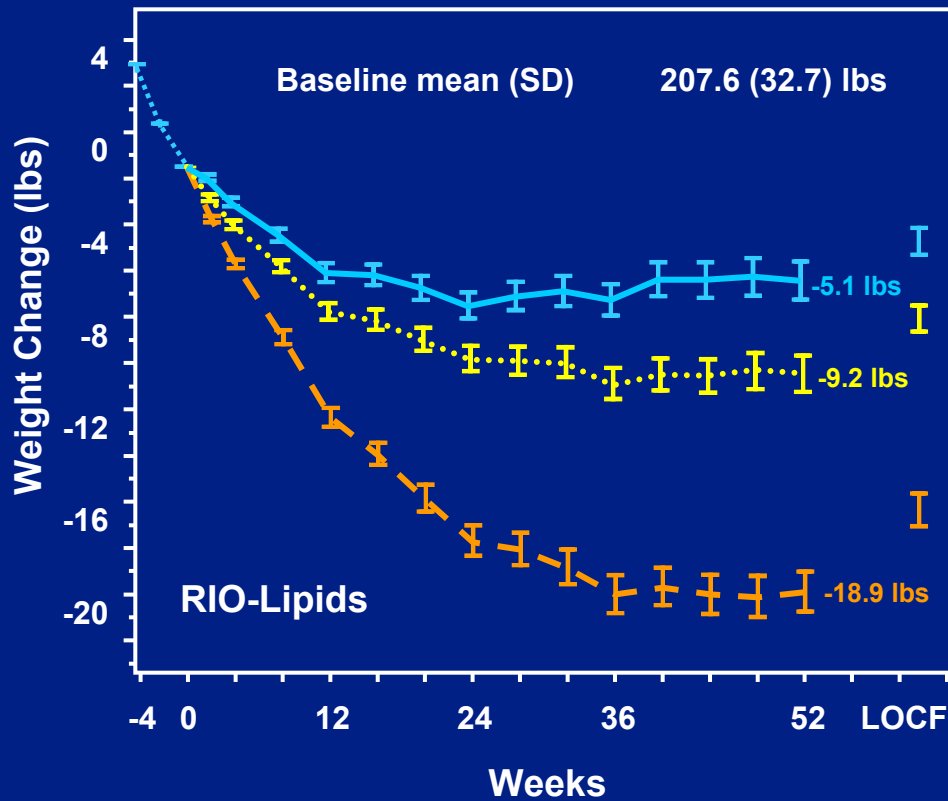
# RIO-Lipids and RIO-Diabetes Weight Loss (lbs) at 1-year: ITT-LOCF and Observed Cases

Difference between groups, mean (SEM)

ITT; LOCF    5 mg vs. Pbo    -3.4 (0.9) ( $P<0.001$ )  
                   20 mg vs. Pbo    -11.9 (0.9) ( $P<0.001$ )

Difference between groups, mean (SEM)

ITT; LOCF    5 mg vs. Pbo    -1.8 (0.7) ( $P=0.013$ )  
                   20 mg vs. Pbo    -8.6 (0.7) ( $P<0.001$ )

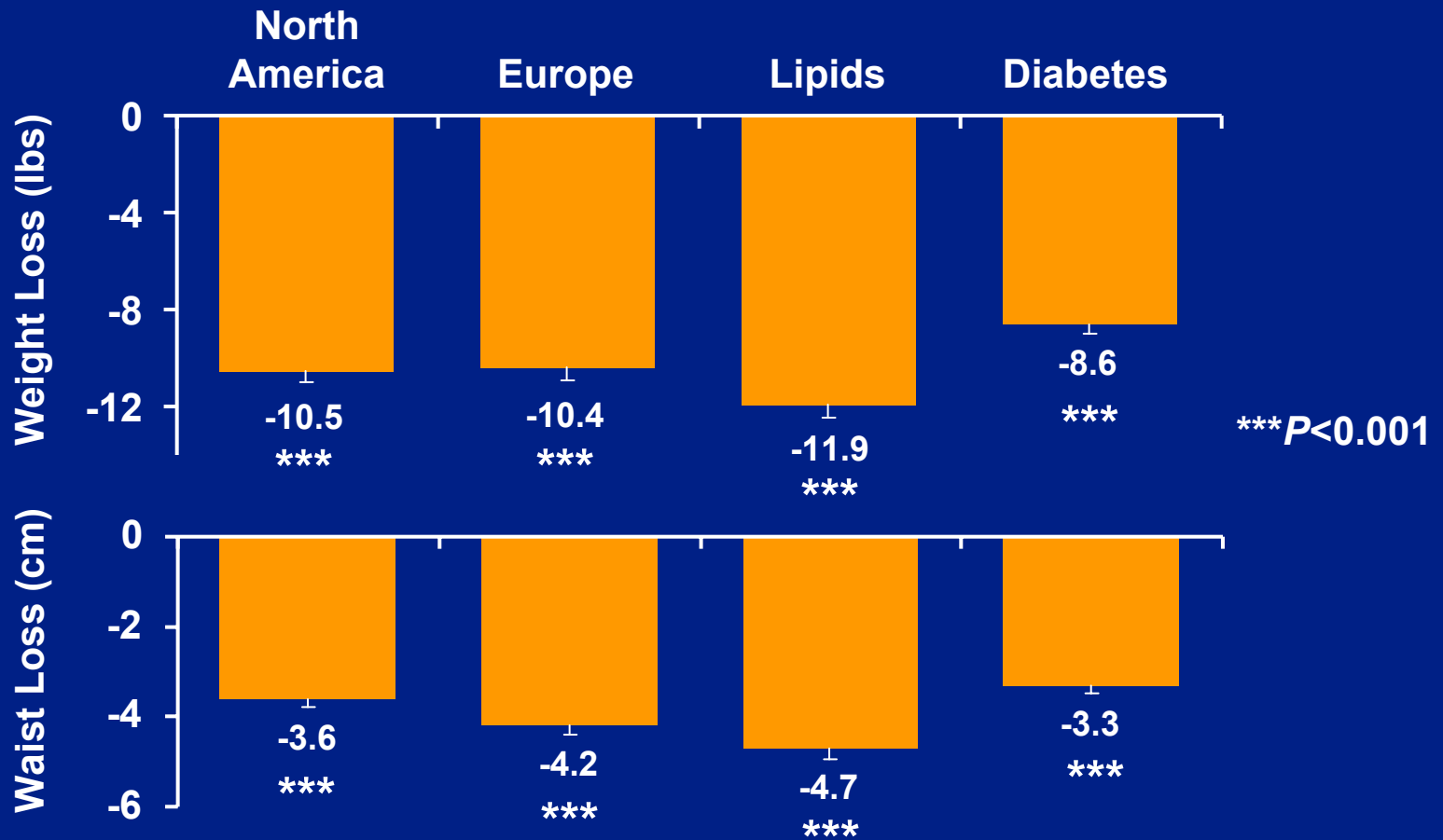




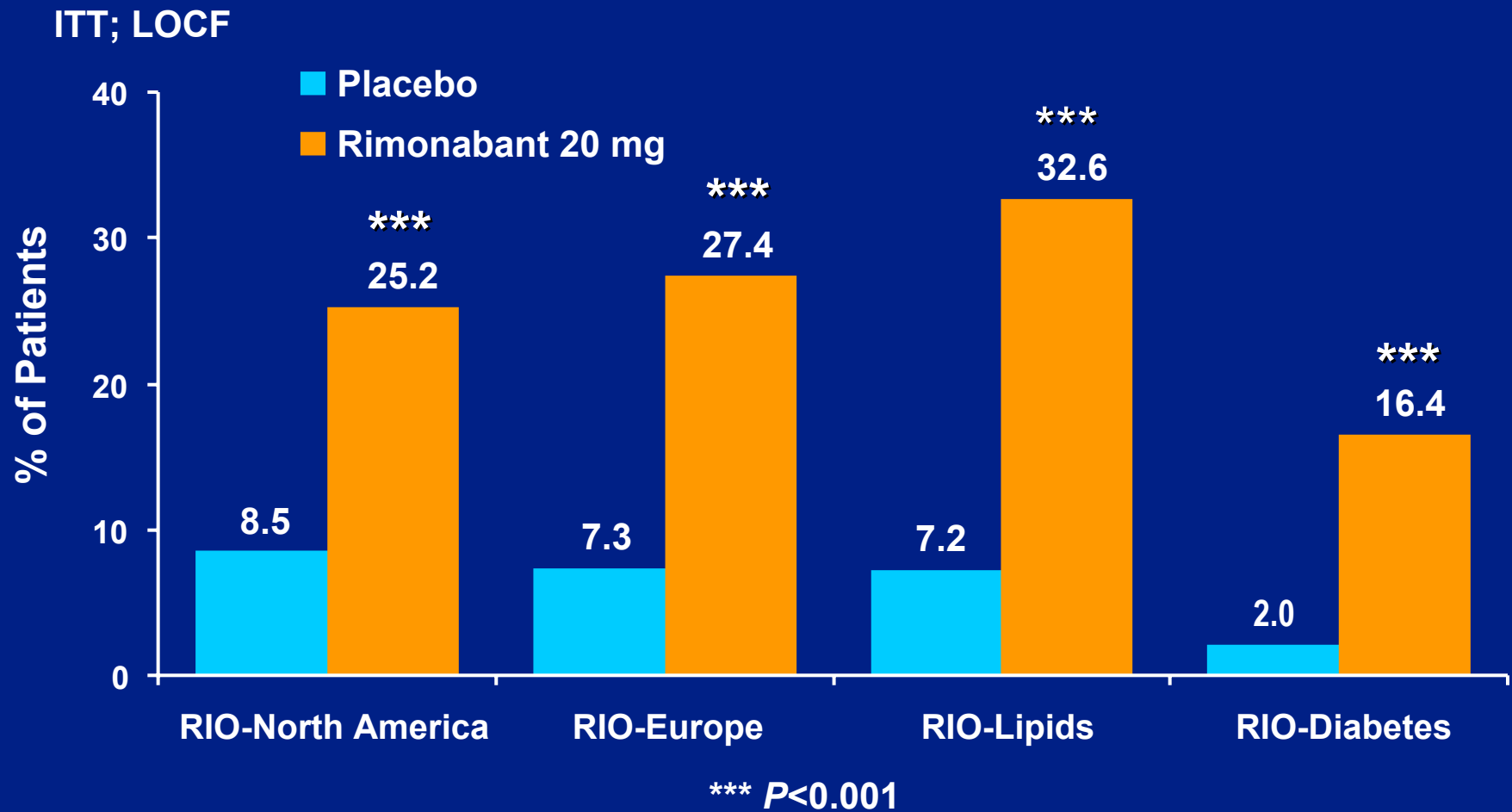
# Weight & Waist Loss

## The Consistency of RIO

Placebo – subtracted mean weight and waist loss after Rimonabant 20 mg (ITT; LOCF)



