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Controlled-Release Phentermine/Topiramate in Severely Obese Adults: A Randomized Controlled Trial (EQUIP)

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A 56-week randomized controlled trial was conducted to evaluate safety and efficacy of a controlled-release combination of phentermine and topiramate (PHEN/TPM CR) for weight loss (WL) and metabolic improvements. Men and women with class II and III obesity (BMI ≥ 35 kg/m^2) were randomized to placebo, PHEN/TPM CR 3.75/23 mg, or PHEN/TPM CR 15/92 mg, added to a reduced-energy diet. Primary end points were percent WL and proportions of patients achieving 5% WL. Secondary end points included waist circumference (WC), systolic and diastolic blood pressure (BP), fasting glucose, and lipid measures. In the primary analysis (randomized patients with at least one postbaseline weight measurement who took at least one dose of assigned drug or placebo), patients in the placebo, 3.75/23, and 15/92 groups lost 1.6%, 5.1%, and 10.9% of baseline body weight (BW), respectively, at 56 weeks ($P < 0.0001$). In categorical analysis, 17.3% of placebo patients, 44.9% of 3.75/23 patients, and 66.7% of 15/92 patients, lost at least 5% of baseline BW at 56 weeks ($P < 0.0001$). The 15/92 group had significantly greater changes relative to placebo for WC, systolic and diastolic BP, fasting glucose, triglycerides, total cholesterol, low-density lipoprotein (LDL), and high-density lipoprotein (HDL). The most common adverse events were paresthesia, dry mouth, constipation, dysgeusia, and insomnia. Dropout rate from the study was 47.1% for placebo patients, 39.0% for 3.75/23 patients, and 33.6% of 15/92 patients. PHEN/TPM CR demonstrated dose-dependent effects on weight and metabolic variables in the direction expected to be beneficial with no evidence of serious adverse events induced by treatment.

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INTRODUCTION

Obesity, a highly prevalent major public health problem, is associated with increased mortality and morbidity, including an increased risk of type 2 diabetes mellitus and cardiovascular disease, physical disabilities, sleep apnea, and reduced quality of life (1). When achieved by medically recommended procedures, weight loss (WL) is associated with reduced morbidities in obese persons (2). Beyond surgery, long-term weight reductions much greater than 3–6 kg remain elusive (3). Hence, generating additional medical treatment options is a priority.

Phentermine hydrochloride is a sympathomimetic amine approved by the US Food and Drug Administration (FDA) in 1959 with a dose range of up to 37.5 mg/day for short-term obesity treatment. Phentermine stimulates increased hypothalamic release of norepinephrine with no detectable effect on serotonin (4). Topiramate, a fructose monosaccharide derivative with sulphamate functionality, was approved for the treatment of epilepsy in 1996 and the prevention of migraine in 2004. Randomized controlled trials (RCTs) show that topiramate monotherapy produces WL among obese individuals of ~6–8 kg at 24 weeks and improvements in lipids, glycemic control, and blood pressure (BP) (5–7). However, topiramate has been associated with adverse events (AEs) that may limit its use as a single agent at optimal doses for WL. With respect to possible mechanisms for the WL effects of topiramate, animal experiments suggest that topiramate-induced WL results from increased energy expenditure, decreased energetic efficiency, and decreased caloric intake (8–10). A significant factor associated with topiramate-induced WL in humans appears to be decreased caloric intake (11–13). However, consistent with animal findings, reduction in caloric intake does not appear to fully explain the observed WL (11,12); thus, as suggested

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by animal studies, topiramate-induced WL in humans may be also related to other mechanisms, such as increased energy expenditure or decreased energy efficiency.

Controlled-release phentermine/topiramate (PHEN/TPM CR) is an investigational WL therapy combining immediate-release phentermine and controlled-release topiramate given in a single daily morning dose. The top dose of PHEN/TPM CR contains phentermine 15 mg (expressed as free-base) and topiramate 92 mg. PHEN/TPM CR contains lower doses of these components than are currently marketed or have been studied for monotherapy in obesity (6,14). Each of the individual components has published dose-related efficacy, tolerability, and AE data (15–17). The combination's efficacy in WL exceeds the maximal response achieved with either individual agent alone at equivalent doses (18), which plausibly results from each component targeting multiple mechanisms that impact energy balance. The goal in developing this combination therapy was to use the dose of each respective agent that provided the greatest level of WL efficacy while minimizing tolerability concerns.

METHODS AND PROCEDURES

Design overview

A double-blind, parallel-group design was used with three arms: placebo ($n = 514$), PHEN/TPM CR 3.75/23 mg ($n = 241$), and PHEN/TPM CR 15/92 mg ($n = 512$). After screening, all eligible patients underwent a blinded 4-week postrandomization titration period and 52 weeks at randomized dose. All interventions were added to a standardized lifestyle program. Total treatment duration was 56 weeks.

Settings and participants

Subjects were enrolled beginning in November 2007 at 91 US sites, consisting of clinical practices, clinical trial sites, and academic centers. The last subject completed all study visits in May 2009. At every site, institutional review board approval and written informed consent were obtained. Eligibility criteria included age 18–70 years, BMI ≥35 kg/m^2 (no upper limit), triglycerides ≤200 mg/dl with treatment of 0–1 lipid-lowering medication, BP ≤140/90 mm Hg with treatment of 0–2 antihypertensive medications, and fasting serum glucose level ≤110 mg/dl. For detailed entry criteria, see **Supplementary Appendix 3** online.

Randomization and interventions

Patients were randomized and stratified by gender via a pseudo-random number generator constrained to a 2:1:2 allocation ratio. This allocation ratio was designed to increase the power of the safety analysis by having more patients receive placebo and by having the highest dose used. All study participants, study physicians, site staff, and sponsor representatives involved in the study conduct were blinded to patient assignment until after the trial was complete. There was an independent, unblinded data and safety monitoring board. The study drug and placebo were visually indistinguishable. Treatment was initiated with a 4-week blinded titration period (typically recommended with clinical topiramate use to minimize AEs), starting with PHEN/TPM CR 3.75/23 or matched placebo and thereafter increased weekly by 3.75/23 mg increments to the assigned dose. Following titration to assigned dose, patients were evaluated for an additional 52 weeks with monthly clinic visits. All patients were provided with standardized lifestyle counseling, based on the *LEARN Manual* (19) and advised to follow a 500-kcal daily reduction in dietary intake, increased water consumption, and increased physical activity.

