

MAGNITUDE OF WEIGHT LOSS CONFERRED BY CONTROLLED-RELEASE, LOW-DOSE PHENTERMINE/TOPIRAMATE (PHEN/TPM CR)

DETERMINES EXTENT OF CARDIOMETABOLIC BENEFIT

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BACKGROUND

- A growing body of literature demonstrates that moderate weight loss (5-10%) confers significant reductions in cardiometabolic risks associated with obesity-related illnesses.^{1,2}
- The National Institutes of Health recommends that obese/overweight persons initially reduce their body weight by at least 10% and maintain this weight loss for 1 year.³
- Although several studies have shown that ≥10% weight loss among obese individuals tends to yield more substantial reductions in cardiometabolic risks compared with <10% weight loss,⁴⁻⁶ direct comparisons of the benefits associated with specific weight-loss thresholds are lacking.

OBJECTIVE

- To compare the cardiometabolic benefits of ≥5%, ≥10%, and ≥15% weight loss among obese/overweight participants enrolled in a 56-week randomized, controlled trial of controlled-release phentermine and topiramate (PHEN/TPM CR).

METHODS

- This phase 3, double-blind, placebo-controlled, randomized trial (CONQUER) evaluated 2 doses of PHEN/TPM CR in 2,487 obese/overweight subjects with ≥2 obesity-related comorbidities (e.g., type 2 diabetes, hypertension, dyslipidemia).
- Subjects were randomized to receive placebo, PHEN 7.5 mg/TPM CR 46 mg (7.5/46), or PHEN 15 mg/TPM CR 92 mg (15/92) once daily in the morning for 56 weeks. Dosing was titrated over 4 weeks and then administered during the subsequent 52 weeks. Efficacy and safety endpoints were evaluated at baseline, weeks 2 and 4 of the titration period, and at 4-week intervals thereafter.
- All participants were managed according to standard of care for their respective comorbidities and received lifestyle modification, including nutrition guidance and increased physical activity, based on the LEARN® program.⁷

