Coadministration of Canagliflozin and Phentermine for Weight Management in Overweight and Obese Individuals Without Diabetes: A Randomized Clinical Trial

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OBJECTIVE

To assess the efficacy and safety of coadministration of canagliflozin (CANA) and phentermine (PHEN) compared with placebo (PBO) and CANA or PHEN monotherapies in individuals who were overweight and obese without type 2 diabetes.

RESEARCH DESIGN AND METHODS

This 26-week, phase 2a, randomized, double-blind, PBO-controlled, multicenter, parallel-group study enrolled individuals who were obese or overweight without type 2 diabetes (*N* = 335, aged 18–65 years, BMI ≥30 to <50 kg/m^2 or BMI ≥27 to <50 kg/m^2 with hypertension and/or dyslipidemia). Participants were randomized (1:1:1:1) to receive PBO, CANA 300 mg, PHEN 15 mg, or coadministration of CANA 300 mg and PHEN 15 mg (CANA/PHEN) orally once daily. The primary end point was percent change in body weight from baseline to week 26; key secondary end points were the proportion of participants achieving weight loss ≥5% and change from baseline in systolic blood pressure.

RESULTS

CANA/PHEN provided statistically superior weight loss from baseline versus PBO at week 26 (least squares mean difference –6.9% [95% CI –8.6 to –5.2]; *P* < 0.001). CANA/PHEN also provided statistically superior achievement of weight loss ≥5% and reduction in systolic blood pressure compared with PBO. CANA/PHEN was generally well tolerated, with a safety and tolerability profile consistent with that of the individual components.

CONCLUSIONS

CANA/PHEN produced meaningful reductions in body weight and was generally well tolerated in individuals who were overweight or obese without type 2 diabetes. Further studies are warranted to evaluate potential use of this combination for long-term weight management.

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Obesity is a complex metabolic disease that is linked to increased risk of diabetes, cardiovascular disease, various cancers, and other metabolic and fat mass abnormalities (1–3). Sustained weight loss of ~5% in overweight or obese individuals may provide clinically meaningful improvements in metabolic and cardiovascular risk factors (4,5). Consistent with these clinical benefits, one of the efficacy thresholds for U.S. Food and Drug Administration approval of obesity therapeutics is ≥5% placebo (PBO)-subtracted reduction in body weight after 1 year of treatment (6–8). Clinical practice guidelines recommend lifestyle modifications as first-line interventions for weight management, with pharmacotherapy and/or bariatric surgery as alternative approaches (4,9,10).

Canagliflozin (CANA), a sodium–glucose cotransporter 2 (SGLT2) inhibitor for the treatment of adults with type 2 diabetes, lowers the renal threshold for glucose reabsorption (RT_G), thereby increasing urinary glucose excretion (UGE) and resulting in a mild osmotic diuresis and a net caloric loss (11,12). Mean overnight RT_G was estimated to be 67.8 mg/dL with CANA 300 mg in a 12-week study in obese and overweight individuals without type 2 diabetes (13), which would be expected to provide UGE of ~60 g/day, based on data from healthy individuals (11). Weight loss observed with CANA in that study of obese and overweight individuals without type 2 diabetes (–2.2 to –2.9 vs. –1.3% with PBO) was generally consistent with caloric loss via UGE (13). In phase 3 studies in patients with type 2 diabetes, CANA improved glycemic control, provided consistent reductions in body weight and blood pressure (BP), and was generally well tolerated (14). Weight loss with CANA and other SGLT2 inhibitors generally plateaus after ~26 weeks of treatment in patients with type 2 diabetes, despite sustained UGE (15–17), with observed weight loss less than predicted based on caloric loss from UGE (18). In addition to achieving a new steady state, other factors may contribute to attenuated weight loss, including compensatory increases in calorie intake and/or changes in energy expenditure. In rodent models, SGLT2 deletion or chronic treatment with the SGLT2 inhibitor dapagliflozin resulted in a compensatory increase in caloric intake (19,20). Mathematical models based on 52- to 90-week studies of SGLT2 inhibitors in patients with type 2 diabetes predict that energy intake after weight loss due to UGE may exceed adaptions in energy expenditure, contributing to difficulties with sustained weight loss (18,21). However, whether energy intake compensations occur in individuals without type 2 diabetes treated with SGLT2 inhibitors over a longer duration has yet to be examined. Overall, clinical trial evidence supports the assertion that weight management is challenging for overweight and obese individuals with and without diabetes (22–25), and multifactorial approaches are likely required.

