Original Article
CLINICAL TRIALS AND INVESTIGATIONS

Obesity

Effects of Lorcaserin on Pre-Existing Valvulopathy: A Pooled Analysis of Phase 3 Trials

Neil J. Weissman[1,2], Steven R. Smith[3,4], Randi Fain[5], Nancy Hall[6], and William R. Shanahan[7]

Objective: To evaluate the effects of lorcaserin in patients with pre-existing Food and Drug Administration (FDA)-defined valvulopathy.

Methods: This is a pooled, *post hoc* analysis of three Phase 3 studies. BLOOM and BLOSSOM patients were 18 to 65 years of age without diabetes and with a body mass index (BMI) of 27 to 29.9 kg/m^2 and $\geq$1 weight-related comorbidity or a BMI of 30 to 45 kg/m^2. BLOOM-DM patients had a BMI of 27 to 45 kg/m^2 and type 2 diabetes. Patients were treated with placebo, lorcaserin 10 mg once daily, or lorcaserin 10 mg twice daily. Serial echocardiographs were obtained at baseline and every 6 months.

Results: Included patients (N = 169) had FDA-defined valvulopathy at baseline and a week 52 echocardiogram. At week 52, 35.5% and 52.7% of patients experienced changes from baseline in aortic and mitral regurgitation, respectively. Numerically greater proportions of patients taking lorcaserin versus placebo had decreases in aortic (33.0% vs. 28.3%) or mitral (41.3% vs. 36.7%) regurgitation. Fewer patients taking lorcaserin versus placebo had increases in aortic (2.8% vs. 6.7%) or mitral (8.3% vs. 21.7%) regurgitation. No adverse event-related discontinuation was due to a valve problem.

Conclusions: These data suggest that lorcaserin does not adversely affect valvular disease in patients with pre-existing FDA-defined valvulopathy.

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Introduction

The serotonin receptor subtype 5-hydroxytryptamine 2C (5-HT$_{2C}$) regulates satiety and food intake via the hypothalamic melanocortin system and is thus an attractive target for weight loss pharmacotherapy (1). Lorcaserin is a selective 5-HT$_{2C}$ receptor agonist indicated in the United States for chronic weight management as an adjunct to a reduced-calorie diet and increased physical activity (2). In preclinical studies, lorcaserin demonstrated ~61-fold selectivity for the 5-HT$_{2C}$ receptor relative to the 5-HT$_{2B}$ receptor (2). This selectivity is important in light of aortic and mitral valve insufficiency associated

[1] MedStar Health Research Institute, Washington, DC, USA. Correspondence: Neil Weissman (neil.j.weissman@medstar.net) [2] Regulatory Science, Georgetown University School of Medicine, Washington, DC, USA [3] Center for the Metabolic Origins of Disease, Sanford Burnham Prebys Medical Discovery Institute, Orlando, Florida, USA [4] Translational Research Institute for Metabolism and Diabetes, Florida Hospital, Orlando, Florida, USA [5] Mallinckrodt Pharmaceuticals, Hampton, New Jersey, USA [6] Medical and Scientific Affairs, Eisai Inc., Woodcliff Lake, New Jersey, USA [7] Anthera Pharmaceuticals, Inc., Hayward, California, USA.

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Author contributions: NJW: conception of work, design of work, data analysis, interpretation of data; drafting of work, critical revision of work for important intellectual content; final approval of the version to be published. He had full access to all data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. SRS: conception of work, design of the work, data analysis, interpretation of data; critical revision of work for important intellectual content; final approval of the version to be published. RF: conception of work, design of work, data analysis, interpretation of data; drafting of work, critical revision of work for important intellectual content; final approval of the version to be published. NH: design of work, statistical/data analysis, interpretation of data; critical revision of work for important intellectual content; final approval of the version to be published. WRS: conception of work, design of work, data analysis, interpretation of data; drafting of work, critical revision of work for important intellectual content; final approval of the version to be published.

