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Randomized Placebo-Controlled Clinical Trial of Lorcaserin for Weight Loss in Type 2 Diabetes Mellitus: The BLOOM-DM Study

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The BLOOM-DM (Behavioral Modification and Lorcaserin for Obesity and Overweight Management in Diabetes Mellitus) study evaluated efficacy and safety of lorcaserin for weight loss in patients with type 2 diabetes. Secondary objectives included evaluations of glycemic control, lipids, blood pressure, and quality of life. This 1-year, randomized, placebo-controlled trial enrolled 604 patients 1:1:1 to placebo, lorcaserin 10 mg once daily (QD) or lorcaserin 10 mg twice daily (BID). Patients were treated with metformin, a sulfonylurea (SFU) or both; had glycated hemoglobin (HbA_{1c}) 7–10%; were 18–65 years old; and had BMI 27–45 kg/m^2. Patients received diet and exercise counseling. Safety monitoring included serial echocardiograms. Mean (± SD) age was 52.7 ± 8.7; 54.2% were women; 60.5% were white, 20.9% were African American, and 13.8% were Hispanic. Mean (± SD) weight was 103.6 ± 17.8 kg; BMI was 36.0 ± 4.5 kg/m^2. Most patients (91.7%) took metformin; 50.2% took a SFU. More patients lost ≥5% body weight with lorcaserin BID (37.5%; $P < 0.001$) or lorcaserin QD (44.7%; $P < 0.001$) vs. placebo (16.1%; modified intent to treat (MITT)/last observation carried forward (LOCF)). Least square mean (± SEM) weight change was –4.5 ± 0.35% with lorcaserin BID and –5.0 ± 0.5% with lorcaserin QD vs. –1.5 ± 0.36% with placebo ($P < 0.001$ for each). HbA_{1c} decreased 0.9 ± 0.06 with lorcaserin BID, 1.0 ± 0.09 with lorcaserin QD, and 0.4 ± 0.06 with placebo ($P < 0.001$ for each); fasting glucose decreased 27.4 ± 2.5 mg/dl, –28.4 ± 3.8 mg/dl, and 11.9 ± 2.5 mg/dl, respectively ($P < 0.001$ for each). Symptomatic hypoglycemia occurred in 7.4% of patients on lorcaserin BID, 10.5% on lorcaserin QD, and 6.3% on placebo. Common adverse events were headache, back pain, nasopharyngitis, and nausea. Lorcaserin was associated with significant weight loss and improvement in glycemic control in patients with type 2 diabetes.

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INTRODUCTION

Activation of the serotonin 2C receptor decreases food intake by increasing satiety and decreasing hunger (1). Although the primary role of the $5HT_{2C}$ receptor is thought to be regulation of ingestive behavior through the hypothalamic melanocortin system, studies conducted using mouse models of diabetes and obesity indicate that the receptor may also have a role in regulating glucose tolerance and hepatic insulin sensitivity (2,3). Lorcaserin is a selective small molecule agonist of the $5HT_{2C}$ receptor that is being developed to take advantage of the anorexigenic property of the receptor for the treatment of obesity.

In two phase 2 trials and two large phase 3 trials, lorcaserin caused significant weight loss in overweight and obese individuals who did not have diabetes (4–7). Weight loss was accompanied by generally favorable changes in lipids, blood pressure, anthropometric measures, and insulin sensitivity. However, the efficacy and safety of lorcaserin in people with type 2 diabetes mellitus has not been previously evaluated.

Excess body weight is a key contributor to type 2 diabetes. Indeed, over 85% of adults diagnosed with type 2 diabetes are classified as overweight (BMI ≥25 kg/m^2 or obese (30 kg/m^2) (8). A cornerstone of treatment is weight reduction through behavioral modification that includes diet and exercise. Weight loss of as little as 5% can significantly improve glycemic control, and may have beneficial effects on weight-related comorbid conditions as well (9,10). Unfortunately, meaningful weight loss has historically been more difficult to achieve among individuals with diabetes than among nondiabetic populations (11–13).

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The BLOOM-DM (Behavioral Modification and Lorcaserin for Obesity and Overweight Management in Diabetes Mellitus) study had as its main objective the evaluation of the efficacy and safety of lorcaserin for weight loss in adults with type 2 diabetes treated with metformin and/or a sulfonylurea (SFU). Secondarily, the impact of lorcaserin on glycemic control was evaluated.

METHODS AND PROCEDURES

Study design

The study was conducted at 58 academic and private research sites in the United States between 27 December 2007 and 9 August 2010 under the guidelines of the Declaration of Helsinki. Institutional review boards reviewed and approved the protocol for each research site. All patients provided written informed consent before participation in the trial.

The overall objective of the 1-year, randomized, double-blind, placebo-controlled trial was to evaluate the safety and efficacy of lorcaserin for weight loss in patients with type 2 diabetes when administered in conjunction with a lifestyle modification program. The prespecified co-primary endpoints were: (i) the proportion of patients achieving ≥5% reduction in baseline body weight at the end of 1 year, (ii) change in weight, and (iii) the proportion of patients achieving ≥10% reduction in baseline body weight. Secondary endpoints included changes from baseline in glycemic control (glycated hemoglobin (HbA_{1c}), fasting plasma glucose, fasting insulin, homeostatic model assessment-insulin resistance (HOMA-IR), ref. (14)), lipids (total cholesterol, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, triglycerides); physical measures (waist circumference, BMI, systolic blood pressure, diastolic blood pressure); and quality of life, as assessed by the Impact of Weight on Quality of Life-LITE questionnaire (IWQOL-LITE) (15).

Patients were randomly assigned in a 1:1:1 ratio, stratified by oral use of metformin or SFU, to receive lorcaserin 10 mg twice daily (BID), lorcaserin 10 mg each morning and placebo each evening ("lorcaserin 10 mg once daily (QD)"), or placebo BID before breakfast and dinner. Patients taking both metformin and SFU were stratified with the SFU group, since the primary purpose of the stratification was to assess risk of hypoglycemia. After ~8 months, the protocol was amended to stop enrollment into the lorcaserin 10 mg QD group because study recruitment was much slower than expected. The patients who had already been enrolled remained in the study. Patients, investigators, and sponsors remained blinded to treatment assignments throughout the trial.

Inclusion/exclusion criteria

Eligible patients had type 2 diabetes mellitus treated with metformin, a SFU or both; had HbA_{1c} at screening visit of 7–10%; were 18–65 years old with BMI 27–45 kg/m^2, inclusive; and were able to participate in a moderate intensity exercise program.

Key exclusion criteria included use of insulin in any form, or use of exenatide or pramlintide (due to potential effects on body weight); prior bariatric surgery; change in weight of ≥5 kg within 3 months; Binge Eating Scale (16) score >17; significant change in cigarette smoking within 3 months; malignancy within 5 years; recent major surgery; history of seizure disorder within 5 years; depression or other major psychiatric disease requiring treatment with prescription medication within 1 year; Beck Depression Inventory-II (BDI-II) (17) 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, or unstable angina. Medication exclusion criteria included prior administration of lorcaserin or drugs associated with cardiac valvulopathy, use of selective serotonin reuptake inhibitors or selective norepinephrine reuptake inhibitors (theoretical risk of serotonin syndrome when combining multiple serotonergic agents), topiramate, and drugs for weight loss. Laboratory exclusion criteria included clinically significant thyroid stimulating hormone and/or T4 abnormalities; triglycerides >499 mg/dl; LDL cholesterol ≥160 mg/dl; aspartate aminotransferase or alanine aminotransferase >2.5 times upper limit of normal; bilirubin >1.5 times upper limit of normal; creatinine >1.5 times upper limit of normal; and positive HIV, hepatitis B or hepatitis C screen.

