

# CONTROLLED-RELEASE, LOW-DOSE PHENTERMINE/TOPIRAMATE (PHEN/TPM CR) REDUCES WEIGHT, IMPROVES GLYCEMIC MARKERS, AND DECREASES PROGRESSION TO TYPE 2 DIABETES MELLITUS (T2DM) IN OVERWEIGHT AND OBESE PATIENTS WITH OBESITY-RELATED COMORBIDITIES

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## BACKGROUND

- Obesity is an escalating global epidemic associated with comorbidities, such as cardiovascular disease and type 2 diabetes (T2DM), as well as increased mortality.<sup>1,4</sup>
- Development of T2DM is closely linked with obesity; the incidence of T2DM is increasing rapidly and mirrors the obesity epidemic.<sup>5</sup>
- Impaired fasting glucose (IFG) and impaired glucose tolerance (IGT) occur in early phases of progression to T2DM and can be exacerbated by weight gain. Both IFG and IGT can generally be improved with weight loss, thus potentially delaying or preventing progression to T2DM.<sup>5,6</sup>
- Phentermine (PHEN) and topiramate (TPM) are pharmacologic agents with demonstrated weight-loss properties. PHEN is currently approved in the United States for short-term weight loss (recommended dose: 37.5 mg/day) as an adjunct to lifestyle modifications. TPM is indicated for treatment of seizures (recommended dose: 400 mg/day) and prevention of migraines (recommended dose: 100 mg/day).<sup>7,8</sup>
- A previous extended-release formulation of TPM at doses titrated up to 175 mg/day (range 50 to 175 mg/day) demonstrated weight loss in clinical trials, although side effects were significant and prevented further development of that formulation as monotherapy.<sup>9,10</sup> A combination of low-dose, controlled-release (CR) PHEN/TPM for once-daily oral dosing was developed to maximize weight loss and comorbid benefits while minimizing adverse events.

## OBJECTIVE

- To evaluate glycemic and insulinemic markers in normoglycemic, prediabetic, and diabetic subjects from the EQUIP and CONQUER clinical trials and determine effects of weight loss on progression to T2DM.

## METHODS

- A pooled analysis of two double-blind, placebo-controlled phase 3 clinical trials is included in this evaluation:
  - EQUIP: 1,267 obese subjects (BMI ≥35 kg/m<sup>2</sup>), excluding subjects with T2DM, were randomly assigned to placebo, PHEN 3.75 mg/TPM CR 23 mg (3.75/23), or PHEN 15 mg/TPM CR 92 mg (15/92) for 56 weeks.
  - CONQUER: 2,487 overweight/obese adult subjects (BMI ≥27 kg/m<sup>2</sup> and ≤45 kg/m<sup>2</sup>) with ≥2 weight-related comorbidities were randomly assigned to placebo, PHEN 7.5 mg/TPM CR 46 mg (7.5/46), or 15/92 for 56 weeks.
- Subjects were instructed to take study drug once daily for 56 weeks. Efficacy and safety endpoints were evaluated at baseline, weeks 2 and 4 of the titration period, and then at 4-week intervals.
- All subjects were provided counseling on lifestyle modification using the LEARN® Program for Weight Management.<sup>11</sup>

