

Lorcaserin (APD356), a Selective 5-HT_{2C} Agonist, Safely Induces Weight Loss in a 12-week Study of Healthy Obese Patients



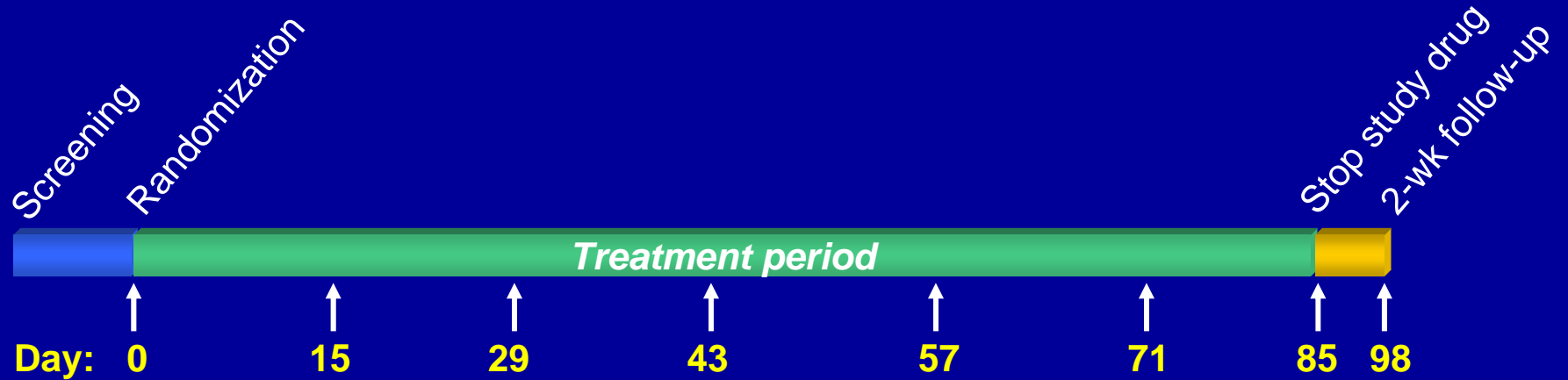
Steven R. Smith, Warren Prosser, David Donahue,
Christen Anderson, William Shanahan, and the
APD356-004 Study Group

Properties of Lorcaserin

- **Potent, highly selective 5-HT_{2C} receptor agonist**
 - ~15-fold selectivity versus 5-HT_{2A}
 - ~100-fold selectivity versus 5-HT_{2B}
- **No preclinical evidence of effects on heart valves or pulmonary vasculature**
- **Efficacious for weight loss in obese patients in a 4-week clinical study at a dose of 15 mg QD**

Study Design

12 week, double blind, randomized, placebo controlled evaluation of the efficacy and safety of lorcaserin in healthy obese patients



	Day: 0	15	29	43	57	71	85	98
ECHO	X						X	
Safety	X	X	X	X	X	X	X	X
Efficacy	X	X	X	X	X	X	X	X

- Lorcaserin doses: 10 mg QD, 15 mg QD, 10 mg BID
- No diet or exercise modifications
- No “run-in” period

