



U.S. Food and Drug Administration

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## **Lorcaserin for weight loss and maintenance of weight loss**

**BMI  $\geq 30$  kg/m<sup>2</sup>, or a BMI  $\geq 27$  kg/m<sup>2</sup> and at least one weight-related comorbid condition**

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## **Lorcaserin for weight loss and maintenance of weight loss**

**BMI  $\geq 30$  kg/m<sup>2</sup>, or a BMI  $\geq 27$  kg/m<sup>2</sup> and at least one weight-related comorbid condition**

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William Shanahan, MD

Sr. Vice President & Chief Medical Officer

Arena Pharmaceuticals

## Lorcaserin Indication

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- Lorcaserin for weight loss and maintenance of weight loss
- BMI  $\geq 30$  kg/m<sup>2</sup>, or a BMI  $\geq 27$  kg/m<sup>2</sup> and at least one weight-related comorbid condition

# Agenda

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## Introduction and Background

### **William Shanahan, MD**

Sr. Vice President and Chief Medical Officer  
Arena Pharmaceuticals

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## Preclinical Carcinogenicity Results

### **Gary Williams, MD**

Professor of Pathology  
Professor of Clinical Public Health  
New York Medical College

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## Clinical Efficacy

### **William Shanahan, MD**

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## Clinical Safety Pharmacovigilance Program

### **Christen Anderson, MD, PhD**

Vice President, Clinical Development  
Arena Pharmaceuticals

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## Risk / Benefit of Lorcaserin

### **Steven Smith, MD**

Scientific Director  
Translational Research Institute  
Florida Hospital • Sanford-Burnham Medical Research  
Institute

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# Rationale for the Development of Lorcaserin – a Selective Serotonin 5-HT<sub>2C</sub> Agonist

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# Serotonin and Weight Management

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- Major neurotransmitter
  - 14 receptors/7 families/subtypes 1-7
- Decreases food intake and reduces body weight in animals

## Need for Selective Serotonergic Agents

- Non-selective 5-HT agonists fenfluramine and dexfenfluramine
  - Release 5-HT and block its re-uptake
  - Primary metabolite (norfenfluramine) a potent 5-HT<sub>2B</sub> agonist
  - Clinically effective
  - Withdrawn due to heart valve effects
  - Strong body of evidence implicates 5-HT<sub>2B</sub> receptor agonism

# 5-HT<sub>2C</sub> Receptor Stimulation Induces Satiety and Weight Loss in Rodents

- 5-HT<sub>2C</sub> agonists decrease food intake and body weight gain
- Satiety effects can be blocked by selective 5-HT<sub>2C</sub> antagonism
- 5-HT<sub>2C</sub> KO mice are hyperphagic, overweight, and resistant to 2C agonists
- Resistance can be eliminated by selective restoration of 2C receptors in POMC neurons in the hypothalamus

# Lorcaserin is Selective for the 5-HT<sub>2C</sub> Receptor

## Functional EC<sub>50</sub> IP<sub>3</sub> Accumulation in Transfected HEK293 cells

Receptor	Human
5-HT <sub>2C</sub>	9 nM (1.8 ng/mL)
5-HT <sub>2A</sub>	133 nM (26.0 ng/mL)
5-HT <sub>2B</sub>	811 nM (158.7 ng/mL)

- In a panel of 82 GPCRs, transporters, and ion channels, no other significant binding was observed.

# In Rats, Lorcaserin In Vivo 5-HT Activity is Restricted to the 2C Receptor

	5-HT <sub>2C</sub>	5-HT <sub>2A</sub>	5-HT <sub>2B</sub>
In Vivo Pharmacology	Decreased weight and food intake: 4.5-18 mg/kg BID	No wet dog shakes or back muscle fasciculations: 4.5-18 mg/kg	No effect on heart valves @ doses up to 100 mg/kg for 2 yrs

## **Lorcaserin for weight loss and maintenance of weight loss**

**BMI  $\geq 30$  kg/m<sup>2</sup>, or a BMI  $\geq 27$  kg/m<sup>2</sup> and at least one weight-related comorbid condition**

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# Lorcaserin Preclinical Carcinogenicity Findings

Gary Williams, MD

Professor of Pathology

Professor of Clinical Public Health

New York Medical College

## Overall Assessment

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Lorcaserin does not pose a cancer risk to humans at the recommended therapeutic dose.

## Key Support For Lack Of Human Relevancy

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- Lorcaserin is not genotoxic
- No tumor increases in the mouse bioassay
- Most tumors increased in the rat are attributable to toxicity and/or rodent specific mechanisms
- Safety margins exist in rats or mice for all tumors

## Tumors With Increased Incidences In The Rat Bioassay

<b>Tissue/ Organ</b>	<b>Sex</b>	<b>Tumor Type</b>	<b>Dose with Significant Tumor Increase</b>
<b>Subcutis</b>	<b>M</b>	<b>Benign Fibroma</b>	<b>Mid Dose</b>
		<b>Malignant Schwannomas</b>	<b>High Dose</b>
<b>Skin</b>	<b>M</b>	<b>Squamous Cell Carcinoma</b>	<b>High Dose</b>
<b>Brain</b>	<b>M</b>	<b>Astrocytoma</b>	<b>High Dose</b>
<b>Mammary gland</b>	<b>F</b>	<b>Adenocarcinoma</b>	<b>High Dose</b>
	<b>F / M</b>	<b>Benign Fibroadenoma</b>	<b>Low F/High M</b>
<b>Thyroid</b>	<b>M</b>	<b>Follicular Adenoma</b>	<b>Low Dose</b>
<b>Liver</b>	<b>M</b>	<b>Hepatocellular neoplasms</b>	<b>High Dose</b>

# Marketed Drugs Which Have Increased The Same Rat Neoplasms As Lorcaserin

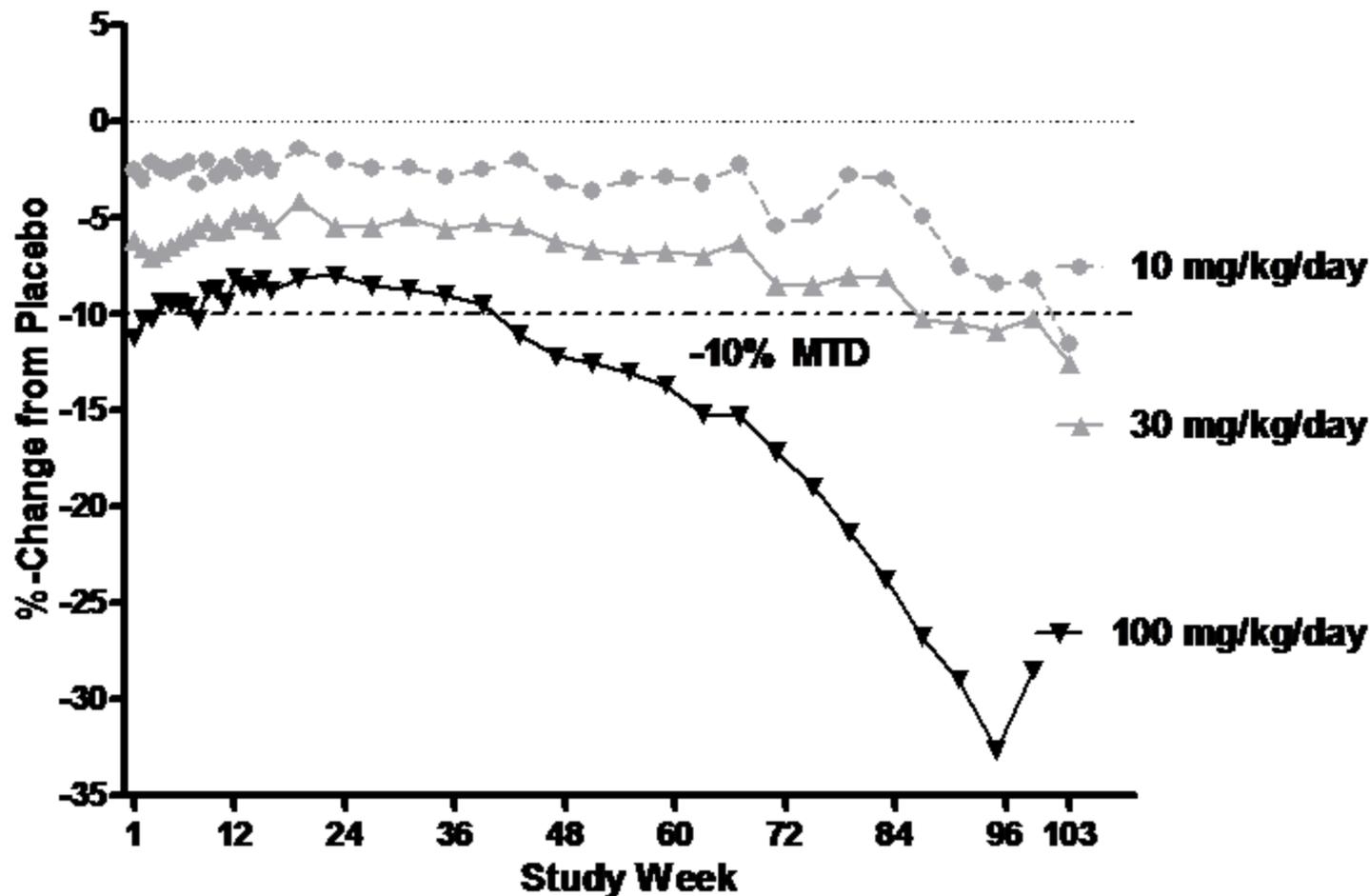
<b>Tumor Type</b>	<b>FDA Approved Drug</b>	<b>Indication</b>
Mammary gland	Reserpine	Mild essential hypertension
Astrocytoma	Prilosec	Treatment in adults of duodenal ulcer and gastric ulcer Treatment of gastroesophageal reflux disease
Subcutaneous	Itraconazole	Antifungal for the treatment of onychomycosis of the toenail
Epidermal	Quinapril	Hypertension Heart Failure
Thyroid	Fluvastatin Nicardipine	Atherosclerosis Stable Angina; Hypertension;
Liver	Fluconazole Simvastatin	Candidiasis Atherosclerosis
Schwannoma (neuroblastoma)	Rifaximin	Antibacterial for the treatment of travelers' diarrhea

# Reasons That Lorcaserin Rat Findings Are Not Relevant To Humans

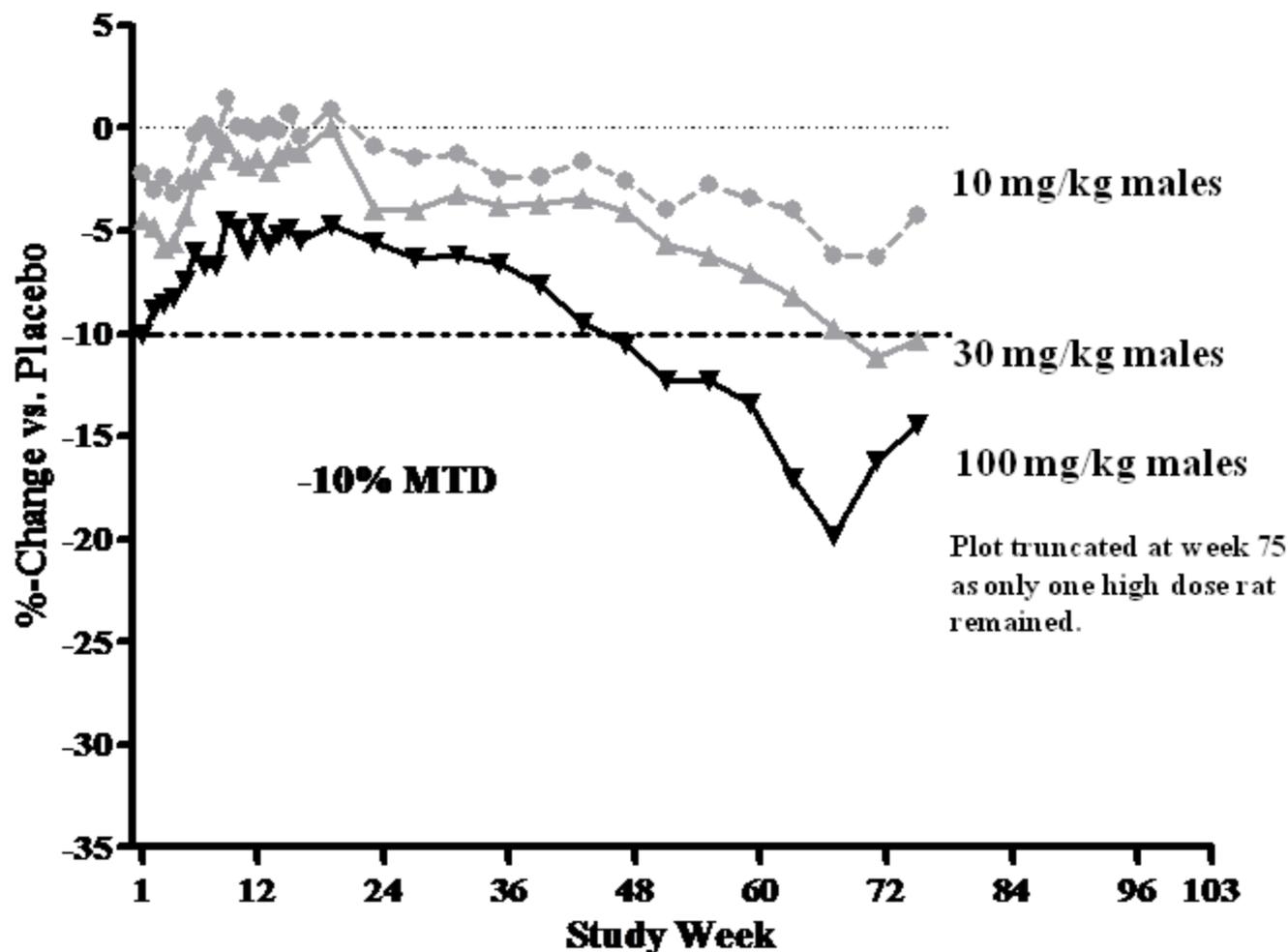
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1. Toxicity
2. Mechanisms
3. Safety margins

# Toxicity Decreased Body Weight In Treated Male Rats Relative To Control



# Decreased Body Weight In High Dose Males Without Tumors Demonstrates Toxicity Independent Of Tumor Development



# Pathological Observations In High Dose Male Rats Indicating Toxicity

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## **Tissues in which tumors were increased**

- Brain gliosis and mild focal mineralization
- Atrophy of epidermis, skeletal muscle, seminal vesicles, parotid gland
- Liver cystic degeneration, vacuolation, and necrosis
- Lymphoid depletion in the spleen and lymph nodes

## **Other tissues:**

- Granulocytic hyperplasia of the bone marrow
- Secretory depletion of the pancreas
- Urinary bladder inflammation
- Extramedullary hematopoiesis (spleen, adrenal, liver)
- Necrosis of tracheal respiratory epithelium

# Independent Study Director Conclusion Regarding High Dose Male Rats

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*“The high exposures achieved in the high-dose group produced signs of general toxicity and confounded the interpretation of observations at the 100 mg/kg/day dose.”*

# Tumors That Occurred In High Dose Males With Toxicity Are Not Relevant To Humans

<b>Tissue/ Organ</b>	<b>Sex</b>	<b>Tumor Type</b>	<b>Dose with Significant Tumor Increase</b>
<b>Subcutis</b>	<b>M</b>	<b>Benign Fibroma</b> <b>Malignant Schwannomas</b>	<b>Mid Dose</b> <b>High Dose</b>
<b>Skin</b>	<b>M</b>	<b>Squamous Cell Carcinoma</b>	<b>High Dose</b>
<b>Brain</b>	<b>M</b>	<b>Astrocytoma</b>	<b>High Dose</b>
<b>Mammary gland</b>	<b>F</b> <b>F / M</b>	<b>Adenocarcinoma</b> <b>Benign Fibroadenoma</b>	<b>High Dose</b> <b>Low F/High M</b>
<b>Thyroid</b>	<b>M</b>	<b>Follicular Adenoma</b>	<b>Low Dose</b>
<b>Liver</b>	<b>M</b>	<b>Hepatocellular neoplasms</b>	<b>High Dose</b>

# Reasons That Lorcaserin Rat Findings Are Not Relevant To Humans

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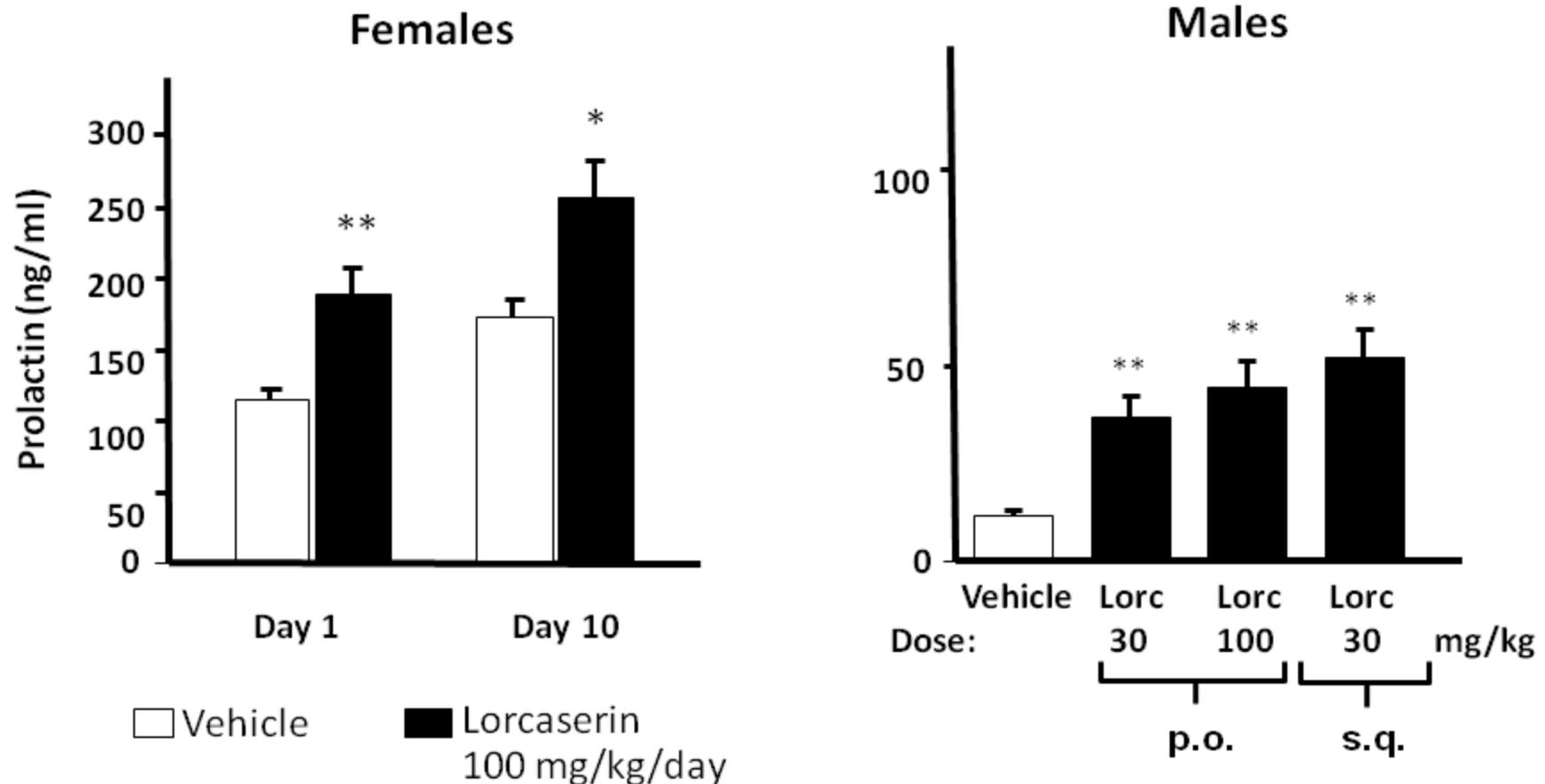
1. Toxicity
2. Mechanisms
3. Safety Margins

