PLEASE NOTE

This reprint includes information that is not contained within the full Prescribing Information (PI) for BELVIQ (loraserin HCl) Tablets, CIV, and is not intended to offer recommendations about BELVIQ that are outside the scope of the PI. Please read the full Indication and Important Safety Information below.

INDICATION

BELVIQ is indicated as an adjunct to a reduced-calorie diet and increased physical activity for chronic weight management in adults with an initial body mass index (BMI) of:

- 30 kg/m^2 or greater (obese), or
- 27 kg/m^2 or greater (overweight) in the presence of at least one weight-related comorbid condition (eg, hypertension, dyslipidemia, type 2 diabetes).

Limitations of Use:

- The safety and efficacy of coadministration of BELVIQ with other products intended for weight loss, including prescription drugs (eg, phentermine), over-the-counter drugs, and herbal preparations, have not been established.
- The effect of BELVIQ on cardiovascular morbidity and mortality has not been established.

IMPORTANT SAFETY INFORMATION

Contraindication

- BELVIQ should not be taken during pregnancy or by women who are planning to become pregnant.

Warnings and Precautions

- BELVIQ is a serotonergic drug. The development of potentially life-threatening serotonin syndrome or Neuroleptic Malignant Syndrome (NMS)-like reactions have been reported during use of serotonergic drugs, including, but not limited to, selective serotonin-norepinephrine reuptake inhibitors, and selective serotonin reuptake inhibitors, tricyclic antidepressants, bupropion, triptans, dietary supplements such as St. John's Wort and tryptophan, drugs that impair metabolism of serotonin (including monoamine oxidase inhibitors), dextromethorphan, lithium, tramadol, antipsychotics or other dopamine antagonists, particularly when used in combination. Patients should be monitored for the emergence of serotonin syndrome symptoms or NMS-like reactions, including agitation, hallucinations, coma, tachycardia, labile blood pressure, hyperthermia, hyperreflexia, incoordination, nausea, vomiting, diarrhea, and muscle rigidity. Treatment with BELVIQ and any concomitant serotonergic or antidopaminergic agents should be discontinued immediately if the above events occur, and supportive symptomatic treatment should be initiated.
- Patients should not take BELVIQ in combination with drugs that have been associated with valvular heart disease (eg, cabergoline). In clinical trials, 2.4% of patients taking BELVIQ and 2.0% of patients taking placebo developed valvular regurgitation: none of these patients was symptomatic. BELVIQ should be used with caution in patients with congestive heart failure (CHF). Patients who develop signs and symptoms of valvular heart disease, including dyspnea, dependent edema, CHF, or a new cardiac murmur, should be evaluated and discontinuation of BELVIQ should be considered.
- Impairment in attention, memory, somnolence, confusion, and fatigue, have been reported in patients taking BELVIQ. Patients should not drive a car or operate heavy machinery until they know how BELVIQ affects them.

Important Safety Information continued on next page.
See the accompanying full Prescribing Information.

BELVIQ® (lorcaserin HCl) IV

- The recommended dose of 10 mg twice daily should not be exceeded, as higher doses may cause euphoria, hallucination, and dissociation. Monitor patients for the development or worsening of depression, suicidal thoughts or behaviors, and/or any changes in mood. Discontinue BELVIQ in patients who develop suicidal thoughts or behaviors.
- Weight loss may increase the risk of hypoglycemia in patients with type 2 diabetes mellitus who are being treated with antidiabetic medications, so measurement of blood sugar levels before and during treatment with BELVIQ is recommended. Decreases in doses of antidiabetic medications or changes in medication regimen should be considered.
- Men who experience priapism should immediately discontinue BELVIQ and seek emergency medical attention. BELVIQ should be used with caution with erectile dysfunction medications. BELVIQ should be used with caution in men who have conditions that might predispose them to priapism (eg, sickle cell anemia, multiple myeloma, or leukemia), or in men with anatomical deformation of the penis (eg, angulation, cavernosal fibrosis, or Peyronie's disease).
- Because BELVIQ may cause a slow heartbeat, it should be used with caution in patients with a history of bradycardia or heart block greater than first degree.
- Consider monitoring for CBC changes, prolactin excess, and pulmonary hypertension.

Most Common Adverse Reactions

- In patients without diabetes: headache (17%), dizziness (9%), fatigue (7%), nausea (8%), dry mouth (5%), and constipation (6%).
- In patients with diabetes: hypoglycemia (29%), headache (15%), back pain (12%), cough (8%), and fatigue (7%).

Nursing Mothers

- BELVIQ should not be taken by women who are nursing.

BELVIQ® (lorcaserin HCl) IV

See the accompanying full Prescribing Information.

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A One-Year Randomized Trial of Lorcaserin for Weight Loss in Obese and Overweight Adults: The BLOSSOM Trial

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Context: Lorcaserin is a novel selective agonist of the serotonin 2C receptor.

Objective: Our objective was to evaluate the effects of lorcaserin on body weight, cardiovascular risk factors, and safety in obese and overweight patients.

Design and Setting: This randomized, placebo-controlled, double-blind, parallel arm trial took place at 97 U.S. research centers.

Patients: Patients included 4008 patients, aged 18–65 yr, with a body mass index between 30 and 45 kg/m^2 or between 27 and 29.9 kg/m^2 with an obesity-related comorbid condition.

Interventions: Patients were randomly assigned in a 2:1:2 ratio to receive lorcaserin 10 mg twice daily (BID), lorcaserin 10 mg once daily (QD), or placebo. All patients received diet and exercise counseling.

Main Outcome Measures: The ordered primary endpoints were proportion of patients achieving at least 5% reduction in body weight, mean change in body weight, and proportion of patients achieving at least 10% reduction in body weight at 1 yr. Serial echocardiograms monitored heart valve function.

