ORIGINAL ARTICLE

Multicenter, Placebo-Controlled Trial of Lorcaserin for Weight Management

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ABSTRACT

BACKGROUND

Lorcaserin is a selective serotonin 2C receptor agonist that could be useful in reducing body weight.

METHODS

In this double-blind clinical trial, we randomly assigned 3182 obese or overweight adults (mean body-mass index [the weight in kilograms divided by the square of the height in meters] of 36.2) to receive lorcaserin at a dose of 10 mg, or placebo, twice daily for 52 weeks. All patients also underwent diet and exercise counseling. At week 52, patients in the placebo group continued to receive placebo but patients in the lorcaserin group were randomly reassigned to receive either placebo or lorcaserin. Primary outcomes were weight loss at 1 year and maintenance of weight loss at 2 years. Serial echocardiography was used to identify patients in whom valvulopathy (as defined by the Food and Drug Administration) developed.

RESULTS

At 1 year, 55.4% of patients (883 of 1595) receiving lorcaserin and 45.1% of patients (716 of 1587) receiving placebo remained in the trial; 1553 patients continued into year 2. At 1 year, 47.5% of patients in the lorcaserin group and 20.3% in the placebo group had lost 5% or more of their body weight (P<0.001), corresponding to an average loss of 5.8±0.2 kg with lorcaserin and 2.2±0.1 kg with placebo during year 1 (P<0.001). Among the patients who received lorcaserin during year 1 and who had lost 5% or more of their baseline weight at 1 year, the loss was maintained in more patients who continued to receive lorcaserin during year 2 (67.9%) than in patients who received placebo during year 2 (50.3%, P<0.001). Among 2472 patients evaluated at 1 year and 1127 evaluated at 2 years, the rate of cardiac valvulopathy was not increased with the use of lorcaserin. Among the most frequent adverse events reported with lorcaserin were headache, dizziness, and nausea. The rates of serious adverse events in the two groups were similar.

CONCLUSIONS

In conjunction with behavioral modification, lorcaserin was associated with significant weight loss and improved maintenance of weight loss, as compared with placebo. (Funded by Arena Pharmaceuticals; ClinicalTrials.gov number, NCT00395135.)

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Activation of the 5-hydroxytryptamine (5-HT, or serotonin) receptor 5-HT_{2C} decreases food intake through the pro-opiomelanocortin system of neurons.[1-3] Lorcaserin is a small-molecule agonist of the serotonin 2C (5-HT_{2C}) receptor designed to promote weight loss. Study of the nonselective serotonergic agonists fenfluramine and dexfenfluramine, which enhance presynaptic serotonin release and block its reuptake, validated serotonin receptors as pharmacologic targets for weight loss.[4] Unfortunately, use of these agents increases the risk of serotonin-associated valvulopathy,[5-8] which is thought to occur through agonism of 5-HT_{2B} receptors expressed on cardiac valvular interstitial cells.[9-11] Lorcaserin was designed to selectively activate central 5-HT_{2C} receptors, with a functional selectivity of approximately 15 times that for 5-HT_{2A} receptors and 100 times that for 5-HT_{2B} receptors.[12,13] In a 12-week clinical trial involving obese patients, the use of lorcaserin was associated with dose-dependent weight loss without apparent effects on heart valves.[14]

The present report describes the Behavioral Modification and Lorcaserin for Overweight and Obesity Management (BLOOM) trial, a 2-year, randomized, placebo-controlled, double-blind clinical trial designed to evaluate the efficacy and safety, including safety regarding cardiac valves, of lorcaserin used for weight management.

Methods

Study Design

This study was conducted at 98 academic and private trial sites from September 11, 2006, through February 5, 2009, under the guidelines of the Declaration of Helsinki. Institutional review boards reviewed and approved the protocol for each site, and all patients provided written informed consent before participation.

The authors — both academic authors and industry authors, who were employees of the sponsor, Arena Pharmaceuticals — and a site investigator and other employees of the sponsor designed the trial, planned the data analyses, reviewed the data, wrote or revised the manuscript, and decided to submit it for publication. An academic author and an industry author wrote the initial draft of the manuscript, which all the authors revised. The authors planned the statistical analyses, and a contract research organization performed them. All authors assume responsibility for the integrity and completeness of the data and the data analyses. All authors had confidentiality agreements with the sponsor during the planning and conduct of the study. The study was conducted in accordance with the protocol (an abbreviated version is available with the full text of this article at NEJM.org).

Study End Points

The trial's objective was to evaluate the safety and efficacy of lorcaserin for weight loss and maintenance of weight loss when administered in conjunction with a lifestyle modification program. The prespecified coprimary end points for year 1 were the proportion of patients with a reduction in the baseline body weight of 5% or more at the end of year 1, the change in weight between baseline and the end of year 1, and the proportion of patients with a reduction in the baseline body weight of 10% or more at the end of year 1. The primary end point for year 2 was the proportion of patients who had had a reduction in the baseline body weight of 5% or more at the end of year 1 and who maintained this reduction during year 2. Key secondary end points included changes from the baseline values for lipids (total cholesterol, low-density lipoprotein [LDL] cholesterol, high-density lipoprotein [HDL] cholesterol, and triglycerides), glycemic variables (fasting glucose, fasting insulin, glycated hemoglobin, and the homeostasis model assessment of insulin resistance), physical measures (waist circumference, body-mass index [BMI], systolic blood pressure, and diastolic blood pressure), inflammatory markers of cardiovascular risk (high-sensitivity C-reactive protein and fibrinogen), and the quality of life (as assessed by means of the Impact of Weight on Quality of Life–Lite questionnaire, on which scores can range from 0 to 100, with higher scores indicating a better quality of life).