Phentermine (PHEN), a sympathomimetic amine anorectic that stimulates satiety centers in the brain via upregulation of dopamine, noradrenaline, and serotonin, is indicated for short-term weight management (26). PHEN may increase BP and pulse rate and is contraindicated in individuals with a history of cardiovascular disease (27). By increasing satiety, the mechanism of PHEN may complement that of CANA, and coadministration may prevent potential increased caloric intake associated with SGLT2 inhibition, resulting in additional weight loss. This study assessed the efficacy and safety of coadministration of CANA and PHEN in overweight and obese individuals without type 2 diabetes over 26 weeks.

RESEARCH DESIGN AND METHODS

Study Design and Participants

This 26-week, randomized, double-blind, PBO-controlled, parallel-group, phase 2a study was conducted at 18 sites in the U.S. Eligible participants were overweight and obese adults without type 2 diabetes who had BMI ≥30 to <50 kg/m^2 or had BMI ≥27 to <50 kg/m^2 with comorbidities of hypertension (i.e., drug treatment for hypertension and/or systolic BP ≥140 mmHg and/or diastolic BP ≥90 mmHg at screening) and/or dyslipidemia (i.e., drug treatment for dyslipidemia and/or fasting LDL cholesterol ≥130 mg/dL [≥3.36 mmol/L], and/or fasting HDL cholesterol <40 mg/dL [<1.03 mmol/L] for men or <50 mg/dL [<1.29 mmol/L] for women, and/or fasting triglycerides ≥150 mg/dL [≥1.68 mmol/L] at screening). As relevant, participants were required to have a stable dose of antihypertensive or lipid-modifying medications for ≥4 weeks before screening, with no anticipated changes during the study. Participants were required to have stable body weight (i.e., change of ≤5% within 3 months before screening). Exclusion criteria included a history of obesity with a known secondary cause (e.g., Cushing disease/syndrome); HbA_{1c} ≥6.5% (48 mmol/mol); diagnosis of diabetes; cardiovascular disease (i.e., myocardial infarction, unstable angina, revascularization procedure, or cerebrovascular accident) within 3 months before screening; history of eating disorder; glaucoma; estimated glomerular filtration rate <70 mL/min/1.73 m^2; fasting triglycerides ≥600 mg/dL (≥6.77 mmol/L); liposuction or treatment with weight loss medications, antipsychotic medications, corticosteroids, antihyperglycemic agents, selective serotonin reuptake inhibitors, or serotonin-norepinephrine reuptake inhibitors within 3 months of screening; or use of monoamine oxidase inhibitors within 14 days of screening. All participants received standardized instruction to implement a nonpharmacological weight loss program (i.e., individualized 600 kcal–deficit diet determined by a formula based on estimated total energy expenditure and 150 min of exercise/week) during a 4-week, single-blind, PBO run-in period and were instructed to follow the program throughout the study. Investigators or designated study staff reinforced these instructions at each follow-up visit through week 26 to promote compliance with study drug and the diet/exercise program. Initiation of other diet or exercise programs was not permitted.

The study was conducted under ethics guidelines set forth by the Declaration of Helsinki and Good Clinical Practices and applicable regulatory requirements. Approval was obtained from institutional review boards and independent ethics committees for participating centers. Participants provided written informed consent before any study-related procedures.

Randomization and Masking

During run-in, all participants took single-blind PBO capsules matching the double-blind study drugs once daily before the first meal of the day. Participants were randomized by an interactive web response system (1:1:1:1) to receive PBO, CANA, PHEN, or coadministration of CANA and PHEN (CANA/PHEN). The sponsor prepared masked computer-generated randomization schedules before the study. Randomization was balanced with randomly permuted blocks of eight participants and stratified

by weight loss during run-in (≤2 kg or >2 kg). For maintenance of blinding, participants randomized to PHEN or CANA also took one capsule of CANA- or PHEN-matching PBO, respectively; participants randomized to PBO received one capsule each of CANA- and PHEN-matching PBO. Participants, study investigators, and local sponsor personnel were masked to treatment assignments until final database lock.