Results: Significantly more patients treated with lorcaserin 10 mg BID and QD lost at least 5% of baseline body weight (47.2 and 40.2%, respectively) as compared with placebo (25.0%, $P < 0.001$ *vs.* lorcaserin BID). Least squares mean (95% confidence interval) weight loss with lorcaserin BID and QD was 5.8% (5.5–6.2%) and 4.7% (4.3–5.2%), respectively, compared with 2.8% (2.5–3.2%) with placebo ($P < 0.001$ *vs.* lorcaserin BID; least squares mean difference, 3.0%). Weight loss of at least 10% was achieved by 22.6 and 17.4% of patients receiving lorcaserin 10 mg BID and QD, respectively, and 9.7% of patients in the placebo group ($P < 0.001$ *vs.* lorcaserin BID). Headache, nausea, and dizziness were the most common lorcaserin-related adverse events. U.S. Food and Drug Administration-defined echocardiographic valvulopathy occurred in 2.0% of patients on placebo and 2.0% on lorcaserin 10 mg BID.

Conclusions: Lorcaserin administered in conjunction with a lifestyle modification program was associated with dose-dependent weight loss that was significantly greater than with placebo. (***J Clin Endocrinol Metab*** **96: 3067–3077, 2011)**

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Abbreviations: AE, Adverse event; Apo, apolipoprotein; BID, twice daily; BMI, body mass index; CI, confidence interval; DEXA, dual-energy x-ray absorptiometry; HDL, high-density lipoprotein; 5-HT$_{2C}$, serotonin 2C; IWQOL-LITE, Impact of Weight on Quality of Life-Lite Questionnaire; LDL, low-density lipoprotein; LOCF, last observation carried forward; LS, least squares; MITT, modified intent to treat; PASP, pulmonary artery systolic pressure; QD, once daily.

Obesity is a global epidemic that is no longer restricted to developed countries (1, 2). Based on 2005 World Health Organization estimates, approximately 1.6 billion adults are overweight and at least 400 million are obese, and the obesity rate is predicted to increase by 75% to 700 million by 2015. Obesity is associated with a number of comorbid conditions, including cardiovascular disease, type 2 diabetes, obstructive sleep apnea, osteoarthritis, depression, and some malignancies (3–5). Weight reduction as little as 5% in obese patients is associated with an improvement in the cardiovascular risk profile, a decrease in the incidence of diabetes, and the reduction of pain associated with osteoarthritis (6–9).

Lorcaserin is a novel selective serotonin 2C (5-HT_{2C}) receptor agonist in clinical development for weight management. The 5-HT_{2C} receptor in the hypothalamus modulates food intake by activating the proopiomelanocortin system of neurons that induces hypophagia (10). Previously available drugs that targeted this receptor, such as fenfluramine and dexfenfluramine, were effective in promoting weight loss. However, these agents were nonselective, and as a result of 5-HT_{2B} receptor activation, some patients developed valvular heart disease; these drugs were subsequently withdrawn from the market (11).

In preclinical models (12, 13) and in clinical trials that did not employ lifestyle modification, lorcaserin significantly reduced body weight. In 4- and 12-wk randomized, double-blind, placebo-controlled studies, significant dose-responsive and progressive weight loss was observed at doses of 10 and 15 mg once daily (QD) and 10 mg twice daily (BID) (14–16). These results were confirmed in a large 2-yr trial incorporating background lifestyle modification in which patients taking lorcaserin 10 mg BID lost significantly more weight than placebo-treated patients after 1 yr of treatment and maintained more weight loss during yr 2 (17). Furthermore, after 2 yr, lorcaserin produced no increase relative to placebo in the incidence of U.S. Food and Drug Administration (FDA)-defined valvulopathy (18).

The BLOSSOM study was designed to assess the efficacy and safety of a dose range of lorcaserin, when administered in conjunction with a nutritional and physical exercise program, to promote weight loss in obese patients and at-risk overweight patients.

Subjects and Methods

Design overview

This 52-wk, randomized, double-blind, placebo-controlled, parallel-group study was conducted between December 2007 and July 2009. The study was conducted in compliance with the Declaration of Helsinki; institutional review boards reviewed and approved the protocol for each study site, and all patients provided written informed consent before participation in the trial. This study is registered at Clinicaltrial.gov, number NCT00603902.

Setting and participants

Men and women ages 18–65 yr (inclusive) were recruited at 97 academic and private clinical trial sites in the United States. Key inclusion criteria were body mass index (BMI) of 30–45 or 27–29.9 kg/m^2 in the presence of hypertension, dyslipidemia, cardiovascular disease, impaired glucose tolerance, or sleep apnea and ability to participate in a moderate-intensity exercise program. Key exclusion criteria included recent cardiovascular events, major surgeries, medical conditions that would preclude participation in a nutritional and physical exercise program, diabetes mellitus, systolic blood pressure 150 mm Hg or higher or diastolic blood pressure 95 mm Hg or higher, triglycerides higher than 499 mg/dl, use of a selective serotonin reuptake inhibitor within 1 yr, previous bariatric surgery, recent use of weight-loss drugs (within 1 month for over-the-counter agents, 3 months for prescription drugs) or very-low-calorie diet, or change in weight of at least 5 kg within 3 months. The trial employed no exclusion criteria based on echocardiographic results.

Randomization and interventions

Patients were randomized in a 2:1:2 ratio to receive one of three interventions for 52 wk: 10 mg lorcaserin BID, 10 mg lorcaserin QD, or placebo. The randomization code was generated programmatically by a statistician not directly involved with the study and was not broken until after database lock.

Patients underwent screening procedures within 6 wk of dosing and randomization on d 1, with follow-up assessments at wk 2 and 4 and monthly thereafter through wk 52. Nutritional and physical exercise counseling were provided at baseline; wk 1, 2, and 4; and monthly thereafter. Patients were instructed to reduce daily caloric intake to 600 kcal below individual estimated energy requirements, using World Health Organization equations (19) and a fixed activity factor of 1.3 (1.4 for any subject who reported ≥1 h of aerobic exercise per day), and were encouraged to exercise moderately for 30 min per day. Food diaries were used as motivational tools and to assist with counseling sessions; data related to self-reported food intake and exercise were not formally analyzed. Body weight, waist and hip circumference, vital signs, concomitant medication use, adverse events (AE), and study compliance were assessed at each visit; laboratory evaluations and physical exams were performed periodically. A 12-lead electrocardiogram was performed at screening and on exit from the study. In a subset of patients, apolipoprotein (Apo) A1 and B were measured at randomization and on exit. The Impact of Weight on Quality of Life-Lite Questionnaire (IWQOL-LITE) (20) and the Beck Depression Inventory-II (21) were administered at randomization and at prespecified intervals thereafter. Echocardiograms were performed at randomization, at wk 24 and 52, and at study discontinuation. Patients who discontinued from the study before wk 36 were encouraged to return at wk 52 for a final echocardiogram.

