Supplementary Appendix

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

Supplement to: Cannon CP, Pratley R, Dagogo-Jack S, et al. Cardiovascular outcomes with ertugliflozin in type 2 diabetes. N Engl J Med 2020;383:1425-35. DOI: 10.1056/NEJMoa2004967

SUPPLEMENTARY APPENDIX

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SUPPLEMENTARY APPENDIX

Supplement to Cannon CP, Pratley R, Dagogo-Jack S, et al. Cardiovascular Outcomes with Ertugliflozin in Type 2 Diabetes. N Engl J Med

TABLE OF CONTENTS

SECTION S1. Committees and Investigators

Scientific Advisory Committee

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VERTIS CV Sites and Investigators

Included below are the Principal Investigators from the 567 sites which randomized at least one patient (n=566) or accepted randomized patients (n=1) across 34 participating countries.

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Merck & Co., Inc. Kenilworth, NJ (Sponsor Representatives):

Jenny Yu (Safety), and previous Sponsor representative: Brett Lauring.

SECTION S2. Supplementary Methods

Data Handling And Record Keeping

Case Report Forms/Electronic Data Record

A Case Report Forms/Electronic Data Record was required to be completed for each included patient. The completed original Case Report Forms/Electronic Data Record are the sole property of the Sponsor and were not be made available in any form to third parties, except for authorized representatives of the Sponsor or appropriate regulatory authorities, without written permission from the Sponsor.

The investigator had ultimate responsibility for the collection and reporting of all clinical, safety and laboratory data entered on the CRFs and any other data collection forms (source documents) and ensuring that they were accurate, authentic/original, attributable, complete, consistent, legible, timely (contemporaneous), enduring and available when required. The CRFs was signed by the investigator or by an authorized staff member to attest that the data contained on the CRFs was true. Any corrections to entries made in the CRFs, source documents were dated, initialed and explained (if necessary) and did not obscure the original entry.

In most cases, the source documents were the hospital’s or the physician's subject chart. In these cases, data collected on the CRFs matched the data in those charts.

In some cases, the CRF, or part of the CRF, also served as source documents. In these cases, a document was available at the investigator’s site as well as at the sponsor and clearly identified those data that were recorded in the CRF, and for which the CRF stood as the source document.

Record Retention

To enable evaluations and/or audits from regulatory authorities or the Sponsor, the investigator agreed to keep records, including the identity of all participating patients (sufficient information to link records, eg, CRFs and hospital records), all original signed ICD, copies of all CRFs, safety reporting forms, source documents, and detailed records of treatment disposition, and adequate documentation of relevant correspondence (eg, letters, meeting minutes, telephone calls reports). The records were to be retained by the investigator according to International Conference on Harmonisation (ICH), local regulations, or as specified in the Clinical Study Agreement (CSA), whichever is longer.

If the investigator was unable for any reason to continue to retain study records for the required period (eg, retirement, relocation), the Sponsor was required to be prospectively notified. The study records were then transferred to a designee acceptable to the Sponsor, such as another investigator, another institution, or to an independent third party arranged by the Sponsor. Investigator records must be kept for a minimum of 15 years after completion or discontinuation of the study or for longer if required by applicable local regulations. The investigator must obtain Pfizer's written permission before disposing of any records, even if retention requirements have been met.

Quality Control And Quality Assurance

During study conduct, the Sponsor or their agent conducted periodic monitoring visits to ensure that the protocol and Good Clinical Practices (GCPs) were followed. The monitors could review source documents to confirm that the data recorded on eCRFs was accurate. The investigator and institution allowed the Sponsor monitors or its agents and appropriate regulatory authorities direct access to source documents to perform this verification.

The study site could also be subject to review by the Institutional Review Board (IRB)/Independent Ethics Committee (IEC), and/or to quality assurance audits performed by the Sponsor, or companies working with or on behalf of the Sponsor, and/or to inspection by appropriate regulatory authorities.

Complete Inclusion and Exclusion Criteria

Inclusion Criteria

1. Patients ≥40 years of age at the time of the initial Screening visit (V1) with a diagnosis of type 2 diabetes mellitus (T2DM) in accordance with American Diabetes Association (ADA) guidelines.

2. Glycated hemoglobin (HbA1c) at the Screening visit (V1) of 7.0–10.5% (53–91 mmol/mol) on stable allowable anti-hyperglycemic agent(s) (AHA) or on no background AHA for at least 8 weeks prior to the Screening visit (V1).

3. Body mass index ≥18.0 kg/m^2.

4. Patients must have evidence or a history of atherosclerosis involving the coronary, cerebral, or peripheral vascular systems as follows (must have at least 1 of the following):

a. Coronary artery disease as indicated by a history of presumed spontaneous myocardial infarction (MI; hospitalized with final diagnosis of MI, excluding peri-procedural or definite secondary MI [e.g., due to profound anemia or hypertensive emergency, troponin increase in sepsis]) in which the most recent event occurred at least 3 months (90 days) prior to the Screening visit (V1); **OR**

b. Coronary artery disease as indicated by a history of coronary revascularization through either a percutaneous coronary intervention at least 3 months (90 days) prior to the Screening visit (V1) or coronary artery bypass graft at least 3 months (90 days) prior to the Screening visit (V1); **OR**

c. Ischemic (presumed thrombotic) cerebrovascular disease as indicated by a history of ischemic stroke (hospitalized with a final diagnosis of non-hemorrhagic stroke [includes completion of a standard evaluation for stroke in an acute care facility or stroke clinic without hospital admission]) with the most recent event occurring at least 3 months (90 days) prior to the Screening visit (V1) or a history of carotid revascularization at least 3 months (90 days) prior to the Screening visit (V1); **OR**

d. Peripheral arterial disease as indicated by:

1. Angiographically-documented peripheral vascular disease; **or**

2. Resting ankle/brachial index of <0.85 (measured by a certified vascular laboratory) plus symptoms of claudication; **or**

3. Amputation, peripheral bypass, or peripheral angioplasty of the extremities secondary to ischemia occurring at least 3 months (90 days) prior to the Screening visit (V1).

5. There is adequate documentation of the objective evidence that the patient has established vascular disease such as investigational site's medical records, copies of such records from other institutions, or a letter from a referring physician that specifically states the diagnosis and date of the most recent occurrence of the qualifying event(s) or procedure(s).

6. Patient meets 1 of the following criteria:

a. Is a male

b. Is a female not of reproductive potential, defined as one who is:

   i) Postmenopausal: defined as at least 12 months with no menses in women ≥45 years of age; **or**

   ii) Has had a hysterectomy and/or bilateral oophorectomy, or had bilateral tubal ligation or occlusion at least 6 weeks prior to the Screening visit (V1).

c. Is a female of reproductive potential and:

   i. Agrees to remain abstinent from heterosexual activity (if this form of birth control is accepted by local regulatory agencies and ethics review committees as the sole method of birth control); **or**

   ii. Agrees to use (or have their partner use) acceptable contraception to prevent pregnancy while the patient is receiving investigational product and for 14 days after the last dose of investigational product. Two methods of contraception will be used to avoid pregnancy. Acceptable combinations of methods include:

      - Use of 1 of the following double-barrier methods: diaphragm with spermicide and a condom; cervical cap and a condom; or a contraceptive sponge and condom;

- Use of hormonal contraception (any registered and marketed contraceptive agent that contains an estrogen and/or a progestational agent [including oral, subcutaneous, intrauterine and intramuscular agents, and cutaneous patch]) with 1 of the following: diaphragm with spermicide; cervical cap; contraceptive sponge; condom; vasectomy; or intrauterine device (IUD);
- Use of an IUD with 1 of the following: condom; diaphragm with spermicide; contraceptive sponge; vasectomy; or hormonal contraception (see above);
- Vasectomy with 1 of the following: diaphragm with spermicide; cervical cap; contraceptive sponge; condom; IUD; or hormonal contraception (see above).

7. Evidence of a personally signed and dated informed consent document indicating that the patient (or a legal representative) has been informed of all pertinent aspects of the trial. The patient may also provide consent for Future Biomedical Research. However, the patient may participate in the main trial without participating in Future Biomedical Research.

8. In the investigator's opinion, patients are willing and likely able to comply with scheduled visits, treatment plan, laboratory tests, and other study procedures whether or not they receive investigational product for the duration of the trial.

Exclusion Criteria

Patients presenting with any of the following will not be included in the trial:

1. Patients who had been previously randomized into this trial.

2. Patients experiencing a cardiovascular event (e.g., MI or stroke) or undergoing coronary angioplasty or peripheral intervention procedure between the Screening visit (V1) and randomization.

3. Patients undergoing any cardiovascular surgery (e.g., valvular surgery) within 3 months (90 days) of the Screening visit (V1).

4. Patients with any planned coronary revascularization or peripheral intervention procedure or other cardiovascular surgery.

5. Patients with New York Heart Association Class IV heart failure (HF) at the Screening visit (V1) (following protocol amendment; exclusion had been Class III–IV prior to protocol amendment).