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with the use of nonselective serotonergic antiobesity compounds (3-7). Nonselective agents, including fenfluramine and dexfenfluramine, affect serotonin transporters and have potent activity at the 5-HT_{2B} receptor, which is expressed on cardiac valvular interstitial cells and whose activation has been strongly implicated in serotonergic cardiac valvulopathy (8-10). In a report of 86 patients exposed to fenfluramine or dexfenfluramine (in combination with mazindol or phentermine) with echocardiograms done before, during, and after treatment, 16.5% of patients developed valvular regurgitation, and its incidence was correlated to duration of treatment (11). In another study, upon cessation of therapy, fenfluramine-associated valvular regurgitation improved or remained stable, while worsening was infrequent (12).

Due to the historical association of antiobesity agents such as fenfluramine–phentermine (fen-phen) with valvular heart disease (13), Phase 3 clinical trials evaluating the efficacy and safety of lorcaserin in patients with overweight and obesity incorporated serial echocardiographic assessments to monitor valvular function (14-16). The primary echocardiographic end point in each study was the proportion of patients developing new Food and Drug Administration (FDA)-defined valvulopathy at week 52 (i.e., mild or greater aortic regurgitation and/or moderate or greater mitral regurgitation (17) not present at baseline) (14-16), a prevalence measure (not a clinical measure) used to evaluate fenfluramine-associated, FDA-defined valvulopathy in the absence of baseline incidence data. A preplanned, integrated analysis showed that, at 1 year, the proportion of patients developing new FDA-defined echocardiographic valvulopathy with lorcaserin 10 mg twice daily (BID) (2.4%) was similar to that with placebo (2.0%) (18). The rate of new FDA-defined valvulopathy was 1.6% in a smaller group of patients receiving lorcaserin 10 mg once daily (QD), and none of these patients with new FDA-defined valvulopathy was symptomatic (19).

Comprehensive monitoring of more than 20,000 standardized serial echocardiograms in the lorcaserin Phase 3 program ruled out $\geq$1.25% of risk difference in the development of new valvular regurgitation after 1 year of lorcaserin use (18,20), but evidence concerning the risk of lorcaserin use in patients with pre-existing valvular disease has not been published. In this *post hoc* analysis, we evaluate the effects of lorcaserin in a subset of patients from the Phase 3 program with pre-existing FDA-defined valvulopathy at baseline. We also present a sensitivity analysis on the potential confounding influences of weight loss and changes in blood pressure (21,22) on valvular regurgitation.

Methods

Ethics

The Phase 3 clinical trial program for lorcaserin consisted of three trials: Behavioral Modification and Lorcaserin for Overweight and Obesity Management (BLOOM), Behavioral Modification and Lorcaserin Second Study for Obesity Management (BLOSSOM), and Behavioral Modification and Lorcaserin for Obesity and Overweight Management in Diabetes Mellitus (BLOOM-DM) (14-16). These were randomized, placebo-controlled, double-blind, multicenter studies conducted from September 2006 to August 2010, in accordance with the guidelines of the Declaration of Helsinki. Institutional review boards reviewed and approved the protocol, and all patients provided written informed consent. Patients did not receive a stipend for participation in these studies, although they could receive a nominal payment to cover time and expenses (generally limited to less than $50 per visit). These studies are registered at Clinicaltrials.gov, identification numbers NCT00395135 (BLOOM), NCT00603902 (BLOSSOM), and NCT00603291 (BLOOM-DM).

Study populations and designs

This is a pooled analysis of data from the BLOOM, BLOSSOM, and BLOOM-DM studies. Complete details of randomization and interventions have been previously published (14-16); briefly, in all three studies, patients were randomized to placebo, lorcaserin 10 mg QD, or lorcaserin 10 mg BID.