Outcomes and follow-up

Outcomes of interest were percent, absolute, and categorical body-WL as well as numerous metabolic and cardiovascular outcomes. Patients were weighed using a calibrated digital scale, and waist circumference (WC) was measured by trained study personnel at each visit. BP measurements were obtained using a calibrated sphygmomanometer with appropriately sized cuff. Fasting blood samples were drawn at baseline and then at weeks 4, 8, 16, 28, and 56 and analyzed in a single central reference laboratory (Medpace Reference Laboratories, Cincinnati, OH). AEs were monitored at each visit with occurrence date, severity, relationship to study drug, action taken with respect to study drug, and outcome. Depression and suicidality were also assessed in detail (see **Supplementary Appendix 2** online). As recommended elsewhere (20), patients who discontinued treatment were encouraged to continue with data assessments through study completion, even though they were no longer taking the drug.

Statistical analyses

Power analysis. Based on standard deviations for percent WL observed in a previous PHEN/TPM CR study (21), this study provided >95% power at the two-tailed 0.05 α-level to reject the null hypothesis of no treatment-placebo difference if the population difference was ~2% to 3% of body weight (BW).

Primary efficacy analyses. The primary efficacy measure was percent WL at end of study, analyzed once as a continuous variable and then as a dichotomous variable with cut-off points at 5%, 10%, and 15% of BW. Secondary efficacy measures were change in WC, systolic BP, diastolic BP, fasting triglycerides, total cholesterol, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, total cholesterol/HDL ratio, and fasting serum glucose. Gender was included as a covariate in all models since it was used as a stratification factor.

For analysis of percent WL as a dependent variable, three main analyses were performed (listed as analyses A–C in **Table 1**) and are reported in detail with additional sensitivity analyses (analyses D–F in **Table 1**) in **Supplementary Appendixes 1–3** online. Analysis A, the analysis prespecified in the study protocol, is an intent-to-treat (ITT) analysis according to FDA standards (22). Note that this analysis included data from patients who discontinued the drug but remained in the study and continued with data assessments through study completion, even though they were no longer taking the drug.

Analysis B was a prespecified secondary per protocol–based analysis that was included to facilitate assessment of the experience in patients who reported using the study drug or placebo for the full intended treatment course. It included only patients for whom end-point data were available and who reported taking their study drug/placebo within 7 days before final end-point measurement. Again, the analysis of covariance model described in **Table 1** was used.

Analysis C was an ITT analysis as defined by Lachin (23) that included all randomized patients. To accommodate missing data, multiple imputation was used as described in **Table 1** (for further detail, refer to Elobeid et al., (24)).

For analyses with percent weight change as a dichotomous outcome, the three analyses described above were used except that analysis of covariance was replaced by a corresponding logistic regression with the same covariates.

Sensitivity analyses for primary efficacy end points. To test the robustness of findings to variations in data analytic procedures, several additional efficacy analyses (analyses D–F in **Table 1**) on percent WL were conducted. For the mixed model described in analysis E of **Table 1**, a random-effects regression model with treatment, gender, baseline, and time as covariates was used, where time was modeled as continuous and calculated from first dose date. Random intercepts and slopes were estimated and an unstructured residual covariance matrix was specified. Results of these analyses are described in **Supplementary Table S2** online.

Analyses for secondary efficacy end points. For all other efficacy measures, reported analyses correspond to analyses A–C described in

Table 1 Efficacy analyses conducted for percent weight loss as a continuous outcome

Analysis	Name	Patients included	Missing data management procedure	Statistical analysis applied
A	Prespecified ITT-LOCF	All randomized patients who received at least one dose of drug/placebo and had at least one postrandomization weight measurement	LOCF	ANCOVA with percent weight loss as dependent variable, sex and baseline body weight as covariates, and treatment assignment as the independent variable
B	Completers only	All randomized patients who had a week 56 measurement and received at least one dose of drug/placebo treatment within 7 days of their week 56 measurement	None	Same as for prespecified ITT-LOCF
C	Randomized-ITT-MI	All randomized patients	MI with $m = 5$ imputations per analysis. Treatment assignment, sex, and all measurements of the efficacy variable under study were used in a two-step imputation process[a]	Same as for prespecified ITT-LOCF
D	Modified-ITT-MI	All randomized patients who received at least one dose of drug/placebo and had at least one postrandomization weight measurement		Same as for prespecified ITT-LOCF
E	Modified-ITT-MM	All randomized patients who received at least one dose of drug/placebo and had at least one postrandomization weight measurement	Not applicable (see above for details of mixed model procedures)	Random-effects regression model with subject-specific intercepts and slopes (see above and footnote[b] for details)
F	On drug LOCF	All randomized patients who received at least one dose of drug/placebo and had at least one postrandomization weight measurement	Last observation within 7 days of last dose of drug/placebo carried forward	Same as for prespecified ITT-LOCF

(100 × (baseline weight – weight at end point)/baseline weight).
ANCOVA, analysis of covariance; ITT, intent-to-treat; LOCF, last observation carried forward; MI, multiple imputation; MM, mixed model.
[a]First, sufficient data were imputed to impose a monotone missing data pattern via a Markov chain Monte Carlo algorithm. Subsequently, any remaining missing data were imputed assuming a monotone missing data pattern and using Rubin's regression method (44). The complete imputed datasets were then analyzed via ANCOVA as described in Table 1. The separate results from the imputed datasets were then pooled into single estimates and tested as described by Schafer (45).
[b]More specifically, a linear mixed model was used with simple linear fixed effects, random intercept, and slopes with unstructured covariance, G in SAS Proc Mixed documentation, and within-subject covariance $\sigma^2 I$, R in SAS Proc Mixed documentation.

Table 1, substituting change (or percent change for some variables as indicated in results section) in the dependent variable of interest for percent WL and baseline values of that dependent variable for baseline BW.

Safety analyses. All AE-preferred terms (defined by MedDRA coding dictionary version 10.1) with a frequency of 5% or more in any treatment group or those that occurred significantly more often with active treatment than placebo (at a two-tailed nominal 0.05 α-level) are listed in Table 4. Due to concerns with past WL drugs (25), we conducted extensive depression and suicidality assessments using the Patient Health Questionnaire (PHQ-9) and Columbia Suicidality Severity Rating Scale (C-SSRS) instruments (see **Supplementary Appendix 2** online).

RESULTS

Baseline characteristics

Baseline data are in Table 2. Groups were not significantly different on any baseline variable. Overall, mean age was 42.7 years, mean BMI was 42.0 kg/m^2, and 83% were female, with substantial representation of black patients (16–18%). Means for BP, fasting glucose, triglycerides, and HDL cholesterol did not meet established thresholds indicative of increased cardiometabolic disease risk (26).

Subject disposition

As shown in Figure 1, 59.9% of randomized patients completed the study regardless of whether they continued taking the assigned drug/placebo (52.9% placebo, 61.0% PHEN/TPM CR 3.75/23, 66.4% PHEN/TPM CR 15/92; $P < 0.0001$ for difference), and 53.7% reported taking the assigned study drug/placebo for the full intended treatment course (46.9% placebo, 57.3% PHEN/TPM CR 3.75/23, 58.8% PHEN/TPM CR 15/92; $P = 0.0003$ for difference). Most common reasons for discontinuation were lost to follow-up or withdrawal of consent (more common in placebo than active groups) or AEs (more common in active than placebo groups). Overall discontinuations were lower in patients receiving active treatments.

