

Weight Loss Achieved with Low-dose, Controlled-release Phentermine/Topiramate (PHEN/TPM CR) is Associated with Improved Blood Pressure, Lipid, and Glycemic Markers among Overweight or Obese Patients with Obesity-related Comorbidities

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OBJECTIVES

- Report outcomes from a Phase 3 randomized controlled study (CONQUER) of an investigational, low dose, controlled-release combination of phentermine hydrochloride and topiramate (PHEN/TPM CR) in two fixed doses for the treatment of overweight and obesity among adults with at least two well-controlled, obesity-related comorbid conditions
- Evaluate efficacy outcomes: weight loss and changes in obesity-related markers (blood pressure, lipids, and glycemic control)
- Estimate number needed to treat (NNT) to achieve at least a 5%, 10%, and 15% weight loss from treatment initiation to 56 weeks

BACKGROUND

OVERVIEW OF U.S. OBESITY EPIDEMIC

- Rates of obesity among U.S. adults are rising alarmingly
 - From 13.5% in 1987¹ to 33.8% in 2008²
- U.S. adult obesity prevalence is expected to reach
 - 41% within 5 years and exceed 51% by the year 2030³
- No state has met the *Healthy People 2010* Surgeon General's 15% obesity goal⁴
 - Adult obesity rates are ≥25% in 32 states⁴
- Obesity accounts for 9.1% (\$150 billion) in annual U.S. healthcare spending⁵
 - By 2030, obesity costs are expected to reach \$958 billion or 18% of healthcare spending³

OVERVIEW OF PHENTERMINE AND TOPIRAMATE

Phentermine (PHEN)⁶⁻⁹

- FDA approved (1959) as short-term adjunct to diet and exercise
- Stimulates hypothalamic neurons to release norepinephrine that may cause:
 - Appetite suppression by increasing blood leptin levels⁹
 - Decreased neuropeptide Y production, which may increase satiety and decrease appetite⁹
- Side effects at recommended dose (37.5 mg/day)

Topiramate (TPM)¹⁰⁻¹³

- Neurotherapeutic agent approved for seizure disorders (1996) and migraine headache prophylaxis (2004)
- Demonstrated weight loss in obese individuals
- Clinically meaningful improvements in glycemic control and blood pressure
- Associated with dose-limiting side effects, which prevent use as a single agent at the doses necessary to produce significant weight loss

