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ORIGINAL ARTICLE

Evaluation of the efficacy and safety of controlled-release phentermine/topiramate in adults with obesity in Korea: A randomized, double-blind, placebo-controlled, phase 4 trial (QUEEN's study)

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Abstract

Aims: This study evaluated the efficacy and safety of a combination of phentermine and delayed-release topiramate (PHEN/TPM CR) versus placebo as an adjunct to standard lifestyle recommendations in Korean adults.

Materials and Methods: This 56-week, randomized, double-blind, placebo-controlled, phase 4 trial enrolled adults (age 19–70 years) with obesity (BMI ≥ 25 kg/m^2) at eight sites in South Korea. After a 12-week lifestyle programme, participants were randomly assigned in a 1:1 ratio to receive PHEN/TPM CR or placebo. PHEN/TPM CR was commenced at 3.75 mg/23 mg daily for 14 days and increased to 7.5 mg/46 mg daily, and to 15 mg/92 mg if 3% weight loss was not achieved after 12 weeks. The primary outcomes were percentage change in body weight from baseline to Week 56.

Results: A total of 232 participants underwent randomization. At 56 weeks, the percentage change in body weight was −8.3% with PHEN/TPM CR and −2.3% with placebo (treatment difference −6.1%; 95% confidence interval [CI], −7.7 to −4.5, $p < 0.001$). Participants receiving PHEN/TPM CR were more likely to achieve ≥5% weight loss compared with those receiving placebo (68.5% vs. 25.0%, odds ratio [OR], 6.4; 95% CI, 3.5 to 11.6; $p < 0.001$). Dizziness, paraesthesia and dry mouth were more common in the PHEN/TPM CR group, although most adverse events were mild or moderate.

Conclusions: Administration of PHEN/TPM CR plus lifestyle intervention in Korean adults with obesity resulted in a greater reduction in body weight and adiposity than lifestyle intervention alone.

KEYWORDS
antiobesity drug, body composition, clinical trial, obesity therapy, phase IV study

1 | INTRODUCTION

Obesity is a chronic disease associated with hypertension, dyslipidaemia and type 2 diabetes mellitus, conditions that increase cardiovascular morbidity and mortality.[1] The World Health Organization defines obesity as body mass index (BMI) ≥ 30 kg/m^2.[2] However, the Korean Society for the Study of Obesity (KSSO) defines obesity in Korean people as a BMI ≥ 25 kg/m^2 based on a substantial increase in obesity-related diseases.[3] The latest version of the KSSO clinical practice guidelines for obesity recommends that pharmacotherapy should be considered in Korean adults with BMI ≥ 25 kg/m^2 who have failed to lose weight with non-medicinal treatment such as diet, exercise and behavioural therapies.[4]

A low fixed-dose phentermine plus controlled-release topiramate (PHEN/TPM CR, Qsymia™) therapy combines phentermine, an appetite suppressant for short-term use, with topiramate, a neurotherapeutic medication.[5] Phase 3 clinical trial results have revealed that PHEN/TPM CR is a clinically effective long-term treatment for obesity.[6,7] In the United States, PHEN/TPM CR was approved by the Food and Drug Administration in 2012 for obesity treatment in adults with BMI ≥ 30 kg/m^2 or ≥27 kg/m^2 in the presence of at least one weight-related comorbidity such as hypertension, type 2 diabetes mellitus or dyslipidemia.[8] PHEN/TPM CR has been available in South Korea since 2020 for the same indications, based on phase 3 trial results.[6,7] However, in South Korea, less than 50% of individuals with BMI ≥ 25 kg/m^2 who have failed to lose weight with non-medicinal treatment have access to PHEN/TPM CR due to this indication.[9] Furthermore, the studies conducted for the approval of PHEN/TPM CR included a low percentage (≤1%) of Asian participants.[6,7] In the present study, we evaluated the efficacy and safety of PHEN/TPM CR versus placebo as an adjunct to standard lifestyle recommendations over 56 weeks in Korean adults with BMI ≥ 25 kg/m^2.

2 | MATERIALS AND METHODS

2.1 | Study design and participants

This randomized, double-blind, placebo-controlled, phase 4 trial was conducted at eight sites in South Korea in accordance with the principles of the International Declaration of Helsinki 2013[10] and the International Conference on Harmonization Good Clinical Practice guidelines.[11] The study protocol was approved by the relevant institutional review board or independent ethics committee at each study site. Adults (aged 19–70 years) with BMI ≥ 25 kg/m^2 were eligible to participate.[3] Detailed inclusion and exclusion criteria are provided in Supplement 1.

