SUPPLEMENTARY DATA

Supplementary Table 1. Summary of Changes in Efficacy Parameters from Baseline at Week 26

Parameter	PBO (n = 82)	CANA (n = 84)	PHEN (n = 85)	CANA/PHEN (n = 83)
Body weight, mITT analysis set (n)	76	78	76	77
Mean ± SD baseline, kg	104.0 ± 18.3	103.3 ± 19.6	102.4 ± 18.6	100.1 ± 18.1
LS mean ± SE percent change	–0.6 ± 0.6	–1.9 ± 0.6	–4.1 ± 0.6	–7.5 ± 0.6
Difference (95% CI) vs PBO		–1.3 (–3.1, 0.4)	–3.5 (–5.3, –1.8)	–6.9 (–8.6, –5.2)*
LS mean ± SE change, kg	–0.6 ± 0.6	–1.9 ± 0.7	–4.1 ± 0.6	–7.3 ± 0.6
Difference (95% CI) vs PBO		–1.3 (–3.1, 0.5)	–3.5 (–5.3, –1.7)	–6.7 (–8.5, –4.9)
Body weight, per-protocol analysis set (n)	55	53	57	60
Mean ± SD baseline, kg	104.2 ± 17.9	105.1 ± 20.0	102.5 ± 19.0	98.1 ± 15.3
LS mean ± SE percent change	–1.1 ± 0.7	–2.6 ± 0.7	–4.6 ± 0.7	–8.1 ± 0.7
Difference (95% CI) vs PBO		–1.5 (–3.4, 0.4)	–3.4 (–5.3, –1.5)	–7.0 (–8.9, –5.1)
LS mean ± SE change, kg	–1.0 ± 0.8	–2.6 ± 0.7	–4.5 ± 0.7	–8.0 ± 0.7
Difference (95% CI) vs PBO		–1.6 (–3.6, 0.4)	–3.5 (–5.5, –1.6)	–7.0 (–8.9, –5.1)
BMI (n)	76	78	76	77
Mean ± SD baseline, kg/m^2	37.8 ± 5.1	37.2 ± 4.8	37.0 ± 5.6	36.6 ± 5.4
LS mean ± SE change	–0.2 ± 0.2	–0.7 ± 0.2	–1.5 ± 0.2	–2.6 ± 0.2
Difference (95% CI) vs PBO		–0.5 (–1.1, 0.2)	–1.3 (–1.9, –0.7)	–2.4 (–3.1, –1.8)
Systolic BP (n)	75	78	76	77
Mean ± SD baseline, mmHg	124.2 ± 12.9	124.8 ± 13.3	124.1 ± 11.5	125.3 ± 13.1
LS mean ± SE change	–2.7 ± 1.3	–3.1 ± 1.3	–1.4 ± 1.2	–6.9 ± 1.2
Difference (95% CI) vs PBO		–0.4 (–3.9, 3.1)	1.3 (–2.1, 4.8)	–4.2 (–7.7, –0.8)†
Diastolic BP (n)	75	78	76	77
Mean ± SD baseline, mmHg	79.6 ± 8.2	80.1 ± 7.9	78.8 ± 8.6	79.5 ± 8.4
LS mean ± SE change	–0.9 ± 0.9	–1.5 ± 0.9	0.1 ± 0.8	–2.5 ± 0.8
Difference (95% CI) vs PBO		–0.6 (–2.9, 1.8)	1.1 (–1.3, 3.4)	–1.6 (–3.9, 0.7)
Pulse rate (n)	75	78	76	77
Mean ± SD baseline, bpm	73.1± 8.8	71.1 ± 9.3	70.6 ± 9.8	73.1± 9.5
LS mean ± SE change	–0.7 ± 1.0	0.7 ± 1.0	4.1 ± 1.0	3.5 ± 0.9
Difference (95% CI) vs PBO		1.3 (–1.4, 4.0)	4.8 (2.1, 7.4)	4.1 (1.5, 6.8)
Any pulse increase ≥5 bpm, n (%)‡,§	36 (49.3%)	38 (52.1%)	58 (84.1%)	56 (74.7%)
Any pulse increase ≥10 bpm, n (%)‡,§	19 (26.0%)	25 (34.2%)	42 (60.9%)	38 (50.7%)
Week 26 pulse increase ≥5 bpm, n (%)‡,‖	17 (23.3%)	23 (31.5%)	33 (47.8%)	32 (42.7%)

