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CLINICAL TRIALS AND INVESTIGATION

Obesity

Coadministration of Lorcaserin and Phentermine for Weight Management: A 12-Week, Randomized, Pilot Safety Study

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Objective: To assess the short-term tolerability of lorcaserin alone or with two dose regimens of phentermine.
Methods: This was a 12-week, randomized, double-blind, pilot safety study of $N = 238$ nondiabetic patients with obesity or overweight with $\geq$1 comorbidity randomized to lorcaserin 10 mg twice daily (BID; LOR BID) alone or with phentermine 15 mg once daily (QD; LOR BID+PHEN QD) or 15 mg twice daily (LOR BID+PHEN BID). Patients reporting $\geq$ 1 of 9 potentially serotonergic adverse events (AEs), mean weight loss (WL), and $\geq$5% WL are reported.
Results: $N = 238$ were randomized, and $N = 235$ were treated. $N = 94$ reported potentially serotonergic AEs: 37.2% LOR BID, 42.3% LOR BID+PHEN QD, and 40.5% LOR BID+PHEN BID. AEs leading to discontinuation were reported approximately twice as often in the LOR BID+PHEN BID group versus the LOR BID group. Mean WL was 3.5 kg/3.3%, 7.0 kg/6.7%, and 7.6 kg/7.2% for LOR BID, LOR BID+PHEN QD, and LOR BID+PHEN BID, respectively. At least 5% WL was achieved by 28.2% LOR BID, 59.0% LOR BID+PHEN QD ($P = 0.0002$ vs. LOR BID), and 70.9% LOR BID+PHEN BID ($P < 0.0001$ vs. LOR BID) patients.
Conclusions: Phentermine added to lorcaserin enhanced short-term weight loss but did not increase incidence of potentially serotonergic AEs; however, phentermine twice daily increased discontinuation compared to both lorcaserin alone and lorcaserin plus phentermine once daily.

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Introduction

Diet and exercise alone are often inadequate to achieve and maintain clinically meaningful weight loss for patients with overweight and obesity (1). Adjunctive pharmacotherapy may increase weight loss beyond that achieved with lifestyle modification (2-4). Increasingly, pharmacotherapy involves combinations of drugs with distinct mechanisms of action (5-7). By targeting different signaling pathways, combination pharmacotherapy may overcome counterregulatory mechanisms that can hamper weight loss, thus improving efficacy (7,8).

Lorcaserin is a selective serotonin (5-HT) 2C receptor agonist approved for weight management in patients with a BMI $\geq$ 30 kg/m^2, or $\geq$ 27 kg/m^2 with $\geq$ 1 weight-related comorbidity, as an adjunct to a reduced-calorie diet and increased physical activity (9). Three phase III clinical trials in adults with overweight or obesity have established the safety and efficacy of lorcaserin (10-12). Following 1 year of treatment, significantly more patients receiving lorcaserin 10 mg twice daily achieved $\geq$ 5% weight loss relative to diet and exercise alone (10-12).

Phentermine, indicated for short-term obesity management, is a sympathomimetic amine thought to suppress appetite through norepinephrine release in the hypothalamus (13,14). In clinical studies, coadministration of serotonergic and noradrenergic drugs has led to additive weight loss (15). However, phentermine may be associated with increased serotonergic activity (16,17). Lorcaserin is a serotonergic agent; therefore, coadministration with phentermine could theoretically result in serotonergic events, adversely impacting safety.

As the safety and tolerability of lorcaserin has been extensively studied (10-12) and phentermine's safety has been well established (14), a major goal of this preliminary study was to understand the tolerability and efficacy of the combination, as well as explore the possibility of both anticipated and unanticipated safety signals. This pilot study focused on physician consensus and published literature regarding serotonergic adverse events (AEs) with the combination of lorcaserin and phentermine. In the absence of a "pure" single serotonergic AE, a composite of AEs as outlined in this paper was chosen. Nine commonly observed AEs in patients taking lorcaserin are potentially associated with serotonin effects and/or commonly attributable to use of selective serotonin reuptake inhibitors (9,18) and were prespecified as potential serotonergic AEs in this study. The data collection followed the approved study protocol. The purpose of this phase IV study, Pilot Evaluation of Tolerability And safety of Lorcaserin plus phentermine (PETAL), was to assess whether combining lorcaserin with immediate-release phentermine is associated with an increased incidence of potentially serotonergic AEs.

Methods

Study overview

This 12-week, randomized, double-blind, parallel-group, pilot safety study was conducted at 12 sites in the United States from October 2013 to September 2014, following Declaration of Helsinki guidelines. Institutional review boards reviewed and approved the protocol; all patients provided written informed consent. Patients did not receive a stipend for study participation.