Demographics at Baseline

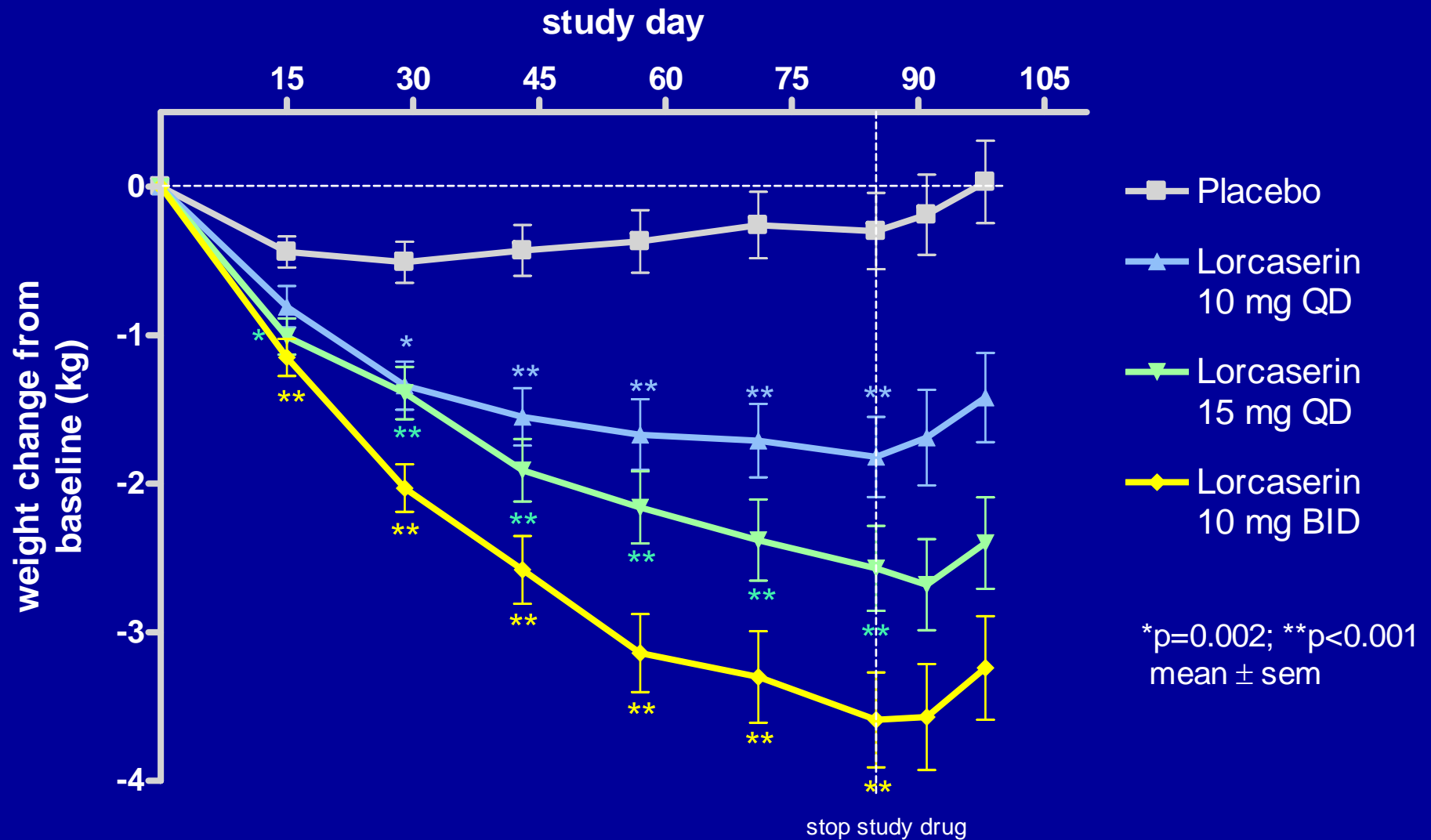
	Lorcaserin				All Patients N=469
	Placebo N=118	10 mg QD N=117	15 mg QD N=118	10 mg BID N=116	
Age (yr)	41.6 ± 10.9	41.5 ± 12.2	41.5 ± 11.3	41.5 ± 11.3	41.5 ± 11.4
Baseline Weight (kg)	100.2 ± 15.0	100.6 ± 15.4	100.3 ± 14.4	98.8 ± 16.9	100.0 ± 15.4
Baseline BMI (kg/m ²)	36.4 ± 4.0	36.2 ± 4.1	36.9 ± 4.2	36.2 ± 4.1	36.4 ± 4.1
Gender (%)					
Male	12.7	17.9	6.8	14.7	13.0
Female	87.3	82.1	93.2	85.3	87.0
Ethnicity (%)					
African American	28.8	30.8	27.1	27.6	28.6
Hispanic	15.3	16.2	19.5	19.8	17.7
Caucasian	55.1	52.1	50.0	52.6	52.5
Other	0.8	0.9	3.4	0	1.2

