Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

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Supplementary Appendix

Supplementary Appendix

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Inclusion and Exclusion Criteria

Inclusion Criteria at Screening Visit

1. Man or woman ≥30 years-old with a clinical diagnosis of type 2 diabetes mellitus (T2DM).
2. Glycated hemoglobin (HbA1c) ≥6.5% to ≤12.0%, (≥6.5% to ≤10.5% in Germany).
3. Estimated glomerular filtration rate (eGFR) ≥30 to <90 mL/min/1.73 m^2 (as determined using the Chronic Kidney Disease Epidemiology Collaboration [CKD-EPI] equation).

   Note*:* An overall global target ratio for randomized cohort of approximately 60%:40% for CKD Stage 3 (i.e., eGFR ≥30 to <60 mL/min/1.73 m^2; first category):CKD Stage 2 (i.e., eGFR ≥60 to <90 mL/min/1.73 m^2; second category) will be monitored centrally. In an effort to limit exposure to investigational product and to ensure sufficient experiences in subjects with Stage 3 CKD, entry of subjects with Stage 2 CKD (i.e., eGFR ≥60 to <90 mL/min/1.73 m^2) may be restricted on a regional and/or site basis should the ratio drift substantially off target over the course of the recruitment period.
4. Urinary albumin:creatinine ratio (UACR) >300 mg/g to ≤5000 mg/g (>33.9 mg/mmol to ≤565.6 mg/mmol).
5. All subjects must be on a stable maximum tolerated labeled daily dose of ACEi or ARB for at least 4 weeks prior to randomization.

   Note: A maximum tolerated labeled daily dose of an angiotensin-converting enzyme inhibitor (ACEi) or angiotensin receptor blocker (ARB) is defined as the maximum approved labeled dose for diabetic nephropathy (for agents with an approved indication for diabetic nephropathy in patients with T2DM, i.e., losartan and irbesartan) or the maximum approved dose for hypertension (for agents without an approved indication for diabetic nephropathy), unless side effects or adverse events limit the use of the maximum approved dose. For subjects who are not

on a maximum labeled daily dose of an ACEi or ARB, investigators will be required to document why a higher dose should not be used.

6. Women must be:

   - postmenopausal, defined as
     - >45 years of age with amenorrhea for at least 18 months, or
     - >45 years of age with amenorrhea for at least 6 months and <18 months and a serum follicle stimulating hormone (FSH) level >40 IU/L, or
   - surgically sterile (have had a hysterectomy or bilateral oophorectomy, tubal occlusion [which includes tubal ligation procedures as consistent with local regulations]), or otherwise be incapable of pregnancy, or
   - heterosexually active and practicing a highly effective method of birth control, including hormonal prescription oral contraceptives, contraceptive injections, contraceptive patch, intrauterine device, double-barrier method (e.g., condoms, diaphragm, or cervical cap with spermicidal foam, cream, or gel), or male partner sterilization, and consistent with local regulations regarding use of birth control methods for subjects participating in clinical studies, for the duration of their participation in the study, or
   - not heterosexually active.

   Note: Subjects who are not heterosexually active at screening must agree to utilize a highly effective method of birth control if they become heterosexually active during their participation in the study.

7. Women of childbearing potential (i.e., those subjects who do not meet the postmenopausal definition above), regardless of age, must have a negative urine pregnancy test at baseline (Day 1) and at screening if required by local regulations.

Note: A serum pregnancy test is acceptable in lieu of a urine pregnancy test if required by local regulations.

8. Willing and able to adhere to the prohibitions and restrictions specified in this protocol.
9. Subjects must have signed an informed consent document indicating that they understand the purpose of and procedures required for the study and are willing to participate in the study. Each subject must also sign a separate informed consent form if he or she agrees to provide an optional DNA sample for research (where local regulations permit). Refusal to give consent for the optional DNA research sample does not exclude a subject from participation in the study.

Inclusion Criterion for Randomization

10. Subjects must have ≥80% compliance (by pill count) with single-blind placebo.

Exclusion Criteria

Potential subjects who meet any of the following criteria will be excluded from participating in the study:

Diabetes-related/Metabolic

1. History of diabetic ketoacidosis or type 1 diabetes mellitus (T1DM).

2. History of hereditary glucose-galactose malabsorption or primary renal glucosuria.

Renal/Cardiovascular

3. Known medical history or clinical evidence suggesting nondiabetic renal disease.

4. Renal disease that required treatment with immunosuppressive therapy or a history of chronic dialysis or renal transplant.

Note: Subjects with a history of treated childhood renal disease, without sequelae, may participate.

5. Uncontrolled hypertension (systolic blood pressure [BP] ≥180 and/or diastolic BP ≥100 mmHg) by Week –2.

Note: Subjects not fulfilling BP criteria at the initial screening visit may have their BP-lowering medication regimen adjusted, followed by re-evaluation up to the Week –2 run-in period (the ACEi or ARB regimen must be stable for at least 4 weeks before Day 1 to be eligible).

6. Blood potassium level >5.5 mmol/L during screening.

Note: Subjects in whom hyperkalemia was associated with the use of nonsteroidal anti-inflammatory drugs (NSAIDs), β-blockers, or mineralocorticoid receptor antagonists (MRAs; e.g., spironolactone or eplerenone), who have been withdrawn from these drugs, and in whom usage of these drugs is not indicated in the view of the treating physician, may be included in the study.

7. Myocardial infarction, unstable angina, revascularization procedure (e.g., stent or bypass graft surgery), or cerebrovascular accident within 12 weeks before randomization, or a revascularization procedure is planned during the trial.

8. Current or history of heart failure of New York Heart Association (NYHA) class IV cardiac disease (The Criteria Committee of the NYHA).

9. Electrocardiogram (ECG) findings within 12 weeks before randomization that would require urgent diagnostic evaluation or intervention (e.g., new clinically important arrhythmia or conduction disturbance).

Gastrointestinal

10. Known significant liver disease (e.g., acute hepatitis, chronic active hepatitis, cirrhosis).

Laboratory

11. Alanine aminotransferase (ALT) levels >2.0 times the upper limit of normal (ULN) or total bilirubin >1.5 times the ULN, unless in the opinion of the investigator and as agreed upon by the sponsor's medical officer, the findings are consistent with Gilbert's disease.

Other Conditions

12. History of malignancy within 5 years before screening (exceptions: squamous and basal cell carcinomas of the skin and carcinoma of the cervix in situ, or a malignancy that in the opinion of the investigator, with concurrence with the sponsor's medical monitor, is considered cured with minimal risk of recurrence).

13. History of human immunodeficiency virus (HIV) antibody positive.

14. Major surgery within 12 weeks before randomization, or has not fully recovered from surgery.

15. Any condition that in the opinion of the investigator or sponsor's medical monitor would make participation not in the best interest of the subject, or could prevent, limit, or confound the protocol-specified assessments.

16. History of atraumatic amputation within past 12 months of screening, or an active skin ulcer, osteomyelitis, gangrene, or critical ischemia of the lower extremity within 6 months of screening (added May 5, 2016).

Medications/Therapies

17. Combination use of an ACEi and ARB.

18. Use of an MRA or a direct renin inhibitor (DRI).

Note: If deemed clinically appropriate at the discretion of the investigator, subjects may be removed from therapy with an MRA or DRI during screening. Subjects who are off therapy with an MRA or DRI for at least 8 weeks prior to randomization may be considered eligible for enrollment.

19. Current use of a sodium glucose co-transporter 2 (SGLT2) inhibitor (within 12 weeks prior to randomization).

20. Current participation in another canagliflozin study or previously exposed to canagliflozin in a prior canagliflozin study.

