



U.S. Food and Drug Administration

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Endocrinologic and Metabolic Drugs Advisory Committee Meeting
East Adelphi, Maryland
September 16, 2010

FDA Clinical Review of Efficacy and Safety
NDA 22529
Lorcaserin hydrochloride
Sponsor: Arena Pharmaceuticals, Inc.

Reviewer: Julie Golden, M.D.
Medical Officer
Division of Metabolism and Endocrinology Products
Office of New Drugs
CDER

Outline

- Historical Overview
- Lorcaserin Clinical Program
- Efficacy
- Safety
 - Valvular Heart Disease
 - Depression- and Suicide-Related Events
 - Cognitive-Related Adverse Events
 - Potential Serotonin-Related Adverse Events
 - Breast Neoplasms and Prolactin Concentrations
 - Abuse-Related Adverse Events

Historical Overview

- Short-term weight loss drugs:
amphetamine congeners
- Long-term weight loss drugs: sibutramine,
orlistat
- Drugs removed from market: fenfluramine,
dexfenfluramine
- Drugs never brought to market:
rimonabant, others

Historical Overview: Fenfluramine and Valvular Heart Disease

- “Fen-phen” craze:
 - Weintraub (1992): 4-year study
 - Prescriptions for fenfluramine and phentermine soared
- Dexfenfluramine (1996)
 - Long-term obesity treatment
 - Patients at high risk: BMI ≥ 30 kg/m² or ≥ 27 kg/m² with co-morbidities

Historical Overview: Fenfluramine and Valvular Heart Disease

- Connolly, et al (1997)
 - 24 women
 - 1-28 months of fen-phen
 - Unusual cardiac valvular morphology and regurgitation
- Graham and Green (1997)
 - 28 patients
 - Left-sided valve involved in all cases
 - Two or more valves affected in 78%
 - Regurgitation graded as moderate or severe in 78%

Historical Overview: Fenfluramine and Valvular Heart Disease

FDA Medical Bulletin (July 1997)

- FDA-defined valvular heart disease
 - Moderate or greater MR and/or mild or greater AR
 - Suggested 1 in 3 exposed patients affected

Historical Overview:

Fenfluramine and Valvular Heart Disease

- Sachdev, et al (2002)
 - Exposed > 90 d 12% vs. unexposed 5.9%
(OR: 2.2, 95% CI: 1.7-2.7)
 - No significant difference exposed < 90 d vs. unexposed
- Loke, et al (2002)
 - AR exposed 8.8% vs. unexposed 3.8%
(RR: 2.32, 95% CI: 1.79, 3.01)
 - MR exposed 2.9% vs. unexposed 1.8%
(RR: 1.55, 95% CI: 1.06, 2.25)

Historical Overview: Anorexigens and Pulmonary Hypertension

- Aminorex: associated with an “epidemic” of PPH in Europe in the 1960s
- Abenhaim, et al (1996): anorexigens associated with 23-fold increase in PPH when used > 3 mos
- Dexfenfluramine AC (1995): ≤ 1 in 1000 patients exposed develop PPH

Historical Overview: Rimonabant and Neuropsychiatric AEs

- 2007 AC: Depression, suicidality, and seizures
 - Trials had high drop-out rates
 - More long-term data were needed
 - Vote: 0 yes, 14 no
- Rimonabant removed from European market in 2008
- Centrally-acting obesity drug development now incorporates standard depression and suicidality inventories in Phase 2 and 3 clinical trials

Historical Overview: Weight Loss Efficacy of Other Obesity Agents

	Active	Placebo
Orlistat 120 mg TID (1)	-6.1 kg	-2.6 kg
Sibutramine 15 mg QD (2)	-6.4 kg	-1.6 kg
Qnexa (phentermine/topiramate) 15/92 mg QD (3)	-10.6 kg	-1.7 kg
NB32 (naltrexone 32 mg/bupropion 360 mg) QD (4)	-6.1 kg	-1.4 kg

(1) Orlistat PI

(2) Sibutramine PI

(3) NDA 22580, FDA Briefing Package, EMDAC meeting, 15 July 2010

(4) Greenway FL, et al. Lancet 2010; 376(9741): 595-605



Lorcaserin Clinical Program

Lorcaserin Database

- 421 randomized in 14 Phase 1 studies
- 821 randomized in 2 Phase 2 trials
- 7190 randomized in 2 completed Phase 3 trials
- Phase 3 trial in type 2 diabetes ongoing

Exposure to Lorcaserin

- Total number of patients randomized in Phase 3 trials:
 - 3198 Lorcaserin 10 mg BID
 - > 180 days: 2135 patients
 - > 360 days: 1589 patients
 - 802 Lorcaserin 10 mg QD
 - > 180 days: 560 patients
 - > 360 days: 400 patients
 - 3190 Placebo

- February 2007 Draft Guidance for Industry: Developing Products for Weight Management
 - *A reasonable estimation of the safety of a weight-management product upon which to base approval generally can be made when a total of approximately 3,000 subjects are randomized to active doses of the product and no fewer than 1,500 subjects are randomized to placebo for 1 year of treatment.*

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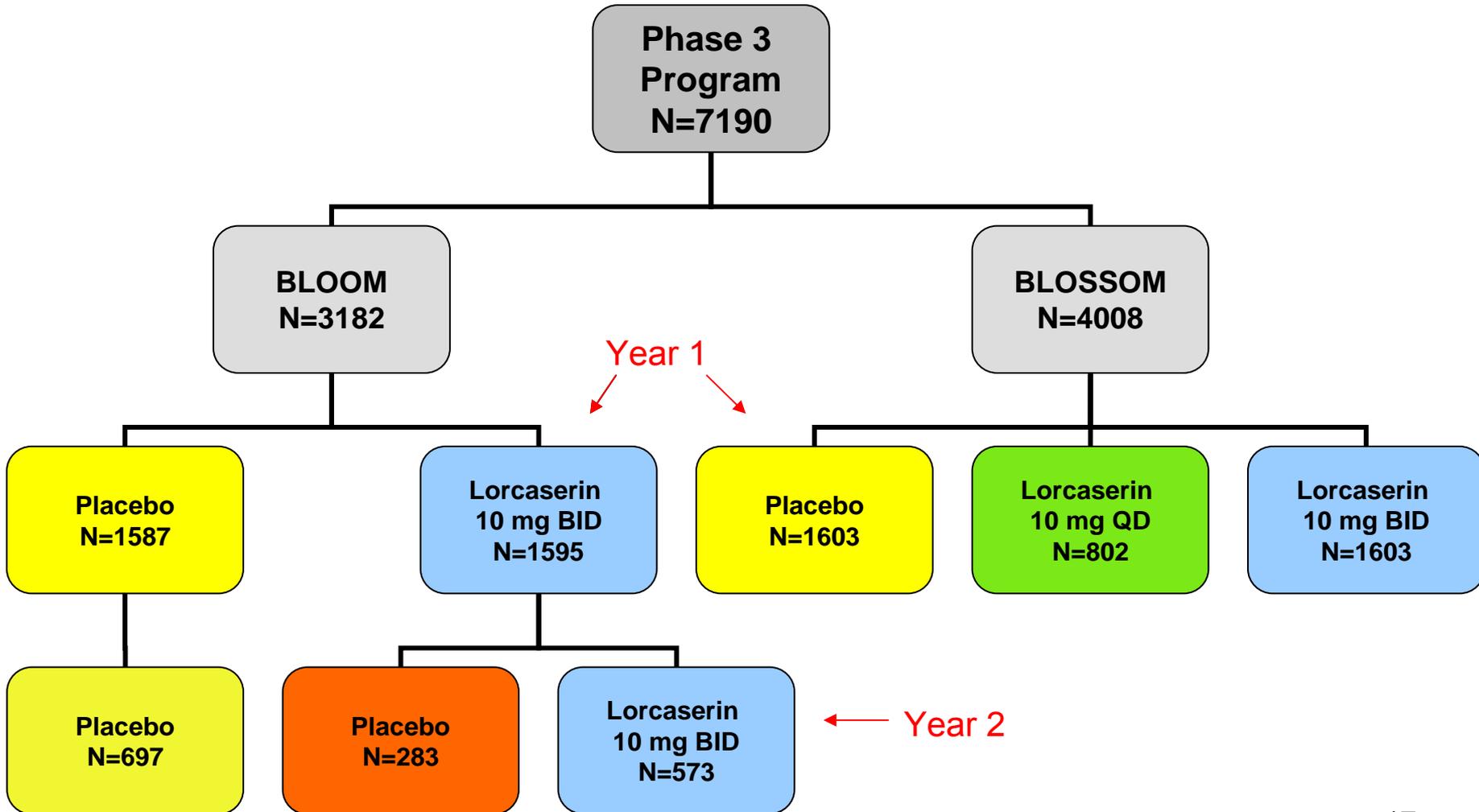
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Lorcaserin Phase 3 Program



Key Exclusion Criteria: Phase 3

- Diabetes mellitus
- Uncontrolled hypertension
- Recent MI, stroke, or arrhythmia
- Unstable angina
- CHF from valvular insufficiency or stenosis
- Valve replacement
- Pulmonary hypertension
- Recent major depression, anxiety, or other psychiatric disease requiring treatment with Rx medication
- Malignancy within past 5 years



Demographics and Baseline Info

	Lorc 10 BID N=3195	Lorc 10 QD N=801	Pbo N=3185
Age, years mean +/- SD	43.8 +/- 11.6	43.8 +/- 11.7	44.0 +/- 11.4
Sex, % female	81.7	81.9	81.0
Race			
White, %	67.7	67.2	66.2
Black, %	18.9	20.0	19.4
Hispanic, %	11.1	10.9	12.4
BMI, kg/m ² mean +/- SD	36.1 +/- 4.3	35.8 +/- 4.3	36.1 +/- 4.2
Weight, kg mean +/- SD	100.4 +/- 15.7	99.8 +/- 16.6	100.2 +/- 15.9
Any Comorbidity, %	44.3	40.2	43.7
Hypertension, %	22.6	21.8	22.7
Dyslipidemia, %	31.0	27.2	30.2
CVD, %	0.6	0.5	0.9
Glucose intol, %	1.5	1.9	1.0
Sleep apnea, %	4.5	3.4	4.0

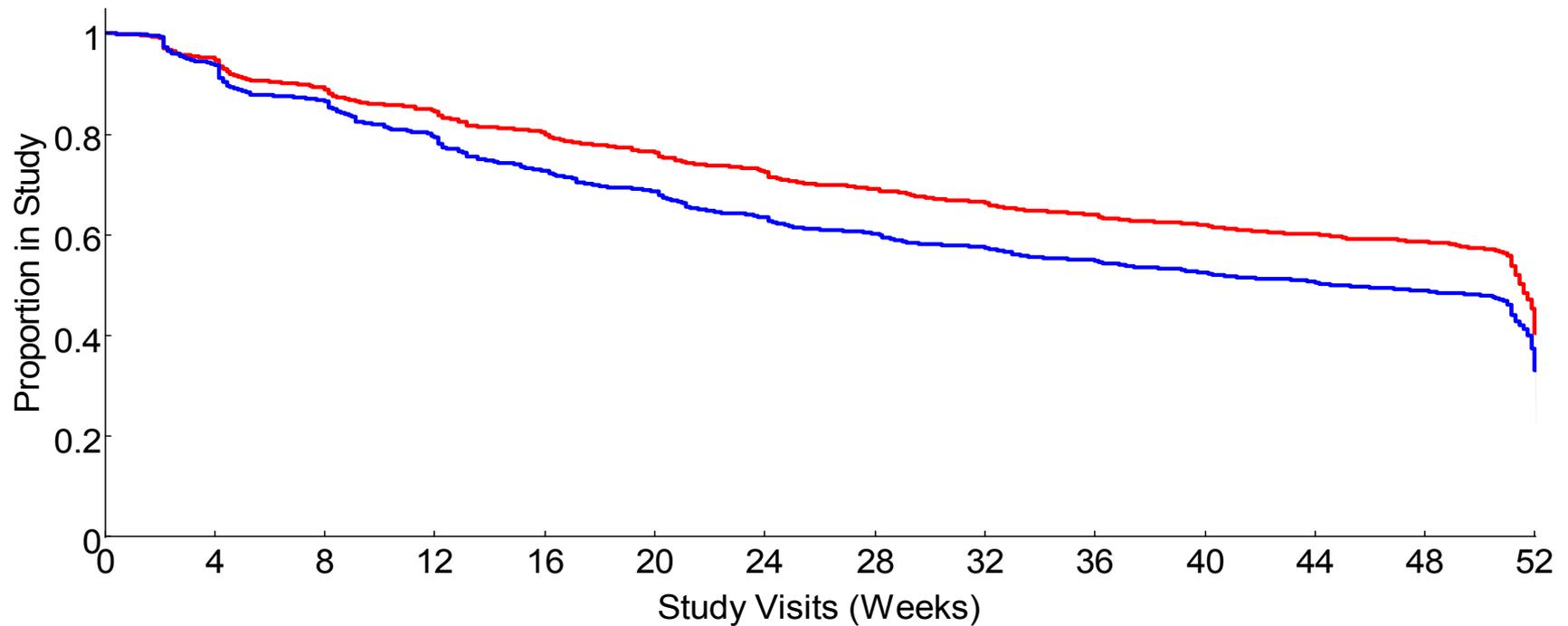
Lorcaserin Phase 3 Program Disposition

	BLOOM		BLOSSOM		
	Lorc 10 BID	Pbo	Lorc 10 BID	Lorc 10 QD	Pbo
Total Randomized	1595	1587	1603	802	1603
Withdrawn early -- Year 1	712 (45%)	871 (55%)	686 (43%)	329 (41%)	769 (48%)
Lack of Efficacy	27 (2%)	88 (6%)	39 (2%)	25 (3%)	62 (4%)
Adverse Event	113 (7%)	106 (7%)	115 (7%)	50 (6%)	74 (5%)



Lorcaserin Phase 3 Program Disposition (BLOOM)

Study 009



∴
— Lorcaserin 10mg bid
— Placebo



Efficacy

Efficacy

February 2007 Draft Guidance for Industry: Developing Products for Weight Management

- *In general, a product can be considered effective for weight management if after 1 year of treatment either of the following occurs:*
 - *The difference in mean weight loss between the active-product and placebo-treated groups is at least 5 percent and the difference is statistically significant*
 - *The proportion of subjects who lose greater than or equal to 5 percent of baseline body weight in the active-product group is at least 35 percent, is approximately double the proportion in the placebo-treated group, and the difference between groups is statistically significant*

Efficacy: Mean Weight Change Week 52 MITT LOCF

	Treatment group	Baseline mean wt (kg)	Adjusted mean % wt change from baseline	Diff in adjusted mean % change (95% CI)	p-value
BLOOM	Placebo	99.7	-2.2	--	
	Lorc 10 BID	100.4	-5.9	-3.7 (-4.1, -3.3)	< 0.001
BLOSSOM	Placebo	100.8	-2.8	--	
	Lorc 10 QD	100.1	-4.7	-1.9 (-2.5, -1.4)	< 0.001
	Lorc 10 BID	100.3	-5.8	-3.0 (-3.4, -2.6)	<0.001

