

LOW-DOSE, CONTROLLED-RELEASE PHENTERMINE/TOPIRAMATE (PHEN/TPM CR) RESULTS IN SIGNIFICANT WEIGHT LOSS AND IMPROVES ATHEROSCLEROTIC BIOMARKERS IN OVERWEIGHT/OBESE PATIENTS WITH OBESITY-RELATED COMORBIDITIES

POSTER
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BACKGROUND

- Obesity significantly increases the risk for coronary heart disease,¹ the leading cause of death in the United States (US).²
- Weight loss of ≥10% significantly improves atherosclerotic biomarkers among the obese.³

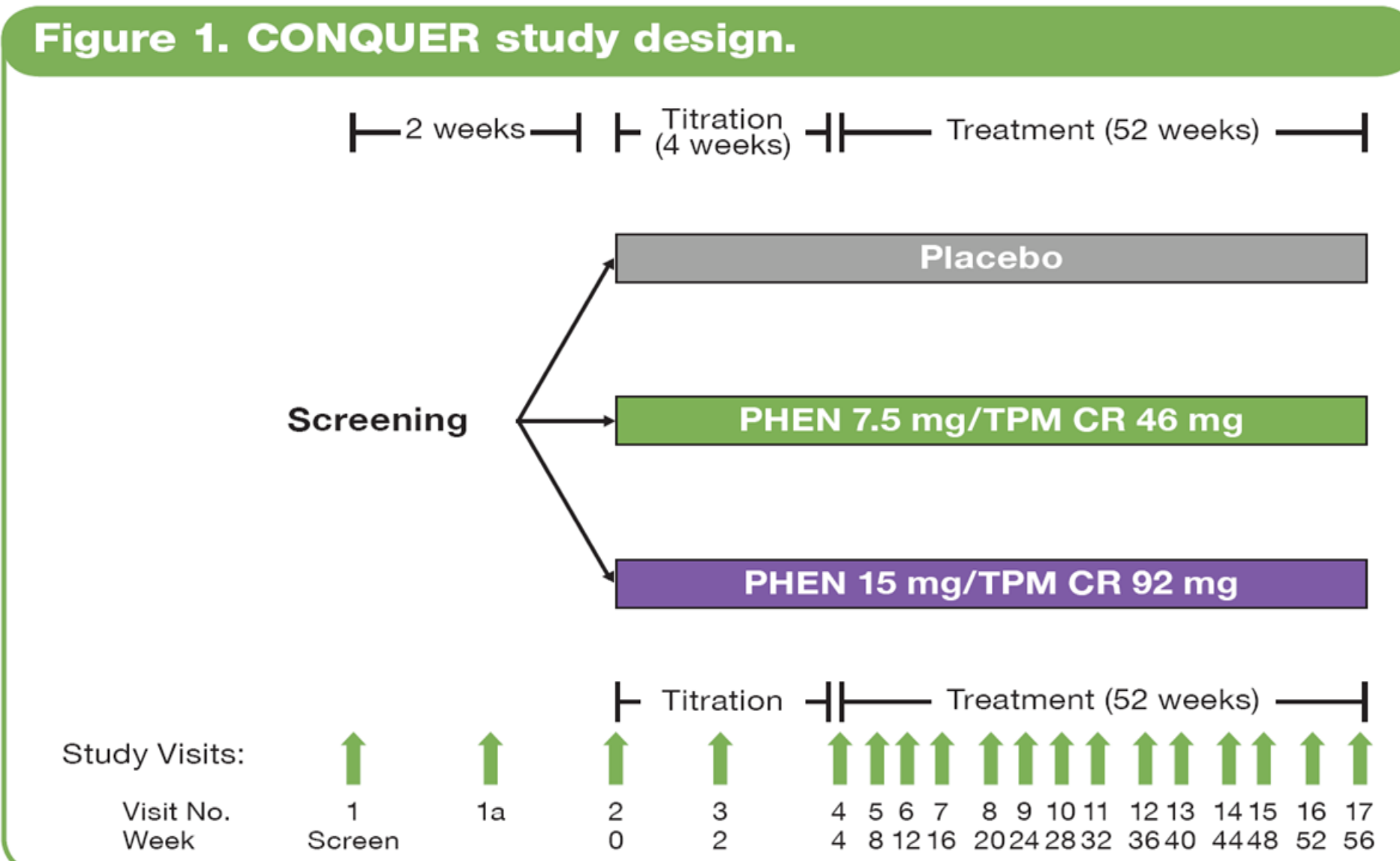
OBJECTIVE

- To determine the effect of controlled-release phentermine and topiramate (PHEN/TPM CR) on weight loss and atherosclerotic biomarkers among obese/overweight participants enrolled in a 56-week randomized, controlled trial.