# Body Weight: Responders with 10% BW Loss at 1-year



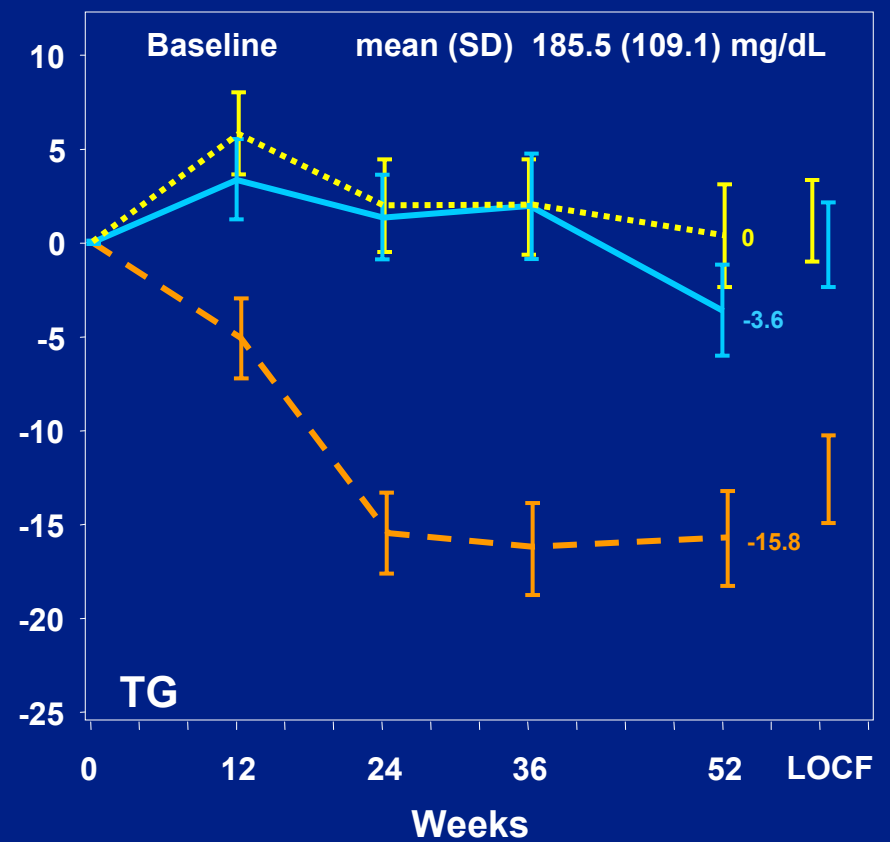
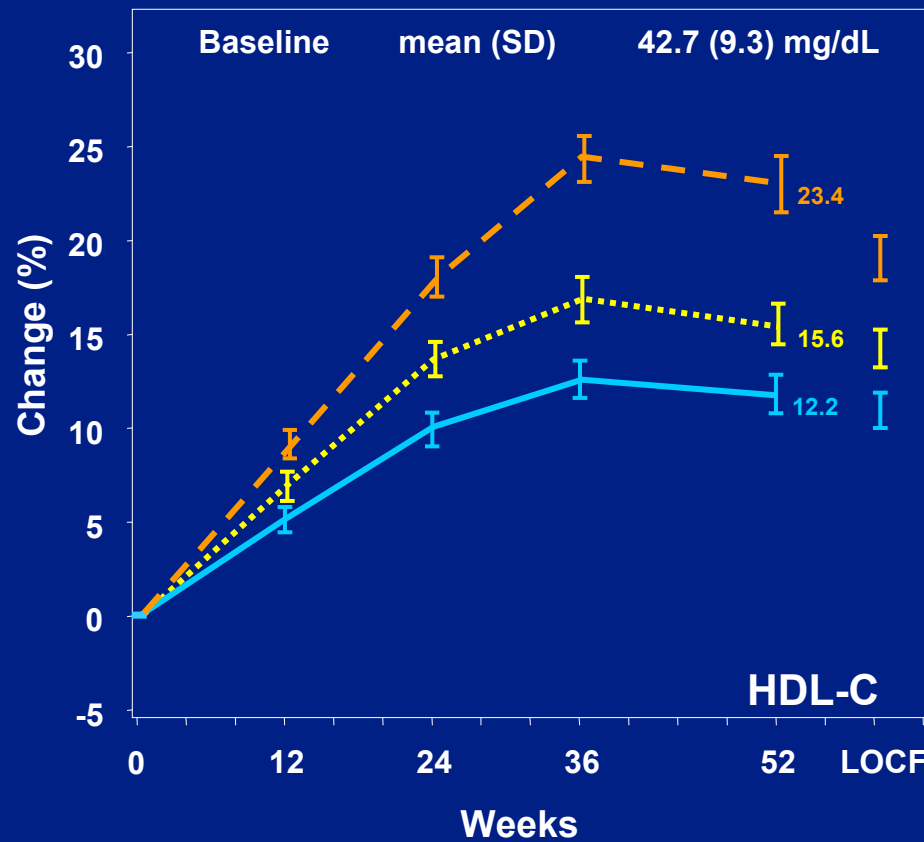
# RIO-Lipids HDL-C and TG (% Change): ITT-LOCF and Observed Cases

Difference between groups, mean (SEM)

ITT; LOCF    5 mg vs. Pbo    3.3 (1.5) ( $P < 0.025$ )  
                  20 mg vs. Pbo    8.0 (1.5) ( $P < 0.001$ )

Difference between groups, mean (SEM)

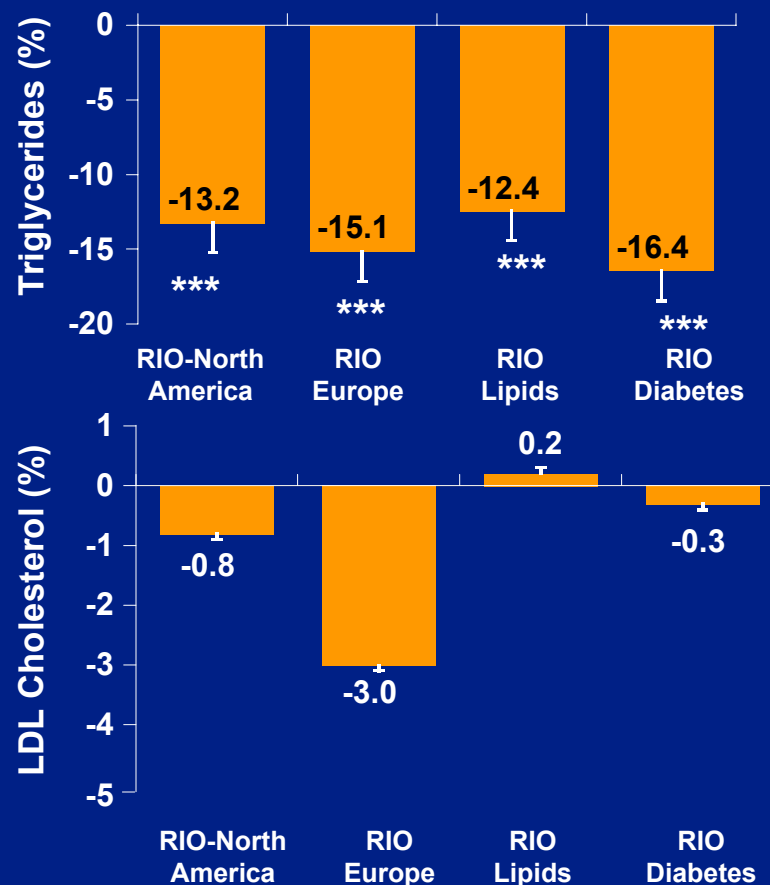
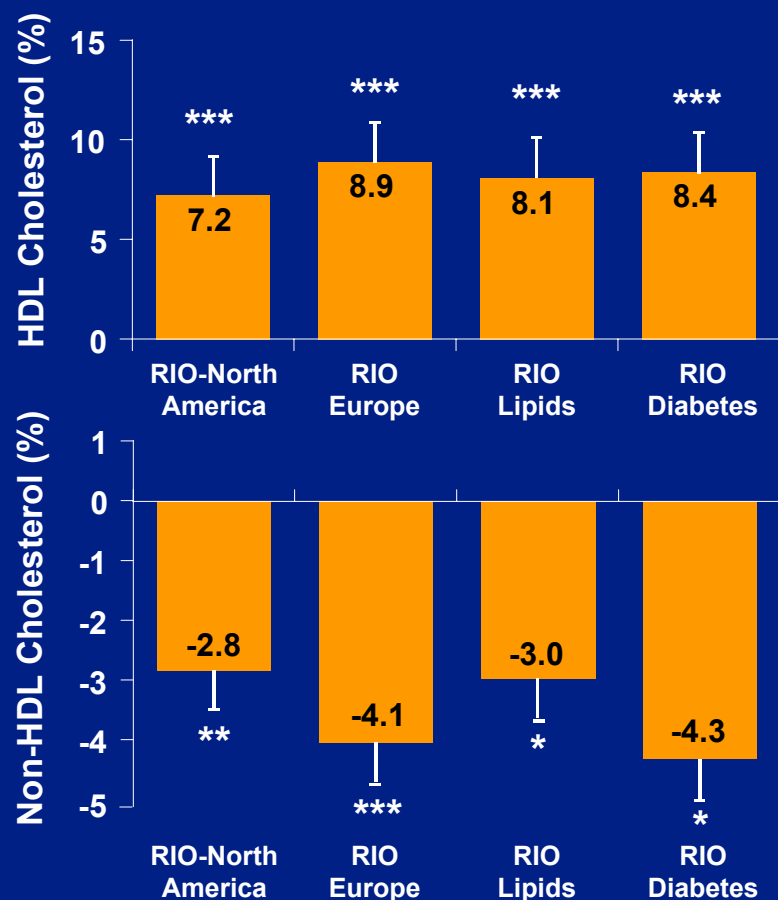
ITT; LOCF    5 mg vs. Pbo    1.3 (3.2) ( $P = 0.677$ )  
                  20 mg vs. Pbo    -12.4 (3.2) ( $P < 0.001$ )