6. Mean value for triplicate screening sitting systolic blood pressure (SBP) >160 mm Hg and/or diastolic blood pressure (DBP) >90 mm Hg after at least a 5-minute seated rest at the Screening visit (V1), confirmed via 1 repeat triplicate set at the Screening visit (V1) if deemed necessary. For patients with a mean triplicate value of sitting SBP >160 mm Hg and/or DBP >90 mm Hg after at least a 5-minute seated rest at the Screening visit (V1) the investigator or the treating physician is allowed to adjust background blood pressure (BP) medication(s) to lower BP values in order for the patient to be re-assessed for enrollment eligibility.

7. Patient has a clinically significant electrocardiogram (ECG) abnormality at Screening visit (V1) that requires further diagnostic evaluation or intervention (e.g., new, clinically significant arrhythmia or a conduction disturbance).

8. History of type 1 diabetes mellitus or a history of ketoacidosis.

9. History of other specific types of diabetes (e.g., genetic syndromes, secondary pancreatic diabetes, diabetes due to endocrinopathies, drug- or chemical-induced, and post-organ transplant).

10. Patient has active, obstructive uropathy or indwelling urinary catheter.

11. Patient has a history of malignancy ≤5 years prior to signing informed consent, except for adequately treated basal cell or squamous cell skin cancer or in situ cervical cancer.

Note (1) A patient with a history of malignancy >5 years prior to signing informed consent should have no evidence of residual or recurrent disease.

Note (2) A patient with any history of melanoma, leukemia, lymphoma, or renal cell carcinoma is excluded.

12. Patient routinely consumes >2 alcoholic drinks per day or >14 alcoholic drinks per week, or engages in binge drinking.

13. Any clinically significant malabsorption condition.

14. Patients with a known hypersensitivity or intolerance to any sodium-glucose co-transporter-2 inhibitor.

15. Screening fasting plasma or finger-stick glucose >270 mg/dl (15 mmol/l), confirmed by a single repeat following counseling on exercise and diet.

16. History of 1 or more severe hypoglycemic episodes within 6 months of Screening visit (V1) or a severe hypoglycemic episode occurring during the interval between the Screening visit (V1) and randomization.

17. Fasting triglycerides >600 mg/dl (6.78 mmol/l) at Screening visit (V1), confirmed by a single repeat if deemed necessary. For patients with fasting triglycerides >600 mg/dl, the investigator or

treating physician is allowed to adjust background lipid altering medication(s) to lower fasting triglycerides in order for the patient to be re-assessed for enrollment eligibility.

18. Patients currently taking BP or lipid altering medications who have not been on a stable dose for at least 4 weeks prior to randomization. Patients who require a change in BP and/or lipid altering medications to meet the entry criteria related to BP and/or triglycerides must be on a stable dose of such therapy for at least 4 weeks prior to randomization.

19. Patients who meet any of the following categories:

- Patient is on a weight-loss program and is not weight-stable.
- Patient is on a weight-loss medication (e.g., orlistat, phentermine/topiramate, lorcaserin) and is not weight-stable.
- Patient is on other medications associated with weight changes (e.g., anti-psychotic agents) and is not weight-stable.
- Patient has undergone bariatric surgery >12 months prior to Visit 1/Screening and is not weight-stable.
- Patient has undergone bariatric surgery within 12 months of Screening visit (Visit 1).

Note: Weight-stable is defined as <5% change in body weight in the last 6 months.

20. Patients currently being treated for hyperthyroidism, patients on thyroid replacement therapy that have not been on a stable dose for at least 6 weeks prior to the Screening visit (V1), and/or patients who have a thyroid stimulating hormone (TSH) outside of the laboratory reference range at the Screening visit (V1). Patients excluded due to TSH criterion may be re-tested after being on a stable thyroid replacement regimen for at least 6 weeks.

21. Estimated glomerular filtration rate <30 ml/min/1.73 m^2 as determined by the 4-variable Modification of Diet in Renal Disease equation, confirmed via a single repeat if deemed necessary.

22. Patients with hemoglobin <10 g/dl (100 g/l). Confirmed via a single repeat if deemed necessary.

23. Aspartate aminotransferase or alanine aminotransferase >2 X the upper limit of normal (ULN) at the Screening visit (V1), or a total bilirubin >1.5 X the ULN unless the patient has a history of Gilbert's.

24. Patient has a medical history of active liver disease (other than non-alcoholic hepatic steatosis), including chronic active hepatitis B or C (assessed by medical history), primary biliary cirrhosis, or symptomatic gallbladder disease.

25. Patient is on or likely to require treatment for ≥14 consecutive days or repeated courses of pharmacologic doses of corticosteroids. These medications are not to be used from the time of the start of the day 1 Visit (Visit 2) to the completion of the trial.

Note: Inhaled, nasal, and topical corticosteroids and physiological replacement doses of adrenal steroids are permitted.

26. The following therapeutic agents are prohibited for the duration of the trial. These medications are not to be used from 8 weeks before the Screening visit (V1) until the completion of the trial:

- Treatment with another SGLT2 inhibitor
- Treatment with rosiglitazone
- Treatment with chlorpropamide.

27. Patients who have donated blood or blood products within 6 weeks of Screening visit (V1) or who plan to donate blood or blood products at any time during the trial.

28. Patients who have undergone a surgical procedure within 4 weeks prior to signing informed consent or have planned major surgery during the trial. Note: A patient who has undergone minor surgery within the 4 weeks prior to Screening visit (V1) and is fully recovered or a patient who has planned minor surgery may participate. Minor surgery is defined as a surgical procedure involving local anesthesia. For exclusion regarding cardiovascular surgery, see exclusion criterion #3.

29. Patients with:

- Known history of Human Immunodeficiency Virus
- Blood dyscrasias or any disorders causing hemolysis or unstable red blood cells.

30. At randomization, patient has developed a new medical condition, suffered a change in status of an established medical condition, developed a laboratory or ECG abnormality, or required a new treatment or medication during the pre-randomization period that meets any previously described trial exclusion criterion or which, in the opinion of the investigator, exposes the patient to risk by enrolling in the trial.

31. Other severe acute or chronic medical or psychiatric condition or laboratory abnormality at the Screening visit (V1) that may increase the risk associated with trial participation or investigational product administration or may interfere with the interpretation of trial results and, in the judgment of the investigator, would make the patient inappropriate for entry into this trial.

32. Patients who have previously been randomized in a trial with ertugliflozin.

33. Participation in other studies involving investigational drug (s) (Phases 1–4) within 30 days before the Screening visit (V1) and/or during trial participation.

34. Patient is pregnant or breast-feeding, or is expecting to conceive during the trial, including 14 days following the last dose of blinded investigational product.

35. Patient is expecting to undergo hormonal therapy in preparation to donate eggs during the period of the trial, including 14 days following the last dose of blinded investigational product.

36. Patients who are investigational site staff members directly involved in the conduct of the trial and their family members, site staff members otherwise supervised by the investigator, or patients who are Pfizer/Merck employees directly involved in the conduct of the trial.

Rationale for Dose Selection of Ertugliflozin

The ertugliflozin doses being evaluated in Phase 3 are 5 mg and 15 mg once daily. Since oral doses of ertugliflozin as high as 300 mg (single dose), 100 mg once daily (up to 14 days) and 25 mg once daily (up to 12 weeks) were safe and well-tolerated, dose selection was based on dose-response modeling of efficacy end-points (HbA1c and fasting plasma glucose [FPG]) from study B1521006 as well as 24-hour urinary glucose excretion (mechanism biomarker) in T2DM patients from study B1521004. For these endpoints, the 5 mg and 15 mg doses consistently elicit a response that is >80% and >90% of the maximum response, respectively (see Table below).

Table. Estimated Percent Maximum Response for Various Endpoints

Ertugliflozin Dose	UGE – T2DM (ED50=0.78 mg)	HbA1C (ED50=1 mg)
5 mg	87%	83%
15 mg	95%	94%

UGE = urinary glucose excretion; ED50 = dose producing half (50%) of the maximal response.

In addition, the dose-response modeling of 24-hour UGE in healthy volunteers estimated the ED50 at 3 mg, which translates to 63% and 83% of maximum effect for 5-mg and 15-mg doses. The selection of the 5 mg and 15 mg doses is also supported by the safety and tolerability profile for ertugliflozin in clinical studies up to 12 weeks in duration. When accounting for species differences in protein binding, the highest Phase 3 dose of 15 mg once daily represents an exposure which is approximately 12-fold [for Cmax] and 11-fold [for area under the concentration-time curve from time 0 to 24 hours (1 day) after dose (AUC(0-24))] lower than exposure at the no observed adverse effect level (NOAEL) in the 6-month toxicology study in the most sensitive species (rat). Thus, both the 5 and 15 mg doses are expected to provide clinically meaningful efficacy and allow for a thorough assessment of the benefit/risk of ertugliflozin in the Phase 3 program.

Randomization Criteria

Patients were assigned a unique identifier via interactive voice response system at the Screening visit (V1), which was retained throughout the duration of participation in the trial. Patients were

randomized into the trial at Day 1 visit (V2), provided that they satisfied all subject eligibility criteria. A computer-generated randomization code using the method of random permuted blocks was utilized to assign patients to 1 of 3 treatment regimens (5 mg ertugliflozin once daily, 15 mg ertugliflozin once daily or matching placebo) on Day 1 visit (V2). For patients enrolled under the original protocol, the randomization was stratified by sub study and by geographic region (within sub study). The stratification factor for sub study had four levels: patients entering the insulin with or without metformin sub study on a background of insulin alone, patients entering the insulin with or without metformin sub study on a background of insulin plus metformin, patients entering the SU monotherapy sub study and patients entering the main cardiovascular study but not any of the aforementioned sub studies. For patients enrolled under Protocol Amendment 1, the randomization was stratified by geographic region only.