Disposition of Patients

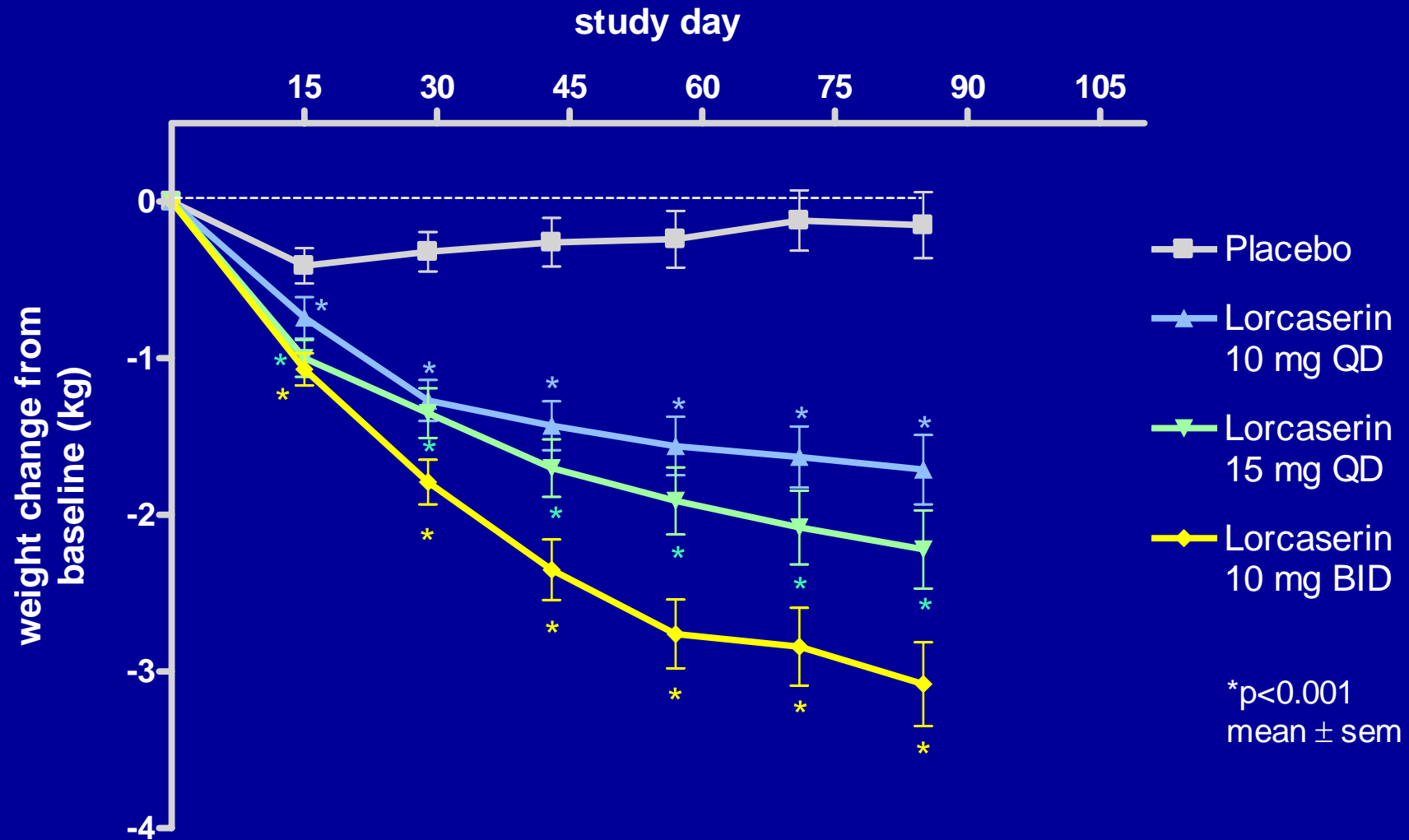
Study Retention Rate = 71%

		Lorcaserin		
	Placebo	10 mg QD	15 mg QD	10 mg BID
Number of Patients				
Randomized	118	117	118	116
Completers	88	86	82	77
ITT	116	114	113	110
Per Protocol	79	80	74	70
Discontinuations				
Adverse Event	3	1	9	2
Protocol Deviation	3	6	4	4
Subject Decision	13	8	7	9
PI Decision	0	0	0	5
LTFU	3	4	10	8
Lack of Efficacy	2	1	1	1
Other	2	4	3	3