2.2 | Randomization

Eligible participants were randomly assigned at a 1:1 ratio to once-daily treatment with placebo and once-daily controlled-release combination of phentermine plus topiramate for 56 weeks with standardized counselling for diet and lifestyle modifications. Randomization was performed centrally on the trial's website with the use of a blocked randomization scheme using SAS statistical software (version 9.4, SAS Institute Inc., Cary, NC, USA). An independent statistical expert, not affiliated with the study, created the randomization table. Investigators, participants and study sponsors were masked to treatment assignment. The study drugs were administered as capsules that were identical in size and appearance (ClinicalTrials.gov Identifier: NCT05378503; https://clinicaltrials.gov/study/NCT05378503).

2.3 | Procedures

Individuals who agreed to participate in the study underwent screening tests. Eligible participants underwent a 12-week lifestyle programme. The dietary intervention aimed for a daily 500 kcal deficit compared with the estimated total daily energy expenditure, which was calculated at the time of randomization. The exercise intervention consisted of moderate or high-intensity exercise (including fast walking, swimming, jogging, biking, aerobics, climbing and other sports) at least five times per week for 30–60 min per session. After the 12-week lifestyle programme, we started PHEN/TPM CR or placebo according to 'recommended dosage and administration of PHEN/TPM CR' from FDA.[8] The 3.75 mg phentermine/23 mg controlled-release topiramate (PHEN/TPM CR 3.75/23) or placebo was administered to participants with failure to lose at least 3% of their body weight for 12 weeks. At week 2, 7.5 mg phentermine/46 mg controlled-release topiramate (PHEN/TPM CR 7.5/46) or placebo was administered to participants until Week 14. At Week 14, participants with failure to lose at least 3% of their body weight received 11.25 mg phentermine/69 mg controlled-release topiramate (PHEN/TPM CR 11.25/69) or placebo until Week 16. At Week 16, 15 mg phentermine/92 mg controlled-release topiramate (PHEN/TPM CR 15/92) or placebo was administered to participants until Week 56. However, PHEN/TPM CR 7.5/46 or placebo was continued until Week 56 in participants with loss of at least 3% of their body weight by Week 14 (Figure S1). All the participants underwent a lifestyle intervention, including regular counselling sessions on diet and exercise. At Week 14 (Visit 3), Week 28 (Visit 4), Week 42 (Visit 5) and Week 56 (Visit 6), the participants attended the clinical trial site for testing to evaluate the efficacy and safety of PHEN/TPM CR. Height, body weight, waist circumference (WC) and vital signs (systolic and diastolic blood pressure, body temperature, and heart rate) were measured at baseline and each visit. Additionally, fertile females underwent pregnancy tests at each visit.

2.4 | Study outcomes

The primary outcome was the percent change in body weight from baseline assessed at Week 56. The secondary outcomes were the

proportion (%) of participants with ≥5% or ≥10% body weight change, and changes from baseline in body weight, BMI, WC, heart rate and blood pressure at Weeks 14, 28, 42 and 56. Exploratory outcomes included the change from baseline in body composition (body fat percentage and visceral fat area) measured using bioelectrical impedance analysis (BIA) with the same equipment used at the study site, blood lipid profile, HbA1c level, fasting blood glucose (FBG) level, fasting insulin level and homeostatic model assessment of insulin resistance (HOMA-R). Safety outcomes included the incidence of adverse events and serious adverse events based on vital signs, laboratory parameters, electrocardiogram results and physical examination.

2.5 | Sample size

Power analysis based on previously reported data[6,7] suggested that 113 participants in each group would provide >95% power to detect a 5.33% difference in the percent change of body weight between placebo and PHEN/TPM CR assuming a standard deviation (SD) of 8.93, a two-sided significance level of $\alpha = 0.05$, and an estimated 35% of loss to follow-up (Supplementary 1).

2.6 | Statistical analysis

The safety set consisted of all participants who received at least one dose of the clinical trial drug. The full analysis set (FAS), the main analysis set of the efficacy assessment, followed the intention-to-treat (ITT) principle and comprised participants who were measured at least once for the primary efficacy endpoint after the start of the investigational product. The per-protocol set (PPS) comprised participants who completed the clinical trial with no major protocol deviations. The last observation carried forward (LOCF) method was applied to the ITT analysis to impute the missing values of the primary efficacy endpoint. When the LOCF method was not applicable, the original data were used without imputation. If the value immediately before the missing value was the baseline value, it was not imputed. Sensitivity analysis was defined as the modified PPS, and the results of both applying and not applying the LOCF to the primary efficacy endpoint only are presented. Other analyses for the secondary outcomes, exploratory outcomes and safety outcomes were conducted using original data without correction for missing values. If a visit date was an outlier of the planned visit window, the measured of that visit was processed as missing. Comparisons between the administration groups for efficacy and exploratory endpoints were performed using the analysis of covariance, including baseline values as covariates, using the PROC MIZED procedure of the SAS program (SAS® Enterprise Guide [version 8.2 or higher] interface, 9.4 64bit [SAS Institute Inc., Cary, NC, USA] or higher). All results from statistical analyses are accompanied by two-sided 95% confidence intervals and the corresponding p values (with significance defined as $p < 0.05$).

