Lorcaserin, a novel serotonin 2C agonist for the treatment of obesity

2013 ICDM
Sung Rae Kim M.D. , Ph.D.
Division of Endocrinology and Metabolism
The Catholic University of Korea

Obesity Medications available prior to 2012

	Indication	Year Approved	Year Disapproved
Sympathomimetics			
Phentermine	Short-term	1959	
Diethylpropion	Short-term	1973	
Phendimetrazine	Short-term	1961	
Benzphentamine	Short-term	1960	
Lipase Inhibitor			
Orlistat	Long-term	1997	
Disapproved Drugs			
Fenfluramine		1973	1997
Dexfenfluramine		1997	1997
Sibutramine		1997	2010
Rimonabant		2006	2009

Disapproved Obesity Medications

Table 1. Anti-obesity medications withdrawn

Drug	Introduced	Mechanism	FDA status
Fenfluramine	1973-U.S.	Sympathomimetic amine (appetite suppression)	Withdrawn 1997: valvular heart disease, pulmonary hypertension
Dexfenfluramine	1996-U.S.	As above	Withdrawn 1997: valvular heart disease, pulmonary hypertension
Rimonabant	2006-Europe	Selective CB1 receptor blocker	Not approved in U.S.: concern over psychiatric side effects Withdrawn 2009: potential of serious psychiatric disorders Temporarily withdrawn 2002
Sibutramine	1997-U.S. 2001-Europe	Selective combined serotonin and noradrenaline reuptake inhibitor (appetite suppression)	Withdrawn 2010: increased risk of heart attack and stroke in high-risk cardiac patients

Modified from Powell et al. Clin Pharmacol Ther 2011;90:40-51 [9] and Ioannides-Demos et al. Drug Saf 2006;29:277-302 [10].
The drug (rimonabant) was an approved drug on the market in Europe.
FDA, U.S. Food and Drug Administration.

Kang JG, Park CY. Diabetes Metab J 2012;36:13-25

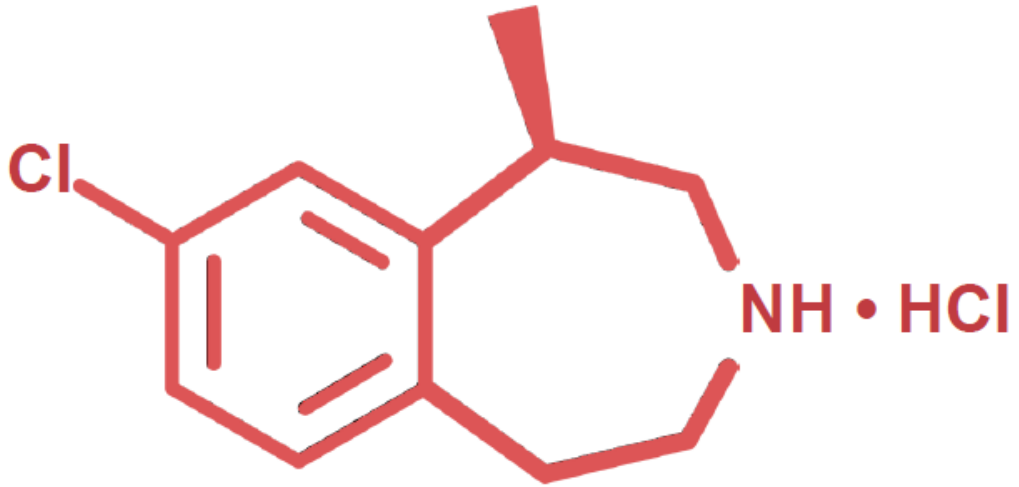
Lorcaserin

- FDA rejected Arena's lorcaserin in October 2010, citing potential cancer risk.
- Arena resubmitted its application with more data to show that the previous findings of tumors in rats did not apply to human.
- At a May 2012 advisory meeting, most panel members said side effects from lorcaserine could be addressed in post approval studies and suggested patients who take the drug should get regular echocardiograms.
- It was approved in June of 2012.
- Lorcaserin is available in the U.S. from June 2013.

Lorcaserin

- Lorcaserin was designed to block appetite signals in the brain in a similar way to fen-phen.
- Fen-phen withdrawn in 1997 after evidence of heart valve damage, assumed related to activation of serotonin 2B receptor on heart tissue.
- When used at the approved dose of 10 milligrams twice a day, lorcaserin dose not appear to activate the serotonin 2B receptor

New Chemical Entity for Chronic Weight Management



- Novel single agent discovered & developed by Arena
- Believed to decrease food consumption and promote satiety by selectively activating serotonin 2C receptors (5-HT_{2C}) in the hypothalamus
- Phase 3 program included 7,794 patients

First Prescription Weight-Loss Treatment Approved by FDA in 13 Years

- **Indicated to be used along with a reduced-calorie diet and increased physical activity for chronic weight management in adult patients with an initial BMI of:**
  - *30 kg/m^2 or greater (obese), or*
  - *27 kg/m^2 or greater (overweight) in the presence of at least one weight related comorbid condition*

Limitations of Use

1. The safety and efficacy of coadministration of BELVIQ with other products intended for weight loss including prescription drugs, OTC drugs and herbal preparations have not been established
2. The effect of BELVIQ on cardiovascular morbidity and mortality has not been established

BELVIQ®
(lorcaserin HCl)

AACE Treatment Guidelines

AACE COMPREHENSIVE DIABETES MANAGEMENT ALGORITHM 2013

COMPLICATIONS-CENTRIC MODEL FOR CARE OF THE OVERWEIGHT/OBESE PATIENT

STEP 1 EVALUATION FOR COMPLICATIONS AND STAGING

CARDIOMETABOLIC DISEASE			BIOMECHANICAL COMPLICATIONS
NO COMPLICATIONS	BMI ≥ 27 WITH COMPLICATIONS		
BMI 25–26.9, or BMI ≥ 27	Stage Severity of Complications		
	LOW	MEDIUM	HIGH

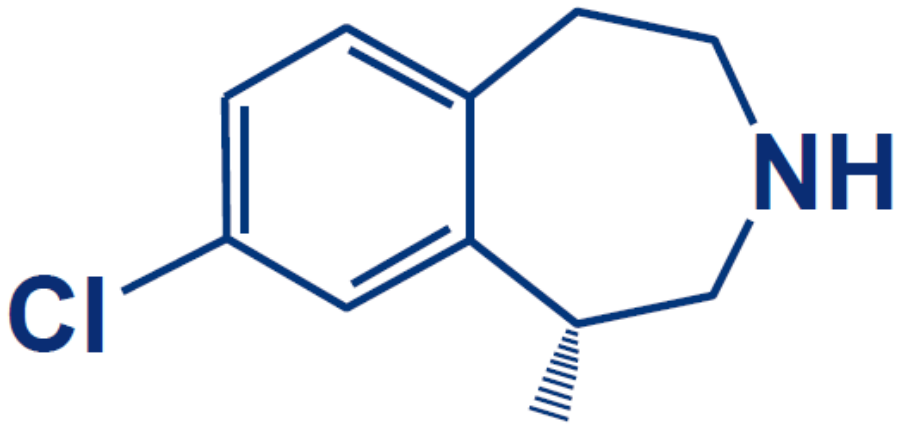
STEP 2 SELECT:

(I) Therapeutic targets for improvement in complications,
(II) Treatment modality and
(III) Treatment intensity for weight loss based on staging

Lifestyle Modification:	MD/RD counseling; web/remote program; structured multidisciplinary program
Medical Therapy:	phentermine; orlistat; lorcaserin; phentermine/topiramate ER
Surgical Therapy (BMI ≥ 35):	Lap band; gastric sleeve; gastric bypass

STEP 3 If therapeutic targets for improvements in complications not met, intensify lifestyle and/or medical and/or surgical treatment modalities for greater weight loss

Lorcaserin is a Selective Serotonin 2C Receptor Agonist



Human	5-HT_{2C}R	5-HT_{2A}R	5-HT_{2B}R
Functional Activity EC_{50} (nM)	39	553	2,380
Relative Selectivity		14	61

Phase 3 Clinical Study Designs and Patient Baseline Characteristics

Phase 3, Double Blind, Randomized Controlled Trials

	Study 009	Study 011	Study 010
Overview	Non-diabetic patients 18-65 yrs old		Type 2 diabetes 18-65 yrs old
BMI Range	27 to 45	27 to 45	27 to 45
N	3,182	4,008	604
Lorcaserin BID Lorcaserin QD	1,595 0	1,603 802	256 95
Length of study	2 years	1 year	1 year
Lifestyle Modification	All patients followed a daily 600 calorie deficit diet + exercise program, with monthly counseling sessions		

Pivotal Study Design: Primary Efficacy Endpoints

- Year 1 (ordered primary endpoints)
  - Proportions achieving ≥ 5% weight loss
  - Absolute weight loss
  - Proportions achieving ≥ 10% weight loss

Baseline Demographics

Parameter	Study 009		Study 011		Study 010	
	PBO n=1,587	LOR n=1,595	PBO n=1,601	LOR n=1,602	PBO n=252	LOR n=256
Mean age (yrs)	44	44	44	44	52	53
Female	84%	83%	78%	81%	54%	54%
Mean weight (kg)	100	100	100	100	103	104
Mean BMI (kg/m^2)	36	36	36	36	36	36
Ethnicity						
Caucasian	66%	68%	67%	67%	66%	59%
African American	19%	19%	20%	19%	18%	22%
Hispanic/Latino	13%	11%	11%	11%	11%	15%
Other	2%	2%	2%	3%	6%	5%

Significant Medical Conditions or Impaired Fasting Glucose in Study 009 and 011

Parameter	Population Prevalence BMI ≥ 30 Male	Female	Study 009	Study 011
Hypertension	38%	32% [a]	21%	24%
Dyslipidemia	20%	25% *[a]	33%	28%
Sleep apnea	> 15%[b]	> 15%[b]	4%	4%
CVD	> 8%	> 6%[c]	5%	5%
Impaired fasting glucose	32.6%	20%[a,d]	26%	25%
Depression	2.9%	6.7%[a]	8%	8%
No comorbid condition			50%	53%
≥ 1 comorbid condition			50%	47%
≥ 2 comorbid condition			16%	17%

* High cholesterol

[a] NHANES III; [b]Wisconsin Sleep Study; [c]AHA Heart Disease and Stroke Statistics; [d]All BMIs

Baseline Characteristics Study 010

	Study 010	
	PBO n=252	Lorcaserin 10 mg BID n=256
HbA1c		
Mean	8%	8%
≥ 9	18%	18%
< 9	82%	82%
Fasting plasma glucose (mg/dL)	160.2	163.8
Primary diabetic medications		
Metformin	91%	92%
SFU	50%	50%
Both	41%	43%
Duration of diabetes (years)	7.0	6.6

Patient Disposition

	Study 009		Study 011		Study 010	
	PBO n=1,587	LOR n=1,595	PBO n=1,601	LOR n=1,602	PBO n=252	LOR n=256
Completed	45%	55%	52%	57%	62%	66%
Completed and Returning Dropouts	57%	65%	59%	64%	65%	68%
Withdrawals:						
Lost to follow up	14%	12%	15%	12%	6%	8%
Adverse events	7%	7%	5%	7%	4%	9%
Lack of efficacy	6%	2%	4%	2%	2%	1%
Other	28%	24%	25%	21%	26%	17%

* Other includes the following withdrawal categories: Withdrawal of Consent, Lost to Follow-up, Protocol Deviation/Non-compliance, Sponsor Decision, PI Decision and Other

FDA Guidance for Primary Endpoints of Weight Loss Drugs

- ≥ 5% difference in mean weight loss between groups at one year

OR

- At least 35% of patients lose ≥ 5% body weight at one year and approximately double the proportion in the placebo-treated group