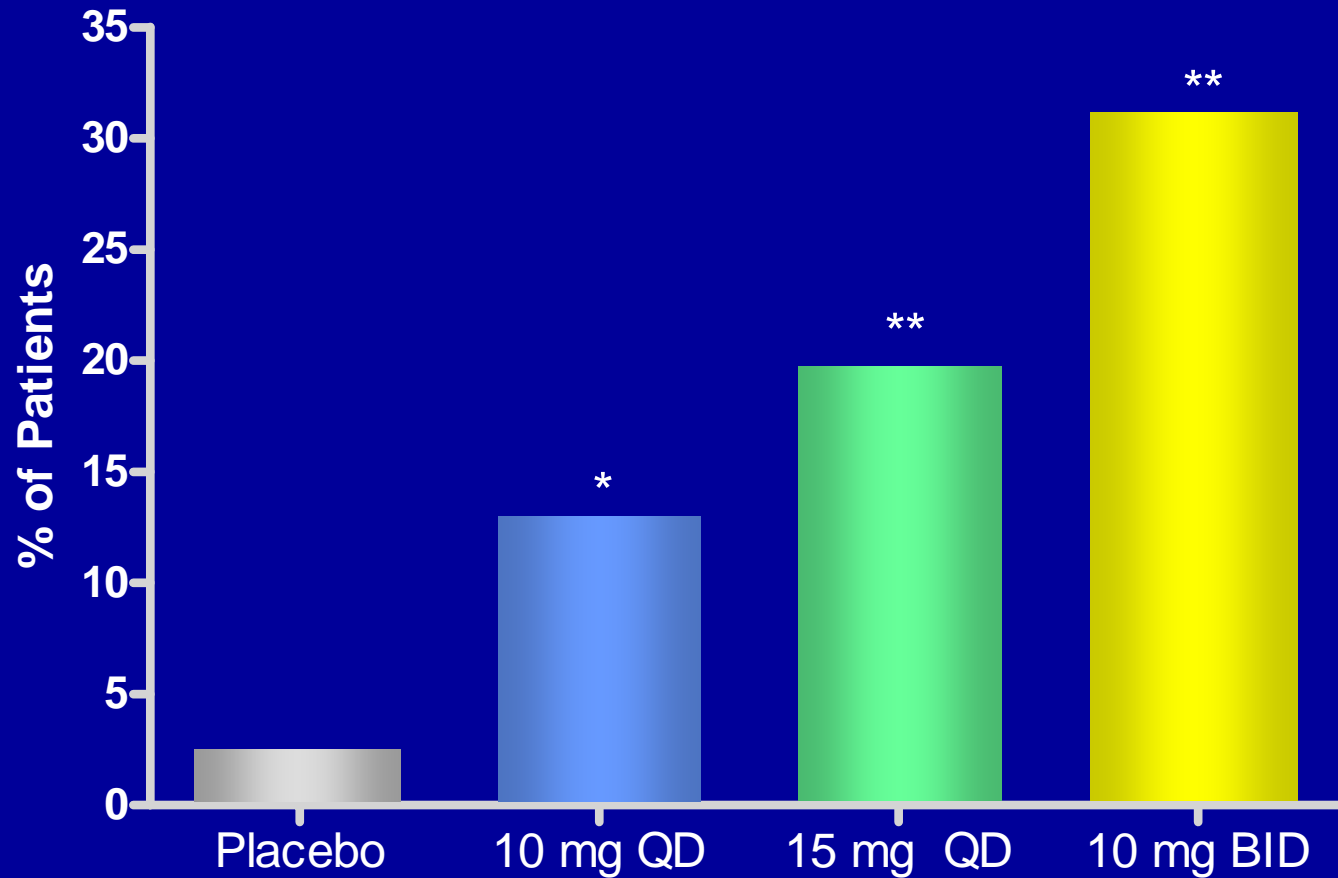
Lorcaserin Causes Dose-Dependent Weight Loss: Completer Analysis