3 | RESULTS

The study was undertaken between September 17, 2021, and October 31, 2023. A total of 290 individuals were screened. The percentage change in body weight from screening at baseline after a 12-week lifestyle programme was −0.16% ± 2.75%. Of these, 232 were randomly assigned to placebo ($n = 116$) or PHEN/TPM CR ($n = 116$, Figure 1). Among them, 67 (28.9%) discontinued the study drugs (35 [30.2%], placebo group; 32 [27.6%], PHEN/TPM CR group). Discontinuation rates were similar between the groups, with the most common reason for discontinuation being withdrawal of consent.

3.1 | Baseline characteristics

There were no significant differences in baseline demographic or clinical characteristics between the groups (Table 1). The mean age was 43.4 years, mean body weight was 83.9 kg and mean BMI was 30.4 kg/m^2. Overall, 64.7% of participants were females. All participants were Asian. Coexisting conditions included type 2 diabetes (17.7% of participants), impaired fasting glucose tolerance (5.6%) and hypertension (23.3%). Baseline demographic or clinical characteristics were similar for ITT (Table S1) and PPS (Table S2).

3.2 | Primary outcome

The percent change in body weight at week 56 was significantly greater in the PHEN/TPM CR group (least-squares mean ± standard error: −8.3% ± 0.6%) than in the placebo group (−2.3% ± 0.6%; treatment difference −6.1% ± 0.8% [95% CI −7.7 to −4.5], $p < 0.001$; Figure 1). The PHEN/TPM CR group exhibited a significantly greater percent change in body weight at Weeks 14, 28 and 42 than the placebo group (all $p < 0.001$; Figure 1, Table S3). Similar findings were observed in the PPS analysis (Table S4). In the subgroup analyses by age, sex, baseline BMI, diabetes, hypertension and final dose (Figure S2), PHEN/TPM CR resulted in greater weight loss than the placebo.

3.3 | Secondary outcomes

At Week 56, the PHEN/TPM CR group showed a significantly greater change in body weight (−6.8 ± 0.5 kg) than the placebo group (−1.8 ± 0.5 kg; treatment difference −5.0% ± 0.7%; 95% confidence interval [CI] −6.4 to −3.7, $p < 0.001$, Table 2). Participants were more likely to lose at least 5% of their baseline body weight with PHEN/TPM CR (68.5%) than with placebo (25%, odds ratio [OR], 6.4; 95% CI, 3.5–11.6; $p < 0.001$; Table 2, Figure 2). Participants were more likely to lose at least 10% of their baseline body weight with PHEN/TPM CR (34.2%) than with placebo (6.5%, OR, 7.4; 95% CI, 3.1–17.6; $p < 0.001$; Table 2, Figure 2). Similar results were observed in the PPS