# Serum Lipids and Lipoproteins at 1-Year the Consistency of RIO

Placebo – subtracted mean data after Rimonabant 20 mg

ITT ; LOCF



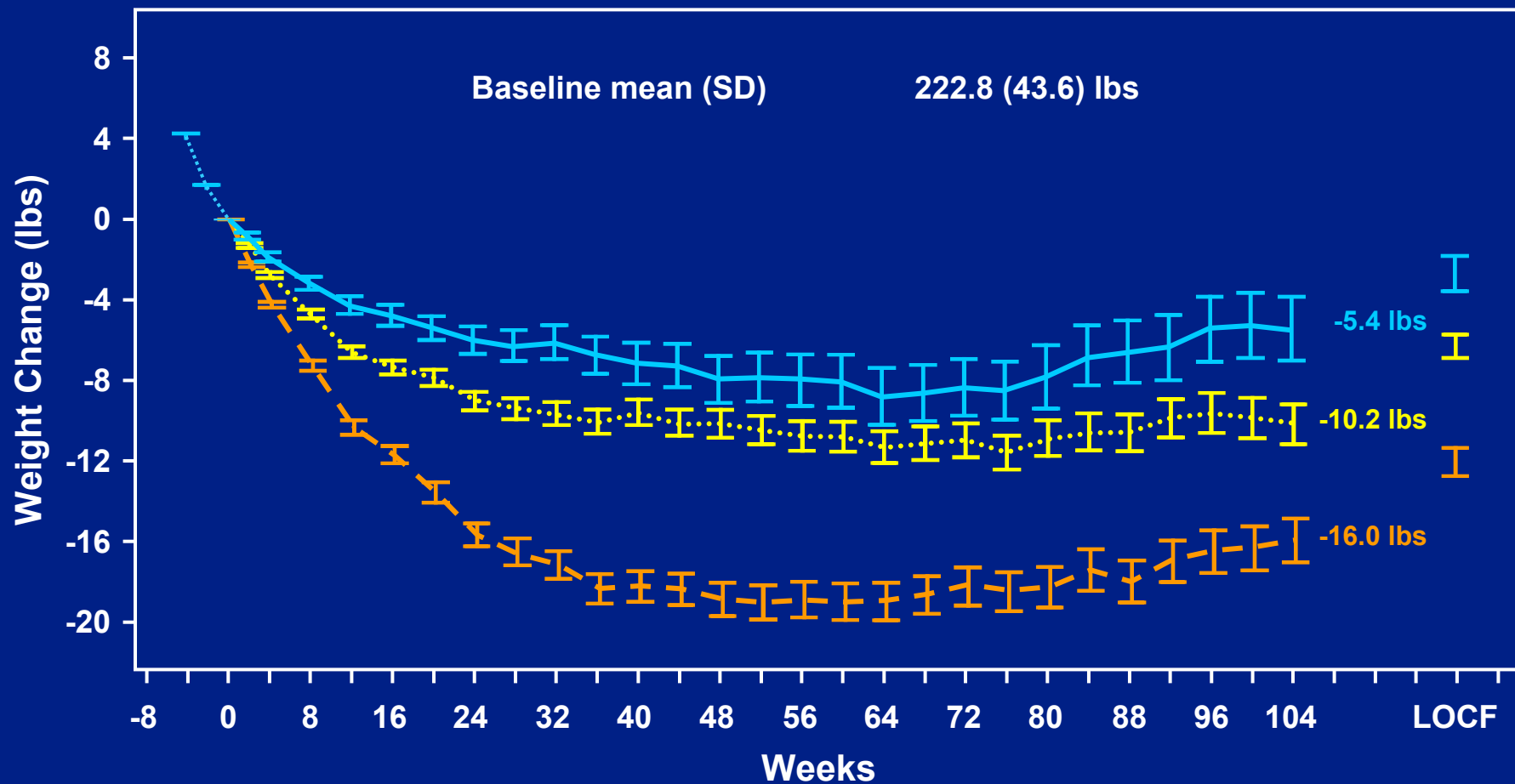
\* $P < 0.05$ ; \*\* $P < 0.01$ ; \*\*\* $P < 0.001$

MM-63

# RIO-Europe: ITT-LOCF and Observed Cases Durable Weight Loss (lbs) at 2 Years (Mean $\pm$ SEM)

Difference between groups, mean (SEM)

ITT; LOCF 5 mg vs. Pbo -3.4 (1.1) ( $P=0.002$ )  
20 mg vs. Pbo -9.3 (1.1) ( $P<0.001$ )



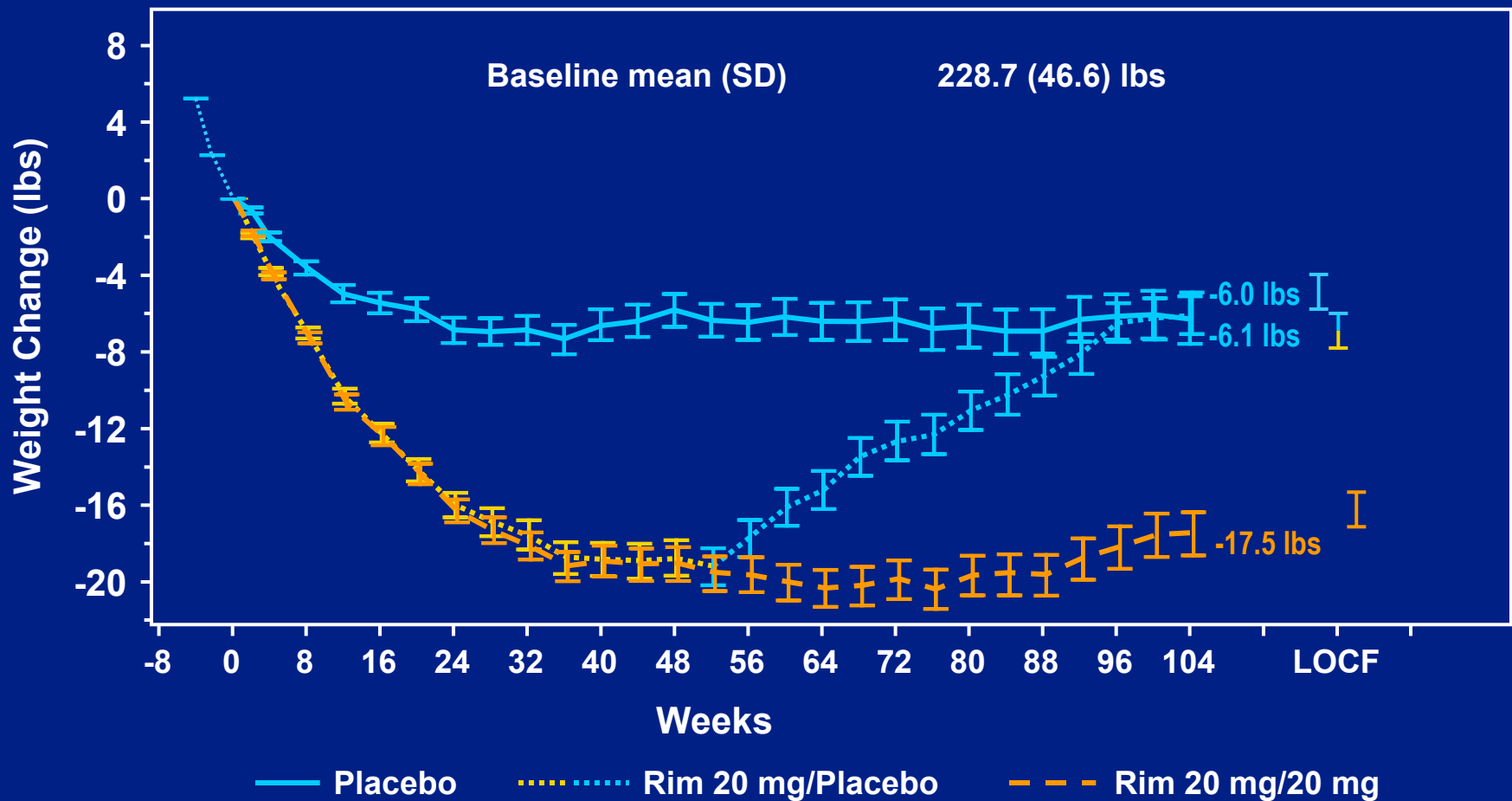
MM-64

# RIO-North America: ITT-LOCF and Observed Cases Durable Weight Maintenance (lbs) at 2 Years (Mean $\pm$ SEM)

Difference between groups, mean (SEM)

ITT; LOCF 20 mg/20 mg vs. 20 mg/Pbo

-9.2 (0.9) ( $P < 0.001$ )