## ASSESSMENTS

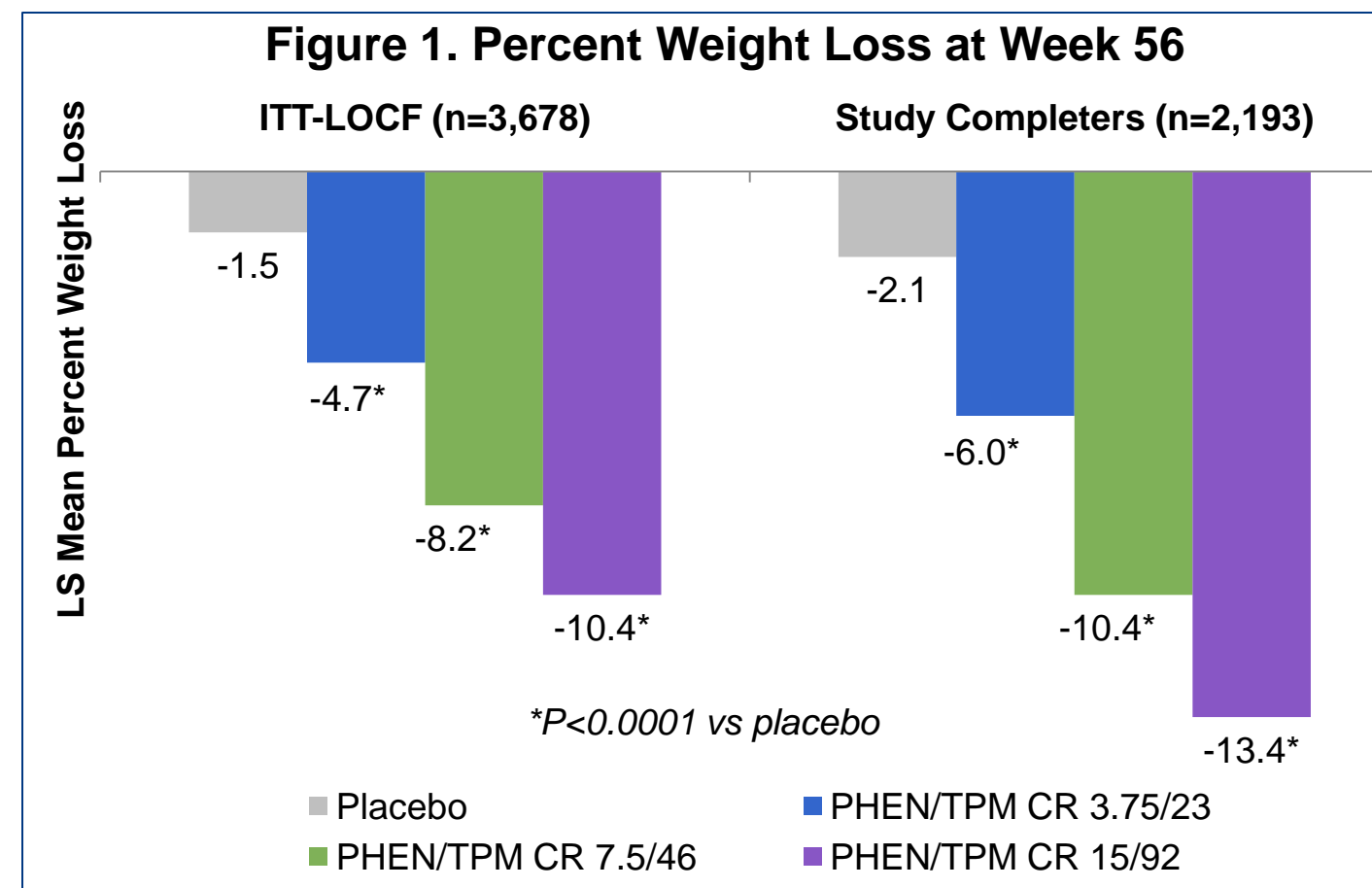
- A primary efficacy endpoint for both phase 3 studies was percentage weight loss from baseline to Week 56 with last observation carried forward (LOCF) for the intent-to-treat (ITT) set and for completers, with the corresponding active treatment versus placebo comparisons.
- For EQUIP, glycemic parameters are presented for Week 56 in the ITT sample and in subjects with baseline fasting glucose (FG) within the upper quartile. For CONQUER, glycemic and insulinemic parameters are presented among ITT and diabetic subjects at 56 weeks.
- An analysis of covariance (ANCOVA) model, with treatment, study, and gender as fixed effects and baseline weight as a covariate, was used to evaluate changes in weight loss and other outcomes.

- Baseline characteristics of the pooled ITT 1-year cohort (EQUIP and CONQUER, n=3,678) are presented in Table 1. Subjects were mostly female (74.3%), age <65 years (93.3%), and overweight or obese (60.5% BMI ≥30 kg/m<sup>2</sup> and <40 kg/m<sup>2</sup>; 34.7% BMI ≥40 kg/m<sup>2</sup>).