METHODS

- A double-blind, placebo-controlled, phase 3 trial (CONQUER) randomized 2,487 obese/overweight subjects with ≥2 weight-related comorbidities (e.g., type 2 diabetes, hypertension, dyslipidemia) to placebo, PHEN 7.5 mg/TPM CR 46 mg (7.5/46), or PHEN 15 mg/TPM CR 92 mg (15/92) for 56 weeks.
- All subjects received lifestyle and exercise guidance based on the LEARN[®] program⁴ and were managed by US standards of care for their comorbidities.⁵⁻⁷
- Subjects received study drug once daily for 56 weeks. Efficacy and safety endpoints were evaluated at baseline, weeks 2 and 4 of the titration period, and at 4-week intervals (Figure 1).
- An analysis of covariance (ANCOVA) model was used to evaluate changes in weight loss and lipids, blood pressure (BP), and glycemic and inflammatory biomarkers.

FIGURE 1. CONQUER STUDY DESIGN



ASSESSMENTS

- The primary efficacy endpoints in the CONQUER trial were percent change in body weight at Week 56 and percentage of subjects with ≥5% weight loss at Week 56 in the intent-to-treat (ITT) population with last observation carried forward (LOCF).
- Secondary efficacy endpoints measured from baseline to Week 56 included:
 - Percentage of subjects achieving ≥10% weight loss; and
 - Change in lipids, BP, glycemic parameters, and inflammatory biomarkers.

RESULTS

- Among enrollees, 70% were female, 86% were Caucasian, and mean age was 51 years. At baseline, subjects had a mean weight of 103.1 kg, mean body mass index of 36.6 kg/m², and waist circumference of 113.2 cm. Table 1 provides comorbid characteristics of subjects in the ITT population (n=2,448).
- Least-squares (LS) mean % weight loss for ITT (n=2,448) and completer populations (n=1,520) was significantly greater for both PHEN/TPM CR groups versus placebo ($P<0.0001$ for all comparisons) (Figure 2).

- In both the type 2 diabetes and prediabetes samples, statistically and clinically significant weight loss ($P<0.0001$) was achieved in a dose-dependent fashion.
- In the ITT population, significantly more patients receiving PHEN/TPM CR achieved ≥10% weight loss versus placebo ($P<0.0001$): 7.4%, 37.3%, and 47.6% for placebo, 7.5/46, and 15/92, respectively. Similar results were obtained in study completers: 9.7%, 49.1%, and 64.3% for placebo, 7.5/46, and 15/92, respectively.
- In the overall sample, significant improvements in total cholesterol, HDL-C and triglycerides at Week 56 were observed with PHEN/TPM CR 7.5/46 and 15/92 versus placebo (Table 2). PHEN/TPM CR 15/92 also resulted in significantly improved LDL-C. Similar benefits were observed in subjects with hypertriglyceridemia.

- After 56 weeks, both doses of PHEN/TPM CR resulted in significantly improved systolic BP (SBP) compared to placebo for the ITT population ($P<0.05$; Figure 3) and for patients with baseline hypertension ($P<0.05$). Diastolic blood pressure (DBP) was also significantly improved among subjects receiving PHEN/TPM CR 15/92 versus placebo ($P<0.05$), and both the PHEN/TPM CR 7.5/46 and 15/92 groups with hypertension experienced significantly improved DBP versus placebo ($P<0.05$).