MM-65

# Presentation Outline

---

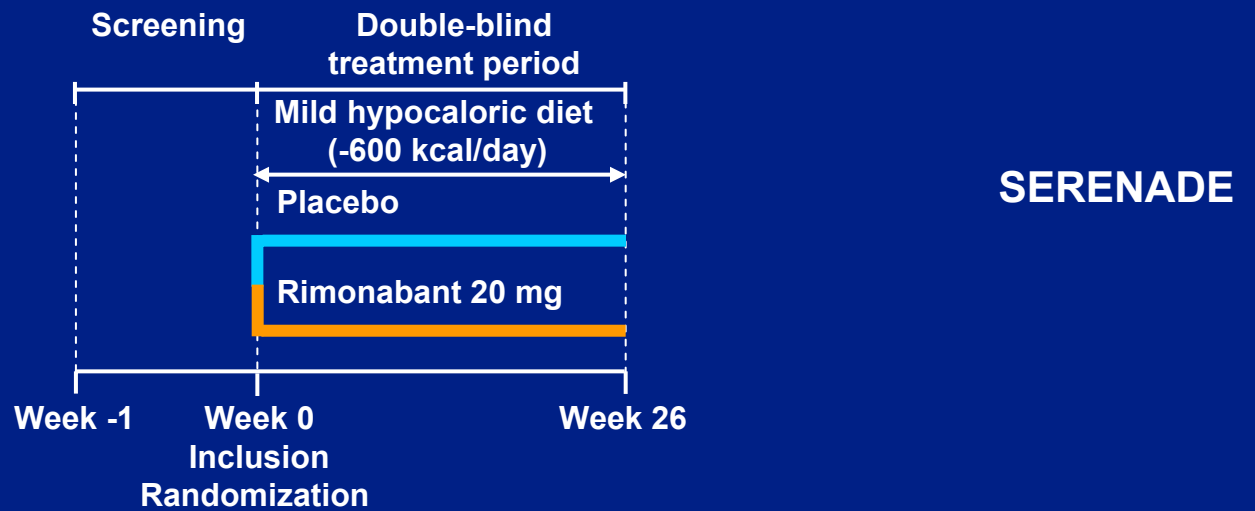
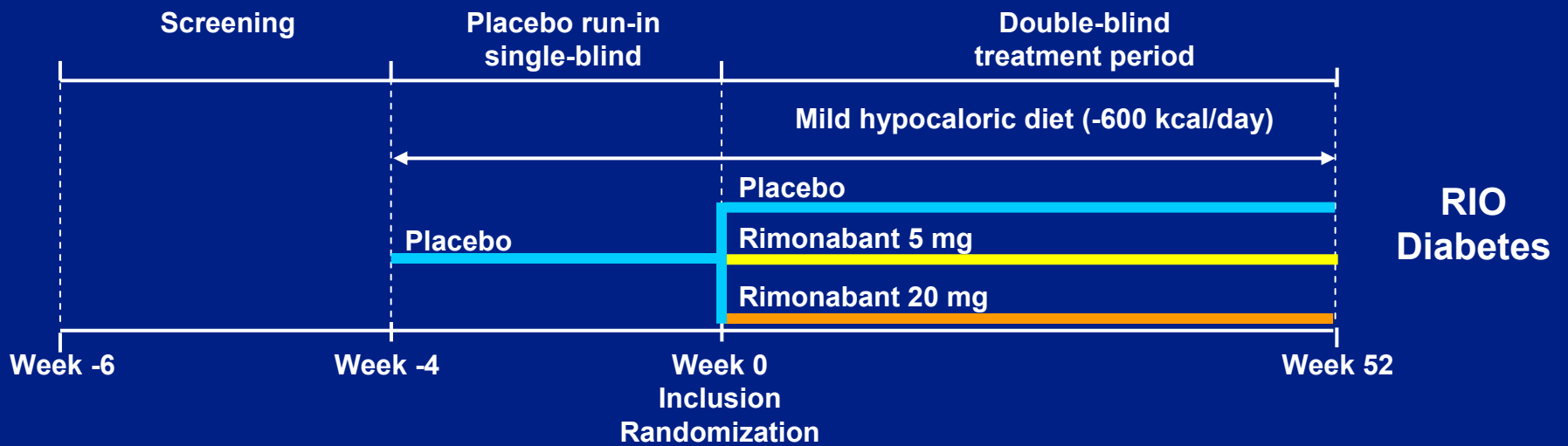
- Medical Need
- Treatment of obesity
- **Glycemic control in type 2 diabetes**
- Relationship between metabolic improvements and body weight loss
- Conclusion

# Glycemic Control in Type 2 Diabetes

Study	Population	Patients	Duration
RIO-Diabetes	Obese or overweight type 2 diabetes uncontrolled with metformin or sulfonylurea	1045	1 yr
SERENADE	Type 2 diabetes not under previous pharmacotherapy	278	6 months



# Study Designs



MM-68

# Baseline Demographics Type 2 Diabetes Patients

		RIO-Diabetes (N=1045)	SERENADE (N=278)
<b>Age (yr)</b>	Mean	55.6	56.6
<b>Race (%)</b>	Caucasian	88.5	84.2
	Black	5.5	2.9
	Other	6.0	11.9
<b>Gender (%)</b>	Females	50.9	50.4
<b>Weight (lbs)</b>	Mean	212.4	212.6
<b>BMI (kg/m<sup>2</sup>)</b>	Mean	33.7	34.5
<b>HbA<sub>1c</sub> (%)</b>	Mean	7.3	7.9
<b>Time since diabetes diagnosis (yr)</b>	Mean	5.1	1.3

# RIO-Diabetes: ITT-LOCF and Observed Cases Lower Weight, Lower HbA<sub>1c</sub> and FPG

**Weight**  
Baseline mean (SD) 212.4 (32.4) lbs

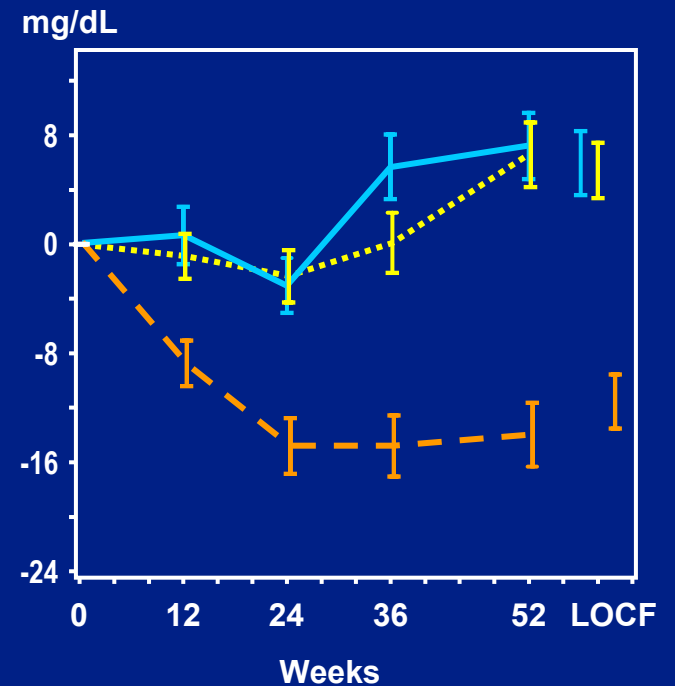
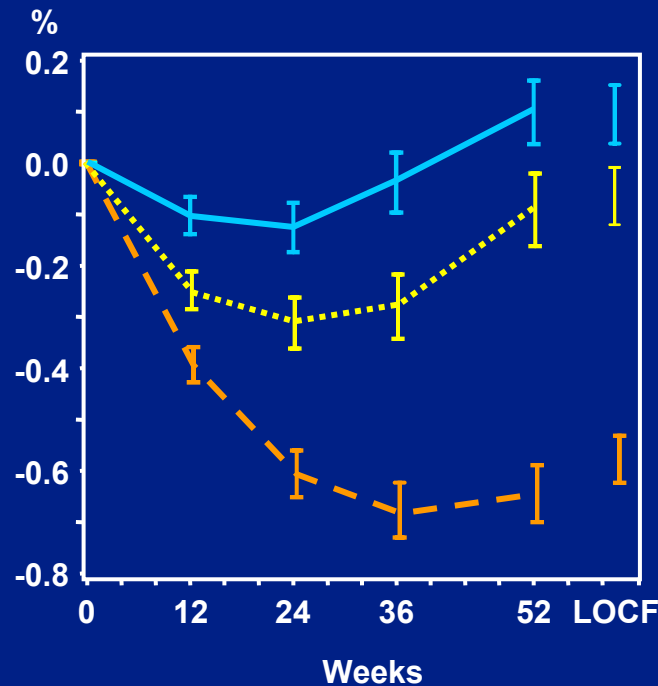
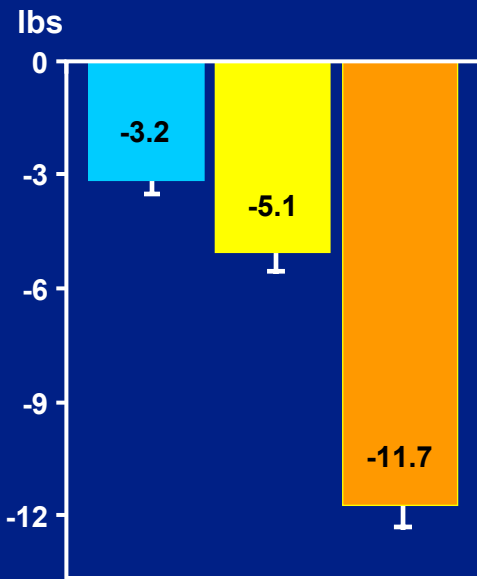
**HbA<sub>1c</sub>**  
7.3 (0.9) %