OUTCOMES MEASURES AND STATISTICAL ANALYSIS

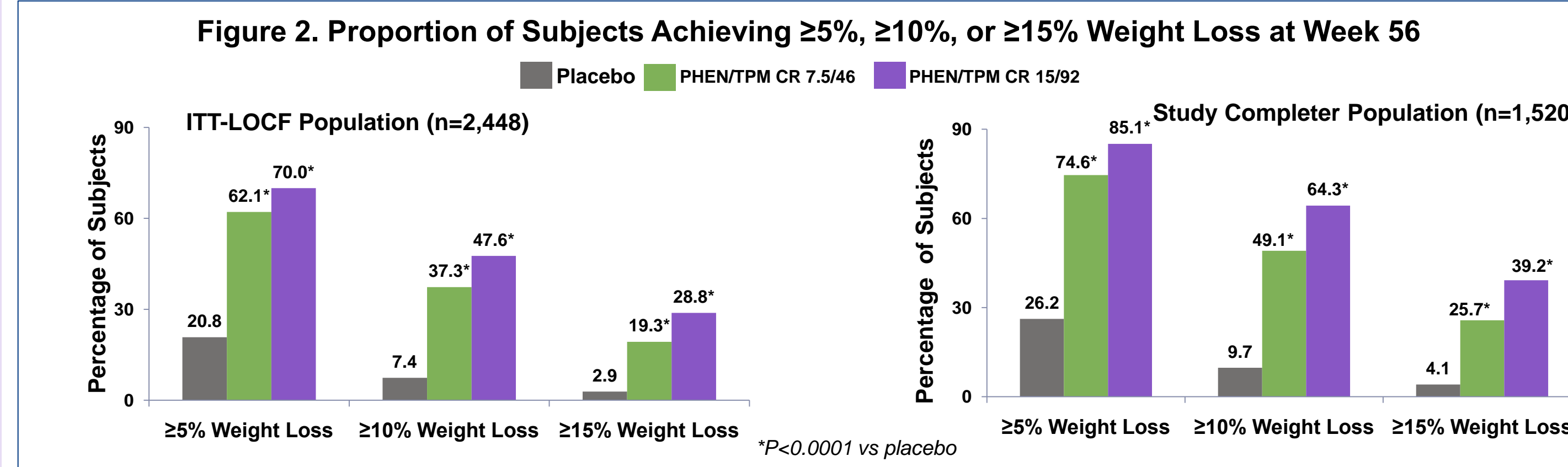
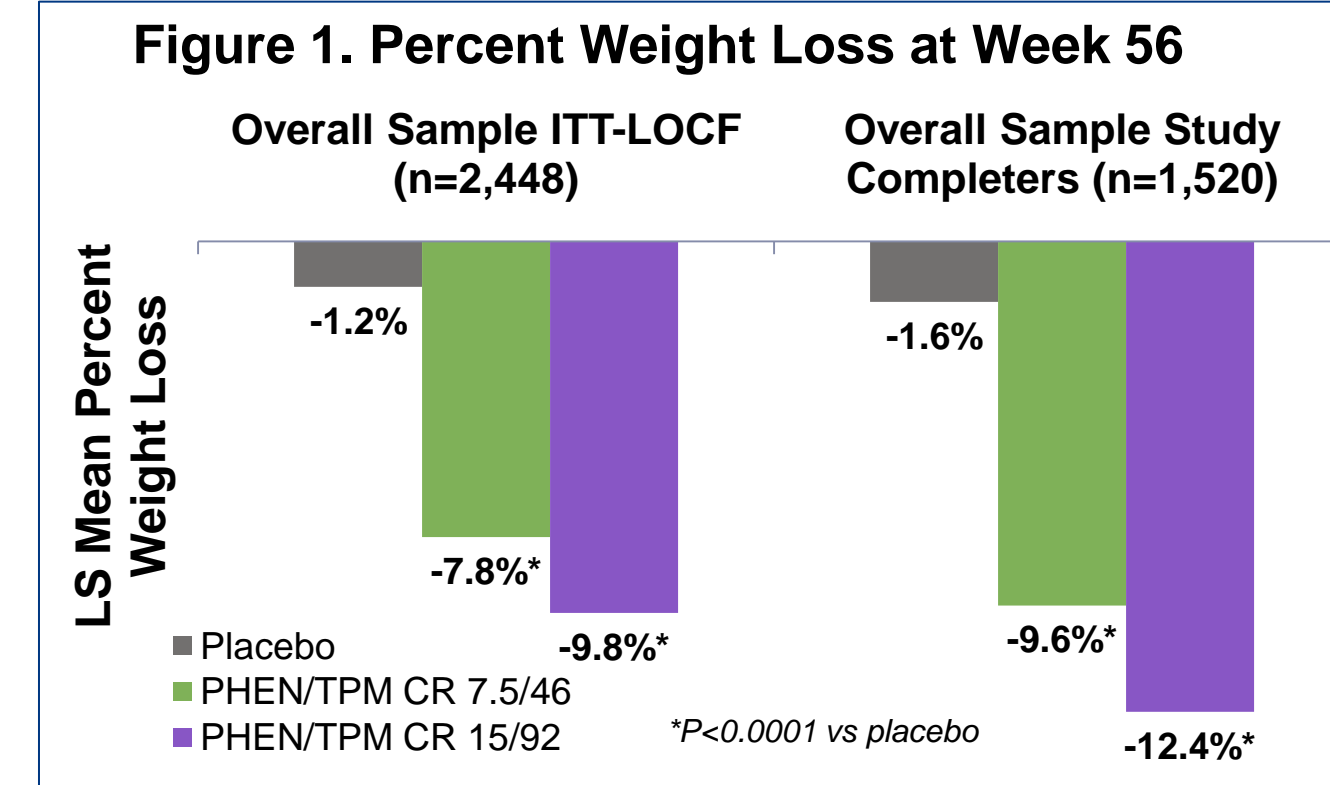
- The primary efficacy endpoints were mean percent weight loss and percentage of subjects with ≥5% weight loss from baseline to Week 56 in the intent-to-treat (ITT) sample with last observation carried forward (LOCF). The last post-dose measurement was used, regardless of whether the subject remained on study drug.
- Additional efficacy endpoints included percentage of subjects achieving ≥10% or ≥15% weight loss; and changes in blood pressure (BP), lipid levels, and glycemic parameters from baseline to Week 56. Safety outcomes were assessed at all study visits.
- The present analysis also examined the effects of varying degrees of weight loss on lipid levels, glycemic parameters, and waist circumference (WC).
- Analysis of percentage of subjects with ≥ 5%, ≥ 10%, or ≥ 15% weight loss at Week 56 with LOCF was performed using a logistic regression model with treatment, gender, and diabetic status as fixed effects and baseline weight as a covariate. For each treatment comparison of interest, the estimated odds ratio (OR), standard error, 95% Wald confidence interval, and P value were derived.

RESULTS

- In the randomized sample (n=2,487), 70% were female and 86% were Caucasian with a mean age of 51 years. At baseline, subjects' mean weight was 103 kg, BMI 36.6 kg/m², WC 113 cm, BP 128/81 mm Hg, total cholesterol 204.5 mg/dL, low-density lipoprotein cholesterol 123.1 mg/dL, fasting serum glucose 106.1 mg/dL (which is within the prediabetes range), and HbA1c 5.9%.