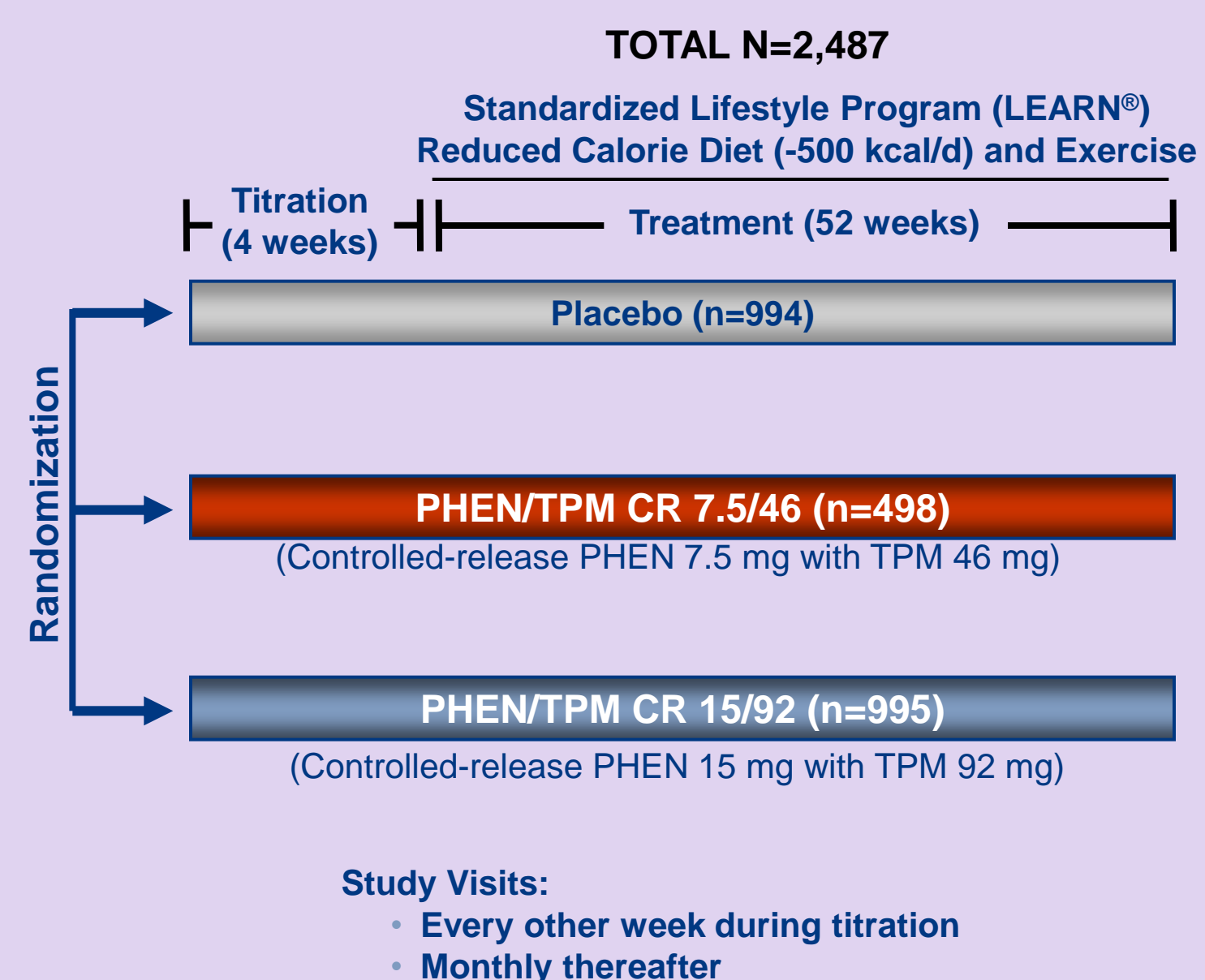
METHODS

Inclusion criteria:

- Age: 18-70
- BMI 27 to 47 kg/m² & ≥ 2 obesity-related comorbidities/risk factors (hypertension, hypertriglyceridemia, elevated fasting blood glucose or diabetes, and/or central adiposity)

Exclusion criteria:

- History of eating disorder, drug or ETOH abuse past year
- Bariatric surgery
- Hx bipolar disorder or psychosis, >1 episode major depression
- Suicidal behavior or ideation
- Antidepressant use not stable for > 3 months



Eligible subjects were randomized to receive daily treatment (1 capsule/morning) of:

- Placebo (PBO),
- Controlled-release PHEN 7.5 mg with TPM 46 mg (PHEN/TPM CR 7.5/46), or
- Controlled-release PHEN 15 mg with TPM 92 mg (PHEN/TPM CR 15/92)

All received lifestyle counseling for weight management

Subjects using medications for the treatment of obesity-related comorbidities (listed above) were required to be on stable doses for at least 1 month prior to screening

Changes in concomitant medications were allowed and determined by the investigator per standard of care guidelines

Subjects requiring insulin or whose comorbid condition could not be well controlled were discontinued from the study