SECTION S3. Background anti-hyperglycemic medication and cardiovascular treatment.

Doses of background anti-hyperglycemic medication were held constant for the initial 18 weeks of the study except for those patients meeting the glycemic rescue criteria (see below) or with clinically significant hypoglycemia. After week 18, changes in anti-hyperglycemic medication were permitted except for prohibited agents (i.e., other SGLT2 inhibitors, chlorpropamide, or rosiglitazone). The investigator or the treating provider were encouraged to make any changes in the background cardiovascular treatment regimen to achieve appropriate targets for secondary disease prevention per treatment guidelines at any time during the study.

Details on the specific glycemic rescue criteria for the initial 18 weeks of the trial are provided in the table below.

Glycemic Rescue Criteria for All patients for the First 18 Weeks

Randomization through Week 6	FPG >270 mg/dL (15.0 mmol/L)
After Week 6 through Week 12	FPG >240 mg/dL (13.3 mmol/L)
After Week 12 through Week 18	FPG >200 mg/dL (11.1 mmol/L)

SECTION S4. Study endpoints

Primary Endpoint

- The primary cardiovascular endpoint is time to first occurrence of the composite endpoint of MACE (a composite of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke).

Key Secondary Endpoints (associated with an alpha-controlled hypothesis that was hierarchically tested)

- Time to first occurrence of:
    - Cardiovascular death or hospitalization for heart failure;
    - Cardiovascular death;
    - Renal composite (a composite of renal death, renal replacement therapy, or doubling of serum creatinine)

Other Secondary Endpoints (not associated with alpha-controlled hypothesis)

- Time to first occurrence of:
    - MACE plus (a composite of cardiovascular death, non fatal myocardial infarction, non fatal stroke or hospitalization for unstable angina);
    - Fatal or non-fatal myocardial infarction;
    - Fatal or non-fatal stroke;
    - Hospitalization for heart failure;
    - Individual components of MACE (cardiovascular death, non-fatal myocardial infarction, non-fatal stroke).

- All-cause death.
- All MACE events (ie, not censored at the time of the first event; not presented in this report).
- All cardiovascular death or hospitalizations for heart failure (ie, not censored at the time of the first event; not presented in this report).

When added to usual background therapy in patients with T2DM and established vascular disease:

- Change from Baseline in HbA1c at Week 18, Week 52 and annually thereafter.
- Proportion of patients with HbA1c <7% (53 mmol/mol) and <6.5% (48 mmol/mol) at 12, 24 and 36 months and annually thereafter (not presented in this report).
- Time to the first occurrence of a subject receiving glycemic rescue therapy during the first 18 weeks of the study (not presented in this report).
- Time to initiation of insulin for patients not on insulin at randomization (not presented in this report).
- Change in insulin dose from Baseline at Week 18, Week 52 and annually thereafter (not presented in this report).
- Change from Baseline in systolic and diastolic (not presented in this report) blood pressure at Week 18, Week 52 and annually thereafter.
- Change from Baseline in body weight at Week 18, Week 52 and annually thereafter.
- Change from Baseline in eGFR and serum creatinine at Week 18, Week 52 and annually thereafter (not presented in this report).

- Change from Baseline in albuminuria as measured by the urinary albumin to creatinine ratio at Week 18, Week 52 and annually thereafter stratified by albuminuria category at baseline (normoalbuminuria, microalbuminuria and macroalbuminuria) (not presented in this report).
- Progression of nephropathy as measured by the progression of normoalbuminuria to microalbuminuria and/or macroalbuminuria as well as measurement of regression of albuminuria (eg, macroalbuminuria → microalbuminuria) (not presented in this report).

Cardiovascular Endpoint Definitions

Cardiovascular Death

Cardiovascular death includes death resulting from an acute MI, sudden cardiac death, death due to HF, death due to stroke, death due to cardiovascular procedure, death due to cardiovascular hemorrhage, and death due to other cardiovascular causes. Only events confirmed by the cardiovascular clinical event adjudication committee were included in the analyses of cardiovascular outcomes. Deaths confirmed by the cardiovascular adjudication committee as having been due to renal causes contributed to the renal outcome.

1. Death Due to Acute MI refers to a death by any cardiovascular mechanism (e.g., arrhythmia, sudden death, HF, stroke, pulmonary embolus, peripheral arterial disease) ≤30 days after a MI related to the immediate consequences of the MI, such as progressive heart failure or recalcitrant arrhythmia.
    a. Death resulting from a procedure to treat a 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.

b. Death resulting from an elective coronary procedure to treat myocardial ischemia (i.e., chronic stable angina) or death due to a 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:

a. Death witnessed and occurring without new or worsening symptoms.
b. Death witnessed within 60 minutes of the onset of new or worsening cardiac symptoms, unless the symptoms suggest acute MI.
c. 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).
d. Death after unsuccessful resuscitation from cardiac arrest.
e. Death after successful resuscitation from cardiac arrest and without identification of a specific cardiac or non-cardiac etiology.
f. Unwitnessed death in a patient seen alive and clinically stable ≤24 hours prior to being found dead without any evidence supporting a specific non-cardiovascular cause of death (information regarding the patient's clinical status preceding death should be provided, if available).

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 MIs, ischemic or non-ischemic 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.

5. Death Due to Cardiovascular Procedure refers to death caused by immediate complications of a cardiac procedure.

6. Death Due to Cardiovascular Hemorrhage refers to death related to hemorrhage such as non-stroke intracranial hemorrhage, non-procedural or non-traumatic vascular rupture (e.g., aortic aneurysm), or hemorrhage causing cardiac tamponade.

7. Death Due to Other Cardiovascular Causes refers to a cardiovascular death not included in the above categories but with a specific, known cause (e.g., pulmonary embolism or peripheral arterial disease).

8. Undetermined Cause of Death refers to a death not attributable to a cardiovascular death or to a non-cardiovascular 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.

Non-Cardiovascular Death

Death occurs and is due primarily to an identifiable non-cardiovascular cause or etiology

1. Renal – Death is due to an identifiable renal etiology (e.g., renal failure).
2. Cancer – Death is due to an identified cancer.
    - Unidentified Primary
    - Prostatic Cancer

- Lung Cancer
- Breast Cancer
- Uterine/Ovarian Cancer
- Colorectal Cancer
- Non-Hodgkin’s Lymphoma
- Melanoma
- Pancreatic Cancer
- Leukemia
- Kidney Cancer
- Oral/Pharyngeal/Esophageal Cancer
- Other Cancer

3. Other Non-Cardiovascular Cause Specific Diagnoses

- Multisystem Failure
- Sepsis
- Trauma
- Suicide
- Cirrhosis
- Other Non-CV Death

Criteria for MI

General Considerations:

The term MI should be used when there is evidence of myocardial necrosis in a clinical setting consistent with MI.

In general, the diagnosis of MI requires the combination of:

- Evidence of myocardial necrosis (either changes in cardiac biomarkers or post-mortem pathological findings); **and**
- Supporting information derived from the clinical presentation, electrocardiographic changes, or the results of myocardial or coronary artery imaging.

The totality of the clinical, electrocardiographic, and cardiac biomarker information should be considered to determine whether or not a MI has occurred. Specifically, timing and trends in cardiac biomarkers and electrocardiographic information require careful analysis. The adjudication of MI should also take into account the clinical setting in which the event occurs. MI may be adjudicated for an event that has characteristics of a MI but which does not meet the strict definition because biomarker or electrocardiographic results are not available.

The Third Universal definition of MI will be used.

Third Universal Definition of MI

- Detection of rise and/or fall of cardiac biomarkers (preferably cardiac troponin [cTN]) with at least one value above the 99th percentile of the upper reference limit (URL) together with evidence of myocardial ischemia with at least 1 of the following:
    - Symptoms of ischemia;
    - New or presumed new significant ST-segment (ST-T) changes or new left bundle branch block (LBBB);
    - Development of pathological Q waves in the ECG;

    - Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality;
    - Identification of an intracoronary thrombus by angiography or autopsy.
- Cardiac death with symptoms suggestive of myocardial ischemia and presumed new ischemic ECG changes or new LBBB, but death occurred before cardiac biomarkers were obtained, or before cardiac biomarker values would be increased.
- Percutaneous coronary intervention (PCI)-related MI is arbitrarily defined by elevation of cTN values (>5 x 99th percentile URL) in patients with normal baseline values (≤99th percentile URL) or a rise of cTN values >20% if the baseline values are elevated and are stable or falling. In addition, either (i) symptoms suggestive of myocardial ischemia, or (ii) new ischemic ECG changes, or (iii) angiographic findings consistent with a procedural complication, or (iv) imaging demonstration of new loss of viable myocardium or new regional wall motion abnormality are required.
- Stent thrombosis associated with MI when detected by coronary angiography or autopsy in the setting of myocardial ischemia and with a rise and/or fall of cardiac biomarker values with at least one value above the 99th percentile URL.
- Restenosis associated with PCI-related MI, defined as ≥50% stenosis at coronary angiography or a complex lesion associated with a rise and/or fall of cTN values >99th percentile URL and no other significant obstructive CAD of greater severity following: (i) initially successful stent deployment, or (ii) dilatation of a coronary artery stenosis with balloon angioplasty (<50%). This classification also requires that the MI does not meet criteria for any other classification of MI.