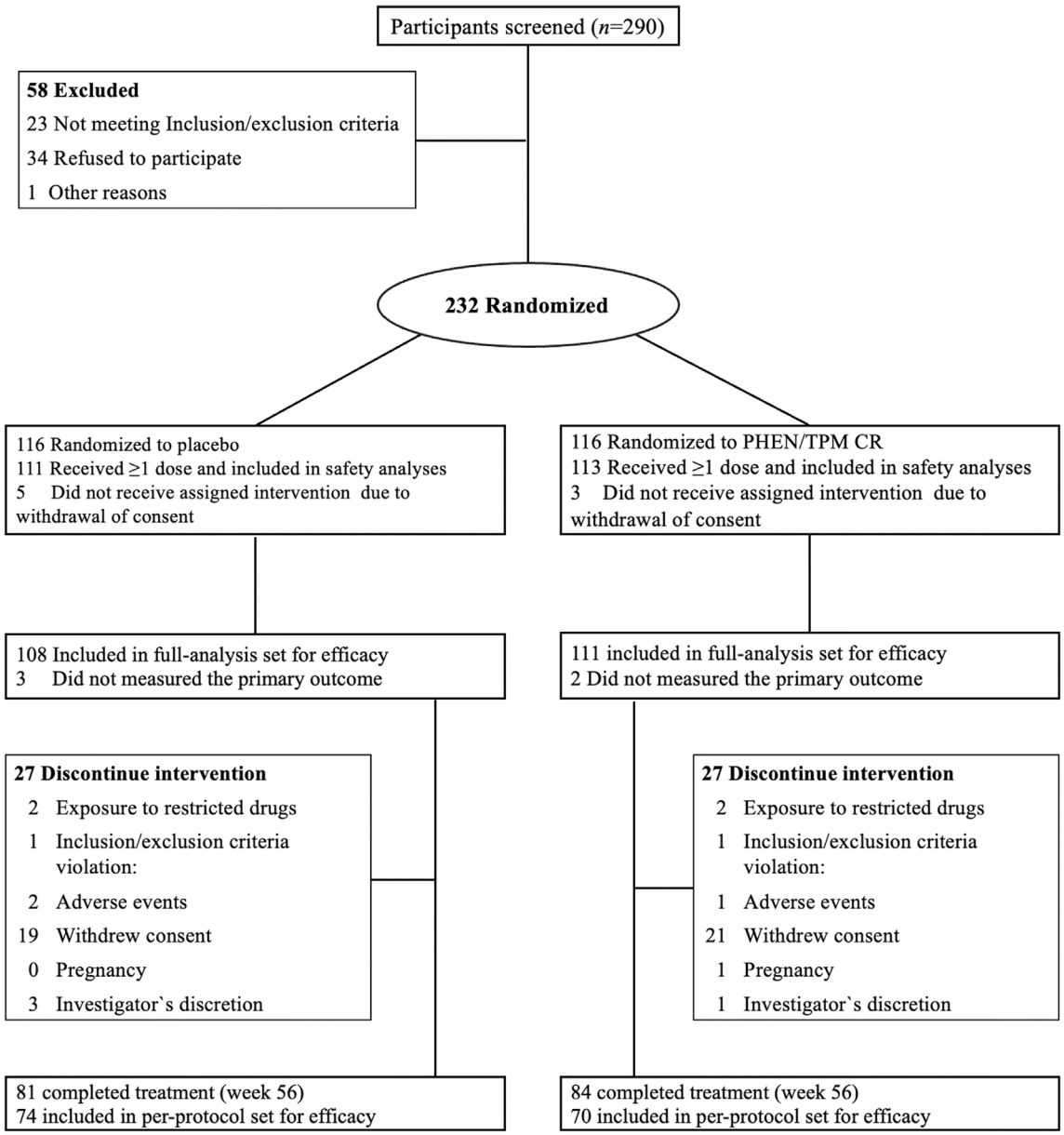


FIGURE 1 CONSORT (Consolidated Standards of Reporting Trials) diagram. After screening, all eligible participants underwent 56 weeks of treatment.

analysis (Table S4, Figure S3). Changes in BMI were −0.7 ± 0.2 kg/m^2 in the placebo group and −2.5 ± 0.2 kg/m^2 in the PHEN/TPM CR group. The treatment difference for placebo versus PHEN/TPM CR was −1.9 kg/m^2 (95% CI −2.4 to −1.4, $p < 0.0001$; Table 2). Treatment with PHEN/TPM CR (−6.4 ± 0.8 cm) was also associated with greater reduction in WC than with placebo (−3.1 ± 0.8 cm; treatment difference: −3.3 cm [95% CI −5.6 to −1.0], $p < 0.0048$; Table 2). Treatment with PHEN/TPM CR was associated with an increase in heart rate (treatment difference: 3.2 beat per minute [95% CI 0.2–6.2], $p = 0.0367$) and diastolic blood pressure (treatment difference: 3.0 mmHg [95% CI 0.6–5.4], $p = 0.0155$) compared with placebo at Week 56. However, there was no significant difference between the groups in systolic blood pressure ($p = 0.201$, Table 2). According to the final dose of PHEN/TPM CR at Week 56, there was only significant treatment difference according to the final dose of PHEN/TPM CR between placebo versus PHEN/TPM CR 15 mg/92 mg in pulse rate and placebo versus PHEN/TPM CR 7.5 mg/46 mg in diastolic pressure (Table S4). And the percent change in body weight was only significant correlation with systolic blood pressure change in the placebo group ($r = 0.250$, $p = 0.032$) and the PHEN/TPM CR group ($r = 0.318$, $p = 0.006$), and diastolic blood pressure in the placebo group ($r = 0.254$, $p = 0.029$), but not with diastolic blood pressure in the PHEN/TPM CR group ($p = 0.157$) and pulse rate both placebo and PHEN/TPM CR group ($p = 0.596$ and $p = 0.780$, respectively). The findings for secondary outcomes in the PPS analysis were similar to those in the ITT analysis (Table S5).

TABLE 1 Participant characteristics at baseline.

