

Lorcaserin (APD356), a Selective 5-HT_{2C} Agonist, Reduces Body Weight in Obese Men and Women

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Lorcaserin (APD356) is a potent, selective 5-HT_{2C} agonist with ~15-fold and 100-fold selectivity vs. 5-HT_{2A} and 5-HT_{2B} receptors, respectively. This study evaluated the safety and efficacy of lorcaserin for weight reduction in obese patients during a 12-week period. The randomized, double-blind, placebo-controlled, parallel-arm study enrolled 469 men and women between ages 18 and 65 and with BMI 30–45 kg/m². Patients received placebo, lorcaserin 10 mg q.d., lorcaserin 15 mg q.d., or lorcaserin 10 mg b.i.d. for 12 weeks, and were counseled to maintain their usual diet and activity. The primary end point was change in weight from baseline to day 85 by completer analysis. Safety analyses included echocardiograms at Screening and day 85/study exit. Lorcaserin was associated with progressive weight loss of 1.8 kg, 2.6 kg, and 3.6 kg at 10 mg q.d., 15 mg q.d., and 10 mg b.i.d., respectively, compared to placebo weight loss of 0.3 kg ($P < 0.001$ for each group). Similar results were seen by intent-to-treat last observation-carried forward (ITT-LOCF) analysis. The proportions of completers achieving $\geq 5\%$ of initial body weight were 12.8, 19.5, 31.2, and 2.3% in the 10 mg q.d., 15 mg q.d., 10 mg b.i.d., and placebo groups, respectively. The most frequent adverse events (AEs) were transient headache, nausea, and dizziness. Echocardiograms showed no apparent drug-related effects on heart valves or pulmonary artery pressure (PAP). Lorcaserin was well tolerated and efficacious for weight reduction in this 12-week study. Longer-term trials employing behavior modification will be needed to more fully assess its safety and efficacy.

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INTRODUCTION

The prevalence of overweight and obesity in the United States has increased at an unprecedented rate over the past two decades (1,2). Excess weight is associated with substantial health risks, as reflected in the increased morbidity and mortality in people with BMI >25 kg/m² (2,3). In particular, obesity is associated with increased risks of hypertension, dyslipidemia, diabetes mellitus, coronary heart disease, congestive heart disease, stroke, osteoarthritis, and sleep apnea (2–12). While aggressive lifestyle management programs are the foundation of a successful weight loss program, a safe and effective pharmacological agent could provide additional benefit for weight loss and weight maintenance.

Stimulation of specific central serotonin receptors represents an effective pharmacological mechanism to suppress appetite. Serotonin and agonists that activate serotonin 2C (5-HT_{2C}) receptors promote feelings of satiety, thereby reducing food intake (13,14). The 5-HT_{2C} receptors are located primarily in the choroid plexus, limbic structures, extrapyramidal pathways, thalamus, and hypothalamus, a major center responsible

for regulating hunger and food intake (15,16); they are virtually absent in peripheral tissues (17). We postulate that pharmacological activation of the 5-HT_{2C} receptor will lead to weight loss in overweight and obese people.

Lorcaserin ([1R]-8-Chloro-2,3,4,5-tetrahydro-1-methyl-1H-3-benzazepine), formerly known as APD356, is a novel, selective 5-HT_{2C} receptor agonist that produces dose-dependent weight loss in preclinical and clinical studies (18–21). The potency (EC₅₀) of lorcaserin at the human 5-HT_{2C} receptor is 9 nmol/l, representing ~15-fold and ~100-fold greater potency than at the 5-HT_{2A} (168 nmol/l) and 5-HT_{2B} (943 nmol/l) receptors, respectively (20). Lorcaserin at concentrations <1 μ mol/l has no functional activity at other 5-HT receptors. This selectivity should minimize adverse effects that are observed with nonselective serotonergic agonists. Fenfluramine and dexfenfluramine act as nonspecific serotonin agonists because of their dual effect to release serotonin and to prevent its reuptake (22–24); their primary metabolites, nordex- and norfenfluramine, are potent 5-HT_{2B} agonists (25). These agents, as well as agents like pergolide that exert agonist activity at serotonin

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receptors (26–28), are associated with increased risk of valvular heart disease. Activation of 5-HT_{2B} receptors has been implicated in the pathogenesis of serotonergic valvulopathy; these receptors are highly expressed in cardiac valvular tissue, but not in brain (17,25–30). Agonist activity at the 5-HT_{2B} receptor is a common feature of drugs associated with valvulopathy (28). Given the rank order in potency for receptor activation and the selective concentration of lorcaserin in the brain (20), lorcaserin is predicted to exert minimal activity at the 5-HT_{2B} receptor at therapeutic concentrations, and substantially less activity at the 5-HT_{2A} receptor than at the 5-HT_{2C} receptor. In the present study, the safety and efficacy of lorcaserin for weight reduction in obese adults were evaluated during a 12-week dosing period.

METHODS AND PROCEDURES

Ethics and compliance

The study protocol was reviewed and approved by either a central or local IRB for each of the sites that participated in the trial. All patients provided informed consent after the study and all related procedures were described to them in detail. The study was conducted in accordance with Good Clinical Practice guidelines (31) and the principles of the Declaration of Helsinki (32).

Hypotheses and study design

The primary hypothesis of the study posited that lorcaserin administration will result in weight loss in healthy obese adults. The study also tested the key secondary hypothesis that lorcaserin use is not associated with changes in heart valve insufficiency or pulmonary artery pressure (PAP).