21. Known allergies, hypersensitivity, or intolerance to canagliflozin or its excipients.

22. Received an active investigational drug (including vaccines) other than a placebo agent, or used an investigational medical device within 12 weeks before Day 1/baseline.

General

23. Pregnant or breast-feeding or planning to become pregnant or breast-feed during the study.

24. Employees of the investigator or study center, with direct involvement in the proposed study or other studies under the direction of that investigator or study center, as well as family members of the employees or the investigator.

Note: Investigators should ensure that all study enrollment criteria have been met and determine that the subject has not had any interval change in clinical status since the time of the initial screening visit. Before randomization, subjects whose clinical status changes after screening such that they now meet an exclusion criterion should be excluded from participation.

Safety Analyses

Adverse events (AEs)	All AEs will be collected and coded using the *Medical Dictionary for Regulatory Activities* (*MedDRA*) from randomization until 30 days after the last date of blinded study medication
AEs of interest	All malignancies, renal cell carcinoma, fatal pancreatitis, hemorrhagic/necrotizing pancreatitis, severe hypersensitivity reactions (e.g., angioedema, anaphylaxis, Stevens-Johnson syndrome), photosensitivity reactions, serious AEs of hepatic injury, nephrotoxicity/acute kidney injury, venous thromboembolic events, fractures, diabetic ketoacidosis (and related AEs including ketoacidosis, metabolic acidosis, or acidosis), amputation, and pregnancy
Hypoglycemia	All episodes of hypoglycemia (both symptomatic and asymptomatic) are recorded on a dedicated hypoglycemia electronic case report form (eCRF)
Safety laboratory tests	Chemistry, hematology, urinalysis
Physical examination	Pulse, blood pressure, weight

Primary Endpoint Criteria

End-stage Kidney Disease (ESKD)

In the absence of universally accepted guidelines that define the onset of ESKD, the following definitions have been developed to identify and adjudicate ESKD events:

1. Diagnosis

Worsening uremia in patients progressing from chronic kidney disease (CKD) to ESKD causes characteristic symptoms which require renal replacement therapy (RRT) in the form of dialysis or transplantation. The requirement of ongoing RRT establishes the diagnosis of ESKD. In some cases, the diagnosis can be made in the absence of RRT when certain criteria are fulfilled:

- Kidney Transplantation: Definitive RRT prescribed when uremic symptoms have already occurred, or are anticipated to occur, due to the progression of irreversible CKD. Death during the transplant surgery will be considered kidney transplantation.
- Chronic Dialysis: ESKD will be diagnosed if dialysis is performed for ≥30 days and is not subsequently known to recover. Indications for dialysis are indicated in Section 2 below.
- Dialysis Not Administered: In cases where dialysis is not available or not administered due to futility or subject refusal, the diagnosis of ESKD will require a sustained estimated glomerular filtration rate (eGFR) of <15 mL/min/1.73 m^2 (by CKD Epidemiology Collaboration [CKD-EPI] formula and confirmed by repeat central laboratory measure at 30 days or more of the initial onset).

2. Onset of ESKD

The mode of onset of ESKD will be adjudicated into the following categories:

- Chronic progression.
- Acute deterioration, diagnosed when the decline in kidney function is sudden and acute kidney injury is superimposed on CKD, resulting in RRT.

3. Confirmation of ESKD

- In cases where RRT is given in the form of dialysis, the patient will be contacted at 90 days after the initiation of dialysis to document if dialysis is continuing.
- If the patient recovers renal function (defined as patient taken off dialysis because the physician evaluates that patient has enough renal function to live independently), the diagnosis of ESKD will be rescinded.
- If the patient is known to have received dialysis for >30 days but <90 days, and not known to recover, ESKD will be confirmed. The reason for the unavailability of information beyond 30 days should be clearly documented by the investigator.
- If dialysis was initiated, but not continued for 30 days due to death, futility of therapy, or transplantation, the patient will be considered to have reached ESKD. In this situation, the reason for discontinuation of dialysis should be clearly documented by the investigator.

4. Date of ESKD

- If an event is adjudicated as ESKD due to kidney transplantation, the date of the transplantation will be the date of the event if transplantation was the first form of RRT given.
- If an event is adjudicated as ESKD due to initiation of dialysis, the date when dialysis was initiated will be the date of the event.

- In cases where dialysis is unavailable, or not administered, the date of ESKD will be when eGFR falls below 15 mL/min/1.73 m^2. If a confirmatory central laboratory value cannot be collected due to death, and there is no evidence of acute kidney injury, the date of the event will be the date in which eGFR falls below 15 mL/min/1.73 m^2. If local and central laboratory tests are collected on the same day, the central laboratory value overrules the local laboratory value. Information around the presence or absence of symptoms of uremia will also be collected for all patients meeting the ESKD endpoint; however, this will not affect the final adjudication decision, which will be based on the primary definition of ESKD as described in Sections 1 to 4 above.
- Symptomatic Uremia: Symptomatic uremia is diagnosed in the presence of the uremic syndrome, which is a constellation of signs and symptom involving several different systems, including:
    - General: Pruritus, dry skin, fatigue, anhedonia;
    - Metabolic: Deterioration in nutritional status, recent significant weight loss, electrolyte or acid-base disturbances (severe hyperkalemia or severe acidosis);
    - Gastrointestinal: Nausea, vomiting;
    - Neurological: Neuropathy, encephalopathy, psychiatric disturbances, seizures;
    - Volume overload, including difficult-to-control or accelerated hypertension;
    - Bleeding diathesis not attributable to other causes;
    - Pleuritis or pericarditis of uremic origin or other;
    - Severe hyperparathyroidism.
- Advanced Asymptomatic Uremia: The initiation of dialysis is generally performed when eGFR declines to <15 mL/min/1.73 m^2 on a subjective basis in anticipation of development of uremic symptoms. If no symptoms are documented for initiation of dialysis, asymptomatic uremia will be diagnosed. In the minority of patients who exhibit no symptoms even at very low eGFR

values (such as <8 mL/min/1.73 m^2), however are initiated RRT in the view of benefits of therapy, the diagnosis will be of advanced asymptomatic uremia.

Doubling of Serum Creatinine

Doubling of serum creatinine will be defined as a ≥2-fold increase in serum creatinine from the baseline assessment that persists for ≥30 days and is not thought to be due to reversible cause.

The baseline serum creatinine, as determined by averaging the 2 values closest to randomization, will be used to compare subsequent values and determine if doubling of serum creatinine has occurred.

Both central serum creatinine values and local laboratory values may be used to calculate the increase in serum creatinine. The investigator will make all reasonable attempts to exclude reversible causes of elevation of serum creatinine such as volume depletion or nephrotoxic medication. The event will be adjudicated positively once the initial doubling of serum creatinine via local or central laboratory results has been confirmed by the central laboratory at ≥30 days, and if the process is determined to be irreversible.

If a confirmatory central laboratory value cannot be collected due to death or dialyses and there is no evidence of acute kidney injury, the event will be adjudicated positively.

The date of the event will be the date on which the creatinine first doubled. If central and local laboratory tests are collected on the same day, the central laboratory value overrules the local laboratory value.

Death

All deaths will be reviewed by the adjudicators to determine the cause of death, which will be classified as either renal death, cardiovascular (CV) death, or non-CV death.

Renal Death

Renal death refers to deaths in patients who have reached ESKD who die prior to initiating RRT and no other cause of death is adjudicated. This may occur in the situations where either the patient refuses RRT or both the physician and the patient consider RRT futile and believe that the patients' current quality of life, with their expected lifespan, outweighs the quality and quantity of life following RRT. This may also occur in situations where dialysis is not available. These events are classified as renal death when death occurs following refusal of dialysis AND no other cause of death is adjudicated. When a more specific cause of death is adjudicated, such as sepsis or trauma, the more specific cause will be designated as the primary cause of death.