Study procedures

Study visits occurred 2 and 4 weeks after randomization, and monthly thereafter. A lifestyle modification program was administered to all patients at each visit, and included advice about exercise, behavior modification techniques, calorie restriction, and food choices. Individual counseling sessions were administered by trained research site staff, and lasted from 15–60 min. Patients were instructed to exercise moderately for 30 min each day, and to reduce daily caloric intake by 600 kcal below estimated daily energy requirements. Individual energy requirements were calculated using World Health Organization equations (18) with an activity factor of 1.3. Each patient was given a OneTouch glucose meter (LifeScan, Milpitas, CA), instructed on its use, and asked to self-monitor blood glucose BID, before breakfast and before dinner. Patients were instructed to call an interactive voice response system if they believed that they were experiencing hypoglycemia; during the call, they were asked to respond to a series of questions to ascertain the nature and severity of the episode, and the steps taken to treat it.

Vital signs, concomitant medication use, and adverse events were assessed at each session. Study drug compliance was evaluated by counting pills at each research site visit. Routine safety laboratory studies (a chemistry panel, complete blood count, and urinalysis) were performed at baseline, week 4, week 12, and every 3 months thereafter. Urine pregnancy tests were performed at each visit for women and serum pregnancy tests were performed at baseline and study completion. HbA_{1c} was measured at weeks 2, 12, 24, 36, and 52. HOMA-IR was calculated using the Oxford University HOMA calculator (14) from plasma insulin and plasma glucose measured at weeks 2, 24, and 52. Patients completed the IWQOL-LITE questionnaire at baseline, and at weeks 24 and 52. The BDI-II was administered at randomization, and at weeks 4, 24, and 52. Electrocardiograms were performed at baseline and week 52. Echocardiograms were performed at baseline, week 24 and week 52.

Echocardiography

Echocardiography was performed as described previously (6). Briefly, a central core echocardiography laboratory (Biomedical Systems, St Louis, MO) trained all sonographers and cardiologists who participated in the clinical trial, and certified the sonography equipment at each research site. A panel of 14 cardiologists interpreted the echocardiograms, with two reading each study independently. Any disagreements (meeting predefined criteria) were adjudicated by a third cardiologist. Aortic and mitral insufficiency were rated on a five point scale (absent, trace, mild, moderate, severe), according to American Society of Echocardiography criteria (19). Valvular regurgitation was also characterized according to Food and Drug Administration (FDA)-defined valvulopathy criteria, which include mild or greater aortic regurgitation (AR) and/or moderate or greater mitral regurgitation (MR). Pulmonary artery systolic pressure was estimated using the tricuspid regurgitant jet velocity (20,21).

Statistical analyses

Sample size. The sample size calculation assumed that ~15% of subjects in the placebo group would achieve ≥5% weight loss, and anticipated that at least twice as many lorcaserin BID-treated patients should achieve this level of weight reduction to be clinically meaningful. Based on a two-sample test of equality of binomial proportions at the 0.05 level of significance, a sample size of 147 patients per group would provide 84% power. Assuming a 40% dropout rate, target enrollment was set at 250 per group. The actual dropout rate was 36%, which is typical for large pharmacological weight management trials (22).

Analysis populations. Primary efficacy analyses used a modified intent to treat (MITT) population with last observation carried forward

(LOCF) imputation for missing data; all randomized patients with at least one post-baseline weight measurement were included. Prespecified sensitivity analyses of weight loss parameters used two additional populations: (i) completer population (patients who completed the study; and (ii) all patients with a body weight recorded at week 52, even if they withdrew from the study prematurely and returned only to have body weight recorded. The analyses of echocardiographic data included all randomized patients with at least one post-baseline echocardiogram, and used LOCF imputation for missing post-baseline data.

Primary and secondary efficacy analyses. The three co-primary endpoints were analyzed using a hierarchical testing procedure in the following order: the proportion of patients who lost ≥5% body weight, mean body weight change, and the proportion of patients who lost ≥10% body weight. Comparisons for categorical weight loss used a logistic regression model with effects for treatment, baseline body weight (kg), baseline antihyperglycemic treatment stratum and baseline HbA_{1c} stratum (<9% or ≥9%). Change in weight used analysis of covariance models with treatment, baseline antihyperglycemic treatment stratum, and baseline HbA_{1c} stratum as factors, and baseline body weight as a covariate. Secondary efficacy endpoints were grouped into families (lipids, glycemic control, blood pressure, and quality of life); within each family, endpoints were prioritized in a prespecified order. For blood pressure (systolic, diastolic), lipid (triglycerides, HDL cholesterol, LDL cholesterol, total cholesterol) and glycemic indicators (HbA_{1c}, fasting glucose, fasting insulin, HOMA-IR), the first endpoint within each family was assessed; each subsequent endpoint was assessed only if the preceding endpoint(s) was (were) significant.

Echocardiographic analysis. The echocardiographic endpoint was the proportion of patients who developed FDA-defined criteria for valvulopathy. The data were analyzed using Pearson's χ^2 test.

RESULTS

The demographic data and baseline characteristics of the enrolled patient population are summarized in **Table 1**. Approximately 54% of the patients were women, and the mean age was ~53 years. Demographic characteristics were well-matched among the