Lorcaserin Causes Dose-Dependent Weight Loss: ITT-LOCF Analysis

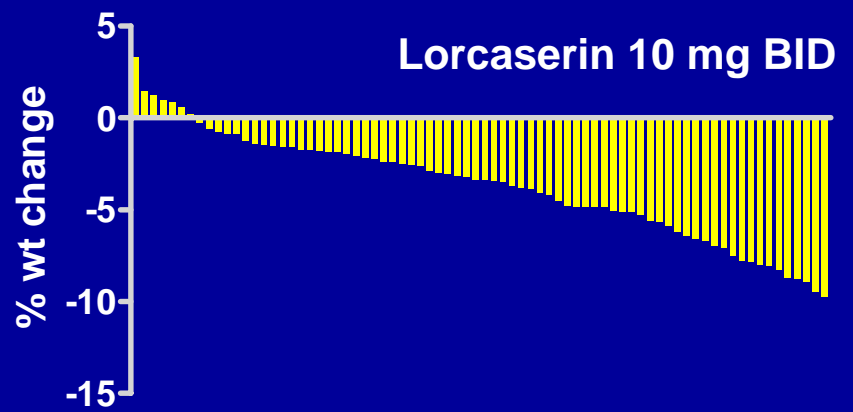
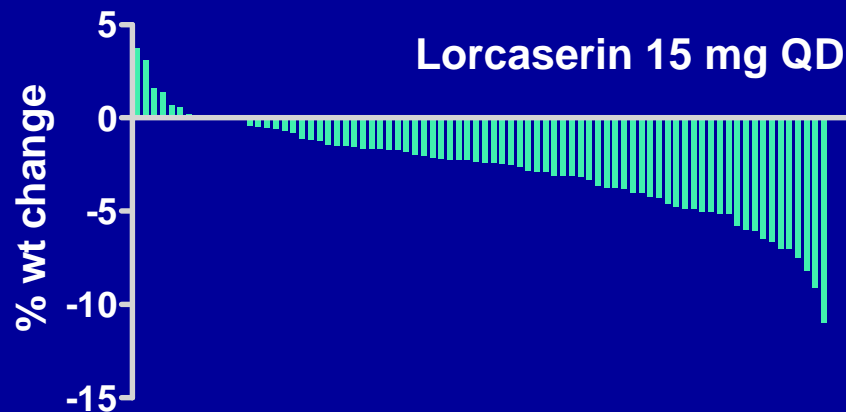
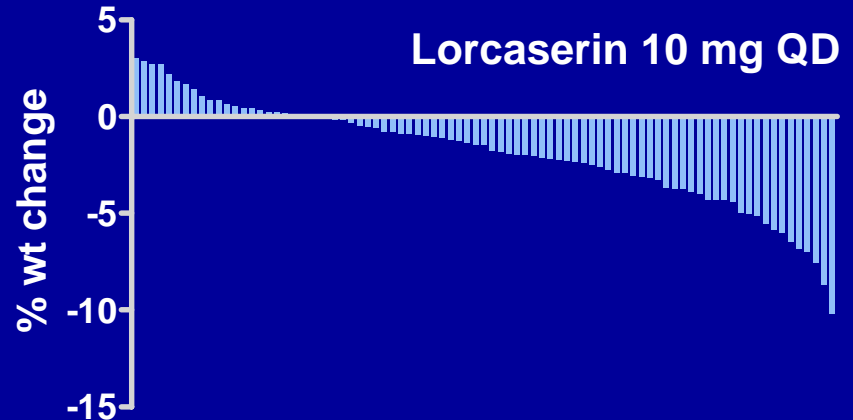
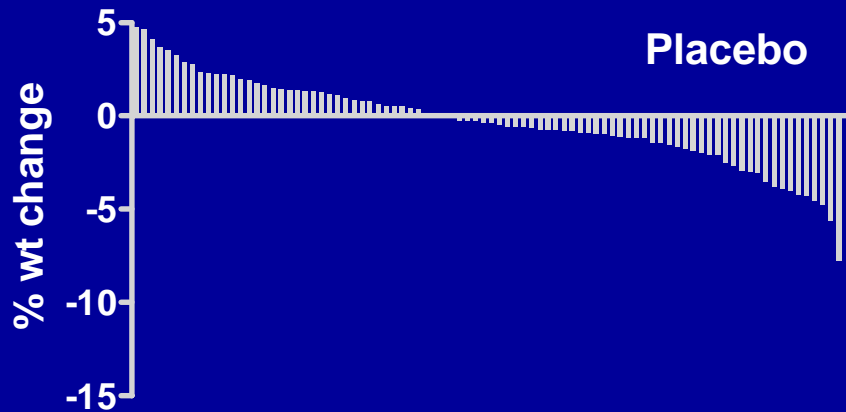