# Mammary Gland Mechanism Overview

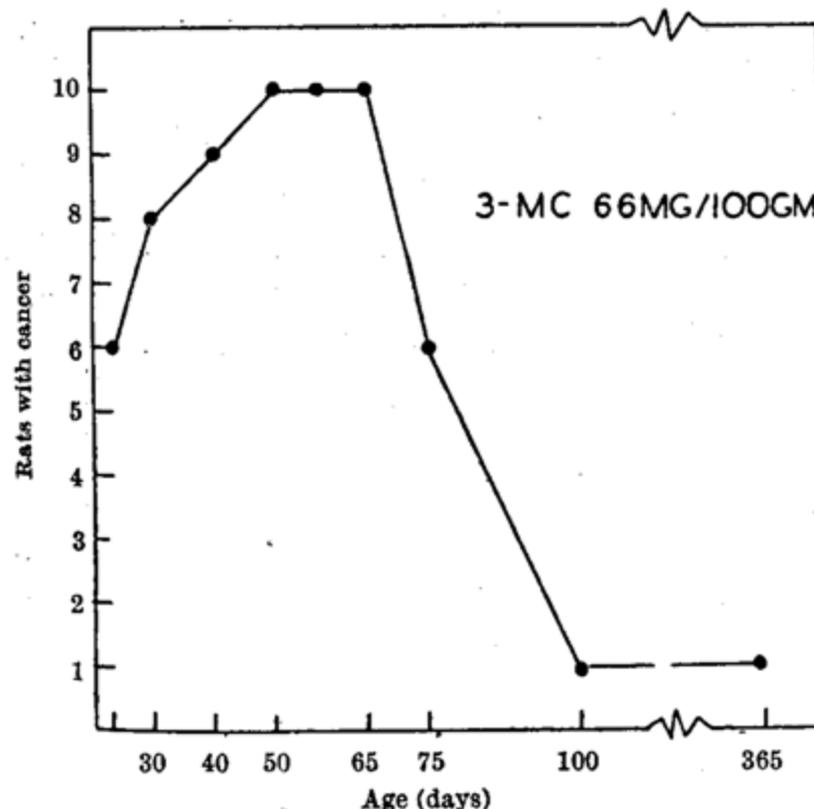
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- Lorcaserin increased prolactin in female and male rats
- Small prolactin increases of short duration may be sufficient to cause mammary tumors because mammary gland development is highly susceptible to tumorigenic stimuli
- Other relevant hormones assessed were not affected by lorcaserin

# Lorcaserin Increased Prolactin Levels In Female And Male Rats

\* $p < 0.01$ ; \*\* $p < 0.05$

# Influence of Age On Induction Of Mammary Cancer In Female Sprague-Dawley Rats Administered 3-Methylcholanthrene Once Only



Age of groups of 10 rats when 3-MC when was administered ;  
tumors palpable after 31 days

Huggins et al., Nature 1961

# Response of Mammary Gland To Prolactin Increase During Development

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- Daily administration of dopamine antagonist produced prolactin increases comparable to lorcaserin
- By 14 days:
  - 9 fold increase in breast volume
  - Increases in epithelial cell compartments

# Prolactin Increase Is Not A Risk Factor For Breast Cancer in Humans

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- Prolactin is not established to be a factor in human breast neoplasia
- Drugs that produce increases in prolactin and mammary neoplasia in rats have not been associated with breast cancer in humans
- Lorcaserin did not increase prolactin in clinical trials

## Lorcaserin Did Not Affect Other Hormones That Can Cause Or Accelerate Rat Mammary Neoplasms

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- Estradiol
- IGF-1
- Progesterone
- LH
- FSH
- GH

# Tumors With Increased Incidences In The Rat Bioassay

<b>Tissue/ Organ</b>	<b>Sex</b>	<b>Tumor Type</b>	<b>Dose with Significant Tumor Increase</b>
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# Reasons That Lorcaserin Rat Findings Are Not Relevant To Humans

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1. Toxicity
2. Mechanisms
3. Safety margins

## Use of Safety Margins For Neoplasms Induced Through Non-genotoxic Mechanisms

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- Non-genotoxic mechanisms have thresholds
- Exposure below threshold conveys no risk
- Margins of safety (ratio of rodent exposure at highest non-tumorigenic dose to human exposure) provide additional assurance of absence of risk
- Margins of safety demonstrated in either mouse or rat bioassays

# FDA Position On Margin Of Safety For Mammary Tumors

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- Safety margin not identified in female rats because fibroadenoma increased at low dose
- Safety margin 5x in male rats based upon combining fibroadenoma and adenocarcinoma as a single tumor for margin calculation

## Combination Of Fibroadenoma And Adenocarcinoma Is Not Justified

- Benign Fibroadenoma is Histogenetically Different from Adenocarcinoma
  - Carcinoma is an epithelial neoplasia
  - Fibroadenoma is an epithelial-stromal
  - Review of authoritative texts confirm these are different types of tumors
- Benign fibroadenoma is not a precursor to adenocarcinoma
- Tumors should be considered separately

# Safety Margins Demonstrated For All Malignant Neoplasms

Tissue/ Organ	Sex	Tumor Type	Safety Margin* (multiple of human exposure)	
			Rat Bioassay	Mouse Bioassay
Subcutis	M	Benign Fibroma	5	7
		Malignant Schwannoma	17	7
Skin	M	Squamous Cell Carcinoma	17	7
Brain	M	Astrocytoma	17	7
Mammary gland	F	Adenocarcinoma	24	4
		Benign Fibroadenoma	<7	4
Mammary gland	M	Adenocarcinoma	>56	7
		Benign Fibroadenoma	17	7
Thyroid	M	Follicular Adenoma	<5	7
Liver	M	Hepatocellular Neoplasms	17	7

\*Based on highest dose not associated with neoplasia

## Summary

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- Lorcaserin is not genotoxic
- All observed neoplasms can be ascribed to toxicity or another rodent-specific mechanism
- Safety margins exist for all tumors

## Conclusion

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Lorcaserin does not pose a cancer risk to humans at the recommended therapeutic dose.

## Lorcaserin Clinical Development Program and Phase 3 Efficacy Results

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William Shanahan, MD  
Sr. Vice President & Chief Medical Officer  
Arena Pharmaceuticals

# Program Objectives

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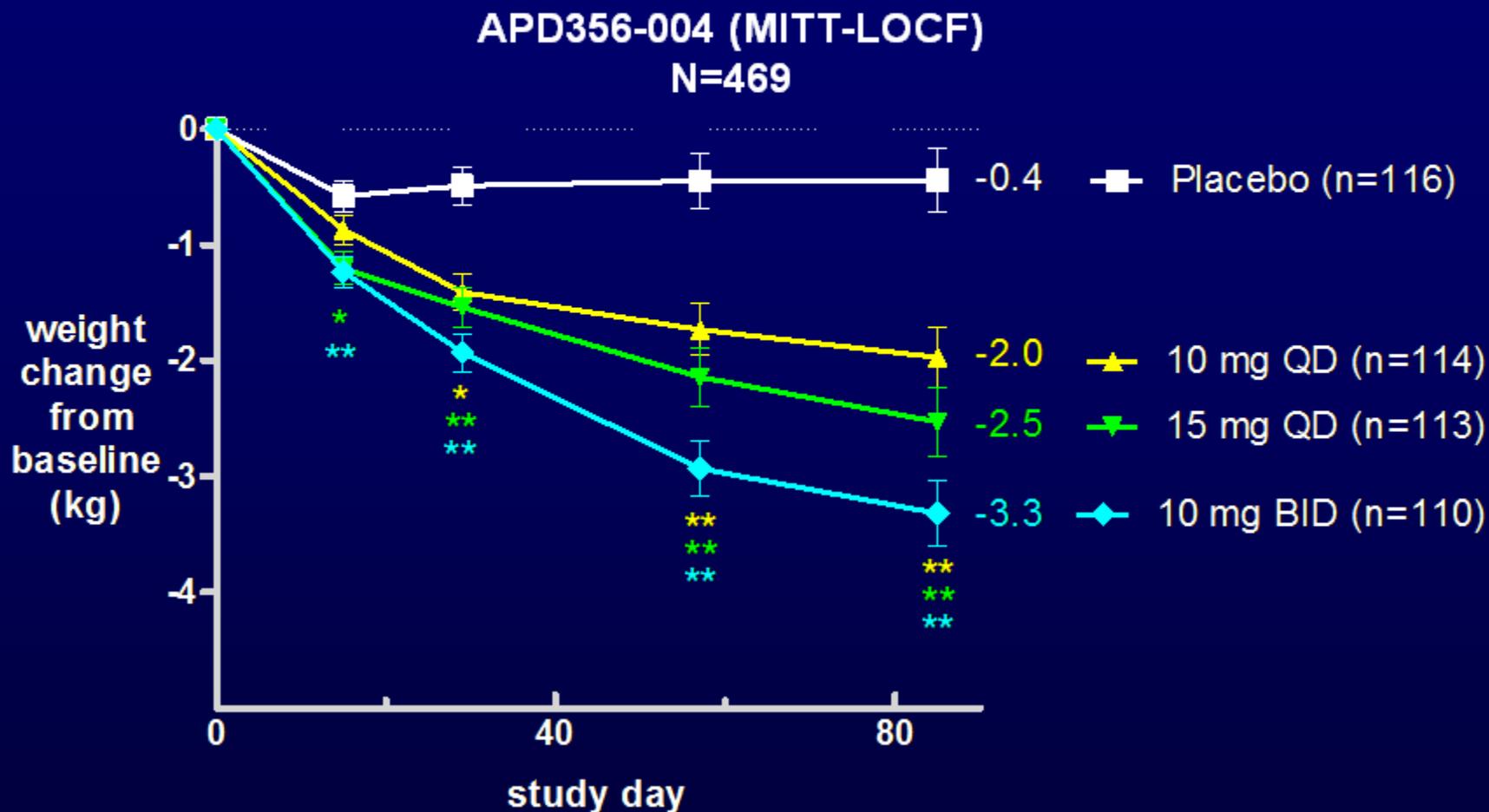
- Demonstrate clinically meaningful weight loss
- Demonstrate safety
  - Powered to rule out cardiac valvulopathy

# Lorcaserin Clinical Studies

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- Phase 1 Studies (N=421)
  - Single ascending dose
  - Effect of food on PK
  - Acute effects on meal size
  - Multiple ascending dose
  
- Phase 2 Studies (N=821)
  - 4 wk dose response (N=352)
  - 12 wk dose response (N=469)

# Dose Responsive Weight Loss Over 12 Weeks Without Lifestyle Modification



\*p=0.002; \*\*p<0.001 mean +/- sem

# Lorcaserin Clinical Studies

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- Phase 1 Studies (N=421)
  - Single ascending dose
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- Phase 2 Studies (N=821)
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  - 12 wk dose response (N=469)
- Phase 3 Pivotal Studies (N=7190)
  - Study 009 2-year (N=3182)
  - Study 011 1-year (N=4008)

# Lorcaserin Clinical Studies

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- Phase 3 Pivotal Studies (N=7190)
  - Study 009 2-year (N=3182)
  - Study 011 1-year (N=4008)
- Additional Studies
  - Abuse potential study
  - Thorough ECG/QT study
  - PK
  - CYP2D6 inhibition

# Primary Efficacy Endpoints Reflect Absolute and Meaningful Weight Loss

- Year 1 (Hierarchically ordered co-primary endpoints)
  - Proportions achieving  $\geq 5\%$  weight loss
  - Absolute weight loss
  - Proportions achieving  $\geq 10\%$  weight loss
- Year 2 (009 only)
  - Proportions achieving  $\geq 5\%$  weight loss at end of Year 1 who maintained  $\geq 5\%$  weight loss at end of Year 2

## Key Inclusion Criteria

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- BMI  $\geq 30$  to  $< 45$  kg/m<sup>2</sup>
- BMI  $\geq 27$  to  $< 30$  kg/m<sup>2</sup>  $\geq 1$  weight-related comorbid condition
  - Hypertension
  - Dyslipidemia
  - Coronary artery disease
  - Impaired glucose tolerance
  - Sleep apnea
- 18-65 years of age at screening

## Key Exclusion Criteria

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- Diabetes mellitus (treated or untreated)
- SSRIs/SNRIs for the treatment of depression within 2 years (009) and 1 year (011)
- FDA-defined valvulopathy (009 only)

# Effective Lifestyle Intervention Employed in Both Pivotal Trials

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- 600 kcal deficient diet
- Moderate exercise – 30 minutes per day
- Visits with lifestyle counselor every 2 weeks x 2; then monthly
- Compliance with lifestyle advice not monitored, but weight loss was substantial in placebo groups of both pivotal trials

## Primary Analysis Statistical Methods

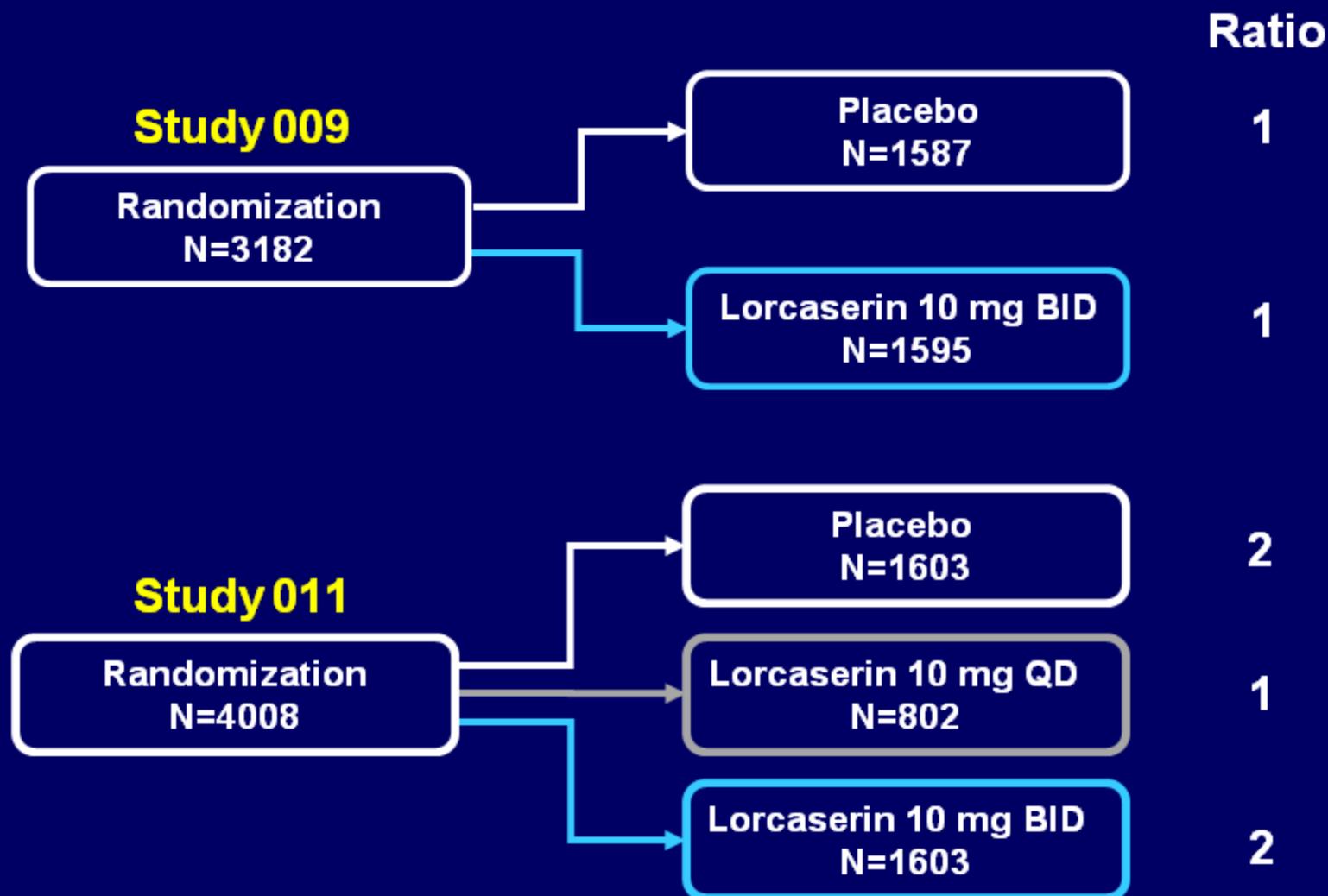
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- MITT: at least one dose of study drug and at least one post baseline weight measurement
- Missing data handled by LOCF