Table 1 Demographic and baseline characteristics of patient population

	Safety population			Completers population		
Mean ± SD	Placebo, *N* = 252	Lorcaserin 10 mg BID, *N* = 256	Lorcaserin 10 mg QD, *N* = 95	Placebo, *N* = 157	Lorcaserin 10 mg BID, *N* = 169	Lorcaserin 10 mg QD, *N* = 75
Age	52.0 ± 9.3	53.2 ± 8.3	53.1 ± 8.0	53.2 ± 8.3	53.9 ± 8.1	53.5 ± 7.4
Sex (*n* (% of patients))						
Women	137 (54.4)	137 (53.5)	53 (55.8)	84 (53.5)	83 (49.1)	41 (54.7)
Men	115 (45.6)	119 (46.5)	42 (44.2)	73 (46.5)	86 (50.9)	34 (45.3)
Weight (kg)	102.6 ± 18.1	103.7 ± 17.0	106.0 ± 19.4	101.6 ± 18.1	104.7 ± 17.9	105.4 ± 19.0
BMI (kg/m^2)	35.9 ± 4.5	36.1 ± 4.5	36.1 ± 4.8	35.5 ± 4.5	36.3 ± 4.5	35.9 ± 4.7
BMI subgroups (*n* (% of patients))						
<30	24 (9.5)	21 (8.2)	12 (12.6)	19 (12.1)	14 (8.3)	10 (13.3)
30–<35	88 (34.9)	82 (32.0)	28 (29.5)	58 (36.9)	52 (30.8)	24 (32.0)
35–<40	86 (34.1)	91 (35.5)	33 (34.7)	51 (32.5)	60 (35.5)	25 (33.3)
40–≥45	54 (21.4)	62 (24.2)	22 (23.2)	29 (18.5)	43 (25.4)	16 (21.3)
Race (*n* (% of patients))						
White	166 (65.9)	150 (58.6)	49 (51.6)	108 (68.8)	106 (62.7)	39 (52.0)
African American	45 (17.9)	55 (21.5)	26 (27.4)	24 (15.3)	36 (21.3)	22 (29.3)
Hispanic	27 (10.7)	39 (15.2)	17 (17.9)	16 (10.2)	23 (13.6)	12 (16.0)
Asian	8 (3.2)	11 (4.3)	3 (3.2)	8 (5.1)	4 (2.4)	2 (2.7)
Other	6 (2.4)	1 (0.4)	0	1 (0.6)	0	0
HbA_{1c}						
Mean (%)	8.1 ± 0.8	8.1 ± 0.8	8.1 ± 0.8	8.1 ± 0.8	8.0 ± 0.8	8.1 ± 0.8
≥9 (*n* (%))	45 (17.9)	47 (18.4)	14 (14.7)	26 (16.6)	32 (18.9)	10 (13.3)
<9 (*n* (%))	207 (82.1)	209 (81.6)	81 (85.3)	131 (83.4)	137 (81.1)	65 (86.7)
Fasting plasma glucose (mg/dl)	159.7 ± 41.7	164.5 ± 48.1	155.4 ± 45.2	160.2 ± 40.9	158.8 ± 43.0	155.6 ± 42.1
Antidiabetic medication (*n*(% of patients))						
Metformin	229 (90.9)	236 (92.2)	88 (92.6)	143 (91.1)	160 (94.7)	70 (93.3)
Sulfonylurea	127 (50.4)	129 (50.4)	47 (49.5)	79 (50.3)	84 (49.7)	40 (53.3)
Both	104 (41.3)	109 (42.6)	40 (42.1)	65 (41.4)	75 (44.4)	35 (46.7)

BID, twice daily; HbA_{1c}, glycated hemoglobin; QD, once daily.

treatment groups. Most patients (81.9%) had HbA_{1c} between 7 and 9% at screening; 18.1% had HbA_{1c} 9–10%. Inclusion criteria required that patients be taking metformin, SFU or both; accordingly, 91.5% took metformin, 50.4% took SFU, and 41.9% took both at study entry. Only 8.5% used SFU alone.

More patients assigned to lorcaserin BID (66.0%) and lorcaserin QD (78.9%) completed the study as compared to placebo (62.1%; **Figure 1**). More discontinuations were attributed to adverse events in the lorcaserin BID (8.6%) and QD (6.3%) groups than in the placebo group (4.3%). Withdrawal of consent was the most frequent reason for early discontinuation in all treatment groups.

Lorcaserin significantly increased the proportion of patients achieving ≥5% body weight loss from baseline to week 52 relative to placebo (**Figure 2a**, **Table 2**). Using MITT with LOCF imputation, 37.5% of patients on lorcaserin BID, 44.7% on lorcaserin QD, and 16.1% of patients on placebo lost at least 5% ($P < 0.001$), while 16.3, 18.1, and 4.4%, respectively, lost at least 10% of baseline body weight ($P < 0.001$). The weight reduction was evident at 2 weeks, and remained significantly greater in the lorcaserin groups than in the placebo group throughout the study (**Figure 2b**). Similar results for weight change were obtained when data from the subgroup of patients who completed the 52-week trial were analyzed (the completer population; **Table 2**, **Figure 2a,b**). Waist circumference and hip circumference decreased significantly more in the lorcaserin groups than in the placebo group at week 52 in the MITT population.

Glycemic control was evaluated by HbA_{1c}, fasting glucose, insulin, and calculated insulin resistance using HOMA-IR (**Table 3**). Mean HbA_{1c} decreased significantly more in the lorcaserin groups as compared to placebo at all time points, as did fasting plasma glucose (**Figure 3**). The proportion of patients who achieved HbA_{1c} ≤7% at week 52 was significantly greater in the lorcaserin BID group (50.4%) and in the lorcaserin QD group (52.2%) than in the placebo group (26.3%). Among the patients with HbA_{1c} <9% at baseline, a greater proportion in all treatment groups achieved HbA_{1c} ≤7% at week 52 as compared with patients in the higher baseline HbA_{1c} stratum; the proportions were significantly higher than placebo in the lorcaserin BID and QD groups (54.9% and 56.4% vs. 28.9%, respectively; **Table 3**). Insulin resistance was reduced significantly more in the lorcaserin BID than in the placebo group, as indicated by the greater reduction in HOMA-IR. Slightly more patients taking lorcaserin than placebo decreased the overall use of oral antidiabetic medications (17.1, 23.4, and 11.7% in the lorcaserin BID, lorcaserin QD, and placebo groups, respectively; $P = 0.087$), and fewer patients taking lorcaserin increased the total daily dose of antidiabetic agents (13.5, 11.7, and 22.2%, respectively; $P = 0.011$).