**Fasting Glucose**  
150 (38) mg/dL

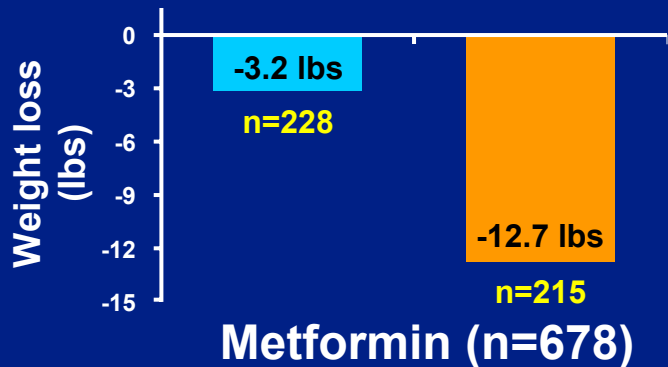
Difference between groups, mean (SEM)  
ITT; LOCF 5mg vs. Pbo -1.8 (0.7) (P=0.013)  
20mg vs. Pbo -8.6 (0.7) (P<0.001)

Difference between groups, mean (SEM)  
ITT; LOCF 5mg vs. Pbo -0.2 (0.1) (P=0.034)  
20mg vs. Pbo -0.7 (0.1) (P<0.001)

Difference between groups, mean (SEM)  
ITT; LOCF 5mg vs. Pbo -0.5 (3.0) (P=0.858)  
20mg vs. Pbo -17.5 (3.0) (P<0.001)

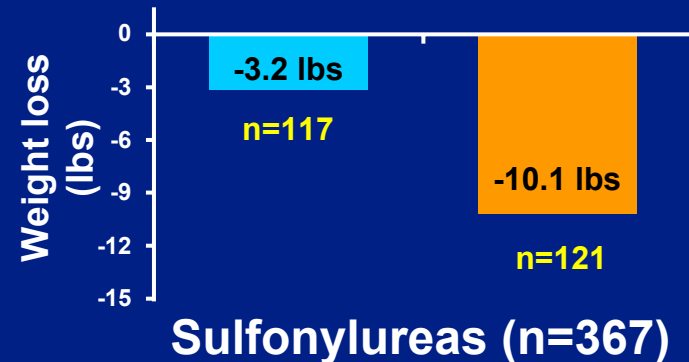


# RIO-Diabetes: Metformin and Sulfonylurea Subgroups Change in Weight (lbs) and HbA<sub>1c</sub> (%)



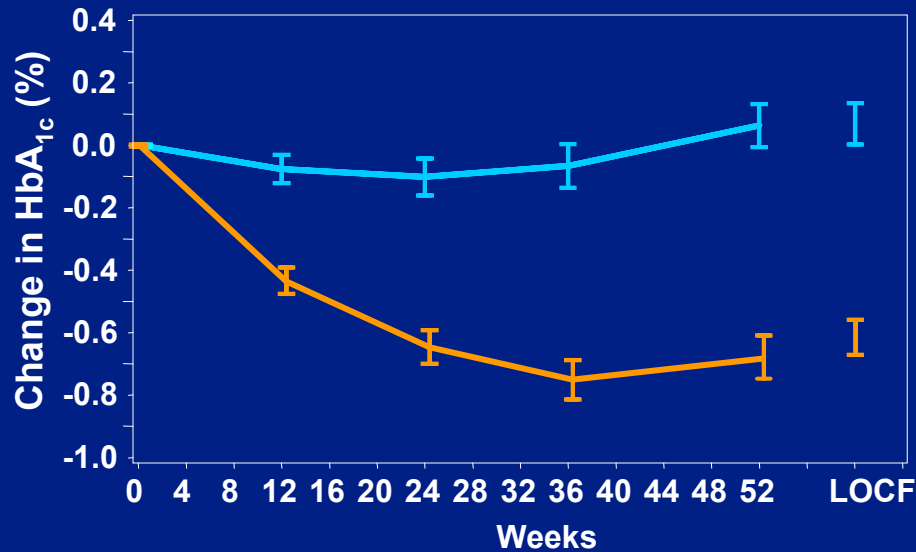
Difference between groups, mean (SEM)

ITT; LOCF 20 mg vs. Pbo -0.7 (0.1) ( $P < 0.001$ )

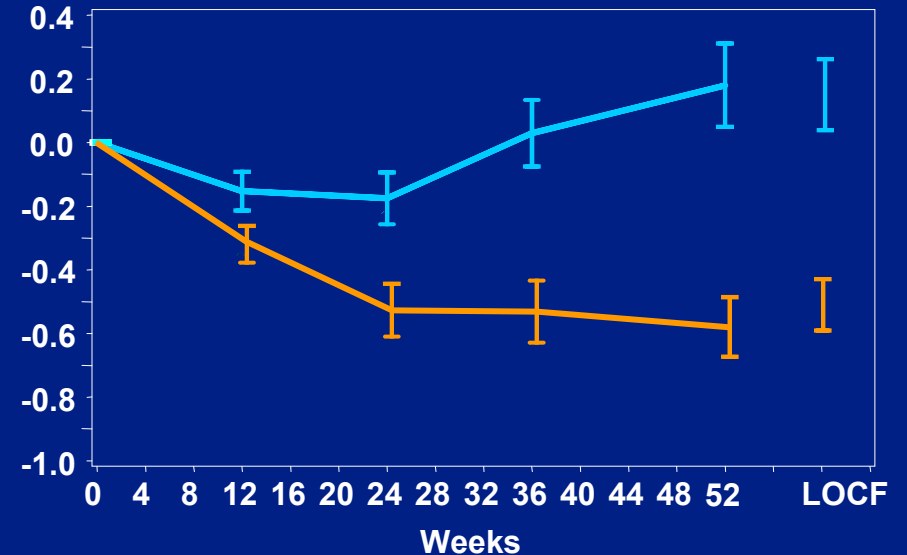


Difference between groups, mean (SEM)

ITT; LOCF 20 mg vs. Pbo -0.7 (0.1) ( $P < 0.001$ )



— Placebo — Rimonabant 20 mg

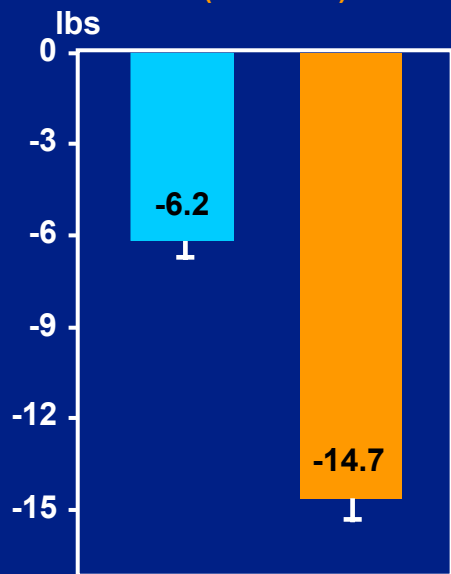


# SERENADE: ITT-LOCF and Observed Cases Lower Weight, Lower HbA<sub>1c</sub> and FPG

## Weight

Baseline mean (SD) 212.6 (46.1) lbs

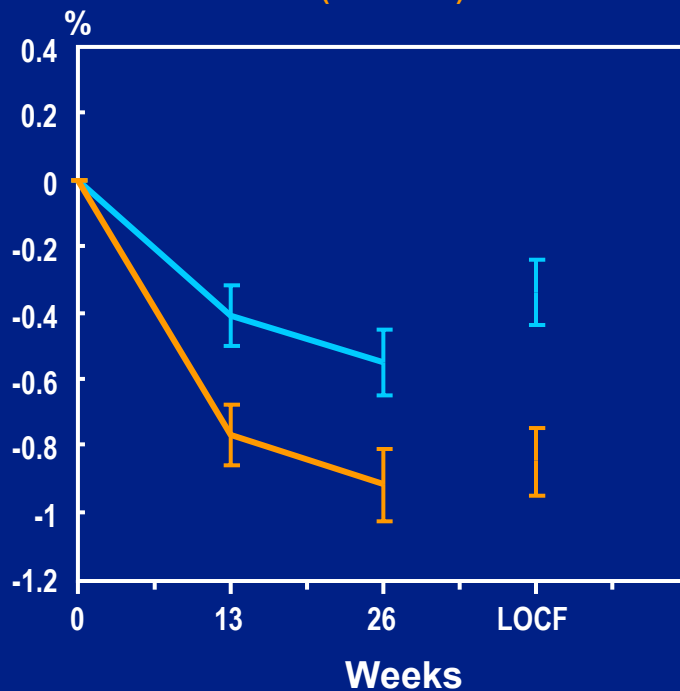
Difference between groups, mean (SEM)  
ITT; LOCF 20 mg vs. Pbo -8.5 (1.3)  
(P<0.0001)



## HbA<sub>1c</sub>

7.9 (0.8) %

Difference between groups, mean (SEM)  
ITT; LOCF 20 mg vs. Pbo -0.51 (0.14)  
(P<0.0002)