Week 26 pulse increase ≥10 bpm, n (%)[‡,‖]	7 (9.6%)	8 (11.0%)	17 (24.6%)	19 (25.3%)

PBO, placebo; CANA, canagliflozin; PHEN, phentermine; mITT, modified intent-to-treat; SD, standard deviation; LS, least squares; SE, standard error; CI, confidence interval; BMI, body mass index; BP, blood pressure; bpm, beats per minute.

[*] P <0.001 vs PBO.

[†] P = 0.015 vs PBO.

[‡] Reported within 2 days of last dose of study drug.

[§] Data are for any post-baseline value.

[‖] Data are for last post-baseline value.

SUPPLEMENTARY DATA

Supplementary Table 2. Changes from Baseline in Fasting Plasma Lipids at Week 26*

Parameter	PBO (n = 82)	CANA (n = 84)	PHEN (n = 85)	CANA/PHEN (n = 83)
Triglycerides, n	68	66	71	69
Mean ± SD baseline, mg/dL (mmol/L)	127.8 ± 65.2 (1.4 ± 0.7)	120.2 ± 62.5 (1.4 ± 0.7)	125.5 ± 84.0 (1.4 ± 0.9)	150.0 ± 109.0 (1.7 ± 1.2)
LS mean ± SE change, mg/dL (mmol/L)	11.4 ± 6.4 (0.13 ± 0.07)	10.3 ± 6.6 (0.12 ± 0.08)	2.4 ± 6.3 (0.03 ± 0.07)	–23.2 ± 6.4 (–0.26 ± 0.07)
Median (IQR) percentage change	16.4% (–11.1, 39.0)	15.7% (–7.1, 63.0)	10.9% (–14.4, 40.0)	–8.4% (–38.2, 35.9)
LS mean ± SE percentage change	18.2% ± 4.8	23.1% ± 4.9	14.1% ± 4.7	5.8% ± 4.8
Difference (95% CI) vs PBO		4.9% (–8.2, 18.0)	–4.1% (–17.0, 8.8)	–12.4% (–25.4, 0.6)
LDL-C, n	68	66	71	69
Mean ± SD baseline, mg/dL (mmol/L)	115.5 ± 30.2 (3.0 ± 0.8)	112.1 ± 30.2 (2.9 ± 0.8)	110.2 ± 29.2 (2.9 ± 0.8)	111.8 ± 31.6 (2.9 ± 0.8)
LS mean ± SE change, mg/dL (mmol/L)	–0.2 ± 2.5 (0.00 ± 0.06)	–0.8 ± 2.5 (–0.02 ± 0.07)	–4.1 ± 2.4 (–0.11 ± 0.06)	1.5 ± 2.5 (0.04 ± 0.06)
Median (IQR) percentage change	–0.6% (–12.0, 13.7)	–0.5% (–11.2, 10.9)	–4.2% (–15.6, 12.7)	1.7% (–6.9, 14.1)
LS mean ± SE percentage change	1.9% ± 2.4	1.6% ± 2.4	–1.4% ± 2.3	3.9% ± 2.3
Difference (95% CI) vs PBO		–0.4% (–6.8, 6.1)	–3.4% (–9.7, 3.0)	1.9% (–4.5, 8.3)
