

Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Smith SR, Weissman NJ, Anderson CM, et al. Multicenter, placebo-controlled trial of lorcaserin for weight management. *N Engl J Med* 2010;363:245-56.

Supplementary Material

Methods

Inclusion/Exclusion Criteria: Eligible patients were 18-65 years of age with body mass index (BMI) 30-45 kg/m², or BMI 27-45 kg/m² with at least 1 comorbidity (hypertension, dyslipidemia, cardiovascular disease, impaired glucose tolerance, or sleep apnea), and able to participate in a moderate intensity exercise program.

Key exclusion criteria included prior bariatric surgery; change in weight of ≥ 5 kilograms within 3 months; Binge Eating Scale¹ score > 17 ; significant change in cigarette smoking within 3 months; diabetes mellitus; systolic blood pressure > 140 or diastolic blood pressure > 90 ; malignancy within 5 years; recent major surgery; history of seizure disorder; depression or other major psychiatric disease within 2 years requiring treatment with prescription medication; Beck Depression Inventory-II (BDI-II)² score of ≥ 20 or an individual response suggesting suicidal thoughts; pregnancy or lactation. Cardiopulmonary exclusion criteria included history of cardiac valve disease or pulmonary artery hypertension; myocardial infarction or stroke within 6 months; active ischemia; mild or greater aortic insufficiency; moderate or greater mitral insufficiency, significant mitral or aortic stenosis; pulmonary artery pressure > 40 mmHg; left ventricular ejection fraction $< 45\%$; or significant congenital or other cardiac disease. Medication exclusion criteria included prior administration of lorcaserin or drugs associated with cardiac valvulopathy, and use of selective serotonin reuptake inhibitor or selective norepinephrine reuptake inhibitors, metformin, topiramate, and drugs for weight loss. Laboratory exclusion criteria included clinically significant thyroid stimulating hormone and/or thyroxine abnormalities; triglycerides > 499 mg/dL; LDL cholesterol ≥ 190 mg/dL; HbA1c $> 6.5\%$; fasting glucose > 126 mg/dL;

aspartate aminotransferase (AST) or alanine aminotransferase (ALT) >2.5 times upper limit of normal; bilirubin >1.5 times upper limit of normal; creatinine >1.25 times upper limit of normal; and positive human immunodeficiency virus, hepatitis B or hepatitis C screen.

Safety and Efficacy Monitoring. At each study visit, research staff evaluated vital signs, concomitant medication use, adverse events, and study compliance. Physical examinations were performed at baseline, Week 4, and every 3 months thereafter. Routine laboratory studies (a 20-item chemistry panel, complete blood count with differential count, urinalysis) were performed at baseline, Week 4, Week 12, and every 3 months thereafter. Women received urine pregnancy tests at each visit and serum pregnancy tests at baseline, Week 52 and Week 104. HbA1c, thyroid function, hsCRP, and fibrinogen were measured every 6 months; fasting glucose and insulin were measured every 4 months. HOMA-IR was calculated using the Oxford University HOMA calculator.³ Patients completed the Impact of Weight on Quality of Life-Lite Questionnaire at baseline, and at Weeks 12, 24, 52, 76, and 104. The Beck Depression Inventory-II was administered at randomization, and at Weeks 4, 12, 24, 36, 52, 64, 76, 88, and 104. Electrocardiograms were performed at baseline, Week 4, Week 24, Week 52, Week 76, and Week 104. Echocardiograms were performed at screening and Weeks 24, 52, 76, and 104.

Data Safety Monitoring Board (DSMB). An independent DSMB evaluated echocardiographic data at Months 6 and 12. The board included 4 voting members: 2 cardiologists, 1 obesity specialist, 1 statistician with expertise in analysis of echocardiographic data, and 1 non-voting statistician who coordinated data unblinding and analysis. At Month 6, the DSMB provided to Investigators and the Sponsor their decision regarding whether to continue the study, but

provided no data or analyses. At Month 12, the DSMB also provided the Sponsor with the overall rate at which the patient population developed FDA-defined valvulopathy.