- CABG-related MI is arbitrarily defined by elevation of cardiac biomarker values (>10 x 99th percentile URL) in patients with normal baseline cTN values (≤99th percentile URL). In addition, either (i) new pathological Q waves or new LBBB, or (ii) angiographic documented new graft or new native coronary artery occlusion, or (iii) imaging evidence of new loss of viable myocardium or new regional wall motion abnormality.

Criteria for Prior MI

Any one of the following criteria meets the diagnosis of prior MI:

- Pathological Q waves with or without symptoms in the absence of non-ischemic causes.
- Imaging evidence of a region of loss of viable myocardium that is thinned and fails to contract, in the absence of a non-ischemic cause.
- Pathological findings of a prior MI.

Clinical Classification of Types of MI

1) Type 1: Spontaneous MI, spontaneous MI related to atherosclerotic plaque rupture, ulceration, fissuring, erosion, or dissection with resulting intraluminal thrombus in one or more of the coronary arteries leading to decreased myocardial blood flow or distal platelet emboli with ensuing myocyte necrosis. The patient may have underlying severe CAD but on occasion non-obstructive or no CAD.
2) Type 2: MI secondary to an ischemic imbalance, in instances of myocardial injury with necrosis where a condition other than CAD contributes to an imbalance between myocardial oxygen supply and/or demand, e.g., coronary endothelial dysfunction, coronary artery spasm, coronary embolism, tachy-/brady-arrhythmias, anemia, respiratory failure, hypotension, and hypertension with or without left ventricular hypertrophy (LVH).

3) Type 3: MI resulting in death when biomarker values are unavailable, cardiac death with symptoms suggestive of myocardial ischemia and presumed new ischemic ECG changes or new LBBB, but death occurring before blood samples could be obtained, before cardiac biomarker could rise, or in rare cases cardiac biomarkers were not collected.
4) Type 4a: MI related to percutaneous coronary intervention (PCI), MI associated with PCI is arbitrarily defined by elevation of cTN values >5 x 99th percentile URL in patients with normal baseline values (≤99th percentile URL) or a rise of cTN values >20% if the baseline values are elevated and are stable or falling. In addition, either (i) symptoms suggestive of myocardial ischemia, or (ii) new ischemic ECG changes or new LBBB, or (iii) angiographic loss of patency of a major coronary artery or a side branch or persistent slow or no-flow or embolization, or (iv) imaging demonstration of new loss of viable myocardium or new regional wall motion abnormality are required.
5) Type 4b: MI related to stent thrombosis, MI associated with stent thrombosis is detected by coronary angiography or autopsy in the setting of myocardial ischemia and with a rise and/or fall of cardiac biomarkers values with at least one value above the 99th percentile URL.
6) Type 4c: Occasionally MI occurs and at angiography, restenosis is the only angiographic explanation. This PCI-related MI type might be designated as an 'MI type 4c', defined as ≥50% stenosis at coronary angiography or a complex lesion associated with a rise and/or fall of cTN values >99th percentile URL and no other significant obstructive CAD of greater severity following: (i) initially successful stent deployment, or (ii) dilatation of a coronary artery stenosis with balloon angioplasty (<50%).

7) Type 5: MI related to CABG, MI associated with CABG is arbitrarily defined by elevation of cardiac biomarker values >10 x 99th percentile URL in patients with normal baseline cTN values (≤99th percentile URL). In addition, either (i) new pathological Q waves or new LBBB, or (ii) angiographic documented new graft or new native coronary artery occlusion, or (iii) imaging evidence of new loss of viable myocardium or new regional wall motion abnormality.

Hospitalization for Unstable Angina

1) Defined as ischemic discomfort (angina, or symptoms thought to be equivalent) ≥10 minutes in duration occurring at rest, or in an accelerating pattern with frequent episodes associated with progressively decreased exercise capacity.

AND

2) Prompting an unscheduled hospitalization **within 24 hours** of the most recent symptoms. Hospitalization is defined as an admission to an inpatient unit or a visit to an emergency department that results in at least a 24-hour stay (or change in a calendar date if the hospital admission and discharge times are not available).

AND

3) At least **one of the** following:
    a. New or worsening ST or T wave changes on resting ECG (in the absence of confounders, such as LBBB or LVH).
        - Transient ST elevation (duration <20 minutes)
            - New ST elevation at the J point in two contiguous leads with the cut-points: ≥0.1 mV in all leads other than leads V2-V3 where the following

cut-points apply: ≥0.2 mV in men ≥40 years (≥0.25 mV in men <40 years) or ≥0.15 mV in women.

- ST depression and T-wave changes
  - New horizontal or down-sloping ST depression ≥0.05 mV in two contiguous leads and/or new T inversion ≥0.3 mV in two contiguous leads with prominent R wave or R/S ratio >1.

b. Definite evidence of inducible myocardial ischemia as demonstrated by:

- early positive exercise stress test, defined as ST elevation or ≥2 mm ST depression prior to 5 mets **OR**
- stress echocardiography (reversible wall motion abnormality) **OR**
- myocardial scintigraphy (reversible perfusion defect) **OR**
- MRI (myocardial perfusion deficit under pharmacologic stress).

AND believed to be responsible for the myocardial ischemic symptoms/signs.

c. Angiographic evidence of new or worse ≥70% lesion and/or thrombus in an epicardial coronary artery that is believed to be responsible for the myocardial ischemic symptoms/signs.

d. Need for coronary revascularization procedure (PCI or CABG) for the presumed culprit lesion(s). This criterion would be fulfilled if revascularization was undertaken during the unscheduled hospitalization, or subsequent to transfer to another institution without interceding home discharge.

AND

4) Negative cardiac biomarkers and no evidence of acute MI.

Stroke

Defined as an acute episode of focal or global neurological dysfunction caused by brain, spinal cord, or retinal vascular injury as a result of hemorrhage or infarction.

Classification of Stroke

A. Ischemic Stroke

An acute focal or global infarction of the brain, retina, or spinal cord caused by infarction of central nervous system tissue. Criteria:

An acute onset of a new focal neurological deficit with clinical or imaging evidence of infarction and not attributable to a non-ischemic etiology (CNS infection, trauma, tumor, metabolic, or neurodegenerative disease).

An acute onset of global ischemia, e.g., of the cerebral hemispheres during a cardiac arrest or systemic hypotension, is another example of ischemic infarction.

A component of hemorrhage may also be the consequence of ischemic stroke; i.e., hemorrhagic transformation.

B. Hemorrhagic Stroke

An acute episode of focal or global cerebral dysfunction caused by non-traumatic intraparenchymal, intraventricular, or subarachnoid hemorrhage.

Criteria:

Evidence of hemorrhage in the brain parenchyma or subarachnoid or subdural spaces that is demonstrated by head imaging or autopsy, not caused by trauma and not within the area of an ischemic infarct, and that is felt to be the primary cause of new neurological symptoms or death.

C. Undetermined Stroke (i.e., Stroke of Unknown Mechanism)

Undetermined stroke is defined as an acute episode of focal or global neurological dysfunction caused by presumed brain, spinal cord, or retinal vascular injury as a result of hemorrhage or infarction but with insufficient information to allow categorization as A or B above.

Transient Ischemic Attack

A neurological deficit of sudden onset that resolves completely and is attributable to focal brain and/or retinal ischemia without imaging evidence of an associated infarction.

Regardless of duration, there must be no associated corresponding neuroimaging abnormality on CT or MRI that would classify it as a minor cerebral infarction.

Criteria:

Rapid onset of a focal neurological deficit that resolves completely and is without evidence of an acute focal infarction of the brain or retina. This cannot be attributable to a non-ischemic etiology (CNS infection, trauma, tumor, metabolic, or neurodegenerative disease).

Heart Failure (HF)

A Heart Failure Event includes hospitalization for HF and may include urgent outpatient visits.

A Heart Failure Hospitalization is defined as an event that meets ALL of the following criteria:

1) The patient is admitted to the hospital with source documentation supporting a most responsible primary diagnosis of HF.
2) The patient's length-of-stay in hospital extends for at least 24 hours (or a change in calendar date if the hospital admission and discharge times are unavailable).
3) The patient exhibits documented new or worsening symptoms due to HF on presentation, including **at least ONE** of the following:

a. Dyspnea (dyspnea with exertion, dyspnea at rest, orthopnea, paroxysmal nocturnal dyspnea)
b. Decreased exercise tolerance
c. Fatigue
d. Other symptoms of worsened end-organ perfusion or volume overload (must be specified and described by the protocol).