Lorcaserin Increases the Proportion of Patients with $\geq 5\%$ Weight Loss at 12 Weeks



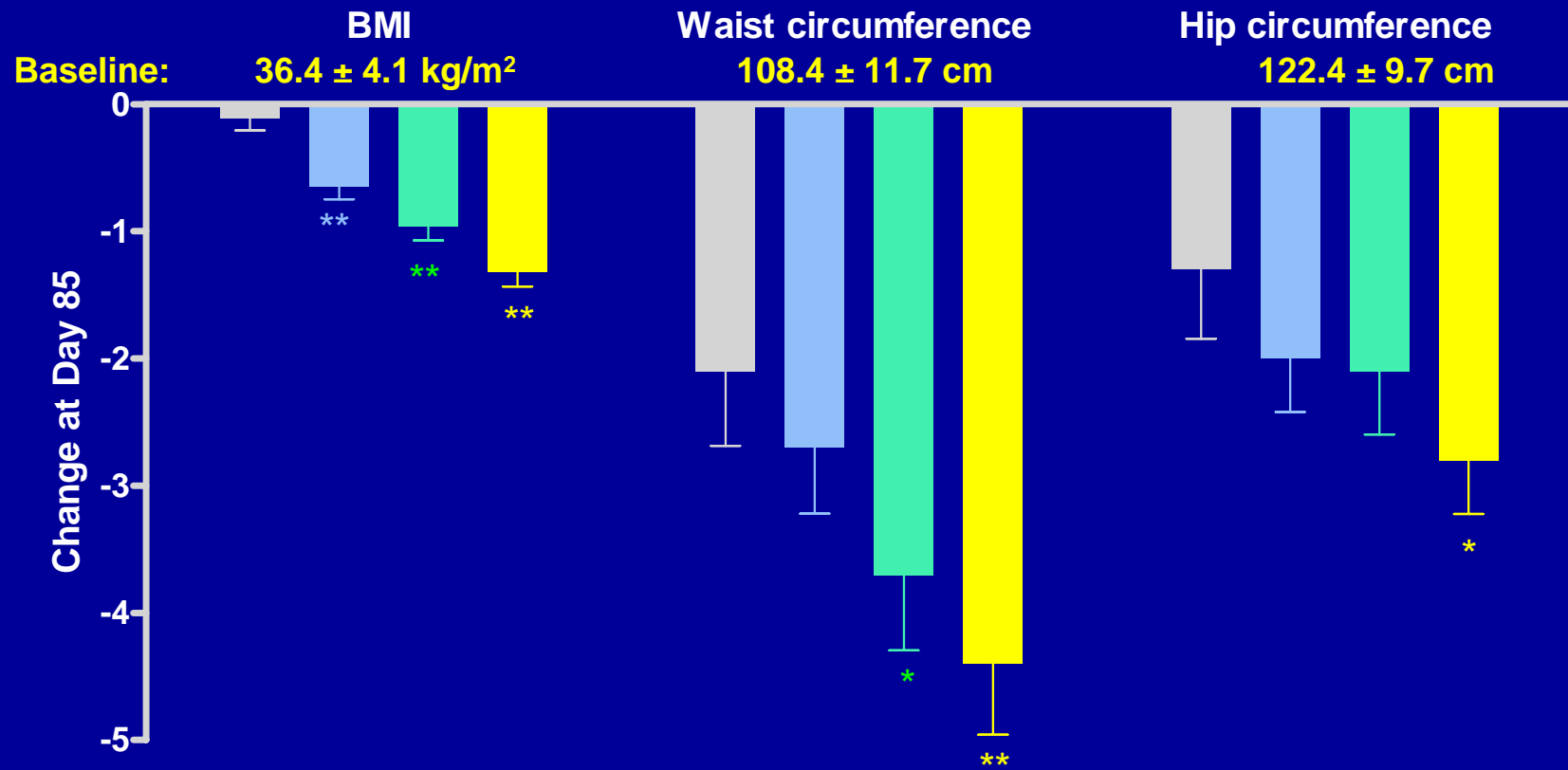
* $p=0.015$; ** $p<0.001$
Completer subset analysis