The study comprised a double-blind, placebo controlled, randomized, parallel-arm design. Patients received placebo, lorcaserin 10 mg q.d., lorcaserin 15 mg q.d., or lorcaserin 10 mg b.i.d. for 12 weeks with a 2-week postdosing follow-up period. The primary end point was change in body weight from baseline (first day of dosing) to study day 85 by completer analysis. Secondary end points included change from baseline in BMI, waist and hip circumference, cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, and triglycerides. A sample size of 39 patients per treatment arm would provide 90% power to detect a 3-kg difference in mean weight change from baseline for each dose level vs. placebo, using a two-sided *t*-test with 5% level of significance, assuming a common s.d. for change of 4 kg. To perform a more thorough safety assessment, the enrollment target was set at 100 patients per treatment arm.

At enrollment, patients were counseled to maintain their usual diet and exercise habits throughout the study; no behavior modification or lifestyle intervention was included. Patients were equally randomized to receive placebo b.i.d., lorcaserin 10 mg each morning and placebo each evening, lorcaserin 15 mg each morning and placebo each evening, or lorcaserin 10 mg b.i.d. Patients returned to the study site biweekly for measurement of weight, waist and hip circumference, laboratory tests, electrocardiogram, adverse event (AE) monitoring, and the Bond and Lader Mood Visual Analog Scale (VAS; 33). Echocardiograms were performed at screening and at day 85 or at early termination. Body weights were measured using digital scales that met National Type Evaluation Program Standards. Waist and hip measurements were made using a standardized procedure (2).

Patients

Obese male and female volunteers, ages 18–65 years, with BMI 30–45 kg/m² were recruited at 42 academic and private medical centers in the United States using existing patient databases and advertisements between June, 2005 and August, 2005. Eligible patients were

nonsmokers who could abstain from alcohol during the study, and were not undergoing or in need of treatment for any chronic disease, with the exception that stable treatment for hypertension and/or dyslipidemia was permitted. Physical exam, routine laboratory tests, and electrocardiogram had no clinically significant abnormalities at screening. Patients were excluded for the following: diabetes, a score of ≥ 12 on the Hospital Anxiety and Depression scale (34), a history of bariatric surgery, any significant changes to diet and exercise within 4 weeks, or previous use of fenfluramine or dexfenfluramine. Patients underwent screening echocardiography, and were excluded if clinically significant abnormalities were detected; these included mitral or aortic stenosis, mitral regurgitation greater than mild, any aortic regurgitation (trace or less allowed for patients ≥ 50), or greater than mild tricuspid or pulmonary regurgitation. Women of childbearing potential were required to use a double-barrier method of contraception throughout the study and for at least 90 days after the last study drug dose.

VASs

The Bond and Lader VAS (33) is a questionnaire that consists of 16 analog scales; responses are analyzed to derive composite scores for self-rated Alertness, Calmness, and Contentment. The test was administered electronically at intervals during the treatment period and at Days 91 and 98 during the follow-up period.

Echocardiographic studies

A central echocardiography core lab (Biomedical Systems, St. Louis, MO) trained and qualified individual sites to perform echocardiograms, provided a detailed protocol to each sonographer, and interpreted all images according to standard criteria (35,36). A pool of three qualified cardiologists interpreted the echocardiograms. The same blinded cardiologist read all echocardiograms for a given patient during the study to minimize variability. Echocardiograms were read at screening; after dosing was completed, day 85 images were read side-by-side with screening images (not blinded to sequence). To optimize the estimates of systolic PAP, agitated saline was infused through an intravenous catheter during the exam. PAP was estimated from the velocity of the regurgitant tricuspid jet, and imputed to a minimum value in the absence of any tricuspid insufficiency. Regurgitation of the mitral, aortic, and tricuspid valves was scored as absent, trace, mild, moderate, or severe. Pulmonic regurgitation was scored absent or present. Changes in valvular regurgitation from baseline to day 85 (“shifts”) were tabulated for each valve separately.

Blood collection and analyses

Blood samples were collected by venipuncture. Blood and urine samples were sent to a central laboratory for analyses. Samples for pharmacokinetic analysis were collected at 2 h (± 15 min) after dosing on day 1 (to approximate C_{max}), and before dosing on Days 15, 29, 57, and 85 or at the early termination visit (to approximate C_{min}). Pharmacokinetic samples were analyzed using a LC/MS/MS method at MDS Bioanalytical Laboratory (MDS, Lincoln, NE).

Statistical analysis

Analysis populations included the safety population (all patients who took at least one dose of study drug), intent-to-treat (ITT; all safety patients with at least one postbaseline body weight measurement), and the completer population (all ITT patients who completed the dosing period and had a postbaseline body weight recorded within 3 days of the day 85 visit). As specified in the protocol, the primary end point was a completer’s analysis of change in weight using two-sided analysis of covariance with treatment, site and gender as fixed effects and the baseline weight and age as covariates. Prespecified subgroup analyses included individual ethnic groups, and patients with elevated cholesterol or low HDL at baseline. Patients were also categorized according to weight loss of $\geq 5\%$ from baseline to day 85. Frequency and percentage were analyzed by Cochran-Mantel-Haenszel tests. Secondary

efficacy end points were analyzed using an analysis of covariance with treatment, site, and gender as fixed effects and baseline value and age as covariates for the completer and ITT samples. For echocardiography data, the binomial distribution for the proportion of patients in each treatment group with increases in valve regurgitation and the proportion with no change/decrease in valve regurgitation were compared; *P* values were based on the Pearson χ^2 -analysis.