**Table 1. Baseline Characteristics of Pooled Analysis of EQUIP and CONQUER: ITT-LOCF 1-Year Cohort**

	Placebo (n=1,477)	PHEN/TPM CR 3.75/23 (n=234)	PHEN/TPM CR 7.5/46 (n=488)	PHEN/TPM CR 15/92 (n=1,479)
Mean (SD) age, years	48.5 (11.4)	43.0 (11.1)	51.1 (10.4)	48.0 (12.0)
Age <65, n (%)	1,382 (93.6)	230 (98.3)	442 (90.6)	1,376 (93.0)
Female, n (%)	1,102 (74.6)	194 (82.9)	341 (69.9)	1,094 (74.0)
Mean (SD) weight, kg	107.5 (20.2)	118.6 (21.9)	102.8 (18.2)	107.1 (19.6)
Mean (SD) waist circumference, cm	115.8 (13.3)	121.5 (15.2)	112.7 (12.4)	115.5 (13.5)
Mean (SD) BMI, kg/m <sup>2</sup>	38.5 (5.7)	42.5 (6.5)	36.3 (4.4)	38.4 (5.7)
BMI ≥30 and <40 kg/m <sup>2</sup> , n (%)	904 (61.2)	91 (38.9)	344 (70.5)	887 (60.0)
BMI ≥40 kg/m <sup>2</sup> , n (%)	502 (34.0)	143 (61.1)	111 (22.7)	521 (35.2)

- After 56 weeks, least-squares (LS) mean percent weight loss in the ITT-LOCF population (n=3,678) and completer population (n=2,193) was significantly greater for all doses of PHEN/TPM CR versus placebo (*P*<0.0001; Figure 1).
- In EQUIP, subjects with T2DM (by history or FG ≥126 mg/dL at baseline) were excluded. In the ITT-LOCF population, there was a significantly greater decrease in FG in the 15/92-treated subjects versus placebo (*P*<0.0001; Table 2). For both doses of PHEN/TPM, subjects with baseline FG in the upper quartile (within the prediabetes range of 100-125 mg/dL) had a significantly greater LS mean change in FG versus placebo (*P*<0.05).
- In CONQUER, at Week 56, HbA1c was significantly reduced in both PHEN/TPM CR groups versus placebo, both in subjects with T2DM (*P*<0.05) and the study population as a whole (*P*<0.0001) (Figure 2).