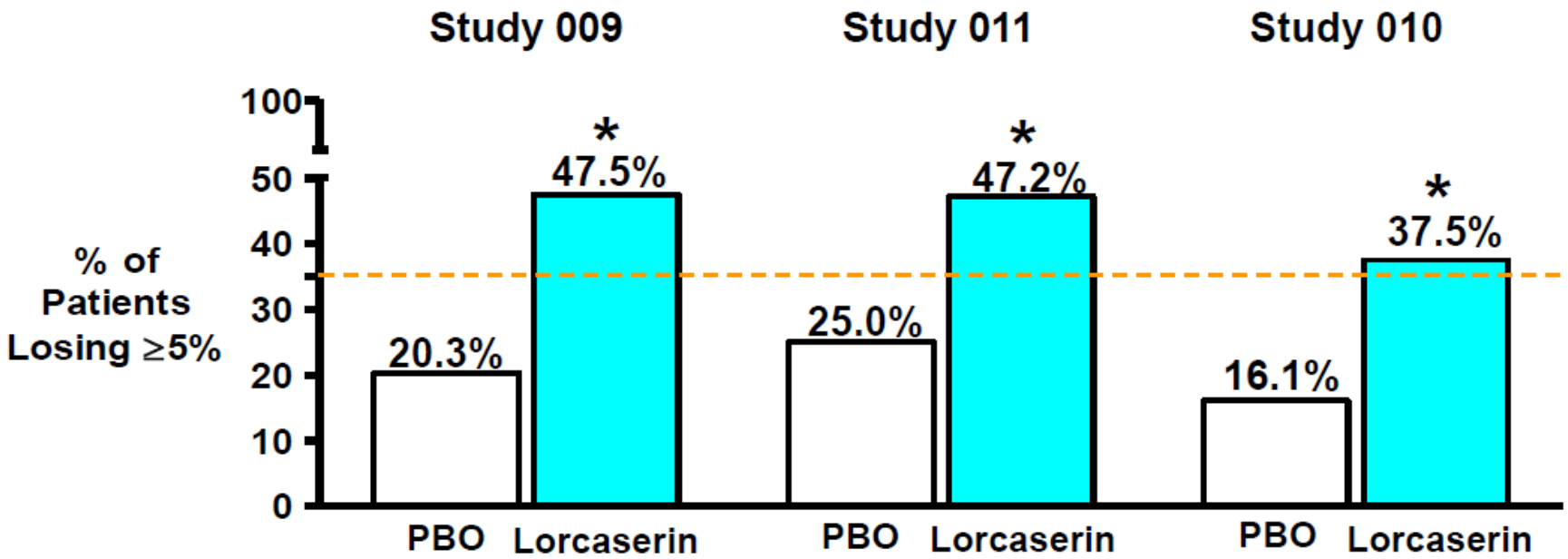
* Adapted from FDA Guidance for Industry Developing Products for Weight Management, February 2007

5% Weight Loss is Correlated with Improvements in Risk Factors

- Generally quoted as 5% based on
  - Improvements in cardiovascular risk factors
  - Improvements in glycemic control
  - Diabetes prevention

Douketis and Macie, et al. *Nature* 2005; Foreyt, et al Lifestyle Obesity Management, 2003 NHLBI website; Abel, et al. *Physiol Rev* 2008; Krauss, et al. *AHA Conference Proceedings: Obesity- Impact on Cardiovascular Disease* 1998; Wilson, et al. *Arch Intern Med* 2002

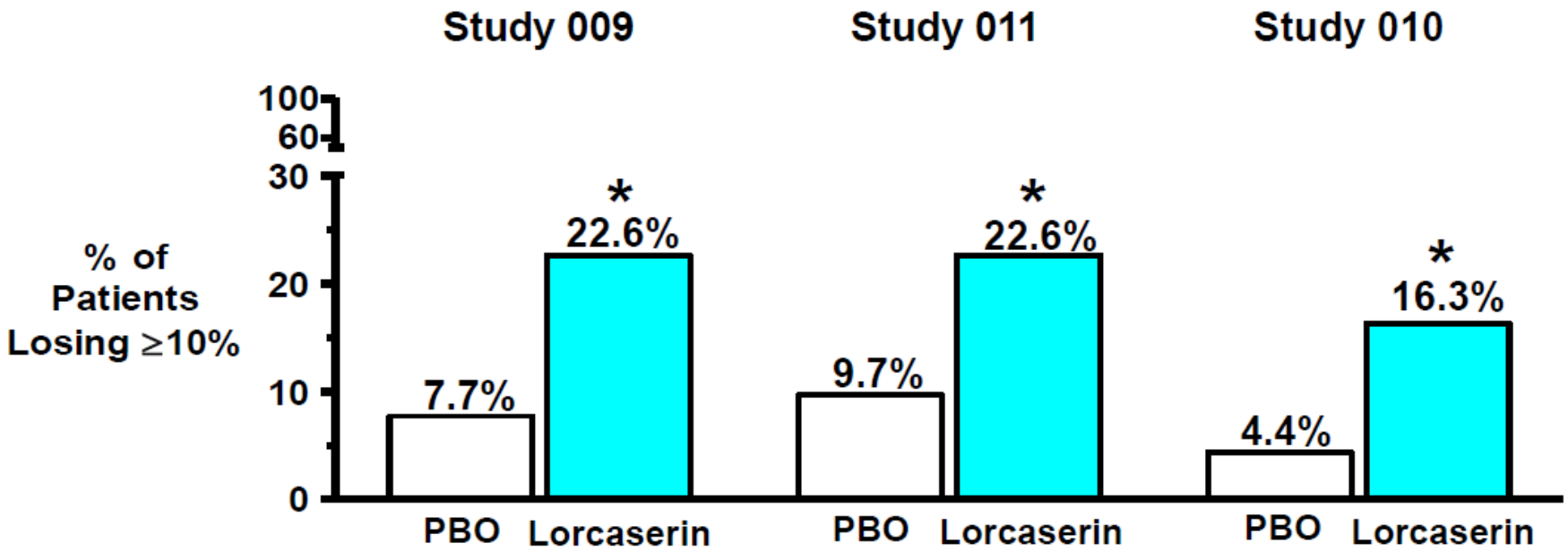
Proportion of Patients Losing ≥ 5% of Baseline Body Weight



	Study 009	Study 011	Study 010
Difference in Proportion vs. PBO	27.2%	22.2%	21.3%
95% CI	24.0%, 30.5%	18.9%, 25.5%	13.8%, 28.9%

* p-value < 0.001 vs. PBO
MITT Population

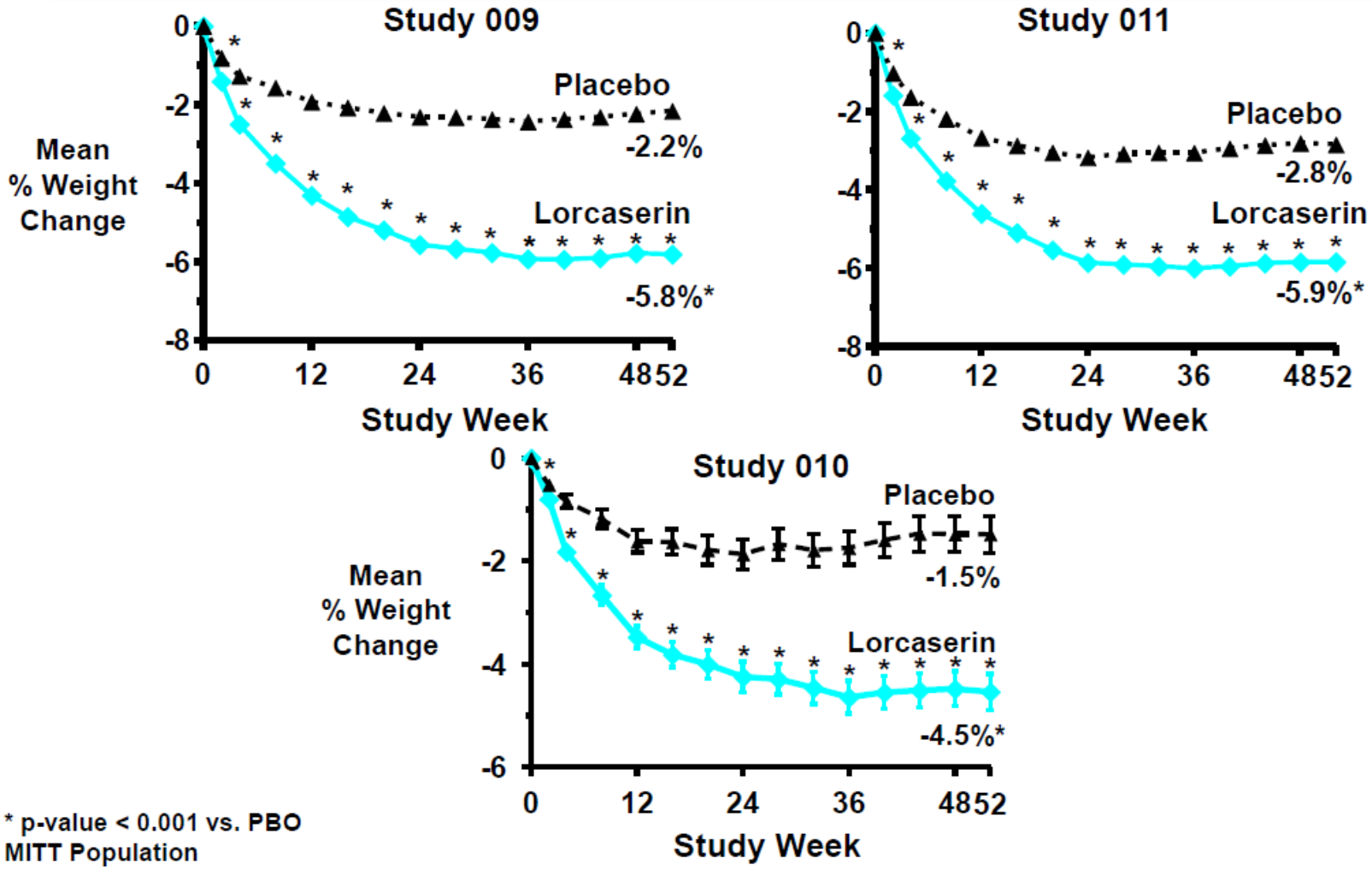
Proportion of Patients Losing ≥ 10% of Baseline Body Weight



	Study 009	Study 011	Study 010
Difference in Proportion vs. PBO	14.9%	12.9%	11.9%
95% CI	12.4%, 17.4%	10.3%, 15.4%	6.7%, 17.1%