Dual-energy x-ray absorptiometry (DEXA)

Body composition was measured in a subset of randomized patients (n = 189) at 16 sites using DEXA at baseline, wk 24, and wk 52. An imaging core laboratory (Bio-Imaging Technologies,

Inc., Newtown, PA) trained sites and technologists, certified the equipment before study commencement, and were responsible for ongoing quality control and processed all DEXA scan data.

Echocardiography

An echocardiography core laboratory (Biomedical Systems, Inc., St. Louis, MO) trained the sonographers and certified the equipment at each site. A pool of 23 experienced cardiologists who were trained by the core laboratory interpreted echocardiograms. Each echocardiogram was independently read in a blinded fashion by two cardiologists with the primary reader for each patient remaining constant. Differences in interpretation were adjudicated by a third cardiologist. Aortic and mitral insufficiency and pulmonary artery systolic pressure (PASP) were determined using previously published standard guidelines (22–24).

Statistical analysis

Statistical analyses were performed using SAS version 9.1 software (SAS, Cary, NC). Three hierarchically ordered primary endpoints were prespecified: the proportion of patients who achieved at least 5% weight loss from baseline, mean weight change from baseline, and the proportion of patients who achieved at least 10% weight loss from baseline.

Sample size

The study sample size was determined by the analysis of the echocardiographic endpoint. Assuming 15% of placebo patients would achieve at least 5% weight loss and a 40% dropout rate at wk 52, a sample size of 720 patients per group provided over 99% power for the primary efficacy endpoint analysis if 30% of lorcaserin-treated patients achieved at least 5% weight loss based on a two-sample test of equality of binomial proportions using a two-sided test with $\alpha = 0.05$.

Analysis populations

Primary and key secondary efficacy analyses used a modified intent-to-treat (MITT) population with last observation carried forward (LOCF) imputation for missing data. The MITT population included all patients who took at least one dose of study drug and had at least one post-baseline body weight recorded. A per-protocol population was also evaluated and included patients who completed 52 wk of study participation and met prespecified criteria for drug compliance, number of study visits, and study visit timing. *Post hoc* sensitivity analyses of the primary efficacy endpoints used the true ITT population (all patients randomized) with LOCF imputation for missing data. Safety evaluations included all patients who received at least one dose of study medication. Echocardiographic analyses used all patients with an echocardiogram at baseline and at least one post-baseline time point, with LOCF imputation.

Primary and secondary efficacy analyses

A hierarchical testing procedure was applied to the primary endpoints. The analyses of the proportion of patients who lost at least 5% or at least 10% body weight used a logistic regression model with effects for treatment, gender, and baseline body weight. Change in weight was analyzed using analysis of covariance models with treatment and gender as factors and baseline body weight as a covariate.

Key secondary endpoints were grouped into four families (lipids, blood pressure, body composition, and quality of life) with prespecified ordering of endpoints. For the lipid family, the first endpoint [low-density lipoprotein (LDL)] was assessed; if LDL was significant, the last three endpoints [total cholesterol, high-density lipoprotein (HDL), and triglycerides] were tested using the Hochberg procedure (25).

Echocardiographic analysis

The primary echocardiographic endpoint was the incidence at wk 52 of new valvulopathy, defined using FDA criteria of mild or greater aortic regurgitation and/or moderate or greater mitral regurgitation (22). Comparisons between treatment groups were made using Pearson's χ^2 test. This study was sized to rule out a greater than 50% increase in the wk 52 incidence of new FDA-defined valvulopathy with 80% power at the 5% significance level (noninferiority analysis) when combined with data from a companion phase 3 study of 3182 patients (17). Shifts in aortic and mitral regurgitation scores were assessed as the change in severity categories.

Results

A total of 4008 patients, of whom 79.8% were female, were randomized; 2224 (55.5%) patients completed the trial: 917 (57.2%), 473 (59.0%) and 834 (52.0%) in the lorcaserin BID, lorcaserin QD and placebo groups, respectively (Supplemental Figure). Patients assigned to lorcaserin BID received study drug for an average (SD) 257 (139) days, lorcaserin QD 265 (137) days, and those assigned to placebo completed 242 (143) days. The demographics and baseline characteristics were similar among treatment groups (Table 1).

Significantly more patients receiving lorcaserin BID and lorcaserin QD lost at least 5% body weight at 1 yr (47.2 and 40.2%, respectively; MITT/LOCF) than in the placebo group (25.0%, $P < 0.0001$ for both; Table 2 and Fig. 1). Lorcaserin BID was associated with significantly greater weight loss than lorcaserin QD ($P < 0.01$). Similarly, significantly more patients achieved at least 10% weight loss in the lorcaserin groups compared with placebo (Table 2). Weight loss and percent weight loss were dose-dependently increased in the lorcaserin groups ($P < 0.001$ for both). The most compliant patients (per protocol) achieved greater weight loss than did the MITT population, as reflected by greater proportions of patients losing at least 5% or at least 10% body weight and greater mean weight loss (Table 3).