HDL-C, n	68	66	71	69
Mean ± SD baseline, mg/dL (mmol/L)	49.3 ± 10.5 (1.3 ± 0.3)	52.7 ± 15. (1.4 ± 0.4)	53.4 ± 13.8 (1.4 ± 0.4)	53.2 ± 15.6 (1.4 ± 0.4)
LS mean ± SE change, mg/dL (mmol/L)	2.7 ± 0.9 (0.07 ± 0.02)	2.6 ± 1.0 (0.07 ± 0.02)	3.7 ± 0.9 (0.10 ± 0.02)	3.4 ± 0.9 (0.09 ± 0.02)
Median (IQR) percentage change	2.2% (–6.1, 15.2)	3.3% (–4.0, 14.6)	4.3% (–3.9, 13.1)	7.9% (–0.9, 15.0)
LS mean ± SE percentage change	6.7% ± 1.9	6.5% ± 1.9	7.8%± 1.8	8.5% ± 1.9
Difference (95% CI) vs PBO		–0.2% (–5.3, 5.0)	1.1% (–4.0, 6.2)	1.9% (–3.3, 7.0)
LDL-C/HDL-C, n	68	66	71	69
Mean ± SD baseline, mol/mol	2.4 ± 0.8	2.3 ± 0.8	2.2 ± 0.8	2.2 ± 0.7
LS mean ± SE change	–0.11 ± 0.06	–0.14 ± 0.06	–0.18 ± 0.06	–0.11 ± 0.06
Median (IQR) percentage change	–5.3% (–18.5, 12.6)	–2.7% (–18.4, 7.6)	–8.2% (–20.3, 10.4)	–3.4% (–16.0, 12.7)
LS mean ± SE percentage change	–2.9% ± 2.7	–3.9% ± 2.8	–6.6% ± 2.6	–2.1% ± 2.7
Difference (95% CI) vs PBO		–0.9% (–8.4, 6.5)	–3.6% (–11.0, 3.7)	0.8% (–6.6, 8.2)
Non–HDL-C, n	68	66	71	69
Mean ± SD baseline, mg/dL (mmol/L)	141.0 ± 34.6 (3.7 ± 0.9)	136.2 ± 32.9 (3.5 ± 0.9)	135.3 ± 34.0 (3.5 ± 0.9)	141.5 ± 38.7 (3.7 ± 1.0)
LS mean ± SE change, mg/dL (mmol/L)	2.8 ± 2.7 (0.07 ± 0.07)	1.8 ± 2.8 (0.05 ± 0.07)	–3.2 ± 2.7 (–0.08 ± 0.07)	–3.3 ± 2.7 (–0.09 ± 0.07)
Median (IQR) percentage change	0.2% (–7.5, 15.2)	1.7% (–5.3, 13.3)	–2.6% (–11.8, 9.0)	–3.2% (–11.7, 10.5)
LS mean ± SE percentage change	3.3% ± 2.0	3.3% ± 2.0	–0.6% ± 1.9	–0.3% ± 2.0
Difference (95% CI) vs PBO		0.0% (–5.5, 5.4)	–3.9% (–9.2, 1.4)	–3.7% (–9.0, 1.7)

PBO, placebo; CANA, canagliflozin; PHEN, phentermine; SD, standard deviation; LS, least squares; SE, standard error; IQR, interquartile range; CI, confidence interval; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol

SUPPLEMENTARY DATA

Supplementary Table 3. Summary of AEs With ≥2% Incidence Over 26 Weeks

Participants, n (%)	PBO (n = 82)	CANA (n = 84)	PHEN (n = 85)	CANA/PHEN (n = 83)
Cardiac disorders	0	0	0	3 (3.6)
Tachycardia	0	0	0	2 (2.4)
Gastrointestinal disorders	12 (14.6)	13 (15.5)	23 (27.1)	17 (20.5)
Abdominal distension	2 (2.4)	0	2 (2.4)	3 (3.6)
Constipation	3 (3.7)	1 (1.2)	11 (12.9)	6 (7.2)
Diarrhea	1 (1.2)	0	2 (2.4)	0
Dry mouth	0	0	2 (2.4)	5 (6.0)
Dyspepsia	2 (2.4)	1 (1.2)	1 (1.2)	2 (2.4)
Nausea	0	7 (8.3)	6 (7.1)	3 (3.6)
Rectal hemorrhage	0	2 (2.4)	0	0
General disorders and administration site conditions	1 (1.2)	4 (4.8)	4 (4.7)	4 (4.8)
Fatigue	0	2 (2.4)	2 (2.4)	0
Immune system disorders	0	2 (2.4)	2 (2.4)	0
Hypersensitivity	0	2 (2.4)	1 (1.2)	0
Infections and infestations	34 (41.5)	32 (38.1)	18 (21.2)	27 (32.5)
Acute sinusitis	2 (2.4)	2 (2.4)	0	0
Bronchitis	2 (2.4)	2 (2.4)	5 (5.9)	1 (1.2)
Conjunctivitis	0	2 (2.4)	0	1 (1.2)
Gastroenteritis	1 (1.2)	3 (3.6)	0	3 (3.6)
Influenza	1 (1.2)	0	4 (4.7)	1 (1.2)
Nasopharyngitis	4 (4.9)	2 (2.4)	2 (2.4)	1 (1.2)
Pharyngitis	0	0	0	2 (2.4)
Pharyngitis streptococcal	1 (1.2)	4 (4.8)	1 (1.2)	0
Sinusitis	3 (3.7)	2 (2.4)	1 (1.2)	3 (3.6)
Tooth infection	4 (4.9)	0	1 (1.2)	2 (2.4)
Upper respiratory tract infection	15 (18.3)	11 (13.1)	5 (5.9)	9 (10.8)
Urinary tract infection	0	3 (3.6)	1 (1.2)	2 (2.4)

Viral infection	0	2 (2.4)	1 (1.2)	1 (1.2)
Vulvovaginal candidiasis	0	3 (3.6)	0	0
Vulvovaginal mycotic infection	0	4 (4.8)	0	4 (4.8)
Injury, poisoning, and procedural complications	3 (3.7)	3 (3.6)	2 (2.4)	3 (3.6)
Fall	2 (2.4)	0	0	0
Muscle strain	1 (1.2)	2 (2.4)	1 (1.2)	1 (1.2)
Investigations	2 (2.4)	3 (3.6)	5 (5.9)	1 (1.2)
Blood creatine phosphokinasae increased	1 (1.2)	1 (1.2)	3 (3.5)	0
Metabolism and nutrition disorders	1 (1.2)	0	4 (4.7)	5 (6.0)
Decreased appetite	0	0	2 (2.4)	1 (1.2)
Polydipsia	0	0	0	2 (2.4)
Musculoskeletal and connective tissue disorders	4 (4.9)	9 (10.7)	3 (3.5)	9 (10.8)
Arthralgia	1 (1.2)	1 (1.2)	1 (1.2)	2 (2.4)
Back pain	1 (1.2)	3 (3.6)	1 (1.2)	0
Osteoarthritis	0	0	1 (1.2)	2 (2.4)
Pain in extremity	0	1 (1.2)	0	2 (2.4)
Nervous system disorders	3 (3.7)	6 (7.1)	5 (5.9)	10 (12.0)
Dizziness	0	1 (1.2)	0	2 (2.4)
Headache	1 (1.2)	3 (3.6)	2 (2.4)	5 (6.0)
Tension headache	0	0	0	2 (2.4)
Psychiatric disorders	4 (4.9)	3 (3.6)	4 (4.7)	5 (6.0)
Anxiety	0	2 (2.4)	0	0
Insomnia	3 (3.7)	0	1 (1.2)	2 (2.4)
Sleep disorder	0	0	0	2 (2.4)
Respiratory, thoracic, and mediastinal disorders	1 (1.2)	5 (6.0)	3 (3.5)	8 (9.6)
Cough	0	2 (2.4)	2 (2.4)	0
Sinus congestion	1 (1.2)	1 (1.2)	1 (1.2)	2 (2.4)
Skin and subcutaneous tissue disorders	3 (3.7)	5 (6.0)	2 (2.4)	4 (4.8)
Rash	0	2 (2.4)	1 (1.2)	0

AE, adverse event; PBO, placebo; CANA, canagliflozin; PHEN, phentermine.