* p-value < 0.001 vs. PBO
MITT Population

Difference in Mean Weight Loss was Statistically Significant

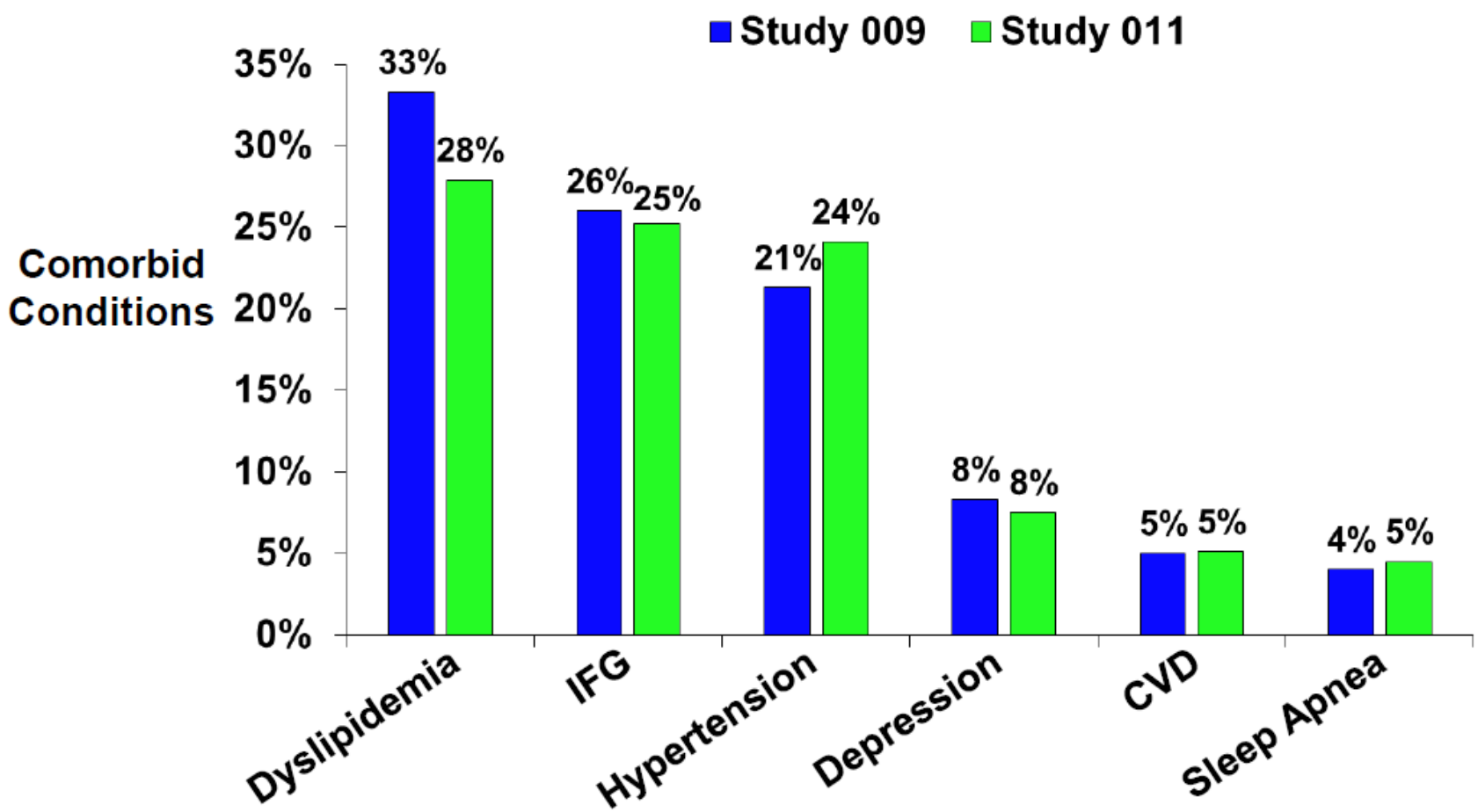


* p-value < 0.001 vs. PBO
MITT Population

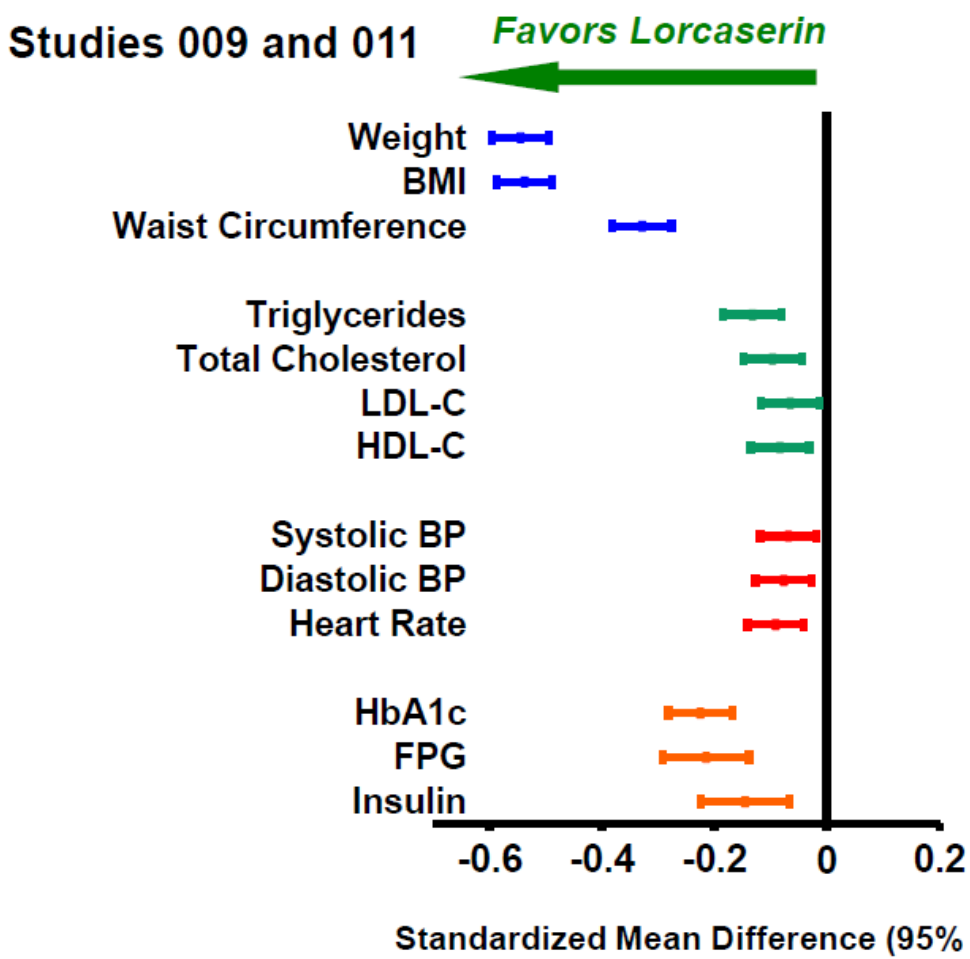
FDA Guidance for Secondary Endpoints of Weight Loss Drugs

- Improvements in markers of cardiovascular risk factors and changes in common weight-related comorbidities

Significant Medical Conditions or Impaired Fasting Glucose



Lorcaserin Showed Favorable Impact on Cardiometabolic Parameters



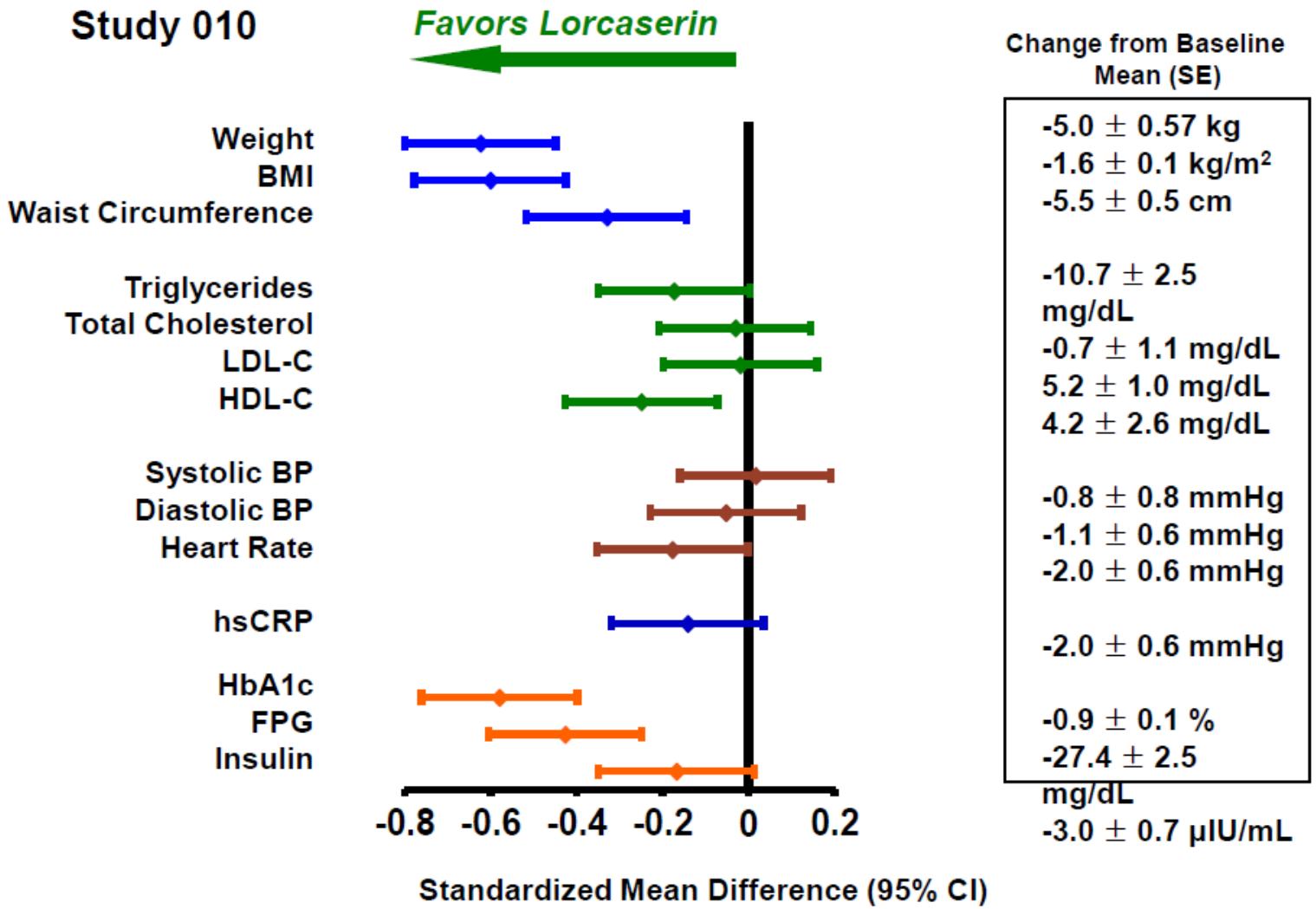
Change from Baseline Mean (SE)
-5.8 ± 0.12 kg
-2.1 ± 0.04 kg/m^2
-6.5 ± 0.15 cm
-5.2 ± 0.73 mg/dL
-0.8 ± 0.25 mg/dL
1.6 ± 0.40 mg/dL
1.8 ± 0.27 mg/dL
-1.7 ± 0.22 mmHg
-1.5 ± 0.16 mmHg
-1.2 ± 0.16 mmHg
-0.1 ± 0.01 %
-0.2 ± 0.19 mg/dL
-0.1 ± 0.01 µIU/mL

Blood Pressure and Heart Rate Change from Baseline at Week 52 Studies 009 and 011

Parameter / Treatment	n at Wk 52	Baseline Mean (SD)	Week 52 Mean (SD)	Change from Baseline LS Mean
Systolic BP (mm Hg)				
Placebo	3,039	121.0 (11.7)	120.2 (12.5)	-1.0 (0.2)
Lorcaserin 10 mg BID	3,096	121.4 (11.9)	119.7 (12.7)	-1.8 (0.2)
Diastolic BP (mm Hg)				
Placebo	3,039	77.7 (8.1)	76.7 (8.8)	-1.0 (0.2)
Lorcaserin 10 mg BID	3,096	77.4 (8.0)	75.9 (8.7)	-1.6 (0.2)
Heart Rate (bpm)				
Placebo	1,557	69.3 (8.7)	67.8 (9.3)	-1.5 (0.2)
Lorcaserin 10 mg BID	1,798	69.0 (8.8)	66.9 (9.1)	-2.2 (0.2)

Population: MITT/LOCF; Except for Heart Rate where Safety Population was used (SEM)