Due to the historical association of serotonergic antiobesity agents with valvular disease (7,13,23), patients with pre-existing FDA-defined valvulopathy were excluded at screening in BLOOM, the first of these three trials (15). BLOOM patients were therefore not included in this analysis, except for three patients who met the criteria for FDA-defined valvulopathy at baseline, were inadvertently randomized, and had a post-baseline echocardiographic assessment that could be brought forward to week 52 (last observation carried forward). These three patients were all randomized to the placebo group and presented with trace-to-mild aortic regurgitation and mild-to-moderate mitral regurgitation at baseline. Their duration in the study ranged from 3 to 193 days. Because lorcaserin use did not increase the incidence of FDA-defined valvulopathy in the BLOOM trial (16), echocardiographic inclusion/exclusion criteria were not applied in the BLOSSOM and BLOOM-DM trials (14,15). However, patients with a history of valve replacement surgery or congestive heart failure caused by insufficiency, damage, or stenosis of any heart valve were excluded from these trials.

BLOSSOM and BLOOM-DM were both 52-week, randomized, controlled studies with three arms: lorcaserin 10 mg QD, lorcaserin 10 mg BID, and placebo (14,15). BLOSSOM patients (N = 4,008) were 18 to 65 years of age without diabetes and with either a body mass index (BMI) of 27 to 29.9 kg/m^2 and at least one other weight-related comorbidity or a BMI of 30 to 45 kg/m^2 (14). BLOOM-DM patients (N = 604) were 18 to 65 years of age with a BMI of 27 to 45 kg/m^2 and type 2 diabetes poorly controlled by oral agents (15). Both studies were conducted at academic and private research sites in the United States (14,15).

Race categories were defined by the sponsor in the primary studies, and patients were classified as Caucasian, African American, Asian, Hispanic, or Other for presentation in this analysis. Patients reported their race, and this information was recorded by the investigator. Race data were collected to identify potential differences in safety, efficacy, or population pharmacokinetics on this basis and to provide information on racial distribution between the treatment groups. Sex distribution (male and female) is also reported.

Echocardiographic assessments

Serial echocardiographs were obtained at baseline and every 6 months in BLOSSOM and BLOOM-DM (14,15). Each blinded echocardiograph was interpreted by two cardiologists at an independent core lab (Biomedical Systems, St. Louis, MO). The same primary reader was maintained for each patient, and the secondary reader was

randomly assigned from a pool of approximately 20 highly experienced level III echocardiographers. In case of a discrepancy, the reading was adjudicated by a third reader. A 5-level rating scale was applied to aortic and mitral valve regurgitation (absent, trace, mild, moderate, or severe) according to American Society of Echocardiography guidelines (18,24).

Analyses

Echocardiographic data from the lorcaserin 10 mg BID and QD groups were pooled for this analysis, since both doses were pharmacologically active, as demonstrated by statistically significant weight loss as compared with diet and exercise alone (14-16). Patient characteristics and shifts in valvular regurgitation grade from baseline to week 52 (last observation carried forward) were summarized descriptively. Because previous reports suggested that the prevalence of valvular regurgitation may increase with increases in blood pressure and with decreases in BMI (18,21,25), the potential for relationships between shifts in regurgitation and changes in blood pressure and body weight were evaluated. Mean changes in blood pressure and body weight between baseline and week 52 and 95% confidence intervals (CIs) were summarized within each treatment group by category of aortic/mitral regurgitation grade shift.

Results

Patient characteristics and disposition

A total of 169 patients (lorcaserin 10 mg QD, $N = 34$; lorcaserin 10 mg BID, $N = 75$; placebo, $N = 60$) met echocardiographic criteria for FDA-defined valvulopathy at baseline and were included in the analysis. Patients with pre-existing FDA-defined valvulopathy accounted for 2.2% of the total Phase 3 population and 3.6% of the BLOSSOM and BLOOM-DM populations. Baseline characteristics were similar in patients receiving lorcaserin and those receiving placebo (Table 1). Mean age was 54 years, more than 70% were women, and mean BMI was 35 kg/m^2.