As a *post hoc* sensitivity analysis, the primary endpoints were reanalyzed using a true ITT population. This sensitivity analysis confirmed the results of the prespecified primary analysis that used a MITT population; of the patients randomized to lorcaserin BID and lorcaserin QD, 46.0 and 38.7% achieved at least 5% weight loss, respec-

TABLE 1. Demographics at baseline

Demographics at randomization	Lorcaserin BID (n = 1602)	Lorcaserin QD (n = 801)	Placebo (n = 1601)
Age (yr)[a]	43.8 (11.8)	43.8 (11.7)	43.7 (11.8)
Sex (% female)	80.5	81.9	78.0
Race [n (%)]			
White	1080 (67.4)	538 (67.2)	1064 (66.5)
Black	306 (19.1)	160 (20.0)	319 (19.9)
Hispanic	174 (10.9)	86 (10.7)	181 (11.3)
Asian	12 (0.7)	3 (0.4)	10 (0.6)
Other	30 (1.9)	14 (1.8)	27 (1.7)
Weight (kg)[a]	100.1 (15.6)	99.8 (16.6)	100.5 (16.2)
Waist (cm)[a]	108.9 (12.2)	108.5 (12.7)	110.2 (12.5)
BMI (kg/m^2)[a]	36.0 (4.3)	35.8 (4.3)	35.9 (4.1)
BMI subgroups [n (%)]			
BMI <30 kg/m^2	75 (4.7)	32 (4.0)	55 (3.4)
BMI ≥ 30 and <35 kg/m^2	655 (40.9)	364 (45.4)	685 (42.8)
BMI ≥ 35 and <40 kg/m^2	542 (33.8)	248 (31.0)	538 (33.6)
BMI ≥ 40 and <45 kg/m^2	323 (20.2)	155 (19.4)	321 (20.0)
BMI ≥ 45 kg/m^2	7 (0.4)	2 (0.2)	2 (0.1)
Comorbid conditions [n (%)]			
Hypertension	388 (24.2)	175 (21.8)	382 (23.9)
Dyslipidemia	455 (28.4)	218 (27.2)	438 (27.4)
Cardiovascular disease	16 (1.0)	4 (0.5)	23 (1.4)
Glucose intolerance	29 (1.8)	15 (1.9)	18 (1.1)
Sleep apnea	72 (4.5)	27 (3.4)	73 (4.6)

[a] Data are mean (SD).

tively, compared with 24.0% in the placebo group ($P < 0.001$ for both). Least squares (LS) mean weight loss [95% confidence interval (CI)] using true ITT analysis with LOCF imputation for missing data in the lorcaserin BID and lorcaserin QD and placebo groups was −5.6% (−5.9 to −5.3%), −4.6% (−5.0 to −4.1%), and −2.7% (−3.1 to −2.4%), respectively.

Changes in anthropometric and metabolic parameters are presented in Tables 2 and 3 for the MITT and per-protocol populations, respectively. In the MITT population, waist circumference and BMI decreased to a significantly greater extent in the lorcaserin BID and lorcaserin QD groups in comparison with placebo. Small changes in LDL cholesterol in the lorcaserin BID group relative to placebo were not statistically significant. As stipulated by the prespecified analysis plan, statistical testing stopped when the change in LDL cholesterol did not differ between placebo and lorcaserin BID. According to this testing scheme, changes in total cholesterol, HDL cholesterol, and triglycerides in the lorcaserin groups did not differ significantly from placebo. *Post hoc* analyses of these parameters, which do not correct for multiplicity, are shown in Table 2. Neither lorcaserin dose significantly affected ApoA1; lorcaserin BID significantly lowered ApoB. Lipid changes observed in the per-protocol population were directionally similar to those in the MITT population, albeit with greater decreases in triglycerides and ApoB and a greater increase in HDL (Table 3). In addition, more patients assigned to lorcaserin BID than placebo decreased total daily use of medications to treat dyslipidemia (2.6 *vs.* 1.4%, respectively), and fewer patients on lorcaserin increased medication use (4.0 *vs.* 5.0%, respectively). Systolic and diastolic blood pressure decreased from baseline at wk 52 in all treatment groups, with no significant differences between placebo and lorcaserin-treated patients. More patients on lorcaserin BID decreased antihypertensive medication use compared with placebo (4.0 *vs.* 3.1%, respectively).

Patients taking lorcaserin BID lost significantly more body fat than did patients taking placebo (−9.9 *vs.* −4.6%, respectively; $P < 0.01$). Smaller changes were observed in lean body mass than in fat mass (Table 2). IWQOL-LITE questionnaire total scores increased (improved) in all treatment groups and were significantly greater in the lorcaserin BID (+11.8) and lorcaserin QD (+11.3) groups than the placebo group (+10.0; $P = 0.0057$ and $P < 0.001$ *vs.* placebo, respectively).

Discontinuation

The most common reasons for study dropout were patient decision and loss to follow-up (Supplemental Fig. 1, published on The Endocrine Society's Journals Online web site at http://jcem.endojournals.org). Lack of efficacy was given as a reason for withdrawal by 2.4 and 3.1% in the lorcaserin BID and lorcaserin QD groups, respectively, and 3.9% in the placebo group. Dropouts due to AE occurred more frequently in the lorcaserin BID and lorcaserin QD groups (7.2 and 6.2%, respectively) than in the placebo group (4.6%).