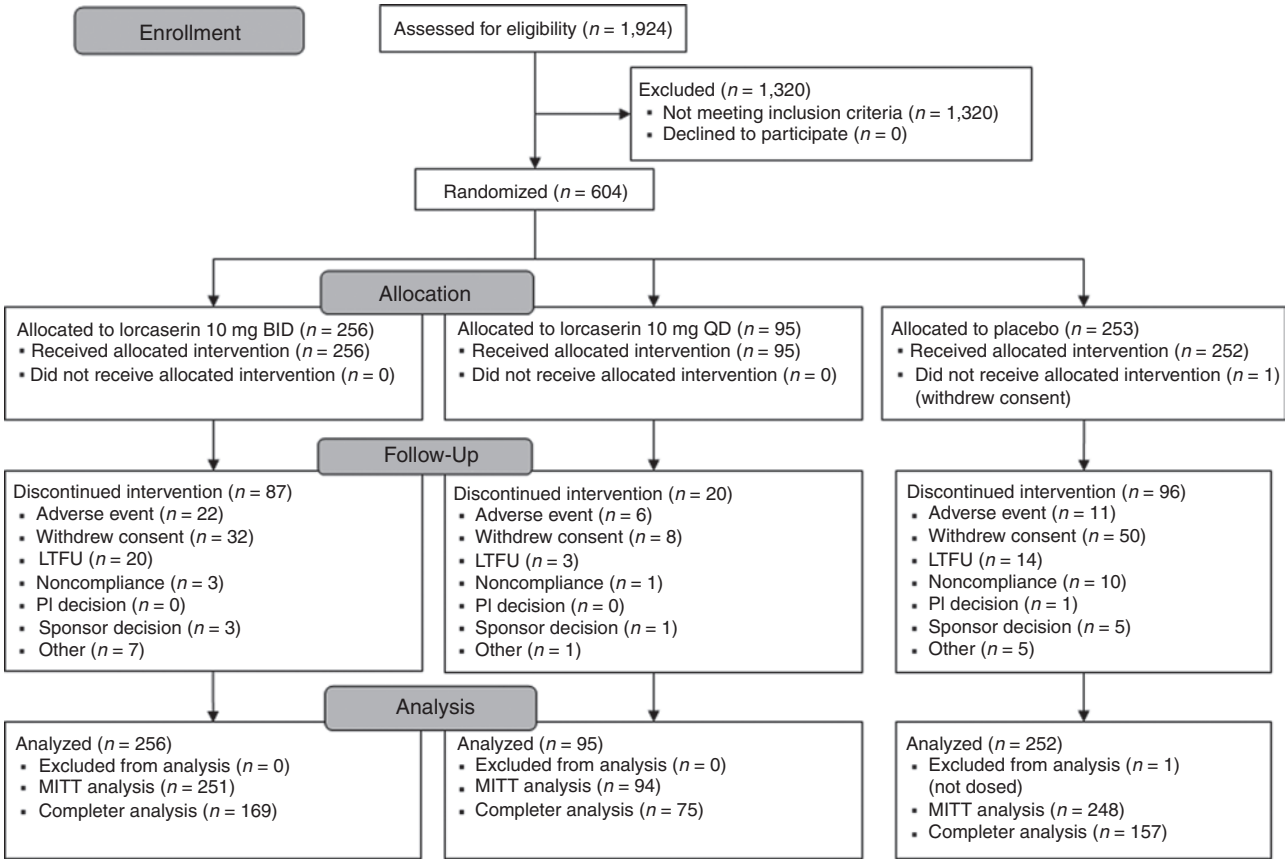

Figure 1 CONSORT figure summarizing patient enrollment and disposition. BID, twice daily; LTFU, lost to follow-up; MITT, modified intent to treat; PI, principle investigator; QD, once daily.

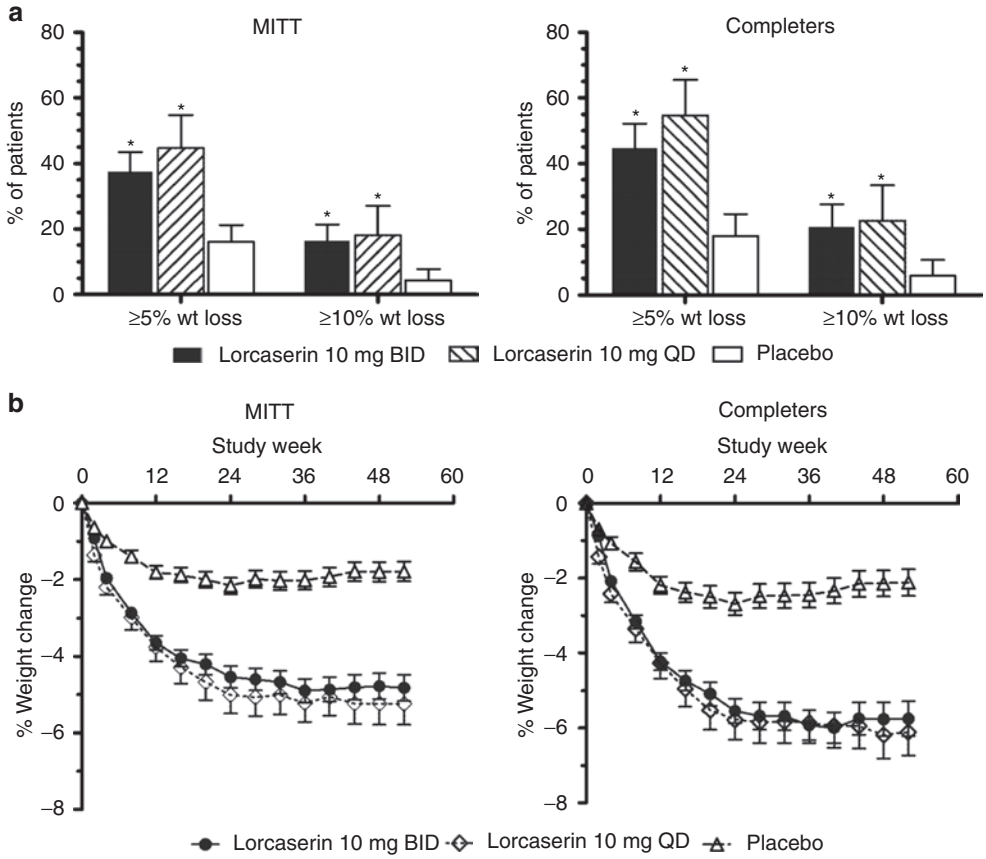

Figure 2 Analyses of body weight change. (**a**) Proportion of patients who lost ≥5% or ≥10% of body weight from baseline to week 52 using the modified intent to treat (MITT) population (left panel) or the completers population (right panel). Lorcaserin 10 mg BID, solid bars; lorcaserin 10 mg QD, hatched bars; placebo, open bars. Values are proportion ± 95% confidence interval. *$P < 0.001$ as compared to placebo. (**b**) Percent change in body weight from baseline to each study visit, using the MITT population (left panel) or the completers population (right panel). Lorcaserin 10 mg BID, closed circles with solid line; lorcaserin 10 mg QD, open diamonds with dotted line; placebo, open triangles with dashed line. Values are mean ± SEM. BID, twice daily; QD, once daily.

Hypoglycemia was more frequent in the lorcaserin groups than in the placebo group, with 7.4 and 10.5% of patients in the BID and QD groups, respectively, and 6.3% of patients on placebo reporting at least one episode of symptomatic hypoglycemia (Table 4). No patient in any treatment group reported severe hypoglycemia, defined as an episode that resulted in confusion, loss of consciousness, or treatment with parenteral agents; no patient in any treatment group withdrew from the study because of hypoglycemia. The combined incidence of all patient-reported adverse events of suspected hypoglycemia or "low blood glucose" (all events regardless of documented low glucose, and with or without symptoms) was higher among patients taking SFU than among those not taking SFU in the placebo (21.6 and 4.1%, respectively), lorcaserin QD (41.3 and 16.7%, respectively), and lorcaserin BID groups (31.7 and 11.2%, respectively).

Changes in cholesterol and triglycerides were small in all treatment groups, and the differences between treatment groups were not significant. According to the prespecified conditional statistical testing paradigm, the changes in LDL, HDL, and total cholesterol were not formally tested since the difference between lorcaserin BID and placebo change in triglycerides was not significant. High-sensitivity C-reactive protein was reduced in all treatment groups, and the IWQOL-LITE questionnaire score increased (improved) in all treatment groups (Table 2).

Systolic and diastolic blood pressure decreased from baseline to week 52 in the lorcaserin BID and placebo groups, with no statistically significant difference between treatments (Table 2). Heart rate decreased significantly more in the lorcaserin BID and lorcaserin QD groups than in the placebo group, 2.0 ± 0.6 beats per minute (bpm) and 2.9 ± 0.9 bpm vs. 0.5±0.6 bpm, respectively ($P = 0.03$ and $P = 0.01$; Table 2). Lorcaserin had no effect relative to placebo on other vital signs, including body temperature and respiratory rate.

Total scores on the BDI-II were low at baseline, and decreased similarly in all treatment groups at week 52 (Table 2).