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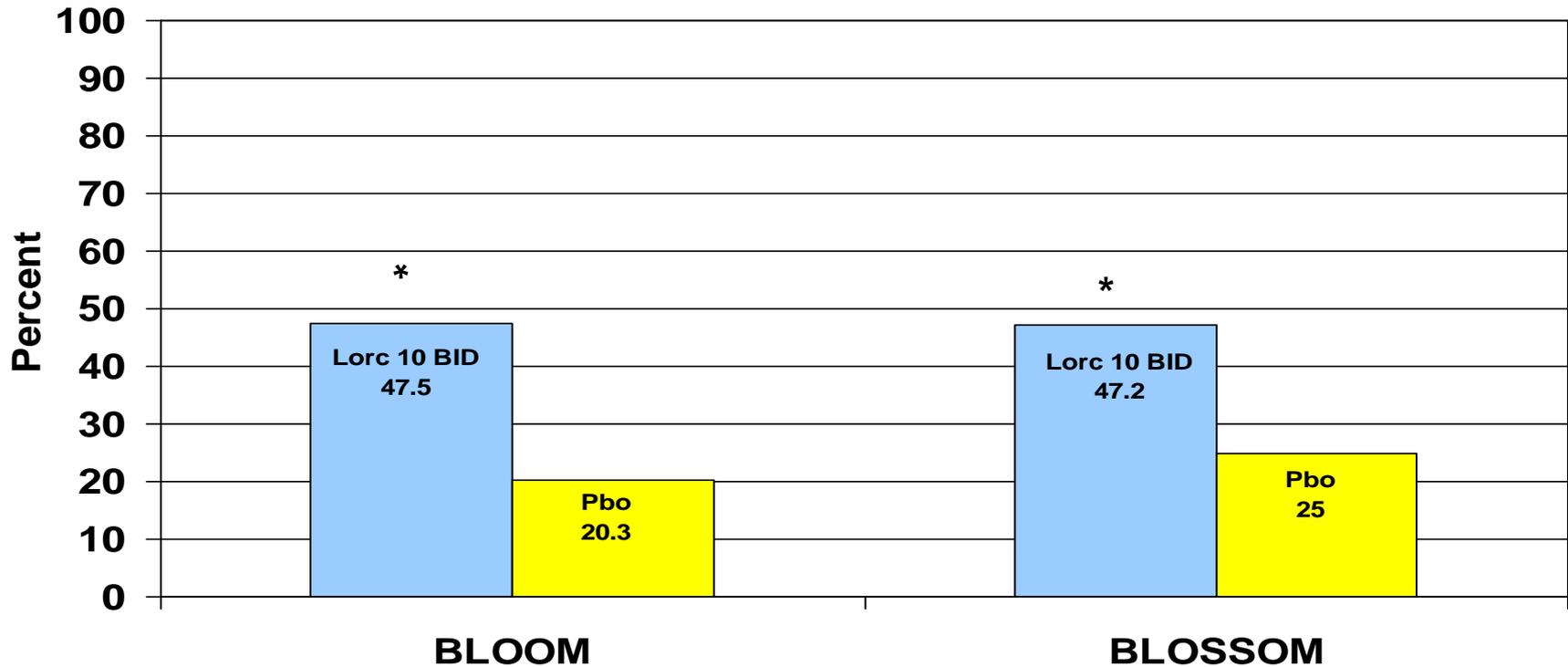
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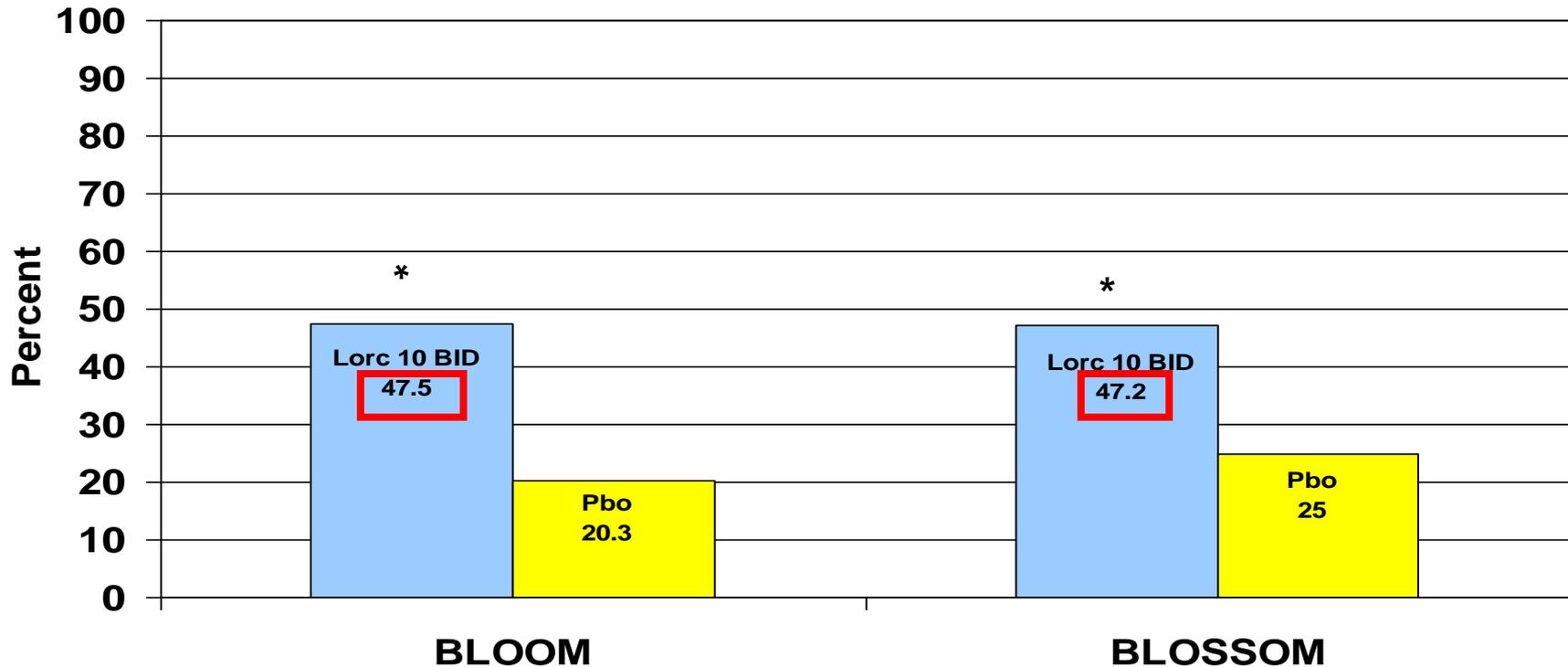
✘ Neither BLOOM nor BLOSSOM met this criterion

Efficacy: Proportion of Patients with $\geq 5\%$ Weight Loss



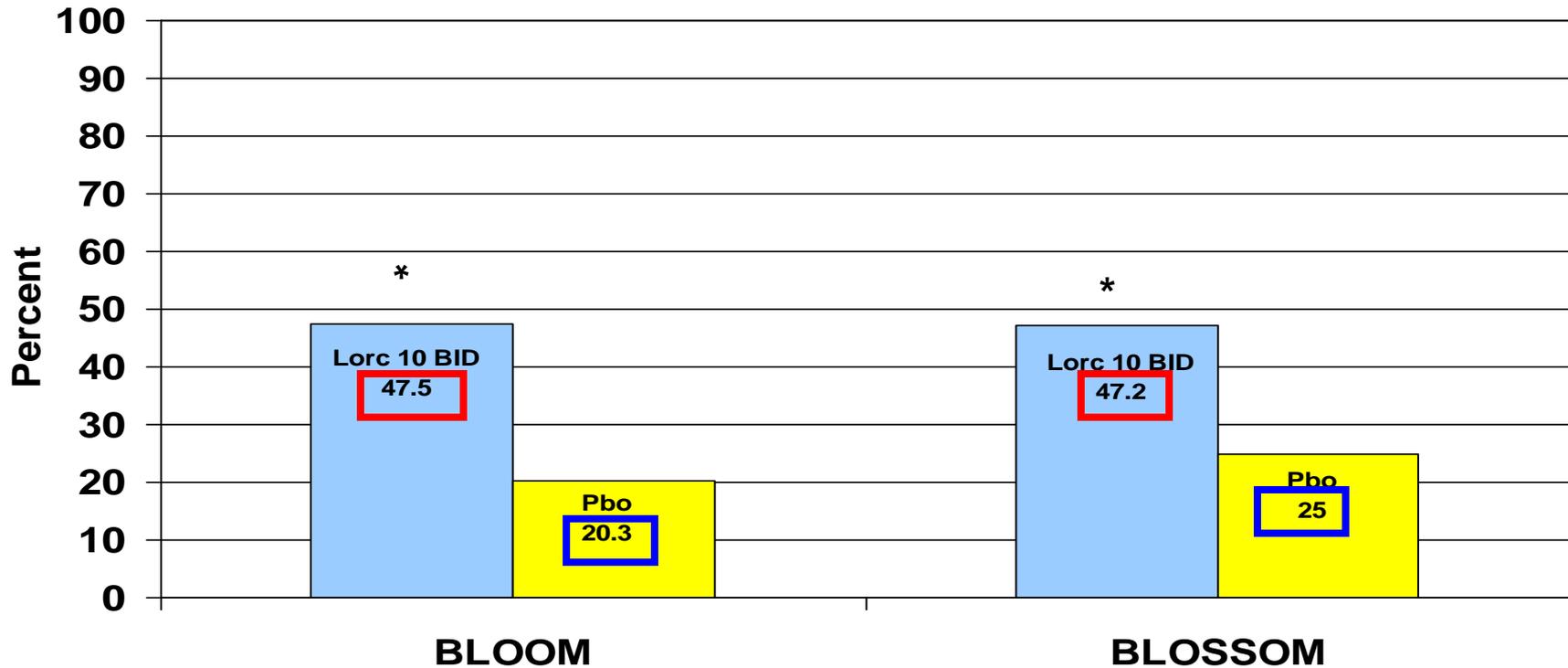
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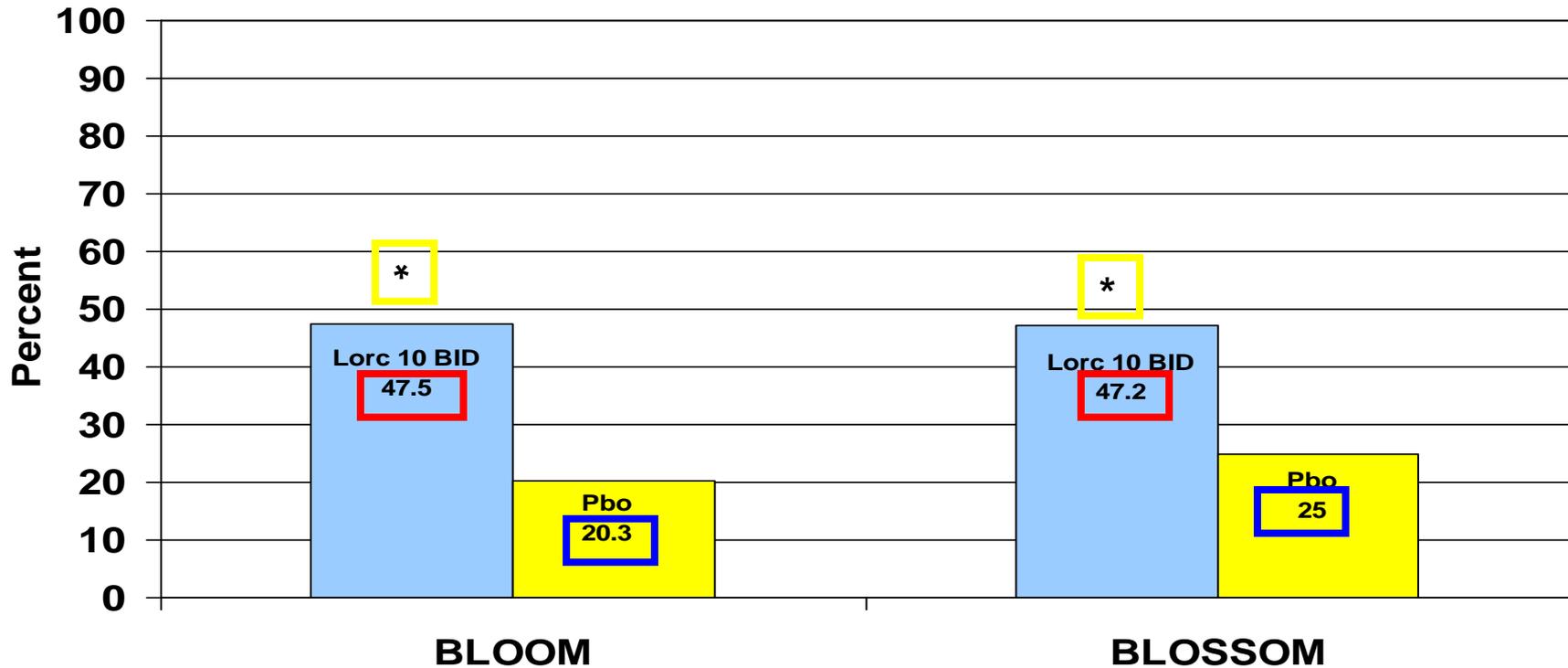
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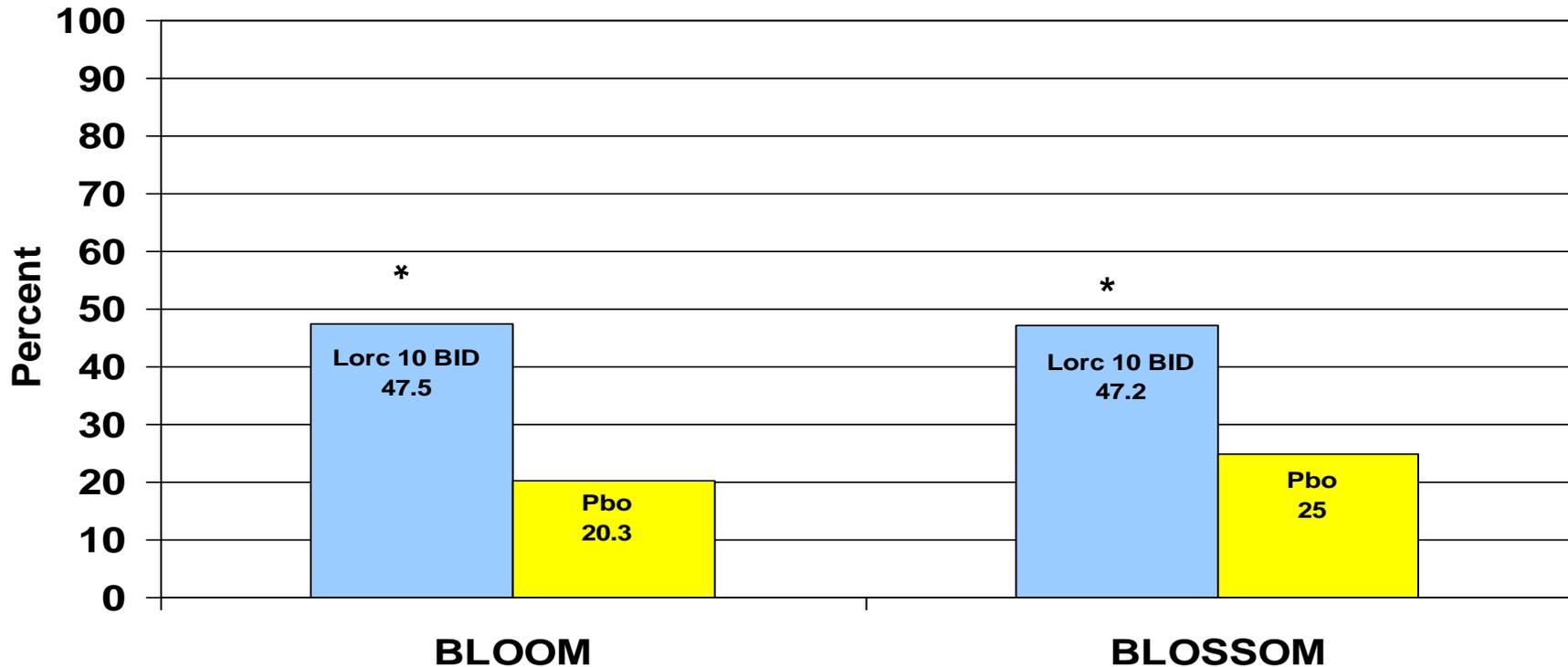
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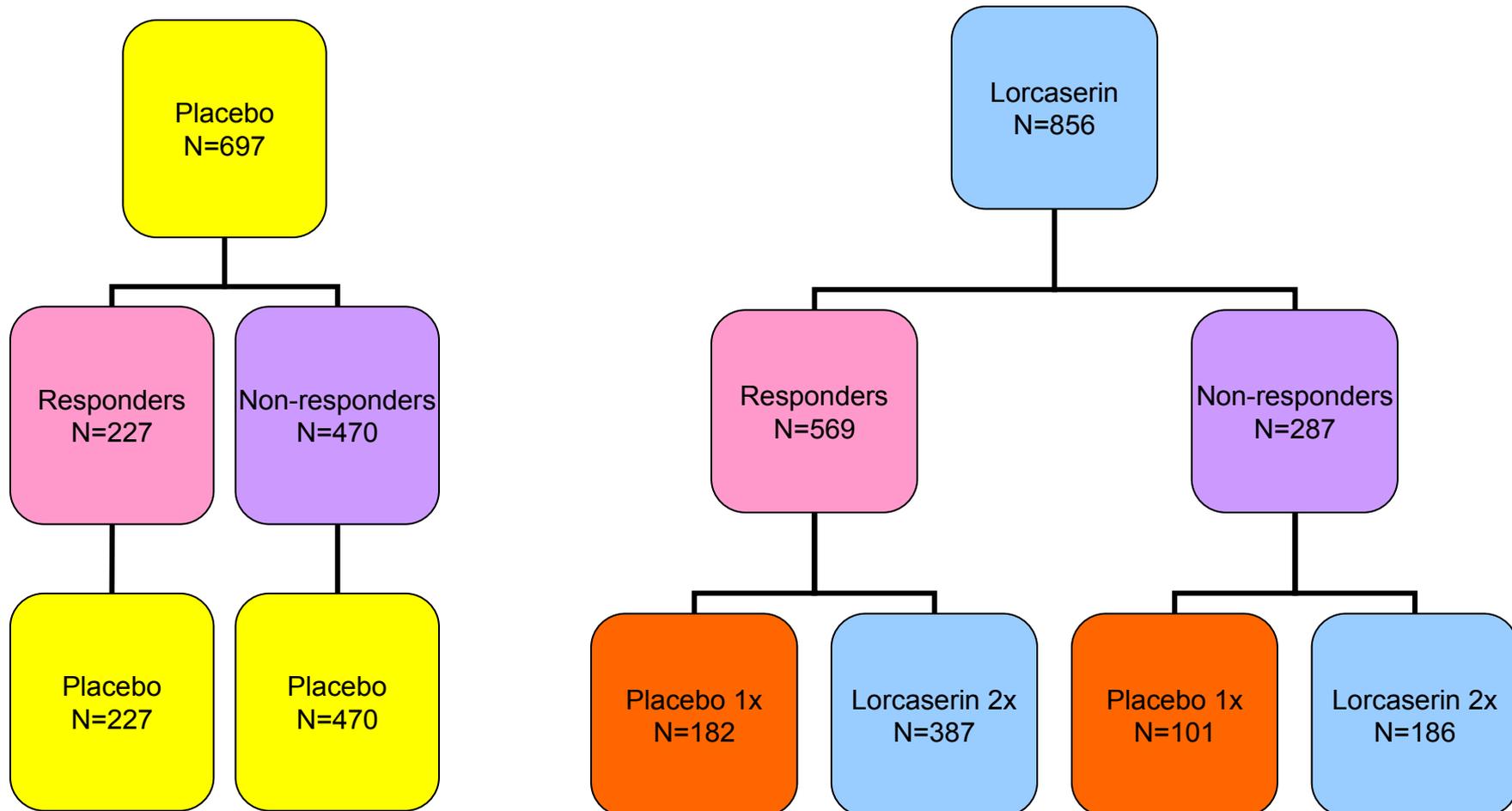
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✓ **BLOOM and BLOSSOM met this criterion**