Patients

Eligible patients were men and women aged 18 to 60 years, with BMIs $\geq$ 30 kg/m^2 or 27 to 29.9 kg/m^2 with $\geq$ 1 weight-related comorbidity (e.g., hypertension, dyslipidemia, sleep apnea). All patients were ambulatory and able to participate in a moderate-intensity exercise program. Key exclusion criteria included recent treatment with monoamine oxidase inhibitors; recent or active history of depression or psychiatric disease requiring prescription medication; concomitant use of selective serotonin reuptake inhibitors or serotonin-norepinephrine reuptake inhibitors; use of fenfluramine, related derivatives, or other medications associated with increased risk of valvulopathy and/or pulmonary hypertension; history of cardiovascular disease within 3 months of screening; systolic blood pressure $\geq$ 150 or diastolic blood pressure $\geq$95 mmHg; valve replacement surgery; clinically significant diagnosed valvulopathy; diabetes mellitus; bariatric surgery; weight change of $>$ 5 kg in the past 3 months; and pregnancy or lactation.

Race/ethnicity was assessed to ensure similar distribution between treatment groups. Race classifications were sponsor-defined as White, Black or African American, Asian, American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, or Other. Ethnicity classifications were sponsor-defined as "Hispanic or Latino" or "Not Hispanic or Latino." Participants reported their race/ethnicity; this information was recorded by the investigator.

Randomization and interventions

Subjects ($N = 238$) were assigned to treatments based on a computer-generated randomization scheme, reviewed and approved by an independent statistician. Participants were randomly assigned in a 1:1:1 ratio to receive lorcaserin HCl 10 mg twice daily plus placebo twice daily (LOR BID), LOR twice daily plus immediate-release phentermine HCl 15 mg once daily plus placebo once daily (LOR BID+PHEN QD), or LOR twice daily plus PHEN twice daily (LOR BID+PHEN BID). Randomization was stratified by BMI ($<$40 or $\geq$ 40 kg/m^2) and performed centrally by an interactive voice/web response system vendor. The sponsor provided study treatments, packaged in a double-blind configuration. Study drug was supplied in a monthly subject medication kit/carton bearing a two-part detachable label. The interactive voice/web response system assigned the specific, unique kit/carton for each monthly scheduled visit. Patients were instructed to take lorcaserin and phentermine/placebo concurrently, once in the morning and again midafternoon, to reduce potential phentermine-associated insomnia (14).

Patients underwent screening within 2 weeks before baseline, with assessments at weeks 1, 2, 4, 8, and 12. A telephone safety assessment was conducted 3 to 4 weeks after patients received their last study medication dose. All patients received ongoing one-on-one counseling with a trained program counselor at each study visit, including instruction to exercise at moderate intensity for 30 min/d and reduce daily caloric intake to 600 kcal below their individual estimated daily energy requirement.

AEs, vital signs, concomitant medications, and body weight were assessed at each visit. Physical exams and blood and urine chemistry laboratory evaluations were performed periodically. Waist and hip measurements were taken at baseline and at week 12/end of treatment (EOT). Electrocardiograms were obtained at screening and week 12/EOT.

Study end points

The primary end point was the proportion of patients reporting at least one of nine common potentially serotonergic AEs (headache, dizziness, vomiting, diarrhea, nausea, fatigue, dry mouth, insomnia, and/or anxiety) (18) from baseline to week 12/EOT, derived from the previously published BLOOM (12) and BLOSSOM (11) studies. Accordingly, it was determined that 75 patients per arm were needed to produce a one-sided 95% confidence interval (CI) of AE rates with a distance of 8.9% between proportion and limit.

Secondary end points were selected from coprimary end points in the BLOSSOM trial (11) and included rates of AEs, serious AEs (SAEs), and AEs leading to discontinuation/withdrawal; laboratory values; change from baseline body weight (kilograms and percent) at week 12 and intermediate time points; proportion of patients achieving $\geq$5% reduction in body weight at week 12/EOT; and change from baseline in waist circumference, hip circumference, and waist/hip ratio at week 12/EOT. A post hoc analysis was performed to determine the percentage of patients achieving $\geq$10% weight loss at week 12/EOT.

Statistical analysis

Analyses of the primary end point used the full analysis set (FAS), which included all randomized patients who received at least one dose of the study drug. This analysis was summarized with descriptive statistics and CIs for the three treatment arms. The Agresti-Coull approach was used to construct event rate CIs. The safety analysis population included all randomized patients who received at least one dose of study drug and had at least one post-baseline safety assessment.

Analyses of efficacy variables were performed on the modified intent-to-treat (MITT) population (all patients who received $\geq$1 dose of study drug and had both baseline and post-randomization weight measurements), with last-observation-carried-forward (LOCF) imputation.

Body weight analyses were also performed on the Completers population, which included all randomized patients who completed the study. Analyses of secondary end points were summarized descriptively.

An exploratory analysis using the Cochran-Armitage trend test was performed to assess any trend in the primary end point event rates and proportion (percent) of patients achieving $\geq$ 5% weight reduction among the three treatment groups. Similarly, mixed model repeated measures were used to explore any trend among treatment groups in change from baseline body weight (kilograms and percent) and pairwise comparisons of treatment difference.

In addition, post hoc exploratory analyses were conducted to test pairwise treatment differences for responder rates ($\geq$5% weight loss at week 12/EOT), safety parameters, and frequencies of AEs included in the primary end point. In these post hoc analyses, an analysis of covariance model with treatment as a factor and baseline BMI group and baseline value as covariates was used on continuous variables; χ^2 or Fisher's exact tests were applied on categorical data.