Serial echocardiograms were conducted at baseline, 6 months, and 12 months. At baseline, 95.7% of patients had some valvular insufficiency; 9 (3.5%) patients assigned to lorcaserin BID, 9 (9.5%) assigned to lorcaserin QD, and 9 (3.6%) assigned to placebo had echocardiographic findings that met FDA-defined valvulopathy criteria. MR graded mild or greater was present in 13% of patients at baseline, and AR graded trace or greater was present in 27.7%. MR and AR regurgitant scores

Table 2 Change from baseline at week 52 in primary and secondary endpoints

	MITT/LOCF population					Completers population				
	Placebo, *N* = 248	Lorcaserin 10 mg BID, *N* = 251	*P* value[a]	Lorcaserin 10 mg QD, *N* = 95	*P* value[a]	Placebo, *N* = 157	Lorcaserin 10 mg BID, *N* = 169	*P* value[a]	Lorcaserin 10 mg QD, *N* = 75	P value[a]
Body weight (kg)	102.3 ± 18.0	103.5 ± 17.2		106.1 ± 19.6		101.7 ± 18.3	104.7 ± 17.9		105.4 ± 19.2	
Change from baseline (kg)	−1.6 ± 0.4	−4.7 ± 0.4	<0.001	−5.0 ± 0.6	<0.001	−1.9 ± 0.5	−5.6 ± 0.5	<0.001	−5.9 ± 0.7	<0.001
%Change from baseline	−1.5 ± 0.4	−4.5 ± 0.4	<0.001	−5.0 ± 0.5	<0.001	−1.7 ± 0.5	−5.5 ± 0.5	<0.001	−5.8 ± 0.7	<0.001
n(%) of patients with ≥5% wt loss	40 (16.1)	94 (37.5)	<0.001	42 (44.7)	<0.001	28 (17.9)	75 (44.6)	<0.001	41 (54.7)	<0.001
n(%) of patients with ≥10% wt loss	11 (4.4)	41 (16.3)	<0.001	17 (18.1)	<0.001	9 (5.8)	35 (20.8)	<0.001	17 (22.7)	<0.001
BMI (kg/m^2)	35.8 ± 4.5	36.1 ± 4.5		36.2 ± 4.8		35.5 ± 4.6	36.3 ± 4.5		35.9 ± 4.8	
Change from baseline	−0.6 ± 0.1	−1.6 ± 0.1	<0.001	−1.7 ± 0.2	<0.001	−0.7 ± 0.2	−2.0 ± 0.2	<0.001	−2.0 ± 0.2	<0.0001
Waist circumference (cm)	113.5 ± 12.6	115.8 ± 11.8		116.7 ± 13.0		114.0 ± 12.7	116.1 ± 12.0		116.1 ± 12.8	
Change from baseline	−3.3 ± 0.5	−5.5 ± 0.5	0.001	−5.0 ± 0.8	0.053	−3.3 ± 0.6	−5.9 ± 0.6	0.0003	−5.6 ± 0.8	0.012
Hip circumference (cm)	118.9 ± 12.0	120.0 ± 11.0		122.1 ± 11.9		119.2 ± 12.6	119.8 ± 11.6		121.1 ± 10.8	
Change from baseline	−2.8 ± 0.5	−4.1 ± 0.5	0.029	−5.3 ± 0.7	0.002	−3.1 ± 0.6	−4.2 ± 0.6	0.143	−5.4 ± 0.9	0.021
Systolic BP (mm Hg)	126.5 ± 13.5	126.6 ± 12.7		126.5 ± 11.4		126.4 ± 13.2	127.3 ± 13.4		126.1 ± 11.5	
Change from baseline	−0.9 ± 0.9	−0.8 ± 0.8	0.891	0.56 ± 1.3	0.288	−1.4 ± 1.1	−1.4 ± 1.0	0.974	0.8 ± 1.4	0.172
Diastolic BP (mm Hg)	78.7 ± 7.9	77.9 ± 8.0		78.1 ± 9.3		77.8 ± 7.6	78.6 ± 8.3		77.5 ± 9.7	
Change from baseline	−0.7 ± 0.6	−1.1 ± 0.6	0.563	0.29 ± 0.9	0.317	−0.7 ± 0.8	−1.2 ± 0.7	0.610	0.4 ± 1.0	0.350
Heart rate (bpm)	72.7 ± 9.0	72.3 ± 9.2		72.9 ± 8.5		72.5 ± 9.4	72.7 ± 9.7		73.3 ± 8.8	
Change from baseline	−0.4 ± 0.6	−2.0 ± 0.6	0.03	−2.9 ± 0.9	0.012	−0.3 ± 0.8	−2.2 ± 0.7	0.037	−3.2 ± 1.1	0.01
Total cholesterol (mg/dl)	172.0 ± 35.7	173.5 ± 35.3		173.9 ± 37.3		170.7 ± 37.6	170.5 ± 35.6		171.2 ± 36.1	
%Change	−0.1 ± 1.2	−0.7 ± 1.1	0.714	1.4 ± 1.7	0.423	1.0 ± 1.5	−0.1 ± 1.4	0.541	3.1 ± 2.0	0.367
LDL cholesterol (mg/dl)	94.6 ± 30.2	95.0 ± 30.4		94.3 ± 29.3		92.9 ± 31.4	93.8 ± 30.5		91.5 ± 28.2	
%Change	5.0 ± 2.6	4.2 ± 2.6	0.802	4.2 ± 4.0	0.846	7.9 ± 3.2	3.0 ± 3.1	0.208	5.0 ± 4.6	0.565
HDL cholesterol (mg/dl)	45.7 ± 12.7	45.3 ± 11.0		45.2 ± 12.0		46.1 ± 12.7	44.7 ± 9.9		45.8 ± 12.0	
%Change	1.6 ± 1.0	5.2 ± 1.0	0.005	4.4 ± 1.6	0.108	2.0 ± 1.3	6.3 ± 1.2	0.005	5.5 ± 1.7	0.071
Triglycerides (mg/dl)	163.5 ± 87.5	172.1 ± 103.6		179.4 ± 111.5		160.2 ± 83.9	164.3 ± 84.6		177.6 ± 120.3	
%Change	−4.8 ± 2.5	−10.7 ± 2.4	0.054	−5.5 ± 3.8	0.866	−5.0 ± 3.2	−11.2 ± 3.0	0.110	−5.2 ± 4.4	0.968
ApoA1 (mg/dl)	138.9 ± 23.1	138.9 ± 21.3		137.9 ± 22.6		139.1 ± 23.3	137.4 ± 20.5		137.3 ± 21.9	
%Change	−1.7 ± 0.8	−0.14 ± 0.7	0.084	0.98 ± 1.1	0.030	−0.8 ± 0.9	1.6 ± 0.8	0.025	2.1 ± 1.2	0.030
ApoB	85.6 ± 21.6	86.0 ± 22.1		86.2 ± 20.7		84.7 ± 22.0	84.8 ± 21.8		83.8 ± 19.6	
%Change	−2.1 ± 1.4	−5.1 ± 1.4	0.090	−2.6 ± 2.1	0.857	−2.0 ± 1.8	−5.4 ± 1.7	0.119	−0.86 ± 2.5	0.697
hsCRP (g/l)	5.4 ± 6.7	6.6 ± 9.6		6.0 ± 7.5		5.4 ± 6.9	5.7 ± 7.5		6.0 ± 7.1	
Change from baseline	−0.6 ± 0.4	−1.3 ± 0.4	0.150	−0.4 ± 0.5	0.686	−0.8 ± 0.4	−1.4 ± 0.4	0.179	0.2 ± 0.5	0.351
IWQOL-LITE score	74.0 ± 17.6	74.7 ± 16.2		74.2 ± 16.2		73.5 ± 18.7	75.0 ± 16.2		76.0 ± 16.0	
Change from baseline	10.2 ± 0.7	11.3 ± 0.7	0.221	12.6 ± 1.1	0.042	10.8 ± 0.8	11.5 ± 0.8	0.482	13.2 ± 1.2	0.058
BDI-II score	4.0 ± 3.6	4.4 ± 4.3		4.1 ± 4.5		3.8 ± 3.5	4.3 ± 4.3		3.5 ± 3.5	
Change from baseline	−0.3 ± 0.3	−0.1 ± 0.3	0.669	−0.01 ± 0.5	0.630	−0.5 ± 0.4	−0.6 ± 0.4	0.887	−0.6 ± 0.5	0.903

Data are presented as follows: baseline value ± SD; change from baseline least squares mean ± SEM.