	Placebo ($N = 116$)	PHEN/TPM CR ($N = 116$)	Total ($N = 232$)
Age, years	42.1 ± 10.8	44.8 ± 10.8	43.4 ± 10.8
Sex, *n* (%)			
Female	76 (65.5)	74 (63.8)	150 (64.7)
Male	40 (34.5)	42 (36.2)	82 (35.3)
Ethnic origin, *n* (%)			
Asian	116 (100)	116 (100)	232 (100)
Body weight, kg	85.5 ± 17.3	82.4 ± 14.6	83.9 ± 16.1
Height, cm	166.7 ± 9.3	164.7 ± 7.9	165.7 ± 8.7
BMI, kg/m^2	30.6 ± 4.4	30.2 ± 4.0	30.4 ± 4.2
BMI group, *n* (%)			
25–26.9 kg/m^2	25 (21.6)	26 (22.4)	51 (22.0)
27–29.9 kg/m^2	42 (36.2)	39 (33.6)	81 (34.9)
30–34.9 kg/m^2	30 (25.9)	39 (33.6)	69 (29.7)
≥35 kg/m^2	19 (16.4)	12 (10.3)	31 (13.4)
Waist circumference, cm	98.8 ± 10.5	98.0 ± 10.8	98.4 ± 10.6
≥90 cm (male) and ≥85 cm (female), *n* (%)	101 (91.0)	100 (88.5)	201 (89.7)
Blood pressure, mmHg			
Systolic	129.0 ± 13.5	127.6 ± 12.1	128.3 ± 12.8
Diastolic	79.3 ± 9.7	79.1 ± 9.4	79.2 ± 9.5
Heart rate, beats per minute	78.9 ± 8.7	79.3 ± 11.3	79.1 ± 10.0
Lipid levels, mg/dL			
Total cholesterol	185.6 ± 41.1	188.9 ± 35.7	187.3 ± 38.5
HDL cholesterol	50.2 ± 12.8	51.4 ± 11.5	50.8 ± 12.2
LDL cholesterol	114.7 ± 34.4	116.7 ± 36.0	115.7 ± 35.1
Triglycerides	158.74 ± 119.47	163.50 ± 125.84	161.14 ± 122.47
Creatinine clearance, mL/min	144.0 ± 44.0	134.9 ± 39.7	139.4 ± 42.1
Estimated GFR—mL/min/1.73 m^2	97.9 ± 17.3	96.7 ± 19.4	97.3 ± 18.3
Glycated haemoglobin, %	5.8 ± 0.7	5.8 ± 0.7	5.8 ± 0.7
Fasting blood glucose, mg/dL	109.9 ± 23.6	109.6 ± 19.0	109.8 ± 21.4
Fasting insulin, μU/mL	15.2 ± 13.5	13.0 ± 7.1	14.1 ± 10.8
Coexisting conditions, *n* (%)			
Type 2 diabetes	22 (19.0)	19 (16.4)	41 (17.7)
Impaired fasting glucose	5 (4.3)	8 (6.9)	13 (5.6)
Hypertension	27 (23.3)	27 (23.3)	54 (23.3)

Abbreviations: BMI, body mass index; GFR, glomerular filtration rate; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

3.4 | Exploratory end points

There was no significant difference in lipid-level changes, fasting insulin and HOMA-IR at Week 56 between the groups (Table 2). However, PHEN/TPM CR was associated with improvement in glucose metabolism including HbA1c ($p = 0.010$), and FBG ($p = 0.041$) compared with placebo at Week 56. In the subset of participants undergoing BIA ($n = 85$), reductions in abdominal visceral fat area (treatment difference: −27.0 cm^2 [95% CI −43.9 to −10.2], $p = 0.002$) and body fat percentage (treatment difference: −4.0% [95% CI −6.3 to −1.7], $p < 0.001$) from baseline to Week 56 were greater in the PHEN/TPM CR group ($n = 41$) than in the placebo group ($n = 44$).

3.5 | Safety

Adverse events were observed in 67 of the 113 participants (59.3%) in the PHEN/TPM CR group, and 42 of the 111 participants (37.8%) in the placebo group ($p = 0.001$). Dizziness, paraesthesia and dry mouth were observed more frequently in the PHEN/TPM CR group than in the placebo group (Table 3). Most adverse events were mild or

TABLE 2 Primary, secondary and exploratory outcomes at Week 56 from baseline for intention to treat population.