Year 2 Efficacy: BLOOM

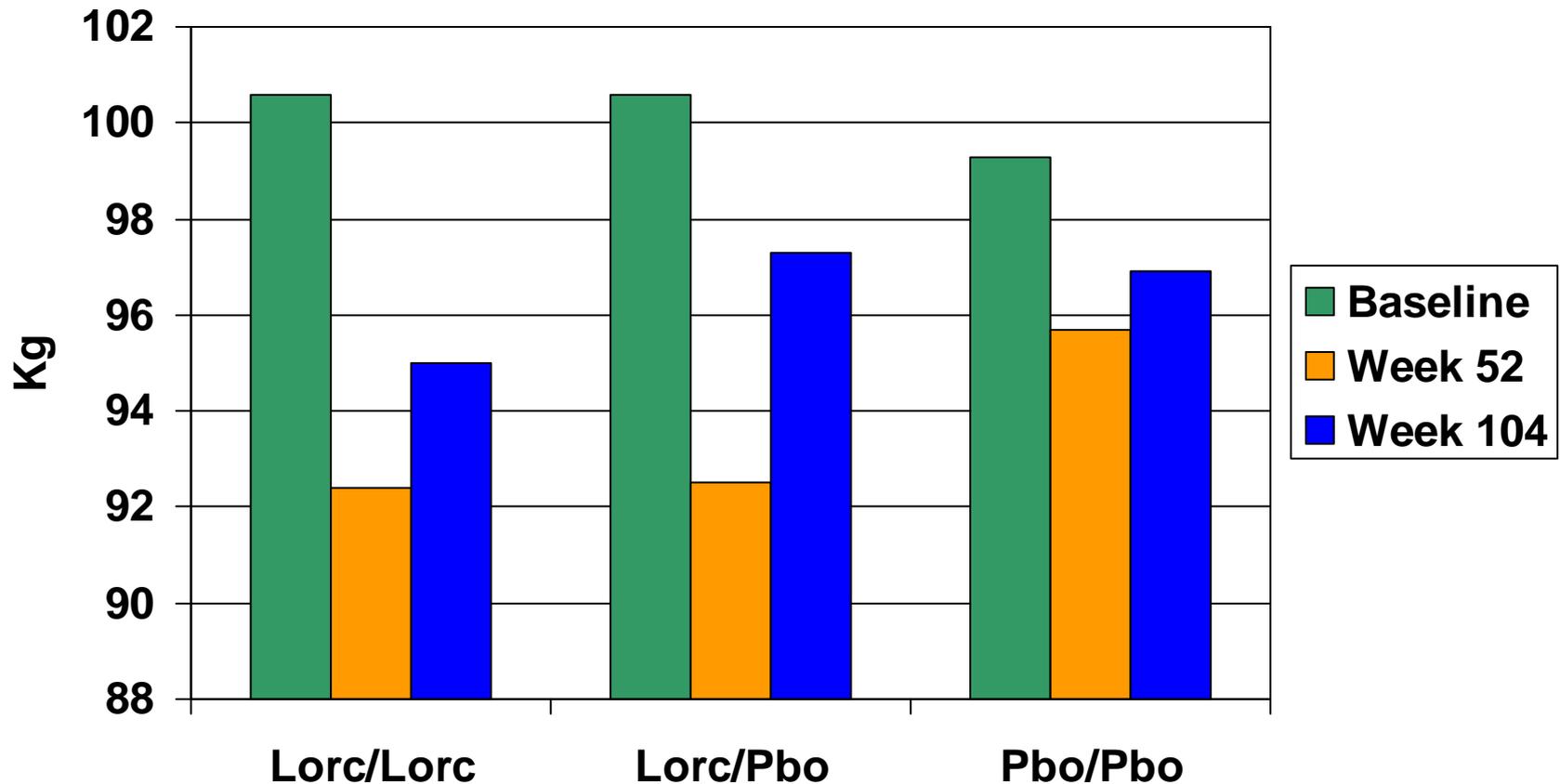


Year 2 Efficacy: BLOOM

- Only 50% of the initially randomized population completed Year 1 and participated in Year 2
- Patients who completed Year 1 of BLOOM lost more weight than those who discontinued early

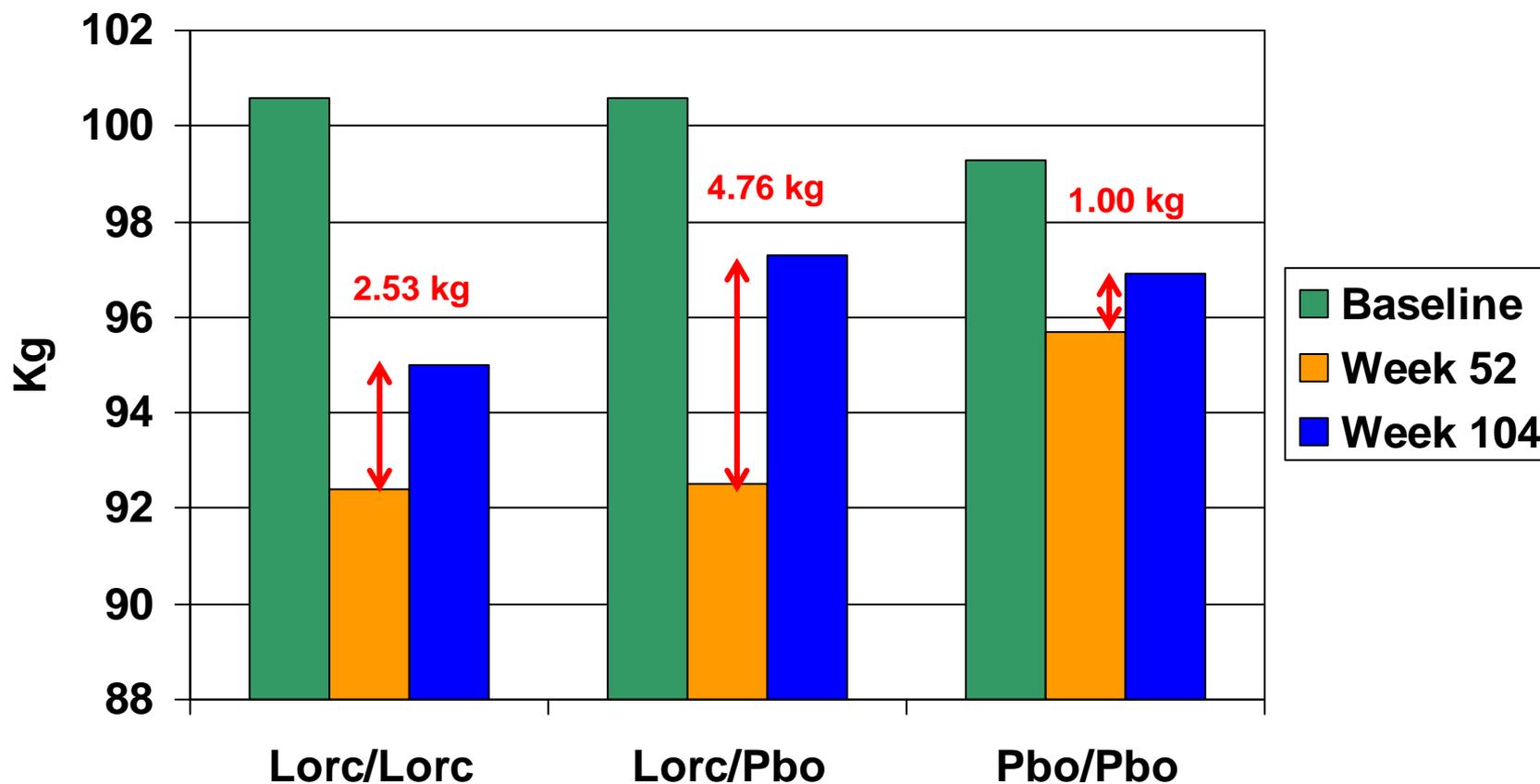
Year 2 Efficacy: BLOOM

Mean Weight over Time

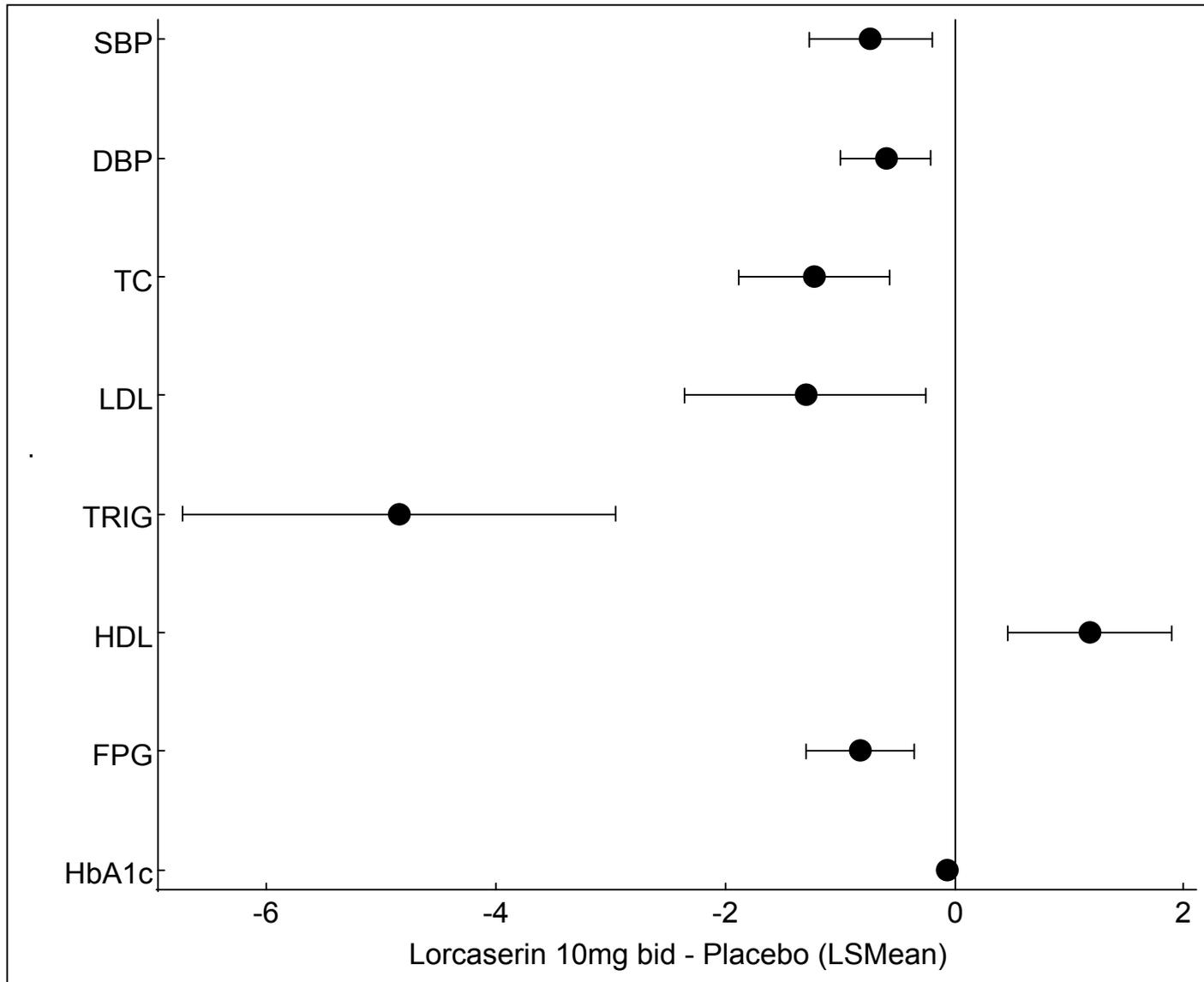


Year 2 Efficacy: BLOOM

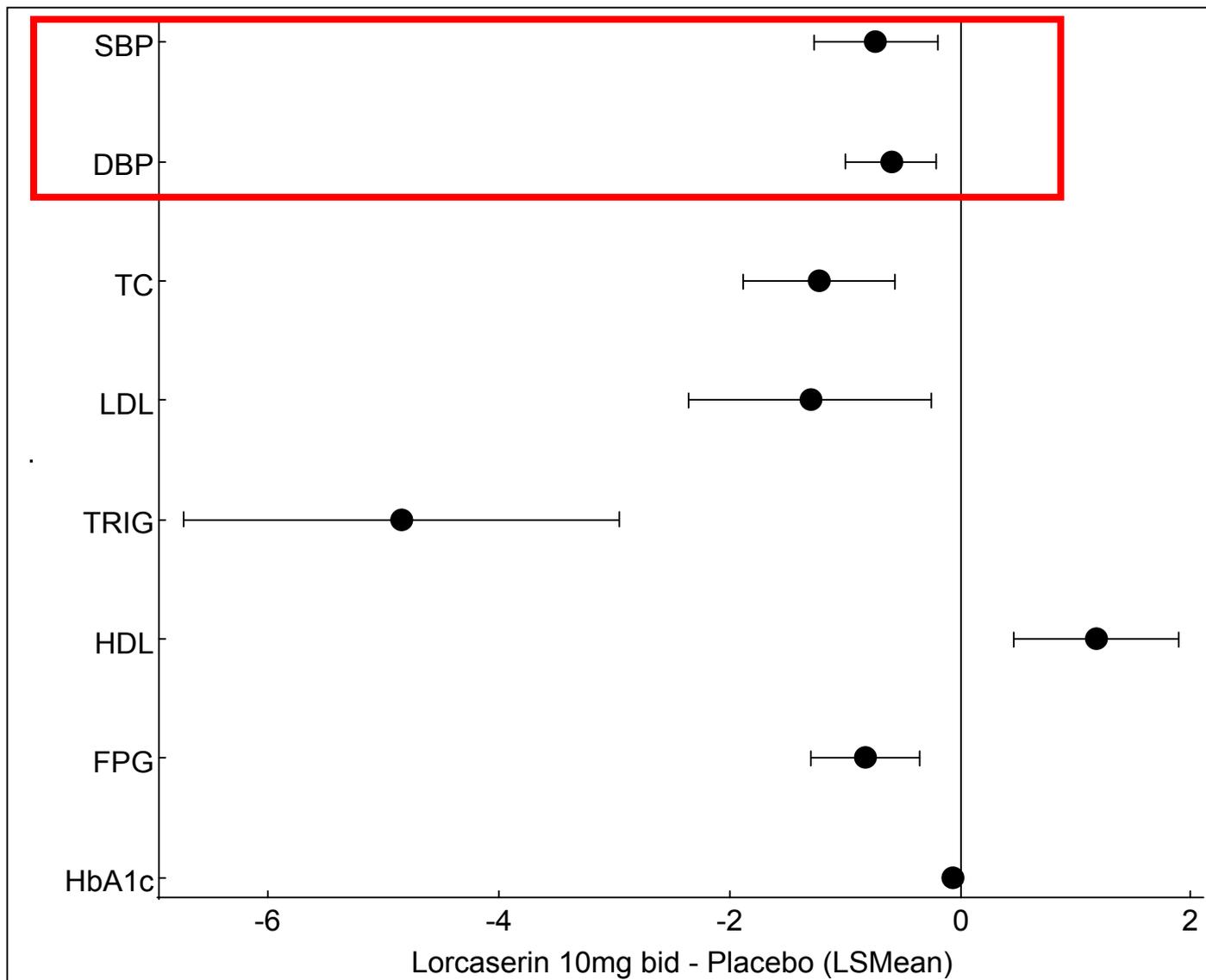
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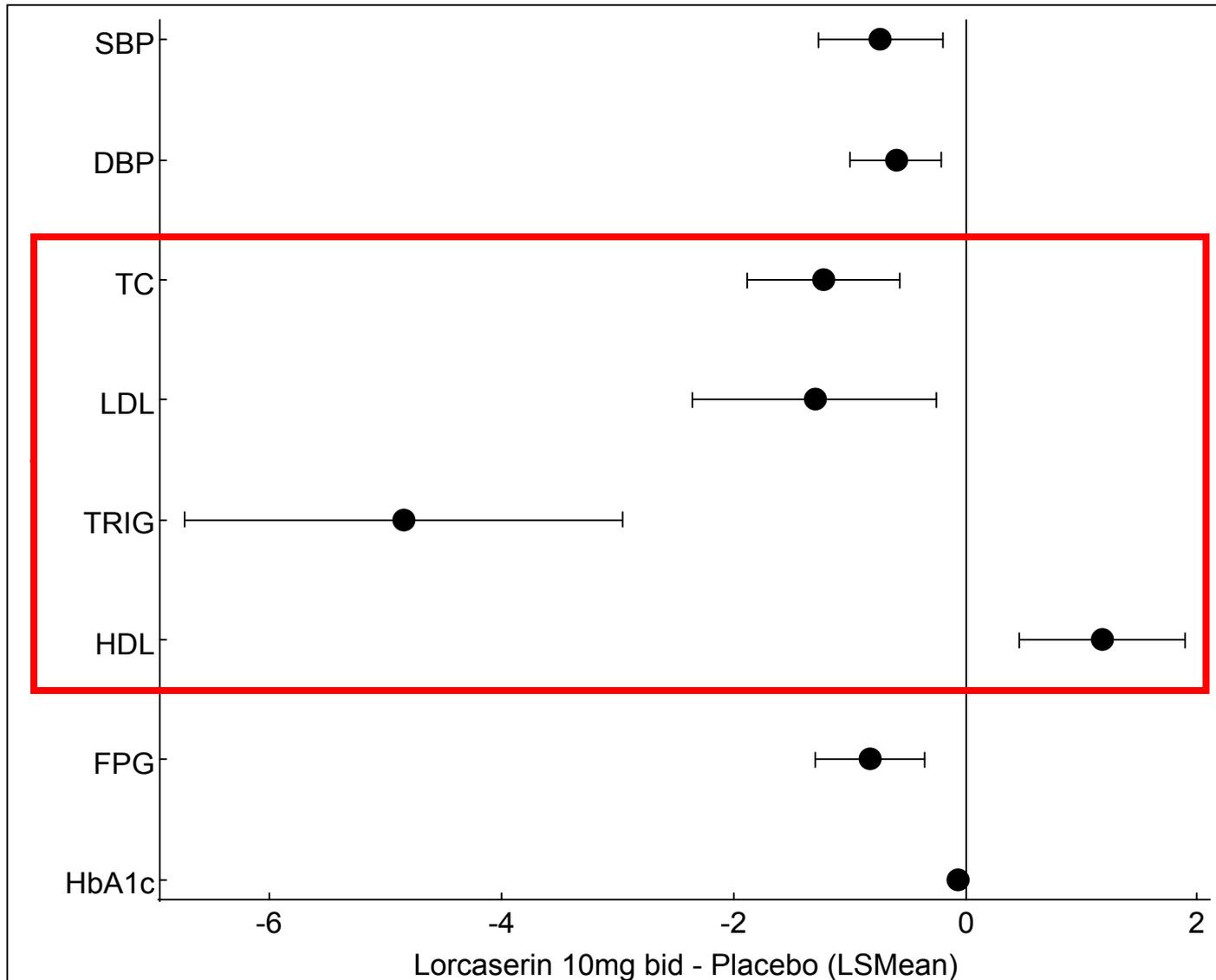
Secondary Endpoints – Week 52 MITT LOCF