Results

Patient disposition and baseline demographics

A total of 344 patients were screened for inclusion in the study; 238 patients were randomized to receive LOR BID, LOR BID+PHEN QD, or LOR BID+PHEN BID. Three patients took no study drug; the remaining 235 made up the FAS population (Table 1).

Of the 235 patients treated, 44 (18.7%) discontinued the study before week 12. Most discontinuations were from the LOR BID+PHEN BID group ($n = 79$), in which 20 patients (25.3%) did not complete the trial. The primary reason for discontinuation was loss to follow-up, which occurred in 8.9% of the total population (21 of 235): six (7.7%), six (7.7%), and nine (11.4%) patients in the LOR BID, LOR BID+PHEN QD, and LOR BID+PHEN BID groups, respectively. The rate at which patients were lost to follow-up throughout the trial was similar among groups (Supporting Information Figure S1A). AEs were cited as the reason for discontinuation in an additional 15 patients: 4 (5.1%), 2 (2.6%), and 9 (11.4%) patients in the LOR BID, LOR BID+PHEN QD, and LOR BID+PHEN BID groups, respectively (Table 2). The rate of discontinuation due to AEs was higher for LOR BID+PHEN BID than for LOR BID and LOR BID+PHEN QD in the second half of the study (Supporting Information Figure S1B). AEs leading to study drug discontinuation in more than one patient within a dose group were headache ($n = 2$ each in LOR BID and LOR BID+PHEN BID) and dizziness ($n = 2$ in LOR BID+PHEN BID). Overall, 191 patients (81.3%) completed the study: 64 (82.1%), 68 (87.2%), and 59 (74.7%) in the LOR BID ($n = 78$), LOR BID+PHEN QD ($n = 78$), and LOR BID+PHEN BID ($n = 79$) groups, respectively.

Baseline demographics and characteristics for the FAS population (Table 1) were similar between groups.

Incidence of nine common potentially serotonergic AEs

The nine common potentially serotonergic AEs included in the primary end point were dry mouth, headache, dizziness, fatigue, insomnia, nausea, diarrhea, vomiting, and anxiety. During the study, 94 patients ($N = 235$) reported at least one of these AEs: 29 (37.2%) in the LOR BID group, 33 (42.3%) in the LOR BID+PHEN QD group, and 32 (40.5%) in the LOR BID+PHEN BID group (Figure 1A). Time to onset and resolution of potentially serotonergic AEs is shown in Supporting Information Figures S2-S9. The potentially serotonergic AE of anxiety is not included in the supplemental figures, as only one event of anxiety occurred during the study.

The Cochran-Armitage test found no evidence of a trend in the primary end point event rates among the three treatment groups ($P = 0.6719$).

Some patients reported more than one potentially serotonergic AE. In total, 152 reported AEs were part of the primary end point (LOR BID, 44; LOR BID+PHEN QD, 52; LOR BID+PHEN BID, 56).

Dry mouth, a known AE for both phentermine and lorcaserin (9,11,12,14,19), was reported at significantly higher rates [one-sided 95% CI] by patients receiving phentermine (LOR BID+PHEN QD, 26.9% [35.9%]; LOR BID+PHEN BID, 22.8% [31.4%]; P values of 0.0006 and 0.0037, respectively, vs. LOR BID, from a post hoc

TABLE 1 Baseline characteristics and demographics (full analysis population)[a]

Demographics	LOR BID (*N* = 78)	LOR BID + PHEN QD (*N* = 78)	LOR BID + PHEN BID (*N* = 79)	Total (*N* = 235)
Age, mean (SD), y	42.5 (11.0)	44.8 (11.1)	41.2 (11.7)	42.8 (11.3)
Sex, *n* (%)				
Male	10 (12.8)	8 (10.3)	17 (21.5)	35 (14.9)
Female	68 (87.2)	70 (89.7)	62 (78.5)	200 (85.1)
Race, *n* (%)				
White	46 (59.0)	50 (64.1)	44 (55.7)	140 (59.6)
Black or African American	29 (37.2)	26 (33.3)	32 (40.5)	87 (37.0)
Asian	0	1 (1.3)	0	1 (0.4)
American Indian or Alaska Native	1 (1.3)	1 (1.3)	1 (1.3)	3 (1.3)
Native Hawaiian or other Pacific Islander	0	0	1 (1.3)	1 (0.4)
Other	2 (2.6)	0	1 (1.3)	3 (1.3)
Ethnicity, *n* (%)				
Hispanic or Latino	11 (14.1)	7 (9.0)	6 (7.6)	24 (10.2)
Not Hispanic or Latino	67 (85.9)	71 (91.0)	73 (92.4)	211 (89.8)
Weight, mean (SD), kg	105.3 (21.0)	105.0 (23.4)	106.6 (19.7)	105.7 (21.3)
BMI, mean (SD), kg/m^2	38.4 (7.5)	38.0 (6.8)	38.5 (6.0)	38.3 (6.8)
Comorbid condition[b], *n* (%)				
Hypertension	13 (16.7)	18 (23.1)	16 (20.3)	47 (20.0)
Dyslipidemia	19 (24.4)	20 (25.6)	11 (13.9)	50 (21.3)
Sleep apnea	3 (3.8)	3 (3.8)	0	6 (2.6)
Impaired glucose tolerance	2 (2.6)	0	0	2 (0.9)
Blood pressure, mean (SD), mmHg				
Systolic	122.5 (12.4)	119.9 (13.6)	122.1 (12.0)	121.5 (12.7)
Diastolic	77.8 (8.3)	78.7 (8.3)	79.3 (8.2)	78.6 (8.2)
Heart rate, mean (SD), bpm	71.9 (9.5)	73.1 (9.5)	72.2 (10.7)	72.4 (9.9)
Waist circumference, mean (SD), cm	112.2 (13.8)	112.2 (15.1)	114.0 (12.0)	112.8 (13.7)
Hip circumference, mean (SD), cm	124.1 (14.3)	123.7 (14.3)	125.4 (12.8)	124.4 (13.8)
Waist/hip ratio, mean (SD)	0.9 (0.1)	0.9 (0.1)	0.9 (0.1)	0.9 (0.1)