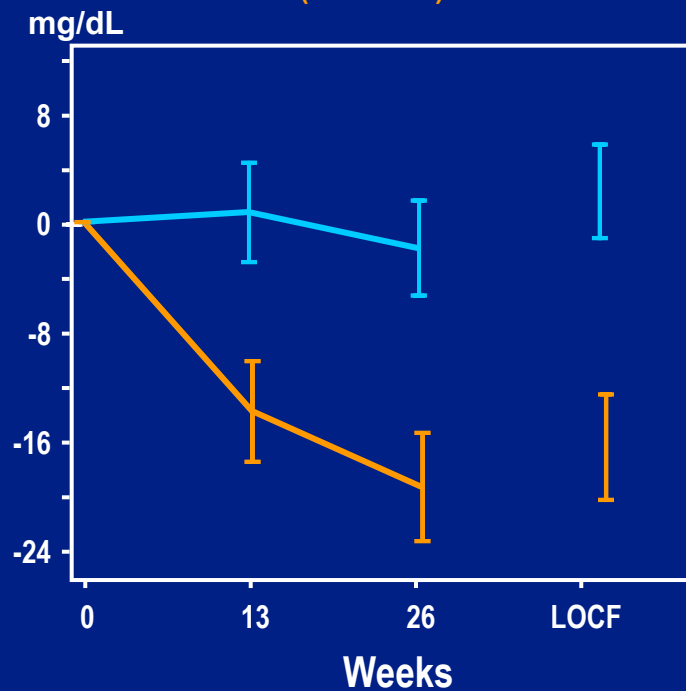


Excluding post rescue medication value

## Fasting Glucose

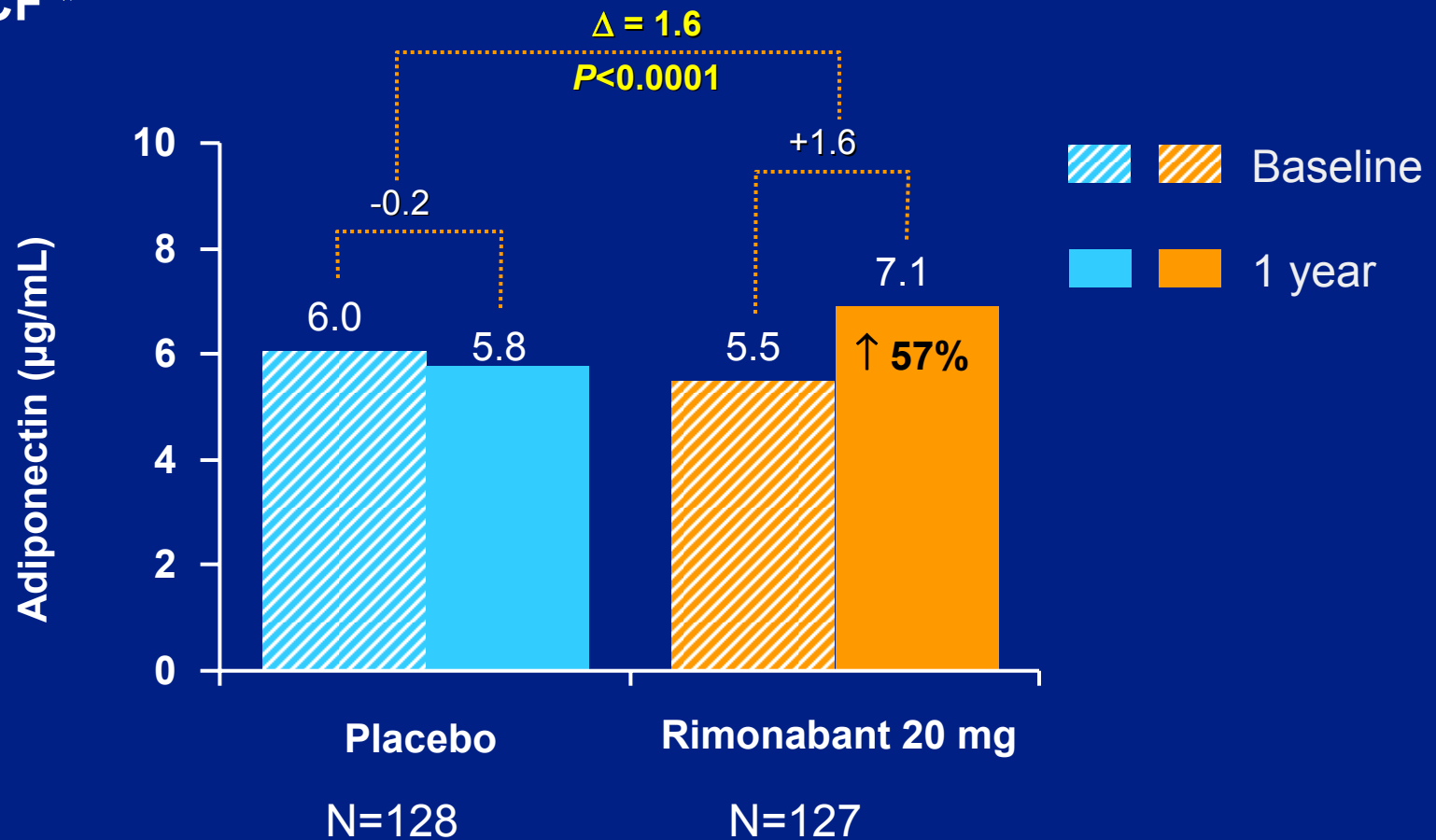
159 (34) mg/dL

Difference between groups, mean (SEM)  
ITT; LOCF 20 mg vs. Pbo -15.0 (4.6)  
(P<0.0012)



# SERENADE: Change in Adiponectin

ITT-LOCF \*



\* Excluding post rescue medication value

MM-73

# Presentation Outline

---

- Medical Need
- Treatment of obesity
- Glycemic control in type 2 diabetes
- **Relationship between metabolic improvements and body weight loss**
- Conclusion

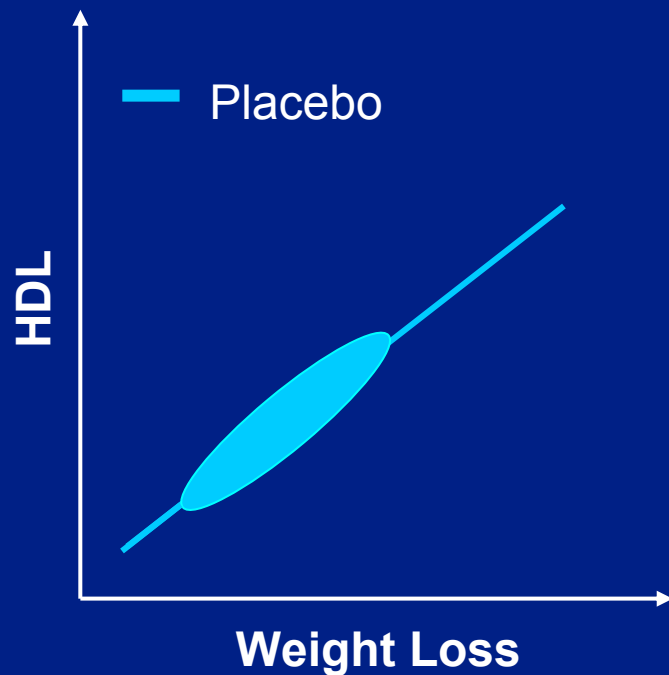
# Relationship of Metabolic Effects on Weight Loss: the Linear Regression Methodology

---



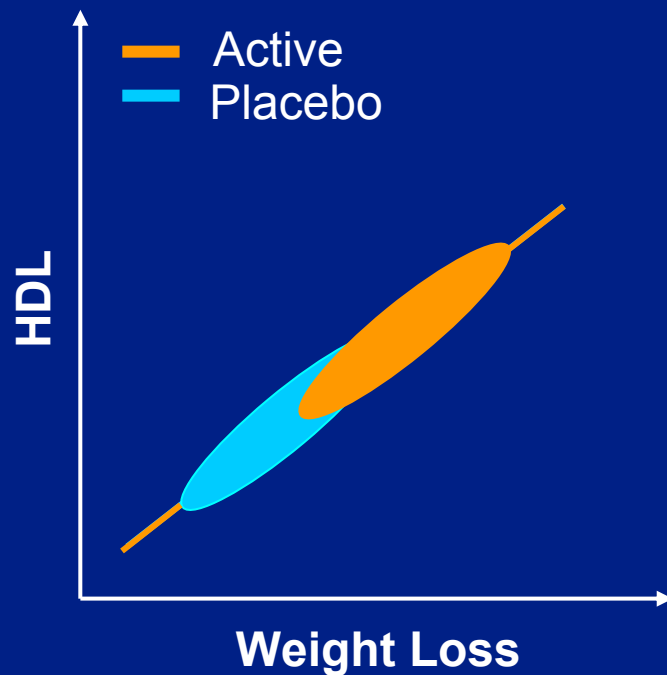
# Relationship of Metabolic Effects on Weight Loss: the Linear Regression Methodology

Overall effect explained  
by weight loss



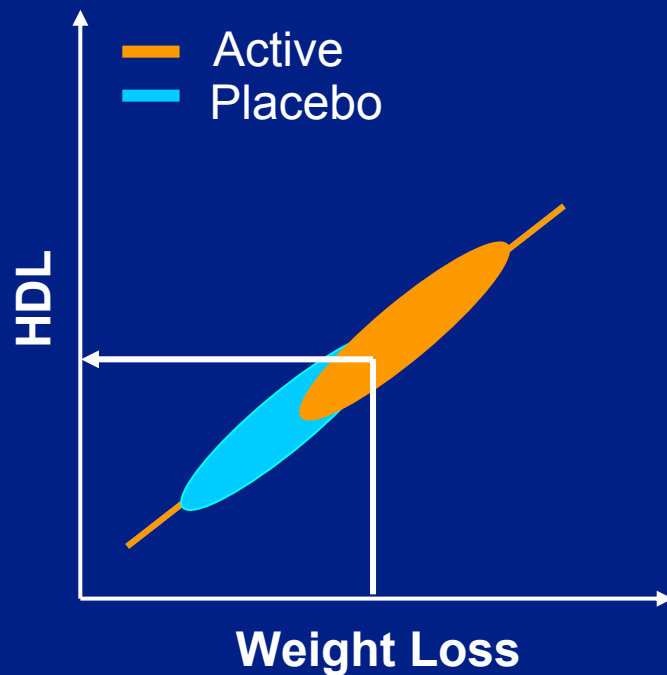
# Relationship of Metabolic Effects on Weight Loss: the Linear Regression Methodology