# Study 009 and Study 011

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# Year 1 Study Design



# Baseline Demographics Balanced Between Groups

	Study 009		Study 011	
	Placebo N=1587	Lorcaserin 10 mg BID N=1595	Placebo N=1603	Lorcaserin 10 mg BID N=1603
Mean age (yrs)	44	43	43	43
Gender (% female)	84%	83%	78%	81%
Mean weight (kg)	99.7	100.4	100.5	100.1
Mean BMI (kg/m <sup>2</sup> )	36.2	36.2	35.9	36.0
Waist (cm)	109.2	109.6	110.2	108.9
Ethnicity				
Caucasian	66%	68%	67%	67%
African American	19%	19%	20%	19%
Hispanic/Latino	13%	11%	11%	11%
Other	2%	1%	2%	3%

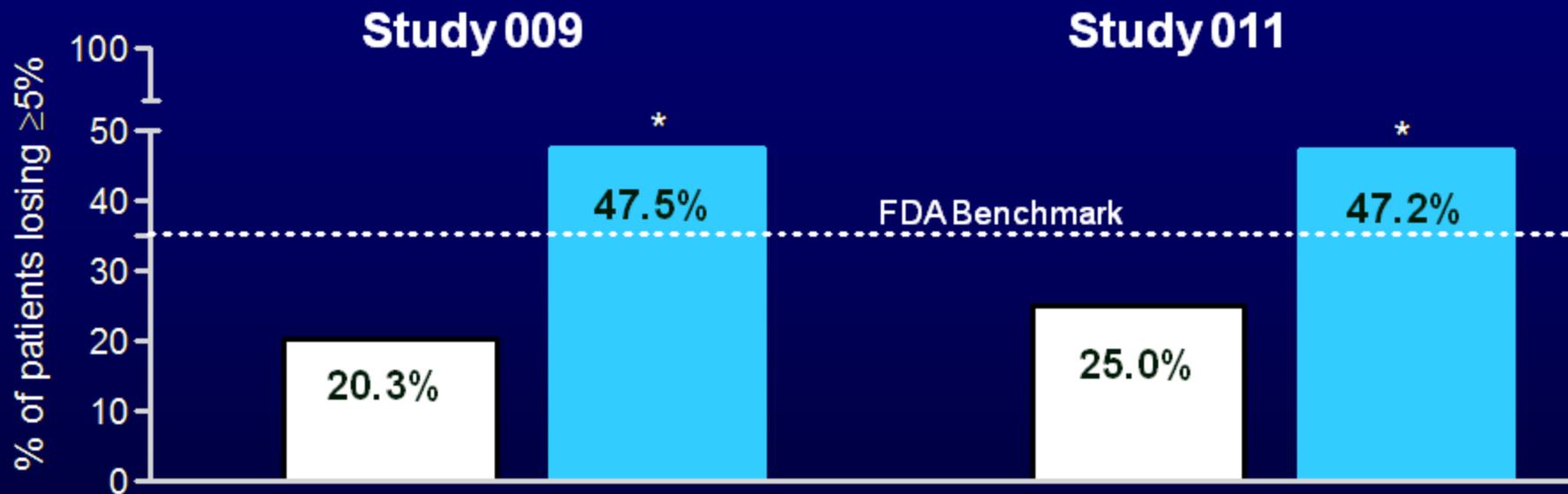
# Baseline History: Significant Medical Conditions or Impaired Fasting Glucose

Parameter	Study 009		Study 011	
	Placebo N=1584	Lorcaserin 10 mg BID N=1593	Placebo N=1601	Lorcaserin 10 mg BID N=1602
Hypertension	21.6%	21.0%	23.9%	24.2%
Dyslipidemia	33.1%	33.5%	27.4%	28.4%
Sleep apnea	3.5%	4.5%	4.6%	4.5%
History of CVD	5.5%	4.5%	5.7%	4.6%
History of depression	8.1%	8.5%	7.7%	7.4%
Impaired fasting glucose	25.7%	26.3%	25.3%	25.1%

# Patient Disposition

	Study 009		Study 011	
	Placebo N=1587	Lorcaserin 10 mg BID N=1595	Placebo N=1603	Lorcaserin 10 mg BID N=1603
Completed	45%	55%	52%	57%
Completed + Returning Dropouts	57%	65%	59%	64%
<b>Withdrawals:</b>				
Withdrawal of consent	22%	18%	20%	16%
Lost to follow up	14%	12%	15%	12%
Adverse events	7%	7%	5%	7%
Lack of efficacy	6%	2%	4%	2%
Protocol deviation / noncompliance	3%	3%	3%	4%
Sponsor decision	2%	2%	2%	1%
PI decision	<1%	<1%	<1%	1%
Other	2%	1%	-	<1%

# Primary Endpoint 1: Proportion of Patients Losing $\geq 5\%$ of Baseline Body Weight



Difference in Proportion vs PBO

27.2%

22.2%

95% CI

24.0%, 30.5%

18.9%, 25.5%

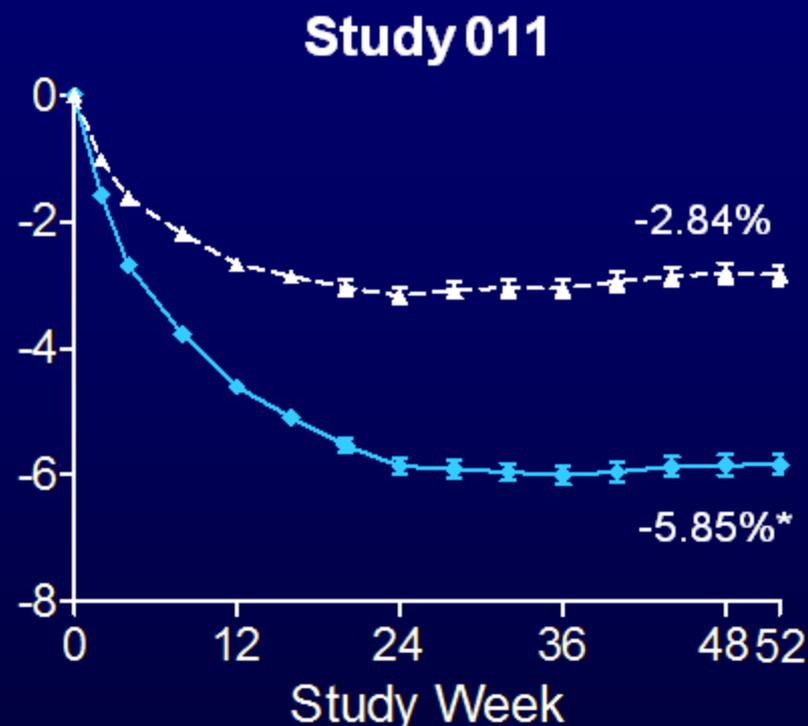
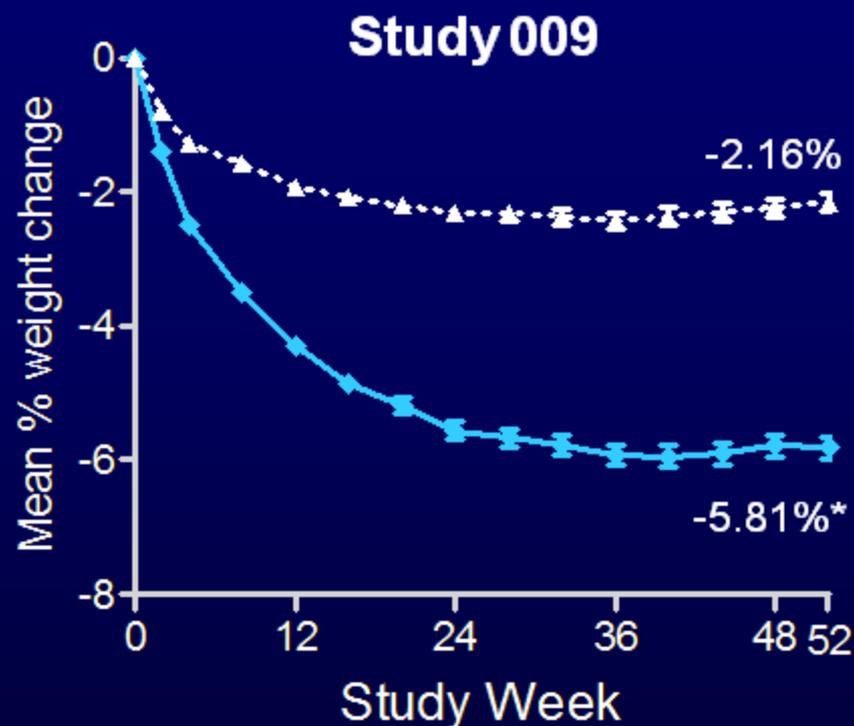
MITT Population

\*P-value <0.001 vs PBO

■ Placebo

■ Lorcaserin

## Primary Endpoint 2: Difference in Mean Weight Loss was Statistically Significant

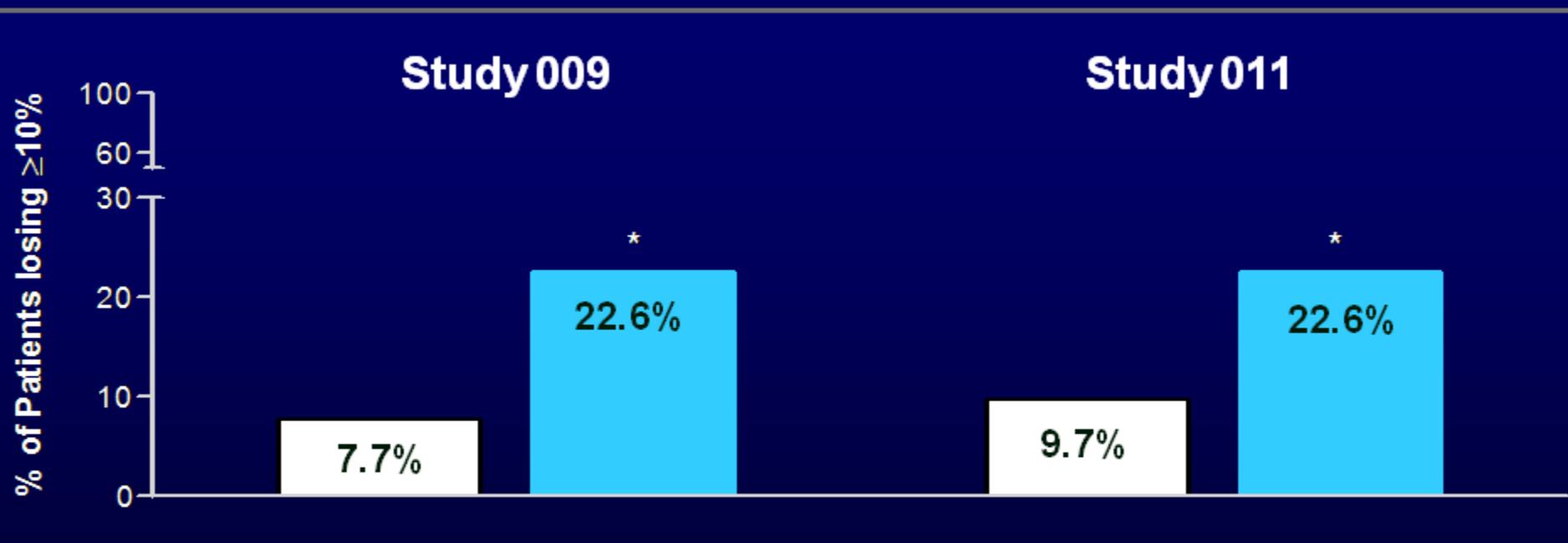


MITT Population \*P-value <0.001 vs PBO

■ Placebo

■ Lorcaserin

# Primary Endpoint 3: Proportion of Patients Losing $\geq 10\%$ of Baseline Body Weight



Difference in  
Proportion vs PBO

14.9%

12.9%

95% CI

12.4%, 17.4%

10.3%, 15.4%

MITT Population

\*P-value <0.001 vs PBO



Placebo



Lorcaserin

# **Sensitivity and Alternative Analyses of the Primary Endpoints**

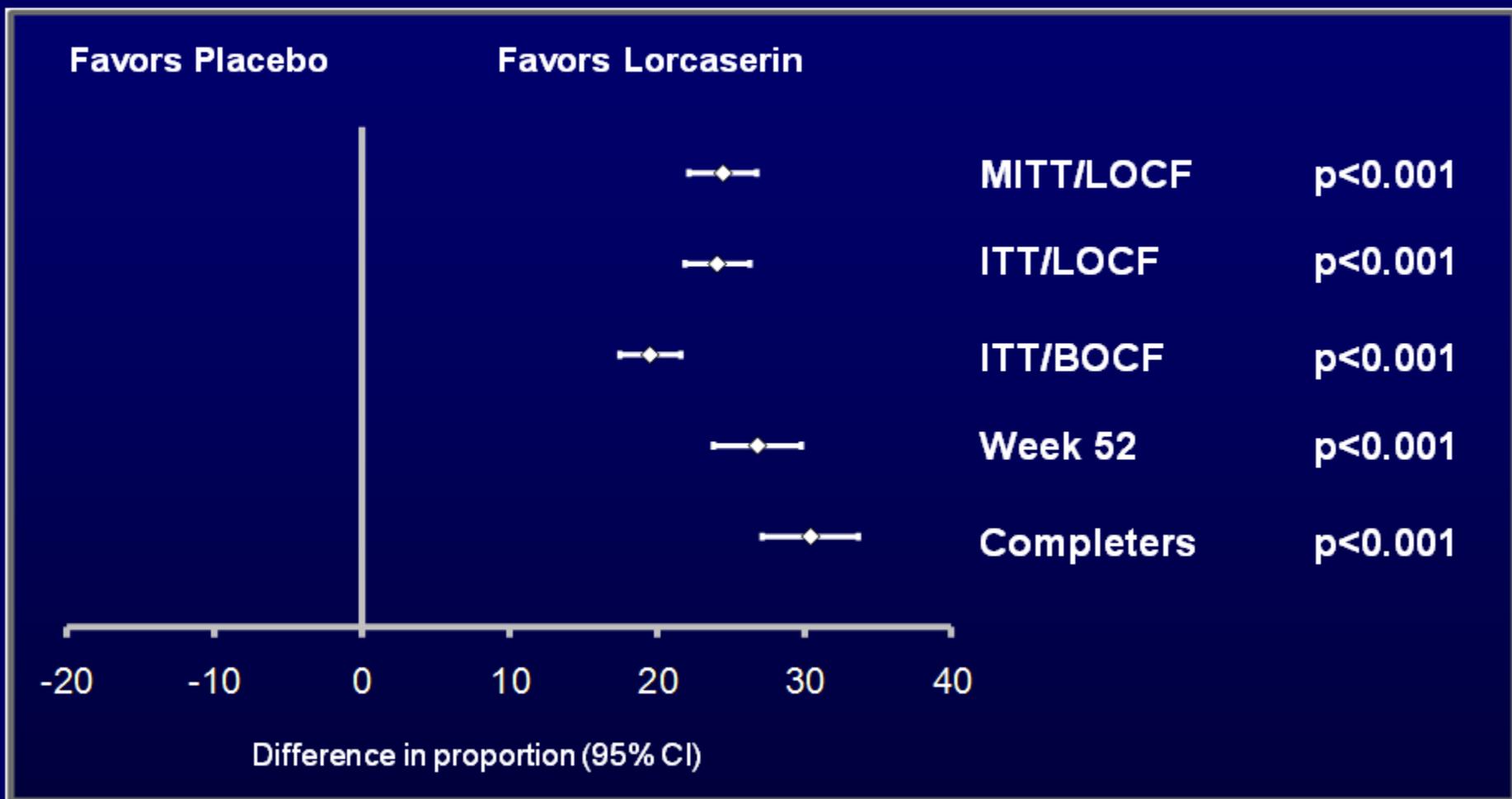
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# Sensitivity and Alternative Analyses: Pooled Phase 3

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- MITT with LOCF imputation: includes all randomized patients who received at least one dose of study medication and had a post-baseline weight measurement
- ITT
  - LOCF imputation
  - BOCF imputation
- Week 52 Population: Completers and those patients who dropped out of the study but returned for the Week 52 visit (returning dropouts)
- Completers

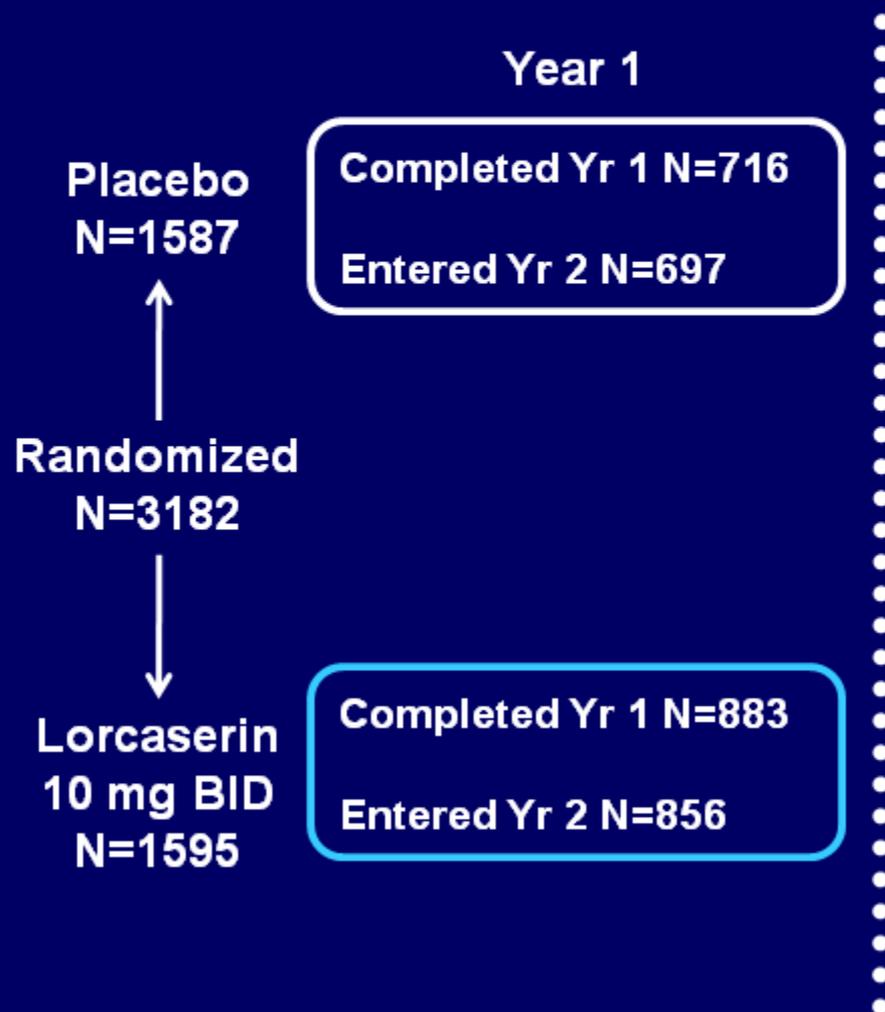
# Placebo-Adjusted Proportion of Patients who Lost $\geq 5\%$ of Baseline Body Weight at Week 52