CV Death

CV death includes death resulting from an acute myocardial infarction (MI), sudden cardiac death, death due to heart failure (HF), death due to stroke, death due to CV procedures, death due to CV hemorrhage, and death due to other CV causes.

1. Death due to acute MI refers to a death by any CV mechanism (e.g., arrhythmia, sudden death, HF, stroke, pulmonary embolus, peripheral arterial disease) ≤30 days after an MI related to the immediate consequences of the MI, such as progressive HF or recalcitrant arrhythmia. We note

that there may be assessable mechanisms of CV death during this time period, but for simplicity, if the CV death occurs ≤30 days of the MI, it will be considered a death due to MI.

Acute MI should be verified to the extent possible by the diagnostic criteria outlined for acute MI or by autopsy findings showing recent MI or recent coronary thrombosis. Death resulting from a procedure to treat an MI (percutaneous coronary intervention [PCI], coronary artery bypass graft surgery [CABG]), or to treat a complication resulting from MI, should also be considered death due to acute MI.

Death resulting from an elective coronary procedure to treat myocardial ischemia (i.e., chronic stable angina) or death due to an MI that occurs as a direct consequence of a CV investigation/procedure/operation should be considered as a death due to a CV procedure.

2. Sudden cardiac death refers to a death that occurs unexpectedly, not following an acute MI, and includes the following deaths:

   - Death witnessed and occurring without new or worsening symptoms;
   - Death witnessed within 60 minutes of the onset of new or worsening cardiac symptoms, unless the symptoms suggest acute MI;
   - Death witnessed and attributed to an identified arrhythmia (e.g., captured on an electrocardiographic (ECG) recording, witnessed on a monitor, or unwitnessed but found on implantable cardioverter-defibrillator review);
   - Death after unsuccessful resuscitation from cardiac arrest;
   - Death after successful resuscitation from cardiac arrest and without identification of a specific cardiac or noncardiac etiology; or

- Unwitnessed death in a subject seen alive and clinically stable ≤24 hours prior to being found dead without any evidence supporting a specific non-CV cause of death (information regarding the patient's clinical status preceding death should be provided, if available)

General Considerations

Unless additional information suggests an alternate specific cause of death (e.g., death due to other CV causes), if a patient is seen alive ≤24 hours of being found dead, sudden cardiac death should be recorded. For patients who were not observed alive within 24 hours of death, undetermined cause of death should be recorded (e.g., a subject found dead in bed, but who had not been seen by family for several days).

3. Death due to HF refers to a death in association with clinically worsening symptoms and/or signs of HF regardless of HF etiology. Deaths due to HF can have various etiologies, including single or recurrent MI, ischemic or nonischemic cardiomyopathy, hypertension, or valvular disease.

4. Death due to stroke refers to death after a stroke that is either a direct consequence of the stroke or a complication of the stroke. Acute stroke should be verified to the extent possible by the diagnostic criteria outlined for stroke.

5. Death due to CV procedures refers to death caused by the immediate complications of a cardiac procedure.

6. Death due to CV hemorrhage refers to death related to hemorrhage such as a nonstroke intracranial hemorrhage, nonprocedural or nontraumatic vascular rupture (e.g., aortic aneurysm), or hemorrhage causing cardiac tamponade.

7. Death due to other CV causes refers to a CV death not included in the above categories but with a specific, known cause (e.g., pulmonary embolism or peripheral arterial disease).

Definition of Non-CV Death

Non-CV death is defined as any death that is not thought to be due to a CV cause. The following is a suggested list of non-CV causes of death:

- Pulmonary;
- Gastrointestinal;
- Hepatobiliary;
- Pancreatic;
- Infection (includes sepsis);
- Noninfectious (e.g., systemic inflammatory response syndrome [SIRS]);
- Hemorrhage that is neither CV bleeding nor a stroke;
- Non-CV procedure or surgery;
- Trauma;
- Suicide;
- Nonprescription drug reaction or overdose;
- Prescription drug reaction or overdose;
- Neurological (non-CV);
- Malignancy; or
- Other non-CV, specify:

Definition of Undetermined Cause of Death

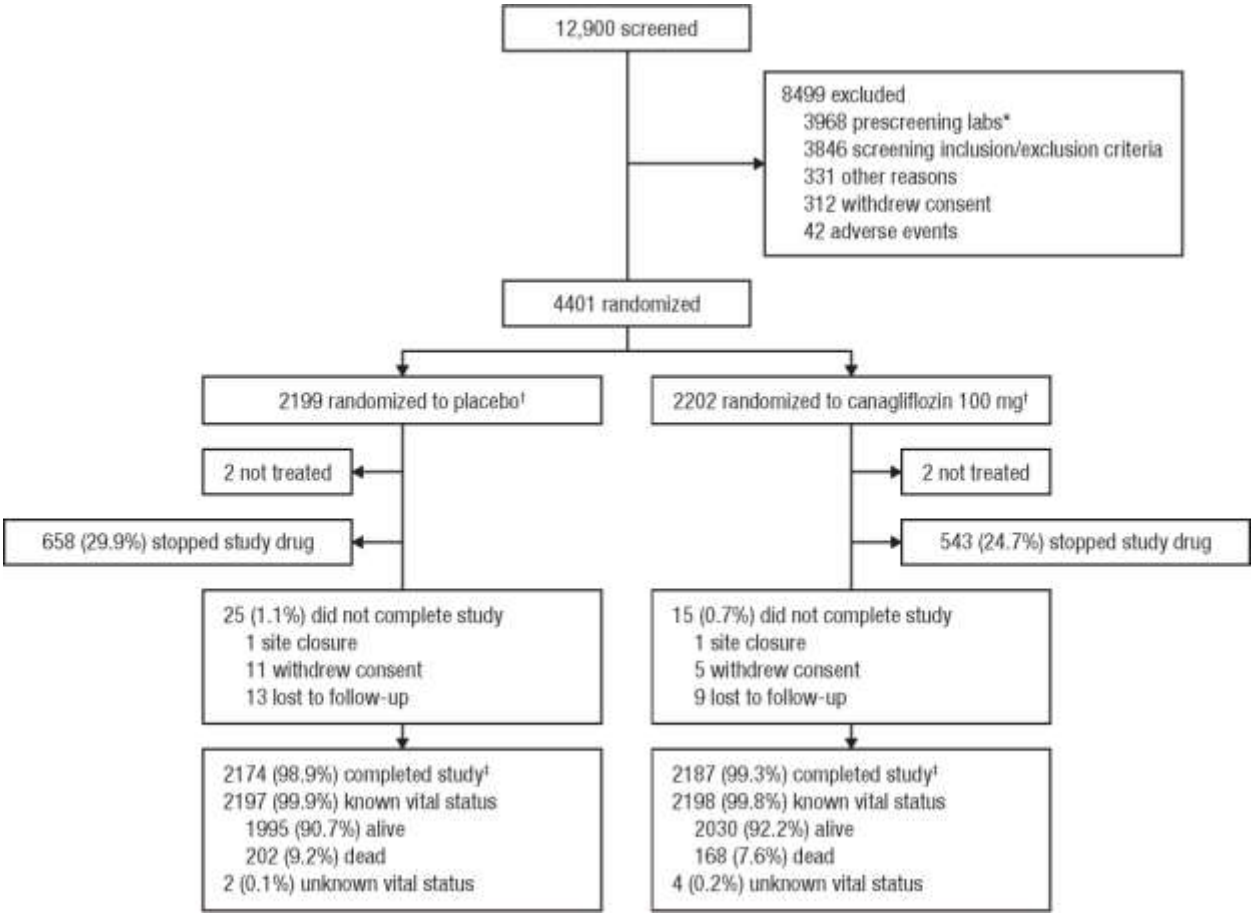
Undetermined cause of death refers to a death not attributable to one of the above categories of CV death or to a non-CV cause. Inability to classify the cause of death may be due to lack of information (e.g., the only available information is “patient died”) or when there is insufficient supporting information or detail

to assign the cause of death. This category of death should be avoided as much as possible and should only apply to a minimal number of patients.