Fifty of 169 patients (29.6%) withdrew before the end of the study, 26 in the lorcaserin group (23.8%) and 24 in the placebo group (40.0%). This rate of attrition is consistent with other trials for obesity management (26-29). Major reasons for withdrawal were withdrawn consent (lorcaserin, 12 patients, 11%; placebo, 12 patients, 20%), adverse events (lorcaserin, 7 patients, 6.42%; placebo, 4 patients, 6.67%), and lost to follow-up (lorcaserin, 4 patients, 3.67%). No adverse event-related discontinuations were due to a valve problem.

Shifts in valvular regurgitation grade

With respect to regurgitation scores at week 52, 35.5% and 52.7% of patients with baseline FDA-defined valvulopathy experienced changes in either direction from baseline in aortic and mitral regurgitation, respectively. The majority of shifts in regurgitation scores were single-grade increases or decreases (Figure 1), and no patient experienced more than a single-grade increase in aortic or mitral regurgitation. With respect to decreases, although the majority were single grade, some were of 2 or 3 grades. Because the patterns of shifts in the lorcaserin 10 mg QD and BID groups were similar, the data from these two groups were pooled.

TABLE 1 Demographic and clinical characteristics of patients with FDA-defined valvulopathy at baseline

	Lorcaserin 10 mg ($N = 109$: QD [$N = 34$]; BID [$N = 75$])	Placebo ($N = 60$)
Age (years)		
Mean (SD)	53.89 (9.01)	53.50 (8.99)
Median (range)	55.00 (19.0-65.0)	55.50 (22.0-65.0)
Age group (years), *n* (%)		
18-24	2 (1.8)	1 (1.7)
25-34	2 (1.8)	1 (1.7)
35-44	11 (10.1)	6 (10.0)
45-54	35 (32.1)	19 (31.7)
55-65	59 (54.1)	33 (55.0)
Sex, *n* (%)		
Male	32 (29.4)	15 (25.0)
Female	77 (70.6)	45 (75.0)
Race, *n* (%)		
Caucasian	77 (70.6)	50 (83.3)
African American	19 (17.4)	4 (6.7)
Asian	5 (4.6)	1 (1.7)
Hispanic	8 (7.3)	4 (6.7)
Other	0 (0.0)	1 (1.7)
Weight (kg)		
Mean (SD)	99.5 (16.8)	95.5 (16.1)
Median (range)	98.3 (64.9-148.7)	92.9 (59.9-141.1)
BMI (kg/m^2)		
Mean (SD)	35.31 (4.24)	34.55 (3.57)
Median (range)	34.60 (27.5-45.0)	34.60 (28.0-44.1)
BMI group, *n* (%)		
<30 kg/m^2	8 (7.3)	3 (5.0)
30 to <35 kg/m^2	53 (48.6)	30 (50.0)
35 to <40 kg/m^2	29 (26.6)	23 (38.3)
40 to <45 kg/m^2	18 (16.5)	4 (6.7)
≥45 kg/m^2	1 (0.9)	0 (0.0)
Systolic blood pressure (mm Hg)		
Mean (SD)	126.18 (12.06)	127.60 (13.90)
Median (range)	126.00 (97.0-152.0)	129.00 (99.0-156.0)
Diastolic blood pressure (mm Hg)		
Mean (SD)	77.80 (8.89)	78.53 (9.02)
Median (range)	76.00 (50.0-94.0)	79.00 (44.0-98.0)
Current tobacco use, *n* (%)[a]		
Yes	33 (30.3)	22 (36.7)
No	76 (69.7)	38 (63.3)

[a]Patients with non-missing tobacco use response.
BID, twice daily; BMI, body mass index; QD, once daily; SD, standard deviation.