RESULTS

Patient disposition

A total of 469 patients were enrolled in the study and randomized at 42 study centers in the United States (Figure 1). Of these, 354 patients completed the treatment phase of the study, and 333 of these met the definition of a “Completer” (day 85 visit must have occurred within a \pm 3-day window). The ITT-LOCF sample comprised 453 patients. The most frequent reasons for study withdrawal were loss to follow-up or patient choice. Eighteen patients (3 placebo, 1 in the 10 mg q.d. group, 9 in the 15 mg q.d. group, and 5 in the 10 mg b.i.d. group) discontinued because of AEs; 25 patients were lost to follow-up; 5 patients discontinued because of lack of efficacy; the remainder of discontinuations were attributed to patient or investigator decision or to protocol deviations. There were no deaths in the study.

Patient demographics

Table 1 summarizes the demographics and baseline characteristics of all randomized patients. Of the 469 patients randomized, the majority were female (87.0%) and between the ages of 25 and 54 years (77.2%). Most patients were white (52.5%), African American (28.6%), and Hispanic (17.7%). Baseline weight was 100.2 ± 15.0 kg (mean \pm s.d.) in the placebo treatment group, and 100.6 ± 15.4 kg, 100.3 ± 14.4 kg, and 98.8 ± 16.9 kg in the lorcaserin 10 mg q.d., 15 mg q.d., and 10 mg b.i.d. treatment groups, respectively. Average BMI was 36.4 ± 4.1 kg/m² and was

consistent among treatment groups. The distribution of age, gender, and ethnicity was similar across all treatment groups.

Change in body weight

Lorcaserin administration was associated with a dose-dependent, progressive decrease in body weight that was evident at the earliest time point (2 weeks) in both the completer and ITT populations (Figure 2, Table 2). The primary end point of change in weight from baseline to day 85 in each lorcaserin treatment group vs. placebo was highly statistically significant for each group (all *P* < 0.001). Weight loss compared to placebo was statistically significant in the 15 mg q.d. and the 10 mg b.i.d. groups at all time points, and in the 10 mg q.d. group at the day 29 and all subsequent time points, for both the completer and ITT populations.

The proportion of patients (completer analysis) who lost $\geq 5\%$ of their body weight from Baseline to day 85 was dose-dependently and significantly increased by lorcaserin, reaching 12.8% in the 10 mg q.d. group (*P* < 0.015), 19.5% in the 15 mg q.d. group (*P* < 0.001), and 31.2% in the 10 mg b.i.d. group (*P* < 0.001). One patient each in the 10 mg q.d. and 15 mg q.d. groups, and no patient in the placebo group or the 10 mg b.i.d. groups, lost >10% of baseline weight.

The number of completers who lost weight was smallest in the placebo group, and increased with increasing dose of lorcaserin (Figure 3). Conversely, the number of patients who gained weight during the 12-week treatment period was smallest in the lorcaserin 10 mg b.i.d. group and greatest in the placebo group. More than 90% of patients in the 15 mg q.d. and 10 mg b.i.d. groups lost weight by ITT or completer analysis. Consistent with this observation, efficacy was observed across the entire range of BMIs allowed in the study.

For the prespecified completer analysis of body weight data by ethnic group, only the African-American and white subgroups

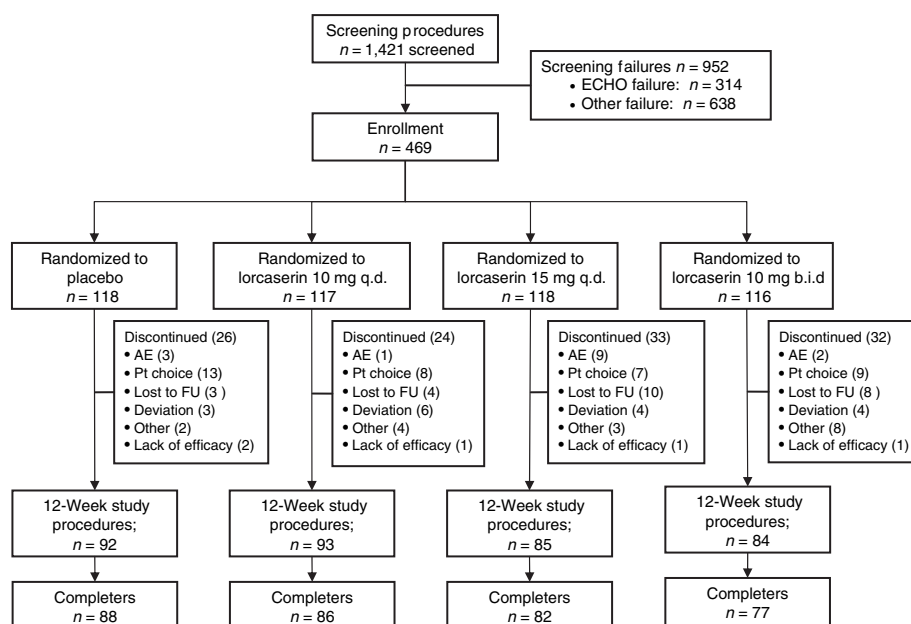


Figure 1 Flowchart of patient dispositions. AE, adverse event; FU, follow-up; Pt, patient.

Table 1 Patient characteristics at baseline (mean ± s.d.)