Study-Group Assignments

For year 1, on study day 1, patients were randomly assigned, in a 1:1 ratio, to receive lorcaserin (at a dose of 10 mg) or placebo twice daily, once before breakfast and once before dinner. All patients who remained in the trial at the end of year 1 were eligible to continue in the study for a second year. For year 2, patients who had been receiving placebo continued to receive it, whereas patients who had been receiving lorcaserin were again randomly as-

signed, in a 2:1 ratio, either to continue to receive lorcaserin or to begin to receive placebo.

PATIENTS

Eligibility criteria included an age of 18 to 65 years and a BMI (the weight in kilograms divided by the square of the height in meters) of 30 to 45 or of 27 to 45 with at least 1 coexisting condition (hypertension, dyslipidemia, cardiovascular disease, impaired glucose tolerance, or sleep apnea). Detailed inclusion and exclusion criteria are provided in the Supplementary Appendix (available at NEJM.org). Key exclusion criteria included moderate or more severe mitral regurgitation or mild or more severe aortic regurgitation (i.e., valvulopathy, as defined by the Food and Drug Administration [FDA]), diabetes mellitus, a systolic blood pressure exceeding 140 mm Hg or a diastolic blood pressure exceeding 90 mm Hg, depression or other major psychiatric disease within 2 years before randomization that necessitated treatment with prescription medication, and pregnancy or lactation.

STUDY PROCEDURES

Patients returned to the research site 2 and 4 weeks after randomization and then on a monthly basis. At each visit, a trained counselor at each site administered standardized nutritional and exercise counseling during individual sessions (lasting 15 minutes to 1 hour, depending on the study week). Patients were instructed to exercise moderately for 30 minutes daily and to reduce the daily calorie intake to 600 kcal below the individual estimate for daily energy requirements. Energy requirements were calculated with the use of equations published by the World Health Organization[15] and an activity factor of 1.3, which assumes an average activity level; a factor of 1.4 was used for patients who reported performing an hour or more of aerobic exercise each day.

Research staff evaluated vital signs, concomitant medication use, adverse events, study compliance and results of physical examinations, routine laboratory studies, pregnancy tests, and electrocardiography. Echocardiography was performed at the screening visit and at weeks 24, 52, 76, and 104. The Beck Depression Inventory II (on which scores can range from 0 to 63, with higher scores indicating more severe depression), as administered at the screening visit and at nine subsequent visits. Efficacy measures included fasting insulin and fasting glucose levels (measured every 4 months), high-sensitivity C-reactive protein and fibrinogen levels, and the score on the Impact of Weight on Quality of Life–Lite questionnaire. Echocardiographic procedures and further study details are listed in the Supplementary Appendix.

STATISTICAL ANALYSIS

The primary efficacy analyses involved data from the intention-to-treat population and last-observation-carried-forward imputation for missing values. Sensitivity analyses were performed as described in the Supplementary Appendix. The three coprimary end points during year 1 were analyzed by means of a closed hierarchical testing procedure. Comparisons regarding categorical weight loss were performed with the use of a logistic-regression model with effects for treatment, sex, and baseline body weight. Analysis of covariance models for weight change used study group and sex as factors and baseline body weight as a covariate. Key secondary efficacy end points were categorized as relating to lipids, blood pressure, or glycemic indicators; within each category, end points were prioritized in a prespecified order. The Supplementary Appendix provides further details concerning the statistical analyses.

The echocardiographic safety end point — the proportion of patients in whom FDA-defined valvulopathy had developed by week 52 — was the primary determinant of sample size. A noninferiority analysis was used to establish that the rate of FDA-defined valvulopathy among patients treated with lorcaserin was no worse than the rate among patients in the placebo group. On the basis of the results of a 3-month phase 2 study of lorcaserin,[14] we estimated that the proportion of patients in the placebo group in whom FDA-defined valvulopathy would develop was approximately 5% per year. On the basis of a noninferiority margin of −0.025 (equivalent to a relative risk of valvulopathy with lorcaserin of 1.5), a rate in the placebo group of 5%, and a one-sided test at the 5% level of significance, we calculated that the total sample size required to provide 80% power was 1879 patients (approximately 940 patients in each of the two study groups). The analysis was performed on data from a modified intention-to-treat population — all patients with a screening echocardiogram and at least one post-baseline echocardiogram — with last-observation-carried-forward imputation. Assuming a dropout rate as high as 40%, 3182 patients were randomly assigned to a study group.

At week 52, a total of 2472 patients had undergone echocardiography at both the screening visit and at least one subsequent visit, and the observed rate of FDA-defined valvulopathy in the placebo group was 2.3%. Hence, our data provide a statistical power of 60% to rule out a relative risk of 1.5 of valvulopathy having developed with lorcaserin use at week 52, by means of last-observation-carried-forward analysis.

RESULTS

PATIENTS AND STUDY COMPLETION

In the trial, 3182 patients were randomly assigned to receive one of the two study drugs; the two groups had similar baseline characteristics (Table 1). The rates of completion of year 1 of the study were 55.4% in the lorcaserin group and 45.1% in the placebo group, and 7.1% and 6.7% of patients, respectively, discontinued the study because of adverse events (see the figure in the Supplementary Appendix). More patients in the lorcaserin group than in the placebo group withdrew from the study owing to headache (2.0% vs. 0.8%) and dizziness (0.8% vs. 0.1%). The overall rate of completion of year 2 of the study was 72.6% of patients who completed year 1, with a slightly higher rate of discontinuation among patients who received placebo in both years (27.3%) than among patients who received lorcaserin in both years (25.7%). The rates and reasons for discontinuation during year 2 were similar among the three groups present in that year: the group receiving placebo in both years, the group receiving lorcaserin in both years, and the group receiving lorcaserin in the first year and placebo in the second.