Figure 3. LS Mean Change in BP at Week 56

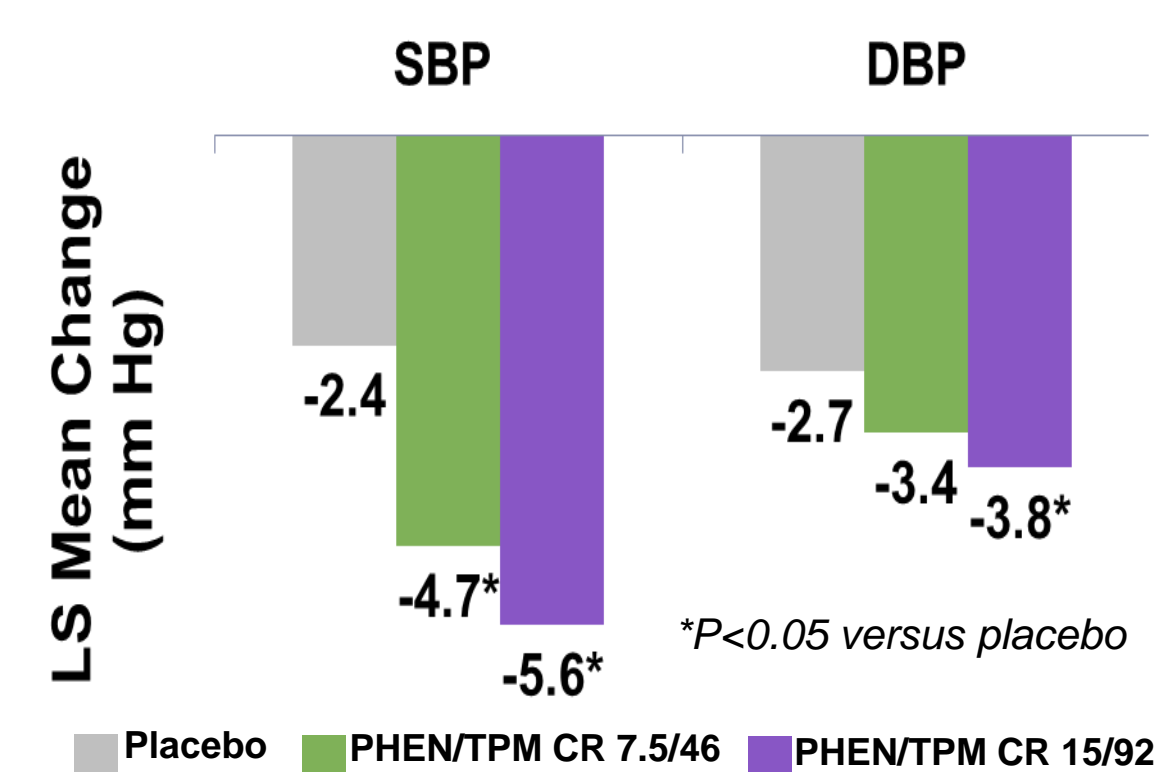


Table 1. Comorbidities in the CONQUER ITT Population

Comorbidities at Baseline (n, %)	ITT-LOCF (n=2,448)
Type 2 diabetes mellitus	388 (15.8%)
Prediabetes*	1,635 (66.8%)
Elevated triglycerides (and/or ≥2 lipid medications)	885 (36.2%)
Hypertension (and/or ≥2 antihypertensive medications)	1,286 (52.5%)

*Defined as impaired fasting blood glucose or impaired glucose tolerance.