Lorcaserin Shifts the Weight Loss Distribution Dose Dependently



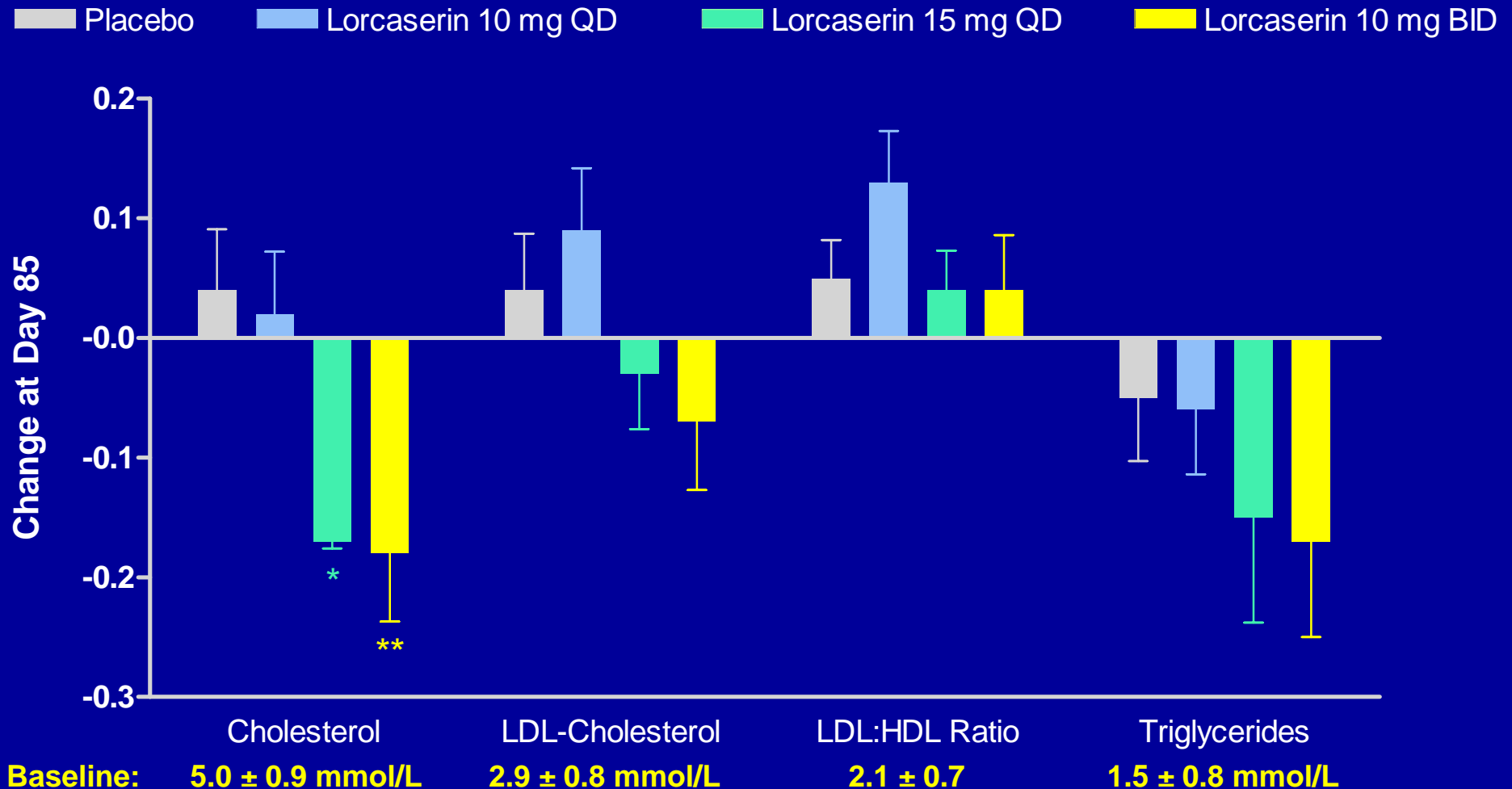
Lorcaserin Reduces BMI, Waist Circumference and Hip Circumference