WEIGHT LOSS

At the end of year 1, 47.5% of patients receiving lorcaserin had lost 5% or more of their baseline body weight, as compared with 20.3% of patients receiving placebo (P<0.001) (Fig. 1A). Patients in the lorcaserin group lost an average (±SE) of 5.81±0.16% of the baseline body weight, as compared with 2.16±0.14% in the placebo group (P<0.001) (Fig. 1B). More patients lost 10% or more of their baseline body weight in the lorcaserin group (22.6%) than in the placebo group (7.7%, P<0.001). In a prespecified analysis of data for patients who completed the protocol-defined study visits (the per-protocol population), those receiving lorcaserin also had greater weight loss than those receiving placebo (Table 2). In the population of all patients with weight data from year 1 (including some who had discontinued the study but returned at 1 year to be weighed), the 1015 patients in the lorcaserin group lost 7.0±0.2% of their baseline body weight, whereas the 888 patients in the placebo group lost 3.0±0.2% (P<0.001). A post hoc analysis of mean weight loss, performed with the use of a repeated-measures method, gave results similar to the last-observation-carried-forward analysis (Table 2).

Among patients in the lorcaserin group who had weight loss of 5% or more at year 1, the loss was maintained in a greater proportion of patients who continued to receive lorcaserin in year 2 than in those who were reassigned to receive placebo (67.9% vs. 50.3%, P<0.001). The mean body weight among patients who received lorcaserin in both years was lower than that among patients who received placebo in both years and lower than that among patients who received lorcaserin in year 1 and placebo in year 2 (Fig. 1C).

WAIST CIRCUMFERENCE AND INSULIN LEVEL

Lorcaserin was associated with significant decreases in waist circumference and BMI during year 1 as compared with placebo (Table 2). Fasting glucose, insulin, and glycated hemoglobin levels and the homeostasis model assessment of insulin resistance decreased significantly more during year 1 in the lorcaserin group than in the placebo group (Table 2). Glucose and insulin levels tended to increase with body weight during year 2 (see the table in the Supplementary Appendix).

Total cholesterol, LDL cholesterol, and triglyceride levels at year 1 were significantly lower in the lorcaserin group than in the placebo group but had increased by year 2 in both groups. In patients who received lorcaserin during year 1 and placebo during year 2, levels of total cholesterol, LDL cholesterol, and triglycerides tended to increase to the levels seen in the placebo group by year 2 (see the table in the Supplementary Appendix).

MARKERS OF CARDIOVASCULAR RISK

High-sensitivity C-reactive protein levels decreased significantly between baseline and year 1 in the lorcaserin group, from 5.5±0.19 mg per liter at baseline to 4.3±0.15 mg per liter, but not in the placebo group. Fibrinogen levels decreased significantly with lorcaserin as compared with

Table 1. Baseline Characteristics of the Patients, According to Study Group.*

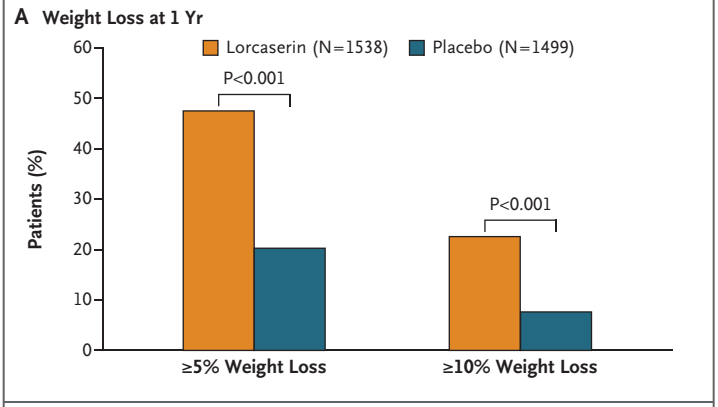
Characteristic	Lorcaserin (N=1595)	Placebo (N=1587)	P Value†
Intention-to-treat population — no.	1538	1499	
Race or ethnic group — no. (%)‡			0.24
White	1081 (67.9)	1046 (66.0)	
Black	298 (18.7)	298 (18.8)	
Hispanic	181 (11.4)	213 (13.4)	
Asian	12 (0.8)	9 (0.6)	
Native American	11 (0.7)	4 (0.3)	
Pacific Islander	1 (0.1)	3 (0.2)	
Other	9 (0.6)	11 (0.7)	
Sex — no. (%)			0.44
Male	272 (17.1)	253 (16.0)	
Female	1321 (82.9)	1331 (84.0)	
Age — yr	43.8±0.3	44.4±0.3	0.16
Weight — kg	100.4±0.4	99.7±0.4	0.21
Height — cm	166.4±0.2	165.9±0.2	0.11
Body-mass index§	36.2±0.1	36.2±0.1	0.73
Waist circumference — cm	109.6±0.3	109.2±0.3	0.30
Blood pressure — mm Hg			
Systolic	120.7±0.3	121.1±0.3	0.27
Diastolic	76.8±0.2	77.1±0.2	0.23
Heart rate — beats per min	69.5±0.2	69.8±0.2	0.37
PASP — mm Hg	25.7±0.1	25.4±0.1	0.24
Cholesterol — mg/dl			
Total	194.2±0.9	196.7±0.9	0.04
LDL	112.1±0.8	113.8±0.8	0.11
HDL	54.7±0.3	55.4±0.4	0.18
Triglycerides — mg/dl	137.4±1.9	137.9±1.9	0.84
Fasting glucose — mg/dl	94.3±0.3	94.1±0.3	0.76
Fasting insulin — μU/ml	15.9±0.3	15.8±0.4	0.83
HOMA-IR	1.95±0.03	1.92±0.03	0.498
Glycated hemoglobin — %	5.66±0.01	5.66±0.01	0.92
High-sensitivity CRP — mg/liter	5.62±0.18	5.50±0.18	0.65
Fibrinogen — mg/dl	365.7±2.0	364.3±2.0	0.62
IWQOL-Lite score	73.92±0.41	73.85±0.42	0.91
BDI-II score	4.2±0.1	4.2±0.1	0.98