TABLE 2. Changes in metabolic and cardiovascular risk factors

	Lorcaserin 10 mg BID, n = 1561	Lorcaserin 10 mg QD, n = 771	Placebo, n = 1541	*P vs.* placebo[a]	
				BID	QD
Patients achieving ≥5% weight loss [n (%)]	737 (47.2)	310 (40.2)[b]	385 (25.0)	<0.001	<0.001
Patients achieving ≥10% weight loss [n (%)]	353 (22.6)	134 (17.4)[b]	150 (9.7)	<0.001	<0.001
Body weight					
Baseline (kg)	100.3 (15.7)	100.1 (16.7)	100.8 (16.2)		
Change (kg)	−5.8 (6.4)	−4.7 (6.4)[b]	−2.9 (6.4)	<0.001	<0.001
Change (%)	−5.8 (6.3)	−4.7 (6.3)[b]	−2.8 (6.3)	<0.001	<0.001
Change (kg) in subgroups [mean (SD)]					
Men	−5.6 (7.2)	−6.0 (8.0)	−3.9 (6.9)	ND	ND
Women	−5.8 (6.4)	−4.4 (6.3)	−2.6 (5.8)	ND	ND
White	−6.7 (7.0)	−5.5 (7.1)	−3.5 (6.6)	ND	ND
Black	−3.9 (5.1)	−3.4 (5.6)	−1.2 (4.1)	ND	ND
Hispanic	−3.4 (5.1)	−1.8 (4.2)	−2.0 (4.6)	ND	ND
BMI <30 kg/m^2	−5.7 (5.3)	−4.7 (4.8)	−3.5 (4.7)	ND	ND
BMI ≥30 and <35 kg/m^2	−5.4 (6.1)	−4.4 (5.7)	−2.6 (5.2)	ND	ND
BMI ≥35 and <40 kg/m^2	−6.3 (7.0)	−5.3 (7.2)	−2.6 (5.9)	ND	ND
BMI ≥40 and <45 kg/m^2	−5.5 (7.0)	−4.8 (8.0)	−3.7 (7.8)	ND	ND
BMI (kg/m^2)					
Baseline	36.1 (4.3)	35.9 (4.3)	36.0 (4.2)		
Change	−2.1 (2.3)	−1.7 (2.3)[b]	−1.0 (2.3)	<0.001	<0.001
Waist (cm)					
Baseline	108.9 (12.2)	108.5 (12.7)	110.2 (12.5)		
Change	−6.3 (8.3)	−5.8 (8.2)	−4.1 (8.0)	<0.001	<0.001
Total cholesterol (mg/dl)					
Baseline	194.2 (37.5)	194.8 (37.8)	193.1 (36.8)		
% change	−0.7 (13.0)	−1.3 (13.0)	0.0 (13.0)	NS	0.03
LDL-C (mg/dl)					
Baseline	116.3 (32.0)	116.7 (32.0)	114.8 (29.9)		
% change	0.3 (19.7)	−0.1 (19.7)	1.7 (19.7)	NS	NS
HDL-C (mg/dl)					
Baseline	51.5 (12.9)	51.8 (13.6)	51.3 (13.2)		
% change	3.7 (15.4)	3.5 (15.4)	1.3 (15.3)	<0.001	<0.01
Triglycerides (mg/dl)					
Baseline	133.3 (78.2)	133.3 (78.0)	135.9 (72.8)		
% change	−4.3 (36.9)	−5.5 (36.9)	−0.9 (36.9)	0.02	<0.01
ApoA1 (g/liter)					
Baseline	1.47 (0.24)	1.49 (0.24)	1.47 (0.24)		
% change	−0.2 (11.2)	0.7 (11.2)	−0.4 (11.2)	NS	NS
ApoB (g/liter)					
Baseline	0.91 (0.22)	0.91 (0.20)	0.91 (0.20)		
% change	−2.9 (15.9)	−0.5 (15.9)	1.4 (15.9)	<0.001	NS
HbA1C (%)					
Baseline	5.6 (0.4)	5.6 (0.4)	5.6 (0.4)		
Change	−0.19 (0.3)	−0.17 (0.3)	−0.14 (0.3)	ND	ND
Systolic BP (mm Hg)					
Baseline	122.1 (12.16)	121.2 (12.18)	121.9 (11.91)		
Change	−1.9 (10.7)	−1.3 (10.8)	−1.2 (11.0)	NS	NS
Diastolic BP (mm Hg)					
Baseline	78.1 (8.13)	78.0 (8.43)	78.3 (8.06)		
Change	−1.9 (7.9)	−1.1 (7.8)	−1.4 (7.8)	NS	NS
Heart rate (bpm)[d]					
Baseline	69.1 (8.8)	68.8 (8.8)	69.0 (8.7)		
Change	−2.3 (8.8)	−1.1 (9.3)	−1.6 (9.0)	ND	ND
Total body fat (%)	n = 85	n = 35	n = 69		
Baseline	44.54 (8.05)	45.68 (9.84)	45.00 (8.97)		
% change	−9.9 (3.1)	−6.1 (3.1)	−4.6 (3.1)	<0.01	NS
Lean body mass (%)	n = 85	n = 35	n = 69		
Baseline	48.00 (9.39)	48.17 (9.03)	50.98 (10.82)		
% change	−1.88 (4.1)	−1.95 (3.8)	−0.32 (3.3)	0.02	NS
IWQOL-LITE[c]					
Baseline	74.7 (16.1)	75.5 (16.0)	75.3 (15.6)		
Change	11.8 (10.1)	11.3 (10.3)	10.0 (10.1)	<0.001	<0.01

Baseline values are presented as mean (SD); change values are LS mean (SD) unless specified otherwise. Analyses used the MITT population with LOCF imputation for missing values. BP, Blood pressure; C, cholesterol; HbA1C, glycosylated hemoglobin; ND, not determined; NS, not significant.

[a] Analysis of difference in proportions or LS means.

[b] $P < 0.01$, lorcaserin QD *vs.* lorcaserin BID.

[c] Converted 0–100 score, 100 being the highest quality of life.

[d] Safety population.