	Placebo (n = 118)	Lorcaserin		
		10 mg q.d. (n = 117)	15 mg q.d. (n = 118)	10 mg b.i.d. (n = 116)
Age (years)	41.6 ± 10.9	41.5 ± 12.2	41.3 ± 11.3	41.5 ± 11.3
Gender (n (%))				
Female	103 (87.3)	96 (82.1)	110 (93.2)	99 (85.3)
Male	15 (12.7)	21 (17.9)	8 (6.8)	17 (14.7)
Ethnicity (n (%))				
White	65 (55.1)	61 (52.1)	59 (50.0)	61 (52.6)
African American	34 (28.8)	36 (30.8)	32 (27.1)	32 (27.6)
Hispanic	18 (15.3)	19 (16.2)	23 (19.5)	23 (19.8)
Pacific Islander	0	0	1 (0.8)	0
American Indian	0	1 (0.9)	2 (1.7)	0
Other	1 (0.8)	0	0	0
Weight (kg)	100.2 ± 15.0	100.6 ± 15.4	100.3 ± 14.4	98.8 ± 16.9
Height (cm)	165.6 ± 7.5	166.5 ± 9.5	164.8 ± 7.0	164.9 ± 8.2
BMI (kg/m ²)	36.4 ± 4.0	36.2 ± 4.1	36.9 ± 4.2	36.2 ± 4.1
Waist circumference (cm)	109.0 ± 12.9	108.7 ± 11.6	108.6 ± 10.9	107.5 ± 11.6
Hip circumference (cm)	122.2 ± 9.4	122.1 ± 9.4	124.0 ± 9.7	121.2 ± 9.8
Waist-to-hip ratio	0.89 ± 0.08	0.89 ± 0.08	0.88 ± 0.07	0.89 ± 0.08
Total cholesterol (mmol/l)	5.0 ± 1.1	4.9 ± 0.8	5.0 ± 0.9	5.0 ± 1.1
HDL cholesterol (mmol/l)	1.4 ± 0.3	1.4 ± 0.4	1.5 ± 0.3	1.5 ± 0.4
LDL cholesterol (mmol/l)	3.0 ± 0.8	2.8 ± 0.7	2.8 ± 0.8	2.8 ± 0.9
LDL-to-HDL ratio	2.2 ± 0.7	2.1 ± 0.7	2.0 ± 0.7	2.0 ± 0.8
Triglycerides (mmol/l)	1.4 ± 0.8	1.5 ± 0.7	1.6 ± 0.8	1.5 ± 1.0
Fasting glucose (mmol/l)	5.2 ± 0.8	5.1 ± 0.6	5.1 ± 1.0	4.9 ± 0.6
Uric acid (μmol/l)	332.5 ± 78.5	327.3 ± 75.5	306.6 ± 70.9	307.8 ± 75.0
Systolic blood pressure (mm Hg)	120 ± 12	122 ± 14	1,220 ± 13	119 ± 12
Diastolic blood pressure (mm Hg)	78 ± 9	77 ± 8	778 ± 8	76 ± 8

HDL, high-density lipoprotein; LDL, low-density lipoprotein.

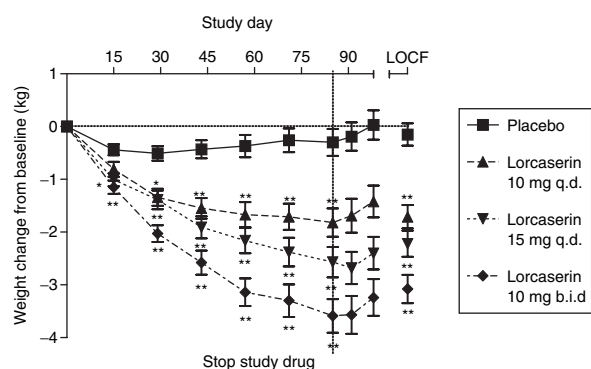


Figure 2 Mean change in weight from baseline. LOCF, last observation-carried forward.

had sufficient numbers of patients to be analyzed individually. Patients of Hispanic, Asian, Native American and other ethnic origins were analyzed together. White patients in the lorcaserin 10 mg q.d. (-2.1 kg) and 10 mg b.i.d. (-3.9 kg) treatment groups,

but not in the 15 mg q.d. (-2.4 kg) group, showed somewhat greater weight reduction at day 85 than did African-American patients (-1.7, -3.4, and -2.9 kg, respectively) or grouped patients of all other ethnic origins (-1.2, -3.0, and -2.6 kg, respectively). This trend was significant at all doses ($P < 0.001$), and was also seen at most other time points; however, the differences in weight loss were small, and in the absence of a consistent effect across all doses, are likely attributable to normal variation.

Secondary efficacy end points

Secondary efficacy end points included physical and laboratory measures that are correlated with cardiovascular risk (Table 3). BMI was significantly ($P < 0.001$) decreased by all doses of lorcaserin at day 85. The decrease in waist circumference from Baseline to day 85 was dose-related, and was significant in the 15 mg q.d. ($P = 0.017$) and the 10 mg b.i.d. ($P = 0.001$) groups. There was also a trend toward decrease in hip circumference with dose, such that waist-to-hip ratio was unaffected by lorcaserin at day 85.

Table 2 Change in weight from baseline to day 85

	Placebo	10 mg q.d.	15 mg q.d.	10 mg b.i.d.
Completers analysis				
Change in weight from baseline to day 85 ^a				
<i>n</i>	88	86	82	77
Mean (s.d.) (kg)	-0.3 (2.4)	-1.8 (2.5)	-2.6 (2.6)	-3.6 (2.8)
CV%	-795.2	-139.2	-100.5	-78.9
Parametric analysis: equal slope ANCOVA model ^b				
LS mean (s.e.m.) (kg)	-0.6 (0.3)	-2.0 (0.3)	-2.9 (0.4)	-3.7 (0.3)
Difference (treatment-placebo)		-1.4	-2.3	-3.1
95% confidence interval		-2.1, -0.6	-3.1, -1.6	-3.9, -2.4
<i>P</i> value		<0.001	<0.001	<0.001
ITT-LOCF analysis				
Change in weight from baseline to day 85 ^a				
<i>n</i>	116	114	113	110
Mean (s.d.) (kg)	-0.2 (2.3)	-1.7 (2.4)	-2.2 (2.6)	-3.1 (2.8)
CV%	-1,554.1	-138.0	-118.8	-90.9
Parametric analysis: equal slope ANCOVA model ^b				
LS mean (s.e.m.) (kg)	-0.4 (0.3)	-2.0 (0.3)	-2.5 (0.3)	-3.3 (0.3)
Difference (treatment-placebo)		-1.5	-2.1	-2.9
95% confidence interval		-2.2, -0.9	-2.7, -1.4	-3.5, -2.2
<i>P</i> value		<0.001	<0.001	<0.001