Overall effect explained  
by weight loss



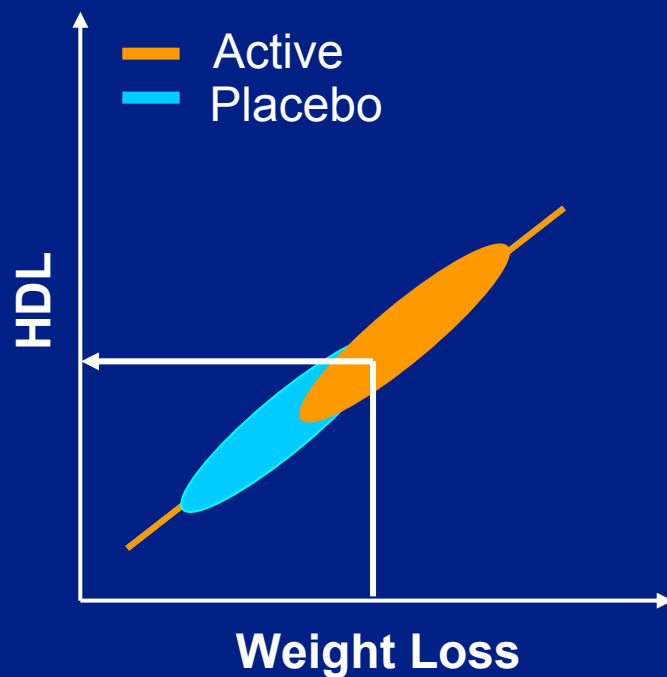
# Relationship of Metabolic Effects on Weight Loss: the Linear Regression Methodology

Overall effect explained  
by weight loss

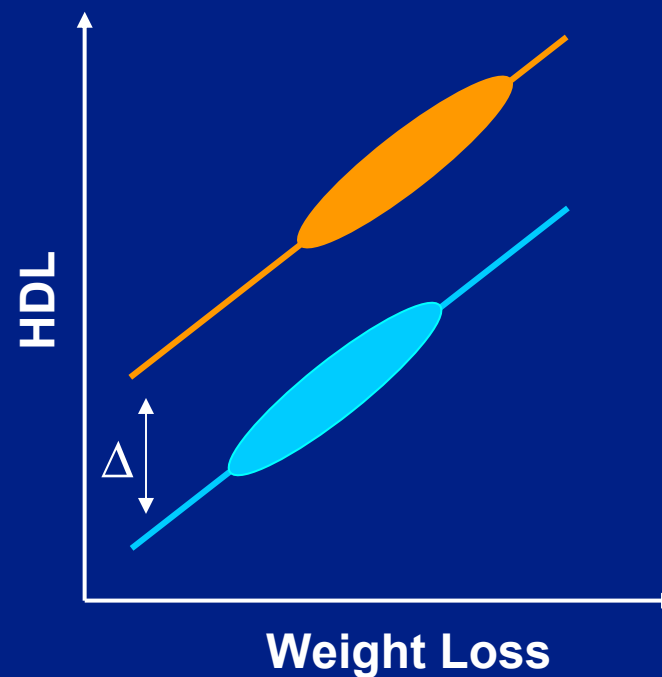


# Relationship of Metabolic Effects on Weight Loss: the Linear Regression Methodology

Overall effect explained  
by weight loss

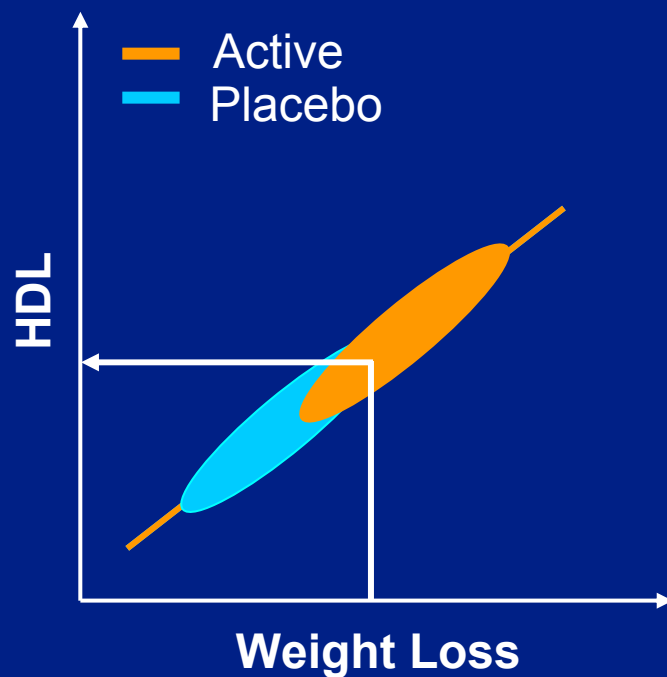


Overall effect NOT explained  
by weight loss ( $\Delta$ )

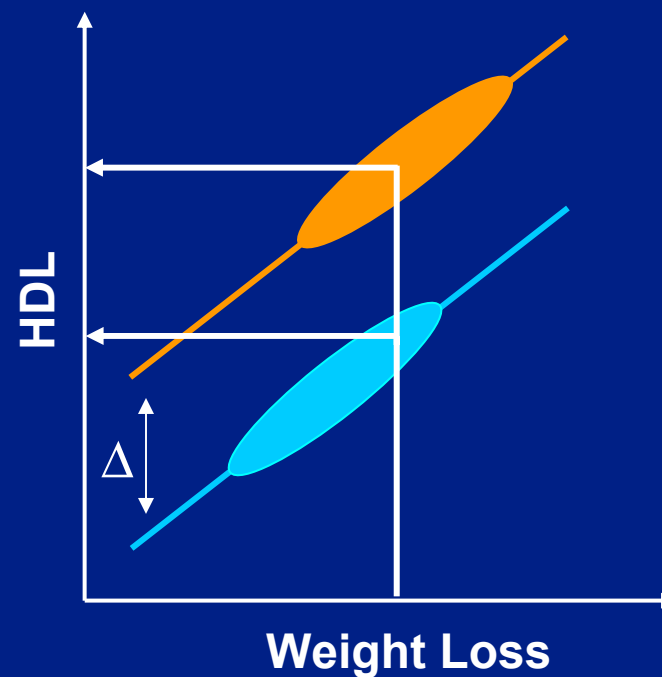


# Relationship of Metabolic Effects on Weight Loss: the Linear Regression Methodology

Overall effect explained  
by weight loss

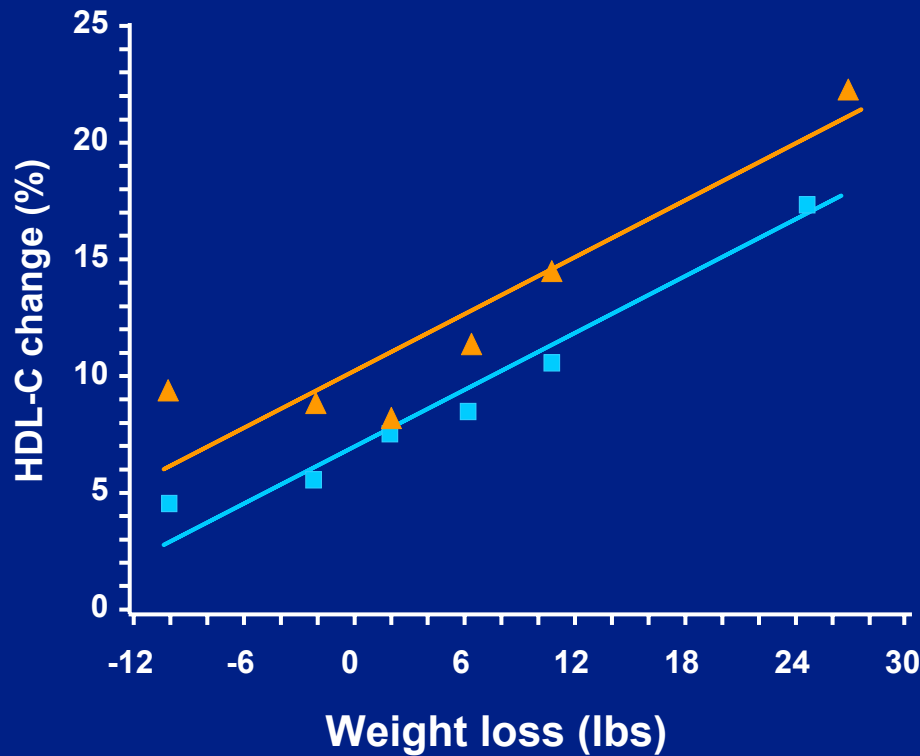


Overall effect NOT explained  
by weight loss ( $\Delta$ )