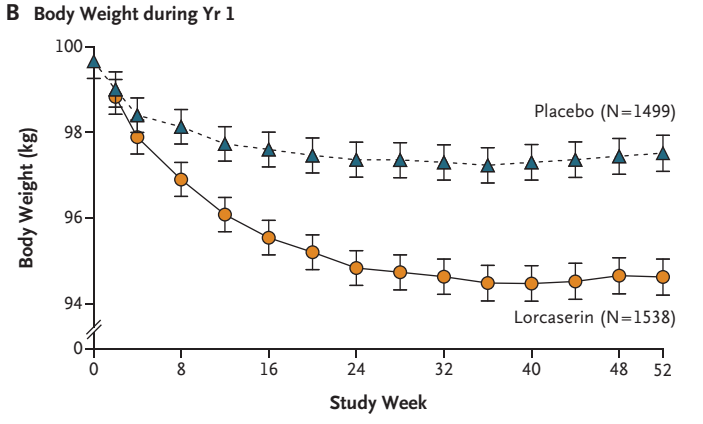
* Plus–minus values are means ±SE. Data for race or ethnic group, age, and sex are reported for the safety population (all patients who received at least one dose of lorcaserin or placebo): 1593 patients in the lorcaserin group and 1584 patients in the placebo group; no missing-value imputation was used for safety analyses. Scores on the Impact of Weight on Quality of Life–Lite (IWQOL-Lite) questionnaire can range from 0 to 100, with higher scores indicating a better quality of life. Scores on the Beck Depression Inventory II (BDI-II) can range from 0 to 63, with higher scores indicating more severe depression. To convert values for cholesterol to millimoles per liter, multiply by 0.02586. To convert values for triglycerides to millimoles per liter, multiply by 0.01129. To convert values for glucose to millimoles per liter, multiply by 0.05551. To convert values for insulin to picomoles per liter, multiply by 6.95. CRP denotes C-reactive protein, HDL high-density lipoprotein, HOMA-IR homeostasis model assessment of insulin resistance, LDL low-density lipoprotein, and PASP pulmonary-artery systolic pressure.

† P values were calculated with the use of a two-sample t-test for continuous end points and a chi-square test for categorical end points.

‡ Race or ethnic group was self-reported.

§ The body-mass index is the weight in kilograms divided by the square of the height in meters.





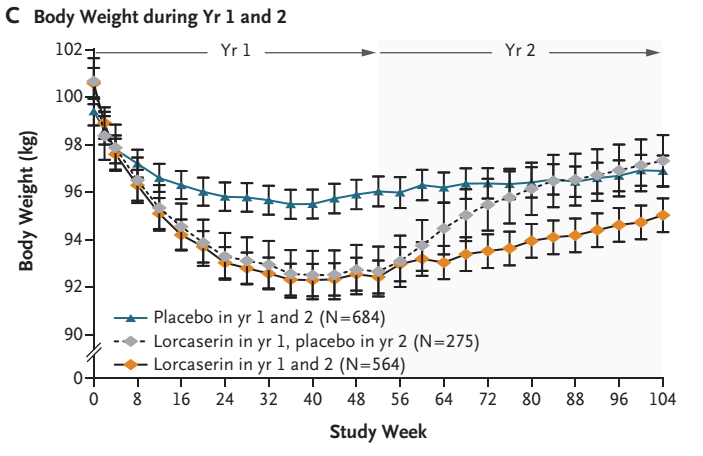


Figure 1. Effects of the Study Drug on Body Weight, According to Study Group.

The proportions of patients who lost 5% or more or 10% or more of their baseline body weight at 1 year are shown (Panel A). For the intention-to-treat population (with last-observation-carried-forward imputation), the mean body weight at each study visit is shown, according to study group, during year 1 among all patients (Panel B) and during years 1 and 2 among only those patients who continued the study past year 1 (Panel C). I bars indicate standard errors.

placebo (Table 2). Systolic and diastolic blood pressures decreased slightly but significantly between baseline and the end of year 1, and between baseline and the end of year 2, with lorcaserin as compared with placebo — as did the heart rate. Quality-of-life scores improved (as measured by an increased score on the 100-point scale of the Impact of Weight on Quality of Life–Lite questionnaire) in both study groups, with a greater improvement in the lorcaserin group than in the placebo group (Table 2).