ApoA1, apolipoprotein A1; ApoB; apolipoprotein B; BDI-II, Beck Depression Inventory-II; BID, twice daily; BP, blood pressure; bpm, beats per minute; HDL, high-density lipoprotein; hsCRP, high-sensitivity C-reactive protein; IWQOL-LITE, Impact of Weight on Quality of Life-LITE Questionnaire; LDL, low-density lipoprotein; LOCF, last observation carried forward; LS, least square; MITT, modified intent to treat.

[a]LS mean change from baseline for lorcaserin 10 mg twice daily compared to control.

Table 3 Glycemic parameters

	MITT/LOCF population					Completers population				
	Placebo, *N* = 248	Lorcaserin 10 mg BID, *N* = 251	*P* value[a]	Lorcaserin 10 mg QD, *N* = 93	*P* value[a]	Placebo, *N* = 157	Lorcaserin 10 mg BID, *N* = 169	*P* value[a]	Lorcaserin 10 mg QD, *N* = 75	*P* value[a]
All patients										
Fasting glucose (mg/dl)	160.0 ± 41.6	163.6 ± 48.3		157.8 ± 41.9		160.2 ± 40.9	158.5 ± 43.0		155.3 ± 42.4	
Change from baseline	−11.9 ± 2.5	−27.4 ± 2.5	<0.001	−28.4 ± 3.8	0.015	−12.3 ± 2.7	−28.3 ± 2.6	<0.001	−27.4 ± 3.7	<0.001
HbA_{1c} (%)	8.0 ± 0.9	8.1 ± 0.9		8.1 ± 0.9		8.0 ± 0.9	8.0 ± 0.8		8.1 ± 0.8	
Change from baseline	−0.4 ± 0.06	−0.9 ± 0.06	<0.001	−1.0 ± 0.09	<0.001	−0.5 ± 0.07	−1.0 ± 0.06	<0.001	−1.1 ± 0.1	<0.001
Fasting insulin (μIU/ml)	16.2 ± 14.7	15.0 ± 10.0		15.4 ± 10.1		15.7 ± 13.8	14.7 ± 9.8		15.1 ± 10.1	
Change from baseline	−1.6 ± 0.7	−3.0 ± 0.7	0.120	−2.3 ± 1.1	0.603	−2.3 ± 0.9	−3.3 ± 0.8	0.299	−2.7 ± 1.2	0.722
HOMA-IR	2.3 ± 1.4	2.3 ± 1.4		2.4 ± 1.5		2.3 ± 1.2	2.3 ± 1.4		2.5 ± 1.5	
Change from baseline	−0.2 ± 0.1	−0.5 ± 0.1	0.022	−0.4 ± 0.2	0.443	−0.4 ± 0.1	−0.6 ± 0.1	0.208	−0.4 ± 0.2	0.857
n(%) with HbA_{1c} ≤7%	61/232 (26.3)	120/238 (50.4)	<0.001	48/92 (52.2)	<0.001	43 (27.4)	94 (55.6)	<0.001	42 (56.0)	<0.001
n(%) with HbA_{1c} ≤6.5%	20/232 (8.6)	57/238 (23.9)	<0.001	26/92 (28.3)	<0.001	13 (8.3)	45 (26.6)	<0.001	23 (30.7)	<0.001
	Placebo, *N* = 204	**Lorcaserin 10 mg BID, *N* = 205**	**Difference vs. placebo (95% CI)**	**Lorcaserin 10 mg QD, *N* = 80**	**Difference vs. placebo (95% CI)**	**Placebo, *N* = 131**	**Lorcaserin 10 mg BID, *N* = 137**	**Difference vs. placebo (95% CI)**	**Lorcaserin 10 mg QD, *N* = 65**	**Difference vs. placebo (95% CI)**
Patients with baseline HbA_{1c} <9										
Fasting glucose (mg/dl)	152.9 ± 38.7	155.0 ± 43.2		154.2 ± 41.9		153.5 ± 38.5	151.5 ± 40.8		153.5 ± 43.0	
Change from baseline[b]	−8.0 ± 2.3	−22.9 ± 2.3	−15.0 (−21.3, −8.7)	−23.9 ± 3.6	−15.9 (−24.2, −7.6)	−8.1 ± 2.4	−25.4 ± 2.4	−17.2 (−24.0, −10.5)	−22.3 ± 3.5	−14.2 (−22.5, −5.8)
HbA_{1c} (%)	7.8 ± 0.7	7.8 ± 0.7		7.9 ± 0.7		7.7 ± 0.7	7.7 ± 0.7		7.9 ± 0.7	
Change from baseline[b]	−0.3 ± 0.06	−0.8 ± 0.06	−0.5 (−0.7, −0.3)	−0.9 ± 0.09	−0.6 (−0.8, −0.4)	−0.3 ± 0.07	−0.8 ± 0.07	−0.5 (−0.7, −0.3)	−0.9 ± 0.1	−0.6 (−0.9, −0.4)
n(%) with HbA_{1c} ≤7%	56/194 (28.9)	106/193 (54.9)	26.1 (16.6, 35.5)	44/78 (56.4)	27.5 (14.8,40.3)	39 (29.8)	83 (60.6)	30.8 (19.5, 42.1)	39 (60.0)	30.2 (16.0, 44.5)
	Placebo, *N* = 44	**Lorcaserin 10 mg BID, *N* = 46**	**Difference vs. placebo (95% CI)**	**Lorcaserin 10 mg QD, *N* = 14**	**Difference vs. placebo (95% CI)**	**Placebo, *N* = 26**	**Lorcaserin 10 mg BID, *N* = 32**	**Difference vs. placebo (95% CI)**	**Lorcaserin 10 mg QD, *N* = 10**	**Difference vs. placebo (95% CI)**
Patients with baseline HbA_{1c} ≥9										
Fasting glucose (mg/dl)	193.6 ± 38.6	202.0 ± 51.5		180 ± 36.5		195.4 ± 35.1	188.7 ± 39.6		168.1 ± 37.0	
Change from baseline[b]	−32.2 ± 6.5	−50.5 ± 6.4	−18.3 (−36.3, −0.3)	−51.5 ± 11.7	−19.3 (−45.7, 7.2)	−34.7 ± 7.1	−44.8 ± 6.4	−10.0 (−29.1, 9.1)	−54.7 ± 12.1	−19.9 (−48.3, 8.5)
HbA_{1c} (%)	9.4 ± 0.7	9.2 ± 0.7		9.4 ± 0.5		9.4 ± 0.7	9.0 ± 0.6		9.3 ± 0.4	
Change from baseline[b]	−1.3 ± 0.18	−1.7 ± 0.17	−0.5 (−1.0, 0.02)	−1.6 ± 0.3	−0.3 (−1.0, 0.4)	−1.3 ± 0.21	−1.7 ± 0.19	−0.4 (−1.0, 0.1)	−1.8 ± 0.3	−0.5 (−1.2, 0.3)
n(%) with HbA_{1c} ≤7%	5/38 (13.2)	14/45 (31.1)	18.0 (0.7, 35.2)	4/14 (28.6)	15.4 (−10.6, 41.4)	4 (15.4)	11 (34.4)	19.0 (−2.5, 40.5)	3 (30.0)	14.6 (−17.0, 46.2)