Echocardiography. An echocardiography core laboratory (Biomedical Systems, St. Louis, MO) trained the sonographers and cardiologists, and certified the equipment at each site. A panel of 19 cardiologists interpreted echocardiograms. Two cardiologists read each echocardiogram, with the primary reader for each patient remaining constant. The secondary reader was randomly selected from the remaining pool of cardiologists. Discrepant echocardiogram interpretations were adjudicated by a third cardiologist. All readings were blinded and independent; no side-by-side reads were performed. Aortic and mitral insufficiency were rated on a five point scale (absent, trace, mild, moderate, severe), according to American Society of Echocardiography criteria.⁴ Pulmonary artery systolic pressure (PASP) was estimated by the tricuspid regurgitant jet velocity.^{5,6} The study also assessed inter- and intra-reader variability by having each cardiologist interpret a set of “standard” echocardiograms assigned by the Medical Director of the echocardiographic core laboratory and masked as study subject echoes. These echocardiograms included examples of each grade of mitral and aortic regurgitation.

Statistical Analyses

Analysis Populations. Primary and key secondary efficacy analyses used an intent to treat (ITT) population with last observation carried forward (LOCF) imputation for missing data. Because Year 2 treatment assignments were not made at baseline, a true intent to treat analysis could not be applied to assessments from baseline to the end of Year 2. Year 2 data were analyzed using modified intent to treat based on the Year 2 treatment assignment, using LOCF imputation for missing values during Year 2. No missing values were imputed from within Year 1 to the end of

Year 2. Pre-specified sensitivity analyses of weight loss parameters evaluated 2 additional populations: (1) a per protocol population that included patients who adhered to protocol-specified procedures; and (2) all patients who had a body weight recorded at Week 52, even if they had discontinued study participation and returned only for the body weight measurement. A post-hoc sensitivity analysis of the primary and key secondary Year 1 efficacy endpoints was performed using a mixed model/repeated measures method.⁸ Safety evaluations included all patients who received at least one dose of study medication. Echocardiographic analyses included all patients with screening and at least one post-screening echocardiogram, with LOCF imputation.

Primary and Secondary Efficacy Analyses. The 3 co-primary Year 1 endpoints were analyzed using a closed hierarchical testing procedure. Comparisons for categorical weight loss used a logistic regression model with effects for treatment, gender and baseline body weight (kg). Change in weight used analysis of covariance (ANCOVA) models with treatment and gender as factors, and baseline body weight as a covariate. Key secondary efficacy endpoints were grouped into 3 families (lipids, blood pressure, and glycemic indicators); within each family, endpoints were prioritized in a pre-specified order. For blood pressure and glycemic indicators, the endpoints were tested in order as follows: the first endpoint within a family was assessed; each subsequent endpoint was assessed only if the preceding endpoint was significant. For the lipid family, the first endpoint (LDL cholesterol) was assessed; if LDL cholesterol was significant, the last three endpoints (total cholesterol, HDL cholesterol and triglycerides) were tested using the Hochberg procedure.⁹

Echocardiographic Analysis. The primary analysis of echocardiographic safety data compared the proportion of patients who developed FDA-defined valvulopathy from screening to Week 52 in lorcaserin versus placebo treated patients. A non-inferiority analysis with a margin of -0.025 (equivalent to a relative risk of 1.5) and based on a one-sided test at the 5% level of significance was used to establish that the rate of FDA-defined valvulopathy in patients treated with lorcaserin is no worse than the rate in the placebo group. This is analogous to inspecting a two-sided 90% confidence interval for the difference in proportion between lorcaserin and placebo. The 2-sided 90% confidence interval was constructed using the normal approximation to the binomial distribution.

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The following investigators participated in the conduct of this trial:

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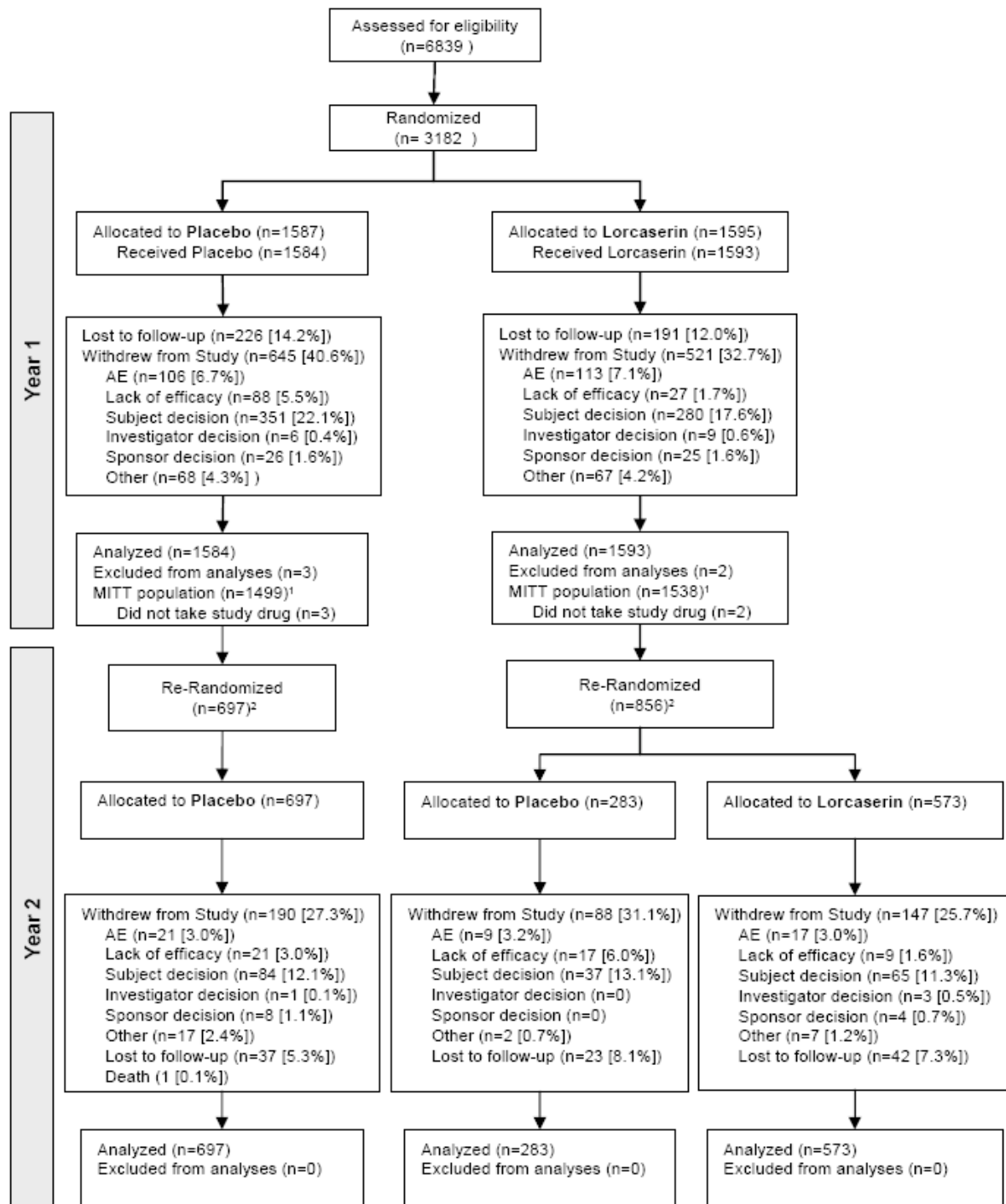
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Supplementary Figure Legend:

Flow diagram of patient screening, randomization and disposition.

