

1 **ONLINE SUPPLEMENTAL MATERIAL**

2 Multiple imputation (MI) was used as a sensitivity analysis to supplement the intent-to-
3 treat with last observation carried forward (ITT-LOCF) approach (**Supplemental Tables**
4 **1 and 2**). MI was applied to all enrolled subjects, thereby adhering strictly to the ITT
5 principle while accommodating missing data. Five imputed data sets were used per
6 analysis. We used a 2-step imputation process involving treatment assignment, gender,
7 and all measurements of the efficacy variable under study. First, sufficient imputations
8 were done to achieve a monotone missing data pattern using a Markov Chain Monte
9 Carlo algorithm. Next, all remaining missing data were imputed under the assumption of
10 a monotone missing data pattern via Rubin's regression method (1). The 5 complete
11 imputed datasets were analyzed with analysis of covariance (ANCOVA) including terms
12 for treatment assignment, sex, and baseline as fixed effect covariates. Finally, using
13 methods described by Schafer (2), the separate results from each of the 5 imputed data
14 sets were pooled into single estimates and tested.

15
16 **Analysis of subjects who completed the study while actively taking study drug was also**
17 **performed to understand the effect of treatment following 108 weeks of exposure**
18 **(Supplemental Tables 3 and 4). Similar to the LOCF analyses, treatment comparisons**
19 **were performed using an ANCOVA with fixed effects for treatment, gender, and diabetic**
20 **status and baseline as a covariate.**

21

1 Conclusions of statistical significance and the order of magnitude of effect estimates
2 were consistent for the MI approach and completer analyses when compared to the
3 ITT-LOCF approach for all variables.

4

5 **REFERENCES:**

6 1. Rubin DB. Multiple imputation for non-response in surveys. Wiley series in probability
7 and mathematical statistics. New York: John Wiley & Sons, 1987.

8 2. Schafer JL. Analysis of incomplete multivariate data (monographs on statistics and
9 applied probability 72). London: Chapman & Hall/CRC, 1997.

10

Supplemental Table 1. Least-Squares Mean (95% CI) Estimates and Treatment Comparisons From Multiple Imputation at Week 108

	Standardized Lifestyle Intervention Across All Treatment Groups					
Parameter	Placebo (n = 227)	Phentermine/ Topiramate CR 7.5/46 (n = 154)	<i>P</i> vs Placebo	Phentermine/ Topiramate CR 15/92 (n = 295)	<i>P</i> vs Placebo	<i>P</i> vs Phentermine/ Topiramate CR 7.5/46
Percent weight loss	-2.5 (-3.4, -1.6)	-10.3 (-11.6, - 9.0)	< 0.0001	-11.2 (-12.2, - 10.3)	< 0.0001	< 0.1693
Waist circumference, cm	-4.2 (-5.2, -3.1)	-10.4 (-11.7, - 9.1)	< 0.0001	-11.1 (-12.0, - 10.2)	< 0.0001	0.4156
Systolic blood pressure, mm Hg	-3.5 (-5.2, -1.9)	-4.6 (-6.6, -2.5)	0.4202	-4.4 (-5.9, -2.9)	0.4053	0.9155
Diastolic blood pressure, mm Hg	-3.6 (-4.7, -2.5)	-3.6 (-5.0, -2.1)	0.9403	-3.1 (-4.2, -2.1)	0.5236	0.6545
Triglycerides, %	-0.5 (-5.6, -1.6)	-13.6 (-20.0, - 7.2)	0.0014	-15.0 (-19.8, - 10.2)	< 0.0001	0.7379

change	4.7)	7.3)		10.1)		
HDL-C, % change	4.9 (2.4, 7.5)	7.8 (4.6, 11.0)	0.1659	12.6 (10.3, 14.9)	< 0.0001	0.0137
LDL-C, % change	-10.8 (-13.7, -7.9)	-4.6 (-8.2, -1.1)	0.0080	-5.8 (-8.4, -3.2)	0.0110	0.5934
Non-HDL-C (% change)	-9.5 (-12.0, -7.0)	-8.7 (-11.8, -5.6)	0.6762	-9.5 (-11.7, -7.2)	0.9838	0.6784

Data are LS mean change (95% CI) or LS mean percent change (95% CI). Standardized lifestyle intervention was used across all treatment groups. CI, confidence interval; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol

**Supplemental Table 2. Percentage of Subjects Achieving Weight Loss Threshold and Treatment Comparisons
From Multiple Imputation at Week 108**

Parameter	Standardized Lifestyle Intervention Across All Treatment Groups					
	Placebo (n = 227)	Phentermine/ Topiramate CR 7.5/46 (n = 154)	<i>P</i> vs Placebo	Phentermine/ Topiramate CR 15/92 (n = 295)	<i>P</i> vs Placebo	<i>P</i> vs Phentermine/ Topiramate CR 7.5/46
≥ 5% weight loss	28.9%	74.3%	< 0.0001	79.7%	< 0.0001	< 0.0001
≥ 10% weight loss	11.6%	50.6%	0.0002	53.0%	< 0.0001	< 0.0001
≥ 15% weight loss	6.9%	23.8%	0.0028	31.6%	0.0009	< 0.0001
≥ 20% weight loss	2.1%	9.4%	0.0817	14.9%	0.0571	0.0030

Data represent percentage of subjects. Standardized lifestyle intervention was used across all treatment groups.