4) The patient has objective evidence of new or worsening HF, consisting of **at least TWO** physical examination findings **OR** one physical examination finding and **at least ONE** laboratory criterion, including:
   a. Physical examination findings considered to be due to heart failure, including new or worsened:
      i. Peripheral edema
      ii. Increasing abdominal distention or ascites (in the absence of primary hepatic disease)
      iii. Pulmonary rales/crackles/crepitations
      iv. Increased jugular venous pressure and/or hepatojugular reflux
      v. S3 gallop
      vi. Clinically significant or rapid weight gain thought to be related to fluid retention.
   b. Laboratory evidence of new or worsening HF, if obtained within 24 hours of presentation, including:

i. Increased B-type natriuretic peptide (BNP)/N-terminal pro-BNP (NT-proBNP) concentrations consistent with decompensation of heart failure (such as BNP > 500 pg/ml or NT-proBNP >2000 pg/ml). In patients with chronically elevated natriuretic peptides, a significant increase should be noted above baseline.

ii. Radiological evidence of pulmonary congestion

iii. Non-invasive diagnostic evidence of clinically significant elevated left- or right-sided ventricular filling pressure or low cardiac output. For example, echocardiographic criteria could include: E/e' >15 or D-dominant pulmonary venous inflow pattern, plethoric inferior vena cava with minimal collapse on inspiration, or decreased left ventricular outflow tract (LVOT) minute stroke distance (time velocity integral [TVI])

OR

iv. Invasive diagnostic evidence with right heart catheterization showing a pulmonary capillary wedge pressure (pulmonary artery occlusion pressure) ≥18 mm Hg, central venous pressure ≥12 mm Hg, or a cardiac index <2.2 l/min/m^2.

5) The patient receives initiation or intensification of treatment specifically for HF, including **at least ONE** of the following:

a. Augmentation in oral diuretic therapy

b. Intravenous diuretic, inotrope, or vasodilator therapy

c. Mechanical or surgical intervention, including:

i. Mechanical circulatory support (e.g., intra-aortic balloon pump, ventricular assist device)

ii. Mechanical fluid removal (e.g., ultrafiltration, hemofiltration, dialysis).

Venous Thromboembolic Events

Pulmonary Embolism (PE); patient must have signs and symptoms associated with a PE and confirmed by:

- An intraluminal filling defect in segmental or more proximal branches on spiral CT scan
- An intraluminal filling defect or a sudden cutoff of vessels more than 2.5 mm in diameter on the pulmonary angiogram
- A perfusion defect of at least 75% of a segment with a normal ventilation result (high-probability) on ventilation/perfusion lung scintigraphy
- An inconclusive finding on spiral CT, pulmonary angiography or lung scintigraphy with demonstration of deep vein thrombosis (DVT) in the lower extremities by compression ultrasound or venography.

DVT; patient must have signs and symptoms associated with a DVT and event must be confirmed by an abnormal compression ultrasound (US) or an intraluminal filling defect on venography.

SECTION S5. Glycemic Sub-studies

Additionally, this trial included 3 add-on glycemic sub-studies in patients receiving specific background anti-hyperglycemic agents (AHAs): two of these were included in the original protocol: a sub-study to evaluate safety and efficacy of ertugliflozin in patients using insulin with or without metformin, and a sub-study to evaluate safety and efficacy of ertugliflozin in patients using sulfonylurea monotherapy. The Protocol Amendment of March 2016 included the addition of a glycemic sub study in patients receiving metformin plus sulfonylurea (SU) at the doses specified and clarification regarding inclusion into this sub study which was done programmatically at the time of the analyses for all the sub studies without changing the randomization scheme (only applicable to patients enrolled prior to amendment).

SECTION S6. Safety analyses

Safety was assessed based on adverse event monitoring, and for certain adverse events (e.g., urinary tract infection, genital mycotic infection, hypovolemia) included *a priori* defined, sponsor-generated custom *Medical Dictionary for Regulatory Activities* (MedDRA) queries. Fracture and pancreatitis events were adjudicated by blinded independent committees, while pre-specified renal and hepatic events were reviewed by a blinded independent committee for assessment of causality with study medication. Potential events of diabetic ketoacidosis were adjudicated by a blinded internal review committee of sponsor representatives that were not involved with the oversight or conduct of the trial. Cases of non-traumatic limb amputations were identified based on a search of adverse events and procedures using a custom MedDRA query and a search of the comment field of serious adverse event narratives.

SECTION S7. Statistical analyses

Original Sample-Size Calculation (Prior to Amendment)

The cardiovascular safety of ertugliflozin was originally planned to be assessed via a meta-analysis across the Phase 2 and Phase 3 development program with the majority of cardiovascular endpoints expected to come from this trial. A total of approximately 700 adjudicated MACE endpoints was initially planned to be collected across the program. The two doses of ertugliflozin (5 and 15 mg) were to be pooled for this analysis.

The primary and secondary objectives of the program wide cardiovascular meta-analysis were to be addressed by testing the hypotheses H0:HR≥1.8 versus H1:HR<1.8 for the MACE plus endpoint and H0:HR≥1.3 versus H1:HR<1.3 for the MACE endpoint where HR represents the risk of ertugliflozin relative to a non-ertugliflozin comparator group as measured by the hazard ratio.

The trial planned to use a group sequential design with up to three interim analyses and a final analysis. The first interim analysis took place at the later of 1) the time at which at least 138 adjudicated MACE plus events accrued throughout the Phase 2 and Phase 3 development program or 2) the time at which all necessary exposure data were available to support the filing of ertugliflozin. This analysis was planned to assess the hazard ratio for the MACE plus endpoint with respect to the 1.8 non-inferiority margin. If the first analysis was conducted with a number of MACE plus events greater than or equal to 138 but less than 175, then a second interim analysis (the final analysis for MACE plus) was to take place, if necessary (ie, if the non-inferiority margin of 1.8 was not met in the first analysis), at the time at which 175 MACE plus events had accrued, the appropriate alpha spending was to be determined from an O'Brien-Fleming type spending function. If the first analysis was conducted with 175 or more MACE plus events, then that would constitute the only analysis for MACE plus and the full alpha of 0.025 (1-sided) would have been utilized.

For these first two analyses, using an O'Brien Fleming type alpha spending function, and analyses at approximately 138 and 175 adjudicated MACE plus endpoints, the meta-analysis would have had approximately 95% power to demonstrate non-inferiority of ertugliflozin to a non-ertugliflozin comparator group when there was truly no difference between treatments (HR=1.0) using the hazard ratio margin of 1.8 and testing at the overall one-sided alpha level of 0.025.

The next interim analysis and the final analysis were planned to occur when approximately 500 and 700 adjudicated MACE endpoints accrued throughout the Phase 2 and Phase 3 development program. These analyses were planned to assess the hazard ratio for the MACE endpoint with respect to the 1.3 non-inferiority margin.

For the last two analyses, using an O'Brien Fleming type alpha spending function and analyses at approximately 500 and 700 adjudicated MACE endpoints, the meta-analysis would have had approximately 90% power to demonstrate non-inferiority of ertugliflozin to a non-ertugliflozin comparator group when there was truly no difference between treatments (HR=1.0) using the hazard ratio margin of 1.3 and testing at the overall one-sided alpha level of 0.025.

The sample size and length of follow up required to achieve these numbers of adjudicated cardiovascular endpoints across the Phase 2 and Phase 3 ertugliflozin development program depended on the accrual rate and annual event rates for this study as well as on the number of endpoints being contributed from the non-cardiovascular portion of the program. With an enrollment period of 18 months and assuming event rates of 2.8% and 2.25% per annum for MACE plus and MACE respectively, and that at least 50 adjudicated MACE endpoints would have accrued in the non-cardiovascular portion of the Phase 2 and Phase 3 development program, a total of approximately 3900 patients randomized in a 1:1:1 ratio to ertugliflozin 5 mg, ertugliflozin 15 mg or placebo would have been sufficient to achieve approximately 138 MACE plus endpoints within approximately 2.0 years and approximately 500 MACE endpoints within approximately 6.3 years from the start of this study. These calculations assumed that patients

would be lost to follow up at a rate of 1% per annum and that patients who were not lost to follow up were followed until the end of the trial.

The protocol was amended in March 2016 to increase the overall sample size to approximately 8000 patients based on updated study objectives and assumptions (details are in the manuscript).

Pre-specified Analyses Prior to Final Analysis

Data from the VERTIS CV study was used in 2 pre-specified analyses conducted prior to the final analysis. All analyses were conducted by a firewalled team, separate from the study team and no results were shared with the study team until after the final database lock. The first analysis (Stage 1) conducted with VERTIS CV data included events that accrued throughout the VERTIS Phase 2 and Phase 3 program including VERTIS CV study data up to the data cut-off date of 18-APR-2016. Meta-analysis of MACE plus (composite endpoint of cardiovascular death, non-fatal myocardial infarction, non-fatal stroke or hospitalization for unstable angina) was conducted to support the initial regulatory submissions and rule out a hazard ratio of 1.8 (an 80% increase in cardiovascular risk relative to the non-ertugliflozin comparator group). The results of the meta-analysis demonstrated that the 1.8 non-inferiority margin was met. In order to meet the post-marketing requirement of the US FDA for a new anti-diabetic agent, a non-inferiority margin of <1.3 (i.e. ruling out a 30% increase in CV risk based on MACE), which only included MACE events that occurred in VERTIS CV, was required. One planned interim analysis occurred, which was conducted to assess efficacy and futility. Results were reviewed by the Data Monitoring Committee (DMC) and the Sponsors were notified only that the study should continue. The DMC did not share details of the interim analysis with the Sponsor.