ADVERSE EVENTS

Upper respiratory infections, headache, dizziness, nasopharyngitis, and nausea were the most common adverse events in the lorcaserin group (Table 3). Differences in the frequency of headache and dizziness between the lorcaserin group and the placebo group were less evident in year 2 than in year 1 and were not explained by different rates of discontinuation between the two groups owing to these adverse events. The incidence of depression, depressive symptoms, or depressed mood was 2.5% in the lorcaserin group and 2.2% in the placebo group during year 1; during year 2, the rates were 3.0% with lorcaserin given in both years, 2.0% with placebo given in both years, and 2.8% with placebo given in year 2 after lorcaserin had been given in year 1. The incidence of suicidal thoughts, according to one item on the Beck Depression Inventory II questionnaire, was 1.3% in each group. The rates of serious adverse events were similar among the three year-2 study groups. One patient in the placebo group died from injuries sustained in a motor vehicle accident; no other deaths occurred.

At year 1, FDA-defined valvulopathy had developed in 2.3% of patients in the placebo group and 2.7% of patients in the lorcaserin group (P=0.70) (relative risk with lorcaserin, 1.1; 95% confidence interval, 0.69 to 1.85). At year 2, the rate of valvulopathy was 2.7% in the placebo group and 2.6% among patients who received lorcaserin during year 1 and year 2 (Fig. 2A). Changes in valvular insufficiency scores for the mitral and aortic valves did not differ significantly (with possible scores of 0 to 5, corresponding to absent, trace, mild, moderate, and severe insufficiency, respectively) among the study groups during the trial (Fig. 2B through 2E). No severe mitral or aortic insufficiency was reported; one patient

Table 2. Changes in Efficacy and Safety End Points between Baseline and 1 Year.*

End Point	Intention-to-Treat Analysis with LOCF Imputation			Repeated-Measures Analysis		
	Lorcaserin (N=1538)	Placebo (N=1499)	P Value	Lorcaserin (N=1538)	Placebo (N=1499)	P Value
Coprimary end points						
Loss of ≥5% of body weight						
Patients (%)	47.5	20.3	<0.001			
Weight change (kg)	−5.8±0.2	−2.2±0.1	<0.001	−7.2±0.1	−2.9±0.1	<0.001
Loss of ≥10% of body weight (%)	22.6	7.7	<0.001			
Key secondary end points						
Waist circumference (cm)	−6.8±0.2	−3.9±0.2	<0.001	−8.1±0.2	−4.3±0.2	<0.001
Body-mass index†	−2.09±0.06	−0.78±0.05	<0.001	−2.61±0.04	−1.01±0.04	<0.001
Blood pressure (mm Hg)						
Systolic	−1.4±0.3	−0.8±0.3	0.04	−1.5±0.3	−0.7±0.4	0.10
Diastolic	−1.1±0.2	−0.6±0.2	0.01	−1.3±0.3	−0.6±0.3	0.055
Cholesterol (%)						
Total	−0.90±0.33	0.57±0.34	0.001	−1.37±0.39	0.57±0.43	0.001
LDL	2.87±0.56	4.03±0.58	0.049	4.10±0.64	5.90±0.70	0.04
HDL	0.05±0.33	−0.21±0.34	0.72	−0.93±0.40	−1.90±0.43	0.08
Triglycerides (%)	−6.15±1.03	−0.14±0.99	<0.001	−9.58±1.15	−1.82±1.26	<0.001
Fasting glucose (mg/dl)	−0.8±0.3	1.1±0.3	<0.001	−1.1±0.3	1.2±0.3	<0.001
Fasting insulin (μU/ml)	−3.33±0.38	−1.28±0.45	0.001	−4.04±0.36	−2.40±0.38	0.001
HOMA-IR	−0.41±0.03	−0.17±0.03	<0.001	−0.51±0.03	−0.28±0.03	<0.001
Glycated hemoglobin (%)	−0.04±0.01	0.03±0.01	<0.001			
High-sensitivity CRP (mg/liter)	−1.19±0.18	−0.17±0.19	<0.001	−1.84±0.18	−0.67±0.19	<0.001
Fibrinogen (mg/dl)	−21.5±2.2	−10.6±2.1	0.001	−24.8±2.4	−12.7±2.6	0.001
IWQOL-Lite score	12.4±0.4	10.7±0.4	<0.001	12.4±0.2	10.6±0.2	<0.001
Coprimary end points in per-protocol population						
No. of patients	583	737				
Loss of ≥5% of body weight						
Patients (%)	66.4	32.1	<0.001			
Weight change (kg)	−8.1±0.3	−3.3±0.3	<0.001			
Loss of ≥10% of body weight (%)	36.2	13.6	<0.001			
Safety end points						
No. of patients	1593	1584				
Heart rate (beats per min)	−2.0±0.3	−1.6±0.4	0.0499			
PASP (mm Hg)	−0.92±0.23	−0.23±0.23	0.14			
BDI-II score	−1.1±0.1	−0.9±0.1	0.26			

* Plus–minus values are means ±SE. The prespecified analysis was the intention-to-treat analysis with last-observation-carried-forward (LOCF) imputation; the post hoc analysis (not performed on proportions or data from secondary analyses or safety analyses) was the repeated-measures analysis. Repeated-measures analysis was also not performed on data from the per-protocol population, since all patients completed 52 weeks of the study. The safety population consisted of all patients who received at least one dose of lorcaserin or placebo; no missing-value imputation was used for safety analyses. Scores on the Impact of Weight on Quality of Life–Lite (IWQOL-Lite) questionnaire can range from 0 to 100, with higher scores indicating a better quality of life. Scores on the Beck Depression Inventory II (BDI-II) can range from 0 to 63, with higher scores indicating more severe depression. To convert values for cholesterol to millimoles per liter, multiply by 0.02586. To convert values for triglycerides to millimoles per liter, multiply by 0.01129. To convert values for glucose to millimoles per liter, multiply by 0.05551. To convert values for insulin to picomoles per liter, multiply by 6.95. CRP denotes C-reactive protein, HDL high-density lipoprotein, HOMA-IR homeostasis model assessment of insulin resistance, LDL low-density lipoprotein, and PASP pulmonary-artery systolic pressure.