ANCOVA, analysis of covariance; CV, coefficient of variation; ITT, intent-to-treat; LOCF, last observation-carried forward; LS, least square.

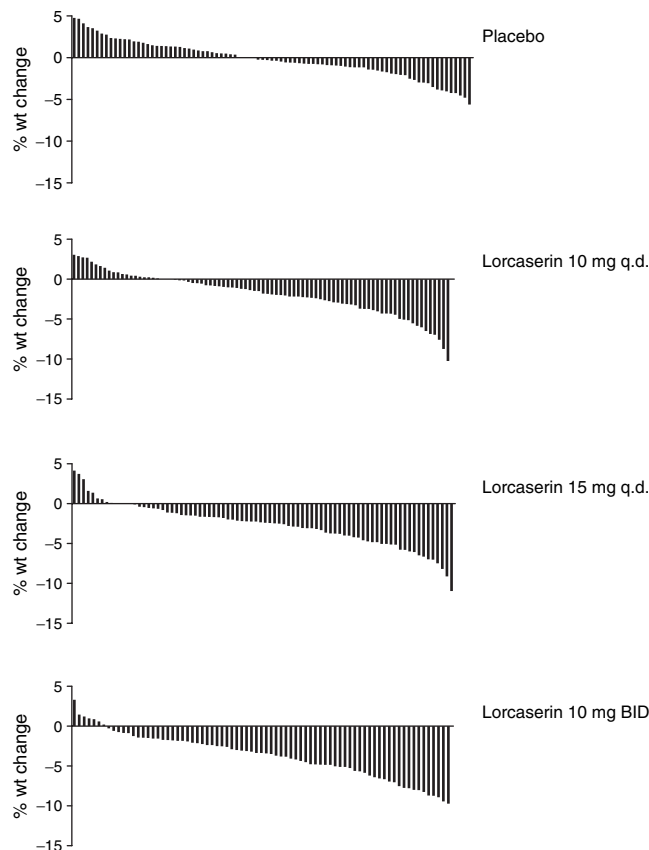
^aBaseline is the last available measurement before first dose of study drug (day 1).

^bChange from baseline weight is analyzed using an equal slope ANCOVA model with treatment, pooled site, and gender as fixed effects and baseline weight and age as covariates.

Total cholesterol was reduced significantly by lorcaserin at 10 mg b.i.d. ($P = 0.006$) and 15 mg q.d. ($P = 0.019$), and there was a nonsignificant trend toward reduction in LDL-cholesterol. LDL-to-HDL ratios were unchanged by lorcaserin at 85 days of treatment because small (-0.1 mmol/l), marginally significant ($P = 0.038$ to 0.053) reductions in HDL in the lorcaserin groups were balanced by nonsignificant reductions in LDL. Although patients with frank diabetes were excluded from the study, fasting glucose was monitored; lorcaserin at 10 mg b.i.d. modestly but significantly decreased fasting glucose at day 85 (-0.2 mmol/l in the 10 mg b.i.d. group). Although serum uric acid was not a prespecified end point, small, dose-responsive decreases were observed (-16.2 μ mol/l in the 10 mg b.i.d. group).

Pharmacokinetics

Mean first day (\pm s.d.) approximate C_{max} values for lorcaserin in the 10 mg q.d., 15 mg q.d. and 10 mg b.i.d. (taken after the first 10-mg dose) completers were 157 ± 62 nmol/l, 230 ± 96 nmol/l and 158 ± 56 nmol/l, respectively; approximate C_{min} values at steady state were 66 ± 61 , 87 ± 69 and 131 ± 78 nmol/l,

**Figure 3** Individual patient weight changes from baseline to day 85.

respectively. Concentrations did not differ among ethnic groups. In phase 1 studies using a 10-mg dose, steady state was reached by day 4, with C_{max} values $\sim 30\%$ higher at steady state than on day 1 (data not shown).

Bond and Lader VAS

No drug-related changes in individual VAS scores or in the composite scores of Alertness, Calmness, or Contentment were observed during the dosing period or during the follow-up period (data not shown).

Safety analysis: echocardiograms

Echocardiograms were obtained at screening and at study day 85/early termination. Overall, there was no apparent drug effect on heart valve function or on PAP. Shifts in valve regurgitation scores during the study are summarized in [Table 4](#). No shifts in regurgitation scores >1 category were observed during the trial. One category shifts in valve regurgitation score were observed with similar frequencies across treatment groups. The distribution of patients with increased regurgitation, vs. those with decreased regurgitation or no change, did not differ among treatment groups for any valve. Three scores of “moderate” mitral valve regurgitation (MR) were reported in the study: two occurred in placebo patients who had “mild” MR at screening and “moderate” or “mild/moderate” MR at day 85, and one occurred in a patient in the lorcaserin 15 mg q.d. group, who had “mild” MR at screening and “mild/moderate” MR at

Table 3 Secondary efficacy endpoints. Change from baseline to day 85, completers analysis (mean (s.d.))