Numerically greater proportions of patients taking lorcaserin versus placebo had decreases in aortic regurgitation (lorcaserin, 33.0% [QD, 26.5%; BID, 36.0%] vs. placebo, 28.3%) or mitral regurgitation (lorcaserin, 41.3% [QD, 50.0%; BID, 37.3%] vs. placebo, 36.7%) from baseline to week 52. A numerically smaller proportion

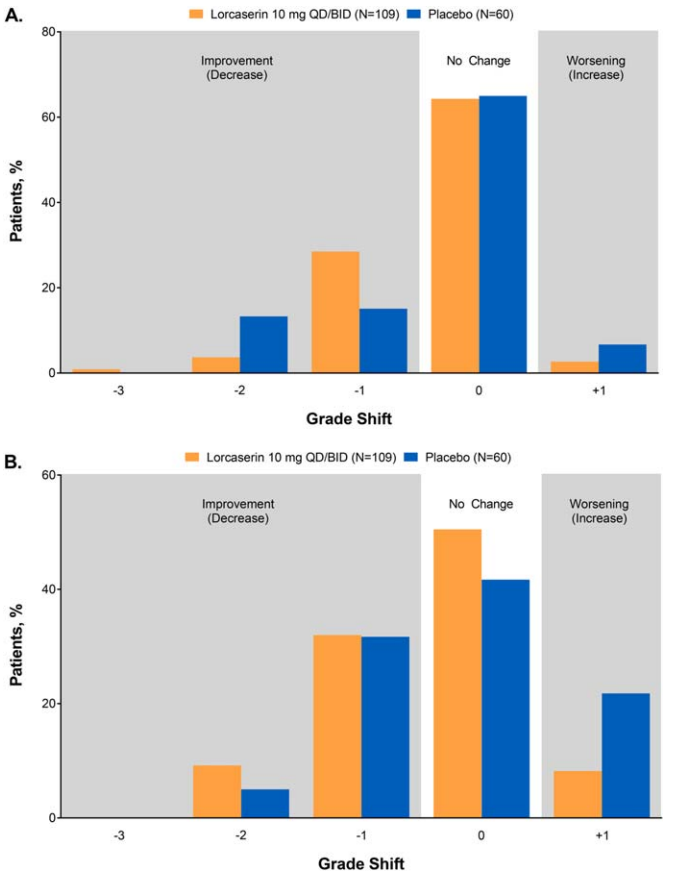

Figure 1 Shifts in (**A**) aortic and (**B**) mitral valvular regurgitation scores in patients with FDA-defined valvulopathy. BID, twice daily; QD, once daily.

of patients taking lorcaserin versus placebo had increases in aortic regurgitation (lorcaserin, 2.8% [QD, 2.9%; BID, 2.7%] vs. placebo, 6.7%) or mitral regurgitation (lorcaserin, 8.3% [QD, 5.9%; BID, 9.3%] vs. placebo, 21.7%) from baseline to week 52. Table 2 provides information on the degree of regurgitation at baseline and week 52. After treatment, aortic valve regurgitation scores improved to absent or trace in 30.3% of lorcaserin-treated patients and 26.7% of placebo-treated patients, and mitral valve regurgitation scores improved to absent or trace in 28.4% of lorcaserin-treated patients and 25.0% of placebo-treated patients. Thus, lorcaserin-treated patients exhibited numerically greater improvements in aortic and mitral regurgitation versus placebo, in both the proportions achieving such improvements and their magnitudes.

Effects of changes in weight and blood pressure on valvular regurgitation

We evaluated the effects of changes in weight on valvular regurgitation in patients with FDA-defined valvulopathy at baseline. In the total population, mean weight change (95% CI) was −5.2% (−6.2 to −4.2); when stratifying by treatment group (lorcaserin, $N = 109$; placebo, $N = 60$), greater weight loss was achieved in lorcaserin-treated patients versus placebo (lorcaserin, −6.2% [−7.5 to −4.9] vs. placebo, −3.4% [−4.8 to −2.0]). Also in the total population, mean change from baseline in weight was −5.2% (−6.7 to −3.7) in patients who showed improvement in mitral regurgitation ($N = 67$) and −5.9% (−9.2 to −2.6) in patients who showed worsening in mitral regurgitation ($N = 22$). Mean change from baseline in weight was −4.8% (−6.5 to −3.2) in patients who showed improvement in aortic regurgitation ($N = 53$) and −8.2% (−16.1 to −0.3) in patients who showed worsening in aortic regurgitation ($N = 7$). Therefore, no association was detected between weight loss and valvular regurgitation.