Weight loss

Patients in the 15/92 group lost significantly more weight than patients in the 3.75/23 group who in turn lost significantly more weight than patients receiving placebo ($P < 0.0001$ for all comparisons; see Figure 2 and Table 3), regardless of analysis used. Using the prespecified ITT-last observation carried forward (LOCF) (Analysis A), patients

Table 2 Baseline data by treatment condition

	Placebo (*n* = 514)	PHEN/TPM CR 3.75/23 (*n* = 241)	PHEN/TPM CR 15/92 (*n* = 512)
Age, years			
Mean (s.d.)	43.0 (11.76)	43.0 (10.96)	41.9 (12.21)
Sex, n (%)			
Female	425 (82.7)	201 (83.4)	424 (82.8)
Male	89 (17.3)	40 (16.6)	88 (17.2)
Ethnicity, n (%)			
Hispanic/Latino	74 (14.4)	29 (12.0)	81 (15.8)
Non-Hispanic/Latino	440 (85.6)	212 (88.0)	431 (84.2)
Race, n (%)			
White	413 (80.4)	192 (79.7)	408 (79.7)
Black	93 (18.1)	39 (16.2)	93 (18.2)
American Indian or Alaskan native	6 (1.2)	2 (0.8)	7 (1.4)
Asian American	3 (0.6)	2 (0.8)	1 (0.2)
Native Hawaiian or other Pacific Islander	2 (0.4)	1 (0.4)	2 (0.4)
Other	4 (0.8)	5 (2.1)	7 (1.4)
Weight, kg			
n	513	240	511
Mean (s.d.)	115.8 (21.46)	118.5 (21.85)	115.2 (20.66)
Height, cm			
n	513	240	511
Mean (s.d.)	165.9 (9.11)	166.6 (8.57)	165.6 (8.62)
BMI, kg/m^2			
n	513	240	511
Mean (s.d.)	42.0 (6.15)	42.6 (6.50)	41.9 (6.04)
Waist circumference, cm			
n	513	240	511
Mean (s.d.)	120.5 (13.92)	121.7 (15.15)	120.1 (14.63)
Low-density lipoprotein cholesterol, mg/dl			
n	512	240	511
Mean (s.d.)	121.3 (32.02)	122.5 (32.96)	119.8 (30.06)
High-density lipoprotein cholesterol, mg/dl			
n	513	240	511
Mean (s.d.)	49.5 (13.09)	50.2 (11.20)	49.8 (11.72)
Total cholesterol, mg/dl			
n	513	240	511
Mean (s.d.)	194.7 (36.36)	196.1 (36.08)	192.5 (33.77)
Triglycerides, mg/dl			
n	513	240	511
Mean (s.d.)	118.8 (39.20)	116.7 (40.12)	114.0 (37.24)
Fasting serum glucose, mg/dl			
n	510	240	511
Mean (s.d.)	93.0 (8.70)	93.8 (9.11)	93.0 (9.47)
Systolic blood pressure, mm Hg			
n	513	240	511
Mean (s.d.)	121.8 (11.45)	122.5 (11.08)	122.0 (11.58)
Diastolic blood pressure, mm Hg			
n	513	240	511
Mean (s.d.)	77.2 (7.85)	77.8 (7.46)	77.4 (7.69)
Heart rate, bpm			
n	513	240	511
Mean (s.d.)	73.2 (8.84)	72.3 (9.18)	73.2 (9.57)
History of depression, *n* (%)	81 (15.8)	47 (19.6)	74 (14.8)
Antidepressant drug use, *n* (%)	68 (13.2)	36 (14.9)	65 (12.7)
History of depression and/or antidepressant drug use, *n* (%)	105 (20.4)	57 (23.7)	95 (18.6)

BPM, beats per minute; PHEN/TPM CR, controlled-release phentermine/topiramate.