Outcomes

The primary end point was percent change from baseline in body weight with CANA/PHEN versus PBO at week 26. Key secondary end points were the proportion of participants with weight loss ≥5% and absolute change from baseline in body weight and systolic BP. Prespecified additional efficacy evaluations included the proportion of participants with weight loss ≥10%, changes from baseline in BMI, diastolic BP, and percent change from baseline in fasting plasma lipids.

Safety and tolerability over 26 weeks included reported adverse events (AEs), laboratory results, and vital sign measurements, including pulse rate. Additional safety analyses were conducted using a predefined list of preferred terms based on the known side effect profiles of CANA (i.e., genital mycotic infections, urinary tract infections [UTIs], fractures, photosensitivity reactions, and AEs related to volume depletion and osmotic diuresis) and PHEN (i.e., psychiatric disorders, cardiac arrhythmias, cognitive disorders, psychomotor disorders, and drug abuse/withdrawal).

Statistical Analyses

A sample size of 60 participants per group was estimated to meet the objective of ensuring that a ≥5% body weight reduction between groups was met with ≥80% probability. With an assumption of 30% dropout during the double-blind period, 86 participants per group would need to be randomized, for a total randomized population of ~344 participants.

Primary, secondary, and exploratory efficacy end points and safety analyses were analyzed using data from the modified intent-to-treat (mITT) population (i.e., all randomized participants who received ≥1 dose of study drug). Primary, secondary, and exploratory efficacy end points were analyzed based on a mixed model for repeated measures (MMRM) approach, with terms for treatment, stratification factor (i.e., weight loss during run-in), visit, treatment-by-visit interaction, baseline value, and baseline-by-visit interaction as fixed effects and participant as a random effect. Differences between each group versus PBO, calculated as least squares (LS) means and two-sided 95% CIs, were estimated. As a supportive analysis, percent change in body weight from baseline at week 26 was also analyzed with an ANCOVA model using the mITT data set with a last observation carried forward (LOCF) approach, with treatment and stratification factor as fixed effects and baseline body weight as a covariate. In addition, percent change in body weight from baseline over time was also evaluated in the per protocol analysis set (i.e., participants who completed 26 weeks of treatment without protocol deviations). The categorical end point of proportion of participants achieving weight loss ≥5% was analyzed longitudinally based on the generalized linear MMRM, with treatment, stratification factor, visit, treatment-by-visit interaction, baseline value, and baseline-by-visit as fixed effects; odds ratios (ORs) and two-sided 95% CIs were estimated at week 26 based on this model. The proportion of participants achieving weight loss ≥10% was analyzed descriptively.

Investigation of the CANA-PHEN interaction with respect to percent weight loss at week 26 was based on incremental benefits among groups (i.e., coadministration vs. each monotherapy arm, and each monotherapy arm vs. PBO). An ANCOVA model was used, with treatment and stratification factors as fixed effects and baseline body weight as a covariate. Treatment effects were considered as two 2-level factors (i.e., CANA or PHEN) plus their interaction; incremental