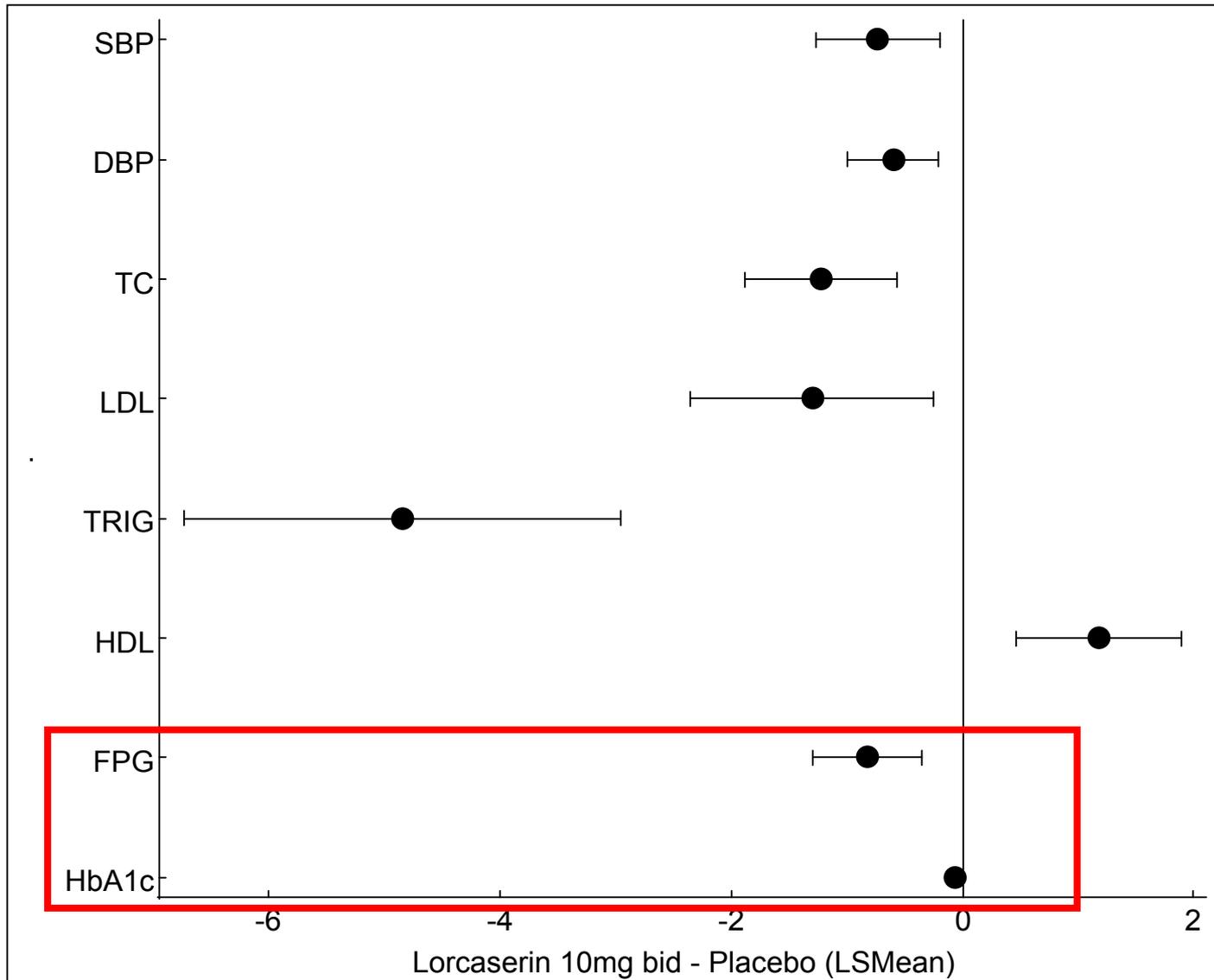
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Secondary Endpoints – Week 52 MITT LOCF



Efficacy Conclusions

- The 52 week mean weight loss difference of 3.0 - 3.7% did not meet draft guidance 5% mean weight loss criterion
- The proportion of patients treated with lorcaserin 10 mg BID who lost $\geq 5\%$ body weight met draft guidance categorical criterion
- Weight was regained in all treatment groups in Year 2 of BLOOM, with the greatest weight regain in Lorc/Pbo

Efficacy Conclusions

- Weight loss was accompanied by modest improvements in blood pressure, lipids, and glycemic parameters
- Efficacy of lorcaserin in patients with diabetes mellitus is unknown
- Impact of lorcaserin treatment on long-term cardiovascular outcomes is unknown



Safety

Safety Assessment

- Off target effects:
 - 5HT2B (heart valves)
 - 5HT2A (psychiatric and cognitive effects)
- Serotonin effects:
 - Serotonin syndrome
- Animal findings:
 - Carcinogenicity



Valvular Heart Disease

Valvular Heart Disease

- Ruling out a 50% or greater increase in the incidence of valvular heart disease (VHD) was considered to be a reasonable, albeit arbitrary initial non-inferiority margin

Phase 3 Echo Procedures

- BLOOM: Screening, weeks 24, 52, 76, 104
- BLOSSOM: Baseline, weeks 24, 52

Phase 3 Echo Procedures

- All echocardiograms read by 2 blinded readers (Reader “A” and Reader “B”) from a central pool
- Whenever possible, all echocardiograms for a single patient were read by the same primary reader
- Secondary reader assigned randomly
- When two readings “matched” results from primary reader entered into database
- A third reader adjudicated discrepant reads

FDA-Defined Valvular Heart Disease

Mitral regurgitation

- Absent
- Trace
- Mild
- Moderate
- Severe

Aortic regurgitation

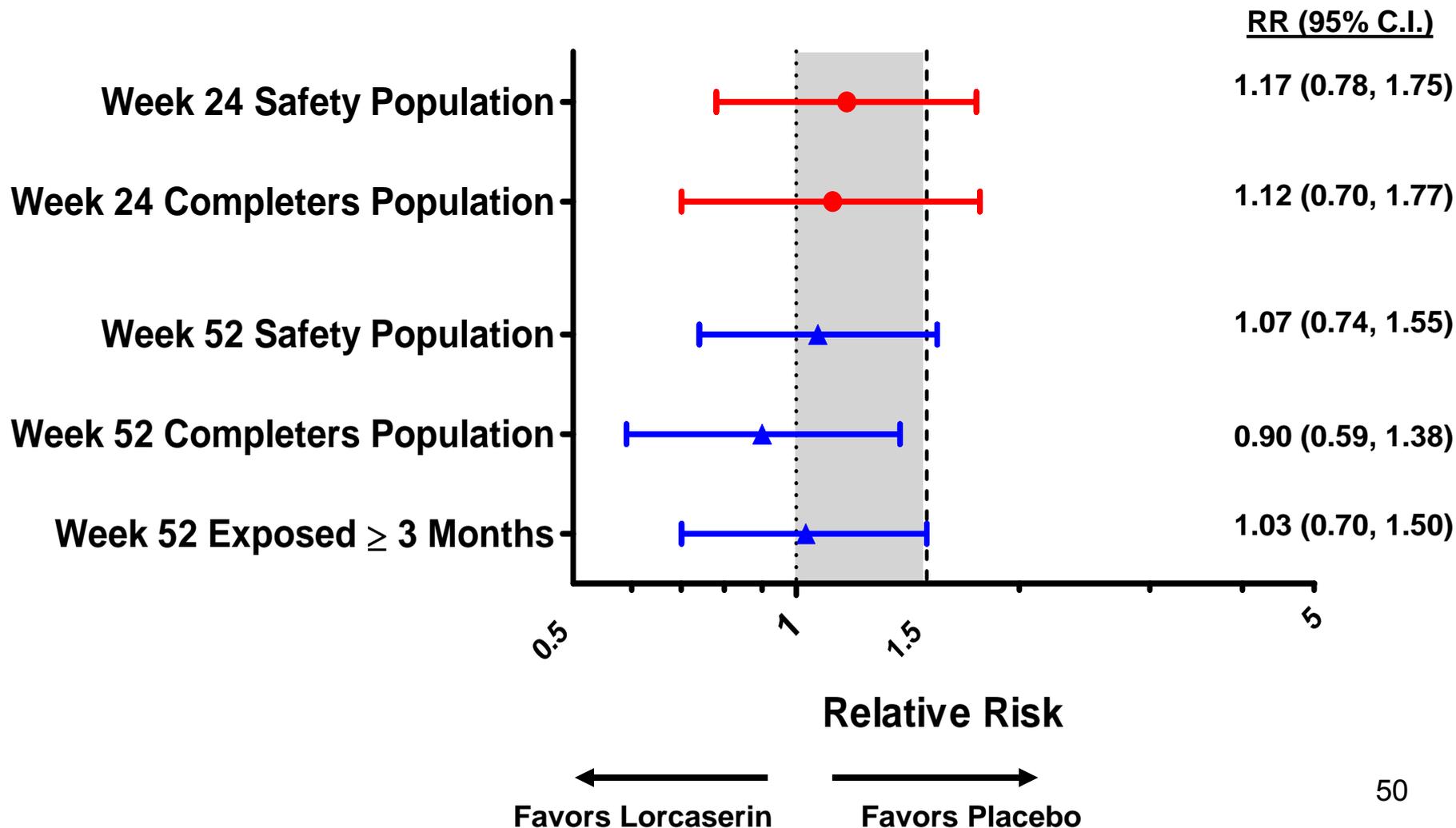
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Valvular Heart Disease

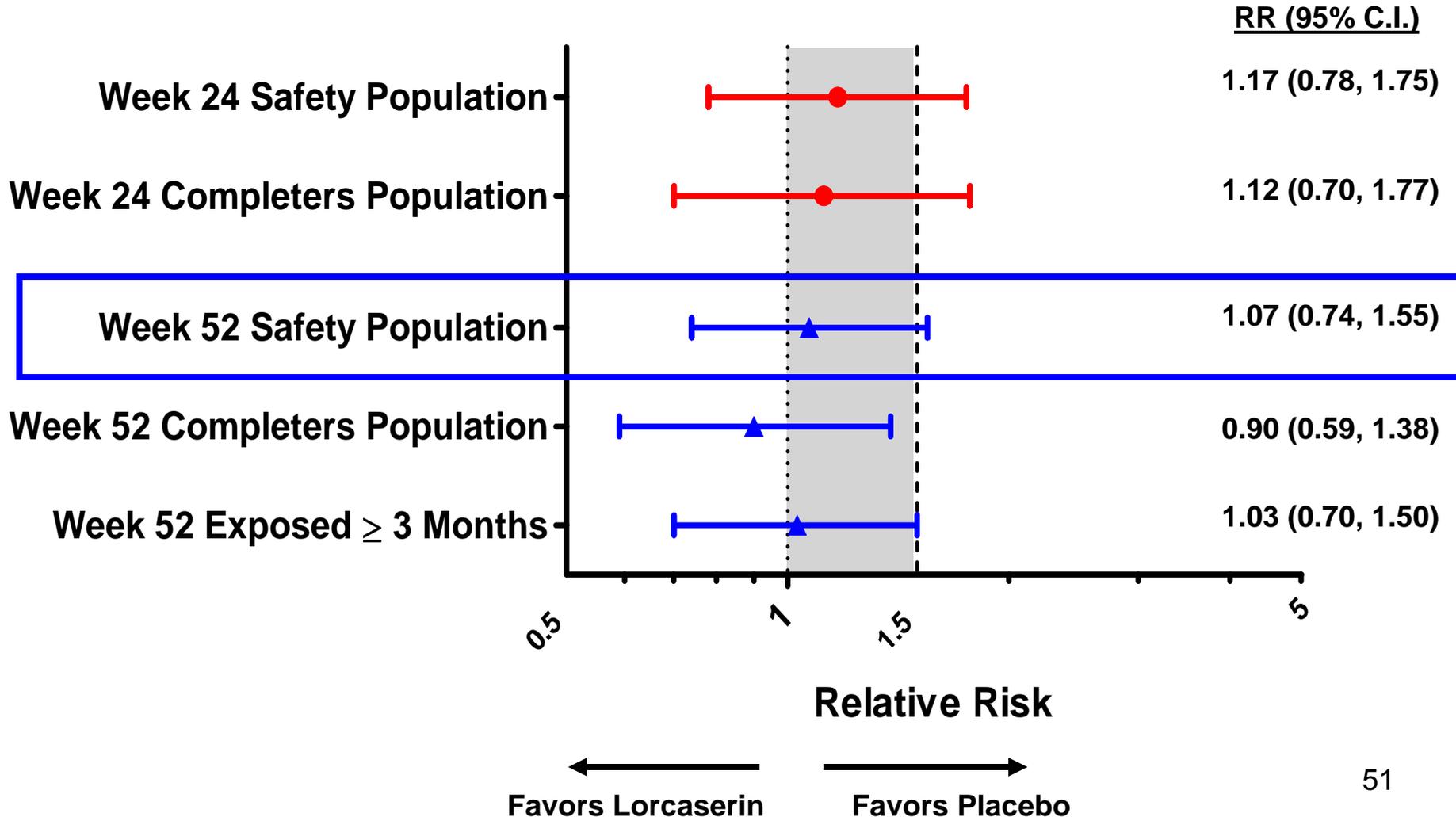
Week 52 Endpoint

- Rule out a relative risk of 1.5 of FDA-defined VHD
- Calculated from Phase 3 pooled data at Week 52 LOCF
- Included patients who discontinued from the trial but returned for a Week 52 echo
- Excluded patients with baseline FDA-defined VHD