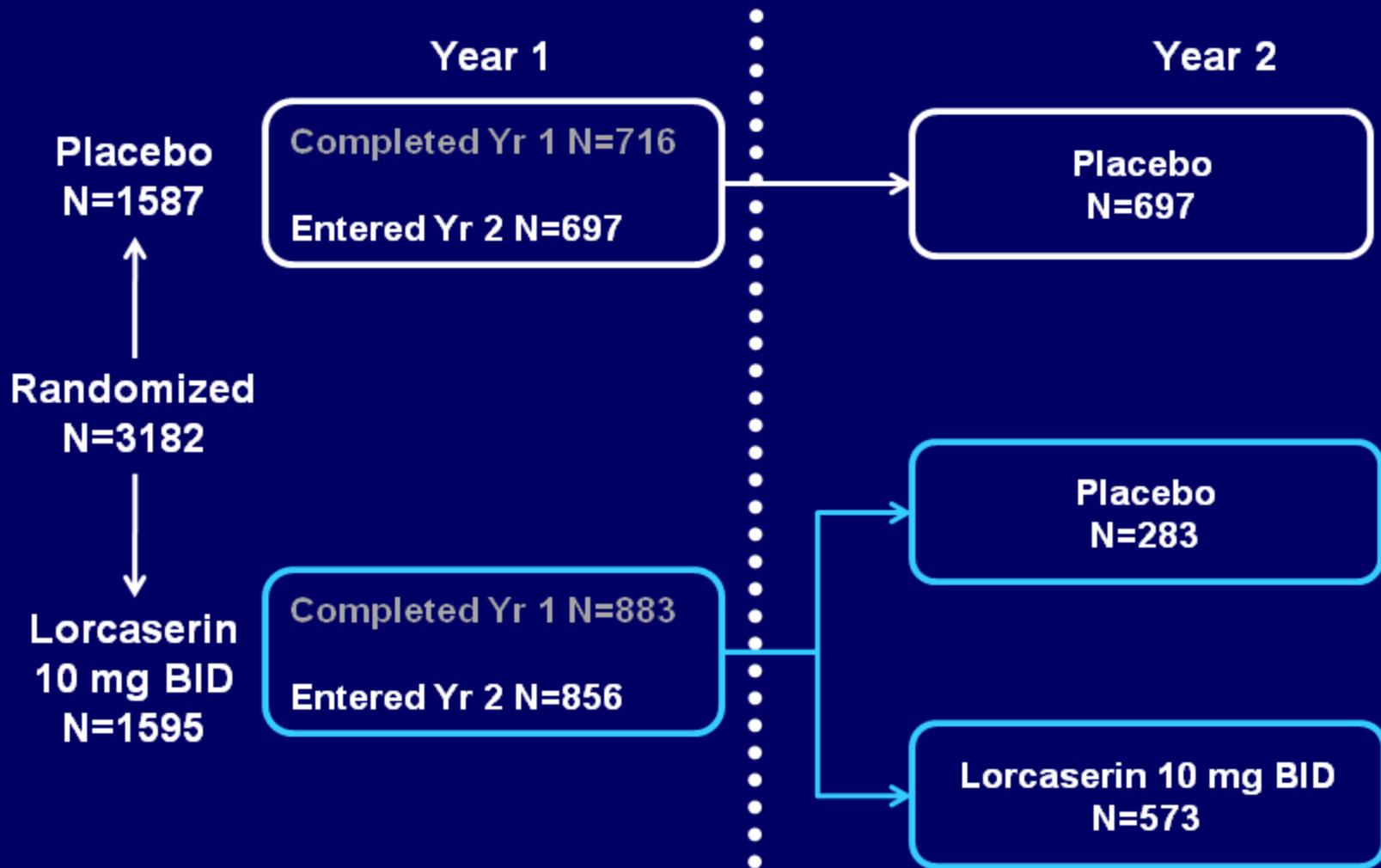
# Year 2: Study 009

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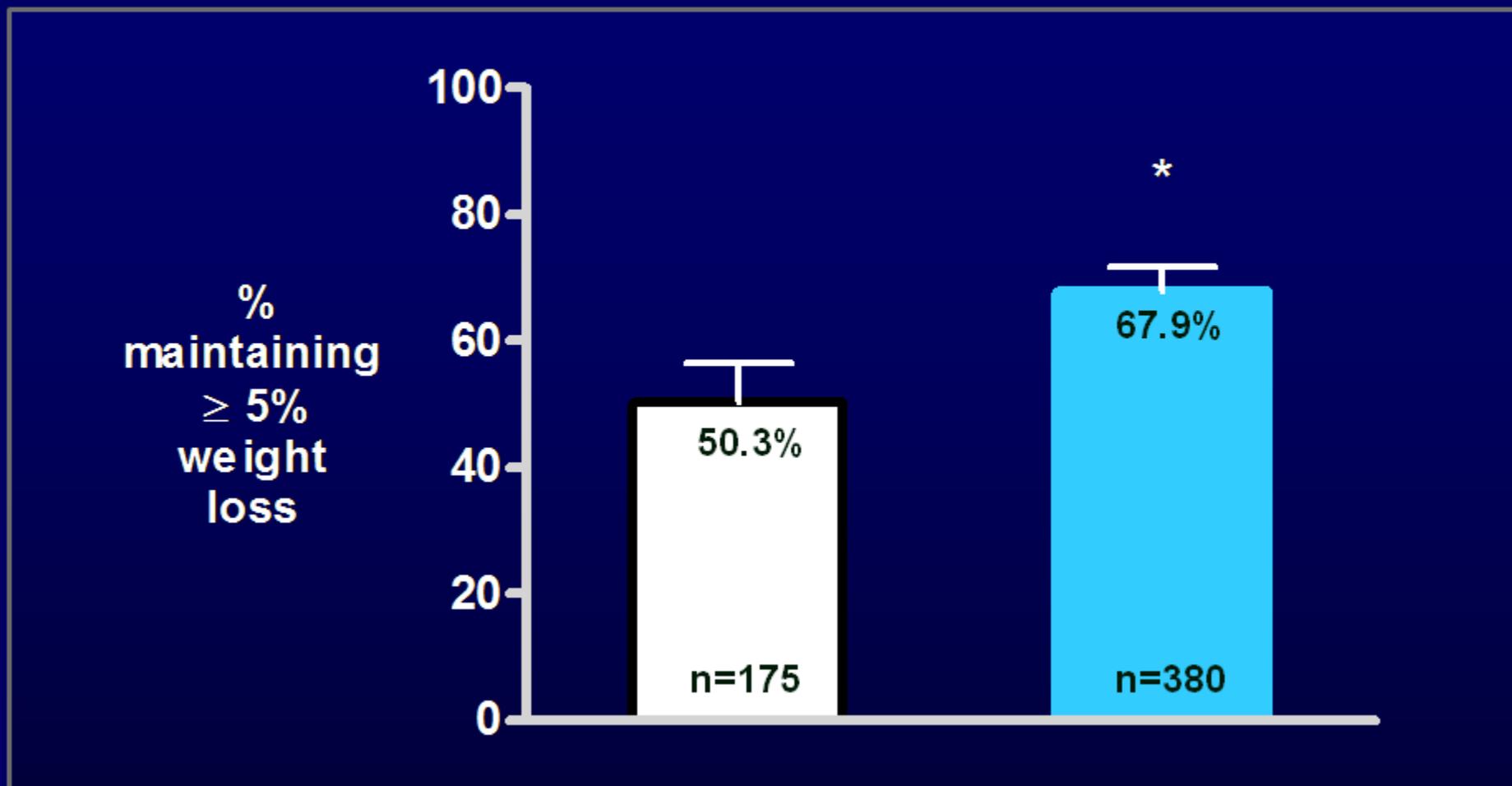
# Year 2 Study 009 Design



# Year 2 Study 009 Design



## Significantly More Patients Remaining on Lorcaserin Maintained Weight Loss in Year 2



mean  $\pm$  95% CI, P-value  $< 0.0001$



Lorcaserin/Lorcaserin



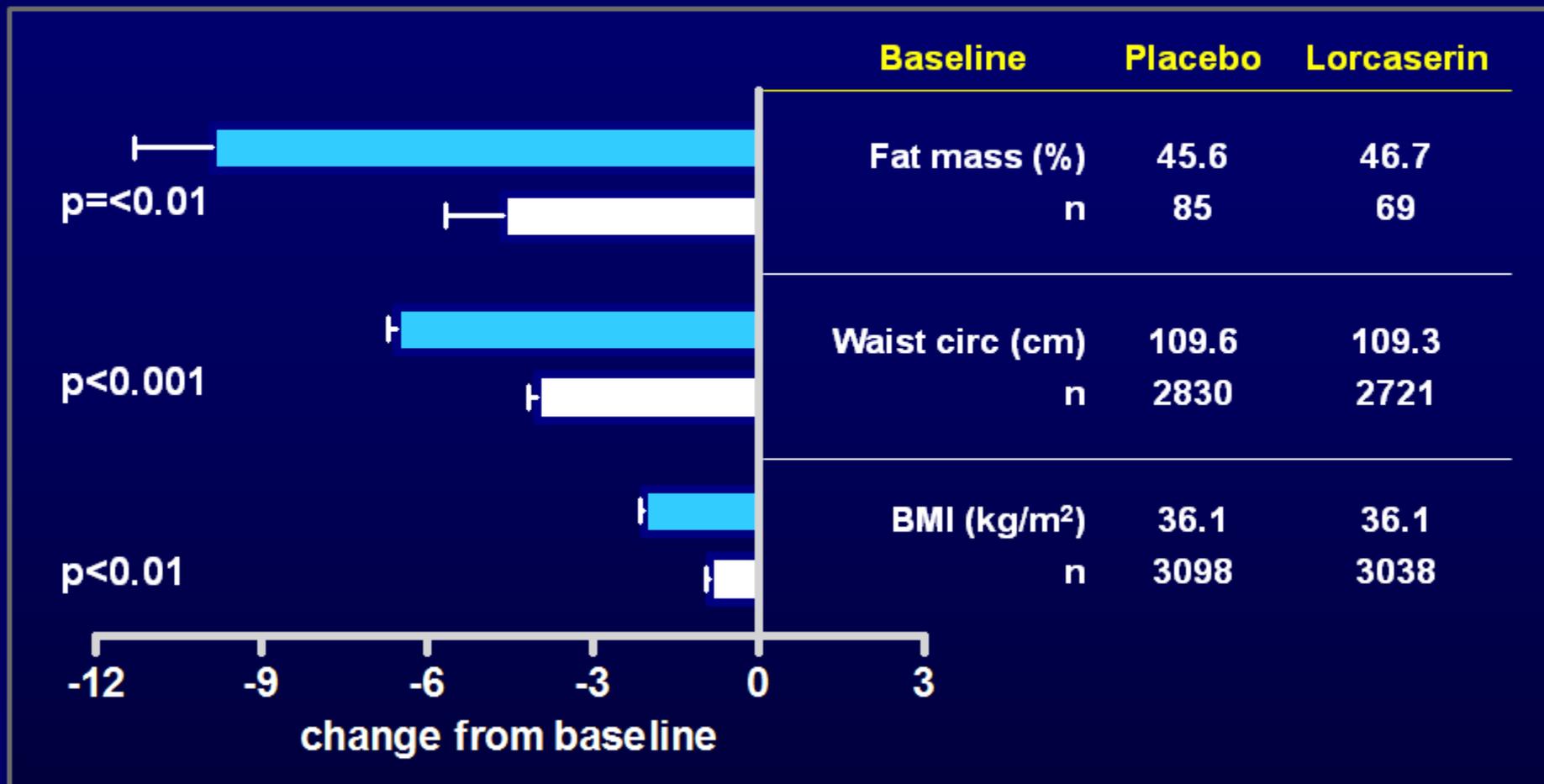
Lorcaserin/Placebo

# Lorcaserin Showed Favorable Impact on Secondary Endpoints

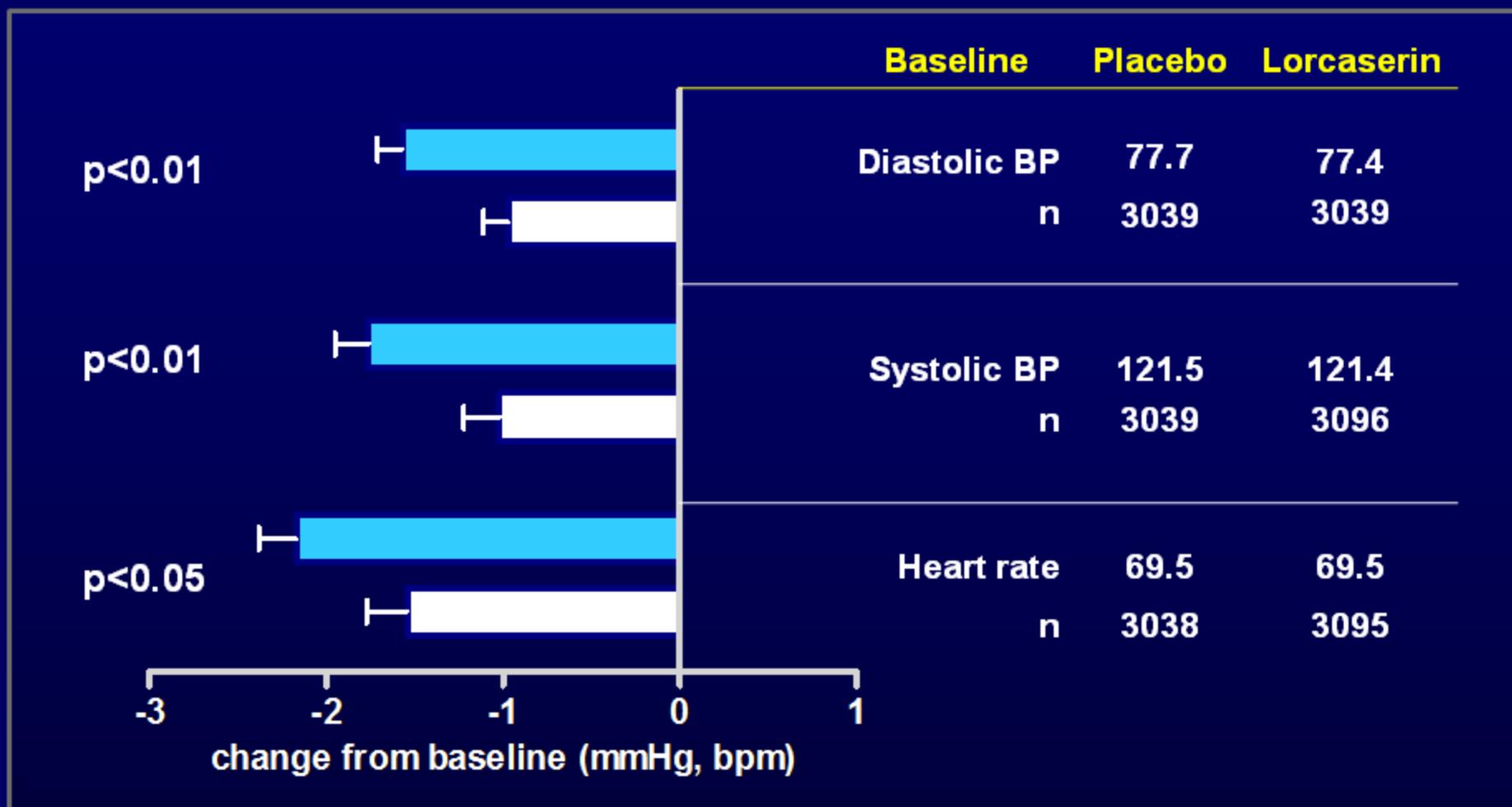
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- Waist circumference
- BMI
- % body fat
- Blood pressure
- Blood lipid assessments
- Glycemic control & insulin resistance
- Inflammatory markers
- Quality of Life