[a]All randomized patients who received at least one dose of the study drug.
[b]Comorbid conditions were self-reported as medical history and supported by medication use and/or baseline laboratory values. Some patients reported ≥ 1 comorbid condition.
BID, twice daily; BMI, body mass index; LOR, lorcaserin HCl 10 mg; PHEN, immediate-release phentermine HCl 15 mg; QD, once daily; SD, standard deviation.

analysis) compared to LOR BID (6.4% [12.8%]). Dizziness and nausea also occurred at numerically higher rates [one-sided 95% CI] in the LOR BID+PHEN BID group (10.1% [17.2%] and 7.6% [14.2%]) and LOR BID+PHEN QD group (5.1% [11.2%] and 6.4% [12.8%]) compared to LOR BID (1.3% [6.0%] and 1.3% [6.0%]).

Headache (one-sided 95% CI) occurred in 17.9% (26.2%) of patients in the LOR BID group, compared to 9.0% (15.9%) for LOR BID+PHEN QD and 13.9% (21.6%) for LOR BID+PHEN BID. Rates of fatigue and diarrhea (one-sided 95% CI) were 10.3% (17.4%) and 6.4% (12.8%) in the LOR BID group, 3.8% (9.5%) and 2.6% (7.8%) in the LOR BID+PHEN QD group, and 6.3% (12.6%) and 0% in the LOR BID+PHEN BID group. Vomiting ($n = 8$) and anxiety ($n = 1$) occurred infrequently in all treatment groups (Figure 1B).

Adverse events

An overview of AEs for the safety analysis population is shown in Table 2. Approximately two-thirds of patients in each group (64.1%, 66.7%, and 68.4% for LOR BID, LOR BID+PHEN QD, LOR BID+PHEN BID, respectively) experienced at least one AE. AEs with the highest absolute frequency reported in at least one of the groups and at ≥5% were headache, fatigue, insomnia, dry mouth, diarrhea, cough, constipation, dizziness, and nausea. Time to onset and resolution of these AEs is shown in Supporting Information Figures S2-S7 and S9-S11. Discontinuation due to AEs was seen in 5.1% of LOR BID, 2.6% of LOR BID+PHEN QD, and 11.4% of LOR BID+PHEN BID patients. The only AEs that led to study drug discontinuation in more than one patient within a dose group were headache (LOR BID, $n = 2$; LOR BID+PHEN BID, $n = 2$) and dizziness (LOR BID+PHEN BID, $n = 2$).

Three SAEs occurred during the study (Table 2): one case of atrial fibrillation (LOR BID+PHEN BID); one patellofemoral arthritis and one appendicitis (both LOR BID+PHEN QD). The investigator considered the SAE of atrial fibrillation in the LOR BID+PHEN BID group to be related to treatment with both study drugs. No deaths occurred during the study.

TABLE 2 Adverse events (safety analysis population)

Patients, *n* (%)	LOR BID (*N* = 78)	LOR BID + PHEN QD (*N* = 78)	LOR BID + PHEN BID (*N* = 79)
AEs	50 (64.1)	52 (66.7)	54 (68.4)
AEs leading to study drug discontinuation[a]	4 (5.1)	2 (2.6)	9 (11.4)
AEs leading to interruption	8 (10.3)	6 (7.7)	6 (7.6)
Treatment-related AEs	38 (48.7)	35 (44.9)	43 (54.4)
Severe AEs[b]	6 (7.7)	5 (6.4)	4 (5.1)
SAEs	0	2 (2.6)	1 (1.3)
Deaths	0	0	0
Headache	14 (17.9)	7 (9.0)	11 (13.9)
Fatigue	8 (10.3)	3 (3.8)	5 (6.3)
Insomnia	7 (9.0)	4 (5.1)	2 (2.5)
Dry mouth	5 (6.4)	21 (26.9)	18 (22.8)
Diarrhea	5 (6.4)	2 (2.6)	0
Cough	5 (6.4)	0	2 (2.5)
Constipation	4 (5.1)	7 (9.0)	11 (13.9)
Dizziness	1 (1.3)	4 (5.1)	8 (10.1)
Nausea	1 (1.3)	5 (6.4)	6 (7.6)