Figure 2. Percent Weight Loss at Week 56

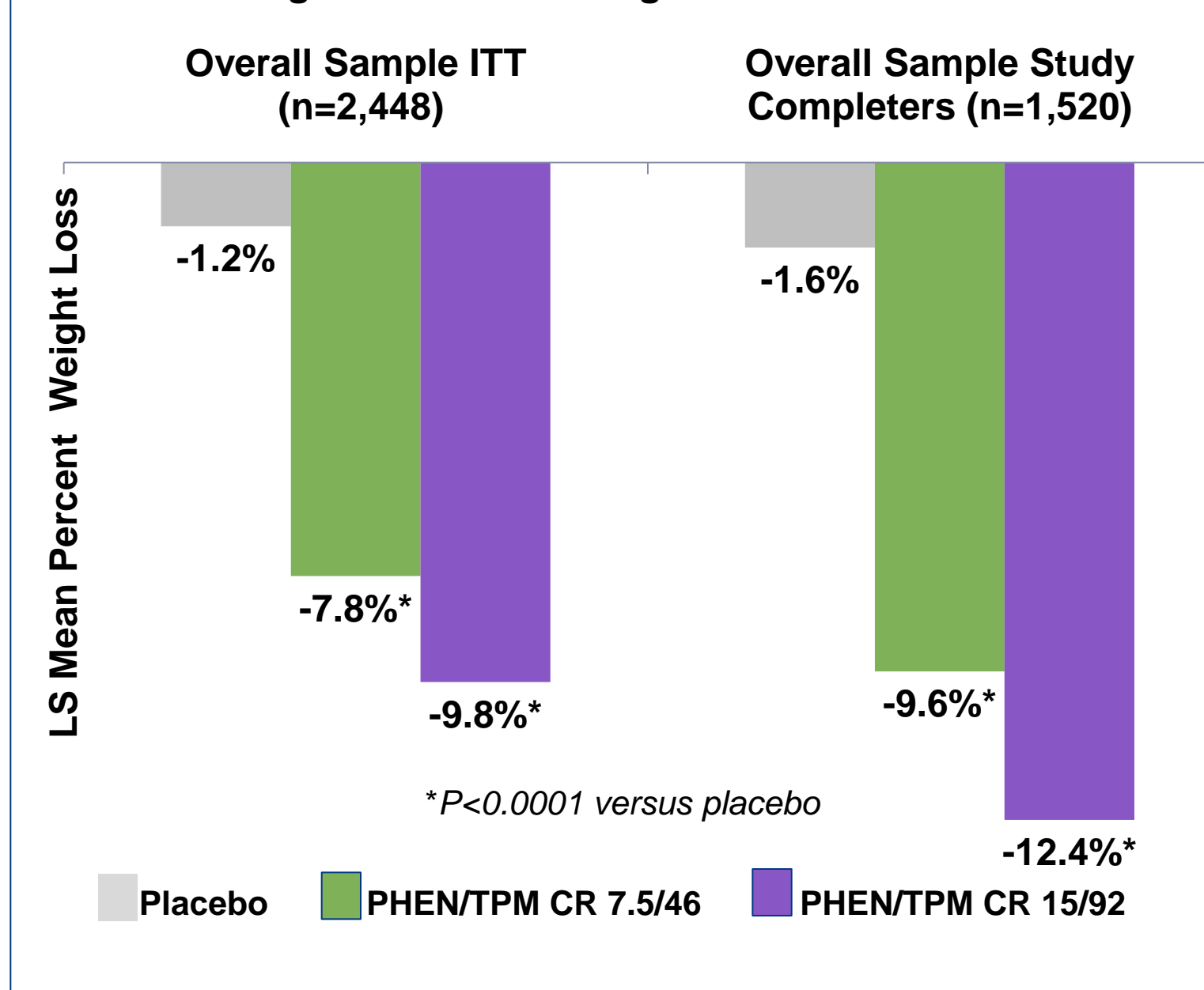


Table 2. Mean % Change in Lipids at Week 56 for the ITT Population

Lipid Parameters	Placebo	PHEN/TPM CR 7.5/46	PHEN/TPM CR 15/92
Overall Sample			
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†
Hypertriglyceridemia Sample			
Total Cholesterol	-4.9	-5.7	-7.8*
LDL-C	-3.6	0.7	-4.3
HDL-C	2.8	9.5*	10.7†
Triglycerides	-8.8	-24.1†	-25.6†

* $P<0.05$ versus placebo, † $P<0.0001$ versus placebo

- Both PHEN/TPM CR doses were associated with significant improvements in inflammatory (C-reactive protein), adipose tissue (adiponectin), and coagulopathic (fibrinogen) markers (Figure 4).

- PHEN/TPM CR was generally well tolerated. The most common treatment-emergent adverse events (AEs) were dry mouth, paresthesia, and constipation (Table 3).

- Discontinuation rates due to treatment-emergent AEs were 8.9% for placebo, 11.6% for PHEN/TPM CR 7.5/46, and 19.2% for PHEN/TPM CR 15/92. Reasons for discontinuations occurring at ≥1% frequency were paresthesias, dizziness, insomnia, depression, and nephrolithiasis. The maximum frequency of any event was 1.6%. One death occurred in a placebo-treated subject.