# Lorcaserin Improved Anthropometric Measures



# Lorcaserin Decreased Blood Pressure and Heart Rate

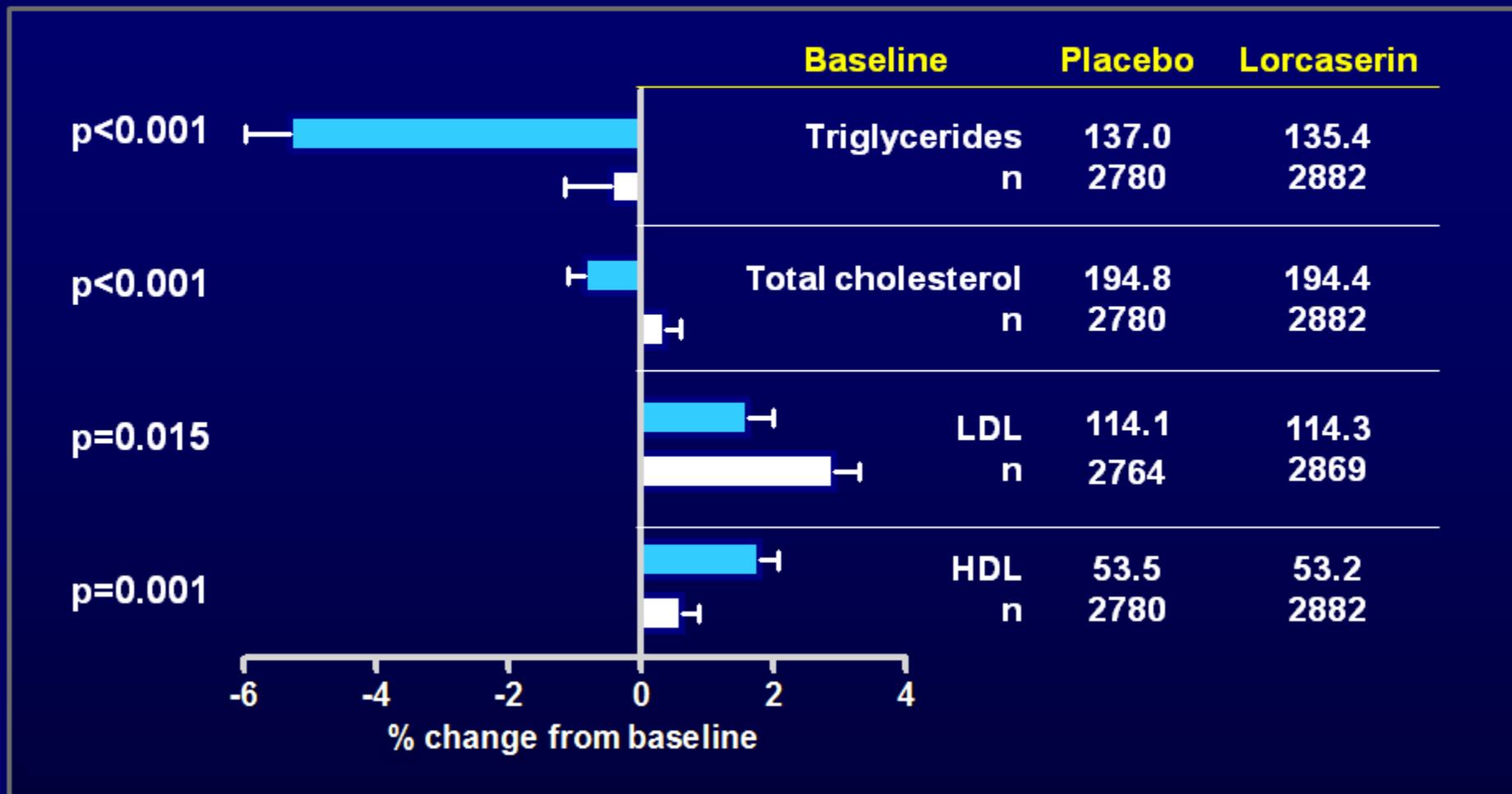


Pooled Phase 3 Studies; mean  $\pm$  sem

■ Placebo

■ Lorcaserin

# Lorcaserin Improved Blood Lipids Relative to Placebo

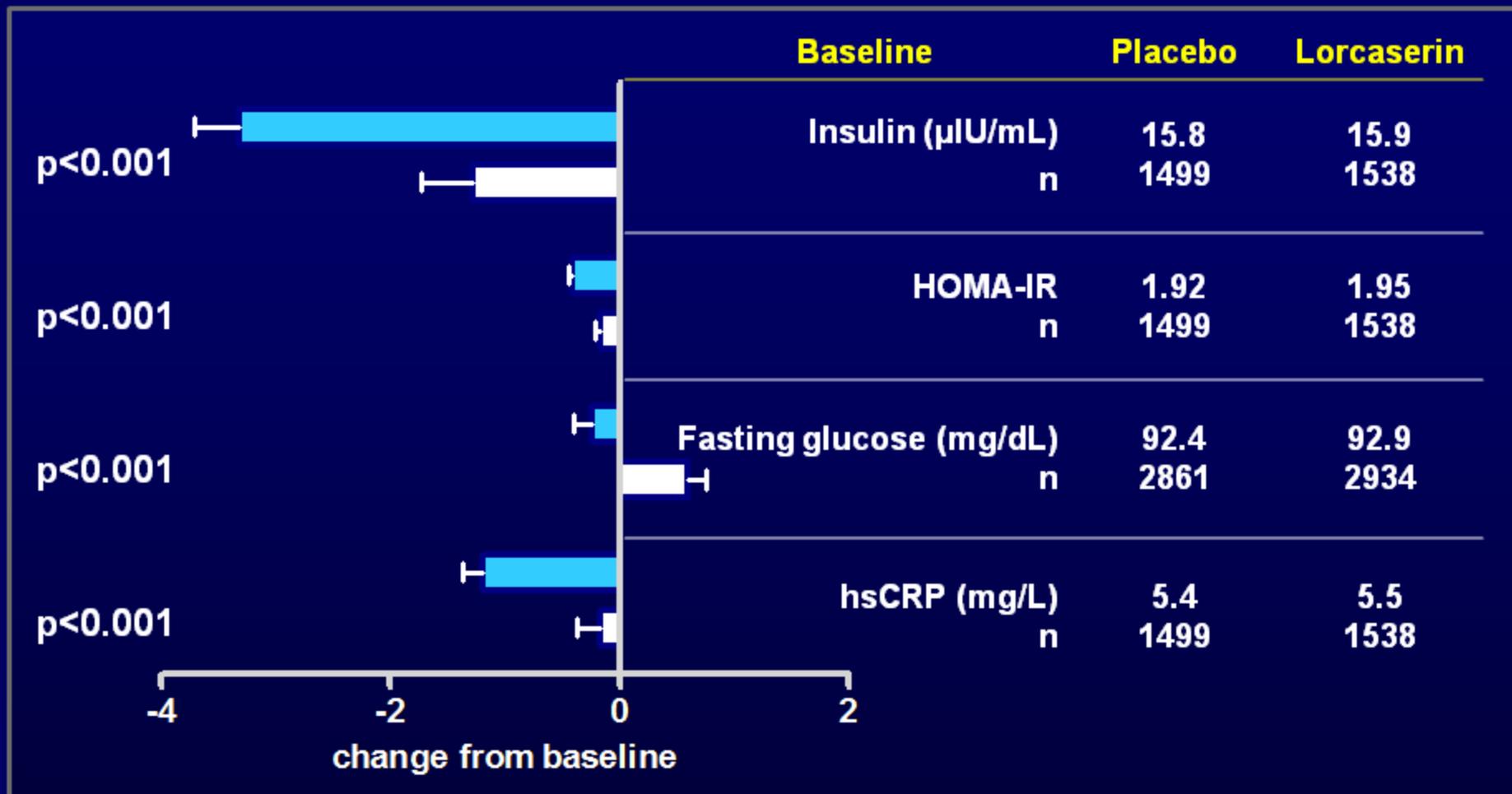


Pooled Phase 3 Studies; mean +/- sem

■ Placebo

■ Lorcaserin

# Lorcaserin Improved Glycemic and Inflammatory Measures



Pooled Phase 3 Studies; mean +/- sem

■ Placebo

■ Lorcaserin

# Changes in Weight-Related Quality of Life

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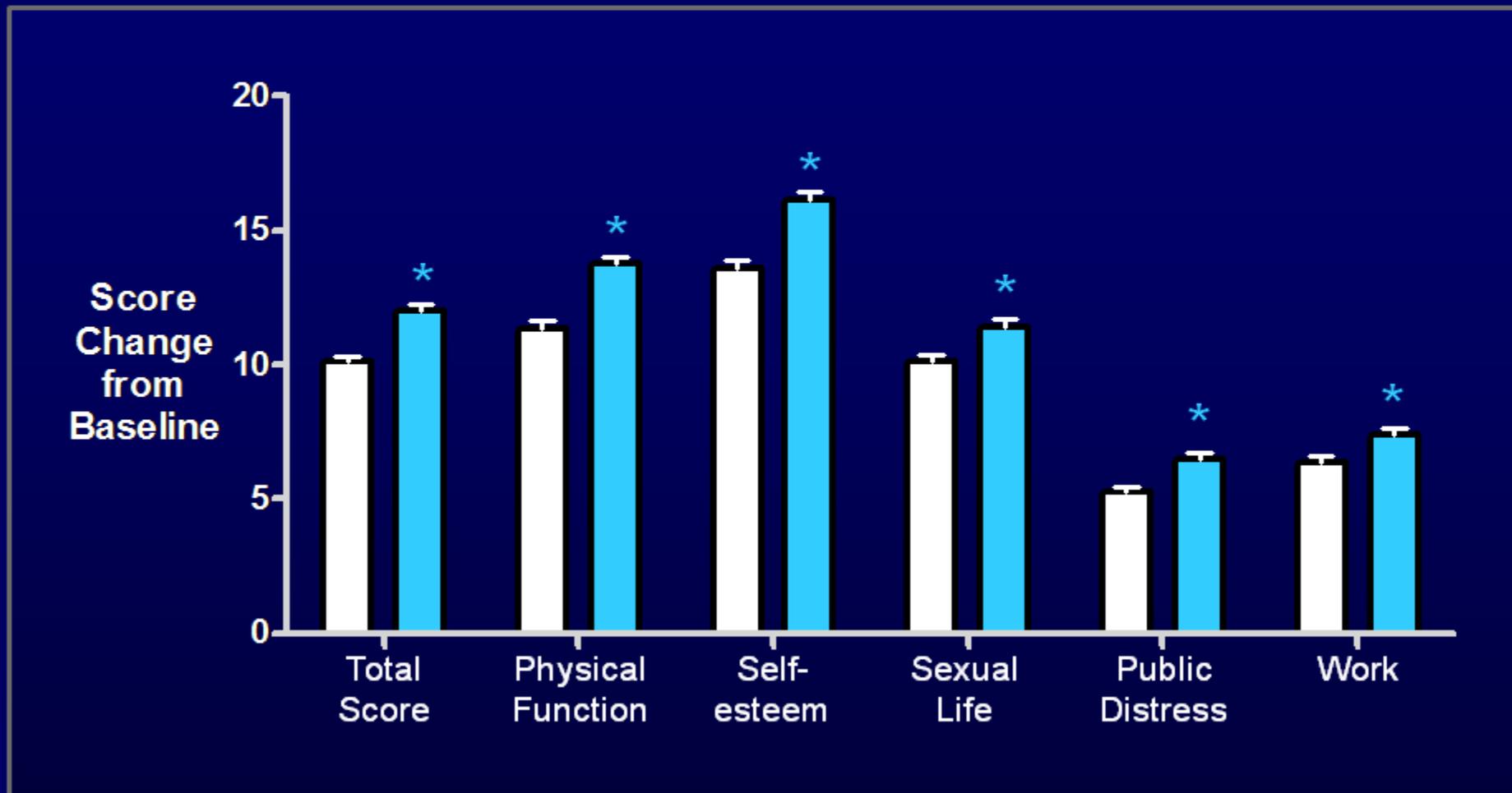
# Weight Related Quality of Life

## Impact of Weight on Quality of Life-Lite (IWQOL-Lite<sup>®</sup>)

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- Psychometrically sound
  - Shown to be valid and reliable
  - Sensitive to weight change
- 7.8-12 point change is clinically meaningful

# Quality of Life Scores Improved with Weight Loss: IWQOL-Lite



mean ± sem \* P-value < 0.001 Higher score = better QoL

■ Placebo

■ Lorcaserin

## Phase 3 Studies Demonstrate Clinically Relevant and Statistically Significant Weight Loss

	Study 009		Study 011	
	Placebo N=1499	Lorcaserin 10 mg BID N=1538	Placebo N=1541	Lorcaserin 10 mg BID N=1561
% losing $\geq 5\%$ baseline body weight	20.3%	47.5%	25.0%	47.2%
% mean weight change	-2.2%	-5.8%	-2.9%	-5.8%
% losing $\geq 10\%$ baseline body weight	7.7%	22.6%	9.7%	22.6%

P-values for all co-primary endpoints < 0.0001

MITT Population

# Lorcaserin Safety

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Vice President, Clinical Development

Arena Pharmaceuticals

## Key Safety Findings

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- Overall safety and tolerability profile supports approval
- Comprehensive echo program rules out pre-specified risk of valvulopathy
- No increase in depression or suicidal ideation.

# Overview of Safety Presentation

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- Adverse event summary
  - Year 1 Pooled Phase 3
  - Year 2 Study 009
- Pre-specified safety assessments
  - Echocardiographic evaluations
  - Depression and suicidal ideation
- Additional analyses
  - Psychiatric and cognitive assessments

# Overview of Clinical Studies and Exposure

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# Approximately 4000 Patients Exposed for up to 2 Years (Pooled Phase 3 Trials, Year 1)

Number of patients	Days of Treatment					Total N	Duration of Treatment (Days)	
	≥ 1D	≥ 6M	≥12M	18M-24M	Missing*		Mean	SD
10 mg BID	3106	2137	1800	461	89	3195	317.3	211.8
Any Dose	3881	2697	2273	461	115	3996	308.4	199.0

\*missing start date, stop date or both

# Overall Summary of Year 1 AEs (Pooled Phase 3 Trials, Year 1)

Patients Reporting AEs:	Placebo (N=3185)		Lorcaserin 10 mg QD (N=801)		Lorcaserin 10 mg BID (N=3195)	
	n	%	n	%	n	%
Any AE	2406	75.5	653	81.5	2645	82.8
Any SAE	73	2.3	27	3.4	87	2.7
AE leading to study withdrawal*	217	6.8	60	7.5	274	8.6
Deaths (Year 1 or 2)	2**	0.1	0	0	0	0

\*includes permanent discontinuation of study drug

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

# Most AEs Rated Mild or Moderate

(Pooled Phase 3 Trials, Year 1)

<b>AEs By Maximum Intensity</b>	<b>Placebo (N=3185)</b>		<b>Lorcaserin 10 mg BID (N=3195)</b>	
	<b>n</b>	<b>%</b>	<b>n</b>	<b>%</b>
<b>No AE</b>	<b>780</b>	<b>24.5</b>	<b>553</b>	<b>17.3</b>
<b>Mild</b>	<b>815</b>	<b>25.6</b>	<b>888</b>	<b>27.8</b>
<b>Moderate</b>	<b>1305</b>	<b>41.0</b>	<b>1406</b>	<b>44.0</b>
<b>Severe</b>	<b>285</b>	<b>8.9</b>	<b>348</b>	<b>10.9</b>

# AEs in Lorcaserin $\geq 1\%$ Over Placebo (Pooled Phase 3 Trials, Year 1)

Preferred Term	Placebo	Lorcaserin
	N=3185	10 mg BID N=3195
	%	%
Headache	10.1	16.8
Upper respiratory tract infection	12.3	13.7
Nausea	5.3	8.3
Dizziness	3.8	8.5
Fatigue	3.6	7.2
Urinary tract infection	5.4	6.5
Constipation	3.9	5.8
Dry mouth	2.3	5.3
Viral gastroenteritis	3.2	4.3
Vomiting	2.6	3.8

## Less Than 10% of Patients Discontinued due to AEs (Pooled Phase 3 Studies, Year 1)

Preferred Term	Placebo N=3185		Lorcaserin 10 mg BID N=3195		Relative Risk* (95% CI)
	n	%	n	%	
Headache	24	0.8	41	1.3	1.7 (1.03, 2.81)
Depression	16	0.5	29	0.9	1.8 (0.98, 3.32)
Dizziness	6	0.2	23	0.7	3.8 (1.56, 9.38)
Nausea	14	0.4	22	0.7	1.6 (0.80, 3.06)

\*Relative risk (Lorcaserin/Placebo) from Mantel-Haenszel method controlling for study.

# Less Than 3% of Patients Reported SAEs

(Lorcaserin > Placebo and  $\geq 2$  Patients: Pooled Phase 3 Studies, Year 1)

Preferred Term	Placebo N=3185		Lorcaserin 10 mg BID N=3195	
	n	%	n	%
Number of Patients Reporting SAEs	73	2.3	87	2.7
Cholecystitis/cholelithiasis	4	0.2	8	0.3
Cellulitis	1	< 0.1	3	0.1
Intervertebral disc protrusion	2	0.1	3	0.1
Myocardial infarction/acute MI	0	-	4	0.1
Diverticulitis	1	< 0.1	2	0.1
Dysmenorrhea	0	-	2	0.1
Dyspnea	0	-	2	0.1
Lung adenocarcinoma	0	-	2	0.1
Menorrhagia	0	-	2	0.1
Multiple myeloma	0	-	2	0.1
Esophagitis	0	-	2	0.1
Pneumonia	1	< 0.1	2	0.1
Pulmonary embolism	1	< 0.1	2	0.1

# Year 2 Adverse Events

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Study 009

# Overall Summary of Year 2 AEs

(Phase 3, Study 009, Year 2)

	Placebo/ Placebo n=697		Lorcaserin/ Lorcaserin n=573		Lorcaserin/ Placebo n=283	
	n	%	n	%	n	%
<b>Any AE</b>	<b>515</b>	<b>73.9</b>	<b>450</b>	<b>78.5</b>	<b>210</b>	<b>74.2</b>
<b>Any SAE</b>	<b>22</b>	<b>3.2</b>	<b>15</b>	<b>2.6</b>	<b>6</b>	<b>2.1</b>
<b>Death</b>	<b>0</b>	<b>-</b>	<b>0</b>	<b>-</b>	<b>1</b>	<b>0.4</b>
<b>AE leading to study withdrawal</b>	<b>19</b>	<b>2.7</b>	<b>21</b>	<b>3.7</b>	<b>12</b>	<b>4.2</b>
<b>AE leading to withdrawal of &gt;1 patient in any group and Lorcaserin/ Lorcaserin &gt; Placebo/Placebo:</b>						
<b>Anxiety</b>	<b>1</b>	<b>0.1</b>	<b>2</b>	<b>0.3</b>	<b>1</b>	<b>0.4</b>

# Most AEs Rated Mild or Moderate

(Phase 3, Study 009, Year 2)

<b>AEs By Maximum Intensity</b>	<b>Placebo/ Placebo n=697</b>	<b>Lorcaserin/ Lorcaserin n=573</b>	<b>Lorcaserin/ Placebo n=283</b>
	<b>%</b>	<b>%</b>	<b>%</b>
<b>No AE</b>	<b>26.1</b>	<b>21.5</b>	<b>25.8</b>
<b>Mild</b>	<b>24.0</b>	<b>25.1</b>	<b>26.9</b>
<b>Moderate</b>	<b>42.5</b>	<b>46.4</b>	<b>39.2</b>
<b>Severe</b>	<b>7.5</b>	<b>7.0</b>	<b>8.1</b>

# AEs in Lorcaserin $\geq 1\%$ Over Placebo

(Phase 3, Study 009, Year 2)

Preferred Term	Placebo/ Placebo n=697	Lorcaserin/ Lorcaserin n=573	Lorcaserin/ Placebo n=283
	%	%	%
Nasopharyngitis	12.6	16.4	13.8
Sinusitis	6.9	8.6	10.6
Urinary tract infection	5.0	7.2	4.9
Headache	4.3	7.2	6.4
Back pain	4.3	5.9	5.7
Diarrhea	4.3	5.9	3.2
Sinus headache	1.0	2.3	1.8
Dyspepsia	0.7	1.9	0.4
Contact dermatitis	0.7	1.9	1.4
Palpitations	0.4	1.4	0.7
Chest pain	0.1	1.4	1.1

# SAE Incidence Remained Low in Year 2

(Events reported by  $\geq 2$  Patients)

Preferred Term	Placebo/ Placebo n=697		Lorcaserin/ Lorcaserin n=573		Lorcaserin/ Placebo n=283	
	n	%	n	%	n	%
Patients Reporting SAEs	24	3.4	15	2.6	6	2.1
Coronary artery occlusion	1	0.1	0	-	1	0.4
Ankle fracture	1	0.1	1	0.2	0	-
Osteoarthritis	1	0.1	2	0.3	1	0.4
Uterine leiomyoma	3	0.4	1	0.2	0	-
Rectocele	0	-	2	0.3	0	-
Pulmonary embolism	1	0.1	0	-	1	0.4

## Lorcaserin Did Not Increase Neoplasia AEs (Years 1 and 2, Pooled Analysis)

Preferred Term	Placebo N=3185		Lorcaserin BID* N=3195	
	n	%	n	%
ALL neoplasm terms	73	2.3	79	2.5
<b>Relative Risk (95% CI) 0.91 (0.40, 2.07)</b>				

- Breast neoplasms
  - n=4 placebo, n=5 lorcaserin
- No brain tumors
- Similar median onset time
  - Study day 212 placebo, 237 lorcaserin

\*Year 2 events in lorcaserin/placebo group counted as lorcaserin.