Table 1—Baseline demographic and disease characteristics

	PBO	CANA	PHEN	CANA/PHEN	Total
n	82	84	85	83	334
Sex, *n* (%)					
Male	15 (18.3)	16 (19.0)	16 (18.8)	14 (16.9)	61 (18.3)
Female	67 (81.7)	68 (81.0)	69 (81.2)	69 (83.1)	273 (81.7)
Age, years	44.8 ± 11.1	45.2 ± 11.0	46.4 ± 11.1	46.3 ± 12.5	45.7 ± 11.4
Race, *n* (%)					
White	73 (89.0)	60 (71.4)	68 (80.0)	61 (73.5)	262 (78.4)
Black or African American	8 (9.8)	20 (23.8)	16 (18.8)	20 (24.1)	64 (19.2)
Asian	1 (1.2)	2 (2.4)	1 (1.2)	1 (1.2)	5 (1.5)
Other	0	2 (2.4)	0	1 (1.2)	3 (0.9)
Body weight, kg	104.3 ± 18.2	103.3 ± 19.1	102.8 ± 17.9	101.1 ± 18.1	102.9 ± 18.3
BMI, kg/m^2	38.0 ± 5.2	37.3 ± 4.7	37.0 ± 5.4	36.8 ± 5.4	37.3 ± 5.2
Weight loss during run-in, %	−1.3 ± 1.8	−1.0 ± 1.6	−1.1 ± 1.8	−0.9 ± 2.2	−1.1 ± 1.9
≤2 kg, *n* (%)	60 (73.2)	61 (72.6)	62 (72.9)	60 (72.3)	243 (72.8)
>2 kg, *n* (%)	22 (26.8)	23 (27.4)	23 (27.1)	23 (27.7)	91 (27.2)
Pulse, bpm	73.5 ± 8.7	71.5 ± 9.4	70.7 ± 10.1	72.4 ± 9.7	72.0 ± 9.5
Systolic BP, mmHg	122.5 ± 13.9	124.5 ± 13.0	123.0 ± 11.8	124.8 ± 12.8	123.7 ± 12.9
eGFR, mL/min/1.73 m^2	95.2 ± 16.2	95.4 ± 15.5	95.3 ± 13.9	97.4 ± 14.5	95.8 ± 15.0
HbA_{1c}, % (mmol/mol)	5.6 ± 0.3 (38 ± 3.3)	5.6 ± 0.4 (38 ± 4.4)	5.6 ± 0.3 (38 ± 3.3)	5.6 ± 0.4 (38 ± 4.4)	5.6 ± 0.4 (38 ± 4.4)

Data are mean ± SD unless otherwise indicated. eGFR, estimated glomerular filtration rate.

benefits were estimated with respective differences in LS means and 95% CIs. Test statistics and *P* values based on the null hypothesis of no incremental benefit were calculated. No multiplicity adjustments were made for this exploratory analysis.

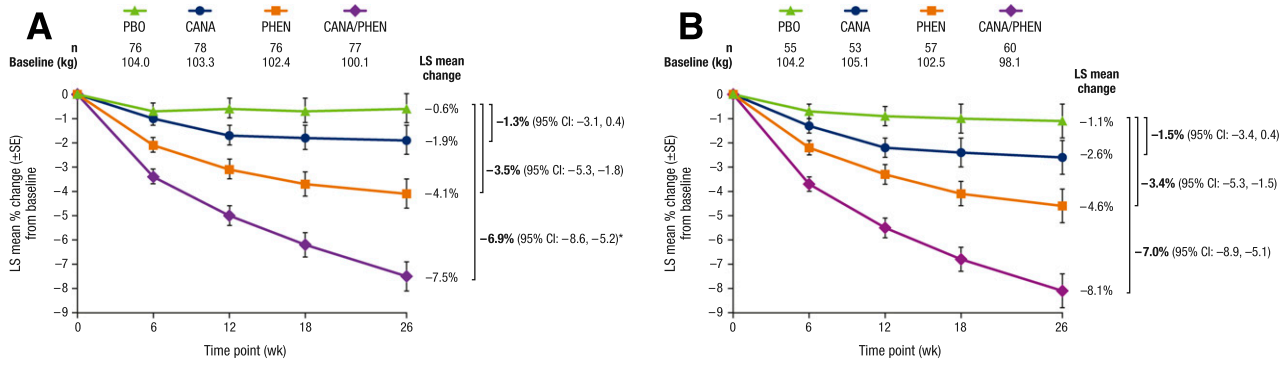
A prespecified hierarchical testing sequence was implemented to strongly control type I error. Two-sided statistical tests were conducted at the 0.05 significance level for comparison of CANA/PHEN with PBO for all primary and key secondary efficacy end points; *P* values were calculated by comparing LS means. *P* values are not reported for exploratory end points with CANA/PHEN versus PBO or for any comparisons of CANA and PHEN versus PBO.

