Supplementary Information

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Supplementary Table 1. Demographic and Clinical Characteristics by Screening eGFR

	eGFR 30-<45 mL/min/1.73 m^2		eGFR 45-<60 mL/min/1.73 m^2		eGFR 60-<90 mL/min/1.73 m^2	
Characteristic*	**Canagliflozin (N=657)**	**Placebo (N=656)**	**Canagliflozin (N=640)**	**Placebo (N=639)**	**Canagliflozin (N=905)**	**Placebo (N=904)**
Age, y	64.4 ± 9.3	64.9 ± 9.4	63.0 ± 9.1	62.9 ± 9.4	61.7 ± 8.9	62.1 ± 8.8
Female, n (%)	220 (33.5)	191 (29.1)	227 (35.5)	230 (36.0)	315 (34.8)	311 (34.4)
Race, n (%)						
White	426 (64.8)	413 (63.0)	432 (67.5)	411 (64.3)	629 (69.5)	620 (68.6)
Black or African American	36 (5.5)	28 (4.3)	34 (5.3)	36 (5.6)	42 (4.6)	48 (5.3)
Asian	131 (19.9)	145 (22.1)	133 (20.8)	140 (21.9)	161 (17.8)	167 (18.5)
Other†	64 (9.7)	70 (10.7)	41 (6.4)	52 (8.1)	73 (8.1)	69 (7.6)
Region, n (%)						
North America	202 (30.7)	189 (28.8)	150 (23.4)	203 (31.8)	222 (24.5)	216 (23.9)
Central/South America	121 (18.4)	127 (19.4)	140 (21.9)	118 (18.5)	215 (23.8)	220 (24.3)
Europe	144 (21.9)	142 (21.6)	151 (23.6)	104 (16.3)	159 (17.6)	164 (18.1)
Rest of the world	190 (28.9)	198 (30.2)	199 (31.1)	214 (33.5)	309 (34.1)	304 (33.6)
Current smoker, n (%)	87 (13.2)	74 (11.3)	80 (12.5)	84 (13.1)	174 (19.2)	140 (15.5)
History of hypertension, n (%)	639 (97.3)	642 (97.9)	620 (96.9)	617 (96.6)	872 (96.4)	870 (96.2)
History of heart failure, n (%)	109 (16.6)	90 (13.7)	88 (13.8)	91 (14.2)	132 (14.6)	142 (15.7)
Duration of diabetes, y	16.9 ± 9.3	17.2 ± 8.8	15.9 ± 8.8	16.3 ± 8.6	14.3 ± 7.9	14.9 ± 8.3
Drug therapy, n (%)						
Insulin	488 (74.3)	461 (70.3)	432 (67.5)	439 (68.7)	532 (58.8)	532 (58.8)
Sulfonylurea	160 (24.4)	182 (27.7)	166 (25.9)	175 (27.4)	286 (31.6)	299 (33.1)
Biguanides	214 (32.6)	233 (35.5)	383 (59.8)	365 (57.1)	679 (75.0)	671 (74.2)
GLP-1 receptor agonist	26 (4.0)	25 (3.8)	20 (3.1)	25 (3.9)	43 (4.8)	44 (4.9)
DPP-4 inhibitor	114 (17.4)	112 (17.1)	123 (19.2)	110 (17.2)	141 (15.6)	151 (16.7)
Statin	480 (73.1)	474 (72.3)	469 (73.3)	434 (67.9)	589 (65.1)	590 (65.3)
Antithrombotic‡	418 (63.6)	399 (60.8)	379 (59.2)	373 (58.4)	544 (60.1)	511 (56.5)
RAAS inhibitor	656 (99.8)	655 (99.8)	640 (100)	638 (99.8)	905 (100)	901 (99.7)
Beta blocker	303 (46.1)	319 (48.6)	262 (40.9)	259 (40.5)	318 (35.1)	309 (34.2)
Diuretic	352 (53.6)	366 (55.8)	303 (47.3)	303 (47.4)	371 (41.0)	362 (40.0)
Microvascular disease history, n (%)						
Retinopathy	300 (45.7)	296 (45.1)	282 (44.1)	272 (42.6)	353 (39.0)	379 (41.9)
Nephropathy	657 (100)	656 (100)	640 (100)	639 (100)	905 (100)	904 (100)
Neuropathy	328 (49.9)	310 (47.3)	299 (46.7)	328 (51.3)	450 (49.7)	432 (47.8)
History of cardiovascular disease, n (%)	345 (52.5)	338 (51.5)	325 (50.8)	326 (51.0)	443 (49.0)	443 (49.0)
Body mass index, kg/m^2	31.6 ± 6.3	31.1 ± 6.0	31.1 ± 5.8	31.4 ± 6.6	31.3 ± 6.3	31.4 ± 6.0
Systolic blood pressure, mmHg	141.4 ± 16.3	140.3 ± 16.6	139.0 ± 15.3	140.2 ± 15.9	139.2 ± 15.2	140.1 ± 14.7