[a]AEs leading to discontinuation in the LOR BID+PHEN BID group included dizziness, headache, abdominal distention, nausea, vomiting, fatigue, local swelling, peripheral edema, gastroenteritis, elevated ALT, elevated AST, abnormal electrocardiogram, myalgia, postural dizziness, migraine, and hot flush. Only dizziness ($n = 2$) and headache ($n = 2$) occurred in more than one patient.
[b]Severe AE is defined as incapacitating, with inability to work or to perform normal daily activity.
AE, adverse event; ALT, alanine transaminase; AST, aspartate transaminase; BID, twice daily; LOR, lorcaserin HCl 10 mg; PHEN, phentermine HCl 15 mg; QD, once daily; SAE, serious adverse event.

Vital signs and other observations related to safety

No clinically relevant changes in hematologic tests, lipids, glycemic parameters, or urinalysis were identified in any treatment group, and there was no evidence of hepatic or renal toxicity.

All treatment groups had numeric reductions in systolic and diastolic blood pressure (mmHg [standard deviation, SD]) from baseline to week 12/EOT in the safety analysis population (LOR BID, -5.5 [11.8]/−2.5 [8.1]; LOR BID+PHEN QD, -3.3 [12.3]/−1.4 [7.8]; LOR BID+PHEN BID, -3.4 [12.9]/−1.7 [8.3]) (Table 3). Blood pressure reductions were seen as early as week 1; at no point during the study did blood pressure rise above baseline.

At week 12/EOT, mean heart rate change from baseline (bpm [SD]) was significantly lower in the LOR BID group (−1.9 [10.6]) relative to LOR BID+PHEN QD (+1.1 [10.4], $P = 0.0157$) and LOR BID+PHEN BID (+3.1 [9.9], $P = 0.0007$) in the safety analysis population (Table 3).

Weight loss

Mean weight loss ± SD at week 12/EOT in the MITT population was 3.5 ± 3.7 kg/3.3 ± 3.4%, 7.0 ± 6.0 kg/6.7 ± 5.4%, and 7.6 ± 4.7 kg/7.2 ± 4.6% for LOR BID, LOR BID+PHEN QD, and LOR BID+PHEN BID, respectively (Figure 2A, Table 3). Mean weight loss at week 12 in the Completers population was 4.0 ± 3.8 kg/3.8 ± 3.3%, 7.6 ± 6.1 kg/7.3 ± 5.4%, and 8.9 ± 4.3 kg/8.7 ± 4.1% for LOR BID, LOR BID+PHEN QD, and LOR BID+PHEN BID, respectively (Figure 2B). An exploratory analysis of change from baseline in body weight (kg/percent) using mixed model repeated measures indicated statistically significant improvements with combination therapy versus LOR BID in both the MITT and Completers populations. Weight loss differences between the LOR BID+PHEN QD and LOR BID+PHEN BID groups were not statistically significant.

In the MITT/LOCF population at week 12/EOT, the percentages of patients achieving ≥5% weight loss were 28.2%, 59.0%, and 70.9% for LOR BID, LOR BID+PHEN QD ($P = 0.0002$ vs. LOR BID), and LOR BID+PHEN BID ($P < 0.0001$ vs. LOR BID; $P = 0.1341$ vs. LOR BID+PHEN QD), respectively. The proportions of patients achieving ≥10% weight loss were 3.8% for LOR BID, 24.4% for LOR BID+PHEN QD ($P = 0.0003$ vs. LOR BID), and 27.8% for LOR BID+PHEN BID ($P < 0.0001$ vs. LOR BID; $P = 0.7169$ vs. LOR BID+PHEN QD) (Figure 2C). Individual patient weight losses in the MITT/LOCF population are displayed in Figure 2E, 2G, and 2I.

In the Completers population at week 12, the percentages of patients achieving ≥5% weight loss were 33.3%, 68.2%, and 84.2% for LOR BID, LOR BID+PHEN QD ($P = 0.0001$ vs. LOR BID), and LOR BID+PHEN BID ($P < 0.0001$ vs. LOR BID; $P = 0.0572$ vs. LOR BID+PHEN QD), respectively. The proportions of patients achieving ≥10% weight loss were 4.8% for LOR BID, 27.3% for LOR BID+PHEN QD ($P = 0.0006$ vs. LOR BID), and 35.1% for LOR BID+PHEN BID ($P < 0.0001$ vs. LOR BID; $P = 0.4344$ vs. LOR BID+PHEN QD) (Figure 2D). Individual patient weight losses in the Completers population are displayed in Figure 2F, 2H, and 2J.