RESULTS

Between 17 September 2014 and 22 June 2015, 335 individuals were randomized and 334 received one or more doses of PBO (*n* = 82), CANA (*n* = 84), PHEN (*n* = 85), or CANA/PHEN (*n* = 83), comprising the mITT analysis set. A total of 231 (69%) participants completed the study; study discontinuation rates were slightly higher with CANA based on more participants lost to follow-up and a greater proportion discontinuing due to AEs (Supplementary Fig. 1). Baseline characteristics were generally balanced across groups (Table 1). The majority of participants were white and female; mean age was 45.7 years. Mean body weight was 102.9 kg, and mean BMI was 37.3 kg/m^2.

Over 26 weeks, the PBO, CANA, PHEN, and CANA/PHEN groups had LS mean percent changes in body weight of –0.6, –1.9, –4.1, and −7.5%, respectively (Fig. 1*A*); absolute changes in body weight were –0.6, –1.9, –4.1, and –7.3 kg, respectively. CANA/PHEN had statistically superior percent weight loss versus PBO (difference of –6.9%; $P < 0.001$). The absolute reduction in body weight with CANA/PHEN was also statistically significant versus PBO (difference of –6.7 kg; $P < 0.001$). The separation in treatment effect on body weight was observed as early as week 6, the first on-treatment visit. Weight loss with CANA/PHEN continued through week 26, with no apparent plateau. The supportive ANCOVA analysis using LOCF also showed superior weight loss with CANA/PHEN versus PBO (difference of –6.5% [95% CI –8.0, –4.9]). In addition, PBO-subtracted changes in body weight in the per-protocol analysis set were consistent with those seen in the primary mITT analysis (Fig. 1*B*).

A statistically significant greater proportion of participants achieved weight loss ≥5% with CANA/PHEN versus PBO at week 26 (66.7 vs. 17.5%; OR 10.2; $P < 0.001$) (Fig. 1*C*). The proportion of participants with weight loss ≥5% with CANA or PHEN alone was 17.9 and 41.7%, respectively (ORs vs. PBO of 1.1 and 4.2, respectively). The proportion of participants with weight loss ≥10% was 8.8, 5.4, 8.3, and 34.9% with PBO, CANA, PHEN, and CANA/PHEN, respectively. PBO-subtracted



Proportion of participants (%)	PBO	CANA	PHEN	CANA/PHEN
Weight loss ≥5%	17.5	17.9	41.7	66.7
Odds ratio (95% CI)‡		1.1 (0.4, 3.1)	4.2 (1.7, 10.1)	10.2 (4.2, 25.1)*
Weight loss ≥10%	8.8	5.4	8.3	34.9

Figure 1—Percent change in body weight over time (mITT analysis set) (*A*), percent change in body weight over time (per protocol analysis set) (*B*), and cumulative distribution of percent change in body weight from baseline at week 26 (*C*). *$P < 0.001$ vs. PBO. †Percentages are based on the number of participants having a nonmissing weight measurement at the week 26 window. ‡ORs, CIs, and *P* values are based on the generalized linear MMRM, including the fixed effects of treatment, weight loss during run-in, visit, treatment-by-visit interaction, treatment-by-subgroup interaction, baseline value, and baseline-by-visit interaction, and participant as a random effect. wk, week.

reductions in BMI with CANA, PHEN, and CANA/PHEN were −0.5, −1.3, and −2.4 kg/m^2, respectively (Supplementary Table 1).

Weight loss with CANA/PHEN was greater than expected assuming simple additivity based on the efficacy of the individual components. The interaction term suggests that the individual contributions of CANA and PHEN were at least additive with coadministration with respect to the percent change in body weight at week 26 (P = 0.0624). Approximately 18% of weight loss with CANA/PHEN was attributed to CANA, ∼50% to PHEN, and ∼32% to the interaction of CANA and PHEN.