Diastolic blood pressure, mmHg	77.4 ± 9.2	77.7 ± 9.8	77.8 ± 9.9	78.1 ± 9.4	79.2 ± 8.9	79.1 ± 9.0
HbA1c, %	8.2 ± 1.3	8.1 ± 1.3	8.2 ± 1.3	8.2 ± 1.3	8.4 ± 1.3	8.4 ± 1.4
Cholesterol, mmol/L						
Total	4.7 ± 1.3	4.5 ± 1.2	4.6 ± 1.3	4.7 ± 1.3	4.8 ± 1.3	4.7 ± 1.3
Triglycerides	2.3 ± 1.5	2.3 ± 1.7	2.3 ± 1.7	2.3 ± 1.6	2.2 ± 1.6	2.1 ± 1.7
HDL cholesterol	1.1 ± 0.3	1.1 ± 0.3	1.1 ± 0.3	1.2 ± 0.3	1.2 ± 0.4	1.2 ± 0.3
LDL cholesterol	2.5 ± 1.1	2.4 ± 1.0	2.4 ± 1.1	2.5 ± 1.1	2.6 ± 1.1	2.5 ± 1.0
Ratio of LDL to HDL	2.4 ± 1.1	2.2 ± 1.0	2.3 ± 1.1	2.3 ± 1.1	2.3 ± 1.1	2.3 ± 1.0
eGFR, mL/min/1.73 m^2[‖]	37.9 ± 9.0	37.5 ± 8.1	53.0 ± 10.4	52.5 ± 9.6	72.1 ± 12.8	71.9 ± 14.0
Median urine albumin:creatinine ratio (IQR), mg/g[#]	1116.0 (498.0-2283.0)	1065.0 (553.0-2343.0)	925.5 (464.5-1791.0)	936.0 (499.0-1868.0)	794.0 (425.0-1517.0)	792.5 (418.5-1587.0)
Median urine albumin:creatinine ratio (IQR), mg/mmol[#]	126.3 (56.3-258.3)	120.4 (62.5-264.8)	104.6 (52.5-202.6)	105.8 (56.5-211.3)	89.8 (48.1-171.5)	89.6 (47.3-179.5)

eGFR, estimated glomerular filtration rate; GLP-1, glucagon-like peptide-1; DPP-4, dipeptidyl peptidase-4; RAAS, renin angiotensin aldosterone system; HDL-C, high-density lipoprotein-cholesterol; LDL-C, low-density lipoprotein-cholesterol; IQR, interquartile range; SD, standard deviation.

*Plus-minus values are mean ± SD.

[†]Includes American Indian or Alaska Native, Native Hawaiian or other Pacific Islander, multiple, other, unknown, and not reported.

[‡]Includes anticoagulation and antiplatelet agents, including aspirin.

[‖]One participant treated with canagliflozin in the screening eGFR 45-<60 mL/min/1.73m^2 subgroup was missing eGFR at baseline.