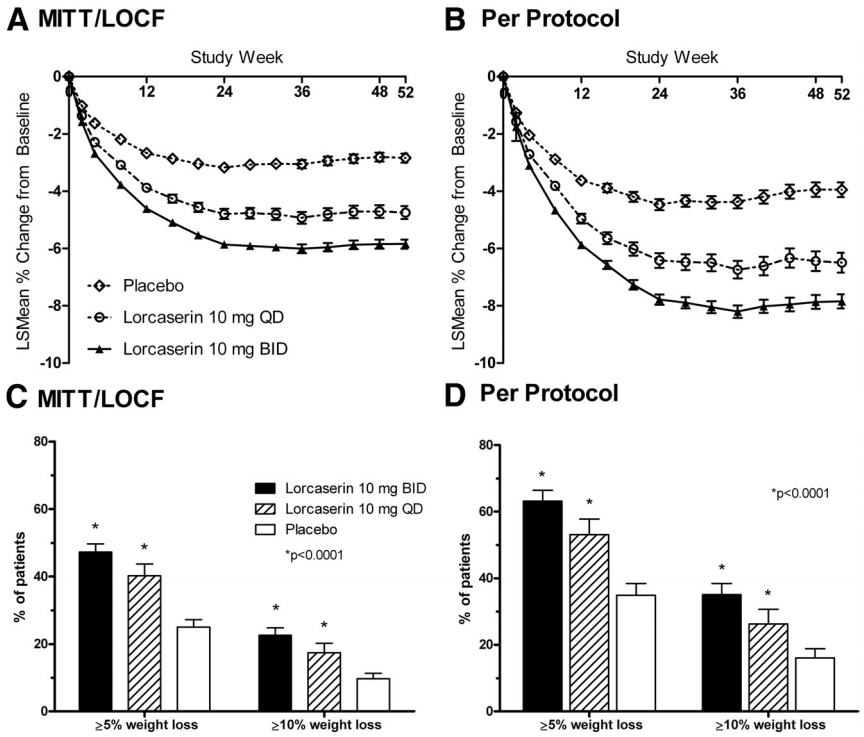

FIG. 1. Body weight change from baseline to wk 52. Weight change by study visit: A, MITT/LOCF analysis; B, per-protocol analysis; ▲, lorcaserin 10 mg BID; ○, lorcaserin 10 mg QD; ◇, placebo. Categorical weight loss: C, MITT/LOCF analysis; D, per-protocol analysis; *black bars*, lorcaserin 10 mg BID; *hatched bars*, lorcaserin 10 mg QD; *white bars*, placebo.

Adverse events

A higher proportion of patients taking lorcaserin BID (82.6%) or lorcaserin QD (81.5%) experienced AE than did those in the placebo group (75.3%; Table 4). The most common AE that occurred more frequently in both lorcaserin groups were headache, upper respiratory infection, nausea, dizziness, and fatigue. Serious AE were reported by slightly more patients taking lorcaserin than placebo; no single event type accounted for the difference (Table 4). One patient assigned to placebo died during the study after experiencing an exacerbation of asthma. Investigators considered six serious AE to be possibly related to the study drug; three occurred in the placebo group (syncope, ventricular tachycardia, and anaphylactic reaction), and three occurred in the lorcaserin BID group (syncope, moderate depression, and acute anxiety attack). The overall incidence of depression and depressed mood was low, and the sum was not higher in the lorcaserin groups than in the placebo group (Table 4). The Beck Depression Inventory-II LS mean (SD) total scores decreased at wk 52 in all treatment groups [−0.8 (3.9), −0.8 (4.1), and −0.7 (3.8) points, in lorcaserin BID, lorcaserin QD, and placebo, respectively]. No lorcaserin-associated changes in clinical laboratory parameters or electrocardiogram parameters were identified.

At wk 52, 2.0% (n = 1208; 95% CI = 1.2–2.8) of patients assigned to lorcaserin BID, 1.4% (n = 622; 95% CI = 0.5–2.4) on lorcaserin QD and 2.0% (n = 1153; 95% CI = 1.2–2.8) on placebo developed new echocardiographic findings of FDA-defined valvulopathy. Shifts in regurgitant scores for the individual heart valves were comparably distributed among treatment groups (Fig. 2). In patients with preexisting valvulopathy identified by the echocardiogram obtained at randomization (5.2% lorcaserin BID, 3.9% lorcaserin QD, and 4.1% placebo), the proportion of patients who experienced any increase in mitral or aortic regurgitation at wk 52 was 12.1% in the lorcaserin BID group ($P = 0.014$) and 11.1% in the lorcaserin QD group ($P = 0.056$) compared with 30.6% in placebo group. LS mean (SD) PASP at baseline for the lorcaserin BID, lorcaserin QD, and placebo treatment groups were 24.8 (5.3), 24.7 (4.8), and 24.5 (5.2) mm Hg, respectively. LS mean (SD) change in PASP from baseline to wk 52 was statistically, but not clinically, greater for the lorcaserin BID group [+0.04 (5.6)] compared with placebo [−0.4 (5.5), $P = 0.01$] whereas the change in the lorcaserin QD group [−0.2 (5.5)] did not differ significantly from placebo ($P = 0.3312$).

Discussion

Lorcaserin administration for 1 yr in conjunction with diet and exercise counseling to obese and overweight adults was associated with clinically and statistically significant weight loss. Significant decreases in body fat content, waist circumference, and quality of life accompanied the reduction in body weight. Although not statistically significant according to the prespecified multiplicity correction, an increase in HDL cholesterol and decreases in triglycerides and ApoB were also observed. Importantly, no increase in blood pressure or heart rate occurred in the populations that received lorcaserin.

The results of this trial are consistent with the results of a companion phase 3 trial of lorcaserin in 3182 patients dosed for up to 2 yr (the BLOOM trial) (17). Indeed, the mean weight loss of 5.8% (MITT/LOCF analysis) among patients treated with lorcaserin 10 mg BID in the present study is identical to that in the companion trial (17). In the present study, which evaluated a once-daily 10-mg dose as well as the twice-daily dose reported previously, weight loss was dose

TABLE 3. Changes in metabolic and cardiovascular risk factors in the per-protocol population