Sensitivity Analyses

Pre-specified sensitivity analyses were conducted using 1) the on-treatment approach that included confirmed events that occurred between the date of the first dose of study medication and the on-treatment censor date (14 days) and 2) the intention-to-treat analysis set where there was no limit on the ascertainment window. The same Cox models used for the primary approach were used for these sensitivity analyses. Missing data was handled by carrying out trial wide "vital sweeps" where all investigators were asked to search all possible sources to ascertain vital status on patients who were lost-to-follow-up. Events identified during vital sweeps were sent for adjudication and included in the analysis as per any other adjudicated event. Patients whose final endpoint status was unknown after the vital sweep was conducted were considered missing. Patients with missing final endpoint status were censored at the earliest of date of last contact, date of death, and date of study end. For on-treatment analyses with 14-day ascertainment windows, patients were censored using date of last dose +14 days, if this was missing, it was imputed based on the date of the subject's last clinic visit and the drug supply dispensed to the patient at that visit. In the absence of any record of discontinuation of study drug, it was assumed that the patient continued to take the drug for as long as the supply would last.

Testing Boundaries And Confidence Intervals

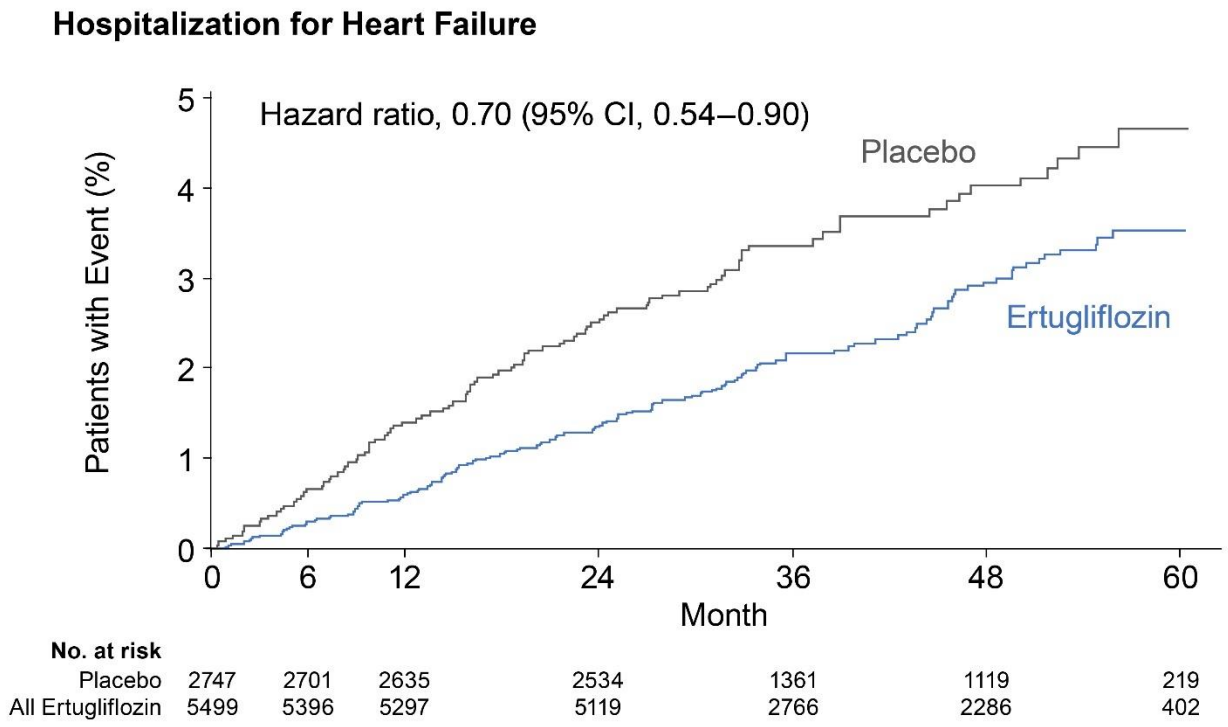
A stratified Cox proportional hazards model that included treatment group as a covariate and timing of enrollment (pre- vs. post amendment) as the stratification factor was used to evaluate the primary major adverse cardiovascular events (MACE) outcome. Testing boundaries and confidence intervals were adjusted according to the actual alpha spent at the interim analysis which was based on the actual numbers of events observed at the interim and final analyses in accordance with a Lan-DeMets O'Brien-Fleming spending function. The upper bound of a 2-

sided 95.6% confidence interval (CI) for the HR (ertugliflozin vs. placebo) was utilized for the non-inferiority test. The key secondary endpoints (CV death/HHF composite, CV death, and the renal composite) were analyzed using Cox models with the same model terms as for the primary outcome. After adjustment for the interim analysis, 2-sided 95.8% CI for the HR were calculated based on the Cox model for each key secondary outcome. Other pre-specified secondary efficacy outcomes (not part of the hierarchical statistical testing sequence) included time to first occurrence of: MACE plus (MACE or hospitalization for unstable angina); fatal or nonfatal myocardial infarction; fatal or nonfatal stroke; hospitalization for heart failure; individual components of MACE; all-cause death. These other pre-specified efficacy outcomes were analyzed using Cox models with the same model terms as for the primary outcome. A point estimate and 2-sided (95% CI for the HR were calculated based on the Cox model for each outcome. For the secondary outcomes that were not part of the hierarchical testing sequence, the widths of the confidence intervals were not adjusted for multiplicity and therefore the intervals should not be used to infer definitive treatment effects.

Subgroup analyses for the primary and key secondary endpoints were conducted by adding terms for the subgroup and subgroup by treatment interaction into the Cox model. Analyses were also carried for each cohort separately using the same Cox model as for the primary analysis.

SECTION S8. Supplemental Figures

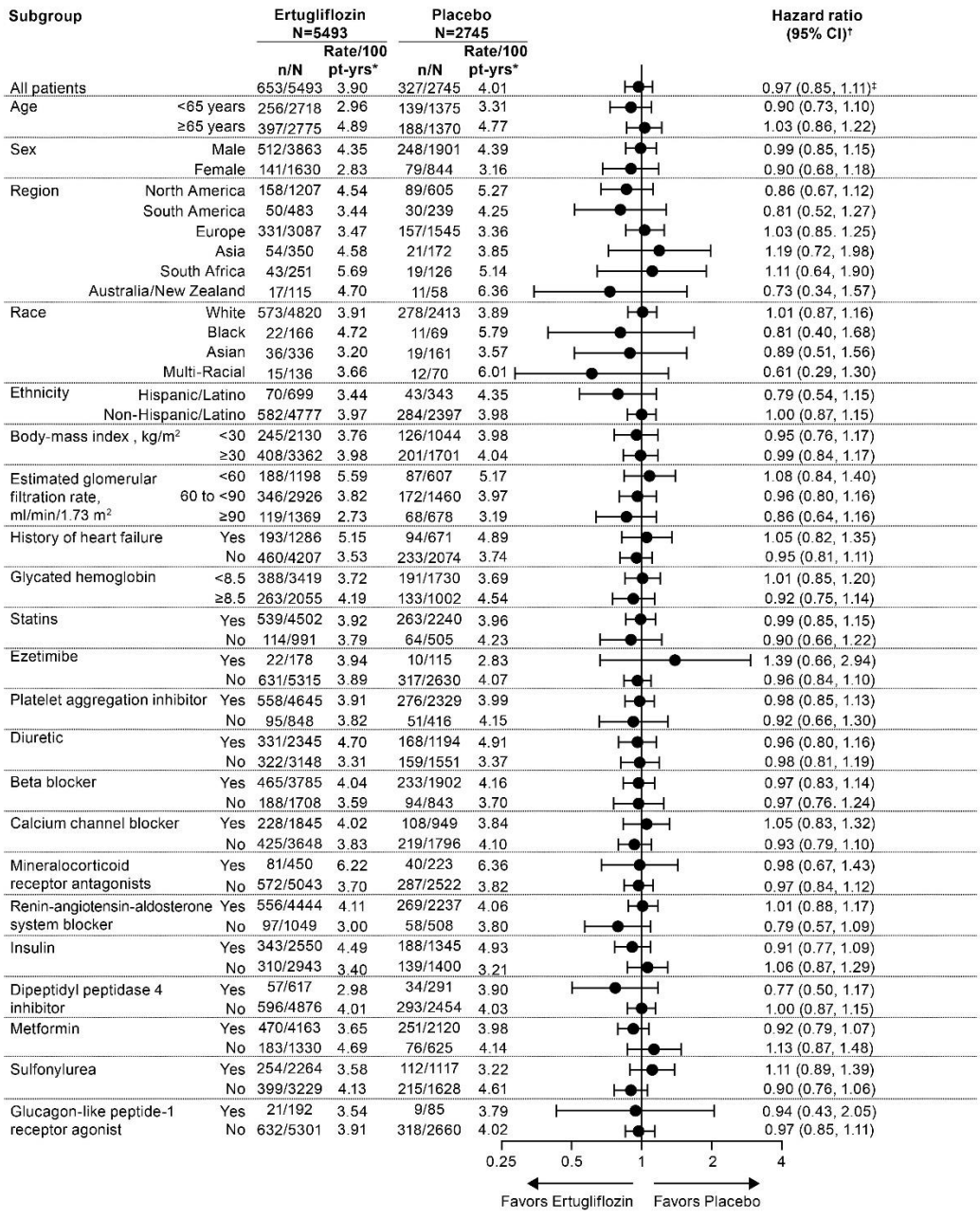
Figure S1. Results of time to first hospitalization for heart failure



Shown is the Kaplan-Meier curve of time to first hospitalization for heart failure.