LS mean reductions in systolic BP over 26 weeks were –2.7, –3.1, –1.4, and –6.9 mmHg with PBO, CANA, PHEN, and CANA/PHEN, respectively (Fig. 2*A*). Reduction in systolic BP was statistically significant with CANA/PHEN versus PBO (difference of –4.2 mmHg; P = 0.015). Reductions in diastolic BP were numerically larger with CANA/PHEN versus PBO (Fig. 2*A*). Consistent with the known effects of PHEN, increases in pulse rate were seen with PHEN and CANA/PHEN versus PBO and CANA (4.1, 3.5, –0.7, and 0.7 bpm, respectively) (Fig. 2*B*). A higher proportion of participants in the PHEN arms had increases in pulse rate ≥5 and ≥10 bpm at any time point and at week 26 compared with those in PBO or CANA groups (Supplementary Table 1). No notable changes were found in fasting plasma lipids with CANA/PHEN versus PBO (Supplementary Table 2).

The overall incidence of AEs was 57.3, 59.5, 54.1, and 66.3% with PBO, CANA, PHEN, and CANA/PHEN, respectively (Table 2). A higher incidence of AEs leading to discontinuation was observed with CANA (10.7%) versus PBO, PHEN, and CANA/PHEN (6.1, 5.9, and 3.6%, respectively). The higher incidence of discontinuation due to AEs with CANA was mainly driven by fatigue in two participants, fungal infections (fungal UTI in one participant and genital mycotic infection in two female participants), and headache in two participants. Three participants discontinued due to AEs with CANA/PHEN: one each due to restlessness and influenza, genital mycotic infection (female), and increased HbA_{1c}. One serious AE of epistaxis was reported in the CANA/PHEN group that was not considered to be related to study drug and did not lead to discontinuation. No deaths occurred in any group.