Per protocol	Lorcaserin 10 mg BID, n = 846	Lorcaserin 10 mg QD, n = 418	Placebo, n = 764	*P vs.* placebo[a]	
				BID	QD
Patients achieving ≥5% weight loss [n (%)]	535 (63.2)	222 (53.1)[b]	267 (34.9)	<0.001	<0.001
Patients achieving ≥10% weight loss [n (%)]	297 (35.1)	110 (26.3)[b]	123 (16.1)	<0.001	<0.001
Weight					
Baseline (kg)	100.2 (15.8)	99.3 (16.8)	101.3 (16.4)		
Change (kg)	−7.7 (7.3)	−6.5 (7.3)[b]	−3.9 (7.3)	<0.001	<0.001
% change	−7.9 (7.1)	−6.5 (7.1)	−4.0 (7.1)	<0.001	<0.001
BMI (kg/m^2)					
Baseline	35.8 (4.2)	35.5 (4.2)	35.9 (4.2)		
Change	−2.8 (2.6)	−2.3 (2.6)	−1.4 (2.7)	<0.001	<0.001
Waist (cm)					
Baseline	109.2 (12.4)	108.0 (12.6)	110.9 (12.9)		
Change	−7.6 (8.4)	−6.9 (8.6)	−4.8 (8.5)	<0.001	<0.001
Total cholesterol (mg/dl)					
Baseline	194.9 (39.7)	194.5 (36.9)	192.4 (34.7)		
% change	−1.15 (13.7)	−1.39 (13.7)	−0.00 (13.7)	NS	NS
LDL-C (mg/dl)					
Baseline	116.7 (32.1)	116.7 (31.8)	113.9 (28.6)		
% change	−0.5 (20.7)	−0.7 (20.7)	1.4 (20.7)	NS	NS
HDL-C (mg/dl)					
Baseline	51.8 (13.3)	51.7 (13.3)	51.4 (13.2)		
% change	5.9 (15.4)	5.3 (15.4)	3.2 (15.4)	<0.001	0.023
Triglycerides (mg/dl)					
Baseline	135.1 (81.4)	131.2 (67.6)	137.5 (89.4)		
% change	−9.1 (35.5)	−8.2 (35.5)	−3.2 (35.5)	0.001	0.022
ApoA1 (g/liter)					
Baseline	1.46 (0.24)	1.48 (0.23)	1.47 (0.23)		
% change	0.4 (11.3)	1.6 (11.3)	−0.4 (11.4)	NS	NS
ApoB (g/liter)					
Baseline	0.91 (0.22)	0.91 (0.20)	0.90 (0.20)		
% change	−3.4 (16.9)	−0.2 (16.9)	1.7 (16.9)	<0.0001	NS
Systolic BP (mmHg)					
Baseline	122.7 (12.02)	121.9 (11.92)	123.4 (11.83)		
Change	−3.3 (10.8)	−1.8 (10.8)	−1.3 (10.8)	<0.001	NS
Diastolic BP (mm Hg)					
Baseline	78.3 (8.13)	78.4 (8.32)	78.8 (7.87)		
Change	−2.9 (7.9)	−1.3 (7.8)	−1.6 (7.7)	<0.001	NS
Total body fat (%)	n = 60	n = 19	n = 37		
Baseline	44.5 (7.9)	43.3 (8.2)	44.6 (9.3)		
% change	−12.3 (13.5)	−9.7 (14.8)	−7.1 (10.6)	0.018	NS
Lean body mass (%)	n = 60	n = 19	n = 37		
Baseline	47.0 (8.2)	46.6 (7.9)	52.4 (10.6)		
% change	−2.3 (4.2)	−2.0 (4.2)	−0.1 (4.0)	0.029	NS
IWQOL-LITE[c]					
Baseline	74.6 (15.9)	76.4 (15.5)	76.4 (14.9)		
Change	12.2 (9.8)	12.6 (9.8)	10.4 (9.9)	<0.001	<0.001

Baseline values are presented as mean (SD); change values are LS mean (SD). BP, Blood pressure; C, cholesterol; NS, Not significant.

[a] Analysis of difference in proportions or LS means.

[b] $P < 0.01$, lorcaserin QD *vs.* lorcaserin BID.

[c] Converted 0–100 score, 100 being the highest quality of life.

dependent as were changes in waist circumference, HDL cholesterol, ApoB, and body fat content. Lorcaserin effects on other lipid parameters were not strictly dose dependent; factors contributing to this finding may include adjustments during the trial in the doses of concomitant medications used to treat dyslipidemia and slight differences in duration of study participation among treatment groups.

To assess the efficacy of lorcaserin when taken continuously for a full year, we also analyzed the subpopulation of patients who completed the trial according to the protocol (the per-protocol population). Among this group, which comprised about half of the randomized subjects, lorcaserin 10 mg BID was associated with 7.9% (7.7 kg) weight loss, compared with 4.0% in the placebo group.

TABLE 4. Adverse events

	Lorcaserin BID (n = 1602)	Lorcaserin QD (n = 801)	Placebo (n = 1601)
Patients with any AE	1323 (82.6)	653 (81.5)	1205 (75.3)
Patients with any serious AE	49 (3.1)	27 (3.4)	36 (2.2)
Discontinuation due to AE	115 (7.2)	50 (6.2)	73 (4.6)
AE with incidence ≥5% in any group			
Headache	250 (15.6)	125 (15.6)	147 (9.2)
Upper respiratory tract infection	204 (12.7)	117 (14.6)	202 (12.6)
Nasopharyngitis	201 (12.5)	95 (11.9)	192 (12.0)
Nausea	145 (9.1)	61 (7.6)	85 (5.3)
Dizziness	140 (8.7)	50 (6.2)	62 (3.9)
Fatigue	134 (8.4)	53 (6.6)	66 (4.1)
Sinusitis	122 (7.6)	67 (8.4)	117 (7.3)
Urinary tract infection	107 (6.7)	61 (7.6)	77 (4.8)
Back pain	101 (6.3)	55 (6.9)	91 (5.7)
Diarrhea	98 (6.1)	53 (6.6)	94 (5.9)
Dry mouth	87 (5.4)	27 (3.4)	37 (2.3)
Constipation	80 (5.0)	41 (5.1)	61 (3.8)
Psychiatric AE of interest			
Depression	31 (1.9)	9 (1.1)	29 (1.8)
Depressed mood	10 (0.6)	7 (0.9)	14 (0.9)
Suicidal ideation	15 (0.9)	5 (0.6)	11 (0.7)

Results are shown as n (%).

Using the MITT/LOCF analysis, patients taking lorcaserin lost an average of 5.8 kg at 52 wk, 2.9 kg more than patients in the placebo group. Predictably, larger changes in cardiometabolic parameters occurred in the per-protocol group than in the MITT population, including statistically significant decreases in systolic and diastolic blood pressure at 10 mg BID.