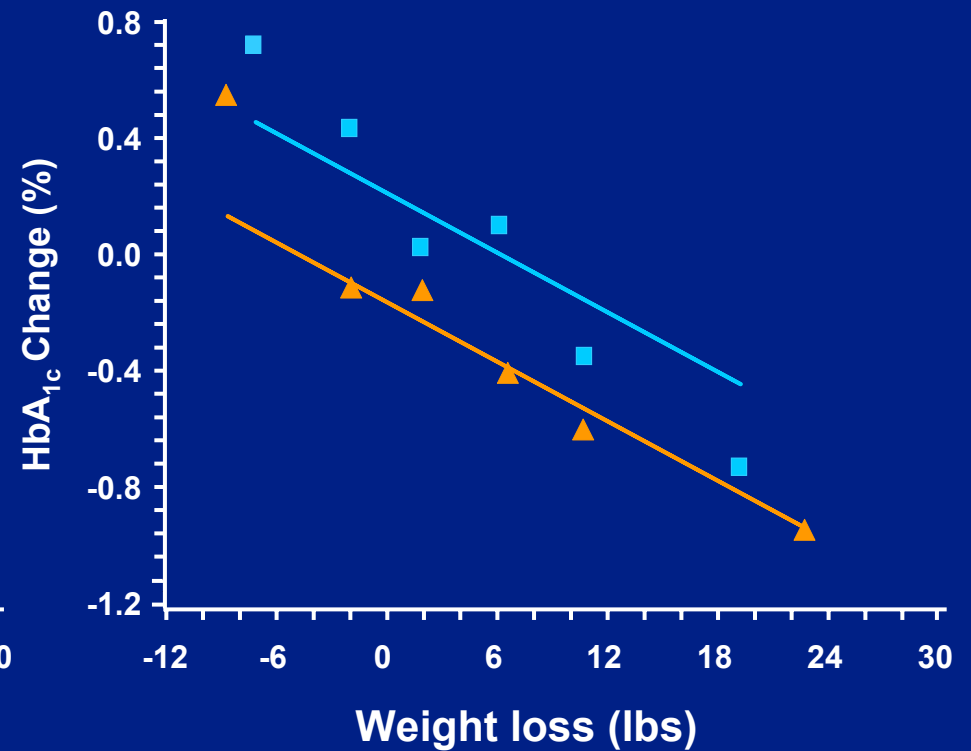


# Relationship Between Weight Loss and Change in HDL-C and HbA<sub>1c</sub>

RIO NA, EU, Lipids, Diabetes



RIO Diabetes

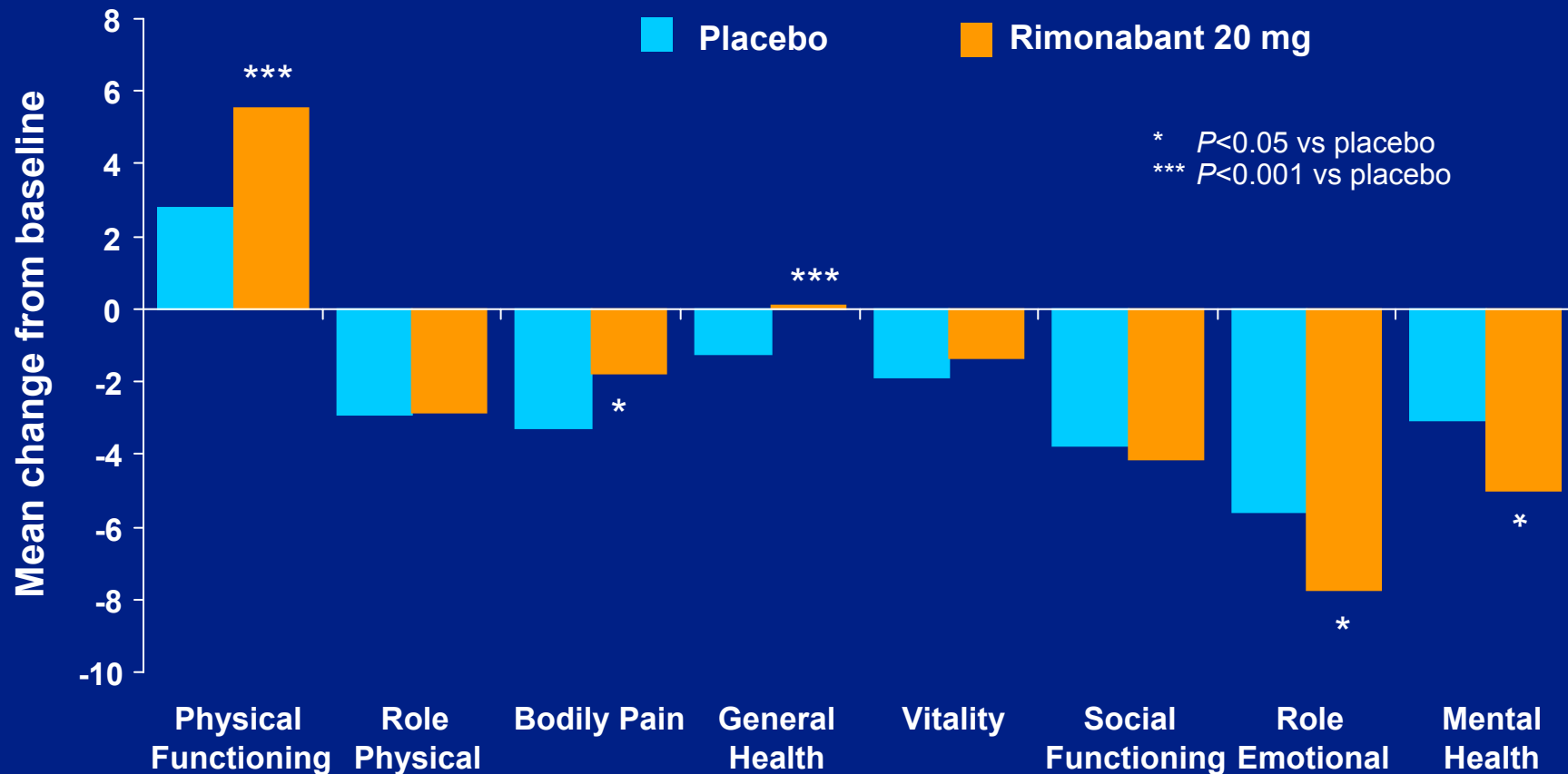


■ Placebo

▲ Rimonabant 20 mg

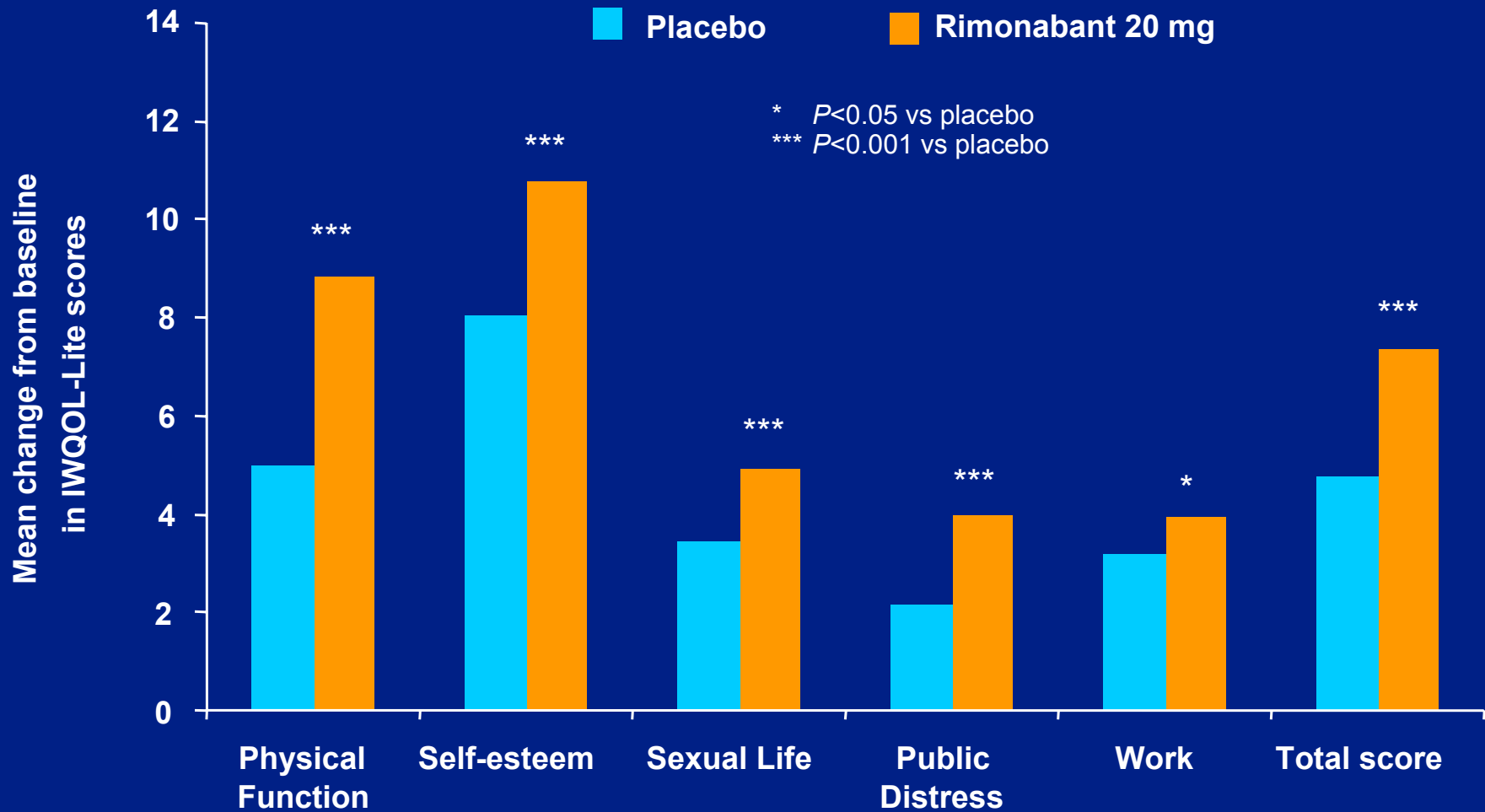
MM-81

# Quality of Life: SF-36 scale (RIO-Pooled – ITT)



Positive change indicates improvement, negative change indicates deterioration

# Quality of Life: IWQOL-Lite Scale (RIO-Pooled ITT)





# Who is the Appropriate Patient for Rimonabant?

- Adult patient
- Prepared to comply with diet / exercise counseling
- Committed to long-term treatment
- Overweight or obese with co-morbidities
  - hypertension
  - abdominal obesity
  - low HDL-C
  - high TG
- Overweight or obese type 2 diabetes
  - not well controlled by metformin or sulfonylureas
  - who are at risk of gaining weight to attain an improved glucose control

# Summary of Efficacy of Rimonabant 20 mg

- Significant reduction in weight and waist circumference
  - significant improvement of HDL-cholesterol and triglyceride levels
  - maintenance of effect up to 2-year
- Significant improvement in HbA<sub>1c</sub> and body weight loss in overweight/obese type 2 diabetes
- Metabolic improvements not fully explained by body weight loss alone
- Robust data replicated in 5 studies comprising over 6900 patients