We also evaluated the effects of changes in blood pressure on valvular regurgitation in these patients. In the total population, mean change in systolic/diastolic blood pressure was −2.2 mm Hg (−4.1 to −0.3)/−0.5 mm Hg (−2.0 to 1.0); when stratifying by treatment group (lorcaserin, $N = 109$; placebo, $N = 60$), slightly greater reductions in systolic/diastolic blood pressure were achieved in lorcaserin-treated patients versus placebo (lorcaserin, −2.4 mm Hg [−4.6 to −0.1]/−0.5 mm Hg [−2.3 to 1.3] vs. placebo, −2.0 mm Hg [−5.6 to 1.7]/−0.5 mm Hg [−3.3 to 2.2]). In the total population, mean change from baseline in systolic/diastolic blood pressure was −4.0 mm Hg (−7.0 to −1.1)/−0.2 mm Hg (−2.6 to −2.3) in patients that showed improvement in mitral regurgitation ($N = 67$) and −2.0 mm Hg (−7.0 to −3.0)/−0.8 (−5.3 to −3.8) in patients that showed worsening in mitral regurgitation ($N = 22$). Mean change from baseline in systolic/diastolic blood pressure was −1.6 mm Hg (−4.9 to 1.7)/−1.0 mm Hg (−4.1 to 2.1) in patients that showed improvement in aortic regurgitation ($N = 53$) and −11.3 (−18.4 to −4.2)/−2.9 mm Hg (−8.4 to −2.7) in patients that showed worsening in aortic regurgitation ($N = 7$). In this analysis, no association was detected between blood pressure changes and valvular regurgitation.

Discussion

Previous nonselective serotonergic agents implicated in FDA-defined cardiac valvulopathy have potent activity at the 5-HT_{2B} receptor (8-10). Lorcaserin, a highly selective serotonergic antiobesity agent that is clinically available for use in patients with obesity or with overweight with a comorbidity, was designed to selectively activate 5-HT_{2C} receptors at therapeutic doses, with a functional selectivity of approximately 14 times that for 5-HT_{2A} receptors and 61 times that for 5-HT_{2B} receptors (2,30). At therapeutic doses, free (unbound to plasma proteins) drug levels of lorcaserin are well below the *in vitro* activation constant for the 5-HT_{2B} receptor (30-32). Thus, the theoretical risk of valvular heart disease associated with lorcaserin use is low.

Analyses reported in a previous publication demonstrated that lorcaserin use was not associated with a meaningfully greater incidence of new echocardiographically identified FDA-defined valvulopathy versus placebo (18). Applying multiple statistical techniques to the data, a consistent risk ratio of approximately 1.1 (lorcaserin BID vs. placebo) was identified (18). Consistent with these data, the current analysis demonstrates that lorcaserin use does not worsen aortic or mitral regurgitation in patients with pre-existing FDA-defined valvulopathy after 1 year of treatment, relative to placebo. Small changes, limited to 1-grade increases and 1- to 3-grade decreases in regurgitation, were noted in similar proportions of lorcaserin- and placebo-treated patients at each valve. Furthermore, a sensitivity

TABLE 2 Changes in valvular regurgitation scores at week 52 among patients with FDA-defined valvulopathy at baseline