	Lorcaserin			
	Placebo (N = 88)	10 mg q.d. (N = 86)	15 mg q.d. (N = 82)	10 mg b.i.d. (N = 77)
BMI (kg/m ²)	-0.1 (0.9)	-0.7 (0.9)*	-1.0 (1.0)*	-1.3 (1.0)*
Waist circumference (cm)	-2.1 (5.5)	-2.7 (4.8)	-3.7 (5.4)***	-4.4 (4.9)*
Hip circumference (cm)	-1.3 (5.1)	-2.0 (3.9)	-2.1 (4.5)	-2.9 (3.7)***
Waist-to-hip ratio	-0.01 (0.05)	-0.01 (0.04)	-0.02 (0.05)	-0.02 (0.04)
Cholesterol (mmol/l)	0.04 (0.48)	0.02 (0.48)	-0.02 (0.05)***	-0.18 (0.52)**
HDL-cholesterol (mmol/l)	0.0 (0.1)	0.0 (0.1)	-0.1 (0.1)***	-0.1 (0.2)***
LDL-cholesterol (mmol/l)	0.0 (0.4)	0.1 (0.5)	0.0 (0.4)	-0.1 (0.5)
LDL-to-HDL ratio	0.50 (0.32)	0.13 (0.42)	0.04 (0.29)	0.04 (0.37)
Triglycerides (mmol/l)	0.0 (0.5)	-0.1 (0.5)	-0.1 (0.8)	-0.2 (0.7)
Fasting glucose (mmol/l)	0 (0.1)	-0.1 (0.5)	-0.1 (0.5)	-0.2 (0.6)***
Uric acid (μmol/l)	-0.4 (36.5)	-5.0 (39.2)	-8.0 (39.5)	-16.2 (39.7)
Systolic blood pressure (mmHg)	-1 (11)	1 (10)	0 (11)	-1 (12)
Diastolic blood pressure (mmHg)	-1 (8)	0 (8)	-1 (9)	-1 (8)
Heart rate (beats/min)	-0.6 (8.0)	1.1 (8.2)	-1.0 (10.3)	-0.3 (8.7)

HDL, high-density lipoprotein; LDL, low-density lipoprotein.

* $P < 0.001$; ** $P < 0.01$; *** $P < 0.05$.

day 85. Two scores of “mild” aortic valve regurgitation were reported in the study: one occurred at screening in a patient in the lorcaserin 10 mg b.i.d. group (no change at day 85), and the other occurred at day 85 in a patient in the lorcaserin 15 mg q.d. group who had “trace” aortic valve regurgitation at screening.

Mean estimated systolic PAP did not differ among treatment groups at screening or at day 85 (Table 5). Changes of ≥ 5 mmHg in PAP in either direction occurred with similar frequencies in all groups, and only a few patients per group had changes of ≥ 10 mmHg (Table 5). The largest individual changes in PAP were a decrease of 15.2 mmHg (from 42 to 26.8) in a patient in the 10 mg q.d. group, an increase of 17.1 mmHg (from 10 to 27.1) in a patient in the 10 mg b.i.d. group, and an increase of 16.8 mmHg (from 8 to 24.8 mmHg) in a patient in the 10 mg q.d. group. The latter 2 changes were likely spurious findings related to abnormally low screening PAP values (no regurgitant tricuspid jet, with imputed minimum values).

Table 4 Summary of echocardiographic changes

	Placebo	10	15	10mg	Total
		mg q.d.	mg q.d.	b.i.d.	lorcaserin
Mitral valve (N (%))					
	N = 99	N = 100	N = 96	N = 96	N = 292
Decrease	21 (21.2)	17 (17)	10 (10.4)	8 (8.3)	35 (11.9)
No change	68 (68.7)	76 (76)	75 (78.1)	77 (80.2)	227 (77.7)
Increase	10 (10.1)	8 (8.0)	11 (11.5)	11 (11.5)	30 (10.3)
P value*	—	0.54	0.82	0.80	0.97
Aortic valve (N (%))					
	N = 99	N = 99	N = 96	N = 96	N = 291
Decrease	2 (2.0)	2 (2.0)	2 (2.1)	1 (1.0)	5 (1.7)
No change	91 (91.9)	95 (96.0)	87 (90.6)	89 (92.7)	271 (93.1)
Increase	3 (3.0)	2 (2.0)	7 (7.3)	6 (6.3)	15 (5.2)
P value*	—	0.62	0.19	0.30	0.41
Tricuspid valve (N (%))					
	N = 95	N = 90	N = 95	N = 89	N = 274
Decrease	12 (12.7)	10 (11.1)	6 (6.3)	9 (10.1)	25 (9.1)
No change	76 (80.0)	77 (85.6)	82 (86.3)	74 (83.2)	234 (85.4)
Increase	7 (7.4)	3 (3.3)	7 (7.4)	5 (5.6)	15 (5.5)
P value*	—	0.20	0.73	0.59	0.37

The number (%) of patients whose valvular regurgitation shifted from baseline values of none, trace or mild is listed for each category of change (increase, no change, decrease). The number of patients with an evaluable echocardiogram is listed for each treatment group and each valve.

*P values are based on Pearson χ^2 -analysis vs. placebo; N values vary because not every valve is evaluable in each person. At Baseline, the distribution of valve regurgitation was: mitral valve regurgitation, 16.1% absent, 48.4% trace, 35.6% mild; aortic valve regurgitation: 79.8% absent, 19.9% trace, 0.3% mild.

Table 5 Estimated pulmonary artery pressures at screening and day 85 (mean \pm s.d.)