† The body-mass index is the weight in kilograms divided by the square of the height in meters.

Table 3. Adverse Events Occurring in 3% or More of Patients and Serious Adverse Events, According to Study Group.

Event	Lorcaserin in Year 1 (N=1593)	Placebo in Year 1 (N=1584)	Lorcaserin in Years 1 and 2 (N=573)	Lorcaserin in Year 1, Placebo in Year 2 (N=283)	Placebo in Years 1 and 2 (N=697)
			number of patients (percent)		
Adverse events					
Headache	287 (18.0)	175 (11.0)	41 (7.2)	18 (6.4)	30 (4.3)
Upper respiratory infection	235 (14.8)	189 (11.9)	83 (14.5)	31 (11.0)	112 (16.1)
Nasopharyngitis	213 (13.4)	190 (12.0)	94 (16.4)	39 (13.8)	88 (12.6)
Dizziness	130 (8.2)	60 (3.8)	10 (1.7)	8 (2.8)	17 (2.4)
Nausea	119 (7.5)	85 (5.4)	20 (3.5)	9 (3.2)	29 (4.2)
Sinusitis	114 (7.2)	130 (8.2)	49 (8.6)	30 (10.6)	48 (6.9)
Diarrhea	109 (6.8)	85 (5.4)	34 (5.9)	9 (3.2)	30 (4.3)
Urinary tract infection	106 (6.7)	96 (6.1)	41 (7.2)	14 (4.9)	35 (5.0)
Constipation	106 (6.7)	64 (4.0)	14 (2.4)	8 (2.8)	11 (1.6)
Back pain	99 (6.2)	89 (5.6)	34 (5.9)	16 (5.7)	30 (4.3)
Fatigue	95 (6.0)	48 (3.0)	15 (2.6)	5 (1.8)	16 (2.3)
Dry mouth	83 (5.2)	37 (2.3)	1 (0.2)	3 (1.1)	2 (0.3)
Gastroenteritis (viral cause)	79 (5.0)	64 (4.0)	18 (3.1)	14 (4.9)	21 (3.0)
Influenza	73 (4.6)	69 (4.4)	38 (6.6)	14 (4.9)	42 (6.0)
Arthralgia	70 (4.4)	75 (4.7)	38 (6.6)	17 (6.0)	43 (6.2)
Cough	65 (4.1)	56 (3.5)	16 (2.8)	8 (2.8)	20 (2.9)
Vomiting	59 (3.7)	42 (2.7)	12 (2.1)	8 (2.8)	14 (2.0)
Pharyngolaryngeal pain	57 (3.6)	43 (2.7)	17 (3.0)	7 (2.5)	18 (2.6)
Bronchitis	56 (3.5)	62 (3.9)	16 (2.8)	8 (2.8)	27 (3.9)
Sinus congestion	53 (3.3)	37 (2.3)	14 (2.4)	3 (1.1)	16 (2.3)
Pain in extremity	52 (3.3)	49 (3.1)	15 (2.6)	8 (2.8)	24 (3.4)
Procedural pain	47 (3.0)	41 (2.6)	0	0	1 (0.1)
Insomnia	41 (2.6)	58 (3.7)	19 (3.3)	11 (3.9)	18 (2.6)
Serious adverse events					
Cardiac disorders	2 (0.1)	0	0	1 (0.4)	3 (0.4)
Congenital, familial, or genetic disorder	0	1 (0.1)	0	0	0
Eye disorder	0	2 (0.1)	0	0	0
Gastrointestinal disorder	3 (0.2)	1 (0.1)	1 (0.2)	0	3 (0.4)
General disorder	1 (0.1)	1 (0.1)	1 (0.2)	0	1 (0.1)
Hepatobiliary disorder	4 (0.3)	4 (0.3)	2 (0.3)	0	0
Immune system disorder	0	0	1 (0.2)	0	0
Infection or infestation	4 (0.3)	2 (0.1)	3 (0.5)	1 (0.4)	2 (0.3)
Injury, poisoning, or procedural complications	5 (0.3)	6 (0.4)	1 (0.2)	1 (0.4)	4 (0.6)
Abnormal laboratory test	0	0	1 (0.2)	0	0
Metabolism or nutrition disorder	1 (0.1)	0	0	0	0
Musculoskeletal disorder	5 (0.3)	8 (0.5)	3 (0.5)	1 (0.4)	3 (0.4)
Neoplasm	4 (0.3)	7 (0.4)	2 (0.3)	2 (0.7)	5 (0.7)

Table 3. (Continued.)

Event	Lorcaserin in Year 1 (N=1593)	Placebo in Year 1 (N=1584)	Lorcaserin in Years 1 and 2 (N=573)	Lorcaserin in Year 1, Placebo in Year 2 (N=283)	Placebo in Years 1 and 2 (N=697)
			number of patients (percent)		
Nervous system disorder	4 (0.3)	3 (0.2)	0	0	2 (0.3)
Pregnancy or perinatal condition	0	1 (0.1)	0	0	0
Psychiatric disorder	1 (0.1)	0	0	0	0
Renal or urinary disorder	0	0	0	0	1 (0.1)
Reproductive system or breast disorder	6 (0.4)	3 (0.2)	2 (0.3)	1 (0.4)	0
Respiratory disorder	3 (0.2)	0	0	1 (0.4)	1 (0.1)

in the placebo group reported moderate aortic regurgitation. Intrareader consistency, evaluated with the use of blinded, standardized echocardiograms, was 79% for the mitral valve and 76% for the aortic valve. Interreader consistency, estimated by comparing each reader's interpretation against the mode, was 71% for the mitral valve and 73% for the aortic valve. These results are similar to those for echocardiographic studies involving a smaller number of readers.[16] The study groups did not differ significantly in the change in mean pulmonary-artery systolic pressure, as estimated by means of Doppler flow, between baseline and 1 year (Table 2) or between year 1 and year 2 (see the Supplementary Appendix).