FDA-Defined Valvular Heart Disease

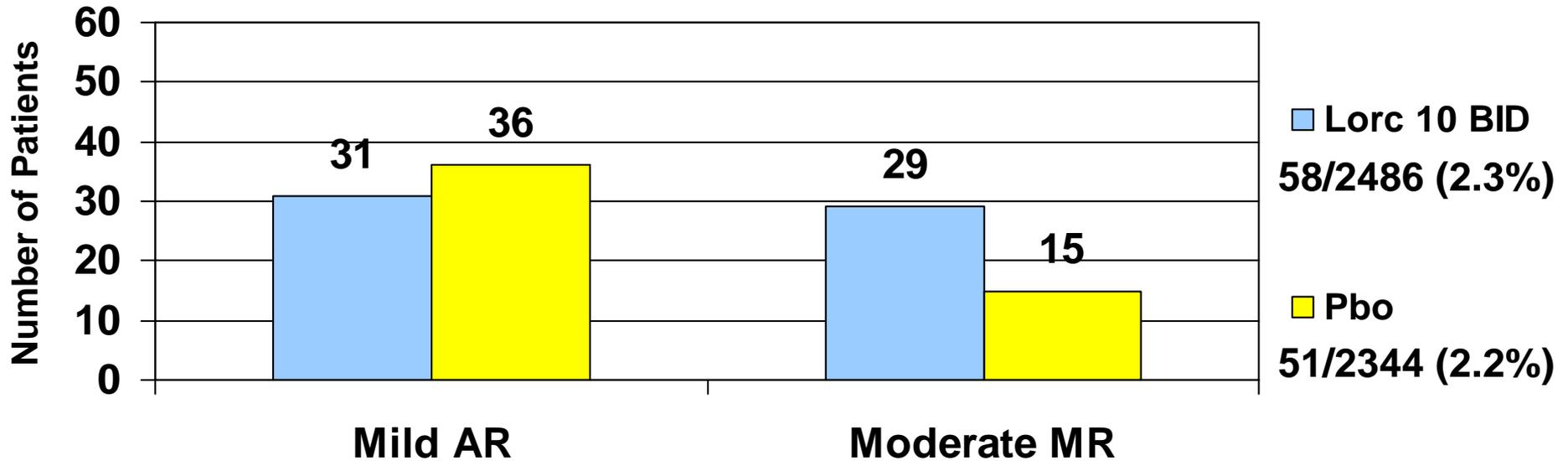


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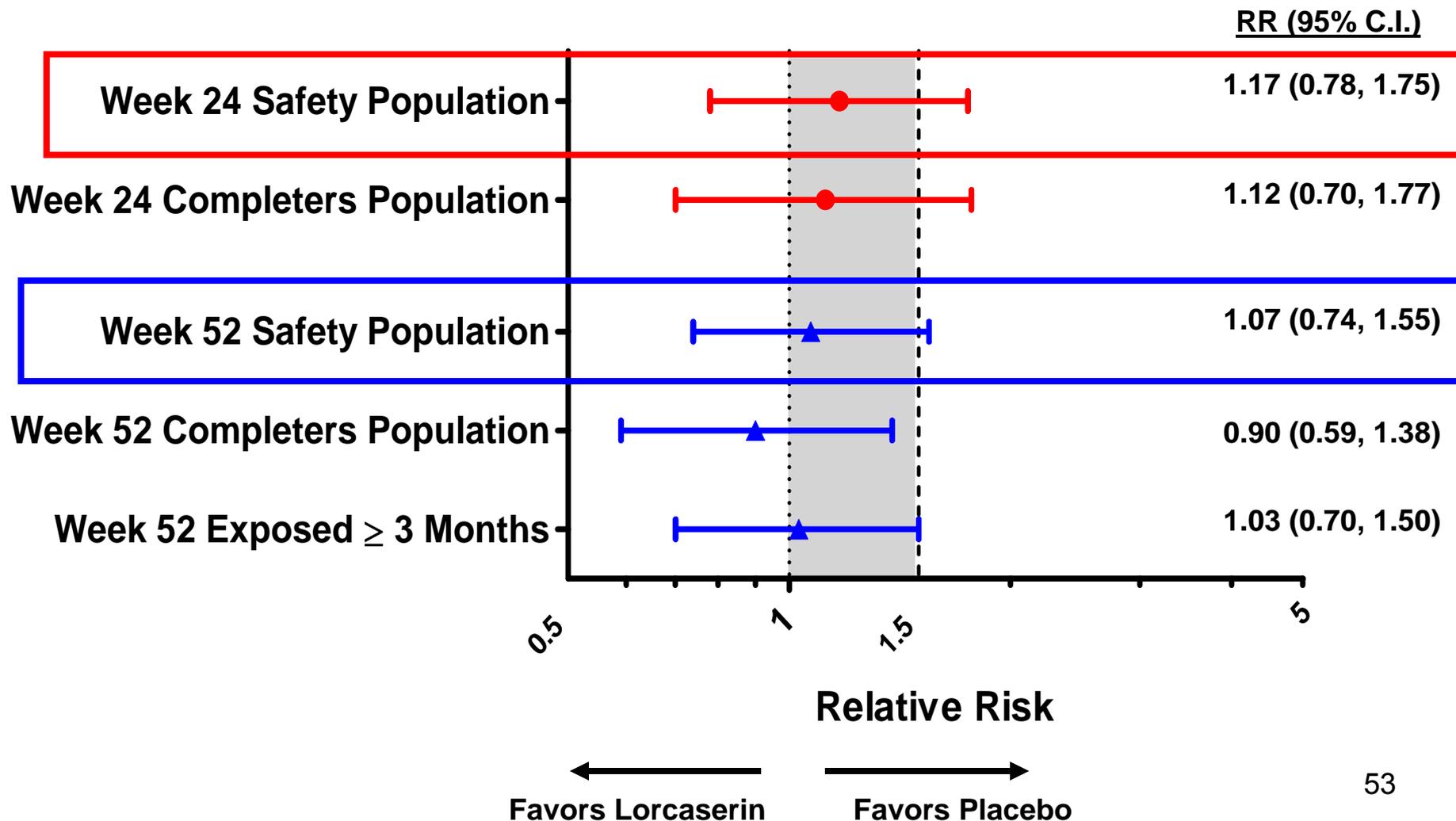


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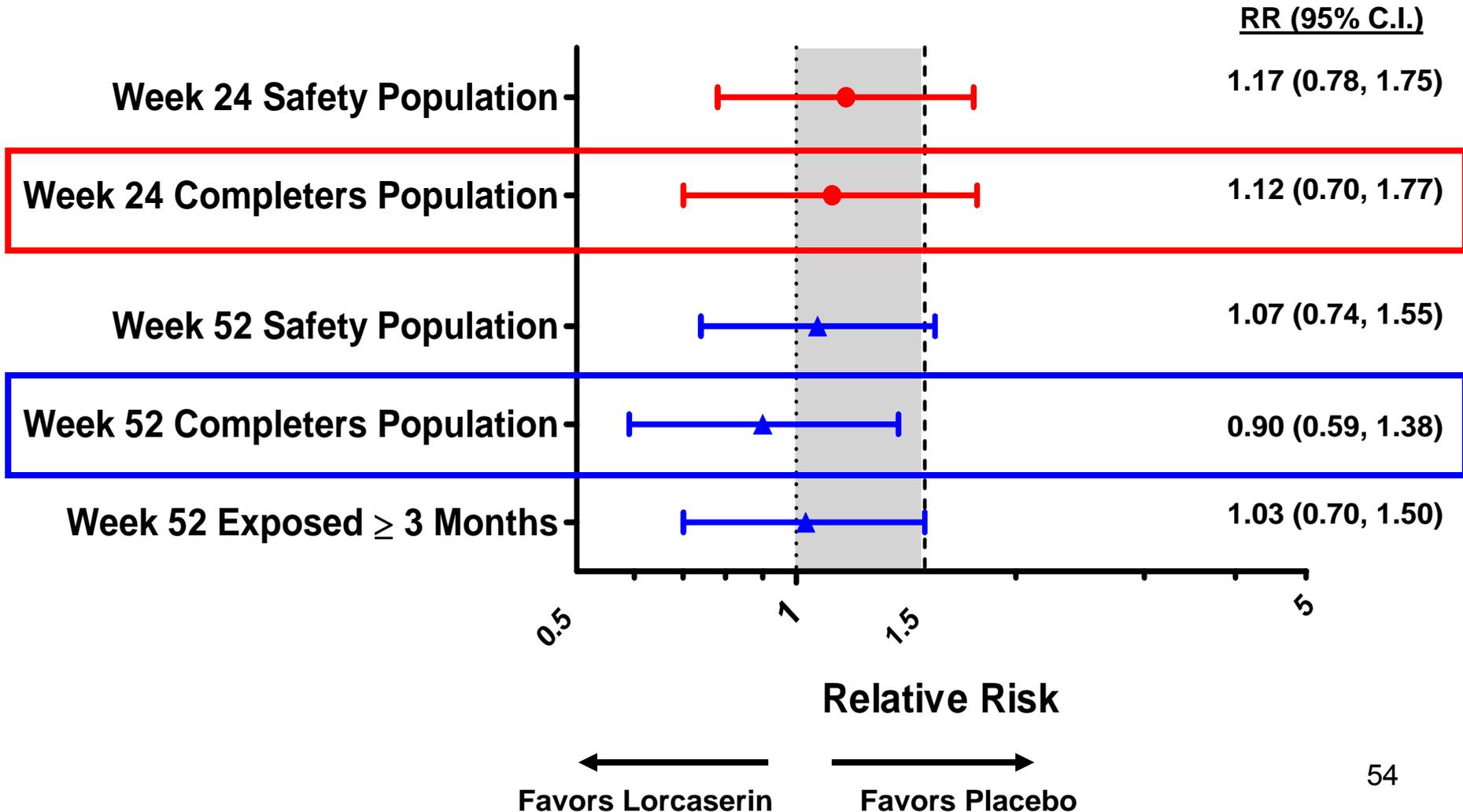
Week 52



FDA-Defined Valvular Heart Disease



FDA-Defined Valvular Heart Disease



Valvular Heart Disease

Relative Risk Week 24 > Week 52

- + VHD at Week 24 \longrightarrow premature discontinuation
- + VHD at Week 24 \longrightarrow – VHD at Week 52

Valvular Heart Disease

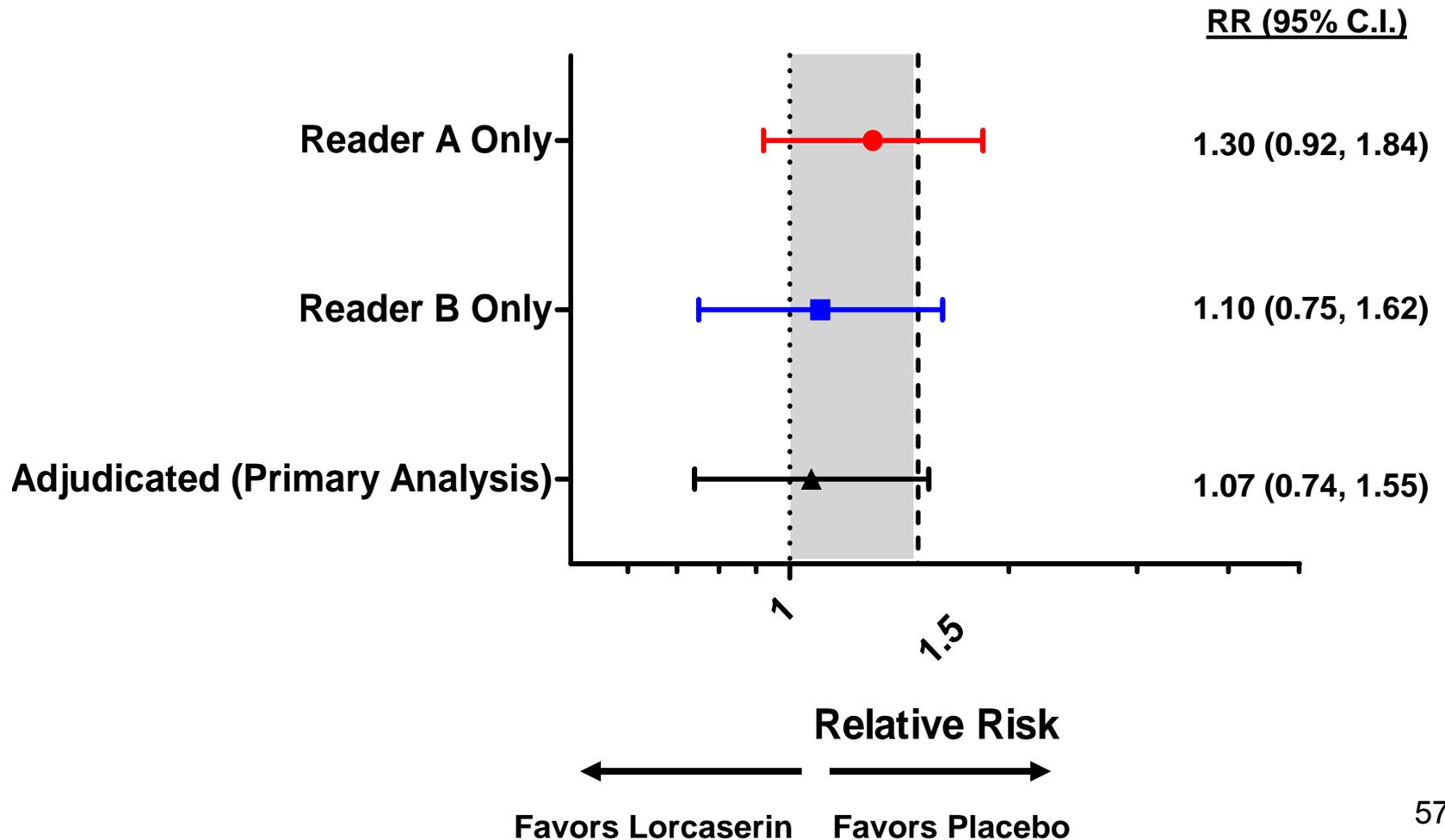
Relative Risk Week 24 > Week 52

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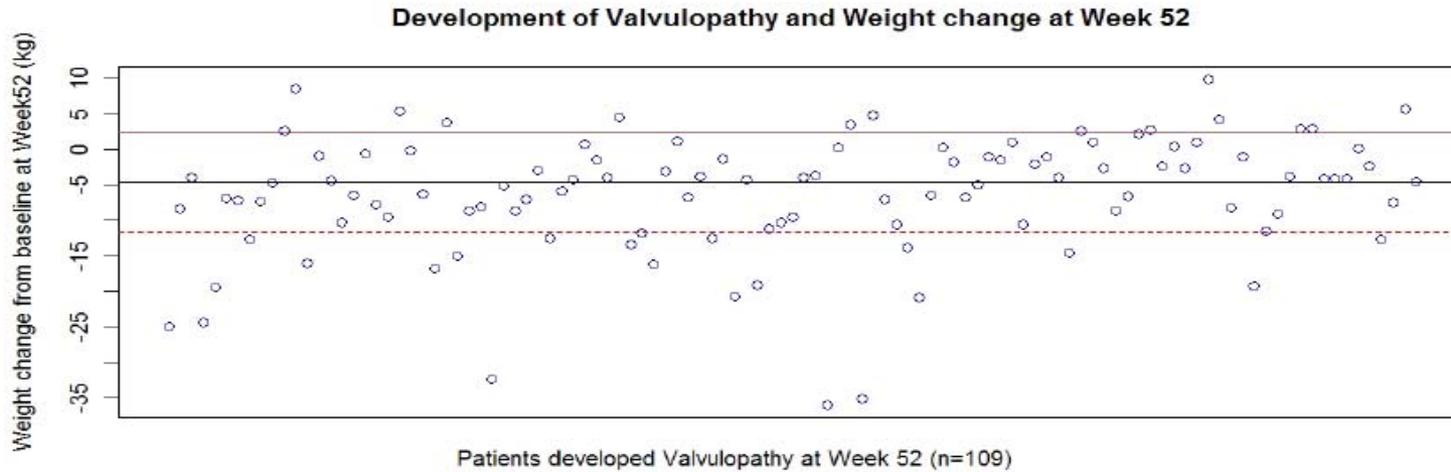
- + VHD at Week 24 → – VHD at Week 52 } “reverters”
 - 27 lorcaserin 10 mg BID / 21 placebo

- Improvement over time?
- Variability of echocardiogram acquisition?
- Impact of echocardiogram inter-reader variability?
- Impact of weight loss?

FDA-Defined Valvular Heart Disease By Reader

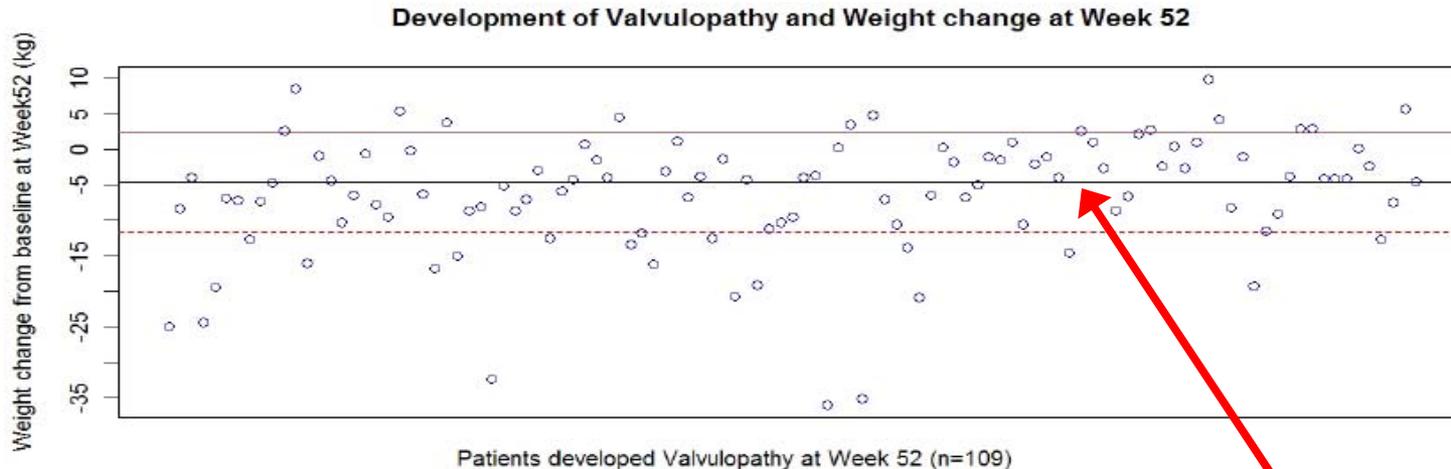


Weight Change and Development of VHD



- Mean= -4.7 kg (patients without Valvulopathy, n=4721)
- Upper (1 SD)
- Lower (1 SD)
- Weight change (Mean=-6.3 kg, patients with Valvulopathy)