Lorcaserin Showed Favorable Impact on Cardiometabolic Parameters



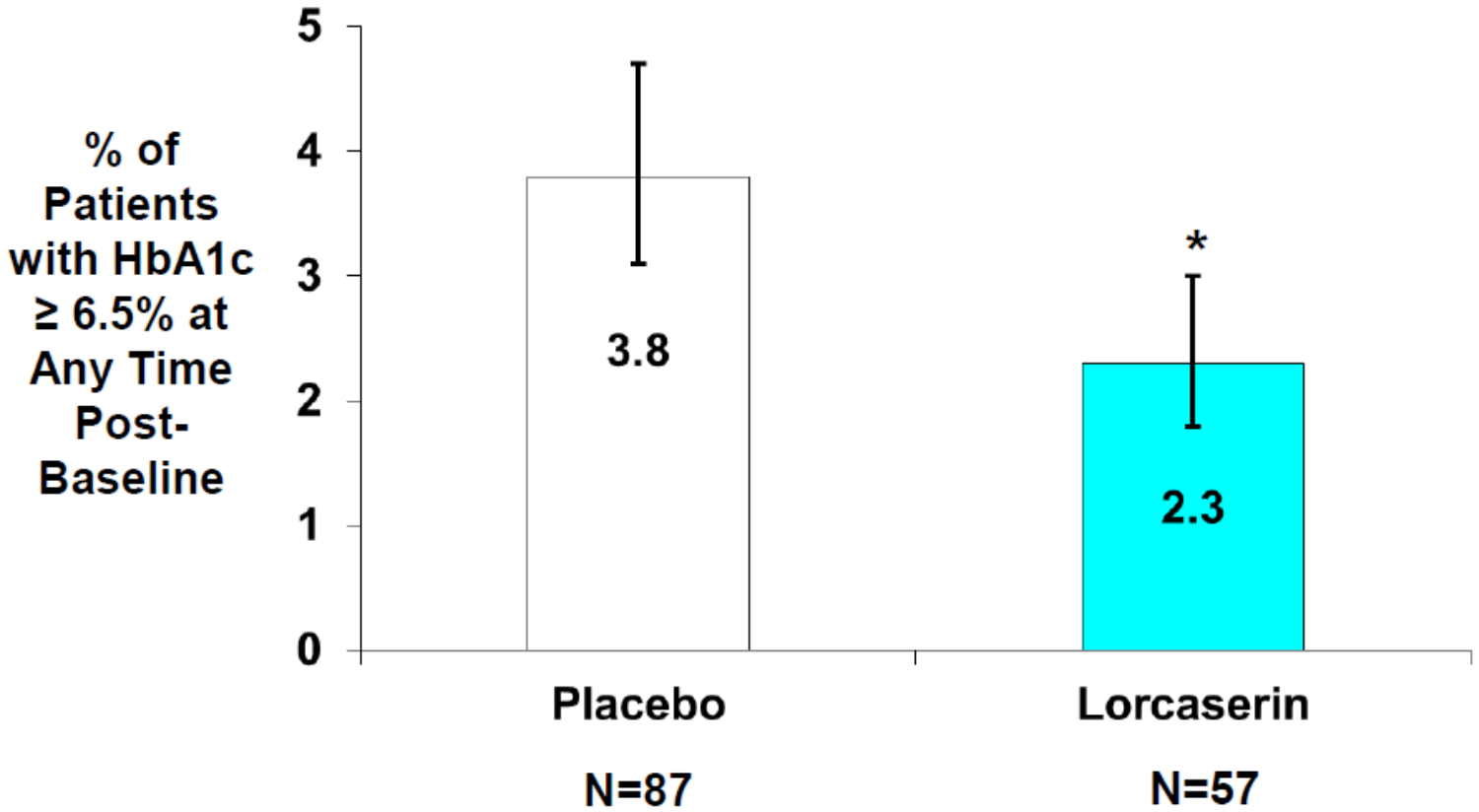
Summary of CV Vital Signs and Change from Baseline in Study 010

Parameter / Treatment	n at Wk 52	Baseline Mean (SD)	Week 52 Mean (SD)	Change from Baseline LS Mean
Systolic BP (mm Hg)				
Placebo	248	126.5 (13.5)	125.6 (13.5)	-0.9 (0.9)
Lorcaserin 10 mg BID	251	126.6 (12.7)	125.8 (12.5)	-0.8 (0.9)
Diastolic BP (mm Hg)				
Placebo	248	78.7 (7.9)	77.5 (8.2)	-0.7 (0.6)
Lorcaserin 10 mg BID	251	77.9 (8.0)	76.8 (8.9)	-1.1 (0.6)
Heart Rate				
Placebo	158	72.4 (9.4)	72.5 (10.2)	0.1 (0.7)
Lorcaserin 10 mg BID	170	72.8 (9.7)	70.7 (9.3)	-2.1 (0.8)

Population: MITT/LOCF; Except for Heart Rate where Safety Population was used (SEM)

Weight Loss and the Prevention of Diabetes

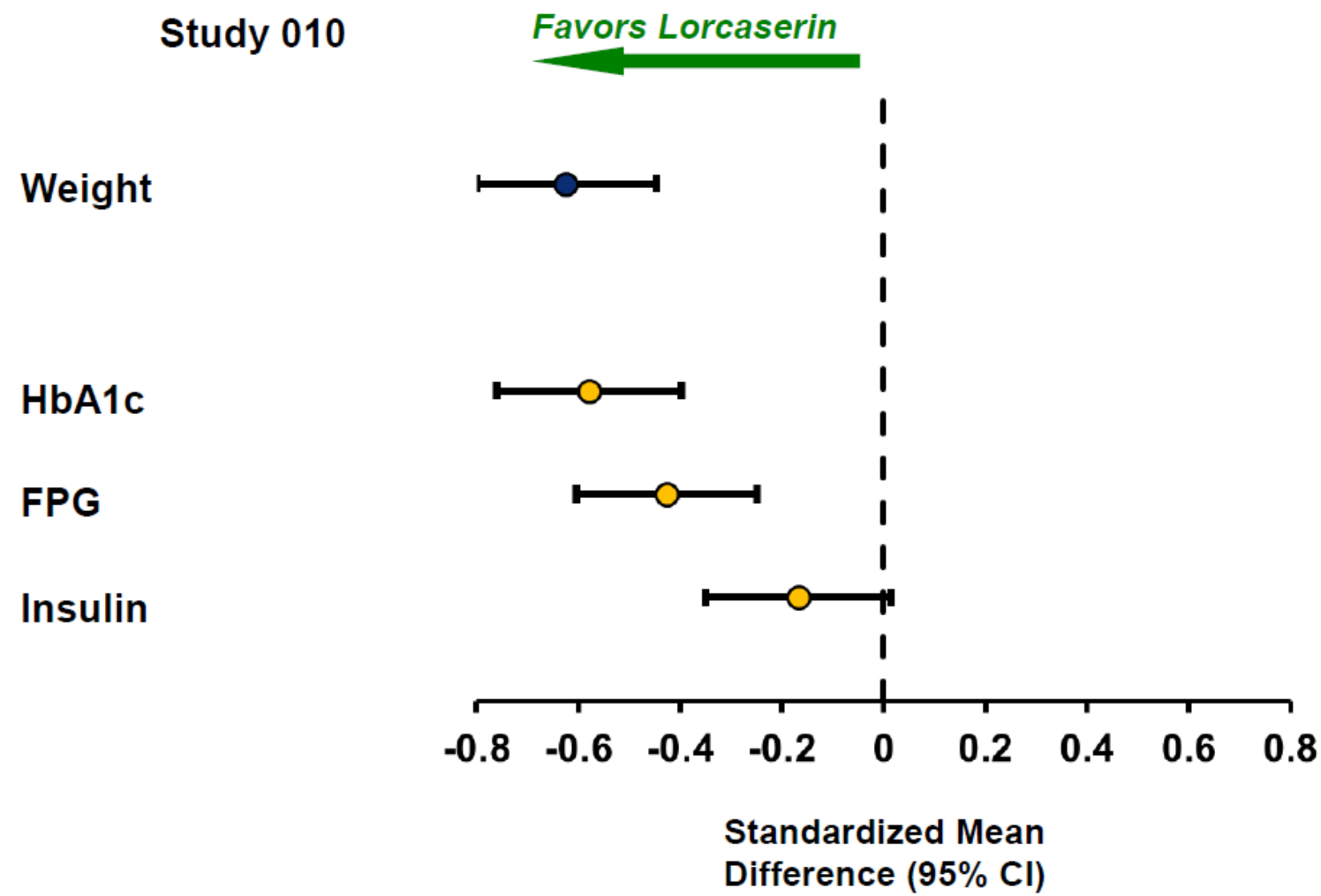
New Onset Type 2 Diabetes in Patients Without Diabetes in Studies 009 & 011