End point	Placebo ($N = 108$)	PHEN/TPM CR ($N = 111$)	Difference, Placebo versus PHEN/TPM CR (95% CI)	*p* value
Primary outcome				
Change in % body weight	−2.3 (0.6)	−8.3 (0.6)	−6.1 (−7.7 to −4.5)	<0.0001
Secondary outcome				
Change in body mass index, kg/m^2	−0.7 (0.2)	−2.5 (0.2)	−1.9 (−2.4 to −1.4)	<0.0001
Change in body weight, kg	−1.8 (0.5)	−6.8 (0.5)	−5.0 (−6.4 to −3.7)	<0.0001
Change in waist circumference, cm	−3.1 (0.8)	−6.4 (0.8)	−3.3 (−5.6 to −1.0)	0.0048
Change in heart rate, per minute	−0.4 (1.1)	2.8 (1.1)	3.2 (0.2–6.2)	0.0367
Change in systolic blood pressure, mmHg				
Systolic blood pressure, mmHg	0.2 (1.2)	−1.9 (1.2)	−2.1 (−5.3 to 1.1)	0.2011
Diastolic blood pressure, mmHg	−1.0 (0.9)	2.0 (0.9)	3.0 (0.6–5.4)	0.0155
			Odds ratio, (95% CI)	
≥5% body weight reduction	27/108 (25.0)	76/111 (68.5)	6.41 (3.5–11.6)	<0.0001
≥10% body weight reduction	7/108 (6.5)	38/111 (34.2)	7.43 (3.1–17.6)	<0.0001
Exploratory outcome			**Difference, Placebo versus PHEN/TPM CR (95% CI)**	
Change in visceral fat area by BIA, cm^2	11.4 (5.9)	−15.6 (6.1)	−27.0 (−43.9 to −10.1)	0.002
Change in body fat percentage by BIA, %	0.7 (0.8)	−3.3 (0.8)	−4.0 (−6.3 to −1.7)	<0.001
Change in lipid levels				
Total cholesterol, mg/dL	−3.4 (3.1)	−4.5 (3.1)	−1.1 (−9.8 to 7.7)	0.804
HDL cholesterol, mg/dL	3.9 (0.9)	5.0 (0.9)	1.1 (−1.4 to 3.6)	0.387
LDL cholesterol, mg/dL	−4.8 (2.8)	−5.2 (2.8)	−0.4 (−8.2 to 7.5)	0.922
Triglycerides, mg/dL	−17.2 (8.3)	−34.0 (8.3)	−16.8 (−39.9 to 6.3)	0.153
Change in glucose metabolism				
HbA1c, %	−0.08 (0.04)	−0.21 (0.04)	−0.13 (−0.23 to −0.03)	0.010
Fasting blood glucose, mg/dL	−2.1 (1.5)	−6.3 (1.5)	−4.3 (−8.4 to 0.2)	0.041
Fasting insulin, μU/mL	−1.8 (0.9)	−3.4 (0.9)	−2.3 (−4.8 to 0.2)	0.072
HOMA-IR	−0.3 (0.3)	−1.0 (0.3)	−0.7 (−1.4 to 0.00)	0.063

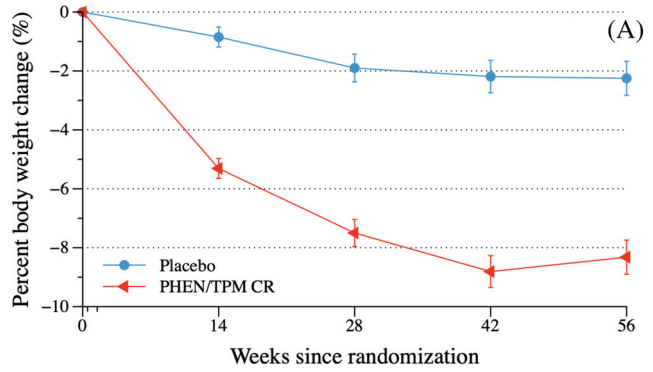
Abbreviations: BIA, bioelectrical impedance analysis; HDL, high-density lipoprotein; HOMA-IR, homeostatic model assessment of insulin resistance; LDL, low-density lipoprotein.

moderate in severity. However, three serious adverse events were observed only in the PHEN/TPM CR group (ankle fracture, missed abortion and ovarian cyst). Missed abortion and ovarian cyst were assessed by the site investigator as related to the trial treatment. A similar percentage of participants with discontinuation of the trial regimen because of adverse events was observed in both groups ($p = 0.620$, Table 3). No fatal adverse events were reported.

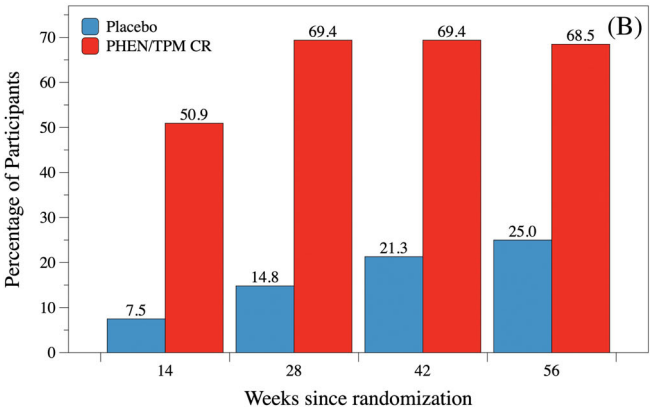
4 | DISCUSSION

This trial revealed that PHEN/TPM CR treatment led to a greater reduction in body weight and adiposity compared with placebo in Korean adults with obesity. PHEN/TPM CR was also linked to improvements in cardiometabolic risk factors such as high blood glucose level and abdominal obesity. These results were consistent regardless of the analytic method employed or the subgroups analysed. This study also demonstrated the safety of PHEN/TPM CR.