- At Week 56, least-squares (LS) mean percent weight loss was significantly greater in both PHEN/TPM CR groups versus placebo (*P*<0.0001 for all comparisons) for the overall ITT-LOCF population (n=2,448) and study completers (n=1,520) (Figure 1).

- The percentages of the ITT-LOCF and study completer populations that achieved ≥5%, ≥10%, and ≥15% weight loss from baseline at Week 56 are shown in Figure 2. Both doses of PHEN/TPM CR were statistically superior to placebo (*P*<0.0001 for all comparisons).



- Table 1 shows the LS mean changes in cardiometabolic parameters from baseline to Week 56 for the overall ITT-LOCF population.

Outcome	LS Mean Change From Baseline at Week 56		
	Placebo	PHEN/TPM CR 7.5/46	PHEN/TPM CR 15/92
Waist circumference (cm)	-2.4	-7.6 [§]	-9.2 [§]
HbA1c (%)	0.1	0.0 [§]	-0.1 [§]
Fasting serum glucose (mg/dL)	2.3	-0.1 [†]	-1.3 [§]
Fasting insulin (μIU/mL)	0.7	-3.5 [‡]	-4.0 [§]
Total cholesterol (%)	-3.3	-4.9 [*]	-6.3 [§]
LDL-C (%)	-4.1	-3.7	-6.9 [*]
HDL-C (%)	1.2	5.2 [§]	6.8 [§]
Triglycerides (%)	4.7	-8.6 [§]	-10.6 [§]
Systolic BP (mm Hg)	-2.4	-4.7 [‡]	-5.6 [§]
Diastolic BP (mm Hg)	-2.7	-3.4	-3.8 [*]
C-reactive protein (mg/L)	-0.78	-2.49 [§]	-2.48 [§]

**P*<0.05 vs placebo, †*P*<0.005 vs placebo, ‡*P*<0.001 vs placebo, §*P*<0.0001 vs placebo.

Parameter	Categorical LS Mean Change at Week 56 From Baseline Levels		
	≥5% to <10% Weight Loss	≥10% to <15% Weight Loss	≥15% Weight Loss
Waist circumference (cm)	-7.9	-12.0*	-18.2*†
HbA1c (%)	0.0	-0.1*	-0.3*†
Fasting serum glucose (mg/dL)	-3.5	-6.8*	-10.0*†
Fasting insulin (μIU/mL)	-3.4	-6.0*	-7.9*†
Total cholesterol (mg/dL)	-13.1	-12.5	-17.3*†
LDL-C (mg/dL)	-9.5	-8.1	-11.6
HDL-C (mg/dL)	1.0	3.5*	6.5*†
Triglycerides (mg/dL)	-17.8	-41.2*	-61.1*†
Systolic BP (mm Hg)	-4.8	-7.4*	-9.4*†
Diastolic BP (mm Hg)	-3.8	-5.0*	-5.6*
C-reactive protein (mg/L)	-1.9	-2.6	-3.2*

**P*<0.05 vs ≥5% to <10%, †*P*<0.05 vs ≥10% to <15%.

- The overall study completion rate was 69.3%. A greater percentage of patients receiving PHEN/TPM CR completed the study than those receiving placebo: 62.0%, 75.1%, and 73.7% for placebo, 7.5/46, and 15/92, respectively.
- PHEN/TPM CR was generally well tolerated. The most common treatment-emergent adverse events experienced in this study were upper respiratory tract infections, constipation, paresthesia, and dry mouth; most were mild or moderate in severity. Rates of serious adverse events were similar across treatment groups; one death was reported in a placebo-treated subject.

CONCLUSIONS

- Treatment with PHEN/TPM CR plus lifestyle modification resulted in significantly greater weight loss and improvements in cardiometabolic parameters (BP, lipid levels, glycemic outcomes, WC, and C-reactive protein) at 56 weeks, compared to placebo (i.e., lifestyle modification alone).
- PHEN/TPM CR was generally well tolerated, with study completion rates >70%.
- This large, randomized, 56-week, placebo-controlled study suggests that well-tolerated drug treatments that result in weight loss ≥10% confer significant cardiometabolic benefit.
- The degree of cardiometabolic benefit conferred appears to be directly associated with the magnitude of weight loss achieved.

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FOR FURTHER INFORMATION

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DISCLOSURES

Barbara Troupin is an employee of VIVUS, Inc. Cheryl Hankin is a consultant to VIVUS, Inc. Research support provided by VIVUS, Inc.