Data are presented as follows: baseline value ± SD; LS mean change from baseline ± SEM except where noted; the treatment by subgroup interactions were not statistically significant for fasting plasma glucose or HbA_{1c}. BID, twice daily; CI, confidence interval; HbA_{1c}, glycated hemoglobin; HOMA-IR, homeostatic model assessment-insulin resistance; LOCF, last observation carried forward; LS, least square; MITT, modified intent to treat; QD, once daily.

[a]LS mean change from baseline for lorcaserin 10 mg BID compared to control for continuous variables; Fisher's exact test for categorical variables. [b]Mean change ± SEM.

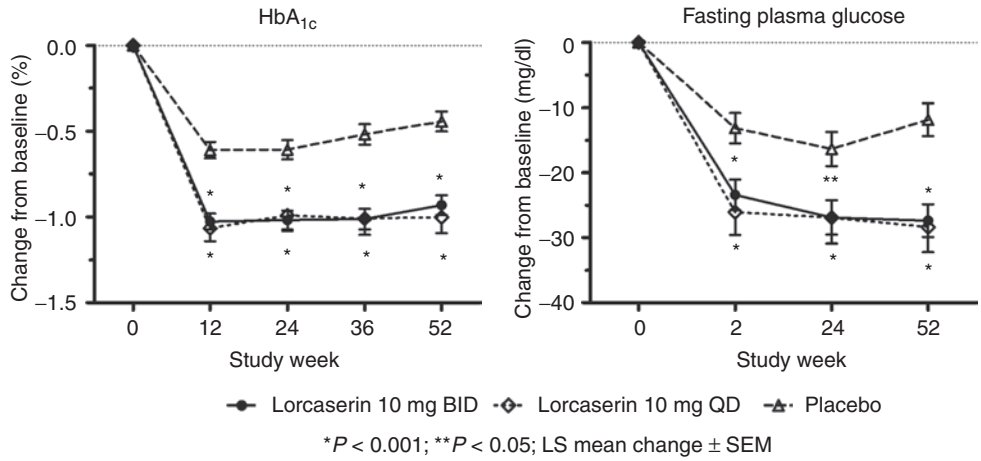

Figure 3 Change in glycemic parameters by study week. Values are mean ± SEM; modified intent to treat with last observation carried forward analysis. Lorcaserin 10 mg BID, closed circles with solid line; lorcaserin 10 mg QD, open diamonds with dotted line; placebo, open triangles with dashed line. Values are mean ± SEM. *$P \leq 0.001$; **$P < 0.05$ compared with placebo. BID, twice daily; HbA_{1c}, glycated hemoglobin; LS, least square; QD, once daily.

Table 4 Adverse events occurring in ≥5% of patients and lorcaserin BID > placebo

	Safety population		
n(% of patients)	Lorcaserin 10 mg BID, *N* = 256	Lorcaserin 10 mg QD, *N* = 95	Placebo, *N* = 252
Headache	37 (14.5)	16 (16.8)	18 (7.1)
Back pain	30 (11.7)	8 (8.4)	20 (7.9)
Nasopharyngitis	29 (11.3)	22 (23.2)	25 (9.9)
Nausea	24 (9.4)	8 (8.4)	20 (7.9)
Urinary tract infection	23 (9.0)	9 (9.5)	15 (6.0)
Cough	21 (8.2)	5 (5.3)	11 (4.4)
Symptomatic hypoglycemia	19 (7.4)	10 (10.5)	16 (6.3)
Fatigue	19 (7.4)	5 (5.3)	10 (4.0)
Gastroenteritis, viral	18 (7.0)	5 (5.3)	11 (4.4)
Dizziness	18 (7.0)	11 (11.6)	16 (6.3)
Influenza	15 (5.9)	8 (8.4)	13 (5.2)
Procedural pain	13 (5.1)	0	5 (2.0)
Hypertension	13 (5.1)	6 (6.3)	8 (3.2)
Gastroenteritis	8 (3.1)	5 (5.3)	5 (2.0)
Depression	6 (2.3)	5 (5.3)	5 (2.0)

BD, twice daily; QD, once daily.

at week 52 changed in both directions (increase and decrease) in all treatment groups, with comparable frequency distributions (Figure 4). At week 24, four patients (1.9%) assigned to placebo, three (3.9%; $P = 0.395$) on lorcaserin QD, and five (2.5%; $P = 0.750$) on lorcaserin BID had new echocardiographic valvulopathy. At week 52, one patient in the placebo group (0.5%), two (2.5%; $P = 0.187$) in the lorcaserin QD group, and six (2.9%; $P = 0.122$) in the lorcaserin BID group had echocardiographic FDA-defined valvulopathy that was not present at baseline. Among patients with pre-existing FDA-defined valvulopathy at study start, 12.5% on placebo, none on lorcaserin QD, and 11.1% on lorcaserin BID experienced any increase from baseline in MR or AR score at week 52 ($P = 0.333$ and $P = 0.929$, respectively, compared to placebo).

The most common adverse events with greater incidence in the lorcaserin group than placebo were headache, back pain, nasopharyngitis, and nausea (Table 4). Serious adverse events occurred in 6.3, 8.4, and 6.7% of the lorcaserin BID, lorcaserin QD, and placebo groups, respectively, and no deaths occurred during the trial.

DISCUSSION

Reduction of excess body weight is fundamental to the treatment of type 2 diabetes. Weight loss is generally associated with improved glycemic control, which in turn may be associated with decreased risk of microvascular complications (23–25). In previous clinical studies, lorcaserin, a selective serotonin 2C receptor agonist, decreased body weight in nondiabetic overweight and obese individuals (4–6). In the present study, lorcaserin was associated with significant weight loss and improved glycemic control in patients with type 2 diabetes mellitus.