Estimated Glomerular Filtration Rate (eGFR) Slope Analyses

The on-treatment eGFR slope for the acute and chronic phase was analyzed using a two-slope model with a knot at week 3, including the fixed effects of treatment, baseline eGFR, screening eGFR strata, continuous time, time spline (one knot at Week 3), with two-way interactions of treatment by time, treatment by time spline, eGFR strata by time, eGFR strata by time spline, and the random effects of intercept, time and time spline. Total slope at week 130 was calculated as a linear contrast of the acute and chronic phases based on the two-slope model.

Figure S1. Study flow diagram.

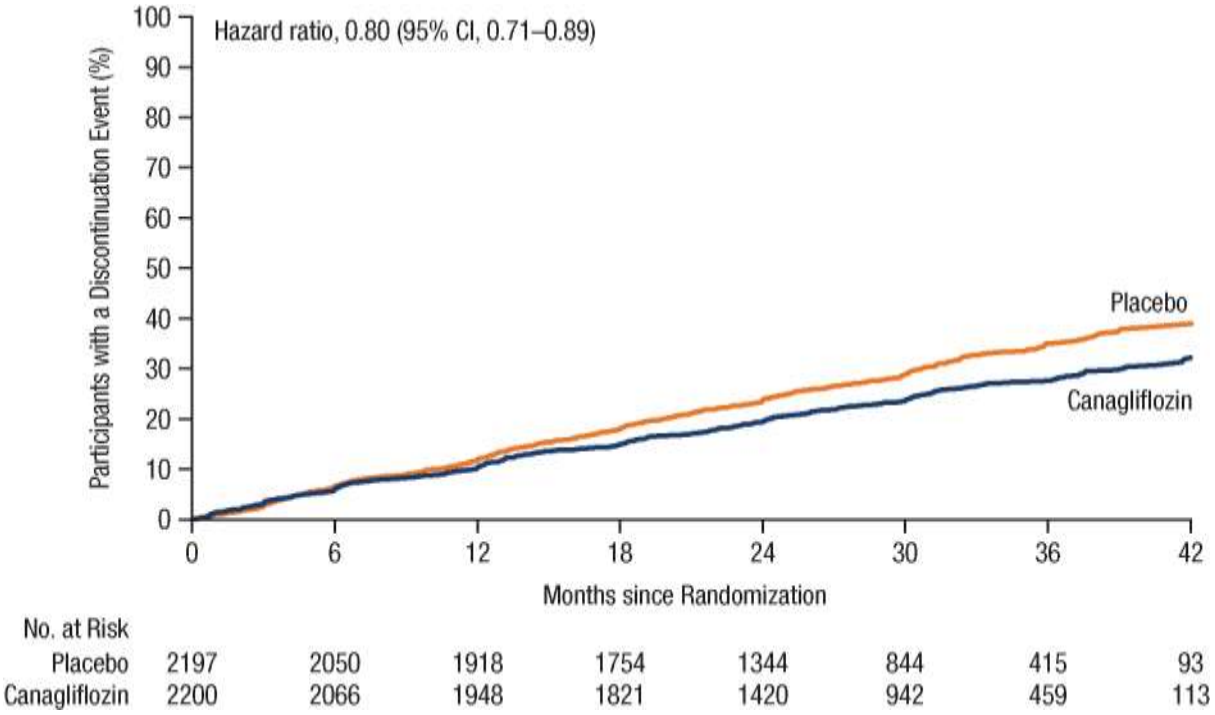


*Includes failed prescreening of estimated glomerular filtration rate and/or proteinuria/albuminuria.

†All randomized participants were in the intent-to-treat population; participants who did not receive study drug were excluded from the on-treatment and on-study analysis sets.

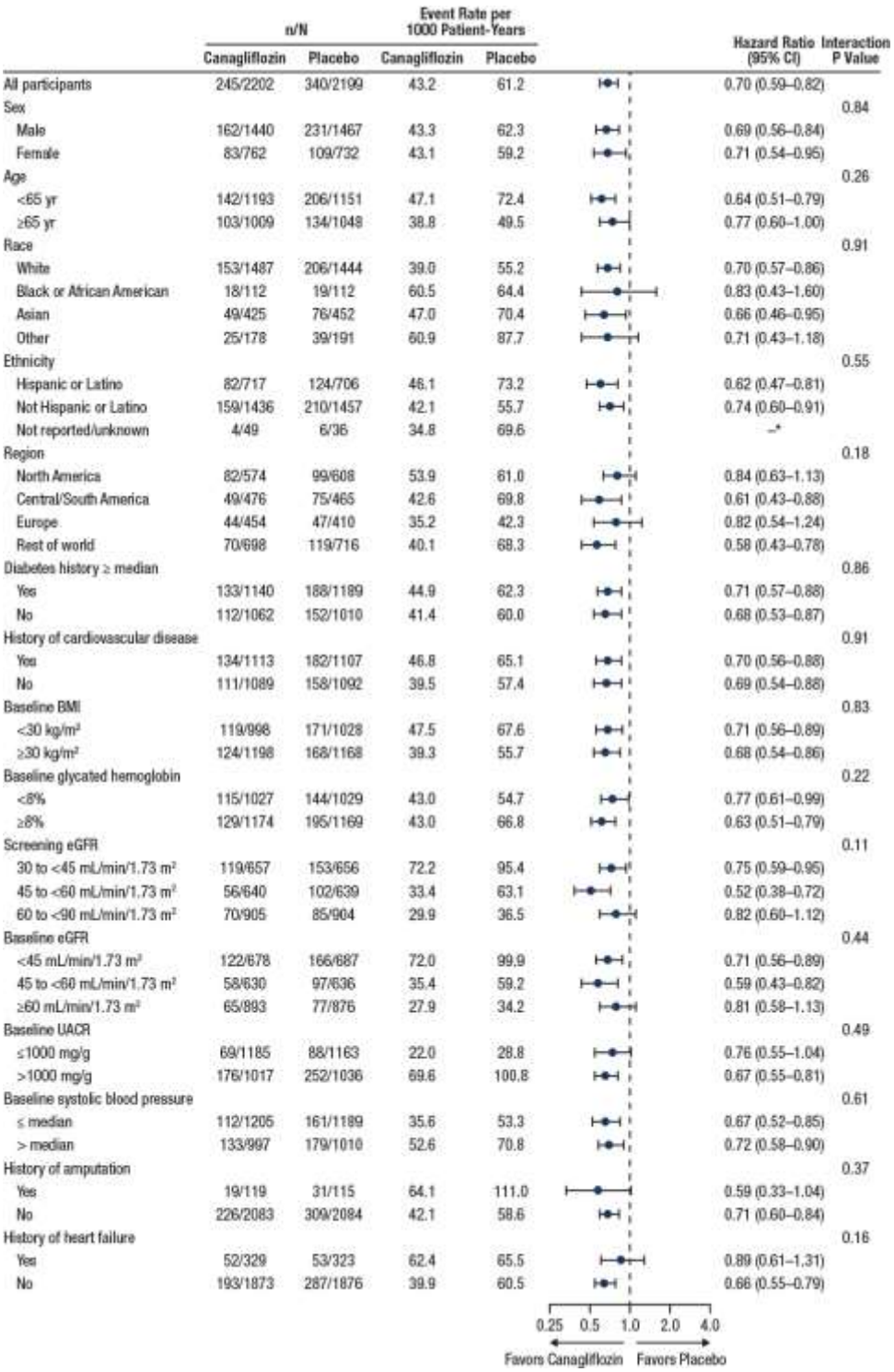
‡Defined as having been followed until a time point between the announcement of the end of study and the end of study, or if the subject had died prior.