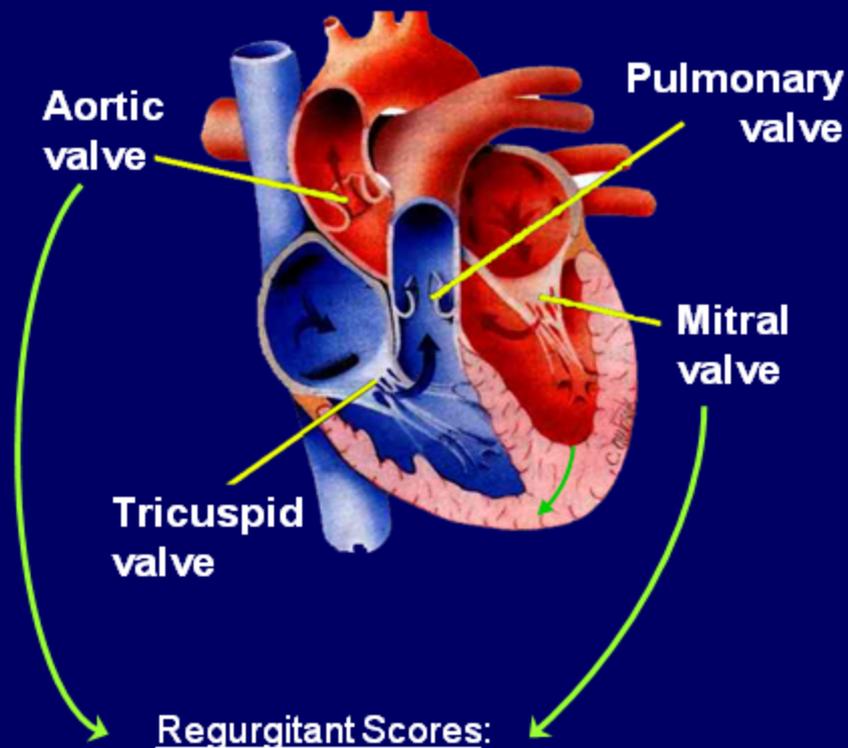
# Lorcaserin Did Not Adversely Impact Vital Signs, Clinical Labs or ECG Parameters

- Heart rate: slight decrease with lorcaserin
- Blood pressure: slight decrease with lorcaserin
- Clinical chemistry, hematology, urinalysis: no adverse lorcaserin effects
- ECG: lorcaserin slightly decreased heart rate in phase 3 chronic studies
  - QT interval: no effect in thorough QT/ECG or phase 3 (>15,000 ECGs performed)

# **Echocardiographic Safety Evaluation of Cardiac Valve Function**

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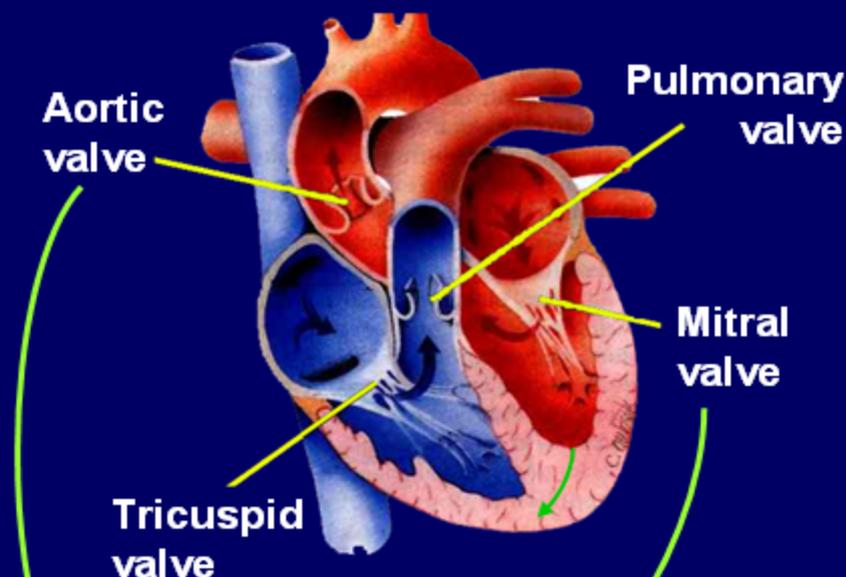
# Echocardiographic Monitoring and Endpoints in Phase 3 Studies



## Regurgitant Scores:

- Absent
- Trace
- Mild
- Moderate
- Severe

# Echocardiographic Monitoring and Endpoints in Phase 3 Studies



- **FDA defines significant valvular regurgitation\* as:**  
**MILD or greater aortic regurgitation *and / or***  
**MODERATE or greater mitral regurgitation**

## Regurgitant Scores:

- Absent
- Trace
- Mild
- Moderate
- Severe

# Clinical Significance of Echocardiographic Readings (Aortic and Mitral Valves)

- Clinical practice
  - Severe regurgitation
    - Asymptomatic: more frequent follow-up
    - Symptomatic: medical/surgical intervention
  - Mild/moderate regurgitation typically monitored with periodic physical exams and echoes (every 1-3 years)
- Echo findings are not static
  - Regurgitation may decrease or increase
  - 5% had FDA-defined valvulopathy at qualification
    - 81% did not at a subsequent echo

# Pre-specified Statistical Analysis Plan for Echocardiographic Data

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- Primary endpoint
  - Proportion of patients with report of new FDA-defined valvulopathy
- Non-inferiority approach to analyze the difference in proportions
  - Margin: 50% increase over placebo
  - Significance level: 5% one-sided test
  - Power: 80%

# Lorcaserin was Non-inferior to Placebo for Development of New Valvulopathy

Analysis Population	Placebo		Lorcaserin		Difference in Proportions	
	n	%	n	%	90% CI	95% CI
Primary*	51	2.18	58	2.33	0.15 (-0.55, <u>0.85</u> )	0.15 (-0.7, <u>1.0</u> )
Observed non inferiority margin for difference in proportion is <u>1.09</u> = 0.5 X 2.18						
Completers (52 wk exposure)	40	2.69	42	2.46	-0.27 (-1.19, <u>0.64</u> )	-0.27 (-1.4, <u>0.87</u> )

**Relative risk analysis may provide lower statistical power than absolute risk (difference in proportions) when the placebo incidence is low.**

\*All patients with baseline and 1 post-baseline echo; LOCF; Pooled Phase 3 Safety Population

# Lorcaserin Did Not Increase Valvulopathy with Exposures up to 2 Years (Year 2, Study 009)

	Placebo		Lorcaserin		Difference in Proportions (90% CI)
	n / N	%	n / N	%	
Week 76	19 / 697	3.1	14 / 486	2.9	-0.2 (-2.0, 1.6)
Week 104	17 / 627	2.7	13 / 500	2.6	-0.11 (-1.7, 1.6)

# Valvulopathy Status Can Change

## Lorcaserin did not Increase Persistence

	Study 009		Study 011	
	Placebo N=1089	Lorcaserin N=1213	Placebo N=1103	Lorcaserin N=1170
	n	n	n	n
Patients with new valvulopathy at Wk 24	21	25	20	27
Valvulopathy at Wk 52	8 / 18	13 / 24	8 / 19	5 / 21

# Valvulopathy Status Can Change

## Lorcaserin did not Increase Persistence

	Study 009		Study 011	
	Placebo N=1089	Lorcaserin N=1213	Placebo N=1103	Lorcaserin N=1170
	n	n	n	n
Patients with new valvulopathy at Wk 24	21	25	20	27
Valvulopathy at Wk 52	8 / 18	13 / 24	8 / 19	5 / 21
	Placebo	L/L	L/P	
Valvulopathy at Wk 76	4 / 12	4 / 9	3 / 9	-
Valvulopathy at Wk 104	4 / 10	3 / 9	2 / 9	-

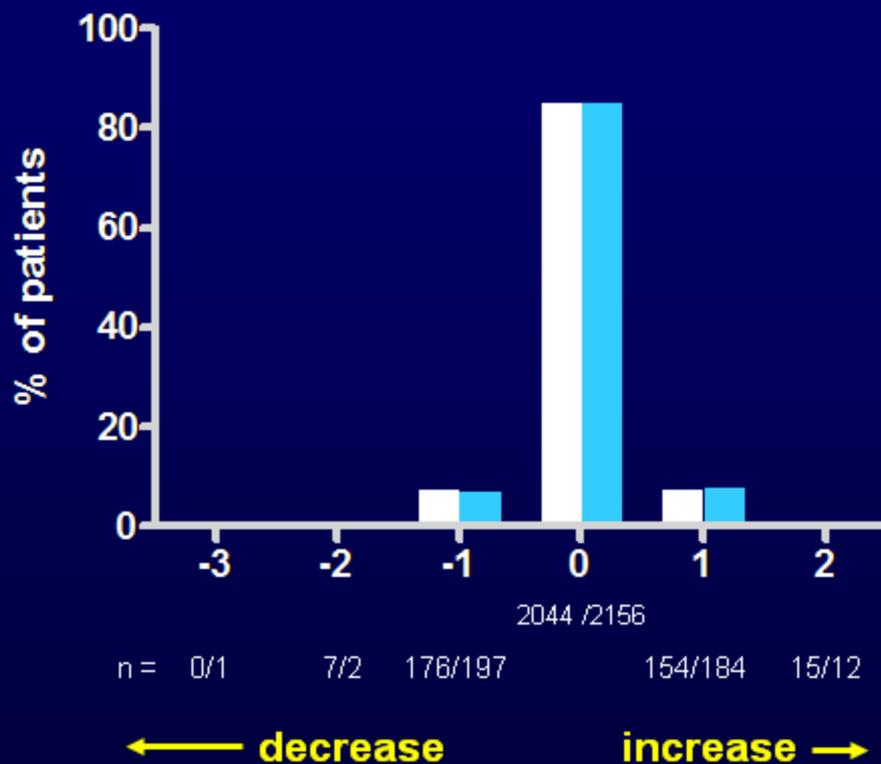
L/L = Lorcaserin Year 1 / Lorcaserin Year 2

L/P = Lorcaserin Year 1 / Placebo Year 2

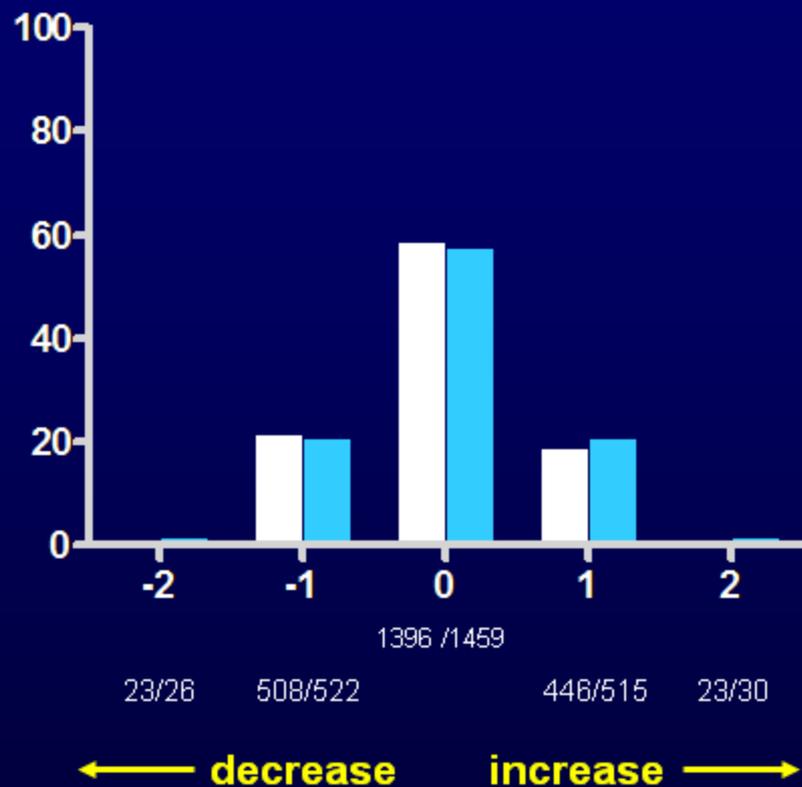
# Lorcaserin Did Not Affect Shifts in Valvular Regurgitation (Year 1, Pooled Phase 3 Studies)