Figure S2. Subgroup Analyses for the Primary Outcome (Composite Outcome of Cardiovascular Death, Nonfatal Myocardial Infarction, or Nonfatal Stroke)

Shown are the results of a prespecified Cox regression analyses of data for subgroups of patients with respect to the primary MACE outcome.



* Patient-years is calculated as the sum of patients´ time to first event or time to censoring (the earliest of patients´ end of study date, death date, last contact date, or 365 days after the last dose).

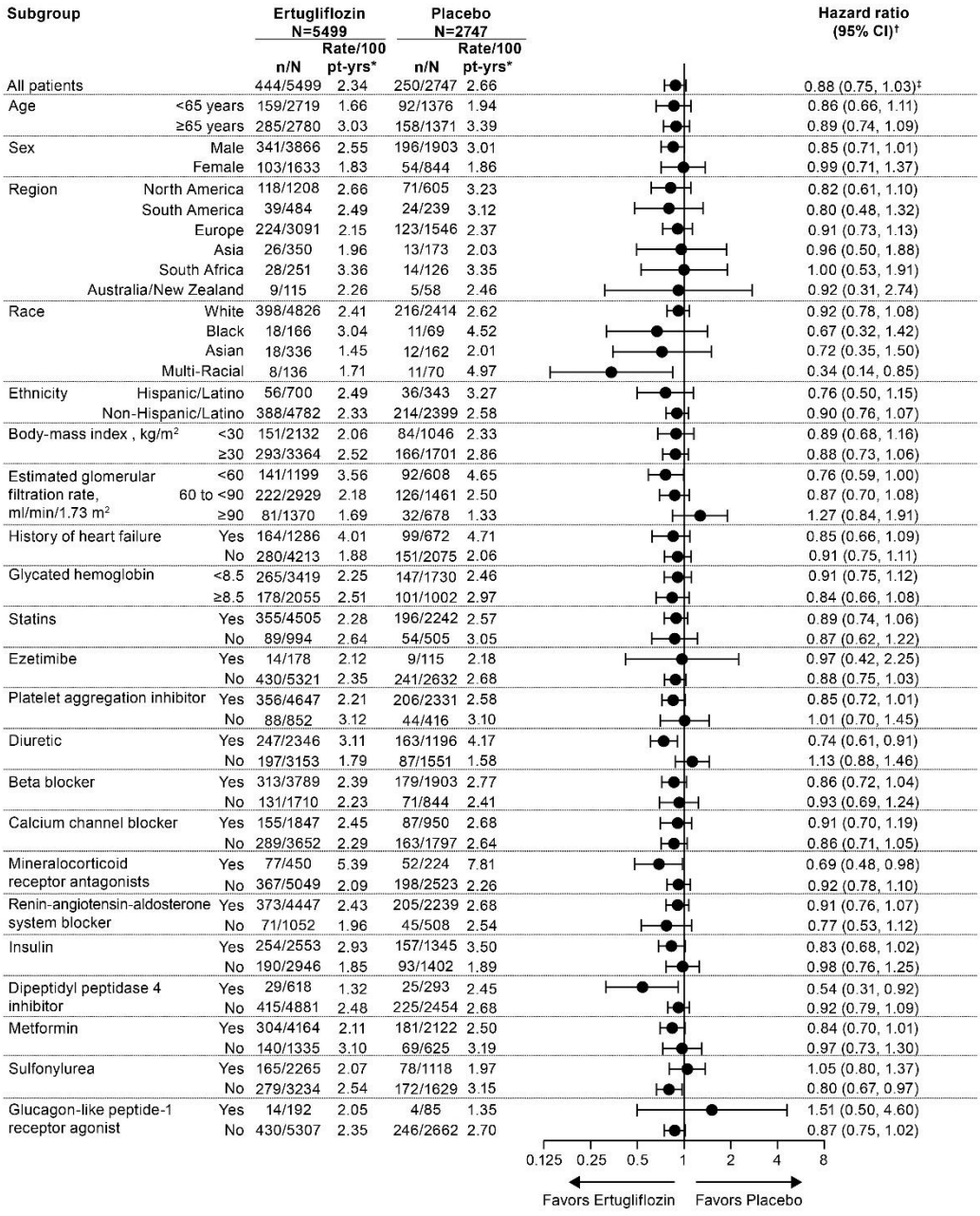
† Ertugliflozin vs. placebo, based on the stratified Cox proportional hazards model that includes treatment, subgroup, and treatment-by-subgroup interaction as explanatory factors and timing of enrollment (pre- vs. post amendment) as a stratification factor. The analysis was only performed for subgroups with at least 20 patients in all of the treatment groups in each subgroup category. For the race subgroup analysis, if the sample size was not at least 20 patients in all of the treatment groups in a certain race category, then that race was combined with the "Other" race category.

‡ 95.6% confidence interval.

MACE denotes major adverse cardiovascular events; pt, patient; yr, year.

Figure S3. Subgroup Analysis of Cardiovascular Death or Heart Failure Hospitalization Outcome

Shown are the results of a prespecified Cox regression analysis of data for subgroups of patients with respect to the key secondary outcome.



* Patient-years is calculated as the sum of patients´ time to first event or time to censoring (the earliest of patients´ end of study date, death date, or last contact date).

† Ertugliflozin vs. placebo, based on the stratified Cox proportional hazards model that includes treatment, subgroup, and treatment-by-subgroup interaction as explanatory factors and timing of enrollment (pre- vs. post amendment) as a stratification factor. The analysis was only performed for subgroups with at least 20 patients in all of the treatment groups in each subgroup category. For the race subgroup analysis, if the sample size was not at least 20 patients in all of the treatment groups in a certain race category, then that race was combined with the "Other" race category.

‡ 95.8% confidence interval.

Pt, patient; yr, year.

Figure S4. Primary Outcome (Composite Outcome of Cardiovascular Death, Nonfatal Myocardial Infarction, or Nonfatal Stroke, on treatment + 365 days approach) and Key Secondary Outcomes by Dose (intention-to-treat approach)

Shown are the Kaplan-Meier curves (Panel A) time to first major adverse cardiovascular events of cardiovascular death, nonfatal myocardial infarction or nonfatal stroke; (Panel B) time to first cardiovascular death or hospitalization for heart failure; (Panel C) time to cardiovascular death; (Panel D) time to first renal composite of renal death, renal replacement therapy, or doubling of serum creatinine; (Panel E)time to first hospitalization for heart failure .