	Lorcaserin 10 mg (*N* = 109: QD [*N* = 34]; BID [*N* = 75])[a]	Placebo (*N* = 60)[a]
Aortic valvulopathy		
Improvement (decrease)		
Moderate to absent (−3)	1 (0.9)	0
Moderate to trace (−2)	0	0
Mild to absent (−2)	4 (3.7)	8 (13.3)
Moderate to mild (−1)	3 (2.8)	1 (1.7)
Mild to trace (−1)	22 (20.2)	7 (11.7)
Trace to absent (−1)	6 (5.5)	1 (1.7)
No change		
Absent to absent	11 (10.1)	8 (13.3)
Trace to trace	4 (3.7)	1 (1.7)
Mild to mild	52 (47.7)	29 (48.3)
Moderate to moderate	3 (2.8)	1 (1.7)
Worsening (increase)		
Absent to trace (+1)	1 (0.9)	3 (5.0)
Trace to mild (+1)	0	1 (1.7)
Mild to moderate (+1)	2 (1.8)	0
Moderate to severe (+1)	0	0
Trace to moderate (+2)	0	0
Mitral valvulopathy		
Improvement (decrease)		
Moderate to absent (−3)	0	0
Moderate to trace (−2)	7 (6.4)	2 (3.3)
Mild to absent (−2)	3 (2.8)	1 (1.7)
Moderate to mild (−1)	14 (12.8)	7 (11.7)
Mild to trace (−1)	13 (11.9)	7 (11.7)
Trace to absent (−1)	8 (7.3)	5 (8.3)
No change		
Absent to absent	4 (3.7)	1 (1.7)
Trace to trace	32 (29.4)	15 (25.0)
Mild to mild	11 (10.1)	4 (6.7)
Moderate to moderate	8 (7.3)	5 (8.3)
Worsening (increase)		
Absent to trace (+1)	2 (1.8)	4 (6.7)
Trace to mild (+1)	5 (4.6)	7 (11.7)
Mild to moderate (+1)	2 (1.8)	1 (1.7)
Moderate to severe (+1)	0	1 (1.7)
Trace to moderate (+2)	0	0

BID, twice daily; QD, once daily.
[a]*n* (%).

analysis showed that neither weight loss nor changes in blood pressure were associated with changes in valvular regurgitation in this population.

The Endocrine Society Clinical Practice Guideline for the Pharmacological Management of Obesity suggests the use of lorcaserin for weight management in patients with established cardiovascular disease (33), since, unlike some other antiobesity agents (29,34), it is not a sympathomimetic agent (33). The current analysis, coupled with the previous analysis of lorcaserin use in patients without FDA-defined valvulopathy at baseline (18), provides additional support for the Endocrine Society recommendation. Combined, these two analyses provide a comprehensive analysis of cardiac valvular safety with lorcaserin use, which may facilitate clinical decision making.

In a pool of more than 20,000 echocardiograms conducted during the Phase 3 clinical trials of lorcaserin, only a small number of patients (2.7%) had FDA-defined valvulopathy at baseline (20). Therefore, these data should be interpreted within the limitations of this analysis. This is a retrospective, *post hoc* subgroup analysis of a limited number of patients with pre-existing FDA-defined valvulopathy. As such, this analysis was not powered to conduct statistical testing between treatment groups. Furthermore, pre-existing valvulopathy was not considered a characteristic for stratification in randomization, so this *post hoc* analysis cannot be considered randomized. Therefore, it is unknown whether the subtle differences in baseline characteristics between the treatment groups introduce bias. Larger prospective studies looking at a diverse population of patients are needed to confirm these results and to conduct subgroup analyses to examine the effects of blood pressure and weight changes on valvular regurgitation. Furthermore, this is not a complete cardiovascular evaluation of lorcaserin use. Valvular regurgitation is only one aspect of cardiovascular health, and general assumptions regarding overall cardiovascular health should not be made based on these data. A 12,000-patient, multiyear assessment of cardiovascular outcomes with lorcaserin use, including serial echocardiographic evaluations in a large subset of the trial population, is ongoing (NCT02019264).

This study provides further data to support that use of lorcaserin does not adversely affect valvular heart disease in patients with pre-existing FDA-defined valvulopathy.

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