	Lorcaserin			
	Placebo (n = 91)	10 mg q.d. (n = 92)	15 mg q.d. (n = 88)	10 mg b.i.d. (n = 86)
PAP (mmHg)				
Baseline	27 \pm 5	27 \pm 6	26 \pm 5	28 \pm 5
Day 85	27 \pm 4	27 \pm 5	27 \pm 5	29 \pm 5
Change from baseline	0 \pm 5	0 \pm 5	1 \pm 4	1 \pm 4
Change in PAP ≥ 5 mmHg (n (%))				
Decrease	12 (13.2)	12 (13.0)	6 (6.8)	4 (4.7)
Increase	12 (13.2)	10 (10.9)	10 (11.4)	13 (15.1)
Change in PAP ≥ 10 mmHg (n (%))				
Decrease	2 (2.2)	1 (1.1)	0	0
Increase	1 (1.1)	4 (4.3)	1 (1.1)	1 (1.2)

PAP, pulmonary artery pressure.

AEs

Lorcaserin was generally well tolerated at all doses tested. The most frequent AEs were headache, nausea and dizziness (Table 6). Each of these tended to be self-limited (e.g., the majority of headaches began on day 1, resolved within hours,

Table 6 Adverse events reported in $\geq 5\%$ of patients in any treatment group during the treatment period (n (%))

Event	Placebo (n = 118)	10 mg q.d. (n = 117)	15 mg q.d. (n = 118)	10 mg b.i.d. (n = 116)	All lorcaserin (n = 351)
Headache	21 (17.8%)	35 (29.9%)	38 (32.2%)	31 (26.7%)	104 (29.6%)
Nausea	4 (3.4%)	10 (8.5%)	11 (9.3%)	13 (11.2%)	34 (9.7%)
Dizziness	0	7 (6.0%)	9 (7.6%)	9 (7.8%)	25 (7.1%)
Upper respiratory infection	11 (9.3%)	2 (1.7%)	4 (3.4%)	4 (3.4%)	10 (2.8%)
Nasopharyngitis	10 (8.5%)	6 (5.1%)	7 (5.9%)	7 (6.0%)	20 (5.7%)
Dry mouth	0	2 (1.7%)	2 (1.7%)	7 (6.0%)	11 (3.1%)
Diarrhea	7 (5.9%)	1 (0.9%)	5 (4.2%)	4 (3.4%)	10 (2.9%)
Fatigue	3 (2.5%)	5 (4.3%)	7 (5.9%)	4 (3.4%)	16 (4.6%)
Vomiting	1 (0.8%)	2 (1.7%)	2 (1.7%)	6 (5.2%)	10 (2.9%)
Urinary tract infection	5 (4.2%)	3 (2.6%)	6 (5.1%)	6 (5.2%)	15 (4.3%)
Dyspepsia	6 (5.1%)	4 (3.4%)	2 (1.7%)	4 (3.4%)	10 (2.9%)

and did not recur), and mild or moderate in severity. Nausea was reported in 9.7% of the lorcaserin-treated patients, and typically occurred early in the study and lasted 1–2 days. The mean weight loss at day 85 did not differ between patients who reported nausea at any time during the study and those who did not (data not shown). Five serious AEs occurred during the study: two events (a kidney stone and an episode of pneumonia) occurred in the same placebo patient. An episode of major depression reported on Study day 100 (10 days after study drug was stopped) was reported in a patient who had a prior history of mood disorder who took lorcaserin 10 mg q.d. A new-onset seizure was reported on Study day 71 in a patient taking lorcaserin 10 mg b.i.d. There was no evidence of a focal process, and a spike, slow-wave pattern typical of an idiopathic seizure disorder was observed by electroencephalography. Finally, a 23 year old woman in the placebo group suffered a miscarriage shortly after study discontinuation.

DISCUSSION

Lorcaserin is a highly selective and potent 5-HT_{2C} agonist that is being evaluated clinically for weight loss. Because of its selectivity, lorcaserin is predicted to have minimal activity at 5-HT_{2A} and even less activity at 5-HT_{2B} receptor subtypes at therapeutic concentrations. The present study evaluated the efficacy and safety of lorcaserin at three doses administered to obese, otherwise healthy adults for 12 weeks. To evaluate drug effects in isolation and to avoid a potentially confounding variable, diet and exercise modifications were not included in this phase 2 trial.

Lorcaserin was associated with progressive, dose-dependent, significant weight loss as compared to placebo over the 12-week study. By completer analysis, weight reductions of 1.8, 2.6, and 3.6 kg were observed at 10 mg q.d., 15 mg q.d., and 10 mg b.i.d., respectively, compared to placebo weight loss of 0.3 kg ($P < 0.001$ for each group), and similar results were obtained by ITT-LOCF analysis. The weight loss was apparent within 2 weeks, and was progressive throughout the 12-week treatment period. Of note, the weight loss in lorcaserin-treated patients was achieved without the

prescription of concurrent calorie restriction or increased physical activity. Lorcaserin was efficacious across all levels of obesity at 15 mg q.d. and at 10 mg b.i.d. Very few patients in the lorcaserin groups who remained in the study failed to respond to the drug; only 7 of the 77 completers in the 10 mg b.i.d. group lost no weight.

The placebo-corrected weight loss of 3.6 kg in the 10 mg b.i.d. group at 12 weeks, which was achieved without concurrent diet or exercise modification, is comparable to weight reductions observed at 12 weeks in longer-term trials of agents like sibutramine (37,38), rimonabant (39,40), or pramlintide (41,42). The maximum magnitude and the durability of the weight loss effect of lorcaserin will be determined in longer-term trials.