Figure S2. Discontinuation from randomized treatment in CREDENCE.



No. at Risk								
Placebo	2197	2050	1918	1754	1344	844	415	93
Canagliflozin	2200	2066	1948	1821	1420	942	459	113

Figure S3. Subgroup analysis of the primary composite endpoint.*



	n/N		Event Rate per 1000 Patient-Years		Hazard Ratio (95% CI)	Interaction P Value
	Canagliflozin	Placebo	Canagliflozin	Placebo		
All participants	245/2202	340/2199	43.2	61.2	0.70 (0.59–0.82)	
Sex						0.84
Male	162/1440	231/1467	43.3	62.3	0.69 (0.56–0.84)	
Female	83/762	109/732	43.1	59.2	0.71 (0.54–0.95)	
Age						0.26
<65 yr	142/1193	206/1151	47.1	72.4	0.64 (0.51–0.79)	
≥65 yr	103/1009	134/1048	38.8	49.5	0.77 (0.60–1.00)	
Race						0.91
White	153/1487	206/1444	39.0	55.2	0.70 (0.57–0.86)	
Black or African American	18/112	19/112	60.5	64.4	0.83 (0.43–1.60)	
Asian	49/425	76/452	47.0	70.4	0.66 (0.46–0.95)	
Other	25/178	39/191	60.9	87.7	0.71 (0.43–1.18)	
Ethnicity						0.55
Hispanic or Latino	82/717	124/706	46.1	73.2	0.62 (0.47–0.81)	
Not Hispanic or Latino	159/1436	210/1457	42.1	55.7	0.74 (0.60–0.91)	
Not reported/unknown	4/49	6/36	34.8	69.6	–*	
Region						0.18
North America	82/574	99/608	53.9	61.0	0.84 (0.63–1.13)	
Central/South America	49/476	75/465	42.6	69.8	0.61 (0.43–0.88)	
Europe	44/454	47/410	35.2	42.3	0.82 (0.54–1.24)	
Rest of world	70/698	119/716	40.1	68.3	0.58 (0.43–0.78)	
Diabetes history ≥ median						0.86
Yes	133/1140	188/1189	44.9	62.3	0.71 (0.57–0.88)	
No	112/1062	152/1010	41.4	60.0	0.68 (0.53–0.87)	
History of cardiovascular disease						0.91
Yes	134/1113	182/1107	46.8	65.1	0.70 (0.56–0.88)	
No	111/1089	158/1092	39.5	57.4	0.69 (0.54–0.88)	
Baseline BMI						0.83
<30 kg/m²	119/998	171/1028	47.5	67.6	0.71 (0.56–0.89)	
≥30 kg/m²	124/1198	168/1168	39.3	55.7	0.68 (0.54–0.86)	
Baseline glycated hemoglobin						0.22
<8%	115/1027	144/1029	43.0	54.7	0.77 (0.61–0.99)	
≥8%	129/1174	195/1169	43.0	66.8	0.63 (0.51–0.79)	
Screening eGFR						0.11
30 to <45 mL/min/1.73 m²	119/657	153/656	72.2	95.4	0.75 (0.59–0.95)	
45 to <60 mL/min/1.73 m²	56/640	102/639	33.4	63.1	0.52 (0.38–0.72)	
60 to <90 mL/min/1.73 m²	70/905	85/904	29.9	36.5	0.82 (0.60–1.12)	
Baseline eGFR						0.44
<45 mL/min/1.73 m²	122/678	166/687	72.0	99.9	0.71 (0.56–0.89)	
45 to <60 mL/min/1.73 m²	58/630	97/636	35.4	59.2	0.59 (0.43–0.82)	
≥60 mL/min/1.73 m²	65/893	77/876	27.9	34.2	0.81 (0.58–1.13)	
Baseline UACR						0.49
≤1000 mg/g	69/1185	88/1163	22.0	28.8	0.76 (0.55–1.04)	
>1000 mg/g	176/1017	252/1036	69.6	100.8	0.67 (0.55–0.81)	
Baseline systolic blood pressure						0.61
≤ median	112/1205	161/1189	35.6	53.3	0.67 (0.52–0.85)	
> median	133/997	179/1010	52.6	70.8	0.72 (0.58–0.90)	
History of amputation						0.37
Yes	19/119	31/115	64.1	111.0	0.59 (0.33–1.04)	
No	226/2083	309/2084	42.1	58.6	0.71 (0.60–0.84)	
History of heart failure						0.16
Yes	52/329	53/323	62.4	65.5	0.89 (0.61–1.31)	
No	193/1873	287/1876	39.9	60.5	0.66 (0.55–0.79)	

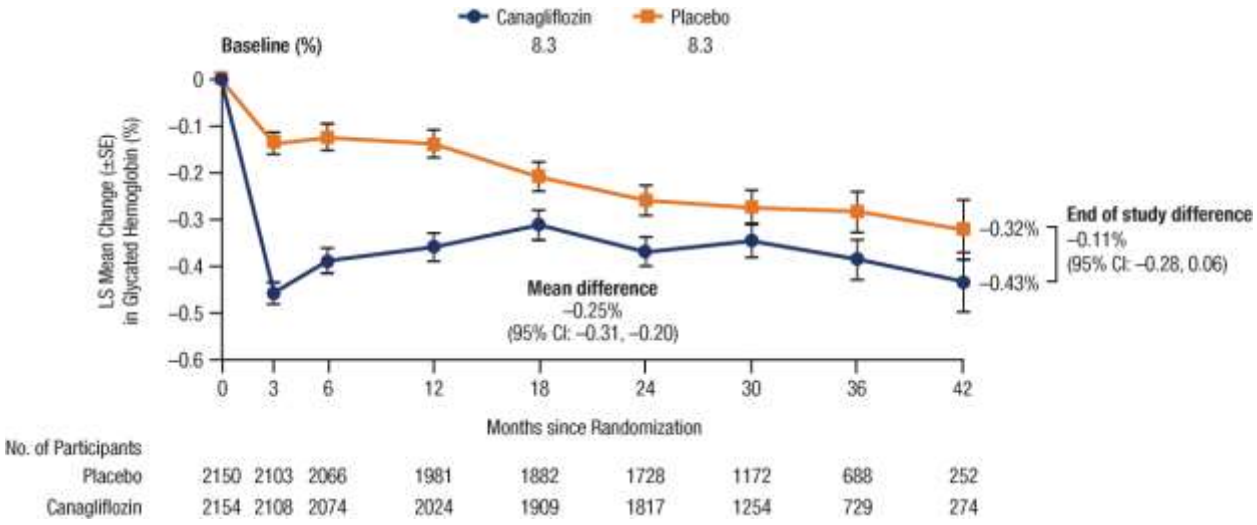
CI, confidence interval; BMI, body mass index; eGFR, estimated glomerular filtration rate; UACR, urine albumin:creatinine ratio.