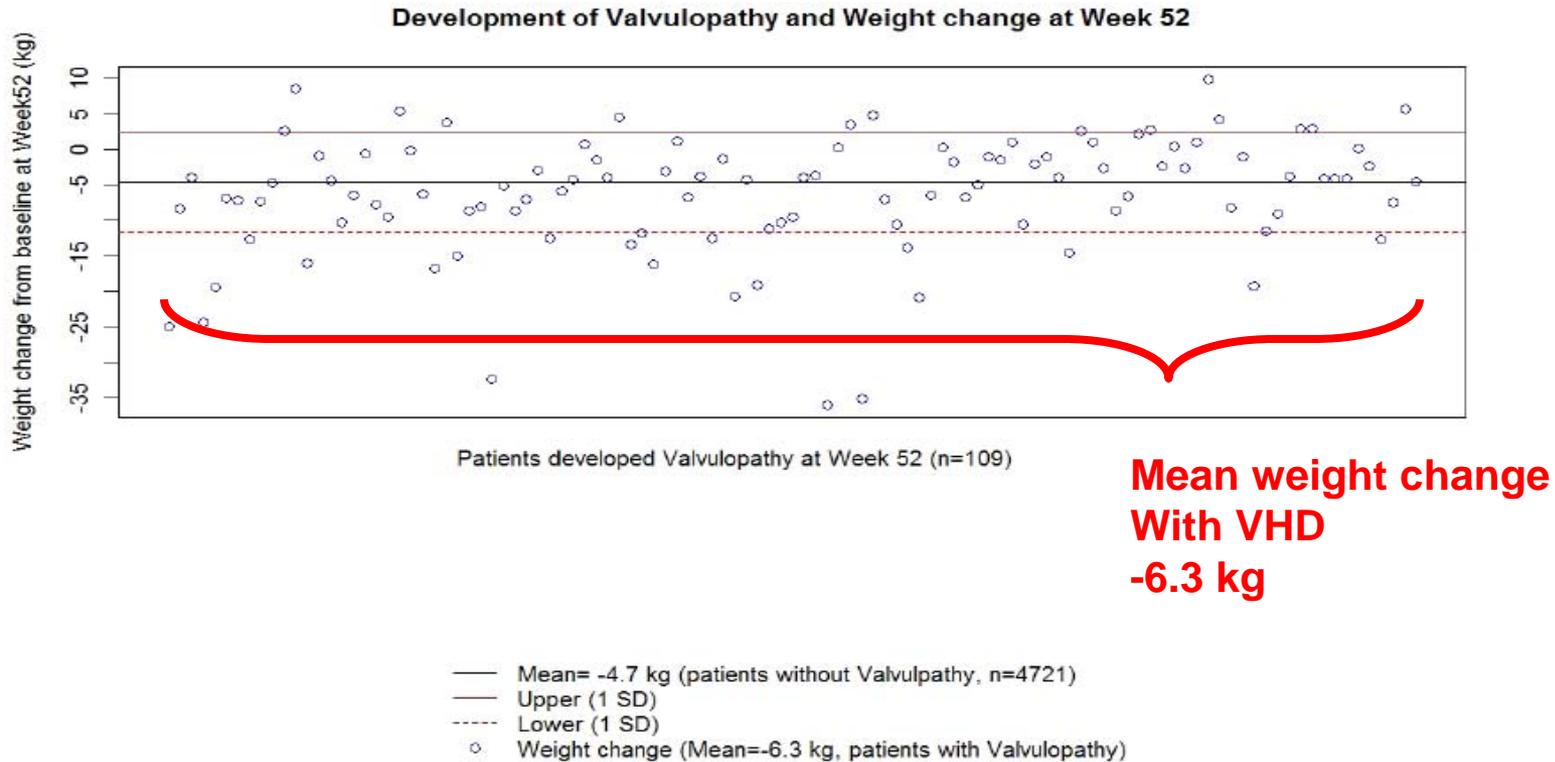
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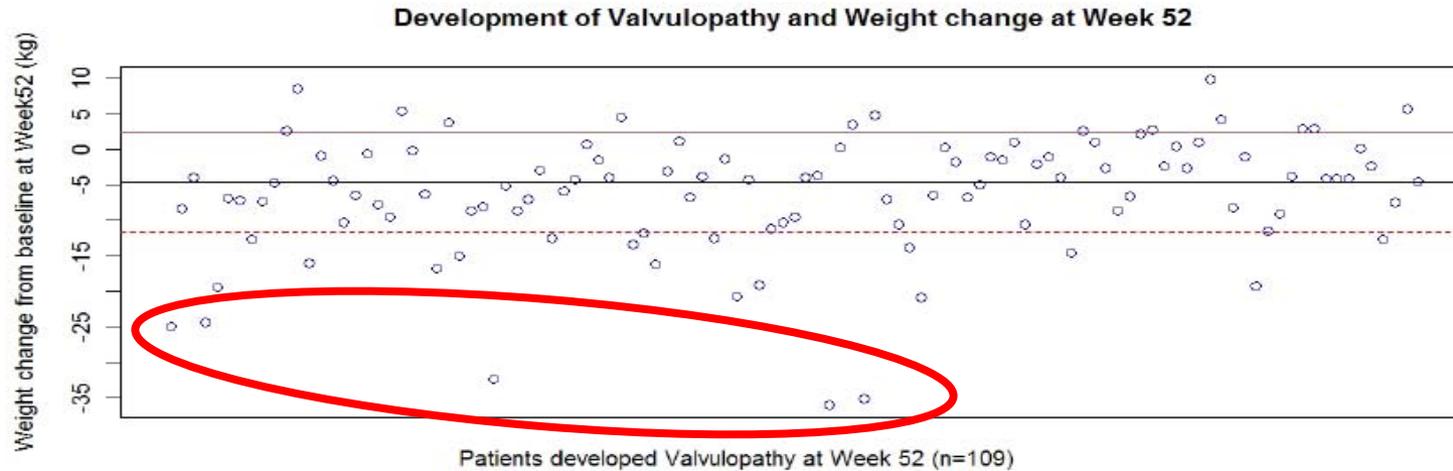
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**Mean weight change
No VHD
-4.7 kg**

Weight Change and Development of VHD

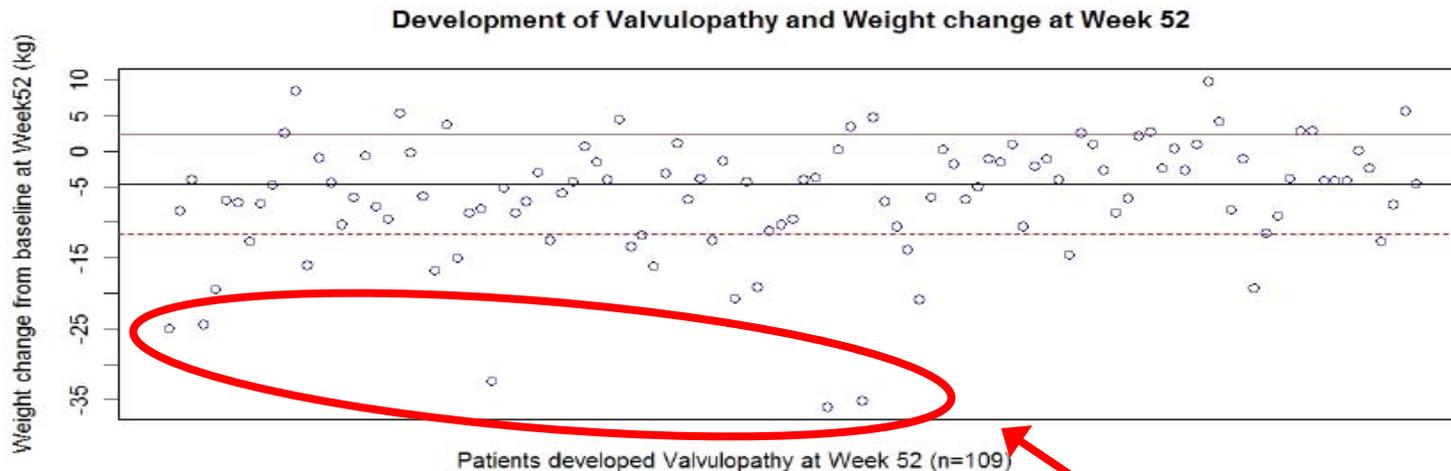


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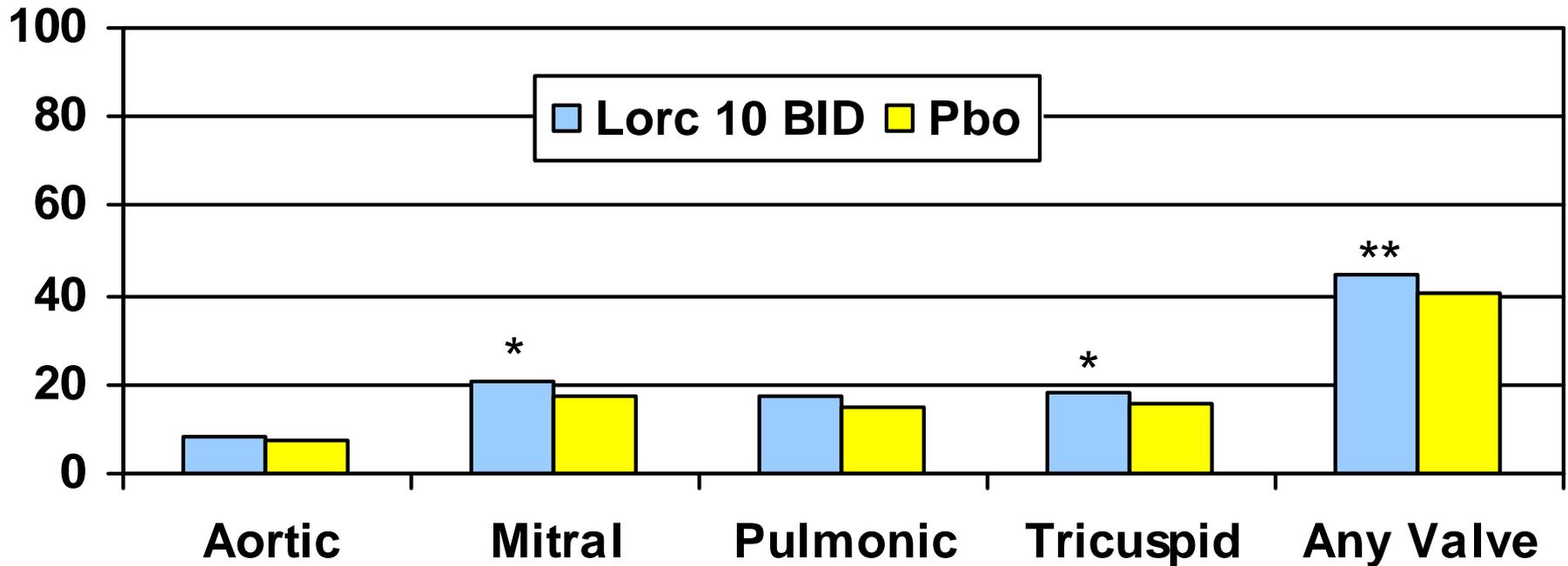
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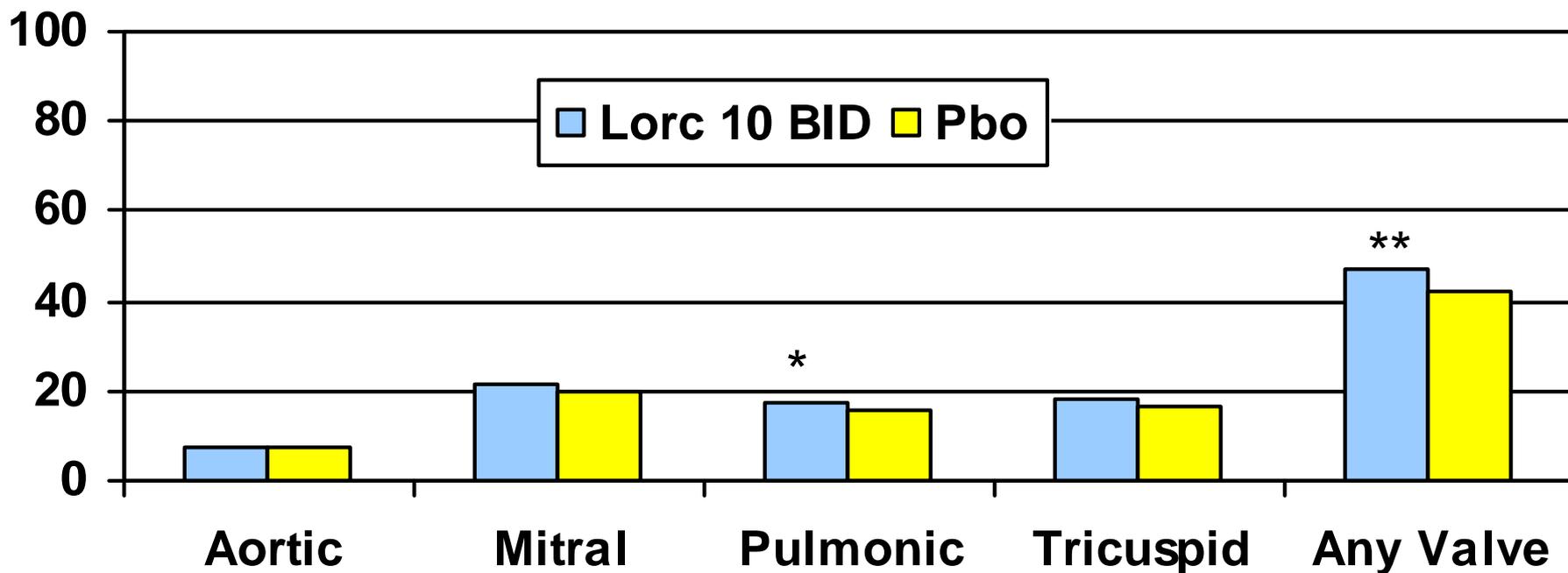
**Mean weight change
With VHD
Minus outliers
-5.1 kg**

Proportion of Patients Who Experienced Any Increase from Baseline in Valvular Regurgitation at Week 24



* p < 0.05 ** p < 0.01

Proportion of Patients Who Experienced Any Increase from Baseline in Valvular Regurgitation at Week 52



* p < 0.05 ** p < 0.01

Conclusions: Valvular Heart Disease

- The pooled analysis failed to demonstrate that lorcaserin was non-inferior (i.e., RR 95% C.I. upper bound < 1.5) to placebo for the risk of developing FDA-defined VHD at 52 weeks
- Lorcaserin is associated with small, but in some cases statistically significant increases in valvular regurgitation vs. placebo



Depression and Suicidality

Depression/Suicidality

- Concern for centrally-acting obesity drugs and suicide risk arose out of the rimonabant experience
- Current recommendations:
 - Psychiatric screening and monitoring in Phase 2 and 3 trials of centrally-acting obesity drugs
 - Exclusion criteria may be loosened in later phases of development if supported by safety
 - Post-approval trials in populations with psychiatric histories may be appropriate

Depression: BDI-II

- Widely-used instrument for measuring the severity of depression
- Self-report
- 21 questions, each scored 0 to 3
- Cutoffs:
 - 0–13: none to minimal depression
 - 14–19: mild depression
 - 20–28: moderate depression
 - 29–63: severe depression

Depression/Suicidality

- Exclusion criteria
 - Major depression, anxiety, or other psychiatric disease requiring treatment with Rx medication within past 2 yrs (BLOOM) / 1 yr (BLOSSOM)
 - BDI-II total score ≥ 20
 - BDI-II question 9 score > 0
- Baseline BDI-II score ~ 4

Depression

- Narrow SMQ
 - Depression
 - Depressed mood
 - Depressive symptom
 - Major depression
 - Decreased interest
 - Dysthymic disorder
 - Feeling of despair
- Broad SMQ
 - Memory impairment
 - Disturbance in attention
 - Initial insomnia
 - Hypersomnia
 - Crying
 - Mood swings
 - Mood altered
 - Affect lability
 - Psychomotor hyperactivity
 - Poor quality sleep
 - Apathy
 - Psychomotor retardation
 - Terminal insomnia
 - Middle insomnia
 - Dyssomnia