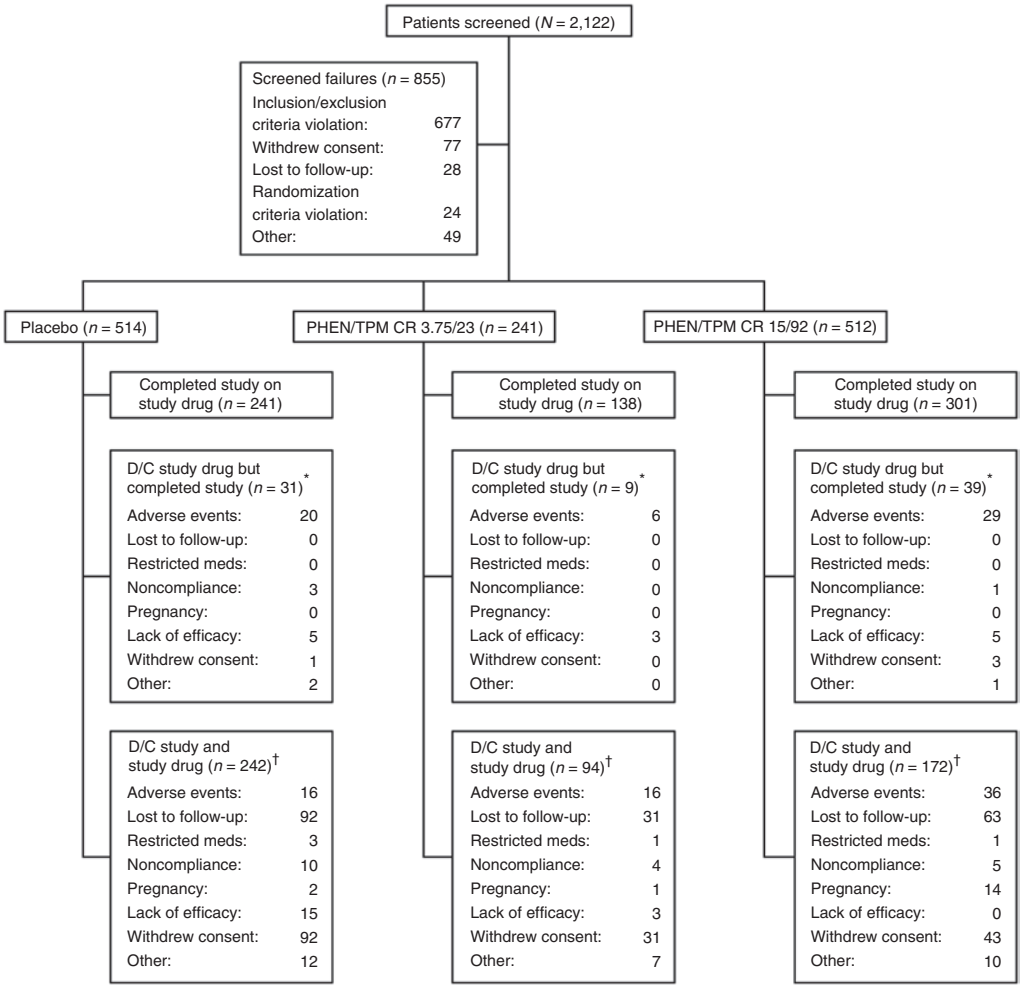

Figure 1 Patient disposition. After screening, all eligible patients underwent 56 weeks of treatment; 4-week blinded, postrandomization titration period, followed by 52 weeks at randomized dose. *Reason for discontinuation as reported while subject was receiving study drug; †Reason for study discontinuation. Subjects were able to discontinue study drug and study for different reason, however, reason was often the same. When they differed, the final reason for discontinuation from the study was used. D/C, discontinued; Meds, medications; PHEN/TPM CR, controlled-release phentermine/topiramate.

receiving 15/92, 3.75/23, and placebo lost 10.9%, 5.1%, and 1.6% of BW, respectively. Moreover, completers (**Table 3**, Analysis B and **Supplementary Table S2 and Figure S1** online) lost 14.4% of BW on 15/92 and 6.7% on 3.75/23 and only 2.1% on placebo. Statistical assumption testing suggested appropriateness of the models, with all sensitivity analyses (Analyses C–F) yielding confirmatory findings (**Table 3** and **Supplementary Appendix 1** and **Table S2** online). We also conducted the baseline observation carried forward analyses (27), and although point estimates changed, conclusions about statistical significance and direction of effects remained unchanged (data not shown).

When analyzed as dichotomous data, regardless of cut-off point (5%, 10%, or 15% of BW), a higher proportion of patients in the 15/92 group exceeded threshold than did patients in the 3.75/23 group, whose proportion exceeded that of placebo patients ($P < 0.05$ for all comparisons). In the prespecified-ITT-LOCF (Analysis A), percentages of patients losing ≥5%, ≥10%, and ≥15% of BW were, respectively, 66.7%, 47.2%, and 32.3% on 15/92; 44.9%, 18.8%, and 7.3% on 3.75/23; and 17.3%, 7.4%, and 3.4% on placebo (all comparisons $P < 0.05$). Among completers, percentages of patients losing ≥5%, ≥10%, and ≥15% of BW were, respectively, 83.5%, 67.7%, and 48.1% on 15/92; 59.1%, 27.7%, and 12.4% on 3.75/23; and 25.5%, 13.0%, and 5.9% on placebo (all comparisons $P < 0.0001$).

We tested whether results differed by baseline BMI by repeating Analysis A after categorizing patients by baseline BMI and then testing for interaction between baseline BMI category and treatment. The interaction was not significant ($P = 0.8056$), indicating that results did not significantly differ by baseline BMI (**Figure 2**).

Secondary end point analysis

The 15/92 group had significantly greater least-squares mean changes, relative to placebo, in WC, systolic BP, diastolic BP, glucose, triglycerides, total cholesterol/HDL ratio, total cholesterol, LDL cholesterol, and HDL cholesterol. The 3.75/23 group had numerically, but not always statistically significant, greater least-squares mean changes compared with placebo, in all these variables (**Table 3**).

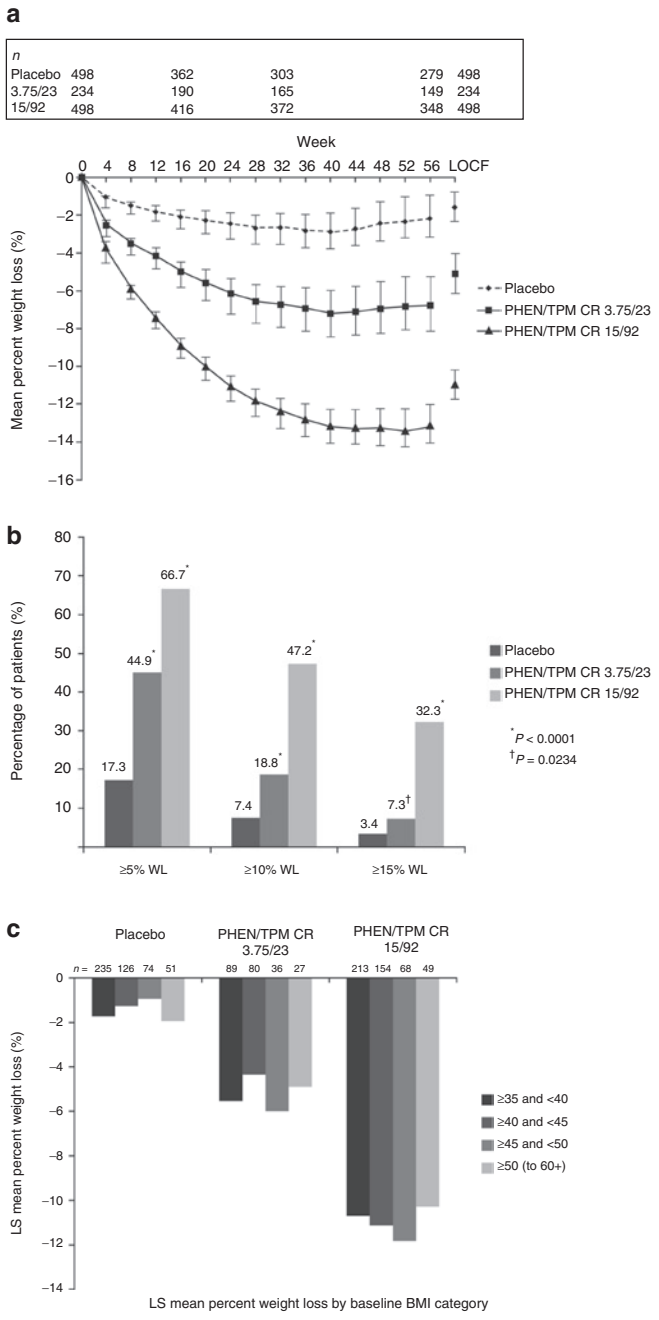

Figure 2 Plot of efficacy results with analysis A (prespecified ITT-LOCF). (**a**) Mean percent WL; (**b**) Patients achieving ≥5%, ≥10%, and ≥15% WL; (**c**) LS mean percent WL by baseline BMI category. Analysis A included data from patients who discontinued drug but remained in study and continued with data assessments through study completion even though no longer taking drug. The supplementary material presents mean percent WL for Analyses B and C. Error bars represent 95% confidence interval. ITT, intent-to-treat; LOCF, last observation carried forward; LS, least-squares; PHEN/TPM CR, controlled-release phentermine/topiramate; WL, weight loss.