DISCUSSION

Lorcaserin was associated with significant weight loss, as compared with placebo, in obese and overweight adults when administered in conjunction with a nutritional and physical exercise program. A benefit of lorcaserin over placebo was also found in an earlier 3-month study that did not involve behavioral modification.[14]

During year 1, the proportion of patients with a loss of 5% or more of the initial body weight in the lorcaserin group was more than twice that in the placebo group. The primary data analysis involved the intention-to-treat principle with last-observation-carried-forward imputation, which could yield misleading results if patients regained weight after withdrawing from the study. However, the results of the primary analysis were confirmed in three sensitivity analyses: analysis of weight change in the per-protocol population, repeated-measures analysis in the intention-to-treat population, and analysis of weight change among all patients who had a body weight recorded at the time of the intended week 52 visit (including some who had withdrawn from the trial but returned to be weighed). Patients in the per-protocol population who were receiving lorcaserin lost 8.2% of the baseline weight, or approximately 8.1 kg, as compared with 3.3 kg in the placebo group. In year 2, patients who continued to take lorcaserin were significantly better able to maintain their year 1 weight loss than those who were switched to placebo, demonstrating a weight-maintenance benefit of long-term lorcaserin use.

The loss of 5 to 10% of body weight can have beneficial effects on hypertension, dyslipidemia, diabetes mellitus, arthritis, and sleep apnea and can also help prevent the development of type 2 diabetes and heart disease.[17-20] Consistent with these findings, the average 5.8% weight loss (in the intention-to-treat, last-observation-carried-forward analysis) in the lorcaserin group at 1 year was associated with improvements in serum lipid levels, insulin resistance, and blood pressure. Lorcaserin use also resulted in decreased waist circumference and decreased levels of markers of inflammation. Tools to predict future risk of coronary heart disease, such as those based on the Framingham Heart Study, incorporate total cholesterol, HDL cholesterol, and systolic blood pressure.[21,22] These measures include variables for which values were improved with the use of lorcaserin for 1 year.

As with any drug, the benefit must be balanced against the risk. The adverse-event profile of lorcaserin was consistent with previous data from a 3-month trial.[14] In particular, the rates of headaches and nausea were greater with lorca-