RESULTS

Baseline Characteristics (N=2,448)		Study Completion Rates by Treatment Condition		
Age (years), mean (SD)	51.1 (SD 10.4)			
Female (%)	70%			
Caucasian (%)	86%			
Weight (kg), mean (SD)	103.1 (17.9)			
Waist circumference (cm), mean (SD)	113.2 (12.3)			
BMI (kg/m ²), mean (SD)	36.6 (4.5)			
HbA1c (mg/dL), mean (SD)	5.9 (0.8)			
Hypertension (%)	52.5%			
Hypertriglyceridemia (%)	36.2%			
Type 2 diabetes/ Impaired glucose tolerance (%)	67.9%			
		Placebo	PHEN/TPM CR 7.5/46	PHEN/TPM CR 15/92
Patients				
Randomized		994	498	995
ITT Population ¹		979	488	981
ITT (% of randomized)		99%	98%*	99%*
Completer Population ²		564	344	634
Completer (% of randomized)		57%	69%*	64%*

* Statistically greater number of patients completed study on PHEN/TPM CR 7.5/46 or PHEN/TPM CR 15/92 vs. placebo, p<0.0001

¹ ITT Population = randomized patients with at least one dose of therapy and one post randomization assessment

² Completer Population = randomized patients completing 56-week study on drug therapy

RESULTS (continued)

Both FDA efficacy benchmarks were satisfied at the lower and higher PHEN/TPM CR doses

FDA PRIMARY EFFICACY BENCHMARKS:	Placebo (n=979)	PHEN/TPM CR 7.5/46 (n=488)	PHEN/TPM CR 15/92 (n=981)
1) MEAN PERCENT WEIGHT LOSS AT 1 YEAR: Δ mean percent weight loss between groups ≥ 5% and statistically significant	1.8%	8.4%*	10.4%*
2) CATEGORICAL WEIGHT LOSS AT 1 YEAR: % Ss in active treatment losing ≥ 5% is ≥ 35% and is ~ 2 Xs placebo. Difference between active and placebo groups is statistically significant.	21%	62%*	70%*

*p<0.0001 vs. placebo

Blood pressure, lipid, and glycemic markers were significantly improved at one year with PHEN/TPM CR compared to placebo

OUTCOMES AT ONE YEAR		PHEN/TPM CR 7.5/46 versus Placebo	PHEN/TPM CR 15/92 versus Placebo
BLOOD PRESSURE	Systolic	↓	<0.0001
	Diastolic	↓	ns
LIPID MARKERS	Triglycerides	↓	<0.0001
	Total Cholesterol/HDL Ratio	↓	ns
	Total Cholesterol	↓	<0.0001
	LDL-C	↓	ns
GLYCEMIC MARKERS	HDL-C	↑	<0.0001
	Hemoglobin A1c	↓	<0.0001
	Fasting Blood Glucose	↓	0.0047
	Insulin Resistance (OGTT)	↓	0.0007
	Insulin Resistance (HOMA)	↓	<0.0001

Number Needed to Treat (NNT) at One Year to Lose:	PHEN/TPM CR 7.5/46		PHEN/TPM CR 15/92	
	NNT	95% CI, p-value	NNT	95% CI, p-value
≥5% from Baseline Weight	3	2.0-2.5, <0.0001	2	1.8-2.1, <0.0001
≥10% from Baseline Weight	4	2.8-3.9, <0.0001	3	2.2-2.6, <0.0001
≥15% from Baseline Weight	6	4.9-7.6, <0.0001	4	3.4-4.2, <0.0001

CONCLUSIONS

In this large randomized, controlled trial, significant weight loss with low dose, PHEN/TPM CR was associated with clinically meaningful improvements in blood pressure, lipid, and glycemic markers. Given that subject inclusion criteria required that comorbid conditions remain well controlled, and that these comorbidities were carefully assessed and treated to standard of care throughout the study, the effect of treatment on these markers may be even greater in "real world" settings. NNT analyses consistently demonstrated the compelling benefits of PHEN/TPM CR on weight loss at 56 weeks.

DISCLOSURE

Authors of this presentation have the following to disclose concerning possible financial or personal relationships with commercial entities that may have a direct or indirect interest in the subject matter of this presentation:
Barbara Troupin: Employee VIVUS, Inc. **Cheryl Hankin:** Consultant to VIVUS, Inc.

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