Safety analyses

Table 4 lists AEs that occurred at a frequency of 5% or higher in any treatment group or occurred at a significantly higher frequency in the 15/92 group than placebo. The most common AEs occurring more often with 15/92 treatment than placebo included paresthesia, dry mouth, constipation, dysgeusia, and insomnia. Other less frequent events occurring more commonly with 15/92 treatment were depression, irritability, alopecia, anxiety, disturbance in attention, and hypoesthesia. Serious AE (SAE) rates were the same across treatment groups: 13 (2.5%) with placebo, 6 (2.5%) with 3.75/23, and 13 (2.5%) with 15/92.

Most AEs reported were mild in severity (**Supplementary Table S3** online). AEs most often resulting in treatment discontinuation in the 15/92 group were insomnia, irritability, anxiety, headache, disturbance in attention, depression, dry mouth, and nephrolithiasis. The exact numbers and percentages of AE-related dropouts were 43 (8.4%) for placebo, 27 (11.3%) for 3.75/23, and 82 (16.0%) for 15/92.

Drug-related SAEs occurred in 2 (0.4%) patients treated with placebo, 1 (0.4%) patient treated with 3.75/23, and 1 (0.2%) patient treated with 15/92. The SAEs reported as drug-related in the placebo group included chest pain and pulmonary embolism, both of which resulted in discontinuation of study drug. The SAE reported in the 3.75/23 group was cholelithiasis that resolved following a 1-week interruption of treatment, and one patient treated with 15/92 was diagnosed with myelogenous leukemia ~6 months after starting treatment and discontinued the study due to this event. These data should be viewed with the understanding that very few SAEs have been reported as drug-related and that investigators' assessments of causality are speculative.

Change from baseline in heart rate was also assessed. By week 56, mean heart rate had decreased 0.2 bpm in placebo, 0.3 bpm on 3.75/23 ($P = 0.9552$ vs. placebo), and increased 1.2 bpm on 15/92 ($P = 0.0830$ vs. placebo). Both doses of PHEN/TPM CR resulted in a decrease in serum bicarbonate (mean changes in mEq/l: −0.3 for placebo, −1.6 for 3.75/23, and −1.7 for 15/92); significant reductions (<17 mEq/l at two consecutive visits) occurred in only 3 (1.3%) patients receiving 3.75/23, 4 (0.8%) patients receiving 15/92, and none receiving placebo.

In addition, depressive symptoms were assessed using the PHQ-9 questionnaire, and suicidality (ideation and behavior) was assessed using the C-SSRS (**Supplementary Appendix 2** and **Table S1** online). Change in mean PHQ-9 total score indicated improvement in depressive symptoms over time in all treatment groups, but no significant differences among groups. There was no significantly increased suicide risk as defined and assessed by the C-SSRS in patients treated with PHEN/TPM CR compared with placebo. Neither suicidal behavior nor suicidal ideation with an intent to act were reported at any time after treatment initiation, and rates of suicidal ideation without intent to act were comparable to rates seen in placebo-treated patients.

There were 15 pregnancies in women exposed to PHEN/TPM CR. Among these, there were three spontaneous abortions, three elective abortions, and nine healthy live births. No congenital malformations were observed.

DISCUSSION

Three salient points emerge from this RCT. First, PHEN/TPM CR caused WL in obese patients. Compared with placebo, both doses of PHEN/TPM CR yielded significantly

Table 3 Weight loss and secondary outcomes at week 56 by treatment condition

	Method	Placebo		PHEN/TPM CR 3.75/23			PHEN/TPM CR 15/92			
	Main analyses	***n***	**LS mean percent change (95% CI)**	***n***	**LS mean percent change (95% CI)**	***P* value vs. placebo**	***n***	**LS mean percent change (95% CI)**	***P* value vs. placebo**	***P* value vs. PHEN/TPM CR 3.75/23**
Analysis of percent weight loss as continuous variable	Analysis A: prespecified ITT-LOCF	498	−1.55 (−0.8 to −2.3)	234	−5.10 (−4.0 to −6.2)	<0.0001	498	−10.92 (−10.2 to −11.7)	<0.0001	<0.0001
	Analysis B: completers only	239	−2.13 (−1.0 to −3.3)	137	−6.67 (−5.2 to −8.1)	<0.0001	297	−14.36 (−13.3 to −15.4)	<0.0001	<0.0001
	Analysis C: randomized-ITT-MI	514	−1.24 (−0.2 to −2.3)	241	−5.25 (−3.9 to −6.6)	<0.0001	512	−12.20 (−11.2 to −13.2)	<0.0001	<0.0001
Analysis of percent weight loss as dichotomous variable	**Lost ≥5% of baseline body weight**	***n***	***n* (%)**	***n***	***n* (%)**	***P* value vs. placebo**	***n***	***n* (%)**	***P* value vs. placebo**	***P* value vs. PHEN/TPM CR 3.75/23**
	Analysis A: prespecified ITT-LOCF	498	86 (17.3)	234	105 (44.9)	<0.0001	498	332 (66.7)	<0.0001	<0.0001
	Analysis B: completers only	239	61 (25.5)	137	81 (59.1)	<0.0001	297	248 (83.5)	<0.0001	<0.0001
	Analysis C: randomized-ITT-MI	514	(24.8%)	241	(51.1%)	<0.0001	512	(74.4%)	<0.0001	<0.0001
	Lost ≥10% of baseline body weight	***n***	***n* (%)**	***n***	***n* (%)**	***P* value vs. placebo**	***n***	***n* (%)**	***P* value vs. placebo**	***P* value vs. PHEN/TPM CR 3.75/23**
	Analysis A: prespecified ITT-LOCF	498	37 (7.4)	234	44 (18.8)	<0.0001	498	235 (47.2)	<0.0001	<0.0001
	Analysis B: completers only	239	31 (13.0)	137	38 (27.7)	0.0004	297	201 (67.7)	<0.0001	<0.0001
	Analysis C: randomized-ITT-MI	514	(11.1%)	241	(23.1%)	<0.0001	512	(57.0%)	<0.0001	<0.0001
	Lost ≥15% of baseline body weight	***n***	***n* (%)**	***n***	***n* (%)**	***P* value vs. placebo**	***n***	***n* (%)**	***P* value vs. placebo**	***P* value vs. PHEN/TPM CR 3.75/23**
	Analysis A: prespecified ITT-LOCF	498	17 (3.4)	234	17 (7.3)	0.0234	498	161 (32.3)	<0.0001	<0.0001
	Analysis B: completers only	239	14 (5.9)	137	17 (12.4)	0.0295	297	143 (48.1)	<0.0001	<0.0001
	Analysis C: randomized-ITT-MI	514	(4.6%)	241	(9.5%)	0.0001	512	(38.4%)	0.0040	0.0005