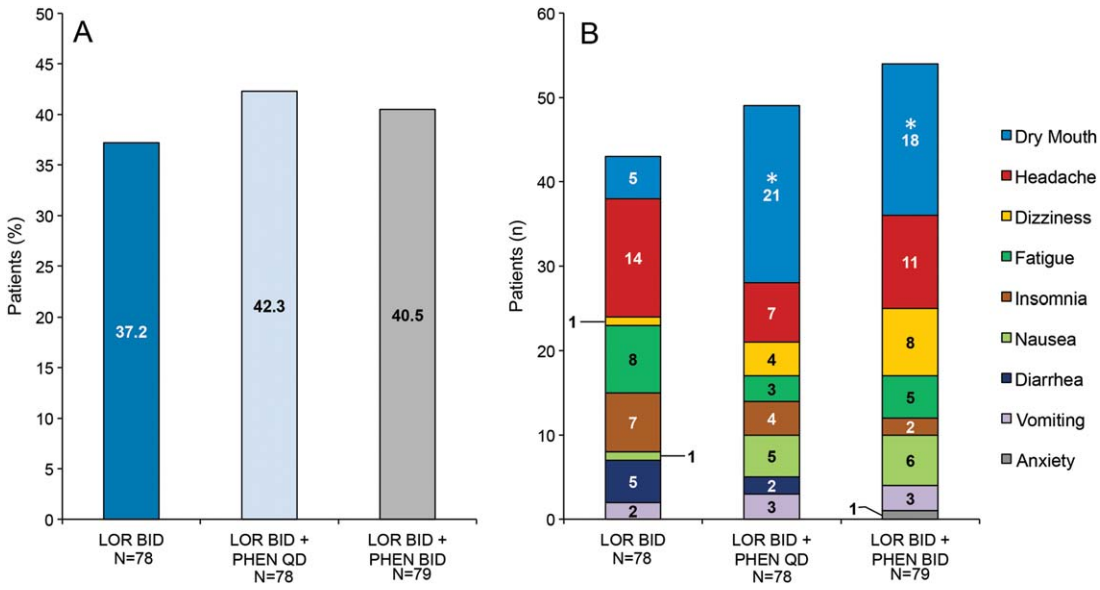

Figure 1 Incidence of prespecified potentially serotonergic AEs in the FAS. (**A**) The proportion of patients (%) reporting at least one of the nine common potentially serotonergic AEs, and (**B**) the number of patients reporting each individual potentially serotonergic AE during the study. The FAS includes all randomized patients who received at least one dose of the study drug. Some patients reported more than one AE that qualified for the primary end point. *$P < 0.05$ vs. LOR BID (as determined by post hoc analysis). AE, adverse event; BID, twice daily; FAS, full analysis set; LOR, lorcaserin HCl 10 mg; PHEN, phentermine HCl 15 mg; QD, once daily.

Exploratory analyses performed across the three treatment groups showed strong evidence in favor of a dose response for the change from baseline in body weight (linear contrasts; $P < 0.0001$) and proportion of patients achieving ≥5% weight loss at week 12/EOT (Cochran-Armitage trend test; $P < 0.0001$).

At week 12/EOT in the MITT/LOCF population, mean changes in waist circumference were −3.4 cm for LOR BID, −4.7 cm for LOR BID+PHEN QD, and −7.1 cm for LOR BID+PHEN BID (Table 3). Mean changes in hip circumference were −2.8 cm for LOR BID, −3.6 cm for LOR BID+PHEN QD, and −6.2 cm for LOR BID+PHEN BID. No between-group differences were seen in mean waist/hip ratios.

Discussion

This pilot study evaluated the short-term safety and tolerability of combination therapy with lorcaserin and immediate-release phentermine, the most commonly prescribed form of phentermine, with secondary efficacy end points for weight management. This study's primary objective was to evaluate whether short-term treatment with lorcaserin 10 mg twice daily plus two doses of immediate-release phentermine (15 mg once daily or 15 mg twice daily) was associated with increased incidence of serotonergic AEs compared to lorcaserin alone. This study suggests that the prespecified potentially serotonergic AEs occurred at a similar rate with combined lorcaserin plus phentermine and with lorcaserin alone. Common AEs during the trial were consistent with prior experience with these agents used as monotherapy (10-12,19). None of the nine prespecified common potentially serotonergic AEs were reported as serious, and no serotonin syndrome events occurred in any treatment group, although the study was not powered to assess serotonin syndrome risk.

Headache and dry mouth were the most frequently reported prespecified potentially serotonergic AEs. Headache has been the most commonly reported AE in lorcaserin monotherapy studies (10-12) and has been associated with phentermine use, with rates >10% in previous studies (20). In the current study, the lorcaserin/phentermine combination did not increase the rate of headache, which trended lower in the combination groups compared with the LOR BID group. Dry mouth has previously been reported as the most common AE associated with phentermine (19,20), and the incidence of dry mouth increased significantly with the addition of phentermine twice daily or once daily to lorcaserin twice daily. Approximately twice as many patients in the LOR BID+PHEN BID group discontinued due to AEs compared to the LOR BID group. Additionally, rates of constipation, dizziness, and nausea were higher in the LOR BID+PHEN BID group than in the LOR BID group. One case of atrial fibrillation was noted in the LOR BID+PHEN BID group. In the phase III clinical studies, lorcaserin did not increase the risk of atrial fibrillation (10-12).