We observed that the efficacy of PHEN/TPM CR on weight loss in present study was consistent with previous phase 3 studies, although the participants in the present study had a lower mean BMI (30.4 kg/m^2) than those in previous phase 3 studies (36.6 and 42.0 kg/m^2).[6,7] The −8.3% change in body weight at Week 56 was observed among the PHEN/TPM CR group in this study, compared with −7.8% with 7.5 phentermine/46 mg controlled-release topiramate (7.5/46) or −9.8% with 15 mg phentermine/92 mg controlled-release topiramate (15/92) in CONQUER study, and −10.9% with 15/92 in EQUIP study.[6,7] Furthermore, the percentage of participants achieving weight reduction of ≥5% or ≥10% was 68.5% and 34.2%, respectively, comparable with the results of previous studies



No. of participants	Baseline	Week 14	Week 28	Week 42	Week 56
Placebo	108	107	108	108	108
PHEN/TPM CR	111	108	111	111	111



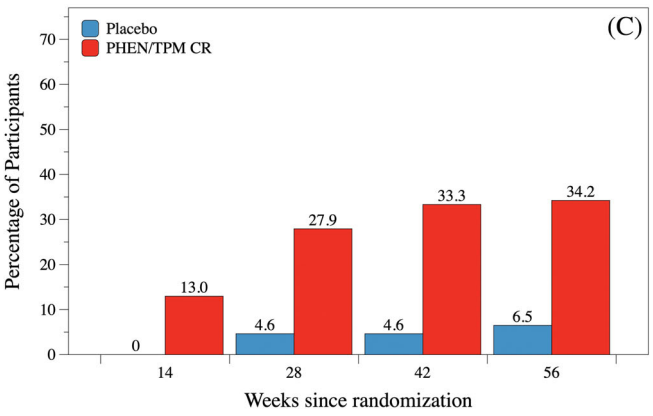


FIGURE 2 Effects of phentermine plus controlled-release topiramate on body weight for intention to treat population. (A) Percent body weight change from baseline to Week 56 (least-squares mean ± standard error). (B) ≥5% weight loss. (C) ≥10% weight loss.

(62% and 37%, respectively with 7.5/46 in CONQUER study).[6] Previous phase 3 studies did not show the result of body composition change after PHEN/TPM CR treatment, but our study showed a greater reduction in body fat percentage in the PHEN/TPM CR group than in the placebo group. Our results suggest that PHEN/TPM CR is an effective treatment for obesity in the Asian population, characterized by a relatively lower BMI than the western population.

PHEN/TPM CR was associated with improvements in cardiovascular and metabolic risk factors, such as WC, visceral fat area, HbA1c level and FBS level. Excess visceral fat is linked to metabolic and cardiovascular diseases.[12] A recent study reported that the reliability of BIA for the assessment of visceral fat area was satisfactory when compared with measurements using CT.[13–15] Previous studies have shown a significant reduction in WC in the PHEN/TPM CR group compared with that in the placebo group.[6,7] The present study demonstrated a reduction in WC and also in visceral fat area in the PHEN/TPM CR group compared with those in the placebo group. PHEN/TPM CR was associated with improvement in blood pressure and lipid, HbA1c, and fasting glucose levels, and HOMA-IR in the CONQUER study,[6] and with improvement in diastolic BP and fasting glucose, LDL cholesterol, HDL cholesterol and total cholesterol levels in the EQUIP study.[7] In the present study, PHEN/TPM CR was also associated with improvement in HbA1c and FBS levels. However, there was no significant improvement in lipid and fasting insulin levels, and HOMA-IR. This finding could be attributed to the lower number of participants ($n = 219$) in the present study than those in the aforementioned studies.[6,7] Substantial improvements in lipid and fasting insulin levels, and HOMA-IR from baseline to Week 56 were observed in the PHEN/TPM CR group (Table S5). The sympathomimetic action of phentermine has been associated with elevated blood pressure and heart rate.[16] However, large phase 3 trials have reported that PHEN/TPM CR is associated with a reduction in blood pressure and a dose-dependent increase in heart rate.[6,7] Similarly, the present study showed that PHEN/TPM CR was associated with a small to modest dose-dependent increase in heart rate. Although there was a small to modest increase in diastolic blood pressure (3.0 mmHg) without dose dependence compared with placebo, the reduction in body weight was positively associated with the reduction of systolic blood pressure in the PHEN/TPM CR group in this study.

In this study, the safety profile of PHEN/TPM CR among Korean adults with obesity was consistent with that observed among Western populations with obesity.[6,7] The frequency of adverse events occurring with PHEN/TPM CR was higher than that observed with placebo, and certain adverse events (dizziness [11.5%], paraesthesia [10.6%] and dry mouth [10.6%]) occurred more frequently in the PHEN/TPM CR group than in the placebo group. And these high number of adverse events with PHEN/TPM CR were predictable with those of the constituent drugs (phentermine and topiramate). Although this study was conducted during the COVID-19 pandemic, the incidence of COVID-19 infection was similar between the placebo group (8.1%) and the PHEN/TPM CR group (5.3%, $p = 0.402$). Most drug-related adverse events and Covid-19 infection were mild or moderate in severity and did not lead to trial product discontinuation. These findings indicated that PHEN/TPM CR is well tolerated in the Korean population with obesity. Additionally, there were no fatal adverse events.