Supplemental Table 3. Least-Squares Mean (95% CI) Estimates and Treatment Comparisons for Completers on Study Drug at Week 108

	Standardized Lifestyle Intervention Across All Treatment Groups								
Parameter	n	Placebo	n	Phentermine/ Topiramate CR 7.5/46	<i>P</i> vs Placebo	n	Phentermine/ Topiramate CR 15/92	<i>P</i> vs Placebo	<i>P</i> vs Phentermine/ Topiramate CR 7.5/46
Percent weight loss	196	-2.2 (-3.3, -1.0)	125	-9.3 (-10.7, -7.8)	< 0.0001	240	-10.7 (-11.8, -9.7)	< 0.0001	0.0879
Waist circumference, cm	196	-4.1 (-5.3, -2.9)	125	-10.1 (-11.6, -8.6)	< 0.0001	240	-10.8 (-11.9, -9.7)	< 0.0001	0.4062
Systolic blood pressure, mm Hg	196	-3.1 (-4.9, -1.3)	125	-4.0 (-6.2, -1.8)	0.5130	240	-4.0 (-5.7, -2.4)	0.4101	0.9683
Diastolic blood pressure, mm Hg	196	-3.7 (-4.9, -2.5)	125	-3.6 (-5.1, -2.1)	0.9104	240	-3.2 (-4.3, -2.1)	0.4890	0.6267
Triglycerides, %	194	-1.8 (-7.2, -1.3)	125	-12.4 (-19.4, -5.4)	0.0113	240	-15.3 (-20.5, -10.1)	0.0001	0.4687

change		3.7)		-5.5)			-10.2)		
HDL-C, % change	194	5.4 (2.5, 8.4)	125	7.6 (3.9, 11.3)	0.3347	240	12.6 (9.9, 15.3)	0.0002	0.0203
LDL-C, % change	193	-11.0 (-14.2, -7.7)	123	-3.9 (-8.0, 0.2)	0.0046	238	-6.3 (-9.4, -3.3)	0.0272	0.3016
Non-HDL-C, % change	194	-10.2 (-13.0, -7.5)	125	-8.5 (-12.0, -5.1)	0.4263	240	-9.9 (-12.5, -7.4)	0.8696	0.4932

Data are LS mean change (95% CI) or LS mean percent change (95% CI). Standardized lifestyle intervention was used across all treatment groups. CI, confidence interval, HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol

Supplemental Table 4. Percentage of Subjects Achieving Weight Loss Threshold and Treatment Comparisons for Completers on Study Drug at Week 108

Parameter	Standardized Lifestyle Intervention Across All Treatment Groups					
	Placebo (n = 196)	Phentermine/ Topiramate CR 7.5/46 (n = 125)	<i>P</i> vs Placebo	Phentermine/ Topiramate CR 15/92 (n = 240)	<i>P</i> vs Placebo	<i>P</i> vs Phentermine/ Topiramate CR 7.5/46
≥ 5% weight loss	30.1%	73.6%	< 0.0001	81.3%	< 0.0001	0.0552
≥ 10% weight loss	12.2%	49.6%	< 0.0001	54.2%	< 0.0001	0.2921
≥ 15% weight loss	7.1%	24.0%	0.0001	32.5%	< 0.0001	0.0530
≥ 20% weight loss	2.0%	9.6%	0.0083	15.4%	< 0.0001	0.0846

Data represent percentage of subjects. Standardized lifestyle intervention was used across all treatment groups.

1 **Supplemental Figure 1. Weight loss by baseline BMI category.**

2 LS mean percent loss (95% CI) from baseline (Week 0) to Week 108. Standardized lifestyle intervention was used across
3 all treatment groups. * $P = 0.0061$ vs placebo; † $P = 0.0057$ vs placebo; ‡ $P < 0.0001$ vs placebo; § $P = 0.0001$ vs placebo.

4 BMI, body mass index; CI, confidence interval; LS, least-squares; PHEN/TPM CR, controlled-release

5 phentermine/topiramate.