## Changes in Regurgitant Score

### Aortic Shifts



### Mitral Shifts



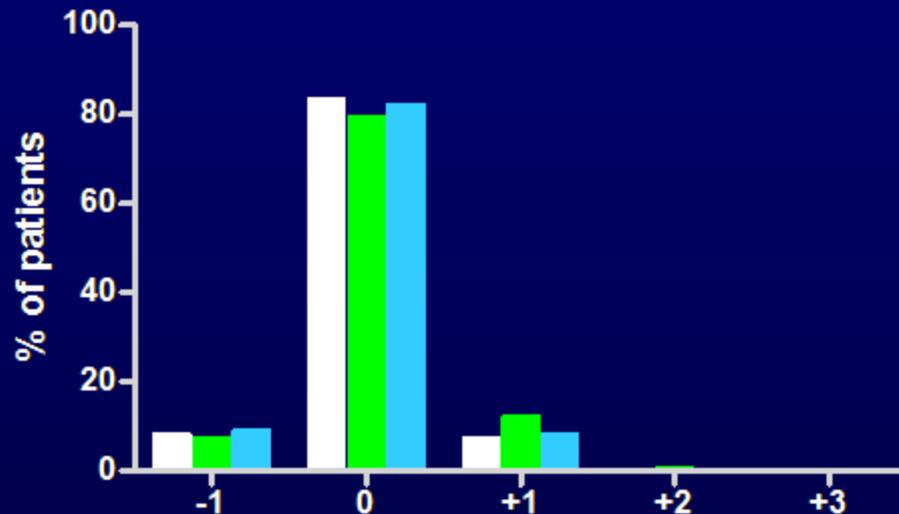
■ Placebo N=2396

■ Lorcaserin 10mg BID N=2552

# Lorcaserin Did Not Affect Shifts in Valvular Regurgitation (Year 2, Study 009)

## Changes in insufficiency score

### Aortic Shifts



524/205/412

n = 52/19/46

45/32/41

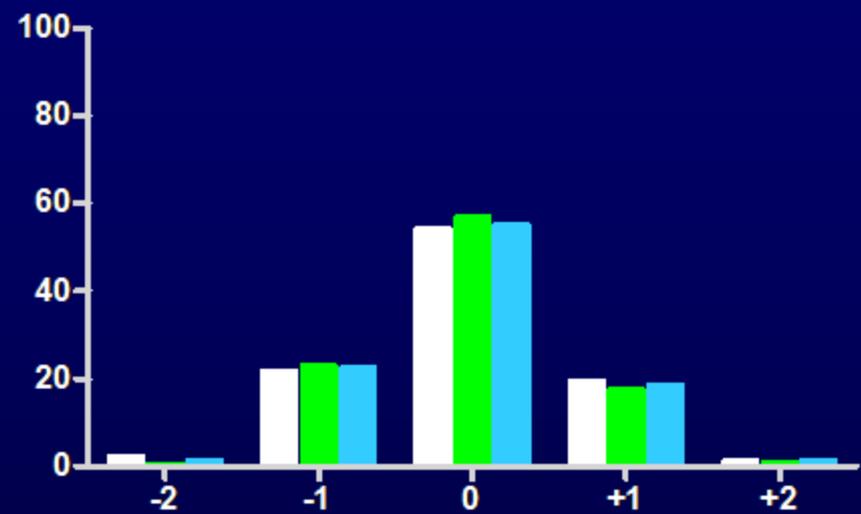
5/2/1

1/0/0

← decrease

increase →

### Mitral Shifts



342/147/276

15/2/8

137/60/114

126/46/94

9/3/8

← decrease

increase →

■ Placebo / Placebo  
N=627

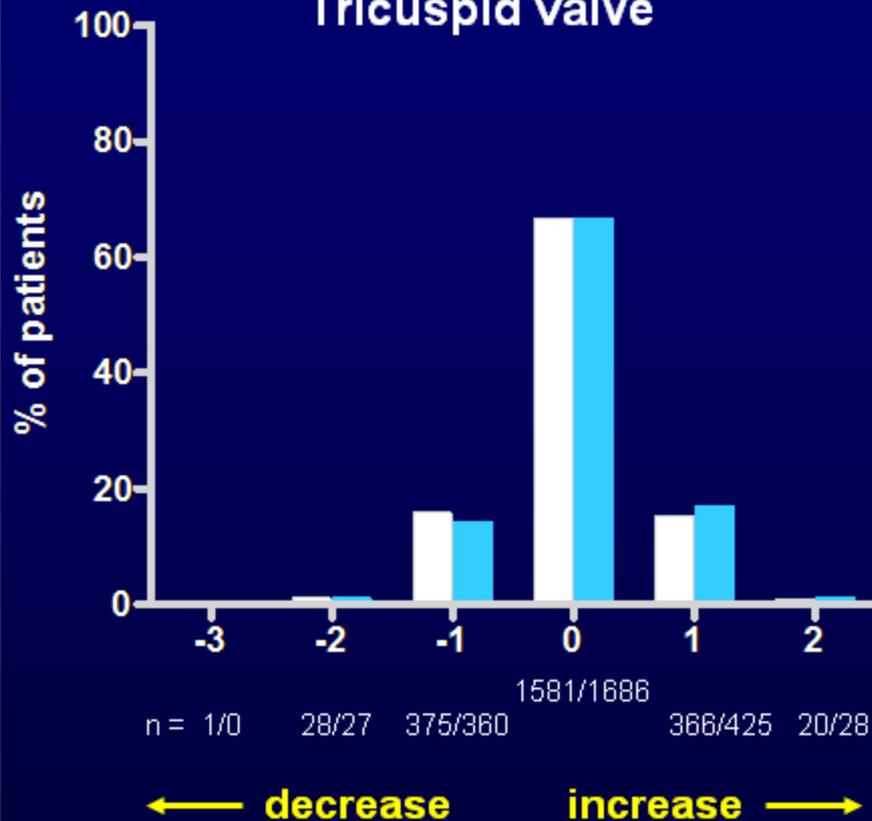
■ Lorcaserin / Placebo  
N=258

■ Lorcaserin / Lorcaserin  
N=500

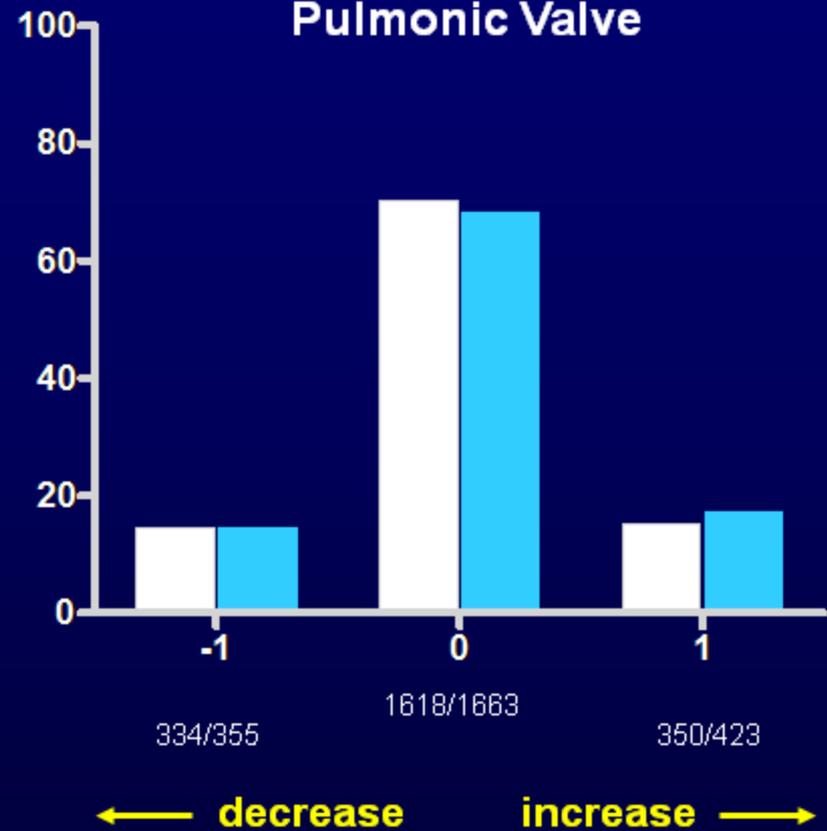
# Lorcaserin Did Not Affect Shifts in Tricuspid or Pulmonic Valvular Regurgitation (Year 1, Pooled Phase 3 Studies)

## Changes in Regurgitant Score

### Tricuspid Valve



### Pulmonic Valve



■ Placebo N=2396

■ Lorcaserin 10mg BID N=2552

# Summary of Echocardiographic Safety Monitoring

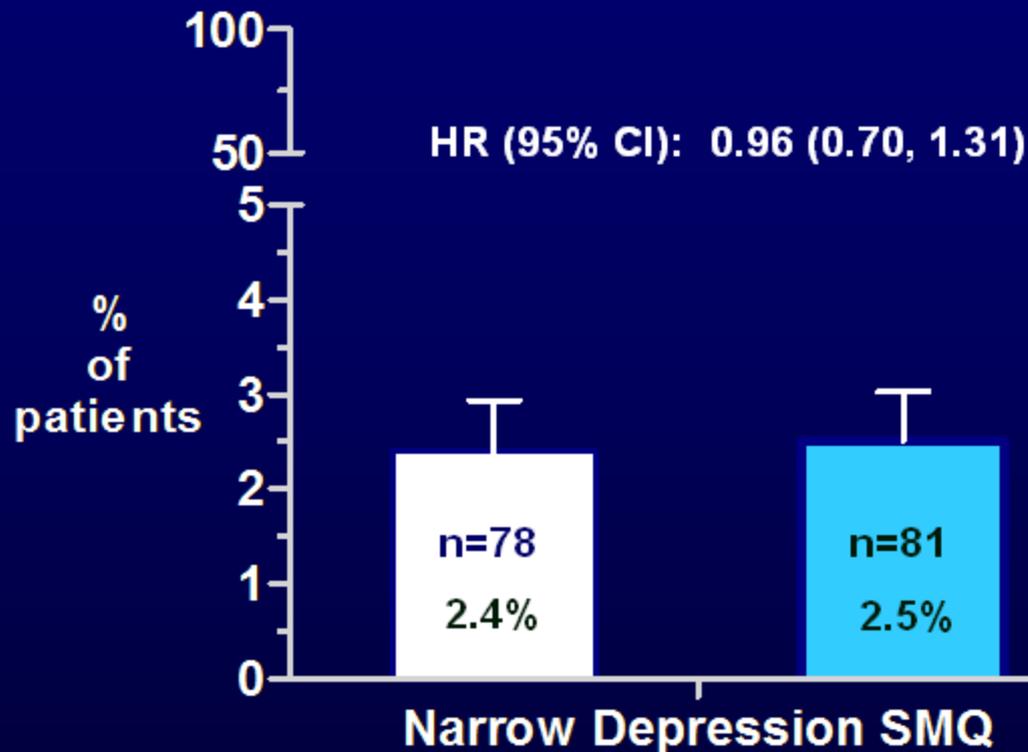
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- More than 20,000 echocardiographs
- More than 7,500 patients
- Lorcaserin did not increase the risk of valvulopathy above the pre-specified margin relative to placebo
- Lorcaserin did not meaningfully affect regurgitant scores at any heart valve

# Assessments of Depression and Suicidal Ideation

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# Lorcaserin Did Not Increase AEs of Depression (Pooled Phase 3 Studies, Year 1)



## Adverse Event Terms

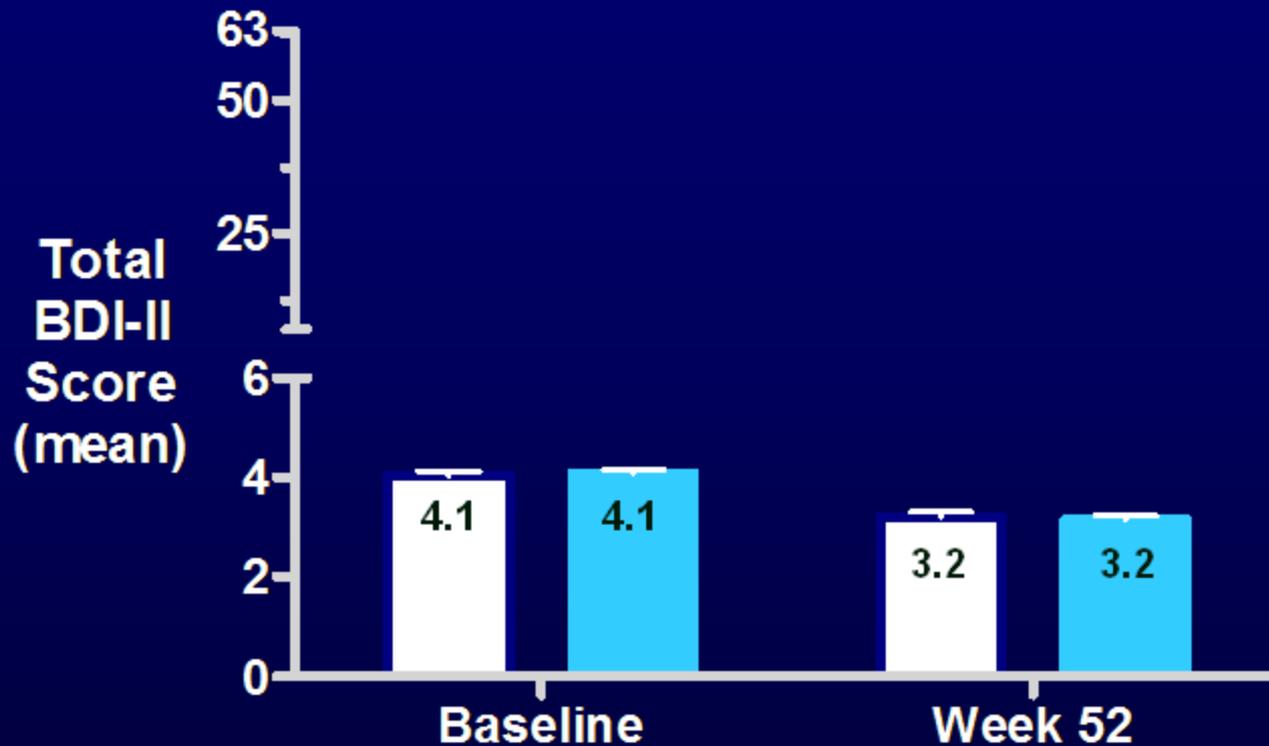
- Depressed mood
- Depression
- Depressive symptom
- Decreased interest
- Dysthymic disorder
- Feeling of despair
- Major depression

Mean (95% CI)

■ Placebo N=3185

■ Lorcaserin 10mg BID N=3195

# Lorcaserin Did Not Increase Total BDI-II Scores (Pooled Phase 3 Studies, Year 1)



## BDI-II Depression Categories

0-13: minimal

14-19: mild

20-28: moderate

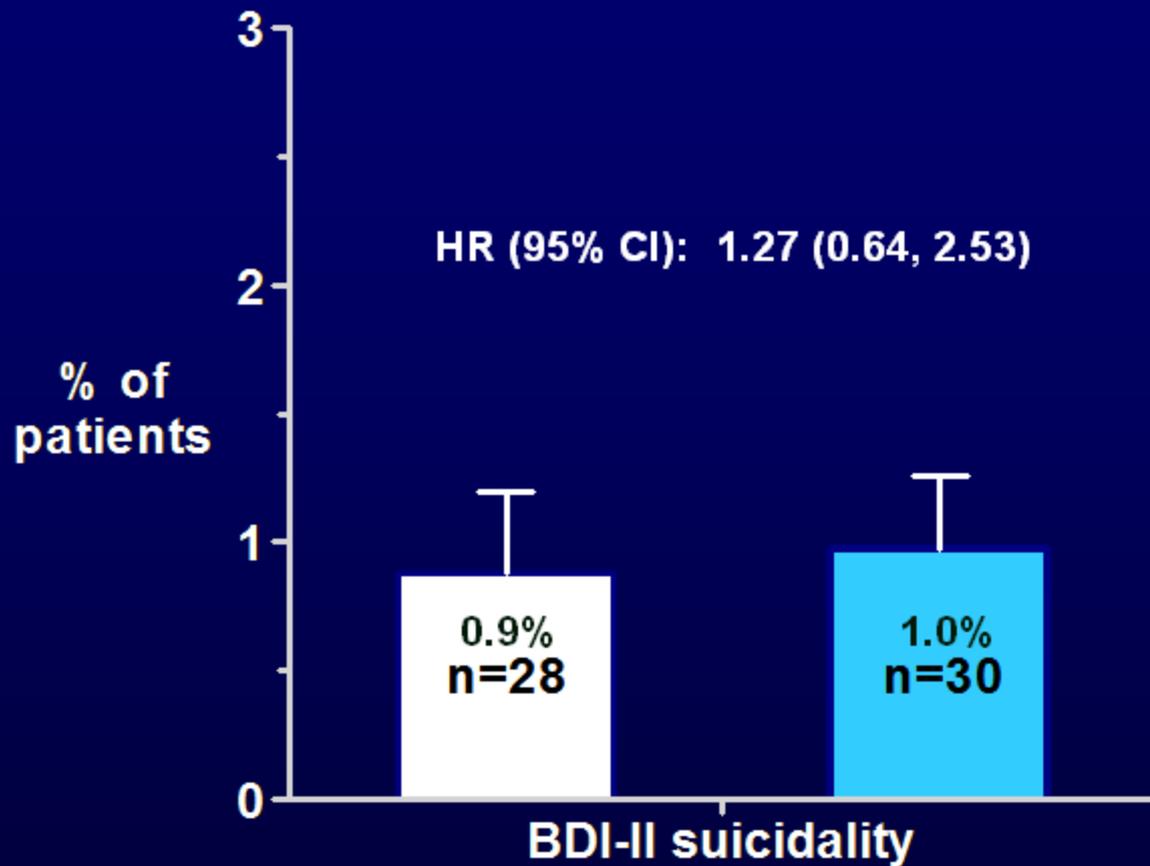
29-63: severe

Mean (SD)

■ Placebo N=2905

■ Lorcaserin 10mg BID N=2981

# Lorcaserin Did Not Increase Suicidal Ideation (Pooled Phase 3 Studies, Year 1)



Mean (95% CI)

■ Placebo N=3185

■ Lorcaserin 10mg BID N=3195

# No Increase in Adverse Events Related to Suicidal Thoughts or Actions (Year 1 or 2)

<b>Preferred Term</b>	<b>Placebo N=3185</b>		<b>Lorcaserin 10 mg BID N=3195</b>	
	<b>n</b>	<b>%</b>	<b>n</b>	<b>%</b>
<b>Suicide attempt/ intentional overdose</b>	<b>1</b>	<b>&lt;0.1*</b>	<b>1</b>	<b>&lt;0.1</b>
<b>Suicidal ideation</b>	<b>1</b>	<b>&lt;0.1</b>	<b>1</b>	<b>&lt;0.1</b>

\*patient in lorcaserin/placebo group; event at Study Week 70 (~ 4 months after stopping lorcaserin)

# Clinical Evaluation of Perceptual/Psychomimetic Adverse Events and Cognitive Function

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# Perceptual Changes: AEs in >1 Patient (Pooled Phase 3 Studies, Year 1)

	Events			
	Placebo N=3185		Lorcaserin N=3195	
	n	%	n	%
<b>Any Perceptual AE</b>	<b>52</b>	<b>1.6</b>	<b>99</b>	<b>3.1</b>
Paraesthesia	15	0.5	39	1.2
Hypoaesthesia	20	0.6	16	0.5
Sensory disturbance	2	0.1	2	0.1
Dysaesthesia	0	-	3	0.1
Hyperaesthesia	1	<0.1	2	0.1
Abnormal dreams	6	0.2	16	0.5
Nightmare	1	<0.1	4	0.1
Confusional state	1	<0.1	6	0.2
Disorientation	4	0.1	4	0.1
Anger	2	0.1	4	0.1
Dissociation	0	-	2	0.1
Dysarthria	0	-	3	0.1

# Perceptual Changes: AEs in >1 Patient (Pooled Phase 3 Studies, Year 1)

	Events				Withdrawal due to Event			
	Placebo N=3185		Lorcaserin N=3195		Placebo N=3185		Lorcaserin N=3195	
	n	%	n	%	n	%	n	%
<b>Any Perceptual AE</b>	<b>52</b>	<b>1.6</b>	<b>99</b>	<b>3.1</b>	<b>4</b>	<b>0.1</b>	<b>15</b>	<b>0.5</b>
Paraesthesia	15	0.5	39	1.2	1	<0.1	4	0.1
Hypoaesthesia	20	0.6	16	0.5	2	0.1	1	<0.1
Sensory disturbance	2	0.1	2	0.1	0	-	0	-
Dysaesthesia	0	-	3	0.1	0	-	0	-
Hyperaesthesia	1	<0.1	2	0.1	0	-	1	<0.1
Abnormal dreams	6	0.2	16	0.5	1	-	0	-
Nightmare	1	<0.1	4	0.1	0	-	0	-
Confusional state	1	<0.1	6	0.2	0	-	2	0.1
Disorientation	4	0.1	4	0.1	0	-	3	0.1
Anger	2	0.1	4	0.1	0	-	3	0.1
Dissociation	0	-	2	0.1	0	-	0	-
Dysarthria	0	-	3	0.1	0	-	1	0.1

# Formal Testing of Cognition: No Impairment at Recommended Dose

- **Single dose studies (10 – 60 mg dose)**
  - Four Choice Reaction Time Task, Memory Scanning, Trail Making Test
  - *Recognition Reaction Time (but not Motor Reaction Time) slightly increased at 60 mg*
- **Multiple dose studies (3 – 20 mg QD x 14 days)**
  - Immediate Word Recall, Simple Reaction Time, Digit Vigilance, Choice Reaction Time, Spatial Working Memory, Numeric Working Memory, Delayed Word Recall, Word Recognition, Picture Recognition
  - *Only effect: Numeric Working Memory Speed was slightly impaired at 20 mg dose*

# Adverse Events Related to Cognition

(Pooled Phase 3 Studies, Year 1)

Preferred Term	Events			
	Placebo (N=3185)		Lorcaserin 10 mg BID (N=3195)	
	n	%	n	%
<b>Patients with any event</b>	<b>17</b>	<b>0.5</b>	<b>61</b>	<b>1.9</b>
Disturbance in attention	9	0.3	20	0.6
Memory impairment	5	0.2	22	0.7
Amnesia	3	0.1	16	0.5
Mental impairment	0	-	4	0.1
Cognitive disorder	0	-	2	0.1
Mental disorder	0	-	1	<0.1

# Adverse Events Related to Cognition

## (Pooled Phase 3 Studies, Year 1)

Preferred Term	Events				Withdrawal due to Event			
	Placebo (N=3185)		Lorcaserin 10 mg BID (N=3195)		Placebo (N=3185)		Lorcaserin 10 mg BID (N=3195)	
	n	%	n	%	n	%	n	%
<b>Patients with any event</b>	<b>17</b>	<b>0.5</b>	<b>61</b>	<b>1.9</b>	<b>3</b>	<b>0.1</b>	<b>5</b>	<b>0.2</b>
Disturbance in attention	9	0.3	20	0.6	1	<0.1	4	0.1
Memory impairment	5	0.2	22	0.7	2	0.1	1	<0.1
Amnesia	3	0.1	16	0.5	0	-	2	0.1
Mental impairment	0	-	4	0.1	0	-	1	<0.1
Cognitive disorder	0	-	2	0.1	0	-	0	-
Mental disorder	0	-	1	<0.1	0	-	0	-