Weight loss is generally associated with proportional improvements in blood pressure (21). In the present analysis, however, blood pressure decreases were numerically greater with lorcaserin twice daily alone, despite greater weight loss in the combination groups. This result may be due to phentermine, a sympathomimetic amine that has been associated with increases in blood pressure and heart rate (8,14,19,20). Lorcaserin is not a sympathomimetic (22). Previously reported results from the phase III studies also demonstrated small decreases in blood pressure and heart rate for patients on lorcaserin (9,23). Given that the sympathetic nervous system drives

TABLE 3 Change from baseline at end of treatment in vital signs and anthropometric measurements

Change from baseline, mean (SD)	LOR BID ($N = 78$)	LOR BID + PHEN QD ($N = 78$)	LOR BID + PHEN BID ($N = 79$)
Safety analysis population[a]			
Systolic blood pressure (mmHg)	−5.5 (11.8)	−3.3 (12.3)	−3.4 (12.9)
Diastolic blood pressure (mmHg)	−2.5 (8.1)	−1.4 (7.8)	−1.7 (8.3)
Heart rate (bpm)[b,c]	−1.9 (10.6)	1.1 (10.4)	3.1 (9.9)
BMI (kg/m^2)[b,c]	−1.3 (1.4)	−2.5 (2.0)	−2.7 (1.7)
MITT population[d]			
Body weight (kg)[b,c]	−3.5 (3.7)	−7.0 (6.0)	−7.6 (4.7)
Body weight (%)[b,c]	−3.3 (3.4)	−6.7 (5.4)	−7.2 (4.6)
Waist circumference (cm)[e]	−3.4 (8.0)	−4.7 (10.3)	−7.1 (5.5)
Hip circumference (cm)[e]	−2.8 (8.1)	−3.6 (11.3)	−6.2 (4.4)
Waist/hip ratio[e]	−0.0 (0.1)	−0.0 (0.0)	−0.0 (0.0)

This is a pilot study and it is not statistically powered. *P* values should be considered exploratory.
[a]*P* value based on ANCOVA model with treatment as factor and baseline value and baseline BMI group as covariates.
[b]LOR BID vs. LOR BID+PHEN QD, $P < 0.05$.
[c]LOR BID vs. LOR BID+PHEN BID, $P < 0.05$.
[d]*P* values based on mixed model repeated measures (MMRM). For MMRM, change from baseline weight (kilograms and percent) is considered a dependent variable, treatment group and visit are considered as fixed effect, and patient as a random effect. The model includes treatment, visit, baseline weight, BMI group, and treatment-by-visit interaction.
[e]Comparative statistics not performed.
ANCOVA, analysis of covariance; BID, twice daily; BMI, body mass index; LOR, lorcaserin HCl 10 mg; MITT, modified intent-to-treat; PHEN, phentermine HCl 15 mg; QD, once daily; SD, standard deviation.

thermogenesis (24), the addition of phentermine to lorcaserin is supported by a mechanistic rationale.

Serotonergic agonists like fenfluramine are associated with cardiac valvulopathy (25). Given the low incidence of this event, assessment of this important AE was not possible in this pilot study. However, lorcaserin has been extensively evaluated (7,794 patients in trials of 1 to 2 years' duration) and has not appeared to increase the risk of FDA-defined valvulopathy (relative risk 1.16, 95% CI [0.81-1.67]) (26).

To date, phentermine has been the most commonly prescribed weight loss drug and has been shown to be effective in combination with topiramate (8,20). Combination therapy can promote additional weight loss compared with monotherapy, and, consequently, physicians are likely to be interested in combining phentermine with other antiobesity agents such as lorcaserin. In this study, combination therapy resulted in significantly greater weight loss than lorcaserin alone in a dose-dependent manner, with a mean change from baseline in body weight of −3.5 kg, −7.0 kg, and −7.6 kg in the MITT/LOCF population for the LOR BID, LOR BID+PHEN QD, and LOR BID+PHEN BID groups, respectively.

We acknowledge several limitations of the study. The sample size is inadequate to assess major SAEs such as cardiovascular events. The duration of the study is too short to assess long-term tolerability and safety, which would require chronic treatment of at least a year. The primary end point was selected to assess a key clinical question regarding tolerability of the combination at two common doses of phentermine. Additionally, the scientific rationale was based on the known pharmacology of each agent and prior clinical experience with lorcaserin and other serotonergic agents. This pilot study was not statistically powered to identify rare AEs, including serotonin syndrome. *P* values should be considered exploratory; therefore, nonsignificance could be due to a true lack of differences or to a lack of power to detect differences. As with all early studies to explore combination pharmacotherapy for weight management, we prospectively chose a relatively small sample size and the primary outcome based on clinical experience with lorcaserin and other serotonergic agents, the known pharmacology, and the literature on serotonergic AEs. We then measured those objectively as described. Additional studies with larger populations and a longer duration are needed to exclude these less common events. In addition, a placebo group was not included in this study, as the intent was to compare AEs of combination therapy to those known for lorcaserin twice daily alone. Finally, our primary end point consisted of nine potentially serotonergic AEs that have been reported with other serotonergic drugs. One limitation of this study is that agents that modulate the adrenergic systems, such as phentermine, also produce several of these same symptoms, including dry mouth.