■ Placebo ■ Lorcaserin 10 mg QD ■ Lorcaserin 15 mg QD ■ Lorcaserin 10 mg BID



* $p < 0.05$; ** $p < 0.001$; data are mean \pm sd for BL, \pm sem for change; Completer subset analysis

Lorcaserin Decreases Cholesterol with Favorable Trends in LDL and Triglycerides



*p<0.05; **p<0.01; data are mean \pm sd for BL, \pm sem for change; Completer subset analysis

Adverse Events

(≥5% of Patients in Any Group)

Lorcaserin

Event (%)	Placebo (n=118)	10 mg (n=117)	15 mg (n=118)	10 mg bid (n=116)
Headache	17.8	29.9	32.2	26.7
Nausea	3.4	8.5	9.3	11.2
Dizziness	0	6.0	7.6	7.8
URI	9.3	1.7	3.4	3.4
Nasopharyngitis	8.5	5.1	5.9	6.0
Dry Mouth	0	1.7	1.7	6.0
Diarrhea	5.9	0.9	4.2	3.4
Fatigue	2.5	4.3	5.9	4.3
Vomiting	0.8	1.7	1.7	5.2
UTI	4.2	2.6	5.1	5.2
Dyspepsia	5.1	3.4	1.7	3.4

All randomized patients

Echocardiograms: Baseline and Day 85

- Echocardiograms performed at screening and Day 85
- Interpreted by a single, blinded, academically-based reader
- All valves except pulmonic rated on scale of 5 for insufficiency:
 - Absent, trace, mild, moderate, severe
 - Pulmonic insufficiency rated as present or absent
- Pulmonary artery systolic pressure estimated

Lorcaserin Has No Effect on Heart Valve Regurgitation at 12 Weeks

Number of Events (%) ¹	No Changes			Increased Regurgitation			Decreased Regurgitation		
	Aortic	Mitral	Tri ²	Aortic	Mitral	Tri	Aortic	Mitral	Tri
Placebo	95.0	68.7	80.0	3.0	10.1	7.4	2.0	21.2	12.7
Lorcaserin 10 mg QD	95.9	76.0	85.6	2.0	8.0	3.3	2.0	17.0	11.1
Lorcaserin 15 mg QD	90.6	78.1	86.3	7.3	11.5	7.4	2.1	10.4	7.4
Lorcaserin 10 mg BID	92.7	80.2	84.3	6.3	11.5	5.6	1.0	8.3	10.1

¹Expressed as % of evaluable valves

²Tri, tricuspid valve

Analysis of completer set with evaluable echocardiograms

Lorcaserin Has No Effect on Pulmonary Artery Pressure at 12 Weeks

Pulmonary Artery Pressure (mm Hg)

	Baseline	Day 85	Change
Placebo	26.9 ± 5.0	26.9 ± 4.4	0.20 ± 5.0
Lorcaserin 10 mg QD	26.5 ± 6.3	27.2 ± 4.6	0.27 ± 4.6
Lorcaserin 15 mg QD	26.3 ± 4.8	27.0 ± 4.5	0.15 ± 3.8
Lorcaserin 10 mg BID	27.6 ± 4.8	28.5 ± 4.5	0.95 ± 4.2

Mean ± sd

Analysis of completer set with evaluable echocardiograms

Summary

- Lorcaserin was well tolerated at all doses
- Lorcaserin caused significant, progressive, dose-dependent weight loss at 10 mg QD, 15 mg QD and 10 mg BID
- Lorcaserin decreased BMI, waist and hip circumference and total cholesterol
- Efficacy was observed across the entire range of obesity studied (BMI 30 - 40+)
- “Non-responder” rate was very low
- No apparent drug effects on heart valves or pulmonary artery pressures were observed

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