# Clinical Safety Summary for Lorcaserin

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- Well tolerated
- Non-inferior to placebo for development of valvulopathy
- No increase in incidence or severity of depression or suicidal ideation
- Small number of patients reported mild, transient adverse events associated with perception or cognition

# Extending Safety Database

## Passive Surveillance



- Spontaneous report analysis
- Trend analyses

## Active Surveillance



- Healthcare claims database review (e.g. i3DrugSafety)
  - Comparator cohort
  - Accrue > 10,000 additional patient-years of exposure
  - Trend analyses
  - Pregnancy registry

## Controlled Clinical Trials



- Obese/overweight diabetic patients (Ongoing)
- Obese/overweight adolescents (Planned)

# Post Approval Echo Monitoring Not Recommended

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- No evidence of valvulopathy related to lorcaserin treatment
- Screening echos could not be standardized in terms of acquisition or interpretation
- Physiological variability of echo findings
- Lack of evidence-based guidelines for incidental echo findings
- Incidental findings will result in undue burden on patients and providers

# Education and Communication

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- Customized website guidance
  - Identify appropriate patients
  - Evaluate patient progress
  - Provide resources for patient support

## **Risk / Benefit of Lorcaserin**

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**Steven R. Smith, M.D.**

Scientific Director

Translational Research Institute For Metabolism and Diabetes

Florida Hospital / Sanford Burnham Medical Research Institute

## FDA (CDER) Industry Guidance for Developing Products for Weight Management (Feb 2007)

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- Excess body fat increases the risk of:
  - Death
  - Type 2 diabetes
  - Hypertension
  - Dyslipidemia
  - Osteoarthritis of the knee
  - Sleep Apnea
  - Some cancers

# Current Treatment Options

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- Behavior modification
- FDA approved for long-term use
  - Sibutramine
  - Orlistat
- Dietary Supplements (not FDA approved)
- Surgery (patients with BMI  $\geq 35$  kg/m<sup>2</sup>)

# What are the characteristics of an ideal weight loss drug?

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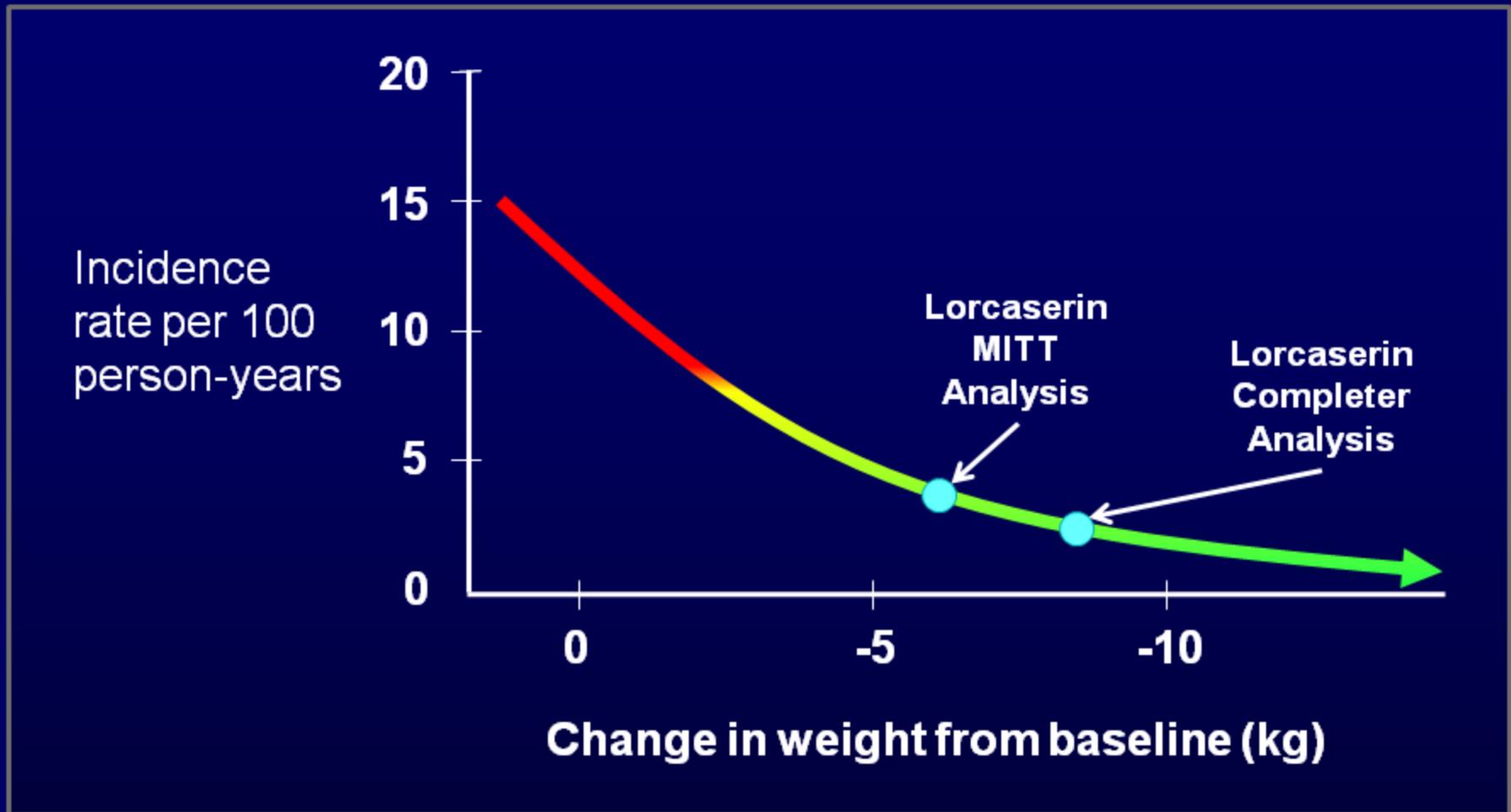
- Clinically significant weight loss
- Predictable tolerability
- Demonstrated safety
- Overall improvement in measures and biomarkers of comorbid conditions
- Improves quality of life

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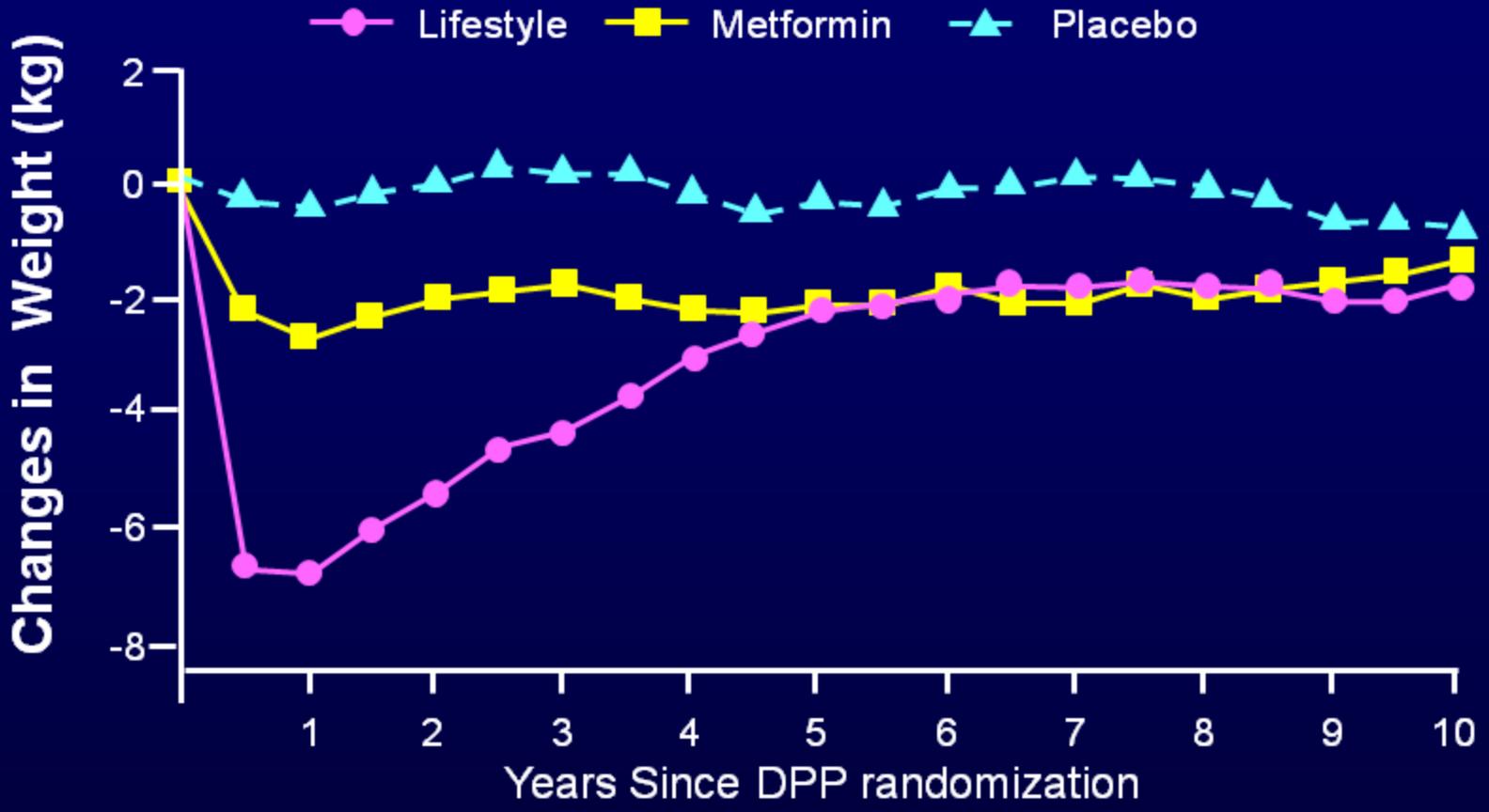
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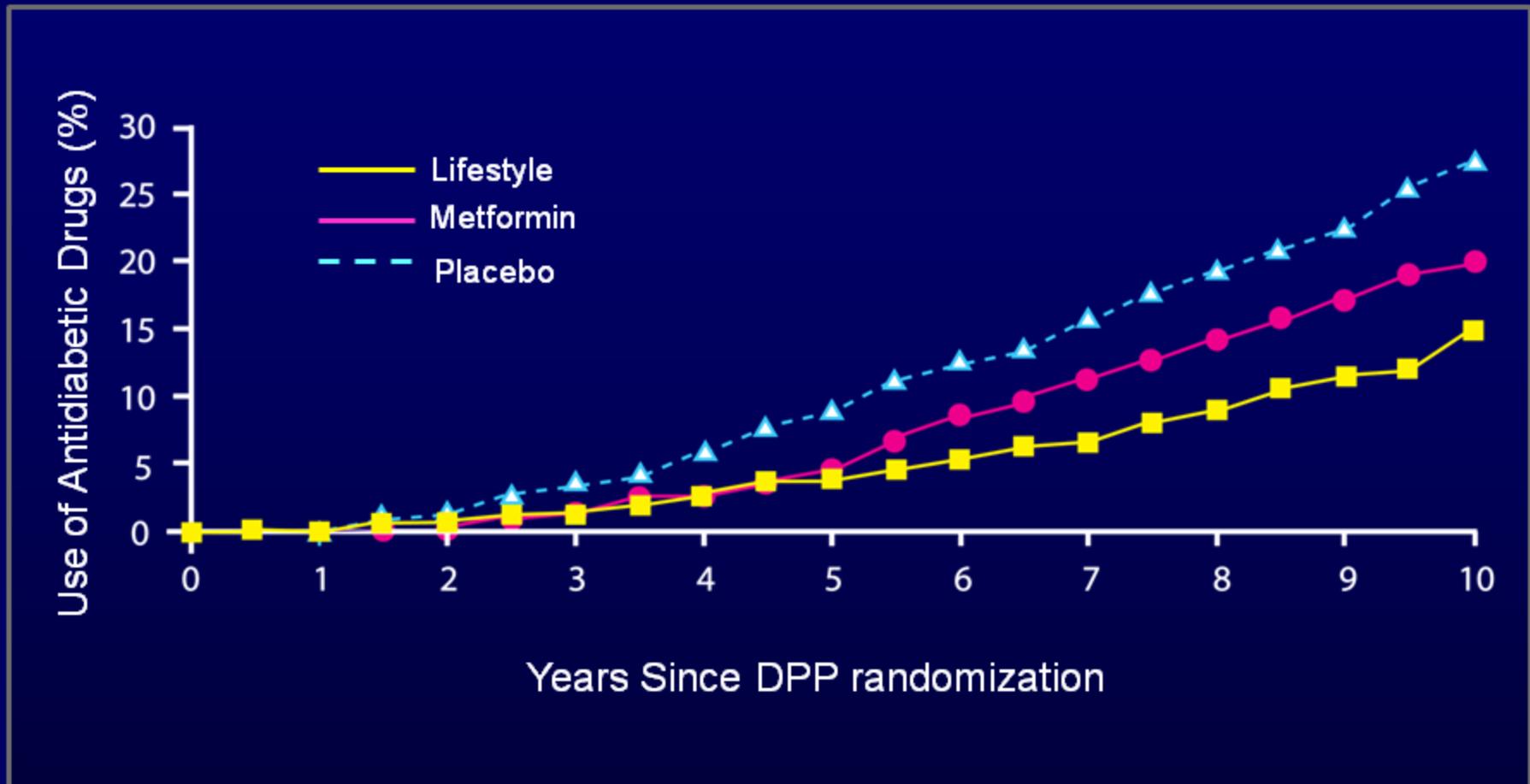
# Lorcaserin Weight Loss in Context to The Diabetes Prevention Program (DPP)



# Diabetes Prevention Program (DPP): 10-Year Results



# Diabetes Prevention Program (DPP): 10-Year Results

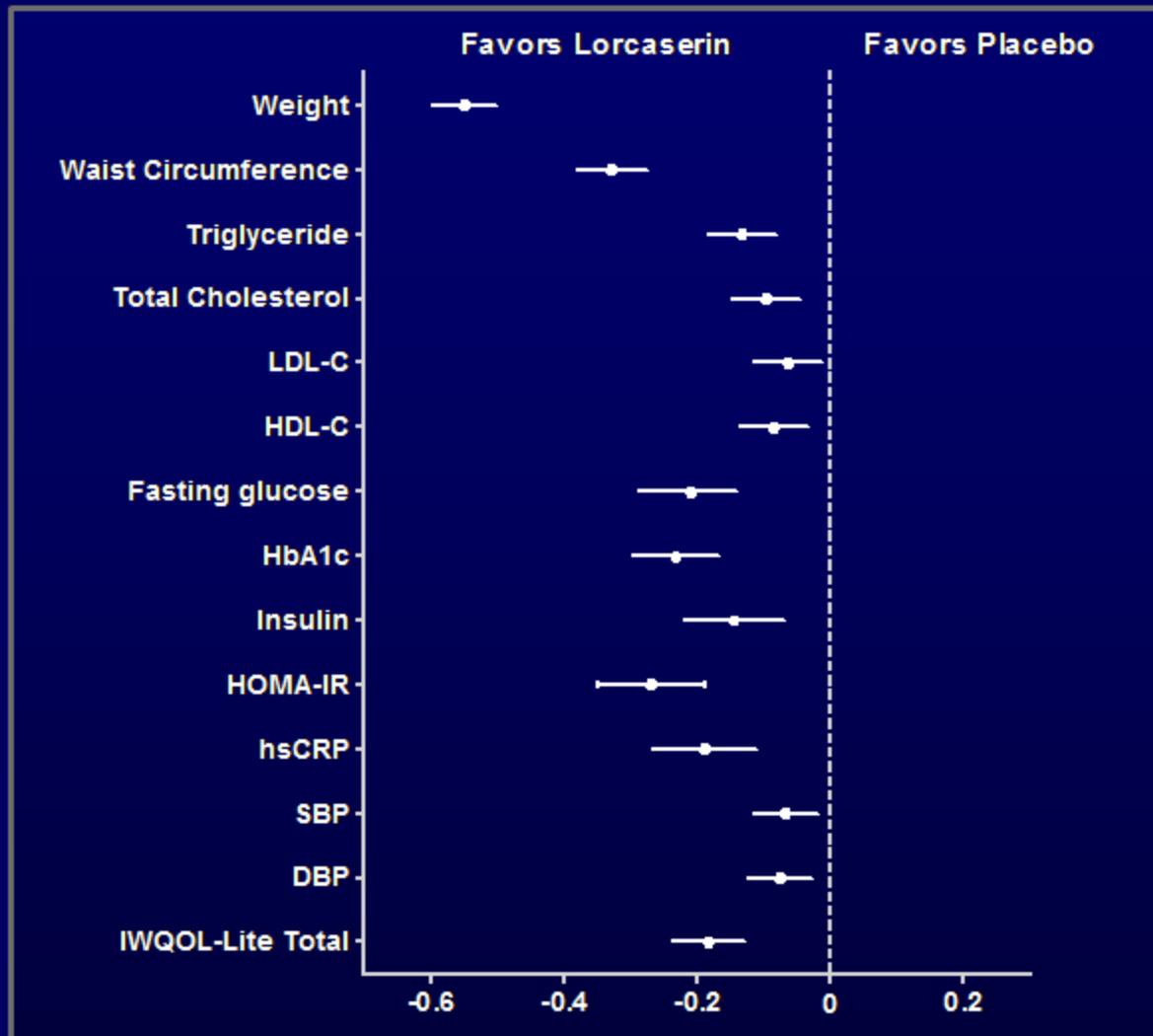


# What are the characteristics of an ideal weight loss drug?

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# Summary of Effect Sizes for Primary and Secondary Endpoints



Pooled Phase 3, Year 1 Standardized Mean Difference (95% CI)

# What are the characteristics of an ideal weight loss drug?

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- ✓ Clinically significant weight loss
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# Body of Evidence Supports Approval of Lorcaserin

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- Clinically meaningful weight loss
- Improved maintenance of weight loss
- Improvements in biomarkers of cardiovascular and metabolic risk
- Well tolerated
- No identified safety signals
- ***Evidence supports approval***

## **Lorcaserin for weight loss and maintenance of weight loss**

**BMI  $\geq 30$  kg/m<sup>2</sup>, or a BMI  $\geq 27$  kg/m<sup>2</sup> and at least one weight-related comorbid condition**

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