Supplementary Figure: Patient Disposition



1 Took study drug but did not have a post-baseline body weight recorded

2 Placebo: 227 responders, 470 non-responders; Lorcaserin: 569 responders, 287 non-responders

Supplementary Table. Changes in Key Efficacy and Safety Parameters: Year 2

Mean (sem) ITT with LOCF	Baseline to Year 2 ¹			Year 1 to Year 2 ²		
	Placebo/ Placebo N=684	Lorcaserin/ Lorcaserin N=564	Lorcaserin/ Placebo N=274	Placebo/ Placebo N=665	Lorcaserin/ Lorcaserin N=553	Lorcaserin/ Placebo N=266
	Mean weight (kg)	N=684	N=564	N=275	N=665	N=553
Starting value ³	99.3 (0.6)	100.6 (0.7)	100.6 (1.0)	95.7 (0.6)	92.4 (0.7)	92.5 (1.1)
Change	-2.43 (0.28)	-5.56 (0.31)	-3.30 (0.42)	1.00 (0.16)	2.53 (0.19)	4.76 (0.31)
Mean weight, PP ⁴ (kg)	N=344	N=308	N=140	N=344	N=308	N=140
Starting value ³	98.3 (0.8)	100.6 (0.9)	99.3 (1.4)	94.5 (0.9)	91.8 (1.0)	90.7 (1.6)
Change	-2.45 (0.38)	-5.97 (0.44)	-3.94 (0.64)	1.27 (0.23)	2.81 (0.26)	4.62 (0.42)
Waist circumference (cm)	N=684	N=564	N=274	N=665	N=553	N=266
Starting value ³	109.4 (0.5)	110.1 (0.5)	109.5 (0.8)	104.1 (0.5)	101.1 (0.6)	100.5 (0.8)
Change	-4.74 (0.33)	-7.13 (0.36)	-5.50 (0.53)	0.51 (0.23)	1.80 (0.25)	3.48 (0.40)
BMI (kg/m ²)	N=684	N=564	N=275	N=665	N=553	N=267
Starting value ³	35.8 (0.2)	36.1 (0.2)	36.1 (0.3)	34.5 (0.2)	33.1 (0.2)	33.2 (0.3)
Change	-0.88 (0.10)	-2.01 (0.11)	-1.21 (0.16)	0.36 (0.06)	0.92 (0.07)	1.74 (0.11)
Systolic BP ⁴ (mmHg)	684	N=564	N=274	N=665	N=553	N=266
Starting value ³	122.5 (0.4)	122.0 (0.5)	121.8 (0.7)	120.3 (0.5)	119.1 (0.5)	119.2 (0.7)
Change	-1.45 (0.49)	-2.47 (0.53)	-0.01 (0.74)	0.71 (0.50)	0.31 (0.51)	2.64 (0.72)
Diastolic BP ⁴ (mmHg)	N=684	N=564	N=274	N=665	N=553	N=266
Starting value ³	77.8 (0.3)	77.6 (0.3)	77.9 (0.5)	76.4 (0.3)	75.5 (0.4)	76.1 (0.5)
Change	-0.73 (0.34)	-1.72 (0.39)	-1.20 (0.52)	0.72 (0.34)	0.37 (0.37)	0.70 (0.47)
Heart rate (bpm) ⁵	N=495	N=412	N=191	N=484	N=407	N=186
Starting value ³	69.3 (0.4)	68.9 (0.4)	69.1 (0.7)	67.5 (0.4)	66.7 (0.5)	66.6 (0.7)
Change	-0.82 (0.43)	-1.65 (0.48)	-0.97 (0.68)	0.89 (0.38)	0.46 (0.43)	1.65 (0.62)

Mean (sem) ITT with LOCF	Baseline to Year 2 ¹			Year 1 to Year 2 ²		
	Placebo/ Placebo N=684	Lorcaserin/ Lorcaserin N=564	Lorcaserin/ Placebo N=274	Placebo/ Placebo N=665	Lorcaserin/ Lorcaserin N=553	Lorcaserin/ Placebo N=266
	PASP (mmHg)	N=272	N=254	N=118	N=309	N=279
Starting value ³	25.9 (0.3)	26.5 (0.3)	26.2 (0.4)	25.8 (0.3)	25.3 (0.3)	26.2 (0.3)
Change	-0.94 (0.32)	-1.61 (0.31)	-0.72 (0.44)	-0.57 (0.28)	-0.33 (0.29)	-0.51 (0.38)
Total cholesterol	N=664	N=547	N=268	N=634	N=526	N=258
Starting value (mg/dL) ³	199.2 (1.3)	196.4 (1.5)	197.7 (2.1)	199.5 (1.4)	192.9 (1.5)	194.5 (2.2)
Change (%)	1.85 (0.57)	0.68 (0.59)	2.01 (0.85)	1.91 (0.54)	2.52 (0.57)	3.76 (0.83)
LDL cholesterol	N=664	N=547	N=268	N=633	N=526	N=258
Starting value (mg/dL) ³	114.8 (1.1)	113.0 (1.3)	114.4 (1.9)	118.8 (1.2)	115.1 (1.3)	116.6 (1.9)
Change (%)	7.44 (0.93)	6.46 (1.04)	7.82 (1.45)	3.39 (0.81)	3.77 (0.88)	5.51 (1.28)
HDL cholesterol	N=664	N=547	N=268	N=633	N=526	N=258
Starting value (mg/dL) ³	56.6 (0.6)	55.6 (0.6)	56.0 (0.9)	55.6 (0.6)	55.0 (0.6)	55.5 (0.8)
Change (%)	-2.96 (0.55)	-1.27 (0.58)	0.16 (0.90)	-0.71 (0.51)	-0.04 (0.55)	0.40 (0.78)
Triglycerides	N=664	N=547	N=268	N=634	N=526	N=258
Starting value (mg/dL) ³	140.2 (2.7)	139.8 (3.1)	137.6 (4.7)	126.2 (2.7)	114.1 (2.5)	112.8 (3.7)
Change (%)	-1.21 (1.69)	-7.91 (1.55)	-2.65 (2.71)	8.06 (1.56)	10.89 (1.78)	15.04 (2.6)
Fasting glucose (mg/dL)	N=621	N=504	N=254	N=597	N=488	N=248
Starting value ³	95.4 (0.4)	95.1 (0.5)	93.7 (0.6)	95.8 (0.4)	93.3 (0.4)	92.7 (0.6)
Change	2.19 (0.41)	0.64 (0.48)	2.00 (0.55)	1.80 (0.39)	2.34 (0.39)	3.02 (0.57)
Fasting insulin (μIU/mL)	N=575	N=451	N=224	N=565	N=432	N=222
Starting value ³	15.4 (0.4)	15.1 (0.4)	14.9 (0.6)	12.4 (0.4)	10.8 (0.4)	10.6 (0.5)
Change	-2.96 (0.51)	-3.35 (0.44)	-2.75 (0.54)	-0.05 (0.50)	1.19 (0.43)	1.83 (0.57)
HbA1c ⁴ (%)	N=638	N=513	N=263	N=638	N=515	N=264
Starting value ³	5.69 (0.01)	5.69 (0.02)	5.65 (0.02)	5.73 (0.02)	5.64 (0.02)	5.61 (0.02)