Table 3 Continued on next page

Table 3 Continued

	Method	Placebo		PHEN/TPM CR 3.75/23			PHEN/TPM CR 15/92			
	Main analyses	*n*	LS mean percent change (95% CI)	*n*	LS mean percent change (95% CI)	*P* value vs. placebo	*n*	LS mean percent change (95% CI)	*P* value vs. placebo	*P* value vs. PHEN/TPM CR 3.75/23
Waist circumference (cm)	Analysis A: prespecified ITT-LOCF	498	−3.1 (−4.0 to −2.2)	234	−5.6 (−6.8 to −4.3)	0.0006	498	−10.9 (−11.8 to −10.0)	<0.0001	<0.0001
	Analysis B: completers only	239	−3.6 (−4.9 to −2.2)	137	−7.5 (−9.2 to −5.7)	0.0001	297	−13.9 (−15.1 to −12.7)	<0.0001	<0.0001
	Analysis C: randomized-ITT-MI	514	−3.6 (−4.8 to −2.3)	241	−6.4 (−8.0 to −4.8)	0.0018	512	−12.3 (−13.4 to −11.2)	<0.0001	<0.0001
Systolic BP (mm Hg)	Analysis A: prespecified ITT-LOCF	498	0.9 (−0.2 to 2.1)	234	−1.8 (−3.4 to −0.3)	0.0019	498	−2.9 (−4.0 to −1.8)	<0.0001	0.2176
	Analysis B: completers only	239	1.0 (−0.6 to 2.7)	137	−1.6 (−3.7 to 0.5)	0.0371	297	−3.6 (−5.1 to −2.1)	<0.0001	0.1005
	Analysis C: randomized-ITT-MI	514	1.3 (−0.3 to 2.8)	241	−1.4 (−3.3 to 0.4)	0.0165	512	−3.0 (−4.4 to −1.6)	<0.0001	0.1211
Diastolic BP (mm Hg)	Analysis A: prespecified ITT-LOCF	498	0.4 (−0.40 to 1.2)	234	−0.1 (−1.2 to 1.0)	0.4257	498	−1.5 (−2.3 to −0.7)	0.0002	0.0269
	Analysis B: completers only	239	0.1 (−1.0 to 1.2)	137	0.2 (−1.2 to 1.6)	0.9401	297	−1.5 (−2.5 to −0.5)	0.0142	0.0320
	Analysis C: randomized-ITT-MI	514	0.4 (−0.5 to 1.4)	241	−0.4 (−1.7 to 0.8)	0.2514	512	−1.5 (−2.4 to −0.6)	0.0004	0.1417
Fasting serum glucose (mg/dl)	Analysis A: prespecified ITT-LOCF	474	1.9 (1.0–2.9)	230	0.8 (−0.5 to 2.1)	0.1209	484	−0.6 (−1.5 to 0.4)	<0.0001	0.0720
	Analysis B: completers only	236	1.9 (0.5–3.2)	134	0.4 (−1.3 to 2.1)	0.1306	295	−1.5 (−2.7 to −0.3)	<0.0001	0.0539
	Analysis C: randomized-ITT-MI	514	1.7 (0.7–2.8)	241	0.7 (−0.8 to 2.1)	0.2299	512	−1.1 (−2.1 to 0)	<0.0001	0.0383
Triglycerides (%)	Analysis A: prespecified ITT-LOCF	479	9.1 (4.7–13.5)	230	5.2 (−0.8 to 11.2)	0.2639	486	−5.2 (−9.6 to −0.8)	<0.0001	0.0027
	Analysis B: completers only	238	1.9 (−3.9 to 7.8)	135	−4.1 (−11.6 to 3.4)	0.1773	297	−14.7 (−19.9 to −9.4)	<0.0001	0.0142
	Analysis C: randomized-ITT-MI	514	8.4 (2.6–14.2)	241	5.1 (−2.4 to 12.6)	0.4545	512	−6.9 (−11.9 to −1.9)	<0.0001	0.0047
Total cholesterol/HDL ratio	Analysis A: prespecified ITT-LOCF	479	−0.09 (−0.16 to −0.03)	230	−0.22 (−0.32 to −0.13)	0.0148	486	−0.35 (−0.41 to −0.28)	<0.0001	0.0230

Table 3 Continued on next page

Table 3 Continued

	Method	Placebo		PHEN/TPM CR 3.75/23			PHEN/TPM CR 15/92			
	Main analyses	*n*	LS mean percent change (95% CI)	*n*	LS mean percent change (95% CI)	*P* value vs. placebo	*n*	LS mean percent change (95% CI)	*P* value vs. placebo	*P* value vs. PHEN/TPM CR 3.75/23
	Analysis B: completers only	238	–0.16 (–0.25 to –0.07)	135	–0.31 (–0.42 to –0.19)	0.0273	297	–0.49 (–0.57 to –0.41)	<0.0001	0.0054
	Analysis C: randomized-ITT-MI	514	–0.12 (–0.20 to –0.04)	241	–0.23 (–0.34 to –0.13)	0.0635	512	–0.40 (–0.48 to –0.33)	<0.0001	0.0042
Total cholesterol (%)	Analysis A: prespecified ITT-LOCF	479	–3.5 (–4.7 to –2.2)	230	–5.4 (–7.1 to –3.7)	0.0502	486	–6.0 (–7.3 to –4.8)	0.0014	0.5432
	Analysis B: completers only	238	–3.6 (–5.4 to –1.8)	135	–6.0 (–8.3 to –3.7)	0.0779	297	–6.2 (–7.8 to –4.5)	0.0202	0.9034
	Analysis C: randomized-ITT-MI	514	–3.0 (–4.5 to –1.6)	241	–5.3 (–7.2 to –3.3)	0.0484	512	–5.9 (–7.3 to –4.5)	0.0011	0.5805
LDL cholesterol (%)	Analysis A: prespecified ITT-LOCF	478	–5.5 (–7.4 to –3.7)	230	–7.7 (–10.3 to –5.2)	0.1338	486	–8.4 (–10.2 to –6.5)	0.0157	0.6584
	Analysis B: completers only	238	–5.0 (–7.7 to –2.4)	135	–7.0 (–10.4 to –3.6)	0.3219	294	–8.1 (–10.5 to –5.7)	0.0567	0.5664
	Analysis C: randomized-ITT-MI	514	–4.8 (–7.0 to –2.6)	241	–7.4 (–10.3 to –4.4)	0.1315	512	–8.4 (–10.4 to –6.3)	0.0116	0.5605
HDL cholesterol (%)	Analysis A: prespecified ITT-LOCF	479	0 (–1.6 to 1.6)	230	0.5 (–1.7 to 2.7)	0.7057	486	3.5 (1.9–5.1)	0.0005	0.0158
	Analysis B: completers only	238	1.2 (–0.9 to 3.3)	135	1.7 (–1.0 to 4.3)	0.7899	297	6.8 (4.9–8.7)	<0.0001	0.0008
	Analysis C: randomized-ITT-MI	514	0.7 (–1.2 to 2.6)	241	0.9 (–1.6 to 3.4)	0.8662	512	5.0 (3.2–6.8)	0.0001	0.0030

BP, blood pressure; CI, confidence interval; HDL, high-density lipoprotein; ITT, intent-to-treat; LDL, low-density lipoprotein; LOCF, last observation carried forward; LS, least-squares; MI, multiple imputation; PHEN/TPM CR, controlled-release phentermine/topiramate.