Lorcaserin-associated weight loss was accompanied by significant, dose-dependent decreases in several markers of cardiovascular risk, including plasma cholesterol, waist circumference and fasting glucose. In addition, serum uric acid, a cardiovascular risk marker that was not a prespecified end point, was modestly reduced in a dose-dependent manner in patients who took lorcaserin. The slight decrease in HDL-cholesterol in this relatively brief trial may reflect the redistribution of HDL subtypes that has been described during the first few weeks of weight loss (43). There were no adverse effects on systolic or diastolic blood pressure.

The most frequent AEs observed in lorcaserin-treated patients were headache, nausea, and dizziness. The absence of effects specifically attributable to the 5-HT_{2A} receptor is consistent with preclinical studies that showed no 5-HT_{2A} behavioral effects. Activation of the 5-HT_{2A} receptor in man is predicted to cause primarily neuropsychiatric effects, potentially including changes in cognition, perception or mood (44–46). There was no lorcaserin-related increase in such events in the present trial, either through reported AEs or through VASs. In rodents, known 5-HT_{2A}-associated behaviors include wet dog shakes, which were not observed at doses of lorcaserin that produced robust reductions in weight gain in rats (20). These observations suggest that therapeutic doses of lorcaserin do not significantly activate central 5-HT_{2A} receptor pathways. In the present trial, the plasma lorcaserin concentration at 2 h after first dosing was

~160 nmol/l after 10 mg lorcaserin and 230 nmol/l after 15 mg. Based on phase 1 clinical data using a 10-mg dose, steady state C_{\max} values are projected to be ~30% higher than the C_{\max} after the first dose (data not shown). The EC_{50} measured in *in vitro* functional assays of lorcaserin activity at the 5-HT_{2A} receptor is 168 nmol/l (20). We are uncertain how to reconcile the apparent lack of central 5-HT_{2A} effects with observed plasma lorcaserin concentrations. Possible explanations include lack of lorcaserin penetration in relevant brain areas, inaccurate predictions from the *in vitro* assay (perhaps because of differing receptor occupancy or receptor number in transfected cells vs. native tissue), partial agonism at the 5-HT_{2A} receptor, differential receptor signaling (47), or other pharmacodynamic phenomena such as protein binding which may limit receptor occupancy *in vivo*.

A second theoretical concern related to lorcaserin receptor specificity is activation of the 5-HT_{2B} receptor. Stimulation of the 5-HT_{2B} receptor has been implicated in the cardiac toxicity of nonselective serotonergic drugs (23–30). In the present study, plasma drug levels were well above the *in vitro* EC_{50} for the 5-HT_{2C} receptor (9 nmol/l), and well below the *in vitro* 5-HT_{2B} receptor EC_{50} of 943 nmol/l. Thus, it is apparent that greater lorcaserin concentrations are required to achieve efficacy *in vivo* than are predicted from *in vitro* EC_{50} data for the 5-HT_{2C} receptor that were obtained using an IP3 generation assay (20). Although the precise reason for this discrepancy is unclear, possible explanations include processes that may limit receptor occupancy or influence receptor signaling *in vivo*, such as protein binding and/or tissue distribution effects, or other similar phenomena as mentioned previously for the 5-HT_{2A} receptor.

Hence, we believe that the *in vitro* 5-HT_{2C} and 5-HT_{2A} potency measurements underestimate the plasma levels of lorcaserin required for significant receptor activation *in vivo*. Similarly, *in vitro* EC_{50} for lorcaserin at the 5-HT_{2B} receptor is also likely to be an underestimate of plasma drug levels required *in vivo* to significantly activate this receptor, and based on these data we believe it is unlikely that lorcaserin will activate 5-HT_{2B} receptors significantly *in vivo*. Consistent with this prediction, lorcaserin administration for 12 weeks was not associated with change in insufficiency of any heart valve; nor was systolic PAP increased.

Retrospective analyses of fenfluramine and dexfenfluramine use suggested that significant valvulopathy (mild or greater aortic regurgitation, or moderate or greater mitral regurgitation) occurred in ~12% of treated patients, vs. ~5.9% of patients who received placebo or who were selected as controls (48). The incidence of fenfluramine-associated valvulopathy appeared to be time-dependent, increasing after 3 months exposure (48,49). The duration of the present trial was probably sufficient to observe heart valve liability of a magnitude comparable to that observed with fenfluramine. However, a more definitive assessment requires longer-term studies of lorcaserin in greater numbers of patients.

Limitations of the present study include its relatively brief duration and the selection of relatively healthy patients for participation. Whether the significant weight loss in the 12-week study predicts greater and sustained weight reduction with longer term use remains to be determined. Moreover, it

is not yet known whether the favorable effects of lorcaserin on some cardiovascular risk markers will be observed in patients with pre-existing cardiovascular comorbidities. The results of echocardiographic safety monitoring were performed in a selected population that lacked selected pre-existing echocardiographic findings; whether the results can be generalized to an unselected population will be determined in future trials. Finally, a definitive evaluation of the cardiac safety of lorcaserin will require a larger trial or longer duration.

In summary, lorcaserin is a novel, selective 5-HT_{2C} agonist that was well tolerated and effective for weight loss in obese, otherwise healthy adults during a 12-week dosing period. Lorcaserin reduced not only body weight, but decreased other cardiovascular and metabolic risk factors as well. These results justify further evaluation of lorcaserin in long-term safety and efficacy trials.

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DISCLOSURE

W.A.P., D.J.D., M.E.M., C.M.A., and W.R.S. are employees of Arena Pharmaceuticals, which sponsored the clinical trial described in the manuscript.

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