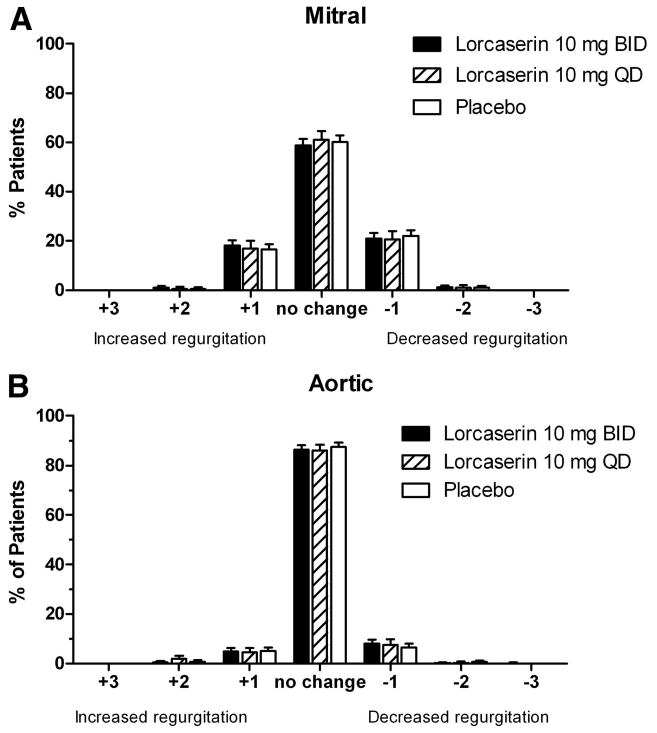

FIG. 2. Shifts in mitral (A) and aortic (B) regurgitant scores from baseline to wk 52. The proportions of patients who experienced shifts across given numbers of categories are presented by treatment group. Regurgitant categories are absent, trace, mild, moderate, and severe. *Black bars*, lorcaserin 10 mg BID; *hatched bars*, lorcaserin 10 mg QD; *white bars*, placebo.

Significant weight loss occurred in men and women, across BMI subgroups, and across racial subgroups, although the magnitude of mean weight loss was greater in Caucasians than in African-Americans or Hispanics. The efficacy difference among racial subgroups was not due to differing lorcaserin exposure, because predose and postdose plasma lorcaserin concentrations did not differ among these subgroups (26).

Decreased food intake due to increased satiety and decreased hunger is the probable mechanism of lorcaserin-induced weight loss. Activation of the 5-HT_{2C} receptor has long been known to reduce food consumption in rodents, an effect predicted to cause weight loss (10, 27–31). In healthy obese human volunteers studied for 2 months, lorcaserin decreased daily caloric intake by about 250 kcal and had no effect on energy expenditure or respiratory quotient; significant weight loss was observed and was concluded to be secondary to reduced food intake (32). The observed magnitude of weight loss in the present study is consistent with this single observed mechanism. The magnitude of changes in lipids and blood pressure are consistent with decreases secondary to the observed weight loss.

Weight loss can be considered clinically significant when associated with favorable changes in cardiometabolic risk factors, comorbid medical conditions, quality of life, or hard outcomes like cardiovascular events or the development of new comorbid conditions like type 2 diabetes. In a general sense, weight loss of 5–10% is associated with improvements

in hypertension, dyslipidemia, glycemic control, symptoms of osteoarthritis of the knee, sleep apnea, and quality of life (33–35). The Diabetes Prevention Program showed that 5% weight loss reduced the 5-yr risk of developing new type 2 diabetes by 58% (36). Within the present study, independent predictors of cardiovascular risk that included waist circumference and blood pressure (in the per-protocol population) decreased significantly with lorcaserin treatment. Quality of life also improved, as measured by the IWQOL-LITE, for which score increases of 7–12 are considered to be clinically meaningful (37). Although not declared statistically significant according to prespecified multiplicity correction, increase in HDL and decrease in triglycerides among patients treated with lorcaserin 10 mg BID were associated with favorable changes in the use of medications used to treat dyslipidemia. In general, such changes in medication use may translate into a meaningful impact on a patient's overall health care.

In this study, the lorcaserin-treated population achieved modest but clinically favorable changes with few adverse effects. Discontinuations due to AE were relatively infrequent, and the most common lorcaserin-associated AE were usually described as mild or moderate in intensity with spontaneous resolution during continued lorcaserin use. Importantly, at 1 yr, lorcaserin did not increase the incidence of FDA-defined cardiac valvulopathy, which can occur with nonselective agents like fenfluramine or pergolide that activate the serotonin 2B receptor (38, 39).

Notable limitations of this study include the exclusion of some preexisting conditions, a high dropout rate that is typical of pharmacological weight-control studies, and the limited statistical power of the echocardiographic safety analysis. The protocol excluded patients with type 2 diabetes, a group among whom weight loss is usually needed but for whom weight loss tends to be more difficult. A separate clinical study is being conducted to evaluate lorcaserin for weight management in patients with type 2 diabetes. Use of serotonergic antidepressants was not allowed during the trial, because serotonin syndrome can occur with concurrent use of two serotonergic agents. Hence, this study does not address possible effects of lorcaserin in a more general population of individuals with pharmacologically treated depression. In clinical trials of weight management, as in clinical practice, patient compliance and trial retention are challenging (40). High discontinuation rates necessitate imputation methods to account for missing data, none of which can ideally predict what might have occurred had the patients remained in the trial and on the study medication. Although LOCF imputation was used for the primary data analyses, a per-protocol population (for which there are no missing data) was also analyzed in this trial to predict the effect of lorcaserin during continued use for 1 yr. It is unclear which approach more accurately predicts the expected efficacy of lorcaserin in a clinical practice setting. The evaluation of cardiac valvulopathy is challenging and requires a large patient population to reliably exclude a small risk. The current study has under 80% statistical power to exclude a relative risk of 1.5 for the development of new FDA-defined valvulopathy. Future analyses of echocardiographic data collected during multiple clinical trials will be required to more fully characterize the risk of valvular heart disease among patients taking lorcaserin.

Lorcaserin used for up to 1 yr was associated with significant weight loss among obese and overweight adults. This study contributes to the overall understanding of lorcaserin's risk-benefit profile for weight management and supports continued evaluation of this potential new weight management tool.

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