Table 4 Adverse events with a frequency of ≥5% in any treatment group or differing significantly in frequency between placebo and either treatment group

	Placebo (*n* = 513)	PHEN/TPM CR 3.75/23 (*n* = 240)		PHEN/TPM CR 15/92 (*n* = 511)	
Adverse event	*n* (%)	*n* (%)	*P* value[a]	*n* (%)	*P* value
Paresthesia	10 (1.9)	10 (4.2)	0.0902	96 (18.8)	<0.0001
Dry mouth	19 (3.7)	16 (6.7)	0.0931	87 (17.0)	<0.0001
Constipation	35 (6.8)	19 (7.9)	0.6495	72 (14.1)	0.0001
Upper respiratory tract infection	56 (10.9)	38 (15.8)	0.0594	63 (12.3)	0.4962
Headache	52 (10.1)	25 (10.4)	0.8979	61 (11.9)	0.3709
Nasopharyngitis	37 (7.2)	30 (12.5)	0.0199	46 (9.0)	0.3050
Dysgeusia	5 (1.0)	3 (1.3)	0.7145	43 (8.4)	<0.0001
Insomnia	25 (4.9)	12 (5.0)	1.0000	40 (7.8)	0.0553
Nausea	24 (4.7)	14 (5.8)	0.4811	37 (7.2)	0.0875
Sinusitis	28 (5.5)	18 (7.5)	0.3269	37 (7.2)	0.2515
Dizziness	21 (4.1)	7 (2.9)	0.5371	29 (5.7)	0.2498
Back pain	26 (5.1)	13 (5.4)	0.8607	28 (5.5)	0.7817
Bronchitis	22 (4.3)	16 (6.7)	0.2100	28 (5.5)	0.3885
Cough	18 (3.5)	8 (3.3)	1.0000	26 (5.1)	0.2218
Influenza	24 (4.7)	18 (7.5)	0.1264	26 (5.1)	0.7740
Depression	6 (1.2)	8 (3.3)	0.0770	24 (4.7)	0.0007
Diarrhea	23 (4.5)	12 (5.0)	0.7151	24 (4.7)	0.8825
Fatigue	17 (3.3)	12 (5.0)	0.3094	23 (4.5)	0.3385
Irritability	3 (0.6)	4 (1.7)	0.2178	23 (4.5)	<0.0001
Vision blurred	16 (3.1)	15 (6.3)	0.0501	23 (4.5)	0.2582
Alopecia	5 (1.0)	5 (2.1)	0.3034	22 (4.3)	0.0008
Anxiety	6 (1.2)	7 (2.9)	0.1288	19 (3.7)	0.0084
Disturbance in attention	3 (0.6)	1 (0.4)	1.0000	18 (3.5)	0.0007
Hypoesthesia	4 (0.8)	2 (0.8)	1.0000	17 (3.3)	0.0039
Dry eye	4 (0.8)	2 (0.8)	1.0000	12 (2.3)	0.0470
Paresthesia oral	2 (0.4)	1 (0.4)	1.0000	11 (2.2)	0.0123
Dry skin	1 (0.2)	0 (0.0)	1.0000	8 (1.6)	0.0208
Anorexia	0 (0.0)	3 (1.3)	0.0321	7 (1.4)	0.0075
Serum bicarbonate decreased	1 (0.2)	0 (0.0)	1.0000	7 (1.4)	0.0381
Feeling jittery	1 (0.2)	3 (1.3)	0.0980	7 (1.4)	0.0381
Amenorrhea	0 (0.0)	0 (0.0)	N/A	6 (1.2)	0.0152
Aphasia	0 (0.0)	0 (0.0)	N/A	6 (1.2)	0.0152
Back injury	0 (0.0)	3 (1.3)	0.0321	5 (1.0)	0.0306
Serum potassium decreased	0 (0.0)	1 (0.4)	0.3187	5 (1.0)	0.0306
Hypogeusia	0 (0.0)	1 (0.4)	0.3187	5 (1.0)	0.0306
Parosmia	0 (0.0)	1 (0.4)	0.3187	5 (1.0)	0.0306
Osteoarthritis	0 (0.0)	4 (1.7)	0.0101	2 (0.4)	0.2488
Rhinitis	0 (0.0)	4 (1.7)	0.0101	1 (0.2)	0.4990

Preferred terms defined by MedDRA Coding Dictionary version 10.1. At a two-tailed nominal α-level of 0.05. No adjustment for multiple testing has been performed.
N/A, not applicable; PHEN/TPM CR, controlled-release phentermine/topiramate.
[a]By Fisher's exact test for comparison to placebo. For each preferred term, two Fisher's exact tests for 2 × 2 contingency tables were conducted, one to compare 3.75/23 with placebo and one to compare 15/92 with placebo.

greater 1-year WL, with a greater proportion of patients losing more than 5%, 10%, or 15% of baseline BW. Results were consistent regardless of analytic method employed. Patients treated with PHEN/TPM CR 15/92 and 3.75/23 lost 10.9% and 5.1% of BW, respectively, when analyzed as ITT-LOCF, compared with 1.6% WL on placebo and 14.4% and 6.7% WL in completers-only analyses compared with 2.1% WL with placebo. Among patients who completed the course of 15/92, 48.1% lost ≥15% of BW, 67.7% lost ≥10%, and 83.5% lost ≥5%. Significant WL also occurred early; patients treated with 15/92 lost between 8% and 10% of BW after 3 months of treatment.

Second, WL induced by PHEN/TPM CR was accompanied by improvements in many cardiovascular and metabolic risk factors, such as WC, systolic BP, and total cholesterol/HDL cholesterol ratio in both doses. PHEN/TPM CR 15/92 treatment was also associated with significant improvements in diastolic BP, fasting glucose, LDL cholesterol, HDL cholesterol, and total cholesterol.