Figure 4. LS Mean Change in C-reactive Protein, Adiponectin and Fibrinogen

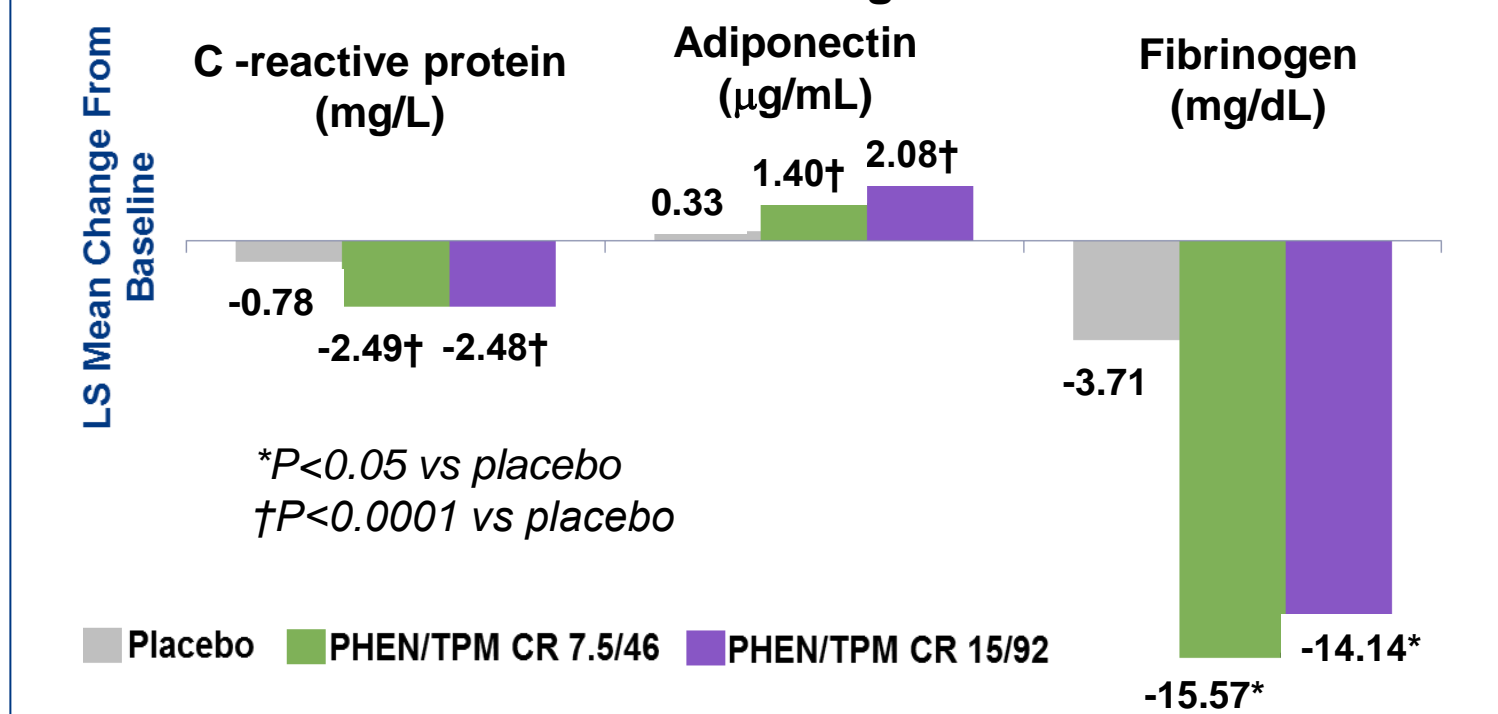


Table 3. Most Common Treatment-Emergent AEs (n=2,485)

Adverse Event (%)	Placebo	PHEN/TPM CR 7.5/46	PHEN/TPM CR 15/92
Dry mouth	2.4	13.5	20.8
Paresthesia	2.0	13.7	20.5
Constipation	5.9	15.1	17.4
Upper respiratory infection	12.9	12.2	13.4
Dysgeusia	1.1	7.4	10.4
Insomnia	4.7	5.8	10.3

CONCLUSIONS

- Treatment with PHEN/TPM CR was more efficacious than placebo, as evidenced by significantly greater weight loss and improved biomarkers of atherosclerotic risk.
- PHEN/TPM CR was generally well tolerated, as demonstrated by low rates of study discontinuations due to adverse events.
- These data indicate that weight loss associated with PHEN/TPM CR may significantly impact multiple atherosclerotic endpoints, and suggest that treatment may prevent the development and/or progression of cardiovascular disease.

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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.