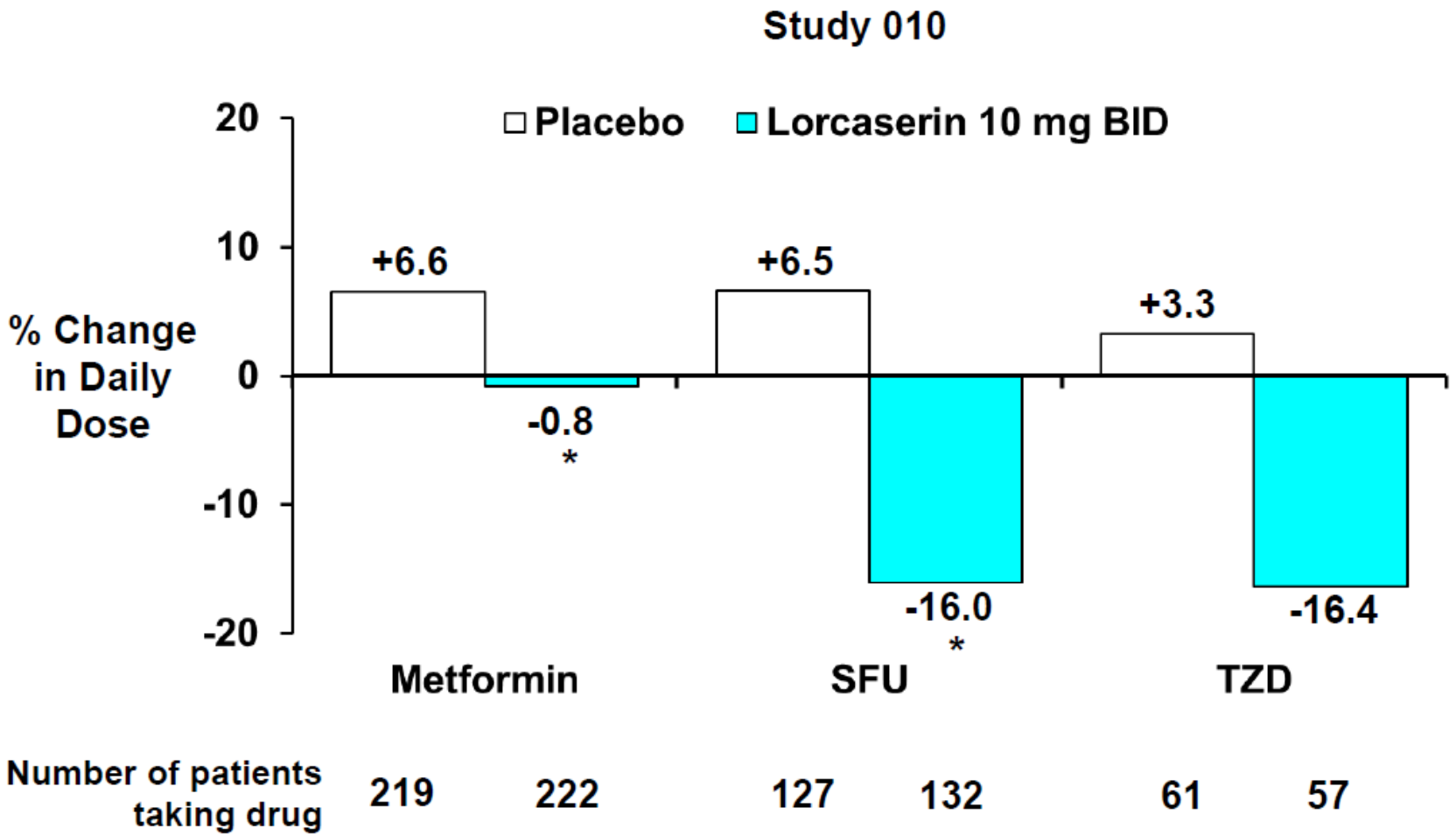
* p=0.003

Benefits to Patients with Diabetes

Lorcaserin Showed Favorable Impact on Metabolic Parameters

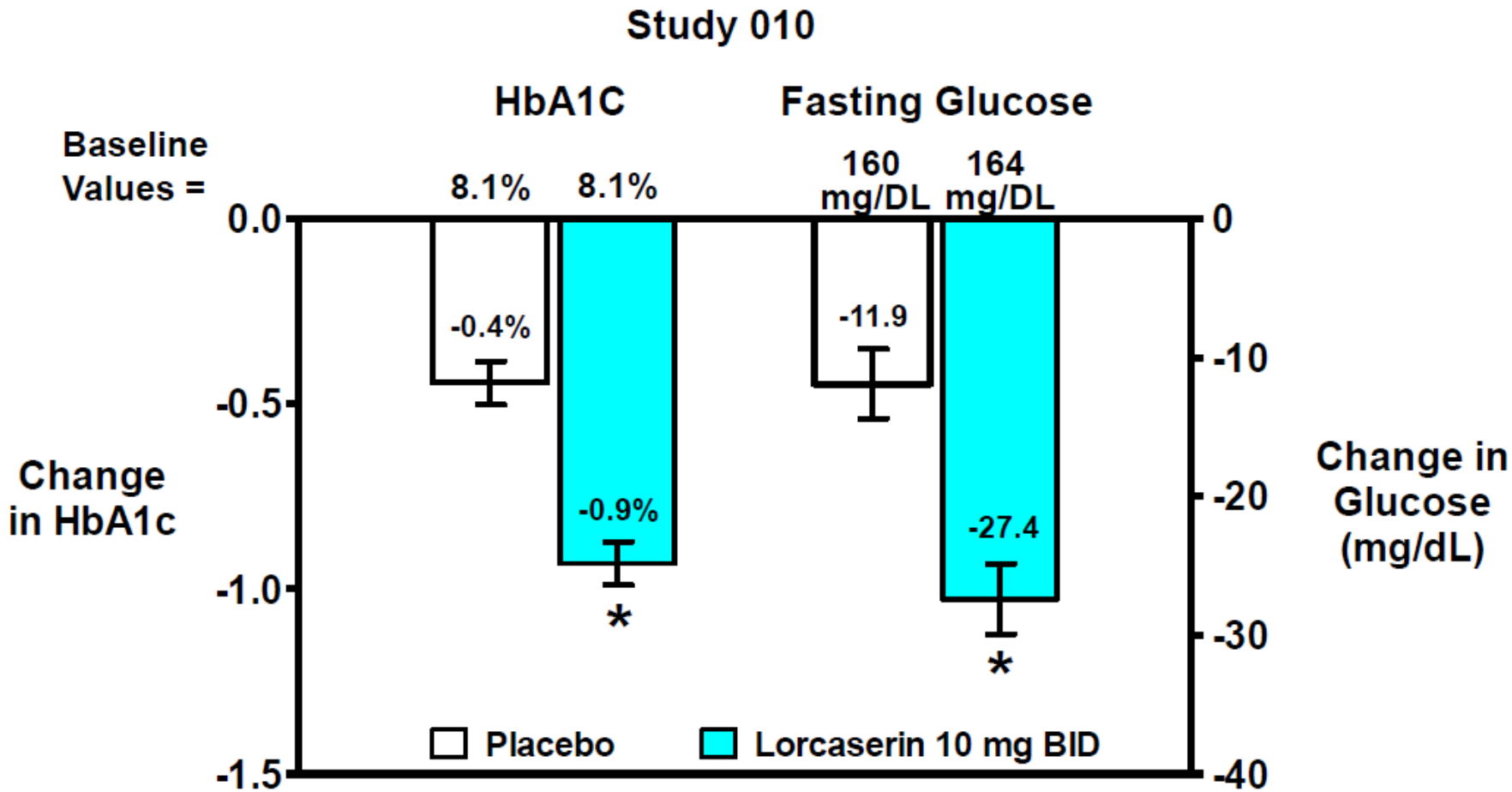


Lorcaserin Reduced Use of Anti-Diabetic Medications



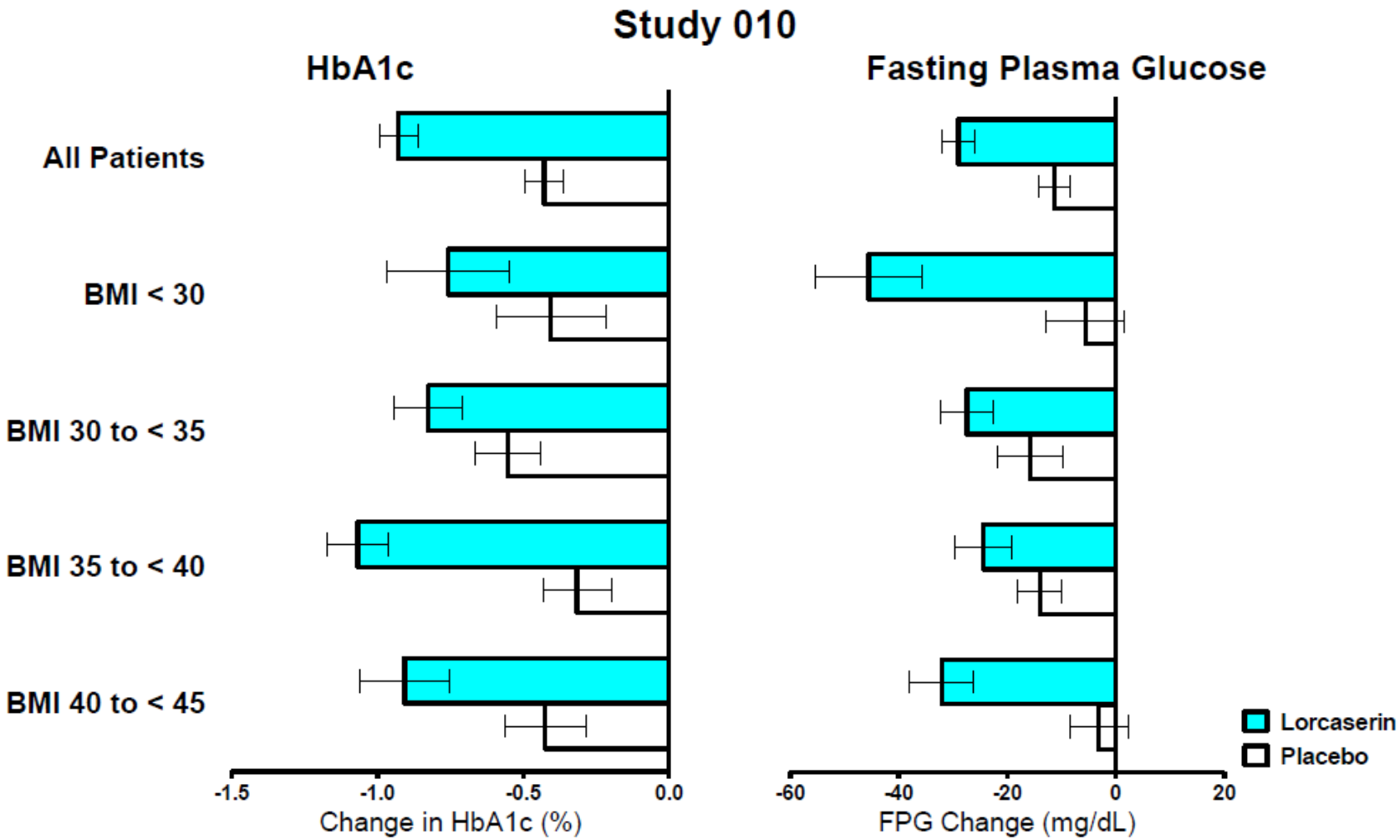
* p < 0.05

Lorcaserin Significantly Improved Glycemic Control at Week 52

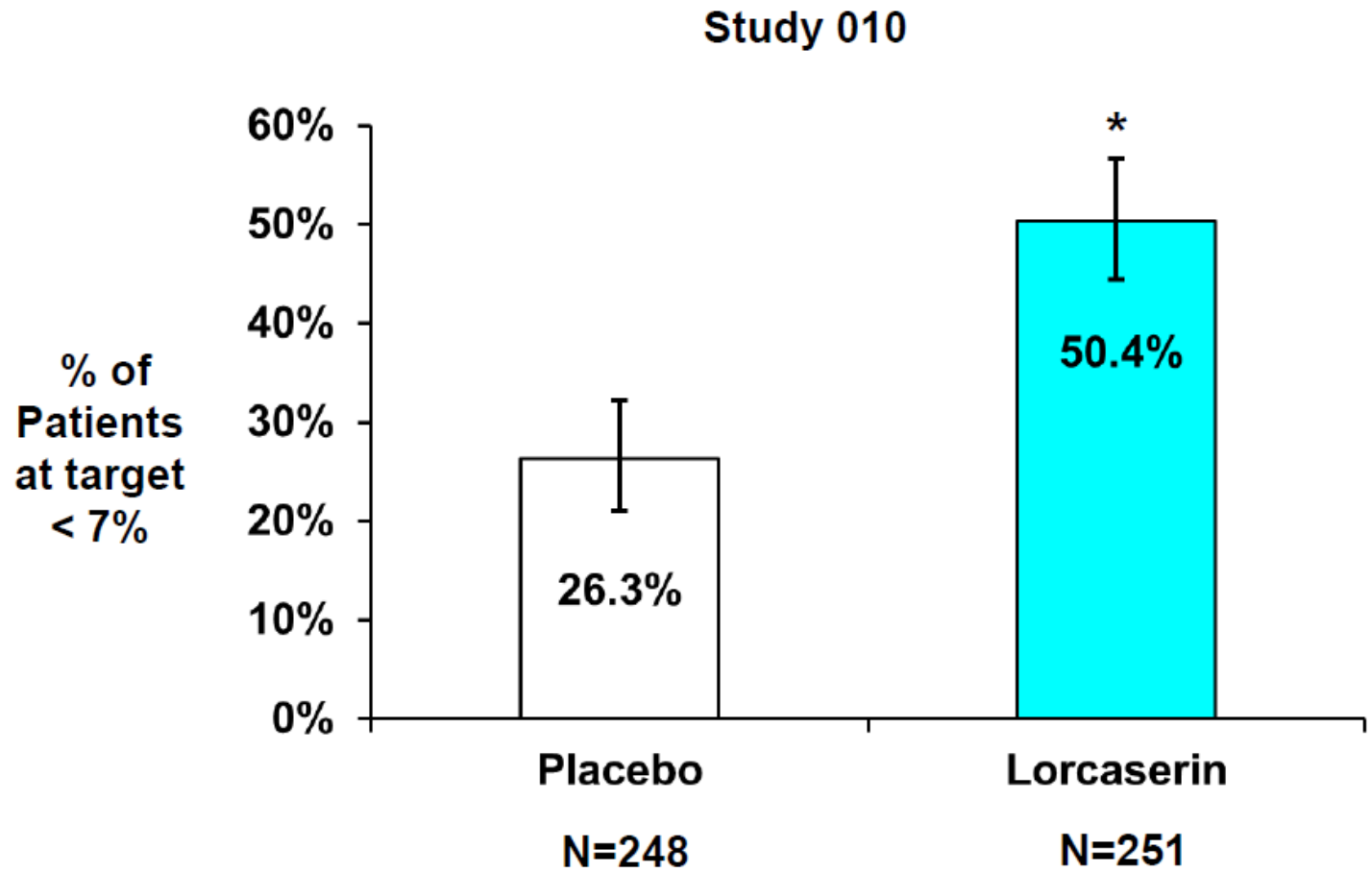


* p < 0.001; MITT/LOCF, LS mean ±sem; Study 010

Improved Glycemic Control Across a Range of BMIs

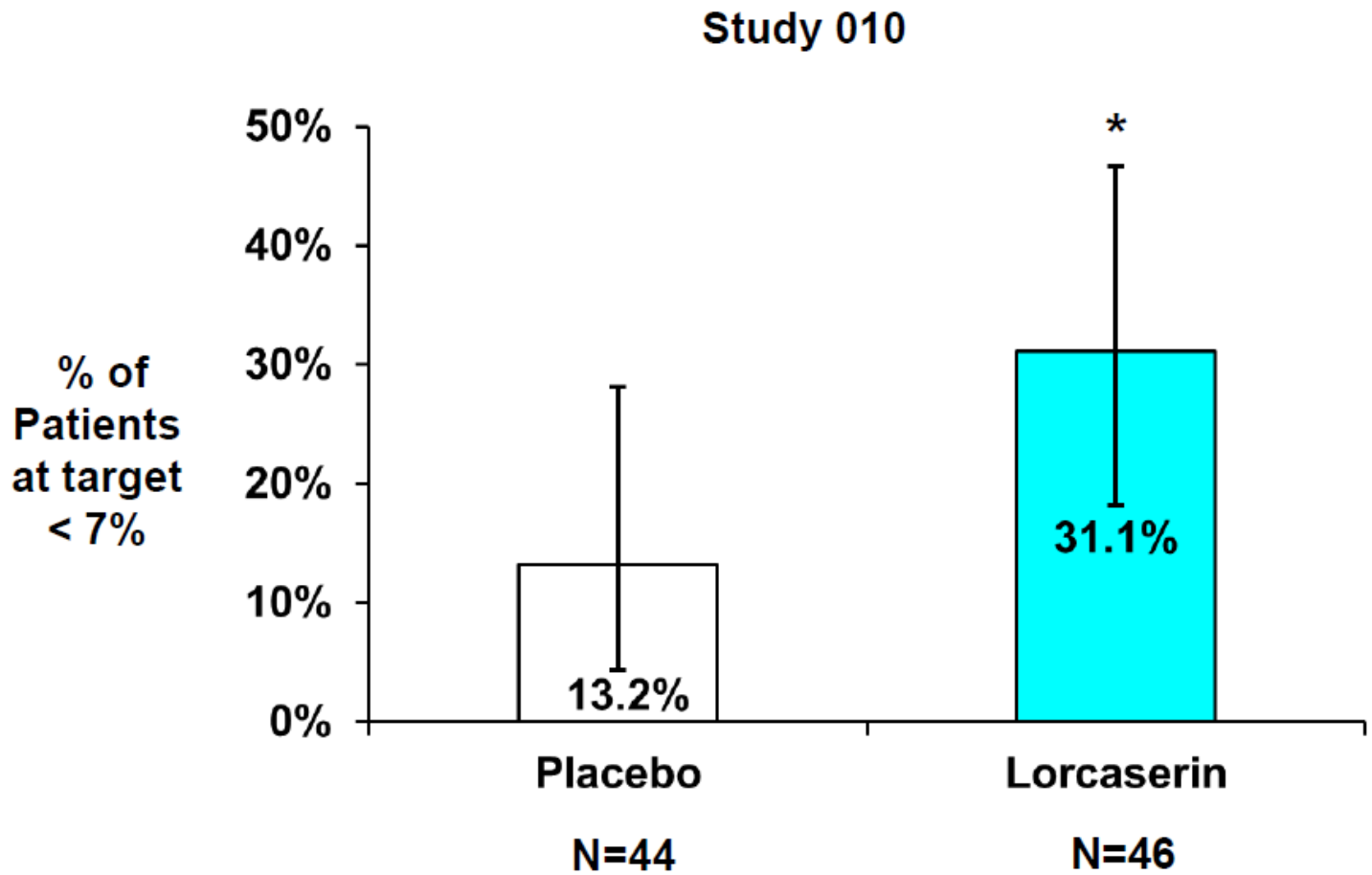


50% of Lorcaserin Patients Reached HbA1c of < 7% at Week 52



p < 0.001; MITT/LOCF; Study 010
Proportion 95%CI

31% of Patients with Baseline HbA1c ≥ 9% Decreased to < 7% at Week 52