Meaningful weight loss has historically been more difficult to achieve among patients with type 2 diabetes than among those without diabetes (11–13). Nevertheless, current American Diabetes Association treatment guidelines recommend that individuals with type 2 diabetes achieve modest weight loss (5–7%) to improve glycemic control and reduce cardiovascular risk (25). In the present study, patients who took lorcaserin BID continuously for 1 year lost an average of 5.5% of their starting body weight—more than three times that of patients in the placebo group. The efficacy of QD lorcaserin was comparable to or greater than that of the BID dose. Weight loss of 5% or more has been linked to improvements in glycemic control, blood pressure, lipids, and quality of life (10,15,26–29). Within this clinical trial, clinically and statistically significant

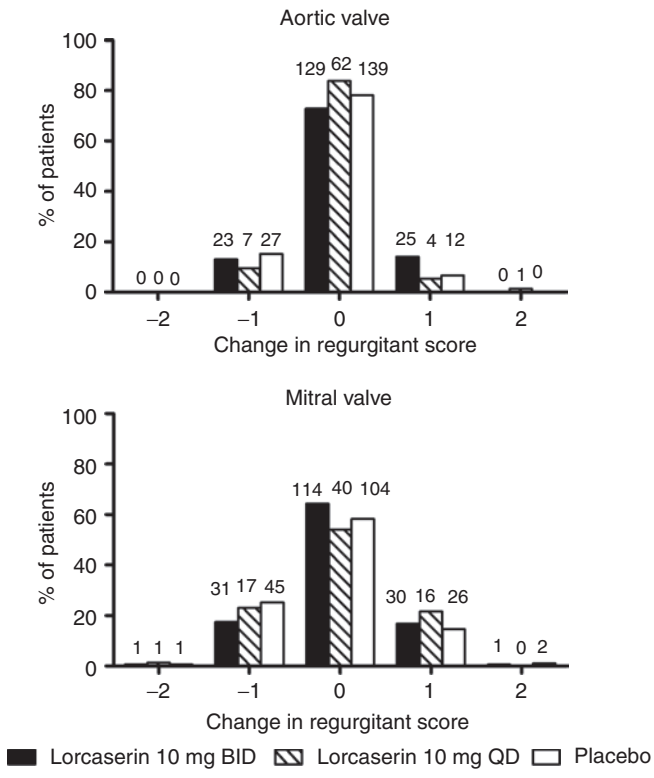

Figure 4 Shifts in echocardiographic valvular regurgitant scores from baseline to week 52. Negative numbers indicate decreased regurgitant score, positive numbers are increased regurgitant scores. Numerals above bars indicate numbers of patients. Lorcaserin 10 mg BID, solid bars; lorcaserin 10 mg QD, hatched bars; placebo, open bars. BID, twice daily; QD, once daily.

improvements in HbA_{1c} and fasting glucose were observed with lorcaserin use, and a larger number of patients in the lorcaserin group reduced total daily use of antidiabetic medications as compared to patients on placebo. Although the study was not designed to optimize or evaluate glycemia primarily, approximately half of the patients assigned to lorcaserin achieved the recommended HbA_{1c} level of <7% (25), almost twice the rate observed in the placebo group. Whether the improvement in glycemic control can be attributed entirely to weight loss is unclear, since antihyperglycemic medications could be adjusted after the 12th week of the trial. Data generated using transgenic rodents have led to speculation that $5HT_{2C}$ agonism may modulate glycemia independent of body weight (2,3). Additional experimentation would be required to determine whether lorcaserin exerts effects on glycemic control that are independent of weight loss.

Although lorcaserin was associated with significant decreases in body weight and anthropometric measures, changes in serum lipids were not consistently different between the lorcaserin and placebo groups. LDL cholesterol, HDL cholesterol, and triglycerides generally trended more favorably in the lorcaserin groups relative to placebo, but according to the prespecified ordered testing procedure, none reached statistical significance. Similarly, blood pressure decreased comparably in the lorcaserin BID and placebo treatment groups, and heart rate decreased more in the lorcaserin group than in the placebo group. The relatively small changes in lipid and blood pressure parameters may be in part because the majority of patients were already using pharmacological agents to manage blood pressure and/or lipids at study entry.

Of note, the effects of lorcaserin on body weight and other parameters were not consistently dose-related in the present study, with essentially equivalent efficacy observed in the 10 mg QD and 10 mg BID dose groups. The absence of dose–response was surprising, since lorcaserin was associated with clearly dose-dependent weight loss in the previous BLOSSOM (Behavioral Modification and Lorcaserin Second Study of Obesity Management) study of nondiabetic overweight and obese patients (7). The trend persisted when only the subgroup of 10 mg BID and placebo patients who enrolled concurrently with the truncated 10 mg QD group was evaluated (data not shown). No differences in baseline characteristics, compliance, or exposure parameters that could explain the lack of dose–response were identified. Differences that were identified include mean age ~10 years greater and a larger proportion of men in the present study compared with the BLOSSOM study, and the presence of diabetes. Within the previous studies of lorcaserin in nondiabetic patients, patients with age greater than the median, and men lost more weight than did younger patients and women (30). However, it is unknown whether these factors were sufficient to equalize weight loss in the QD vs. BID lorcaserin.

The safety and tolerability profile of lorcaserin in this diabetic population was comparable to that reported for patients without diabetes (6), and no lorcaserin-related adverse changes in clinical laboratory values, vital signs or electrocardiogram parameters emerged. Because lorcaserin is a centrally acting agent, patients were monitored for possible depression using the BDI-II. The instrument provided no evidence of increased depression or suicidal ideation in either treatment group.

Echocardiographic monitoring in this study served two key purposes: first, as a safety tool to monitor for significant changes in individual patients; and second, to add to the overall clinical echocardiographic database with lorcaserin. As such, the BLOOM-DM trial by itself enrolled too few patients to provide a statistically powerful population analysis. The majority of cases of valvular regurgitation observed in all groups during the study were changes from absent to trace (AR and MR) or trace to mild (MR) regurgitation and vice versa. The baseline prevalence of FDA-defined valvulopathy was consistent with that in our previous study of 4,008 nondiabetic adults (7) and with the Framingham Offspring Study results (31). In the present study, only one patient assigned to placebo (<1% of patients) developed new FDA-defined valvulopathy at week 52—well below the expected value based on two previous studies of 3,182 patients (2.3%) (6) and 4,008 patients (2.0%) (7). In contrast, the 2.9% of patients with new echocardiographic valvulopathy in the lorcaserin BID group is similar to the previously observed values between 2.7 (6) and 2.0% (7). Overall, the imbalance in week 52 FDA-defined valvulopathy is likely to be attributable to an unexpectedly low incidence in the placebo

group of the present study, which may be the result of the small sample size.

The study design has some limitations. Lorcaserin was evaluated only in patients whose diabetes was treated with oral agents that included metformin and/or a SFU. Whether the efficacy and safety results are generalizable to a broader diabetic population awaits experimental confirmation. The interpretation of lipid and blood pressure changes that occurred during the study may be confounded by the prevalent use of drugs to treat dyslipidemia and hypertension, and medication adjustments during the trial. Finally, the discontinuation rate was relatively high, ranging from 22.1% of patients in the lorcaserin QD group to 37.9% in the placebo group. Attrition in pharmacological weight loss trials is a well-known challenge that can complicate data interpretation (32). In the absence of a universally accepted analysis methodology to account for loss of study participants through attrition, the present analysis considered both a completer population that avoided imputation altogether and a traditional LOCF approach; both approaches provided similar overall conclusions regarding the efficacy of lorcaserin.

In summary, lorcaserin use for up to 1 year in obese and overweight patients with type 2 diabetes was associated with statistically significant and clinically meaningful weight reduction. Because significant improvements in glycemic control were also observed, lorcaserin could represent a useful weight management tool for overweight and obese type 2 diabetic patients in the future.

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DISCLOSURE

M.F., M.S., J.Z., B.R., C.M.A., and W.R.S. were employees of Arena during the conduct of the study. P.O., S.R.S., and N.J.W. acted as advisors to Arena Pharmaceuticals, for which they received compensation.
See the online ICMJE Conflict of Interest forms for this article.

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