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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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Purpose: We report outcomes from a Phase 3 randomized controlled study (CONQUER) of a low dose, controlled-release combination of phentermine hydrochloride (PHEN) and topiramate (TPM) in two fixed doses for the treatment of overweight and obesity among adults with at least two well-controlled, obesity-related comorbid conditions. Efficacy endpoints included weight loss and changes in obesity-related markers (blood pressure, lipids, and glycemic control). We also estimated the number needed to treat (NNT) to achieve at least a 5%, 10%, and 15% weight loss from treatment initiation to 56 weeks.

Methods: This randomized, double-blind, placebo-controlled study consisted of a 2-week screening period followed by a 56-week treatment period (4-week titration and 52-week fixed-dose). Subjects were males and females aged 18 to 70 years (inclusive) with Body Mass Index (BMI) between 27 to 45 kg/m² (inclusive) and at least two of the following obesity-related comorbid conditions: hypertension (elevated blood pressure or controlled blood pressure using at least two antihypertensives), hypertriglyceridemia (elevated fasting triglycerides or controlled using at least two antilipidemics), elevated fasting blood glucose or diabetes (diet and exercise controlled or treated with metformin only), and/or central adiposity (waist circumference ≥ 102 cm for men or ≥ 88 cm for women). Eligible subjects were randomized to receive daily treatment (one capsule each morning) of controlled-release PHEN 15 mg with TPM 92 mg (PHEN/TPM 15/92 CR), controlled-release PHEN 7.5 mg with TPM 46 mg (PHEN/TPM 7.5/46 CR), or placebo (PBO); randomization was stratified by gender and diabetes status across treatment groups. All subjects were counseling at monthly study visits on a lifestyle program for weight management including caloric reduction and increased physical activity. Visits took place at the end of weeks 2 and 4, and at 4-week intervals thereafter. Subjects using medications for the treatment of obesity-related comorbidities listed above were required to be on stable doses for at least one month prior to screening; changes in concomitant medications were allowed and determined by the investigator per standard of care guidelines; subjects who required insulin or whose comorbid condition could not be well controlled were discontinued from study treatment. Efficacy analyses are reported for the modified intent-to-treat (ITT) population, defined as all randomized subjects who provided a baseline measurement of body weight, received at least one dose of study drug, and had at least one post-dose assessment of body weight within 7 days of the last dose of study drug. For subjects who did not return at Week 56, the last post-dose assessment was carried forward to the Week 56 time point. Least squares (LS) mean, SE, 95% CI and two-sided p-values for percent of change from baseline were calculated from an analysis of covariance model with treatment, gender, and diabetic status as fixed effects and baseline weight as a covariate.

Results: Among 2,448 subjects in the ITT population, 981 were randomized to receive PHEN/TPM 15/92 CR, 488 to PHEN/TPM 7.5/46 CR, and 979 to placebo. Overall, mean age was 51.1 years (SD 10.4), 30.2% were male, and 86% Caucasian. Mean baseline weight was 103.1 kg (SD 17.9), waist circumference was 113.2 cm (12.3), BMI was 36.6 kg/m² (SD 4.5), and glycosylated hemoglobin (HbA1c) was 5.9 mg/dL (SD 0.8). At study initiation, more than one half (52.5%) of all subjects met criteria for comorbid hypertension, 36.2% for hypertriglyceridemia, and over two thirds (67.9%) diabetes and/or impaired glucose tolerance. The most common adverse events were tingling, constipation and dry mouth. Most events were assessed as mild by the investigator.

Subjects receiving the full and lower dose of PHEN/TPM CR had a 9.8% (10.2 kg) and 7.8% (8.1 kg) weight loss, respectively, which were significantly ($p < 0.05$) greater than the weight loss achieved by the placebo group (1.8%; 1.4 kg). At Week 56, systolic and diastolic blood pressure were significantly ($p < 0.05$) reduced (-5.6 mmHg and -3.8 mmHg, respectively) among subjects who received the full dose of PHEN/TPM CR, and systolic blood pressure was significantly reduced among subjects who received the lower dose of PHEN/TPM CR (-4.7 mmHg and -3.4 mmHg), compared with placebo (-2.4 mmHg and -2.7 mmHg). Significantly greater reductions in triglycerides (-10.6% vs. +4.7%), total cholesterol (-6.3% vs. -3.3%), and LDL-C (-6.9% vs. -4.1%) were observed in the full dose PHEN/TPM CR compared with the placebo group ($p < 0.05$ for all comparisons) at Week 56; HDL-C was significantly increased in the full dose treatment compared with the placebo group (6.8% vs. 1.2%, $p < 0.05$). Lower dose PHEN/TPM CR also resulted in significantly greater reductions in triglycerides and total cholesterol, and an increase in HDL-C, compared with placebo. Subjects who received the full dose of PHEN/TPM CR had significantly improved glycemic control, as evidenced by a greater reduction in HbA1c compared with placebo at Week 56 (-0.1% vs. +0.1%, $p < 0.05$).

Based on number needed to treat analysis, at the full dose, 1 of 2 (95% CI 1.8 to 2.1, $p < 0.0001$) overweight/obese patients can be expected to lose at least 5%, 1 of 3 (95% CI, 2.2 to 2.6, $p < 0.0001$) at least 10%, and 1 of 4 (95% CI, 3.4 to 4.2, $p < 0.0001$) at least 15% of baseline weight at 56 weeks. At the lower dose, an estimated 1 of 3 (95% CI 2.0 to 2.5, $p < 0.0001$) overweight/obese patients can be expected to lose at least 5%, 1 of 4 (95% CI, 2.8 to 3.9, $p < 0.0001$) at least 10%, and 1 of 6 (95% CI, 4.9 to 7.6, $p < 0.0001$) at least 15% of baseline weight at 56 weeks.

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.