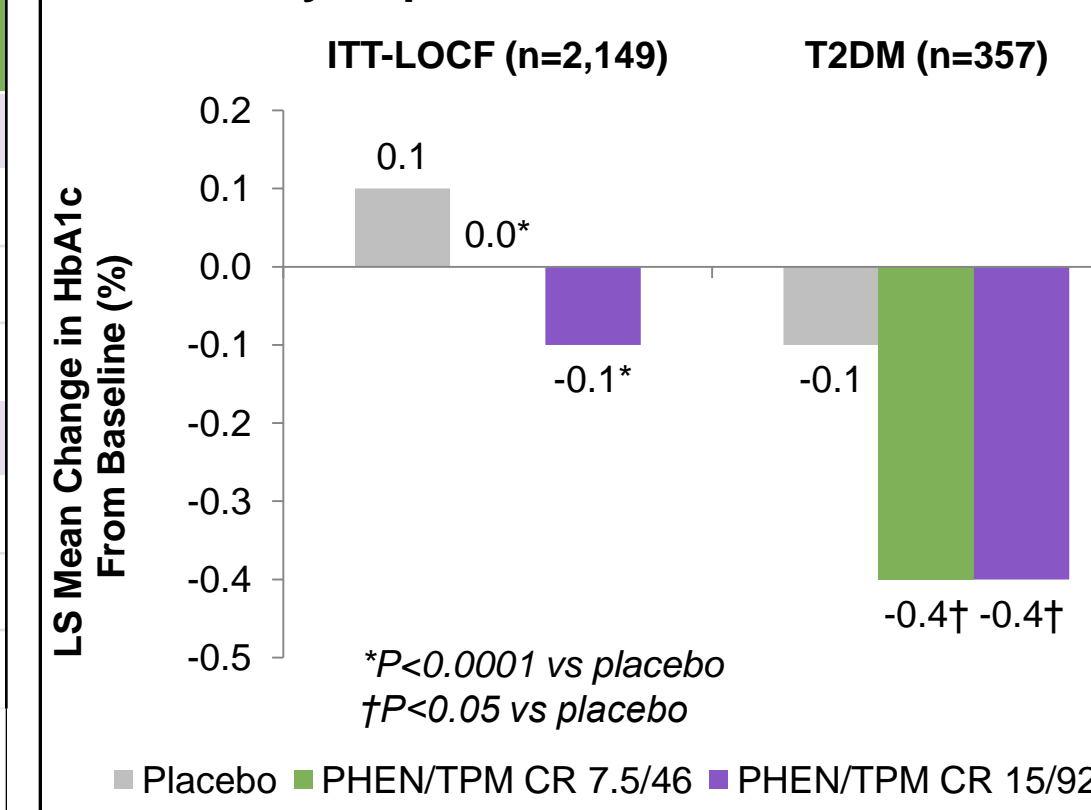


**Table 2. Change in FG at Week 56 for EQUIP ITT-LOCF Population and Subjects in Upper Quartile of FG at Baseline**

	Baseline Mean (mg/dL)	LS Mean Change at Week 56 (mg/dL)
<b>ITT-LOCF (n=1,188)</b>		
Placebo	93.1	1.9
PHEN/TPM CR 3.75/23	93.9	0.8
PHEN/TPM CR 15/92	93.0	-0.6*
<b>Subjects in Upper Quartile of FG at Baseline (n=261)</b>		
Placebo	105.0	-3.5
PHEN/TPM CR 3.75/23	105.6	-9.3†
PHEN/TPM CR 15/92	105.2	-6.2‡