Third, certain AEs (paresthesia, dry mouth, constipation, and dysgeusia) occurred at a higher frequency with 15/92 treatment, with twice (16.2% vs. 8.4%) as many patients treated with 15/92 compared with placebo withdrawing due to one or more AE. An indication of tolerability can be obtained from the AE data. The most common AEs associated with PHEN/TPM CR treatment were paresthesia, dry mouth, constipation, dysgeusia, and insomnia; however, none of these events caused study discontinuation in more than 1% of patients. Mood-related (depression, anxiety, and irritability) and cognition-related (disturbance in attention) AEs occurred at higher frequencies among patients receiving 15/92. Mood assessments with standardized rating scales (PHQ-9) showed an improvement in mood-related symptoms overall (see **Supplementary Table S1** online). The low incidence of treatment-emergent depression in this trial should be viewed in the context of exclusion of patients with substantial depressive symptoms at study entry (PHQ-9 score of >10 was an exclusion criterion, and the mean (s.d.) PHQ-9 score of 2.8 (2.8) was low, suggesting minimal depressive symptoms). However, the study allowed participation of patients with a self-reported history of depression, patients with adequately controlled depression based on PHQ-9 scores, and those on stable doses of antidepressants. Neither suicidal behavior nor suicidal ideation with intent to act was reported at any time after treatment initiation. There was no significantly increased suicide risk, as defined and assessed by the C-SSRS, in patients treated with PHEN/TPM CR compared with placebo.

In this study, there were no birth defects among infants whose mothers were exposed to study treatment. However, given the FDA's recent reclassification of topiramate use during pregnancy (FDA has recently added a warning about increased risk of cleft lip and cleft palate with topiramate and its pregnancy category has now been changed to category D) and the general belief that WL during pregnancy is not wise, the use of PHEN/TPM during pregnancy is not recommended. For more and recent information on this topic, refer to Mølgaard-Nielsen *et al.* (28).

Phentermine has been associated with elevations in BP (29). In this study, PHEN/TPM CR led to reduced BP. Phentermine has also been associated with elevations in heart rate (29). Here, there was an increase in resting heart rate seen in the 15/92 subgroup (1.2 bpm above the baseline value of 73.2 bpm; $P = 0.083$ compared with placebo), whereas heart rate was unaltered in the 3.75/23 subgroup (a decrease of 0.3 bpm from baseline; $P = 0.955$ compared with placebo).

This heart rate increase in the 15/92 group is plausibly attributable to the sympathomimetic action of phentermine, given that increased heart rates have been observed in patients treated with the higher doses of phentermine monotherapy approved for short-term therapy of obesity (29). In the 15/92 treatment group, the increased heart rate was accompanied by a reduction of 2.9 mm Hg in systolic BP (ITT-LOCF; $P < 0.0001$ compared with placebo) and a 1.5 mm Hg decrease in diastolic BP ($P = 0.0002$ compared with placebo). By comparison, in the SCOUT Trial, the sibutramine treatment group exhibited a significantly increased heart rate combined with a significant elevation in BP compared with placebo (30). In terms of overall cardiac risk, larger future studies can test the hypothesis that the beneficial effects of PHEN/TPM CR on weight, BP, lipids, and glycemic measures mitigate any AEs on heart rate.

Although most pharmaceutical obesity RCTs include BMIs ranging from 27–40, or 45 at most, this study included patients with class II and III obesity (BMI ≥35 kg/m^2) without any upper BMI limit. WL magnitude resulting from PHEN/TPM CR administration was estimated to be consistent across this broader BMI spectrum (ranging from 35.0–78.7). This finding refutes a common notion that nonsurgical treatments are not efficacious among extremely obese persons. For example, the National Heart, Lung, and Blood Institute guidelines on obesity treatment state, "Extremely obese persons often do not benefit from the more conservative treatments for WL and weight maintenance" (31). Our results show that this is not necessarily true. This finding is germane to the 14% of the US adult population classified as "extremely obese" (32).

A study limitation was the 40% dropout rate (47.1%, 39.0%, and 33.6% for patients receiving placebo, 3.75/23, and 15/92, respectively). This dropout rate is consistent with what one would expect at 56 weeks in obesity trials based on a published meta-analytic prediction equation (24) and lower than the 50% dropout recently reported with two other phase 3 obesity RCTs (33,34). Although our approach to retaining subjects, even if they discontinued the drug, and our use of ITT analyses with established missing data management procedures may have mitigated these high dropout rates, retention of patients in WL trials of 1 year or longer remains challenging. Nevertheless, we used several different ways of handling the missing data, all of which obtained confirmatory results. These statistical methods rest on fewer and less restrictive assumptions than do complete case analyses (35). Moreover, retention rate was significantly higher with active treatment compared with placebo. Although speculative, this may have been due in part to greater WL efficacy in the treatment groups. Greater early WL may provide tangible encouragement for patients to

pursue lifestyle guidance and has been shown to be associated with greater success in WL programs (36). There were other limitations, including the overrepresentation of women (83%). Further studies with larger groups of men may be informative. The trial included mostly white persons and many participants did not have significant obesity-associated comorbid diseases. A publication of another RCT of PHEN/TPM CR covers this broader population (37). Furthermore, the study report herein excluded patients with recurrent depression, although patients on stable antidepressants were allowed. In future studies, determining the extent to which WL effects of this combination therapy are maintained for 2 years and beyond will also be informative. It will also be valuable to monitor potential adverse outcomes for periods beyond 1 year. Gathering information regarding efficacy and safety, including rate-pressure product of this drug therapy in patients with these and other significant comorbidities, in future studies may be valuable.

Currently available pharmacologic agents generally offer efficacy of ≤9% body-WL (3,38), and although modest WL is associated with improvements in weight-related comorbidities (39,40), greater benefits are seen with increased WL (39,41). Some bariatric surgery procedures are associated with mean WL of ~33% before some weight gain tends to reoccur (42). Data suggest that lap-banding results in ~22% WL after 24 months (43). PHEN/TPM CR 15/92 was associated with 14.4% WL in study completers (Analysis B) at 1 year, arguably the relevant comparison to surgical treatment. This appears to represent a result between that of other available pharmacologic agents and that of lap-banding, although randomized head-to-head comparison studies would be required before any definitive statements about relative efficacy of treatments can be made.

In this RCT of PHEN/TPM CR, both 3.75/23 and 15/92 in conjunction with lifestyle modification produced statistically significant WL compared with placebo. PHEN/TPM CR 15/92 provided WL and concomitant improvement in comorbidities that exceeds weight losses reported at 1 year for other currently available pharmaceutical treatments. PHEN/TPM CR demonstrated dose-dependent beneficial effects on weight and metabolic variables with no evidence of SAEs induced by treatment.

SUPPLEMENTARY MATERIAL

Supplementary material is linked to the online version of the paper at http://www.nature.com/oby

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