Conclusion

This pilot study suggests that coadministration of phentermine 15 mg once daily or twice daily with lorcaserin 10 mg twice daily did not appear to increase the incidence of nine prespecified potentially serotonergic AEs but did significantly increase weight loss compared to lorcaserin 10 mg twice daily alone. Further study of lorcaserin/phentermine combination therapy for weight management should be considered.

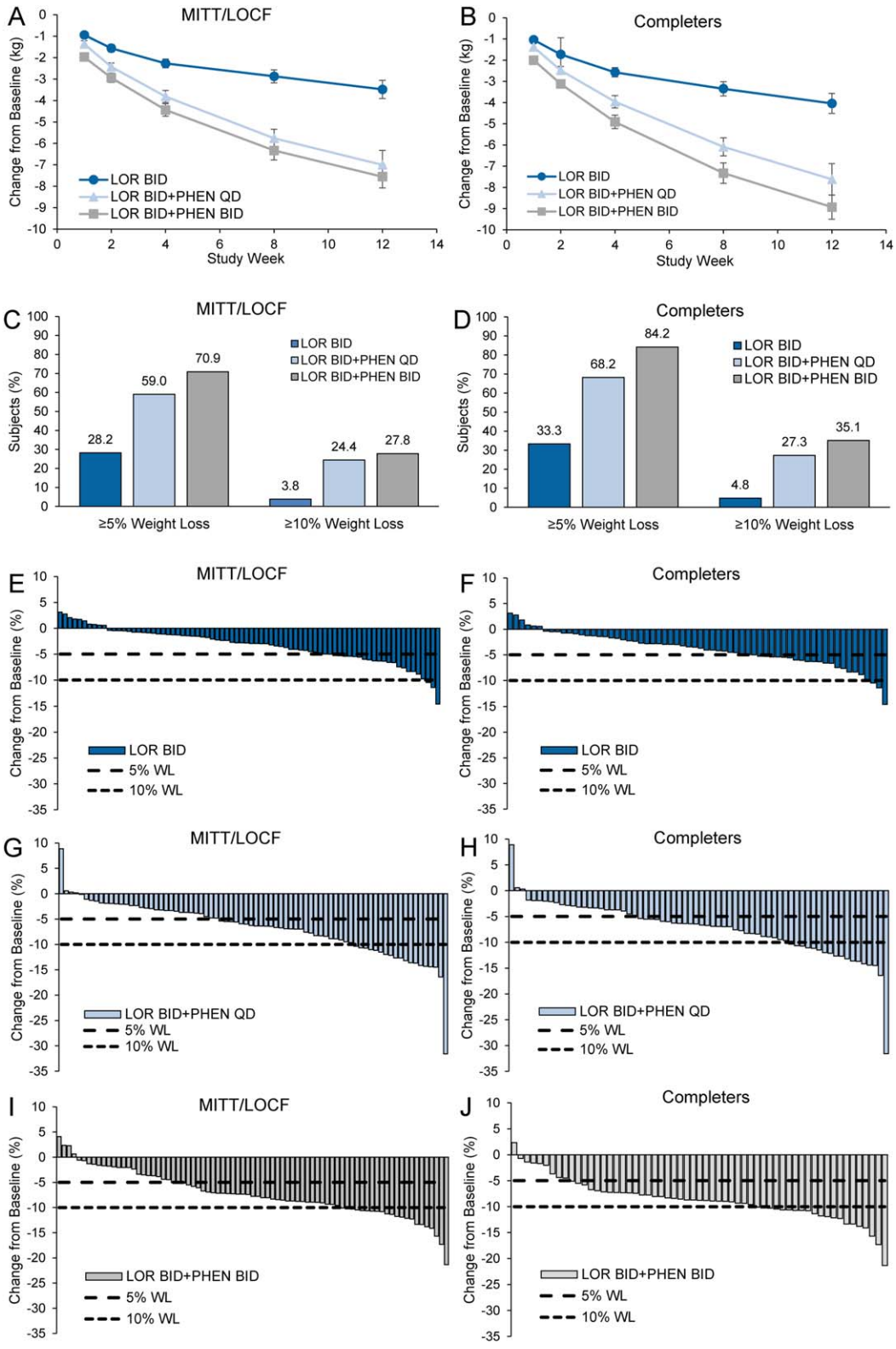

Figure 2 Weight loss secondary end points in the MITT and Completers populations. (**A,B**) Body weight change from baseline; (**C,D**) proportion of patients achieving ≥5% and ≥10% weight loss at week 12/EOT; and percent change from baseline in body weight for each individual in the (**E,F**) LOR BID group, (**G,H**) LOR BID+PHEN QD group, and (**I,J**) LOR BID+PHEN BID group. BID, twice daily; EOT, end of treatment; LOCF, last observation carried forward; LOR, lorcaserin HCl 10 mg; MITT, modified intent-to-treat; PHEN, phentermine HCl 15 mg; QD, once daily. [Color figure can be viewed at wileyonlinelibrary.com]

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