\**P*<0.0001, †*P*<0.001, ‡*p*<0.05

**Figure 2. LS Mean Change in HbA1c at Week 56 for CONQUER ITT-LOCF Study Population and T2DM Subset**



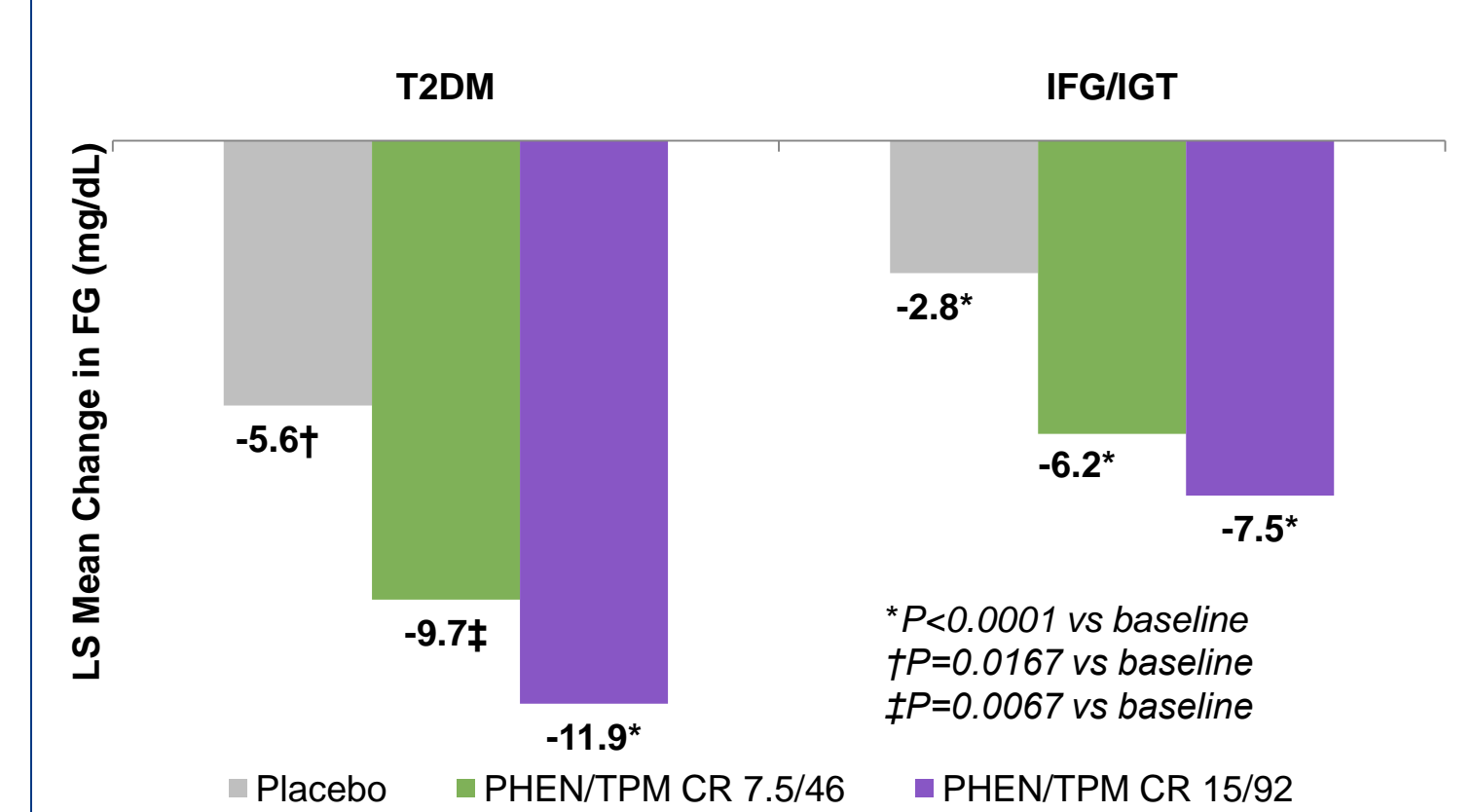
## RESULTS

- In CONQUER, which included 388 (15.8%) subjects with T2DM at baseline, oral glucose tolerance testing at Week 56 demonstrated significant reductions in insulin and glucose levels with PHEN/TPM CR treatment versus placebo (*P*<0.0005). After 56 weeks of treatment, the whole-body insulin sensitivity index increased by about 60% across the entire population (Table 3).
- For CONQUER, changes in FG from baseline for the T2DM and IFG/IGT are shown in Figure 3. In the T2DM subpopulation, LS mean change in FG was similar for both doses of PHEN/TPM but not statistically significant compared to placebo. Subjects with IFG/IGT (n=1,635 [66.8%]) showed significant improvements in FG versus placebo (*P*<0.005).
- In the CONQUER trial, 47 new cases of T2DM were documented as adverse events: 27 (2.7%), 9 (1.8%), and 11 (1.1%) for placebo, 7.5/46, and 15/92, respectively.
- PHEN/TPM CR was generally well tolerated. Constipation, dry mouth, paresthesia, and dysgeusia were the most commonly reported treatment-emergent adverse events; these events were dose related and appeared across EQUIP, CONQUER, and pooled 1-year data.
- More subjects taking PHEN/TPM CR than placebo completed all study visits, with the highest completion rate in the 7.5/46 group.

**Table 3. Whole-body Insulin Sensitivity Index – Change From Baseline to Week 56 in CONQUER Subjects (ITT-LOCF)**

	Baseline Mean	LS Mean Change	P Value vs Placebo
Placebo (n=918)	3.54	0.50	—
PHEN/TPM CR 7.5/46 (n=459)	3.36	1.71	<0.0001
PHEN/TPM CR 15/92 (n=925)	3.65	1.98	<0.0001

**Figure 3. LS Mean Change in FG for the T2DM and IFG/IGT Subpopulations in the CONQUER Trial**



## CONCLUSIONS

- These results demonstrate that treatment with PHEN/TPM CR consistently leads to significant weight loss and clinically meaningful improvements in glycemic parameters.
- In these pooled analyses, weight loss led to improvements in glycemic markers, which indicate improvements in glycemic regulation and insulin sensitivity.
- There were fewer T2DM diagnoses among subjects receiving PHEN/TPM CR with lifestyle modification than among those receiving placebo (i.e., lifestyle modification alone). This suggests that weight loss conferred by PHEN/TPM CR may alter the course of the disease and delay progression to T2DM.
- The tolerability profile of PHEN/TPM CR was consistent across studies, showing high completion rates across a range of relevant patient populations.

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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.