The strengths of our study include the randomized, double-blind, placebo-controlled, multicentre design. Notably, this is the first trial to assess the efficacy and safety of PHEN/TPM CR in an Asian population with BMI ≥ 25 kg/m^2. Further strengths are the inclusion of a 12-week lifestyle intervention run-in phase before randomization and

TABLE 3 Adverse events.

	Placebo ($N = 111$)		PHEN/TPM CR ($N = 113$)		Total ($N = 224$)		
	No. of participants (%)	No. of events	No. of participants (%)	No. of events	No. of participants (%)	No. of events	
Any adverse event	42 (37.8)	109	67 (59.3)	303	109 (48.7)	412	0.001
Adverse drug reaction	24 (21.6)	64	49 (43.4)	216	73 (32.6)	280	<0.001
Serious adverse events	0	-	3 (2.7)	3	3 (1.3)	3	N.A.
Adverse events leading to trial product discontinuation	2 (1.8)	3	1 (0.9)	2	3 (1.3)	5	0.620
Drug-related	0	-	0	-	0	-	N.A.
Drug-unrelated	2 (1.8)	3	1 (0.9)	2	3 (1.3)	5	0.666
Fatal adverse events	0	-	0	-	0	-	N.A.
Adverse events reported in ≥3% of participants in either group							
Headache	13 (11.7)	[17]	12 (10.6)	[18]	25 (11.2)	[35]	0.795
Dizziness	5 (4.5)	[10]	13 (11.5)	[19]	18 (8.0)	[29]	0.054
Paraesthesia	2 (1.8)	[2]	12 (10.6)	[72]	14 (6.3)	[74]	0.006
Dysgeusia	0	[0]	4 (3.54)	[6]	4 (1.79)	[6]	N.A.
Dry mouth	1 (0.9)	[1]	12 (10.6)	[27]	13 (5.8)	[28]	0.002
Nausea	4 (3.6)	[5]	4 (3.5)	[5]	8 (3.6)	[10]	0.979
Dyspepsia	1 (0.9)	[3]	5 (4.4)	[11]	6 (2.7)	[14]	0.102
Constipation	2 (1.8)	[4]	4 (3.5)	[7]	6 (2.7)	[11]	0.420
COVID-19	9 (8.1)	[9]	6 (5.3)	[7]	15 (6.7)	[16]	0.402
Nasopharyngitis	3 (2.7)	[3]	4 (3.5)	[4]	7 (3.1)	[7]	0.719
Insomnia	3 (2.7)	[3]	6 (5.3)	[9]	9 (4.0)	[12]	0.321
Urticaria	1 (0.9)	[1]	4 (3.6)	[5]	5 (2.2)	[6]	0.181
Palpitations	4 (3.6)	[4]	2 (1.8)	[2]	6 (2.7)	[6]	0.395

dose escalation, which reflect real-world clinical practice. Finally, this is the first report on improvements in body composition (visceral fat area and body fat percentage) as determined using BIA following PHEN/TPM CR treatment. However, this study also has some limitations. First, only Korean nationals were included. However, we postulate that similar findings can be observed in other Asian populations. Second, end point assessment results were not available for 29% of the randomized participants. The percentage of participants who completed treatment (71%) was similar or higher than that reported in previous studies with PHEN/TPM CR (CONQUER study: 69.2%; EQUIP study: 51.5%).[6,7] To overcome this limitation, data analysis was conducted using different statistical methods, with similar results. Third, our study was conducted with relatively small population comparing previous phase 3 studies. The number of study was sufficient to assess the primary outcome but may not be sufficient to assess the safety of PHEN/TPM CR.

5 | CONCLUSION

In this randomized, double-blind, placebo-controlled trial, Korean adults with obesity demonstrated a significant reduction in body weight with PHEN/TPM CR compared with that with placebo in conjunction with lifestyle modifications. Over two thirds of the participants achieved at least a 5% reduction in body weight from baseline. In the PHEN/TPM CR group, the reduction in body weight was accompanied by reductions in visceral fat and body fat percentage and improvement in glucose metabolism.

AUTHOR CONTRIBUTIONS

SMH, WJK and CBL designed the trial and did data analysis. All authors interpreted the data and were involved in the conduct of the trial. All authors contributed to data collection. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication. All authors contributed to the data interpretation. SMH drafted the first and subsequent versions of the report, with input and critical revisions by all authors, who reviewed and approved the final report as submitted.

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CONFLICT OF INTEREST STATEMENT

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PEER REVIEW

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. Data will be shared with researchers who submit a research proposal approved by the independent review board after publication. Individual participant data will be shared in data sets in a de-identified and anonymised format.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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