SUPPLEMENTARY DATA

Supplementary Table 4. Mean Percent Changes in Clinical Laboratory Parameters from Baseline to Week 26[*,†]

Parameter	PBO	CANA	PHEN	CANA/PHEN
ALT, n	55	52	58	59
Mean baseline, U/L	25.0 ± 14.1	23.6 ± 10.3	22.8 ± 9.6	24.6 ± 11.5
Mean percentage change	–1.4% ± 32.3	–11.9% ± 32.8	–8.3% ± 31.6	–17.4% ± 22.6
Bilirubin, n	55	52	58	59
Mean baseline, μmol/L	8.5 ± 3.6	8.6 ± 4.5	8.4 ± 4.8	8.2 ± 4.0
Mean percentage change	–4.7% ± 34.1	–1.1% ± 43.6	–7.4% ± 29.0	10.8% ± 50.6
Bicarbonate, n	55	52	57	59
Mean baseline, mEq/L	23.9 ± 1.9	23.7 ± 2.0	24.2 ± 2.3	24.3 ± 2.4
Mean percentage change	–2.1% ± 11.6	–3.1% ± 12.4	0.3% ± 9.1	–0.5% ± 11.0
BUN, n	55	52	58	59
Mean baseline, mmol/L	4.8 ± 1.2	4.9 ± 1.5	4.8 ± 1.3	5.3 ± 1.3
Mean percentage change	10.9% ± 21.7	10.2% ± 24.1	2.9% ± 31.0	10.6% ± 25.3
Creatinine, n	55	52	58	59
Mean baseline, μmol/L	73.2 ± 14.2	74.1 ± 15.0	73.9 ± 14.1	73.0 ± 11.9
Mean percentage change	–1.8% ± 10.0	–2.2% ± 10.9	–4.7% ± 9.6	–1.4% ± 11.1
eGFR, n[‡]	55	52	58	59
Mean baseline, mL/min/1.73 m^2	92.2 ± 16.9	92.5 ± 14.9	90.5 ± 15.1	92.7 ± 13.6
Mean percentage change	3.3% ± 10.8	3.4% ± 10.0	6.8% ± 11.2	2.8% ± 12.1
GGT, n	55	52	58	59
Mean baseline, U/L	25.3 ± 18.3	24.9 ± 22.9	22.4 ± 15.7	24.4 ± 15.4
Mean percentage change	9.0% ± 53.3	–1.1% ± 22.4	–3.3% ± 24.7	–7.7% ± 28.6
Hemoglobin, n	54	52	57	59
Mean baseline, g/L	138.0 ± 12.6	135.4 ± 16.6	137.2 ± 13.4	137.4 ± 12.1
Mean percentage change	0.0% ± 4.8	5.6% ± 5.8	–0.1% ± 4.3	3.9% ± 6.8
Potassium, n	55	52	58	59
Mean baseline, mEq/L	4.3 ± 0.4	4.2 ± 0.3	4.2 ± 0.3	4.3 ± 0.3
Mean percentage change	–0.8% ± 9.9	–0.8% ± 8.0	–2.0% ± 8.0	–0.3% ± 9.3
Urate, n	55	52	58	59
Mean baseline, μmol/L	316.9 ± 84.1	335.0 ± 77.1	344.6 ± 75.9	337.2 ± 81.6
Mean percentage change	5.6% ± 14.2	–17.0% ± 17.2	–2.7% ± 13.4	–23.1% ± 14.4

PBO, placebo; CANA, canagliflozin; PHEN, phentermine; ALT, alanine aminotransferase; BUN, blood urea nitrogen; eGFR, estimated glomerular filtration rate; GGT, gamma glutamyl transferase; SD, standard deviation; BSA, bovine serum albumin.