Mean (sem) ITT with LOCF	Baseline to Year 2 ¹			Year 1 to Year 2 ²		
	Placebo/ Placebo N=684	Lorcaserin/ Lorcaserin N=564	Lorcaserin/ Placebo N=274	Placebo/ Placebo N=665	Lorcaserin/ Lorcaserin N=553	Lorcaserin/ Placebo N=266
	Change	-0.09 (0.01)	-0.17 (0.01)	-0.12 (0.02)	-0.13 (0.01)	-0.12 (0.01)
HOMA-IR	N=555	N=434	N=225	N=544	N=417	N=210
Starting value ³	1.91 (0.04)	1.96 (0.05)	1.86 (0.07)	1.64 (0.04)	1.42 (0.04)	1.39 (0.06)
Change	-0.37 (0.04)	-0.45 (0.05)	-0.27 (0.07)	-0.06 (0.04)	0.13 (0.04)	0.29 (0.07)
hsCRP (mg/L)	N=633	N=510	N=260	N=609	N=498	N=254
Starting value ³	5.5 (0.3)	5.0 (0.2)	5.4 (0.4)	5.2 (0.3)	3.8 (0.2)	3.9 (0.3)
Change	-0.15 (0.38)	-0.44 (0.27)	0.16 (0.39)	0.18 (0.35)	0.70 (0.24)	1.56 (0.34)
Fibrinogen (mg/dL)	N=562	N=463	N=233	N=552	N=455	N=235
Starting value ³	361.0 (3.0)	361.9 (3.3)	367.4 (5.0)	356.4 (3.2)	343.0 (3.5)	340.5 (4.7)
Change	13.91 (3.25)	5.14 (3.65)	5.36 (5.11)	22.66 (3.10)	23.00 (3.52)	39.84 (5.32)
IWQOL-LITE score	N=589	N=481	N=234	N=595	N=483	N=238
Starting value ³	74.3 (0.7)	73.5 (0.8)	74.6 (1.0)	85.9 (0.6)	87.2 (0.5)	88.5 (0.7)
Change	12.82 (0.56)	14.22 (0.61)	13.07 (0.78)	1.12 (0.34)	0.56 (0.35)	-0.87 (0.59)
BDI-II score	N=664	N=546	N=268	N=666	N=547	N=268
Starting value ³	3.6 (0.2)	3.8 (0.2)	3.9 (0.2)	2.3 (0.1)	2.4 (0.2)	2.5 (0.3)
Change	-1.23 (0.18)	-1.35 (0.20)	-0.98 (0.35)	-0.01 (0.13)	0.03 (0.14)	0.46 (0.30)

¹ Change from Baseline to Year 2, ITT-LOCF from Year 1

² Change from Year 1 to Year 2, ITT-LOCF from Year 1

³ Starting value is value at Baseline for Baseline to Year 2 changes and Year 1 value for Year 1 to Year 2 changes

⁴ PP, per protocol; BP, blood pressure; HbA1c, glycosylated hemoglobin

⁵ Safety population