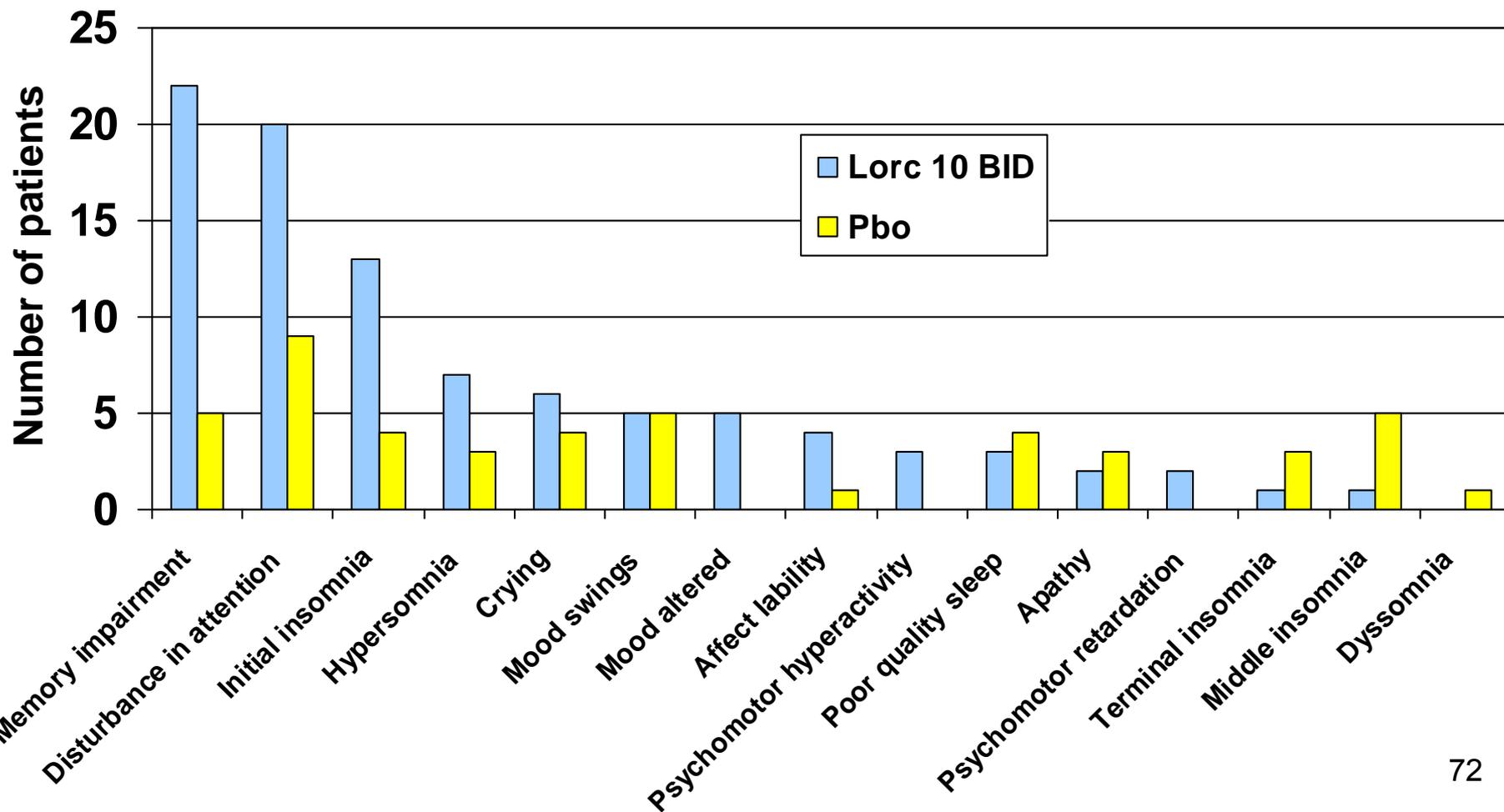
Depression Adverse Events

Year 1

	Lorc 10 BID N=3195	Lorc 10 QD N=801	Pbo N=3185
Narrow SMQ	81 (2.5)	17 (2.1)	78 (2.4)
Broad SMQ	86 (2.7)	15 (1.9)	44 (1.4)
SAEs*	5 (0.2)	0	0
DAEs	42 (1.3)	6 (0.7)	24 (0.8)

***Includes SAEs of suicidality, depression, nervous breakdown, and psychiatric crisis**

Broad Depression SMQ



BDI-II

- **BLOOM**
 - Year 1: Screening and Weeks 4, 12, 24, 36, and 52/exit
 - Year 2: Weeks 64, 76, 88, and 104/exit
- **BLOSSOM**
 - Screening and Weeks 4, 24, and 52/exit



BDI-II: Categorical Total Score

Week 52, LOCF

	BLOOM		BLOSSOM	
	Pbo	Lorc 10 BID	Pbo	Lorc 10 BID
Severe Depression (score: 29 – 63)	2 (0.1%)	4 (0.3%)	2 (0.1%)	6 (0.4%)
Moderate Depression (score: 20 – 28)	19 (1.2%)	15 (0.9%)	15 (0.9%)	9 (0.6%)
Mild Depression (score: 13 – 19)	35 (2.2%)	35 (2.2%)	36 (2.3%)	40 (2.5%)
None to Minimal Depression (score: 0 – 13)	1372 (86.6%)	1423 (89.3%)	1433 (89.5%)	1455 (90.8%)
Unknown	156 (9.9%)	116 (7.3%)	115 (7.2%)	92 (5.7%) 74



BDI-II: Categorical Total Score

Week 52, LOCF

	BLOOM		BLOSSOM	
	Pbo	Lorc 10 BID	Pbo	Lorc 10 BID
Severe Depression (score: 29 – 63)	2 (0.1%)	4 (0.3%)	2 (0.1%)	6 (0.4%)
Moderate Depression (score: 20 – 28)	19 (1.2%)	15 (0.9%)	15 (0.9%)	9 (0.6%)
Mild Depression (score: 13 – 19)	35 (2.2%)	35 (2.2%)	36 (2.3%)	40 (2.5%)
None to Minimal Depression (score: 0 – 13)	1372 (86.6%)	1423 (89.3%)	1433 (89.5%)	1455 (90.8%)
Unknown	156 (9.9%)	116 (7.3%)	115 (7.2%)	92 (5.7%)



BDI-II: Categorical Total Score

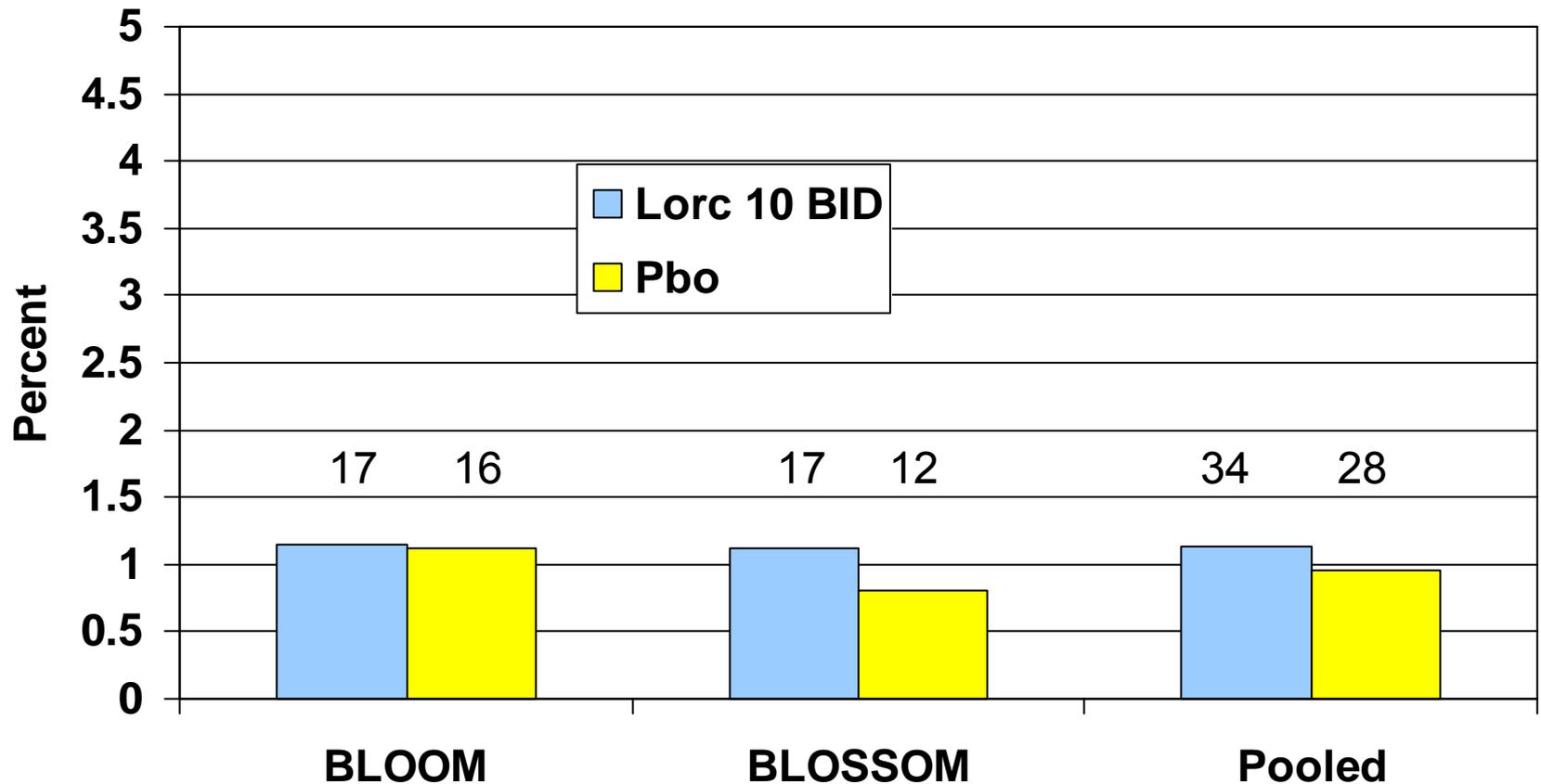
Week 52, LOCF

	BLOOM		BLOSSOM	
	Pbo	Lorc 10 BID	Pbo	Lorc 10 BID
Severe Depression (score: 29 – 63)	2 (0.1%)	4 (0.3%)	2 (0.1%)	6 (0.4%)
Moderate Depression (score: 20 – 28)	19 (1.2%)	15 (0.9%)	15 (0.9%)	9 (0.6%)
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None to Minimal Depression (score: 0 – 13)	1372 (86.6%)	1423 (89.3%)	1433 (89.5%)	1455 (90.8%)
Unknown	156 (9.9%)	116 (7.3%)	115 (7.2%)	92 (5.7%)

Suicidality

- Suicidality evaluated in the lorcaserin trials using suicide question in the BDI-II (question 9) and reviewing adverse events
- Question 9 on the BDI-II specifically asked patients to rate their degree of suicidal thoughts or wishes on the following scale:
 - 0 I don't have any thoughts of killing myself
 - 1 I have thoughts of killing myself, but I would not carry them out
 - 2 I would like to kill myself
 - 3 I would kill myself if I had the chance

Suicidality: BDI-II question 9 score > 0 Year 1



Suicide/Self-Injury SMQ

Year 1, Pooled

	Lorc 10 BID N=3195	Lorc 10 QD N=801	Pbo N=3185
Total	19 (0.6)	6 (0.7)	14 (0.4)
Suicidal ideation	18 (0.6)	5 (0.6)	13 (0.4)
Self-injurious ideation	0	0	1 (<0.1)
Suicide attempt	1 (<0.1)	0	0
Depression suicidal	0	1 (0.1)	0

Suicide/Self-Injury SMQ

Year 1, Pooled

	Lorc 10 BID N=3195	Lorc 10 QD N=801	Pbo N=3185
Total	19 (0.6)	6 (0.7)	14 (0.4)
Suicidal ideation	18 (0.6)	5 (0.6)	13 (0.4)
Self-injurious ideation	0	0	1 (<0.1)
Suicide attempt	1 (<0.1)	0	0
Depression suicidal	0	1 (0.1)	0

Suicide/Self-Injury SMQ

Year 2, BLOOM

	Lorc/Lorc N=573	Lorc/Pbo N=283	Pbo/Pbo N=697
Total	1 (0.2)	1 (0.4)	0
Suicidal ideation	1 (0.2)	1 (0.4)	0
Intentional overdose	0	1 (0.4)	0

Suicide/Self-Injury SMQ

Year 2, BLOOM

	Lorc/Lorc N=573	Lorc/Pbo N=283	Pbo/Pbo N=697
Total	1 (0.2)	1 (0.4)	0
Suicidal ideation	1 (0.2)	1 (0.4)	0
Intentional overdose	0	1 (0.4)	0

Suicidal Behavior

- **Patient 180-S141: lorcaserin 10 mg BID**
 - 36-year-old WF
 - Medical history: migraines
 - Attempted suicide by ingesting husband's metformin, Lipitor, and antihypertensive medications on 2 consecutive evenings (Study Days 106 and 107)
 - Hospitalized; treated with trazodone and fluoxetine; study drug discontinued; withdrawn from study
 - Told husband she had been “feeling low” ~3-4 weeks prior to the event
 - Patient's husband reported that she had been recently fired from her job due to embezzlement of company funds past 2-3 months; “totally out of character”

Suicidal Behavior

- **Patient 145-S044: Lorc / Pbo**
 - 48-year-old WF
 - No history of depression or other mental health problems
 - AE of depression was reported on Study Day 491
 - Study Day 495, attempted suicide (PT: intentional overdose) by ingesting ibuprofen, levothyroxine, and cyclobenzaprine
 - Hospitalized; treated with venlafaxine; study drug discontinued; withdrawn from study
 - Evening of the event reported drinking alcohol but not intoxicated
 - Upsetting conversation made her feel bad about herself and decided to commit suicide

Conclusions:

Depression and Suicidality

- Depression
 - More depression AEs in the lorcaserin group were considered serious or led to study drug discontinuation
 - Lorcaserin associated with non-specific depression symptoms (broad SMQ)
 - BDI-II inconclusive
- Suicidality
 - Prospective monitoring limited to single question on BDI-II
 - More patients randomized to lorc 10 mg BID answered positively to question 9 or experienced suicidality AEs⁸⁵



Cognitive-Related Events

Cognitive-Related Preferred Terms of Interest

- Amnesia
- Aphasia
- Apraxia
- Cognitive disorder
- Confusional state
- Disorientation
- Disturbance in attention
- Dysphasia
- Memory impairment
- Mental disorder
- Mental impairment
- Psychomotor retardation
- Speech disorder

Cognitive-Related AEs, Pooled Phase 3 Trials

	Lorc 10 BID N=3195	Lorc 10 QD N=801	Pbo N=3185
Total	76 (2.4)	7 (0.9)	24 (0.8)
Memory impairment	22 (0.7)	0	5 (0.2)
Disturbance in attention	20 (0.6)	2 (0.2)	9 (0.3)
Amnesia	16 (0.5)	2 (0.2)	3 (0.1)
Confusional state	6 (0.2)	2 (0.2)	1 (<0.1)

Cognitive-Related AEs, Pooled Phase 3 Trials

	Lorc 10 BID N=3195	Lorc 10 QD N=801	Pbo N=3185
Cognitive DAEs	15 (0.5)	3 (0.4)	3 (0.1)
Cognitive AEs leading to study drug interruption	4 (0.1)	0	1 (<0.1)
“Ongoing” cognitive AEs	13 (0.4)	1 (0.1)	3 (0.1)

Conclusions:

Cognitive Adverse Events

- Cognitive AEs in lorcaserin 10 mg BID 3x placebo
- Cognitive DAEs/interruptions in lorcaserin 10 mg BID 4-5x placebo
- “Ongoing” cognitive AEs in lorcaserin 10 mg BID 4x placebo; however, majority of cognitive AEs resolved on drug



Potential Serotonin-Related Adverse Events

Serotonin Syndrome

- Excess serotonergic agonism at CNS and peripheral receptors
- Mental status changes, autonomic hyperactivity, and neuromuscular abnormalities
- Spectrum of clinical findings: “Signs of excess serotonin range from tremor and diarrhea in mild cases to delirium, neuromuscular rigidity, and hyperthermia in life-threatening cases.”

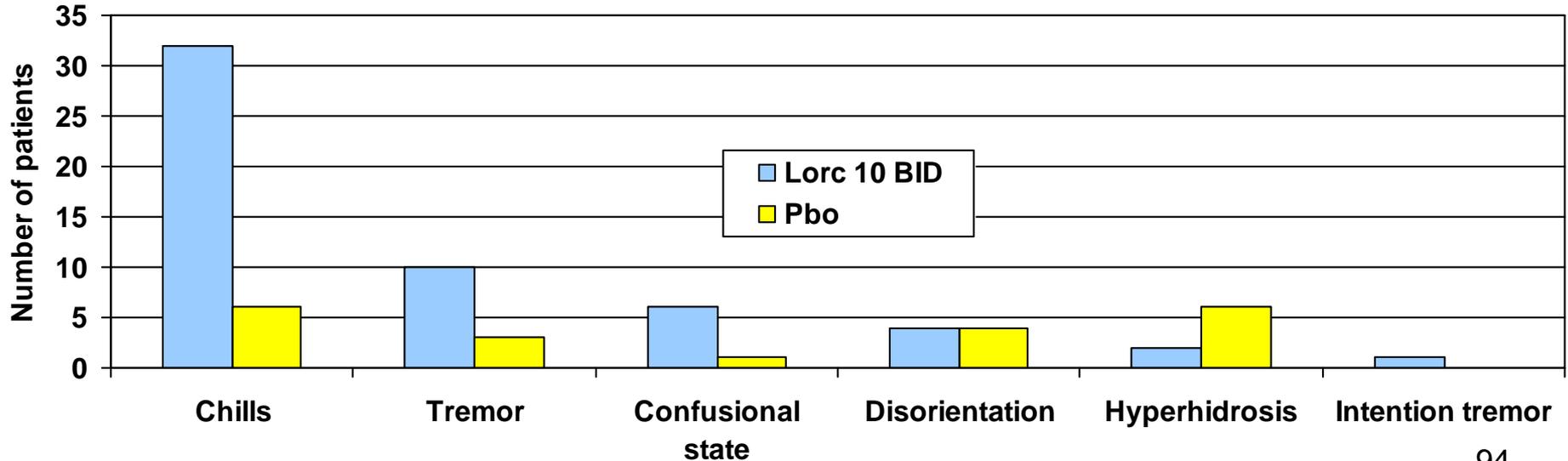
Serotonin Syndrome

Concomitant Medications – Phase 3

- Triptans and dextromethorphan permitted
 - Triptans: 2%
 - Dextromethorphan: 12%
- Other serotonergic drugs excluded: SSRIs, bupropion, and tricyclics
 - SSRIs: 0.9%
 - Bupropion: 0.2%
 - Other tricyclics: 0.1%

Potential Serotonin-Related Adverse Events

	Lorc 10 BID N=3195	Lorc 10 QD N=801	Pbo N=3185
Serotonin-Related AEs	55 (1.7)	13 (1.6)	18 (0.6)