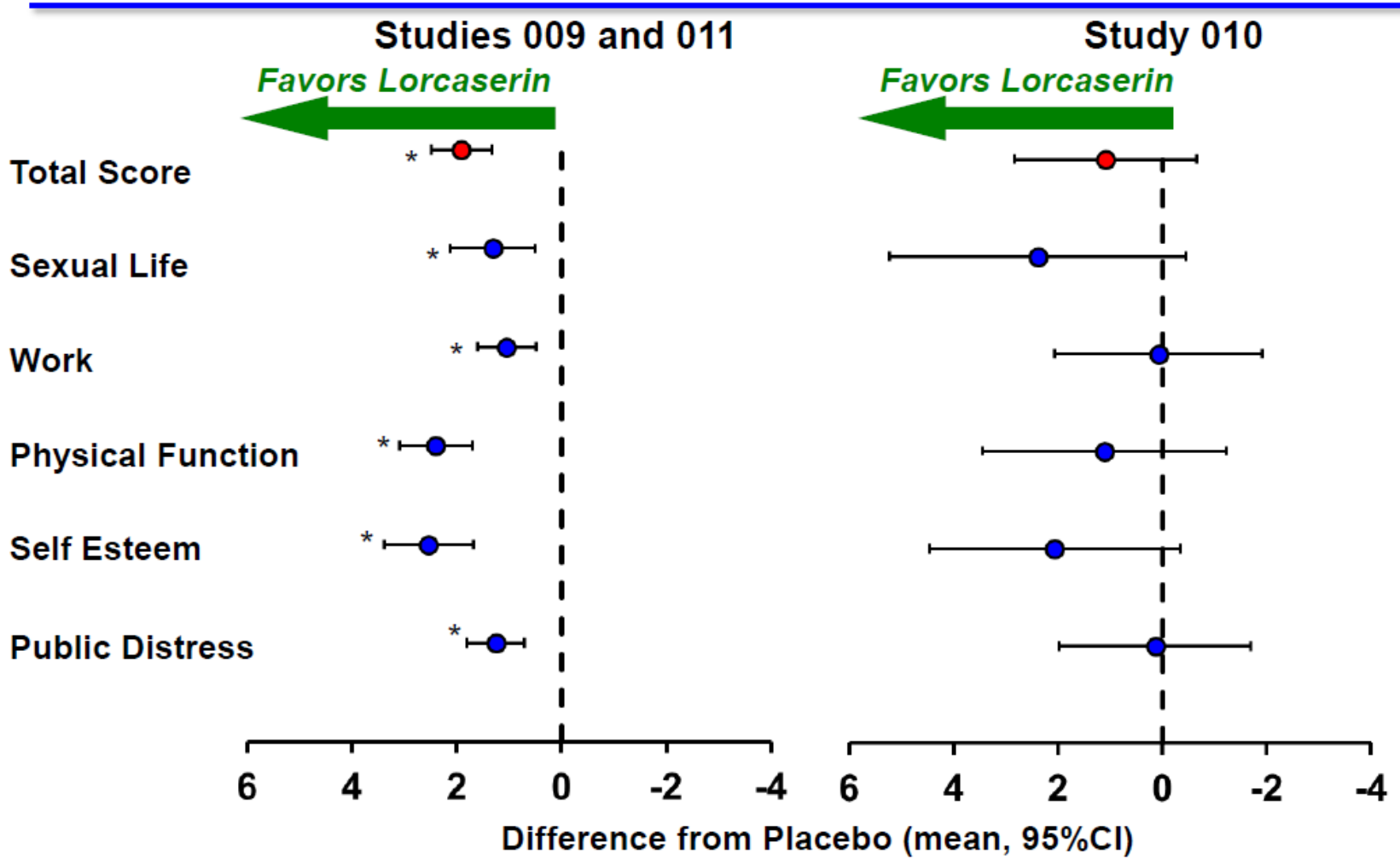


MITT/LOCF; Study 010
Proportion 95%CI

Quality of Life

IWQOL-Lite

Lorcaserin Improved Quality of Life: IWQOL-Lite Instrument



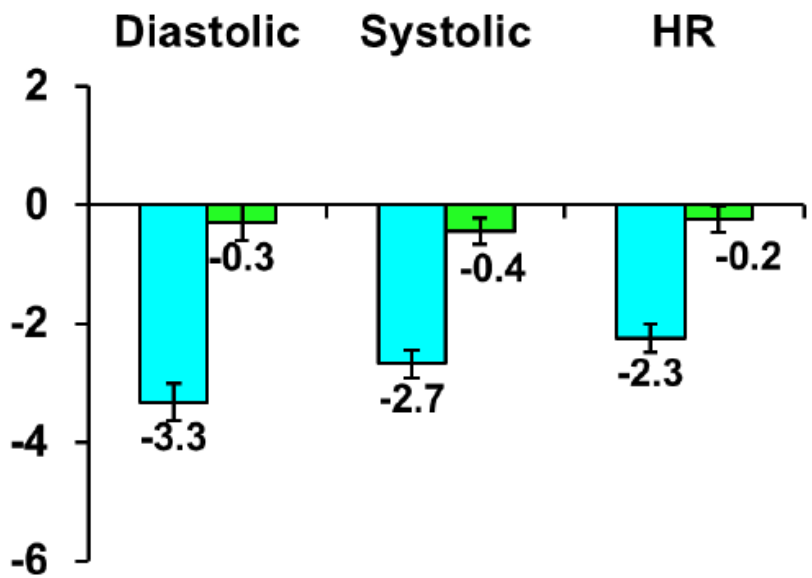
* All differences between placebo and lorcaserin were statistically significant p < 0.001

Patients Achieving ≥ 5% Weight Loss

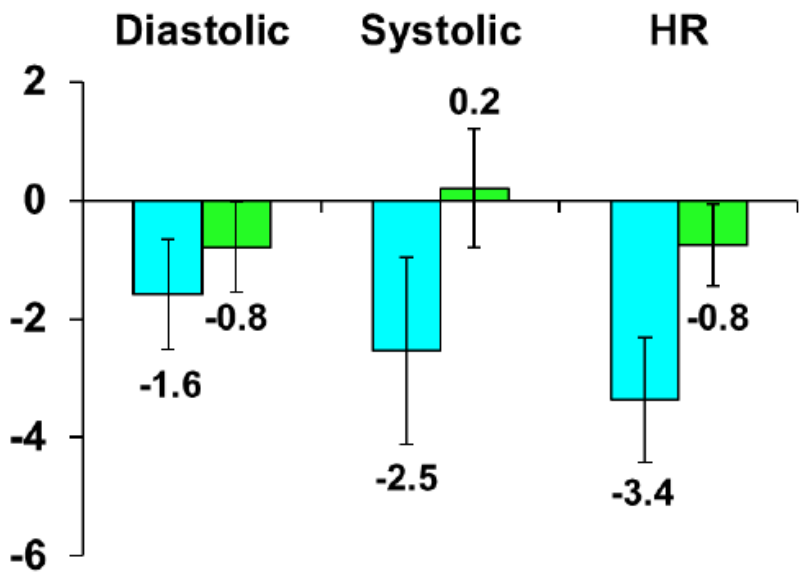
Patients achieving ≥ 5% Weight Loss	Study 009		Study 011		Study 010	
	PBO	LOR	PBO	LOR	PBO	LOR
% of ITT Population	14.2%	35.6%	18.3%	36.2%	11.5%	30.5%
% Total Weight Loss	10.7%	11.7%	11.1%	12.0%	8.9%	10.8%
Mean weight loss (lbs)	23.4	25.6	24.7	26.0	20.3	24.0
Change in BMI	-3.8	-4.2	-4.0	-4.3	-3.2	-3.8
Number of Patients	225	567	293	581	29	78