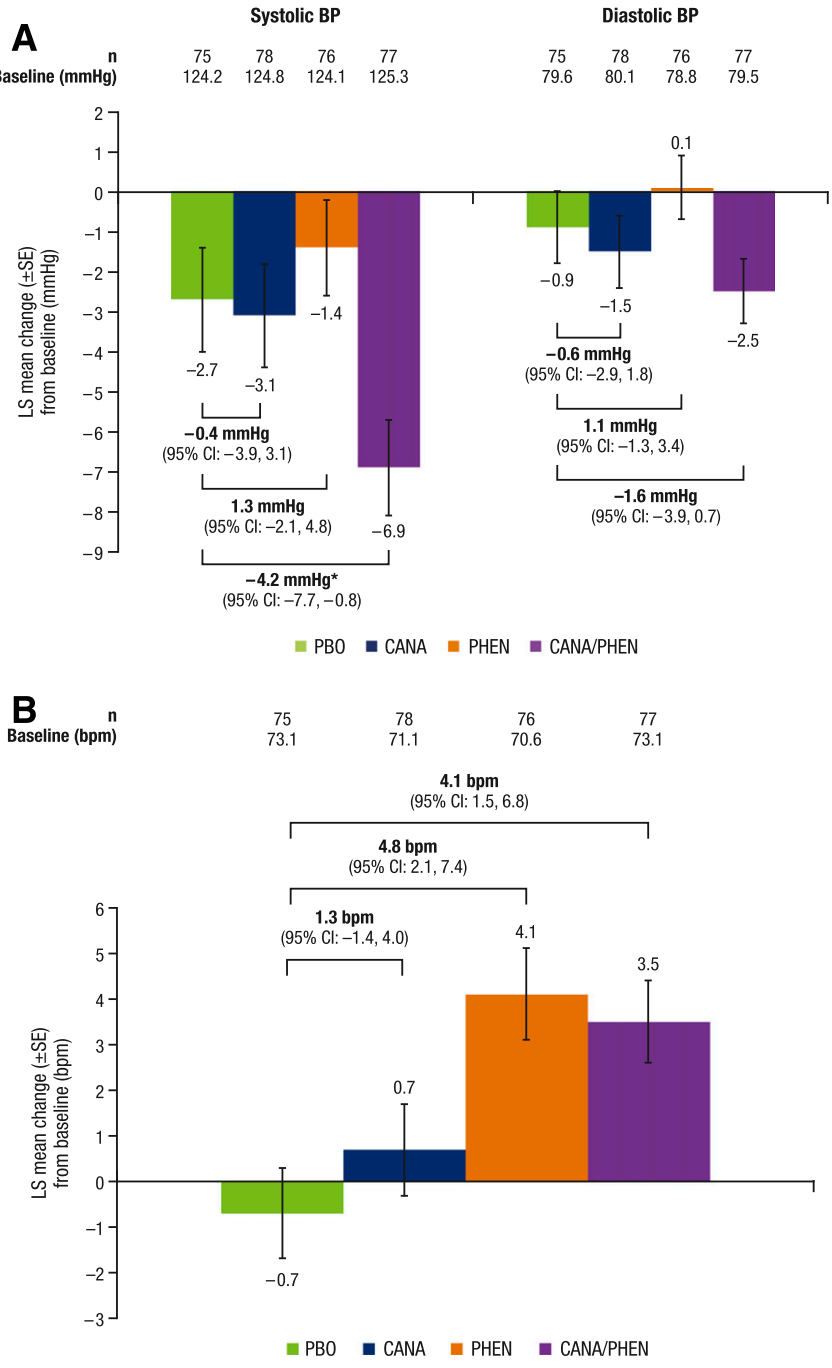


Figure 2—Change from baseline in BP at week 26 (*A*) and change from baseline in pulse at week 26 (*B*). *P = 0.015 vs. PBO.

No treatment-emergent fractures, male genital mycotic infections, renal- or photosensitivity-related AEs, or AEs of diabetic ketoacidosis or related events were reported in any group. Treatment-emergent AEs with ≥2% incidence in any group are summarized in Supplementary Table 3. The incidence of female genital mycotic infections was 10.3 and 7.2% with CANA and CANA/PHEN, respectively, compared with no events with PBO and PHEN; most events were generally mild or moderate in intensity, with one severe event with CANA. The incidence of UTIs was low overall, with a numerically higher incidence with CANA/PHEN and CANA versus PHEN and PBO (2.4, 4.8, 1.2, and 0%, respectively). All UTIs were mild or moderate, with no reports of upper UTIs. The incidence of osmotic

Table 2—Summary of overall safety and selected AEs over 26 weeks

	PBO	CANA	PHEN	CANA/PHEN
n	82	84	85	83
Any AE	47 (57.3)	50 (59.5)	46 (54.1)	55 (66.3)
AEs leading to discontinuation	5 (6.1)	9 (10.7)	5 (5.9)	3 (3.6)
AEs related to study drug*	8 (9.8)	21 (25.0)	15 (17.6)	25 (30.1)
Serious AEs	0	0	0	1 (1.2)
Deaths	0	0	0	0
Selected AEs				
Genital mycotic infections				
Female†‡	0	7 (10.3)	0	5 (7.2)
Male	0	0	0	0
UTIs§	0	4 (4.8)	1 (1.2)	2 (2.4)
Osmotic diuresis–related AEs‖	0	2 (2.4)	3 (3.5)	8 (9.6)
Volume depletion–related AEs¶	0	1 (1.2)	1 (1.2)	0
Psychiatric disorder–related AEs#	4 (4.9)	2 (2.4)	2 (2.4)	4 (4.8)
Heart rate–related AEs**	1 (1.2)	1 (1.2)	0	3 (3.6)

Data are *n* (%) participants, unless otherwise indicated. *Possibly, probably, or very likely related to study drug, as assessed by investigators. †Includes urogenital infection fungal, vulvovaginal candidiasis, and vulvovaginal mycotic infection. ‡The number of female participants were as follows: PBO, *n* = 67; CANA, *n* = 68; PHEN, *n* = 69; CANA/PHEN, *n* = 69. §Includes UTI and UTI fungal. ‖Includes dry mouth, dry throat, polydipsia, pollakiuria, and thirst. ¶Includes dizziness postural. #Includes agitation, anxiety, insomnia, sleep disorder, and stress. **Includes heart rate increased, heart rate irregular, palpitations, and tachycardia.

diuresis–related AEs was 0, 2.4, 3.5, and 9.6% with PBO, CANA, PHEN, and CANA/PHEN, respectively. One participant (1.2%) in the CANA group and one participant (1.2%) in the PHEN group experienced a volume depletion–related AE; none were reported with CANA/PHEN or PBO.