*Subgroup analysis was conducted when the total number of events was greater than 10 for both treatment groups (canagliflozin group and placebo) and there was at least 1 event in both groups.

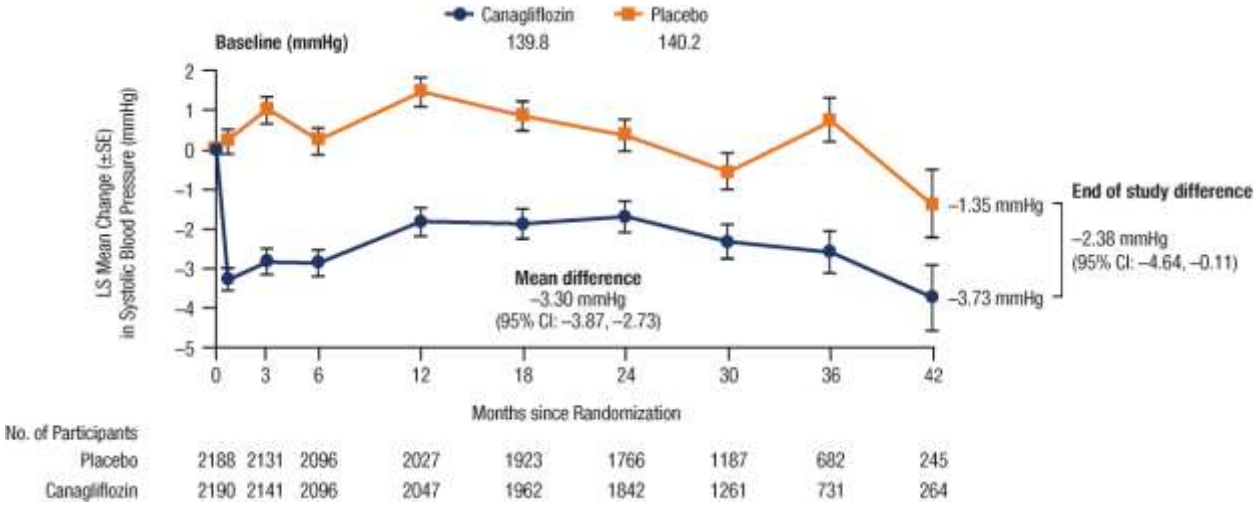
P values are based on the test of subgroup by treatment interaction in a stratified Cox proportional hazard model, without adjustment for multiple testing.

Figure S4. Effects on intermediate outcomes (ITT).*

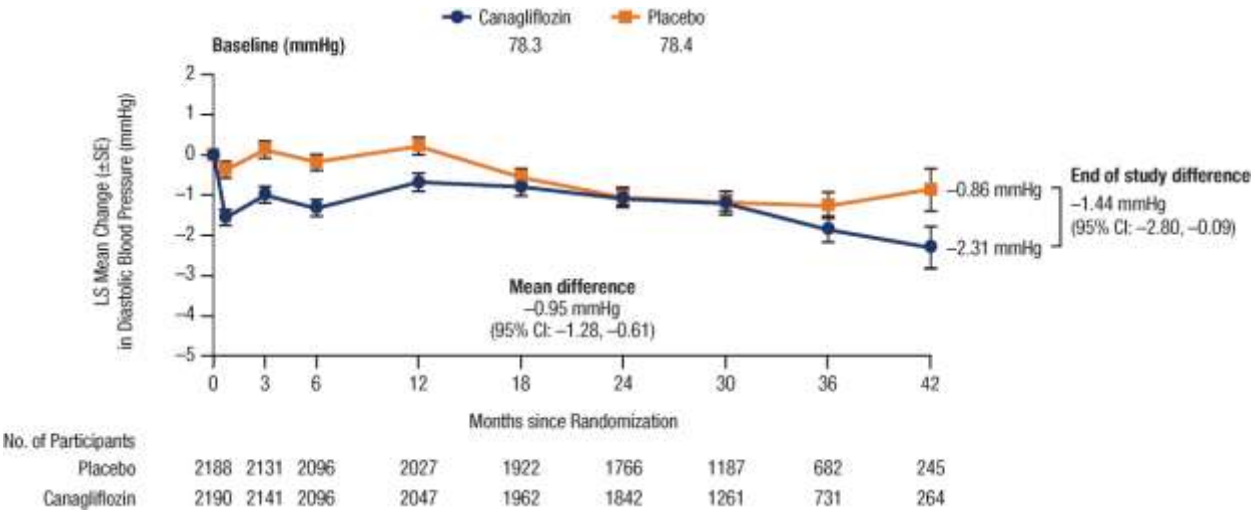
A) Glycated hemoglobin



B) Systolic blood pressure

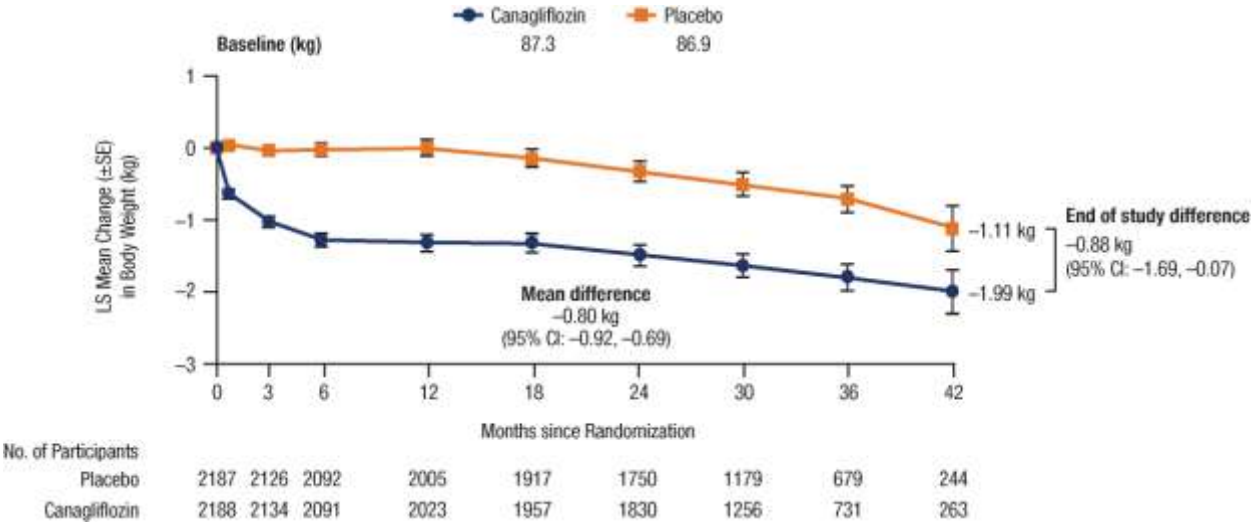


C) Diastolic blood pressure



No. of Participants									
Placebo	2188	2131	2096	2027	1922	1766	1187	682	245
Canagliflozin	2190	2141	2096	2047	1962	1842	1261	731	264

D) Body weight



No. of Participants									
Placebo	2187	2126	2092	2005	1917	1750	1179	679	244
Canagliflozin	2188	2134	2091	2023	1957	1830	1256	731	263

ITT, intention-to-treat; LS, least square; SE, standard error.

*Mean differences shown are based on the on-treatment analysis.