ITT-BOCF

Responder Analysis:
Heart Rate, Systolic BP, and Diastolic BP



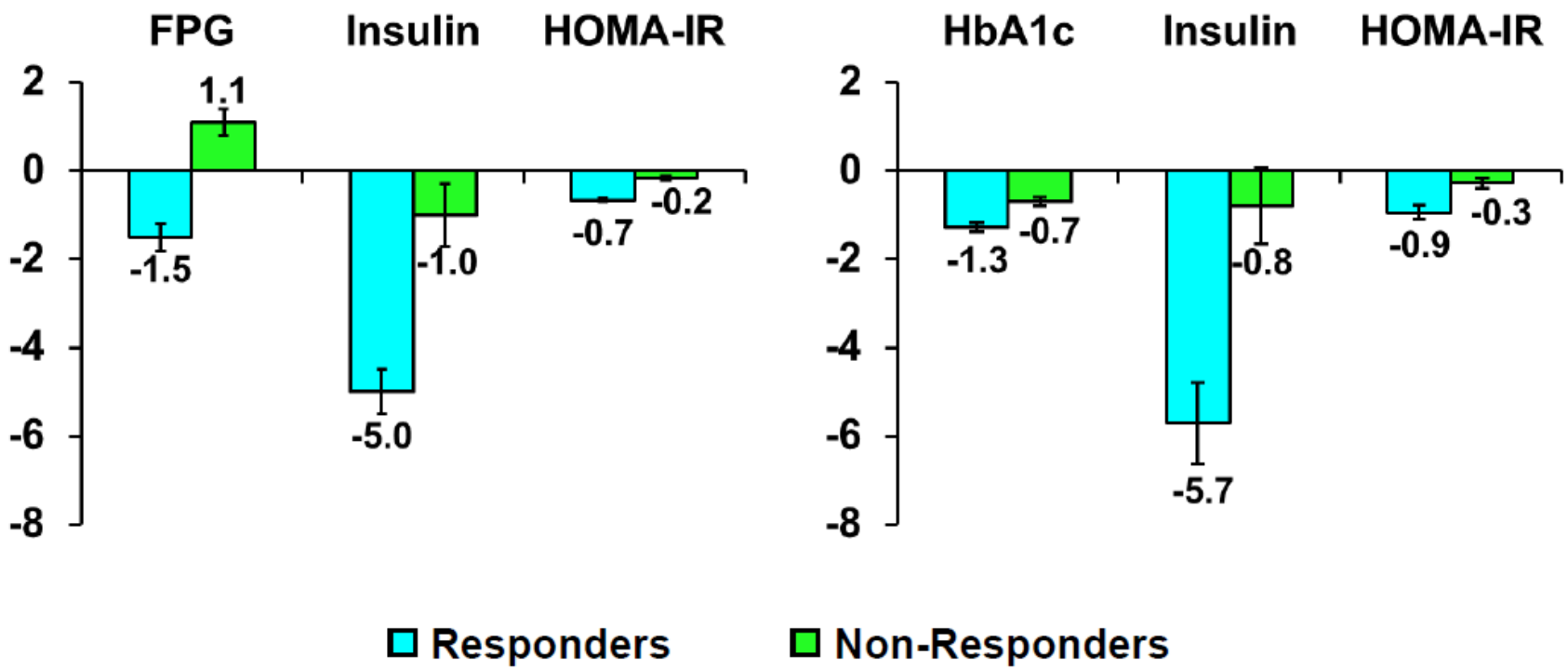
(MITT- LOCF), Studies 009 and 011



(MITT- LOCF), Study 10

Responders Non-Responders

Responder Analysis: Glycemic Parameters



(MITT- LOCF), Studies 009 and 011

(MITT- LOCF), Study 10

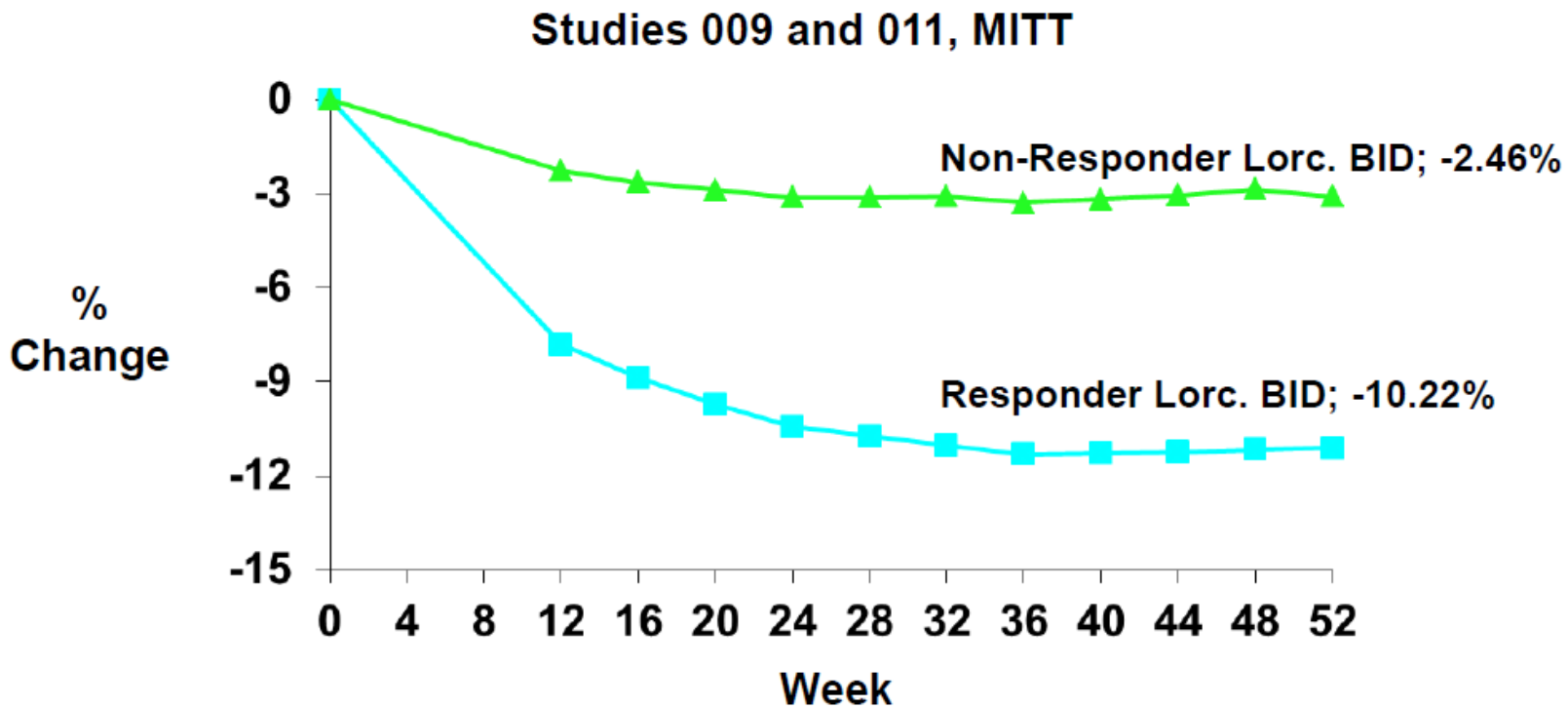
Identifying Responders

Predicting Lorcaserin Responders: How Long to Dose to Identify Non-Responders?

Week of Prediction	% Weight Loss	Sensitivity (95% CI)	Specificity (95% CI)	AUC for ROC[a]
Week 2	1.5	0.66 (0.63, 0.69)	0.63 (0.59, 0.67)	0.69
Week 4	2.5	0.75 (0.72, 0.78)	0.63 (0.58, 0.67)	0.75
Week 8	3.9	0.75 (0.72, 0.76)	0.70 (0.66, 0.74)	0.80
Week 12	4.6	0.80 (0.77, 0.83)	0.72 (0.68, 0.76)	0.85

[a] Higher number signifies better prediction.

Those Who Lost 4.5% Total Body Weight by Week 12 Were Week 52 Responders



Week 12	Completed Week 12	Completed Week 52
≥ 4.5% wt loss	1,369/3,098 (44.2%)	1,083/1,369 (79.1%)
< 4.5% wt loss	1,168/3,098 (37.7%)	680/1,168 (58.2%)

Summary and Conclusions

- We treat weight loss to
  - Reduce cardiovascular risk
  - Prevent diabetes / improve glycemic control
  - Provide benefits important to individual health
- Lorcaserin → clinically meaningful weight loss
  - Improvements in CV and metabolic risk biomarkers
  - Improvements in HbA1c and FPG
  - Approx. 1/3 of patients lost 11% or 25 lbs

Review of Safety

Overall Summary of AEs

	Pooled Studies 009 and 011		Study 010	
	Placebo n=3,185	Lor BID n=3,195	Placebo n=252	Lor BID n=256
	YEAR 1			
Any AE	75.5%	82.8%	84.5%	92.2%
Any SAE	2.3%	2.7%	6.7%	6.3%
Dropouts due to AE	5.6%	7.1%	4.3%	8.6%
	YEAR 2			
Any AE	73.9%	78.5%	--	--
Any SAE	3.2%	2.6%	--	--
Dropouts due to AE	2.7%	3.7%	--	--
Death, n (%)*	2 (0.06%)	0	--	--

* 1 death during Year 2: patient on placebo in Year 2, lorcaserin in Year 1

AEs with Lorcaserin Incidence ≥ 1% Over Placebo (Based on 009 and 011 incidence)

	Pooled Studies 009 and 011		Study 010	
	Placebo n=3,185	Lorcaserin 10 mg BID n=3,195	Placebo n=252	Lorcaserin 10 mg BID n=256
Headache	10.1%	16.8%	7.1%	14.5%
Upper respiratory infection	12.3%	13.7%	14.7%	13.7%
Dizziness	3.8%	8.5%	6.3%	7.0%
Nausea	5.3%	8.3%	7.9%	9.4%
Fatigue	3.6%	7.2%	4.0%	7.4%
Urinary tract infection	5.4%	6.5%	6.0%	9.0%
Constipation	3.9%	5.8%	4.8%	4.3%
Dry mouth	2.3%	5.3%	1.2%	1.6%
Viral gastroenteritis	3.2%	4.3%	4.4%	7.0%
Vomiting	2.6%	3.8%	3.6%	3.5%
Oropharyngeal pain	2.5%	3.5%	4.8%	4.3%

Discontinuations due to AEs ≥ 0.4% in Studies 009 and 011 or > 2 Patients in Study 010

	Pooled Studies 009 and 011		Study 010	
	Placebo n=3,185	Lorcaserin 10 mg BID n=3,195	Placebo n=252	Lorcaserin 10 mg BID n=256
Any Withdrawal for AE	5.6%	7.1%	4.3%	8.6%
Headache	0.8%	1.3%	0	0.4%
Depression	0.5%	0.9%	0	0.8%
Dizziness	0.2%	0.7%	0	0.4%
Nausea	0.4%	0.7%	0	0
Anxiety	0.3%	0.4%	0.8%	0

SAEs: Lorcaserin Incidence > Placebo and > 2 Patients; Year 1

	Pooled Studies 009 and 011		Study 010	
	Placebo n=3,185	Lorcaserin 10 mg BID n=3,195	Placebo n=252	Lorcaserin 10 mg BID n=256
Any SAE	2.3%	2.7%	6.7%	6.3%
Cholecystitis/cholelithiasis	0.2%	0.3%	0	0.4%
Cellulitis	< 0.1%	0.1%	0.8%	0
Intervertebral disc protrusion	0.1%	0.1%	0	0.4%
Myocardial infarction	0	0.1%	0.8%	0

Post Hoc Cardiovascular Clinical Events Committee Adjudication of SAEs in Studies 009 and 011

Adjudicated AE Term	Placebo N=3,185	Lorcaserin 10 mg BID N=3,195	Lorcaserin 10 mg QD N=801	Lorcaserin/ Placebo Yr 2 N=1,553
Unstable angina	2	1	0	1
MI, spontaneous	0	4	0	0
MI, silent	1	0	0	0
Stroke, ischemic	1	0	0	0
TIA	2	0	0	0
Total cardiac	3	5	0	1
Overall Total	6	5	0	1

Abbreviations: MI = myocardial infarction; TIA = transient ischemic attack

SAEs of Ischaemic Heart Disease and Cerebrovascular Disorders: Not Adjudicated for MACE; Study 010

		Lorcaserin 10 mg	
	Placebo	BID	QD
	N=252	N=256	N=95
Preferred Term	n	n	n
Number of patients with any SAE	2	1	4
Coronary artery occlusion	0	1	0
Myocardial infarction	2	0	0
Angina pectoris	0	0	1
Coronary artery disease	0	0	1
Total Cardiac	2	1	2
Cerebrovascular accident	0	0	2

CV Safety Assessment

- No identified CV safety signal for lorcaserin
- EMDAC meeting on March 28-29 provided recommendations for CV safety studies for obesity drugs
- We are committed to working with the FDA to design appropriate post-marketing studies to assess CV safety as necessary

Echocardiographic Safety Evaluation of Cardiac Valve Function

FDA-Defined Valvulopathy

- Aortic and Mitral Regurgitation
  - Rated from absent to severe
- FDA defines significant valvular regurgitation as:

MILD or greater aortic regurgitation

OR

MODERATE or greater mitral regurgitation

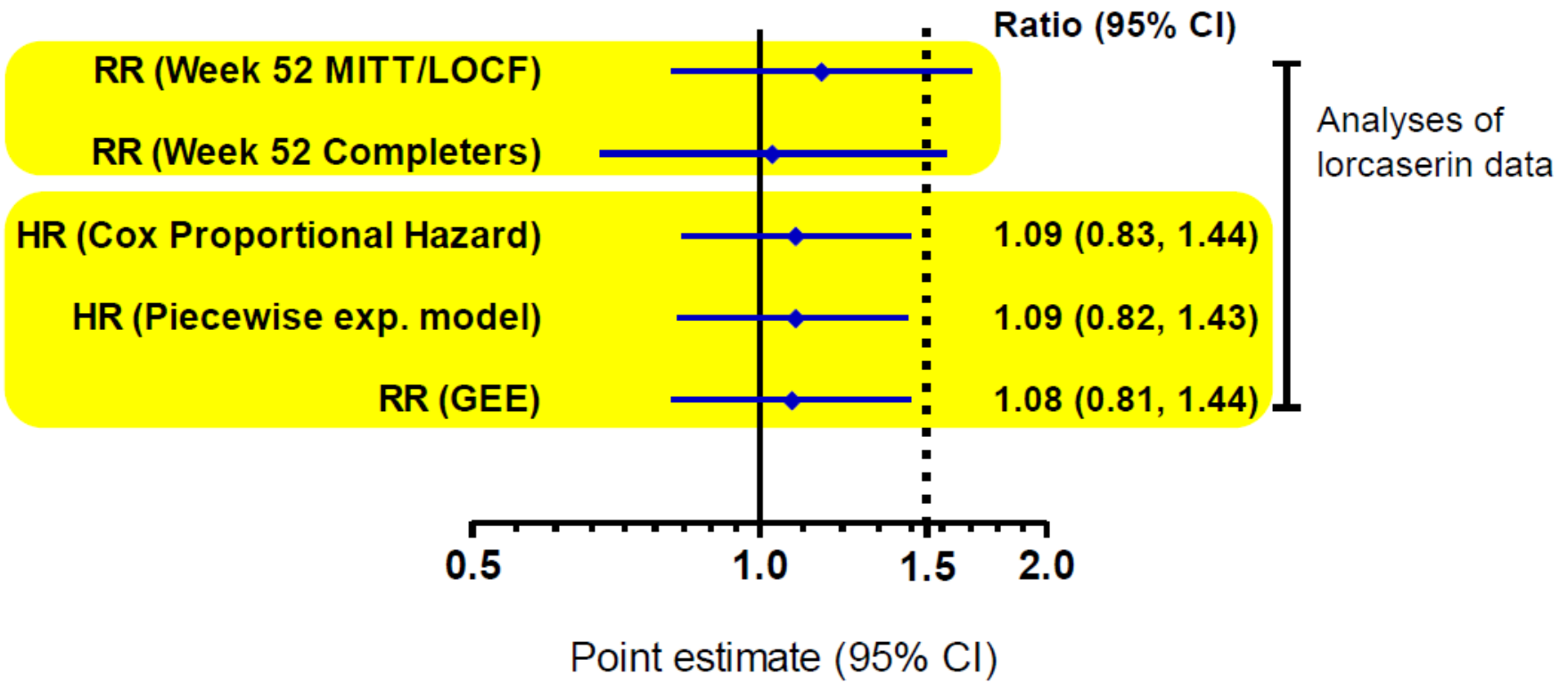
Cardiac Valvular Function Assessed by Serial Echocardiographs

- > 20,000 echocardiographs
- 7,800 patients
- Evaluated at baseline or screening, and every 6 months thereafter
- 426 patients received lorcaserin BID for 2 years

Cardiac Valvular Function

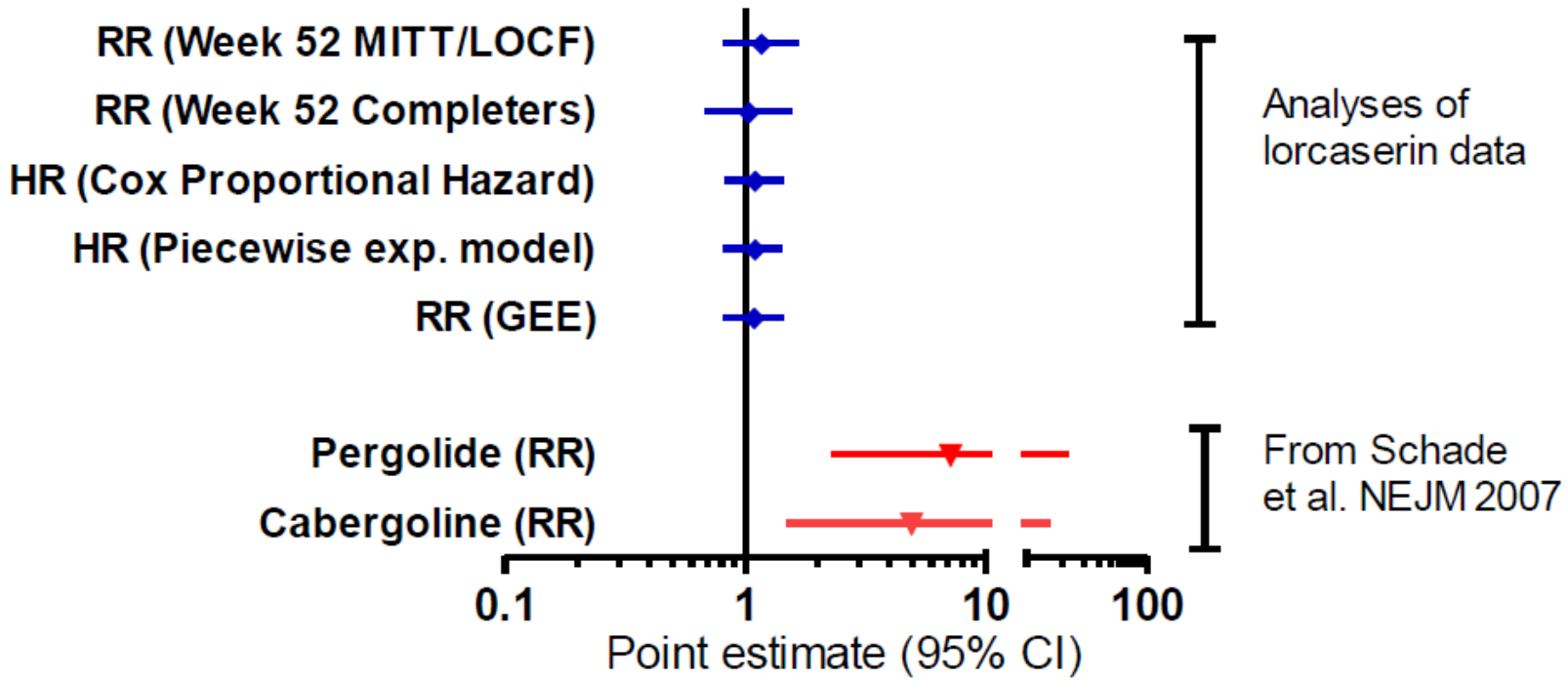
- Week 52 rates of valvulopathy
  - Lorcaserin = 2.37%
  - Placebo = 2.04%

Risk Analyses for FDA-defined Valvulopathy Phase 3 Studies



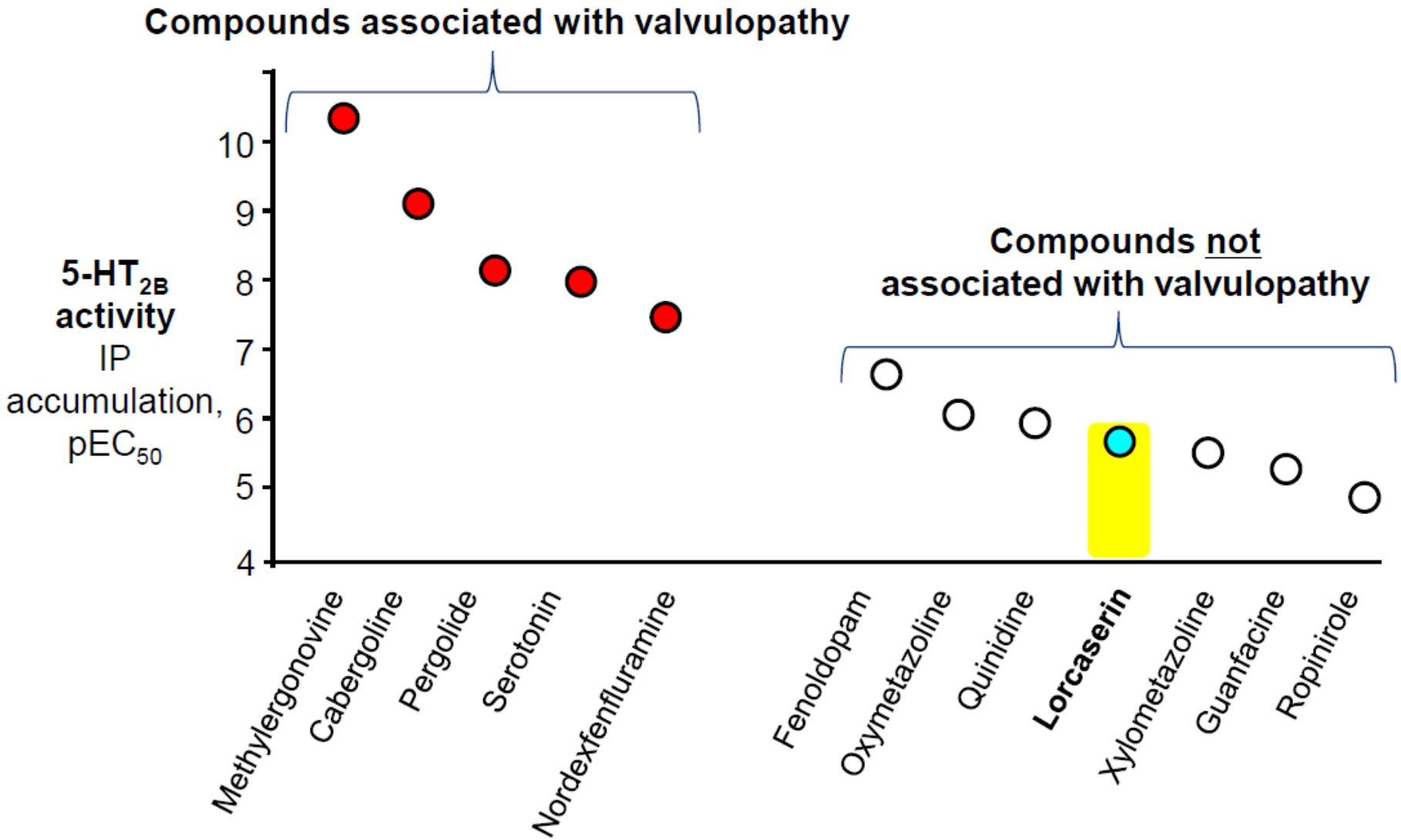
RR = relative risk; HR = hazard ratio;
GEE = generalized estimating equations

Risk Analyses for FDA-Defined Valvulopathy Phase 3 Studies



RR = relative risk; HR = hazard ratio;
GEE = generalized estimating equations

Lorcaserin is Not Associated with Valvulopathy



Valvulopathy Summary

- Appropriately powered risk ratio analyses rule out a 1.5 fold or greater incidence of FDA valvulopathy with lorcaserin treatment for up to 2 years
- Receptor pharmacology studies strongly suggest that lorcaserin will not activate the 5-HT2B receptor at therapeutic doses

Clinical Summary

- Medically meaningful weight loss in three phase 3 trials
  - Improvements in anthropometric, cardiovascular and quality of life parameters
  - Significant weight loss in patients with type 2 diabetes
    - Improvements in glycemic control: HbA1c, fasting glucose, and use of medications to treat diabetes
- Safety data across all studies are consistent

Thank you for your attentions !!