No cognitive disorders, psychomotor disorders, or drug abuse/withdrawal–related AEs were observed in any group. The incidence of psychiatric disorder–related AEs (e.g., agitation, anxiety, insomnia) was low and generally similar across groups (4.9, 2.4, 2.4, and 4.8% with PBO, CANA, PHEN, and CANA/PHEN, respectively). The incidence of pooled AEs of palpitations, tachycardia, increased heart rate, and irregular heart rate was higher with CANA/PHEN (3.6%) versus PBO, CANA, and PHEN (1.2, 1.2, and 0%, respectively); none were serious or led to study drug discontinuation.

Changes in laboratory parameters at week 26 were consistent with the expected profiles of CANA and PHEN, and no clinically meaningful differences were observed between groups (Supplementary Table 4).

CONCLUSIONS

This study describes the weight loss effects of coadministration of CANA, an SGLT2 inhibitor, and PHEN, a sympathomimetic amine, in overweight and obese individuals without type 2 diabetes. Given the multifactorial complexities involved in weight loss in obese and overweight individuals, combination therapies have potential as effective therapeutic approaches to weight management. CANA/PHEN provided statistically superior weight loss compared with PBO over 26 weeks. The relative contribution of each component of the CANA/PHEN combination was clearly additive and perhaps synergistic. In addition, a statistically significant proportion of participants treated with CANA/PHEN had weight loss $\geq$5% and reductions in systolic BP versus PBO. Larger reductions in systolic BP with CANA/PHEN than with either component alone may be related to the greater weight loss seen in this group. CANA/PHEN was generally well tolerated, with a safety and tolerability profile consistent with the individual components and no new or unexpected safety signals. Changes in pulse rate were consistent with the known effects of PHEN and observations from other approved weight loss agents, including PHEN/topiramate and liraglutide (28,29). The participants in this study were representative of those typically recruited to weight loss studies and, despite differences in study designs, weight loss with CANA and PHEN monotherapies was generally consistent with the results of previous studies of these agents (13,30).

In the absence of changes in food intake, daily caloric loss due to UGE with SGLT2 inhibition in patients with type 2 diabetes is predicted to give weight loss of ~3.6% over 26 weeks (31). However, in phase 3 studies of SGLT2 inhibitors in patients with type 2 diabetes, weight loss was less than predicted, which has been attributed to compensatory increases in food intake (18,21). In this study, PBO-subtracted weight loss with CANA monotherapy was below the predicted weight loss due to UGE. However, the incremental weight loss seen with CANA/PHEN versus PHEN (3.4% greater reduction in body weight) is very similar to predicted weight loss due to UGE, suggesting that the reduced appetite or increased satiety activity of PHEN may compensate for potential adaptive increases in caloric intake after weight loss with CANA. Additionally, the complementary renal effects with CANA and central nervous system activity with PHEN may support synergistic weight loss. In contrast to what has been observed with other weight loss agents (22–25), weight loss with CANA/PHEN is likely to be greater in people with type 2 diabetes, due to greater UGE and associated urinary caloric loss in these individuals.

A limitation of this analysis was the inclusion of a 4-week run-in period, which may have impacted the results of the study by potentially filtering out less committed patients. In addition, this study did not measure caloric intake; thus, further studies are required to directly evaluate the effects of CANA/PHEN on energy balance. Additional work is necessary to elucidate the physiological signals that drive compensatory increases in food intake with SGLT2 inhibitors and the combined effects of CANA and PHEN on these signals. It would also be beneficial to assess whether the pattern of changes in fat mass with CANA/PHEN is consistent with those seen with CANA in patients with type 2 diabetes (i.e., approximately two-thirds of weight loss due to loss of fat mass and one-third due to loss of lean mass) (32–34). Longer studies are needed to determine the overall effects of weight loss, increased heart rate, and decreased BP on cardiovascular outcomes and long-term weight management in overweight

and obese individuals with or without type 2 diabetes.

In conclusion, these analyses show that, compared with PBO, coadministration of CANA and PHEN provides clinically meaningful weight loss that appears to be synergistic over 26 weeks, and was generally well tolerated in overweight and obese adults without type 2 diabetes, suggesting potential for use in long-term weight management.

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