[#]Eligibility was based on screening urine albumin:creatinine ratio >300 mg/g to ≤5000 mg/g (33.9-<565.6 mg/mmol).

Supplementary Table 2. Effects of Canagliflozin on HbA1c, Body Weight, Systolic Blood Pressure and UACR According to Screening eGFR*

	eGFR 30-<45 mL/min/1.73 m^2		eGFR 45-<60 mL/min/1.73 m^2		eGFR 60-<90 mL/min/1.73 m^2	
	Canagliflozin	**Placebo**	**Canagliflozin**	**Placebo**	**Canagliflozin**	**Placebo**
HbA1c, %, n	620	631	618	619	877	877
Mean (SD) baseline	8.1 (1.3)	8.2 (1.3)	8.2 (1.3)	8.2 (1.3)	8.4 (1.3)	8.4 (1.4)
LS mean change (SE)	–0.37 (0.04)	–0.23 (0.04)	–0.36 (0.04)	–0.12 (0.04)	–0.49 (0.03)	–0.14 (0.03)
Difference vs placebo (95% CI)	–0.15 (–0.24, –0.05)		–0.24 (–0.33, –0.14)		–0.34 (–0.42, –0.26)	
Body weight, kg, n	646	648	634	634	899	893
Mean (SD) baseline	88.1 (20.6)	86.2 (19.9)	86.2 (19.5)	86.9 (22.0)	87.5 (21.6)	87.4 (20.3)
LS mean change (SE)	–1.07 (0.13)	–0.34 (0.13)	–1.11 (0.13)	–0.30 (0.13)	–1.21 (0.10)	–0.39 (0.10)
Difference vs placebo (95% CI)	–0.72 (–0.94, –0.51)		–0.80 (–1.00, –0.61)		–0.82 (–0.99, –0.65)	
Systolic blood pressure, mmHg, n	647	648	635	634	899	894
Mean (SD) baseline	141.5 (16.3)	140.2 (16.6)	139.0 (15.4)	140.2 (15.9)	139.2 (15.1)	140.2 (14.6)
LS mean change (SE)	–2.55 (0.45)	1.14 (0.45)	–2.92 (0.41)	0.56 (0.42)	–3.13 (0.32)	–0.25 (0.32)
Difference vs placebo (95% CI)	–3.69 (–4.81, –2.57)		–3.48 (–4.56, –2.39)		–2.88 (–3.71, –2.06)	
UACR, mg/g, n	598	603	604	598	860	854
Median baseline	1112.0	1057.0	905.5	902.5	774.0	789.0
Geometric mean (95% CI)	641.5 (592.0,695.2)	963.7 (889.1,1044.5)	530.0 (487.8, 575.8)	845.9 (777.8, 919.9)	447.8 (413.5, 485.1)	619.9 (572.2, 671.7)
Percent change in the geometric mean relative to placebo (95% CI)	33 (27; 40)		37 (31; 43)		28 (20; 35)	

UACR, urinary albumin:creatinine ratio; eGFR, estimated glomerular filtration rate; SD, standard deviation; SE, standard error; CI, confidence interval.

*Linear mixed effects models for repeated measures were used to analyze changes in intermediate outcomes over time.

Supplementary Table 3. Number of Events in Participants Whose Final eGFR Was <30 mL/min/1.73m^2 From the Point Their eGFR First Fell Below 30 mL/min/1.73m^2

	Canagliflozin (n=417)	**Placebo (n=512)**
Primary composite endpoint	130	205
Composite of cardiovascular death or hospitalization for heart failure	46	73
Cardiovascular death, myocardial infarction, or stroke	46	66
Hospitalization for heart failure	23	40
Composite of doubling of serum creatinine, end-stage kidney disease, or renal death	111	181
Cardiovascular death	30	44
Mean (SD) follow-up period from eGFR <30 mL/min/1.73m^2 (months)	20.5 (13.30)	18.4 (11.99)

eGFR, estimated glomerular filtration rate.