Table S1. Detailed Baseline Demographic and Disease Characteristics by Randomized Groups*

Characteristic	Canagliflozin (n = 2202)	Placebo (n = 2199)	Total (N = 4401)
Age—yr	62.9 ± 9.2	63.2 ± 9.2	63.0 ± 9.2
Female sex—no. (%)	762 (34.6)	732 (33.3)	1494 (33.9)
Race—no. (%)			
White	1487 (67.5)	1444 (65.7)	2931 (66.6)
Black or African American	112 (5.1)	112 (5.1)	224 (5.1)
Asian	425 (19.3)	452 (20.6)	877 (19.9)
Other†	178 (8.1)	191 (8.7)	369 (8.4)
Region—no. (%)			
North America	574 (26.1)	608 (27.6)	1182 (26.9)
Central/South America	476 (21.6)	465 (21.1)	941 (21.4)
Europe	454 (20.6)	410 (18.6)	864 (19.6)
Rest of the world	698 (31.7)	716 (32.6)	1414 (32.1)
Current smoker—no. (%)	341 (15.5)	298 (13.6)	639 (14.5)
History of hypertension—no. (%)	2131 (96.8)	2129 (96.8)	4260 (96.8)
History of heart failure—no. (%)	329 (14.9)	323 (14.7)	652 (14.8)
Duration of diabetes—yr	15.5 ± 8.7	16.0 ± 8.6	15.8 ± 8.6
Drug therapy—no. (%)			
Insulin	1452 (65.9)	1432 (65.1)	2884 (65.5)
Sulfonylurea	612 (27.8)	656 (29.8)	1268 (28.8)
Biguanides	1276 (57.9)	1269 (57.7)	2545 (57.8)
GLP-1 receptor agonist	89 (4.0)	94 (4.3)	183 (4.2)

DPP-4 inhibitor	378 (17.2)	373 (17.0)	751 (17.1)
Statin	1538 (69.8)	1498 (68.1)	3036 (69.0)
Antithrombotic‡	1341 (60.9)	1283 (58.3)	2624 (59.6)
RAAS inhibitor	2201 (>99.9)	2194 (99.8)	4395 (99.9)
Beta blocker	883 (40.1)	887 (40.3)	1770 (40.2)
Diuretic	1026 (46.6)	1031 (46.9)	2057 (46.7)
Microvascular disease history—no. (%)			
Retinopathy	935 (42.5)	947 (43.1)	1882 (42.8)
Nephropathy	2202 (100)	2199 (100)	4401 (100)
Neuropathy	1077 (48.9)	1070 (48.7)	2147 (48.8)
Atherosclerotic vascular disease history—no. (%)‖			
Coronary	653 (29.7)	660 (30.0)	1313 (29.8)
Cerebrovascular	342 (15.5)	358 (16.3)	700 (15.9)
Peripheral	531 (24.1)	515 (23.4)	1046 (23.8)
Cardiovascular disease history—no. (%)	1113 (50.5)	1107 (50.3)	2220 (50.4)
History of amputation—no. (%)	119 (5.4)	115 (5.2)	234 (5.3)
Body mass index—kg/m^2	31.4 ± 6.2	31.3 ± 6.2	31.3 ± 6.2
Systolic blood pressure—mmHg	139.8 ± 15.6	140.2 ± 15.6	140.0 ± 15.6
Diastolic blood pressure—mmHg	78.2 ± 9.4	78.4 ± 9.4	78.3 ± 9.4
Glycated hemoglobin—%	8.3 ± 1.3	8.3 ± 1.3	8.3 ± 1.3
Cholesterol—mg/dL (mmol/L)			
Total	180.9 ± 51.3 (4.7 ± 1.3)	179.8 ± 49.7 (4.6 ± 1.3)	180.4 ± 50.5 (4.7 ± 1.3)
Triglycerides	198.8 ± 140.5	197.0 ± 148.1	197.9 ± 144.4

	(2.2 ± 1.6)	(2.2 ± 1.7)	(2.2 ± 1.6)
HDL cholesterol	44.5 ± 13.8	44.5 ± 13.1	44.5 ± 13.4
	(1.2 ± 0.4)	(1.2 ± 0.3)	(1.2 ± 0.3)
LDL cholesterol	97.0 ± 42.7	95.9 ± 39.9	96.4 ± 41.3
	(2.5 ± 1.1)	(2.5 ± 1.0)	(2.5 ± 1.1)
Ratio of LDL to HDL	2.3 ± 1.1	2.3 ± 1.0	2.3 ± 1.1
eGFR—mL/min/1.73 m^2[¶]	56.3 ± 18.2	56.0 ± 18.3	56.2 ± 18.2
eGFR ≥90 mL/min/1.73 m^2—no. (%)	105 (4.8)	106 (4.8)	211 (4.8)
eGFR ≥60 to <90 mL/min/1.73 m^2—no. (%)	788 (35.8)	770 (35.0)	1558 (35.4)
eGFR ≥45 to <60 mL/min/1.73 m^2—no. (%)	630 (28.6)	636 (28.9)	1266 (28.8)
eGFR ≥30 to <45 mL/min/1.73 m^2—no. (%)	594 (27.0)	597 (27.1)	1191 (27.1)
eGFR ≥15 to <30 mL/min/1.73 m^2—no. (%)	83 (3.8)	89 (4.0)	172 (3.9)
eGFR <15 mL/min/1.73 m^2—no. (%)	1 (<0.1)	1 (<0.1)	2 (<0.1)
Median urine albumin:creatinine ratio (IQR)—mg/g	923.0	931.0	927.0
	(459-1794)	(473-1868)	(463-1833)
Normoalbuminuria—no. (%)[#]	16 (0.7)	15 (0.7)	31 (0.7)
Microalbuminuria—no. (%)[#]	251 (11.4)	245 (11.1)	496 (11.3)
Nephrotic range macroalbuminuria—no. (%)**	233 (10.6)	270 (12.3)	503 (11.4)
Non-nephrotic range macroalbuminuria—no. (%)[††]	1702 (77.3)	1669 (75.9)	3371 (76.6)

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

*Plus–minus values are means ±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.

[||]Some participants had ≥1 type of atherosclerotic disease.

[¶]Values for baseline eGFR categories calculated based on N of 2201 for canagliflozin, 2199 for placebo, and 4400 for the total population.

[#]Eligibility was based on screening urine albumin:creatinine ratio >300 mg/g to ≤5000 mg/g.

**Nephrotic range macroalbuminuria is defined as urine albumin:creatinine ratio >3000 mg/g.

[††]Non-nephrotic range macroalbuminuria is defined as urine albumin:creatinine ratio >300 mg/g and ≤3000 mg/g.

Table S2. Baseline Use and New Initiation of Concomitant Antihyperglycemic Therapy (On Treatment)

	Baseline use			New Initiation		
Participants, n (%)	**Canagliflozin (n = 2200)**	**Placebo (n = 2197)**	**Total (N = 4397)**	**Canagliflozin (n = 2200)**	**Placebo (n = 2197)**	**Total (N = 4397)**
Alpha glucosidase inhibitors	66 (3.0)	73 (3.3)	139 (3.2)	10 (0.5)	16 (0.7)	26 (0.6)
Biguanides	1275 (58.0)	1268 (57.7)	2543 (57.8)	55 (2.5)	80 (3.6)	135 (3.1)
DPP-4 inhibitors	378 (17.2)	373 (17.0)	751 (17.1)	92 (4.2)	105 (4.8)	197 (4.5)
GLP-1 receptor agonists	89 (4.0)	94 (4.3)	183 (4.2)	54 (2.5)	57 (2.6)	111 (2.5)
Insulin	1451 (66.0)	1431 (65.1)	2882 (65.5)	98 (4.5)	132 (6.0)	230 (5.2)
Sulfonylurea	611 (27.8)	656 (29.9)	1267 (28.8)	61 (2.8)	95 (4.3)	156 (3.5)
Thiazolidinediones	71 (3.2)	65 (3.0)	136 (3.1)	21 (1.0)	30 (1.4)	51 (1.2)

Table S3. Reasons for Premature Discontinuation of Randomized Treatment

Participants, n (%)	Canagliflozin (n = 2200)	Placebo (n = 2197)
Any reason	543 (24.7)	658 (29.9)
Adverse event*	263 (12.0)	285 (13.0)
Personal reasons	164 (7.5)	199 (9.1)
Poor compliance	16 (0.7)	18 (0.8)
Safety or tolerability	13 (0.6)	19 (0.9)
Dialysis or renal transplant	18 (0.8)	28 (1.3)
Disallowed therapy	2 (0.1)	17 (0.8)
Protocol violation	3 (0.1)	3 (0.1)
Site closure	3 (0.1)	3 (0.1)
Other	61 (2.8)	86 (3.9)

*137 participants prematurely discontinued treatment due to an adverse event with a fatal outcome.