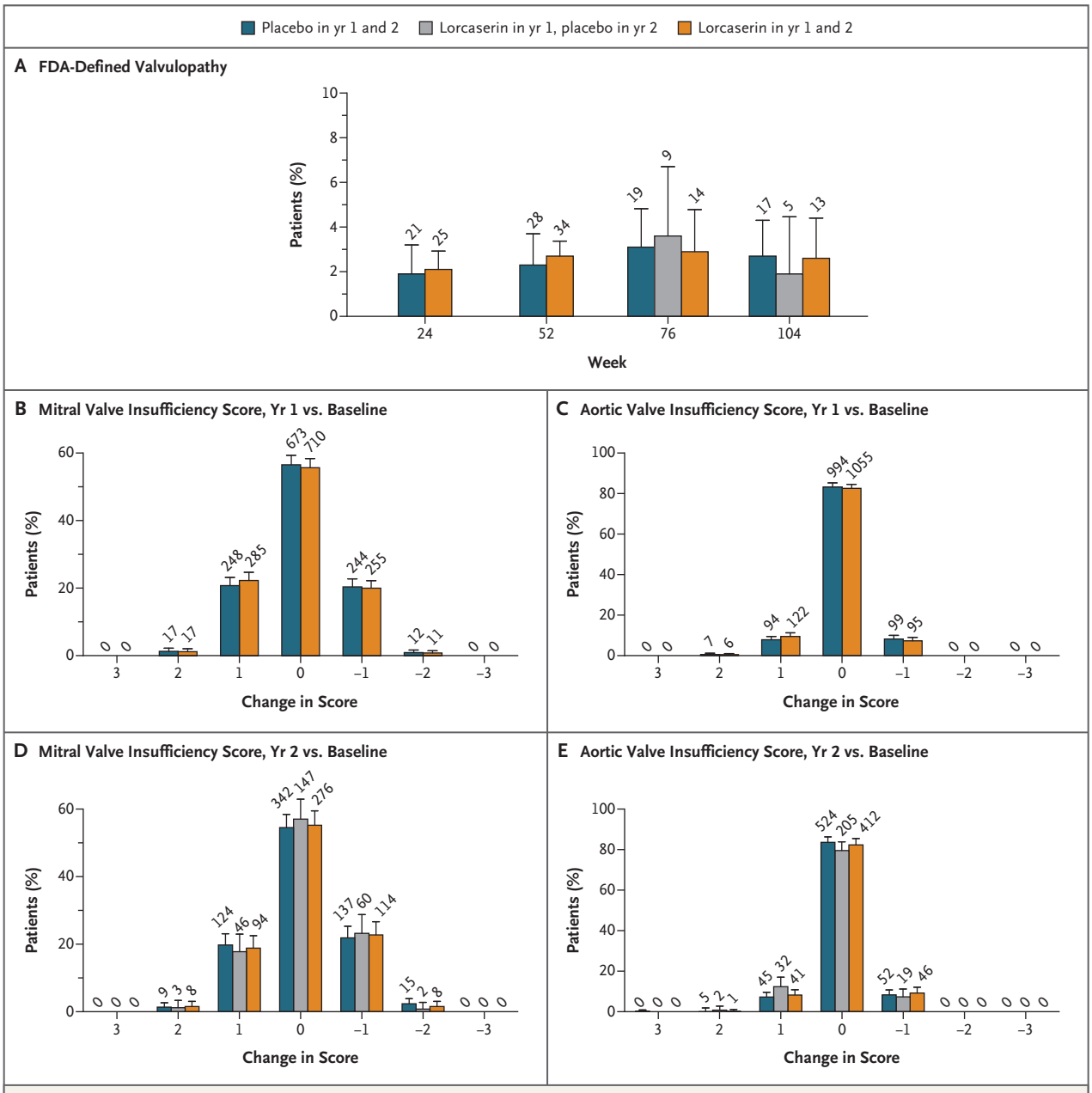


Figure 2. Findings on Echocardiography, According to Study Group.

The data given are the mean percentages of patients, with numbers of patients listed above each bar. The proportion of patients in whom echocardiographic criteria for valvulopathy, as defined by the Food and Drug Administration (FDA), were met during the study is shown (Panel A). Also shown are categorical changes in valvular insufficiency scores between baseline and year 1 (for the mitral and aortic valves [Panels B and C, respectively]) and baseline and year 2 (for the mitral and aortic valves [Panels D and E, respectively]). Possible insufficiency scores range from 0 to 5, corresponding to absent, trace, mild, moderate, and severe insufficiency, respectively. Negative values indicate less valvular insufficiency (improvement). T bars indicate the upper limit of the 95% confidence interval.

serin than with placebo. These adverse events tended to be mild and generally resolved, even with continued use of the study drug. Neuropsychiatric adverse events were not more frequent in the lorcaserin group than in the placebo group. The rates of depression and related adverse events were low in all the study groups at year 1 and throughout year 2, as was the incidence of anxi-

ety. The incidence of suicidal thoughts, ascertained by means of the Beck Depression Inventory II questionnaire, was low and did not differ significantly among the study groups. The overall incidence of suicidal ideation in our trial was below the prevalence of 9.5% reported previously, on the basis of the Beck Depression Inventory II, in a study of more than 12,000 healthy adults.[23]

Activation of the 5-HT_{2B} receptor in cardiac valvular interstitial cells is thought to cause serotonin-associated valvulopathy, which is characterized by the thickening of heart valves (particularly the mitral and aortic valves) and valvular insufficiency.[9-11] Serotonergic agents such as ergotamine, methysergide, pergolide, and cabergoline,[24-27] and especially the weight-loss drug fenfluramine,[6-8] increase the risk of valvulopathy. Each of these agents has significant agonist activity in vitro at the 5-HT_{2B} receptor. In contrast, agents that activate the 5-HT_{2A} or 5-HT_{2C} receptor, but not the 5-HT_{2B} receptor, are not associated with valvulopathy.[11,28] Lorcaserin caused no significant increase, relative to placebo, in the incidence of FDA-defined valvulopathy,[5] a finding that supports the hypothesis that valvulopathy is not associated with activation of the 5-HT_{2C} receptor. When the aortic and mitral valves were studied separately, the rates of increased and decreased valvular insufficiency did not differ significantly between the study groups. Variability in echocardiographic interpretation for individual readers (as measured with the use of blinded reads of "standard" echocardiograms) in the current trial compared favorably with that measured in other trials involving echocardiographic end points with two readers.[16]

The sample size and power calculations in our trial were based on the assumption that FDA-defined valvulopathy would develop in 5% of patients in the placebo group within 1 year, an assumption that was in turn based largely on data from a previous 3-month, phase 2 study of lorcaserin.[14] Because only 2.3% of patients in the placebo group actually had a finding of FDA-defined valvulopathy at week 52, the statistical power to rule out a relative risk with lorcaserin of 1.5 is 60%, which is below the desired power of 80%.

Limitations of the trial include the fact that the rate of discontinuation at 1 year was nearly 50%, similar to the rates in other large, long-term, randomized trials of obesity.[29-31] This limitation is partially mitigated by the evaluation of all patients who returned for a weigh-in at week 52, even if they had withdrawn from the trial. This analysis included 63.6% (1015 of 1595) of patients in the lorcaserin group and 56.0% (888 of 1587) of patients in the placebo group, and the results were intermediate between those from the intention-to-treat analysis and the per-protocol analysis. Second, the applicability of our data to broader populations is not known. In particular, patients with binge-eating disorder, a BMI above 45, or diabetes mellitus were not included in our trial. The actual incidence of FDA-defined valvulopathy was below the pretrial estimates; as a result, the trial was slightly underpowered regarding the primary echocardiographic safety end point. Finally, the results cannot be compared directly with those of other antiobesity pharmacologic trials owing to differences in study design. For example, our trial had neither a placebo run-in period nor a dose-adjustment period. Despite their differing study designs, the BLOOM trial and published phase 3 studies of other single agents report similar placebo-adjusted and categorical weight losses.

In conclusion, lorcaserin used in conjunction with behavioral modification was associated with significant weight loss and improved maintenance of weight loss. Lorcaserin was also associated with improved values for biomarkers that may be predictors of future cardiovascular events, including lipid levels, insulin resistance, levels of inflammatory markers, and blood pressure.

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