Potential Serotonin-Related Adverse Events

- AE attributed to possible serotonin toxicity in Phase 2 trial
 - 44 yo WF (lorcaserin 10 mg BID) experienced a constellation of symptoms that included tremor, palpitations, headache, and vomiting on Study Days 1 and 5
- AE of “serotonin syndrome” in BLOSSOM
 - 29 yo WF (lorcaserin 10 mg BID) with vertigo, nausea, vomiting, diarrhea with some minor blood spots in stools, and a BP increase to 135/105 after concomitant treatment with dextromethorphan

Conclusions:

Potential Serotonin-Related Adverse Events

- The imbalance of potential serotonin-related AEs seen in the lorcaserin Phase 3 program was primarily due to chills and tremor
- As with any serotonergic agent, serotonin syndrome remains a theoretical concern



Breast Neoplasms and Prolactin

Breast Neoplasms and Prolactin

- Lorcaserin-related increase in mammary tumors in the rat carcinogenicity study
- Potential for a prolactin-mediated cause of mammary tumors in rats suggested by sponsor
- Prolactin acutely increased via 5HT_{2C} activation



Breast Neoplasms

Treatment	ID	AE Term
Lorc 10 BID	117-S033	Ductal carcinoma <i>in situ</i>
	122-S109	Atypical ductal hyperplasia
	146-S015	Left breast cancer
	170-S005	Tubular cancer, left breast
	196-S018	Breast cancer
	2105-S070	Breast cancer
	2270-S040	Breast cancer
Lorc 10 QD	2141-S039	Ductal carcinoma <i>in situ</i>
Pbo	113-S228	Breast cancer
	119-S064	Invasive ductal carcinoma with mucinous differentiation
	139-S043	Left breast cancer
	161-S087	Breast cancer
	2203-S032	Intraductal papilloma of breast

Prolactin

- Normal prolactin range: **2.5-17 ng/mL** in men and **1.9-25 ng/mL** in women
- Peak values ~ 2-3 x nadir
- Symptomatic hyperprolactinemia with antipsychotic medications usually associated with prolactin 5-10 x ULN

Prolactin

- Measured in a BLOSSOM substudy
- Pre-dose
 - Baseline and Week 4, 12, 24, and 52/ET
- 2 h post-dose
 - Baseline and Week 4, 12, 24, and 52/ET



Prolactin

% Patients with Increase in at Least 1 Quartile from Pre-dose to 2 hrs Post-dose

	Lorc 10 BID N=3195	Lorc 10 QD N=801	Pbo N=3185
Baseline	26%	19%	6%
Week 4	24%	19%	16%
Week 12	29%	23%	16%
Week 24	27%	24%	20%
Week 52	31%	25%	16%

Prolactin

% Patients with Increase in at Least 1 Quartile from Baseline to Post-baseline

	Lorc 10 BID N=3195	Lorc 10 QD N=801	Pbo N=3185
Week 4	24%	26%	24%
Week 12	27%	29%	26%
Week 24	28%	21%	29%
Week 52	33%	25%	30%

Conclusions:

Breast Neoplasms and Prolactin

- An increased risk of breast cancer not identified in the Phase 3 trials
- Prolactin is increased acutely, but does not appear to be associated with chronic increases



Abuse-Related Adverse Events

Abuse-Related AEs

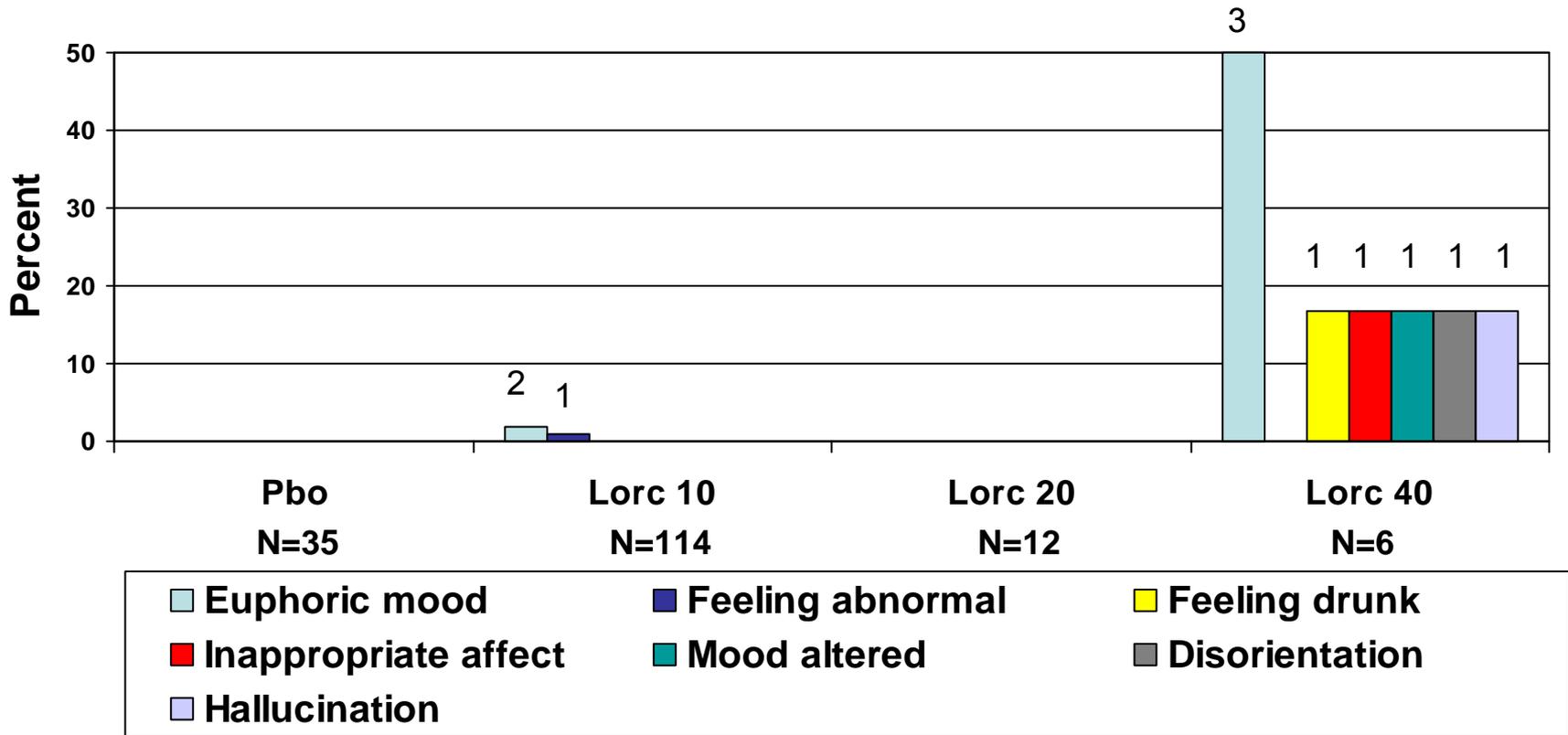
- Certain schedule I hallucinogens, such as LSD are 5HT_{2C} and 5HT_{2A} agonists
- Lorcaserin is also a 5HT_{2C} and 5HT_{2A} receptor agonist

Abuse-Related AEs: Preferred and Verbatim Terms

- **Euphoria-related terms**
 - Euphoric mood
 - Elevated mood
 - Feeling abnormal
 - Feeling drunk
 - Feeling of relaxation
 - Dizziness
 - Thinking abnormal
 - Hallucination
 - Inappropriate affect
- **Terms indicative of impaired attention, cognition, mood, and psychomotor events**
 - Somnolence
 - Mood disorders and disturbances
 - Mental impairment disorders
 - Drug tolerance, Habituation, Drug withdrawal syndrome, Substance-related disorders
- **Dissociative/psychotic terms**
 - Psychosis
 - Aggression
 - Confusion and disorientation

Abuse-Related Adverse Events

Single Dose Studies, Healthy Participants



Abuse-Related Adverse Events

Participant 25, Study APD356-001a

48 yo WF, Lorcaserin 40 mg

- 8:52 am dosed
- 9:33-10:05 euphoria, moderate
- 9:40-12:00 disorientation, severe
- 9:40-12:30 feeling drunk, moderate
- 9:59-11:45 feeling abnormal, moderate
- 10:00-11:55 crying, moderate
- 10:20-10:30 hallucination, severe

Analyte	Tmax (h)	Cmax (ng/mL)
Lorcaserin	1.50	176.90

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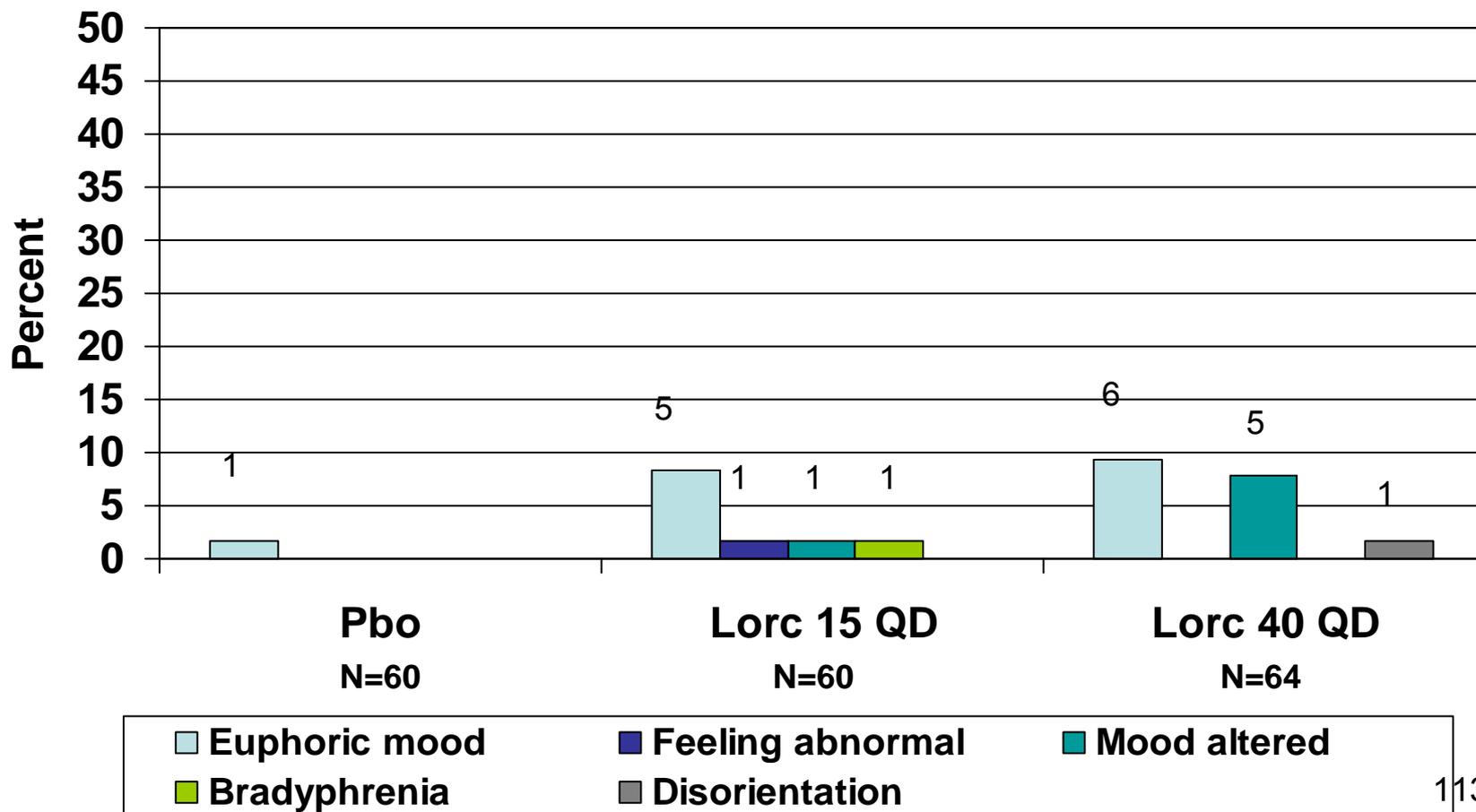
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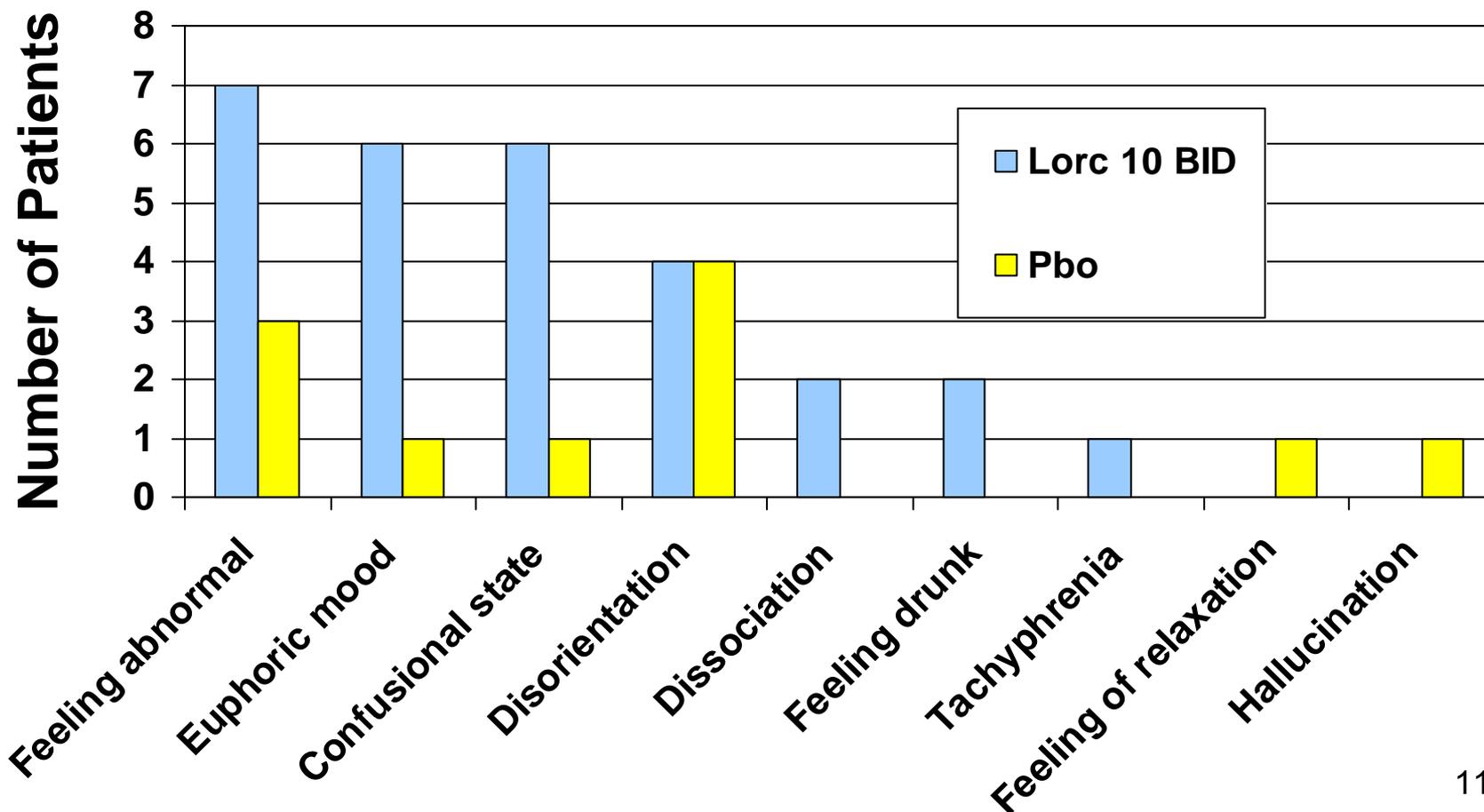
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Abuse-Related Adverse Events Thorough QT Study, Healthy Participants



Abuse-Related Adverse Events

Pooled Phase 3



Abuse-Related Adverse Events

Human Abuse Potential Study

- Lorcaserin 20-60 mg produced a relatively high incidence of dose-related euphoria (6-19%) compared to placebo (0%)
- The incidence of euphoria from lorcaserin was similar to that reported for zolpidem (13-16%) and less than that reported for ketamine (50%)

Conclusions: Abuse-Related AEs

- AEs of euphoria, hallucinations, and dissociation variably seen with lorcaserin in Phase 1 studies
- Euphoria seen infrequently in Phase 3, yet at greater frequency with lorcaserin than placebo

Lorcaserin Benefit:Risk Profile

- Potential Benefits*

- 5% categorical weight loss
 - Lorcaserin 47%
 - Placebo 23%
- Mean weight loss: 3.3%
- Modest improvements in weight-related comorbidities

* Efficacy in patients with diabetes unknown

- Potential Risks

- Valvular heart disease
 - RR 1.07 (95% C.I.: 0.74, 1.55)
- Depression/suicide
 - Imbalance in SAEs, DAEs, and suicidality scores
- Cognitive impairments
 - 3x increase in AEs
- Serotonin syndrome
 - Serotonergic agent
- Carcinogenicity
 - Rat carcinogen
- Abuse liability
 - Dose-related euphoria
- PPH?

Historical Overview: Weight Loss Efficacy of Other Obesity Agents

	Active	Placebo
Orlistat 120 mg TID	-6.1 kg	-2.6 kg
Sibutramine 15 mg QD	-6.4 kg	-1.6 kg
Qnexa (phentermine/topiramate) 15/92 mg QD	-10.6 kg	-1.7 kg
NB32 (naltrexone 32 mg/bupropion 360 mg) QD	-6.1 kg	-1.4 kg
Lorcaserin 10 mg BID	-5.8 kg	-2.5 kg

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