Table S4. Summary of Safety Results*

	n/N		Event rate per 1000 patient-years		
	Canagliflozin	**Placebo**	**Canagliflozin**	**Placebo**	**Hazard ratio (95% CI)†**
All adverse events	1784/2200	1860/2197	351.4	379.3	0.87 (0.82–0.93)
All serious adverse events	737/2200	806/2197	145.2	164.4	0.87 (0.79–0.97)
Serious adverse events related to study drug	62/2200	42/2197	12.2	8.6	1.45 (0.98–2.14)
Amputation	70/2200	63/2197	12.3	11.2	1.11 (0.79–1.56)
Fracture‡	67/2200	68/2197	11.8	12.1	0.98 (0.70–1.37)
Cancer					
Renal cell carcinoma‡	1/2200	5/2197	0.2	0.9	–†
Breast§	8/761	3/731	4.1	1.6	2.59 (0.69–9.76)
Bladder	10/2200	9/2197	1.7	1.6	1.10 (0.45–2.72)
Acute pancreatitis‡	5/2200	2/2200	1.0	0.4	–†

Hyperkalemia[¶]	151/2200	181/2197	29.7	36.9	0.80 (0.65–1.00)
Acute kidney injury	86/2200	98/2197	16.9	20.0	0.85 (0.64–1.13)
Diabetic ketoacidosis[‡, #]	11/2200	1/2197	2.2	0.2	10.80 (1.39–83.65)
Osmotic diuresis	51/2200	40/2197	10.0	8.2	1.25 (0.83–1.89)
Volume depletion	144/2200	115/2197	28.4	23.5	1.25 (0.97–1.59)
Hypoglycemia	225/2200	240/2197	44.3	48.9	0.92 (0.77–1.11)
Urinary tract infection	245/2200	221/2197	48.3	45.1	1.08 (0.90–1.29)
Genital mycotic infection					
Male	28/1439	3/1466	8.4	0.9	9.30 (2.83–30.60)
Female	22/761	10/731	12.6	6.1	2.10 (1.00–4.45)
Hypersensitivity/cutaneous reactions	23/2200	30/2197	4.5	6.1	0.75 (0.44–1.30)
Hepatic injury	28/2200	32/2197	5.5	6.5	0.86 (0.52–1.43)
Renal-related adverse events (including acute kidney injury)	290/2200	388/2197	57.1	79.1	0.71 (0.61–0.82)

Photosensitivity	1/2200	1/2197	0.2	0.2	–[†]
Venous thromboembolism	21/2200	16/2197	4.1	3.3	1.28 (0.67–2.45)

CI, confidence interval.

*The numbers for amputation and fracture were based on the on-study analysis set, while the other safety endpoints were based on the on-treatment analysis set.

[†]Hazard ratios and 95% CIs were calculated for outcomes with >10 events.

[‡]The analyses for fracture, renal cell carcinoma, acute pancreatitis, and diabetic ketoacidosis and were based on confirmed and adjudicated results.

[§]Includes female participants only.

[¶]Adverse events of hyperkalemia were spontaneously reported by the investigator. The summary counts provided for the adverse event of hyperkalemia include the MedDRA preferred terms of “hyperkalemia” and “blood potassium increased.”

[#]All potential ketone-related events were adjudicated for diabetic ketoacidosis by an independent adjudication committee based on clinical presentation and predefined biochemical parameters.

Table S5. Summary of Adverse Events by Body System or Organ Class

Body system or organ class, n (%)	Canagliflozin (n = 2200)	Placebo (n = 2197)
All adverse events	1784 (81.1)	1860 (84.7)
Blood and lymphatic system disorders	120 (5.5)	200 (9.1)
Cardiac disorders	300 (13.6)	393 (17.9)
Congenital, familial and genetic disorders	9 (0.4)	6 (0.3)
Ear and labyrinth disorders	77 (3.5)	77 (3.5)
Endocrine disorders	57 (2.6)	55 (2.5)
Eye disorders	234 (10.6)	257 (11.7)
Gastrointestinal disorders	463 (21.0)	475 (21.6)
General disorders and administration site conditions	288 (13.1)	382 (17.4)
Hepatobiliary disorders	70 (3.2)	74 (3.4)
Immune system disorders	22 (1.0)	20 (0.9)
Infections and infestations	932 (42.4)	1016 (46.2)
Injury, poisoning and procedural complications	307 (14.0)	304 (13.8)
Investigations	343 (15.6)	451 (20.5)
Metabolism and nutrition disorders	604 (27.5)	690 (31.4)
Musculoskeletal and connective tissue disorders	443 (20.1)	468 (21.3)

Neoplasms benign, malignant and unspecified (including cysts and polyps)	132 (6.0)	122 (5.6)
Nervous system disorders	396 (18.0)	419 (19.1)
Pregnancy, puerperium and perinatal conditions	2 (0.1)	0
Product issues	2 (0.1)	4 (0.2)
Psychiatric disorders	93 (4.2)	112 (5.1)
Renal and urinary disorders	339 (15.4)	423 (19.3)
Reproductive system and breast disorders	101 (4.6)	92 (4.2)
Respiratory, thoracic and mediastinal disorders	263 (12.0)	310 (14.1)
Skin and subcutaneous tissue disorders	313 (14.2)	324 (14.7)
Social circumstances	1 (<0.1)	1 (<0.1)
Surgical and medical procedures	0	1 (<0.1)
Vascular disorders	365 (16.6)	387 (17.6)

Table S6. Baseline Characteristics of Participants With Diabetic Ketoacidosis Adverse Events

	Participants with Diabetic Ketoacidosis* (n = 12)	All Participants (n = 4401)
Background insulin treatment—no. (%)	11 (91.7)	2884 (65.5)
Background metformin treatment—no. (%)	4 (33.3)	2545 (57.8)
Duration of diabetes—yr	23.8	15.8
Glycated hemoglobin—%	8.9	8.3
Glycated hemoglobin >10%—no. (%)	3 (25.0)	450 (10.2)
eGFR—mL/min/1.73 m^2	54.0	56.2
Screening eGFR ≥30 to <45 mL/min/1.73 m^2—no. (%)	7 (58.3)	1313 (29.8)
History of diabetic ketoacidosis	2 (16.7)	4 (0.1)

*****Precipitating factors (primarily recent or concurrent illness, recent reduction in insulin dose, or drugs affecting carbohydrate metabolism) were identified by the adjudication committee for 83% of cases (10 of 12 events) in the canagliflozin group and 100% (1 event) in the placebo group. With the exception of 1 case, concomitant blood glucose levels were >250 mg/dL (>13.9 mmol/L).