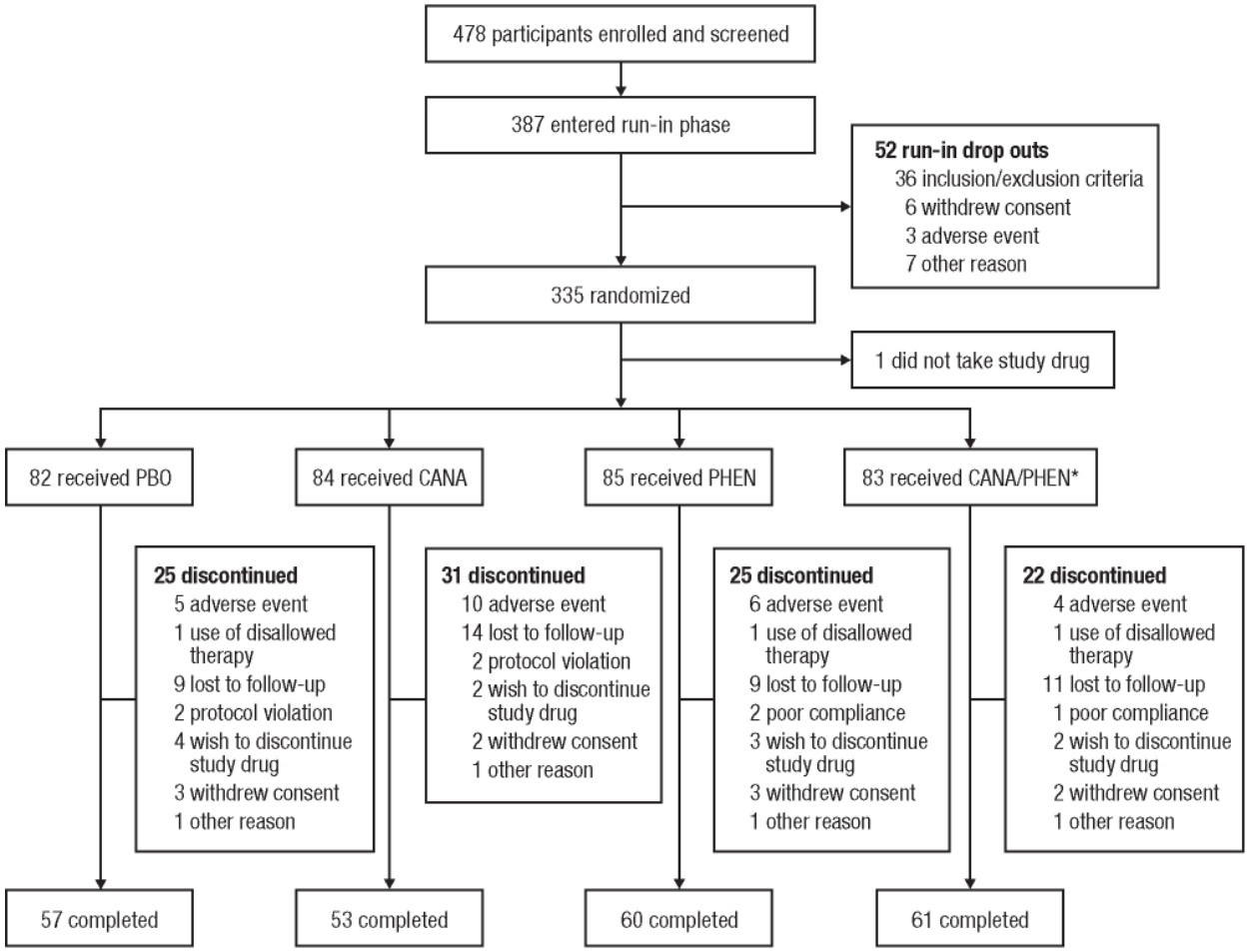
[*]Reported within 2 days of last dose of study drug.

[†]Data are mean ± SD.

[‡]From creatinine adjusted for BSA.

SUPPLEMENTARY DATA

Supplementary Figure 1. Study flow diagram.



PBO, placebo; CANA, canagliflozin; PHEN, phentermine.
*84 participants randomly assigned.