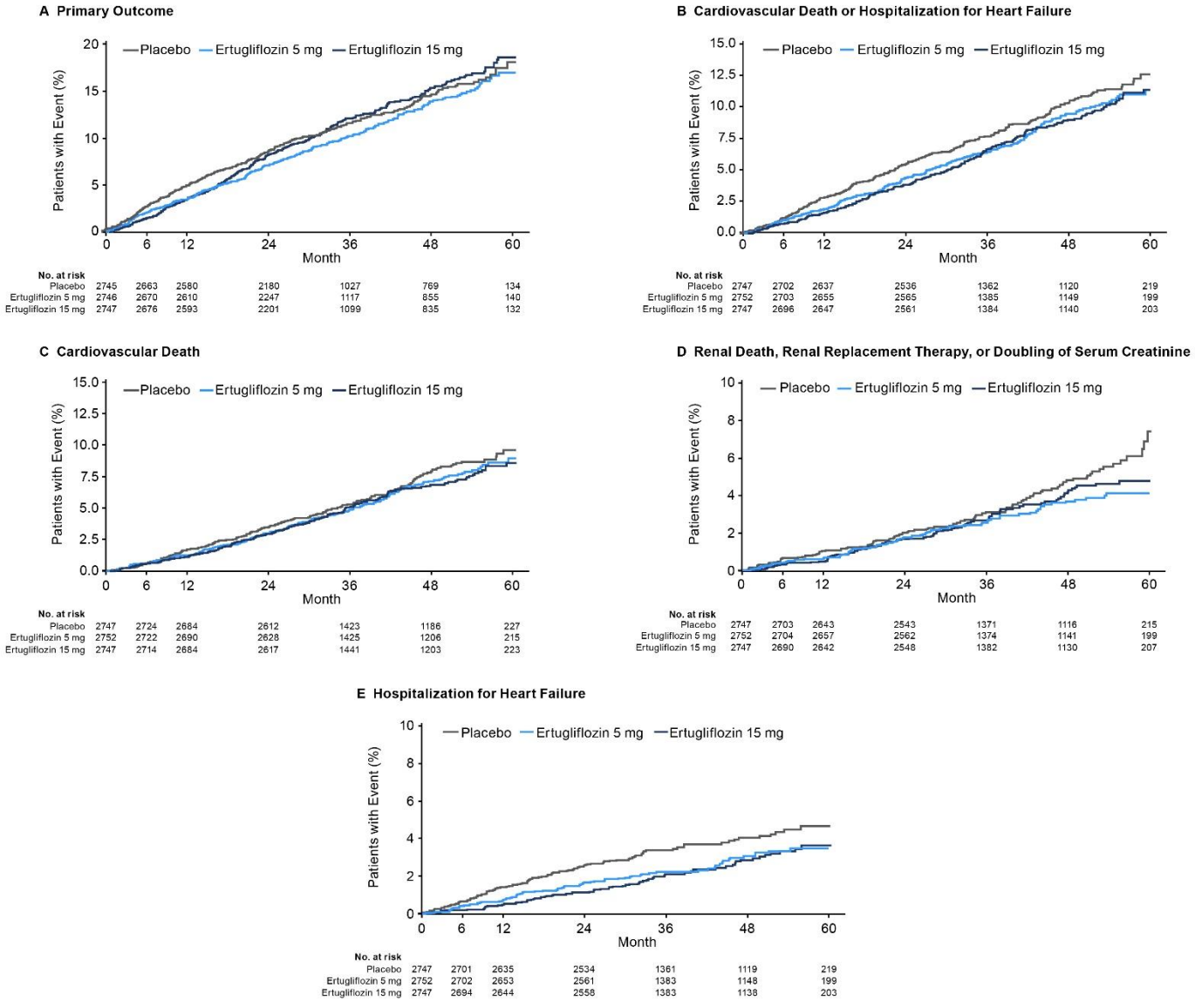


Figure S5. Glycated Hemoglobin

Shown are least squares mean (±SE) change in glycated hemoglobin in the three treatment groups, analyzed using a longitudinal data analysis model to estimate least squares mean changes for patients who received at least one dose of a study drug and had at least one measurement (baseline or post-baseline). The model used fixed effects for treatment, time, trial, baseline estimated glomerular filtration rate (eGFR), and the interaction of time by treatment.

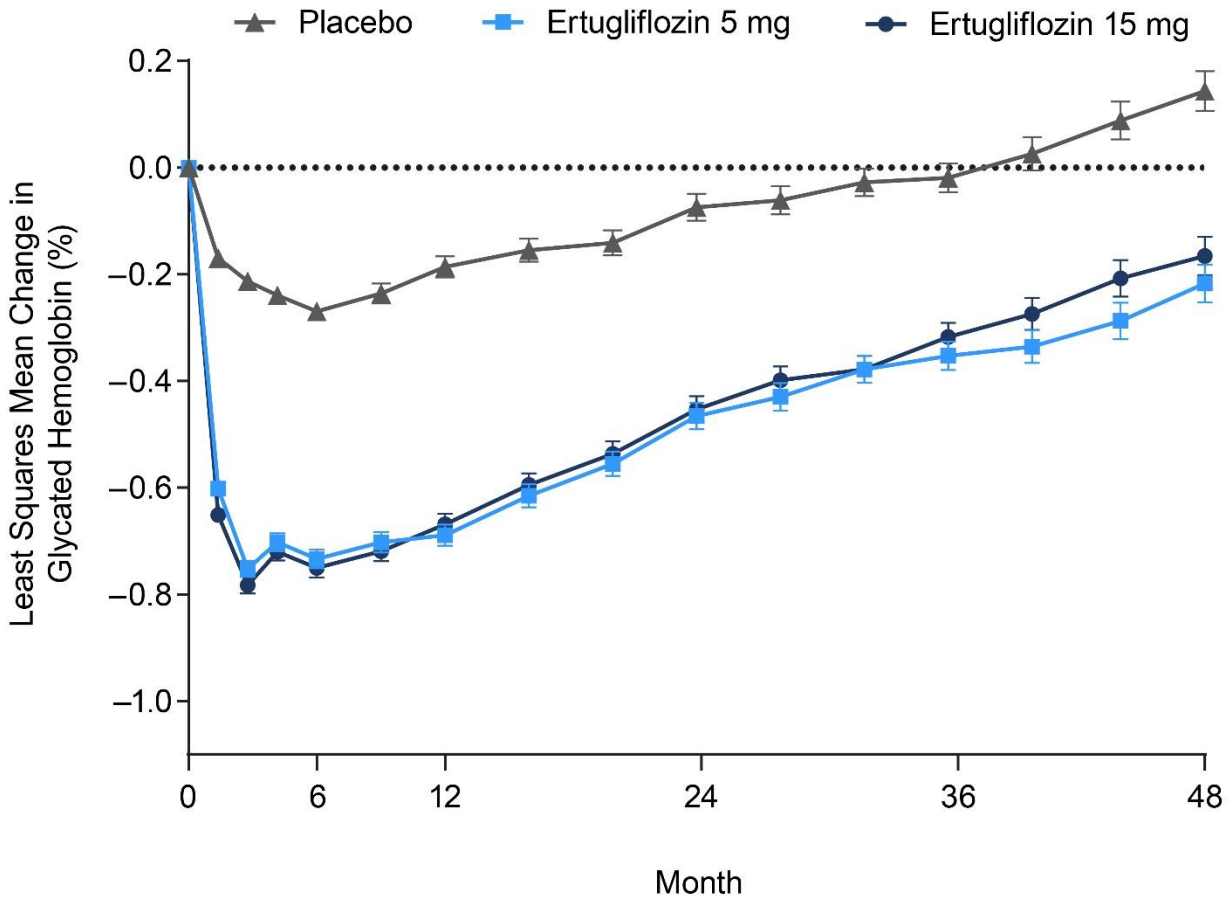


Figure S6. Body Weight

Shown are least squares mean (±SE) change in body weight in the three treatment groups, analyzed using a longitudinal data analysis model to estimate least squares mean changes for patients who received at least one dose of a study drug and had at least one measurement (baseline or post-baseline). The model used fixed effects for treatment, time, trial, baseline estimated glomerular filtration rate (eGFR), and the interaction of time by treatment.

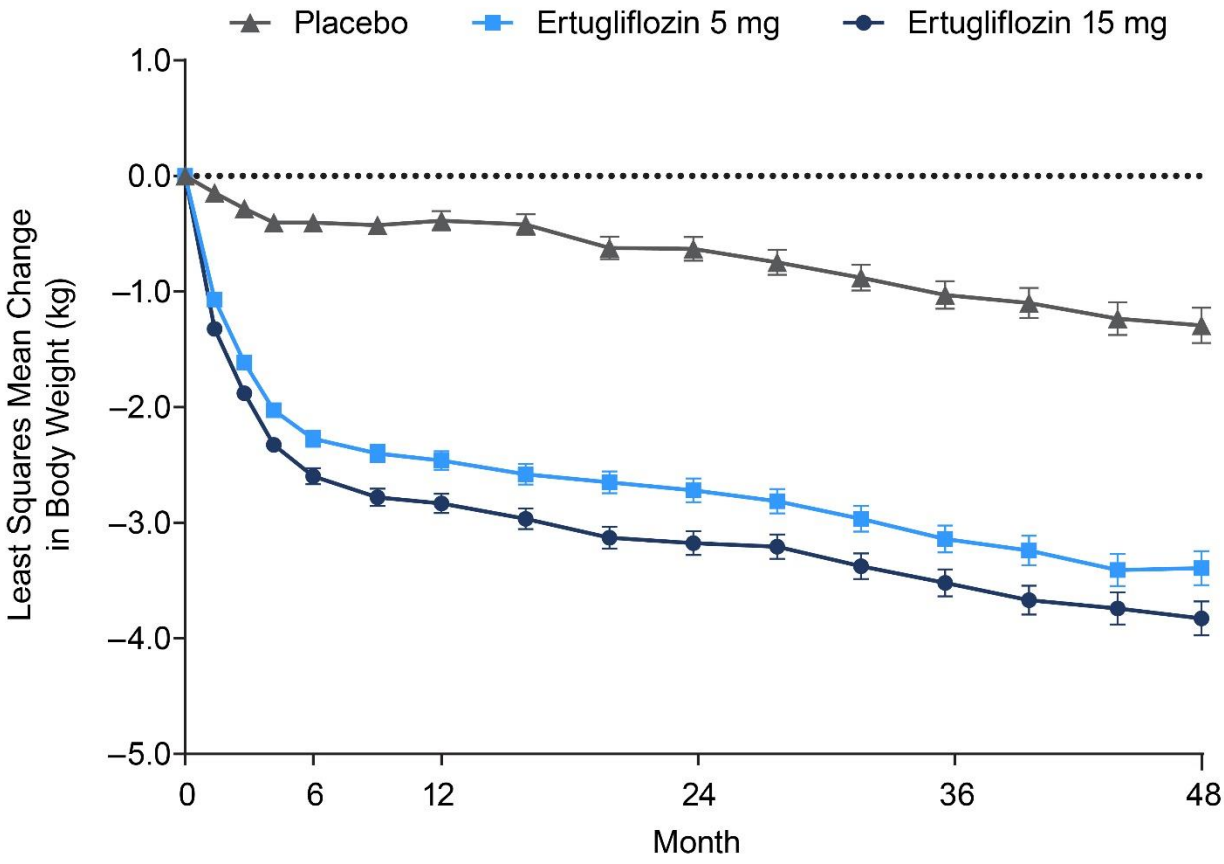
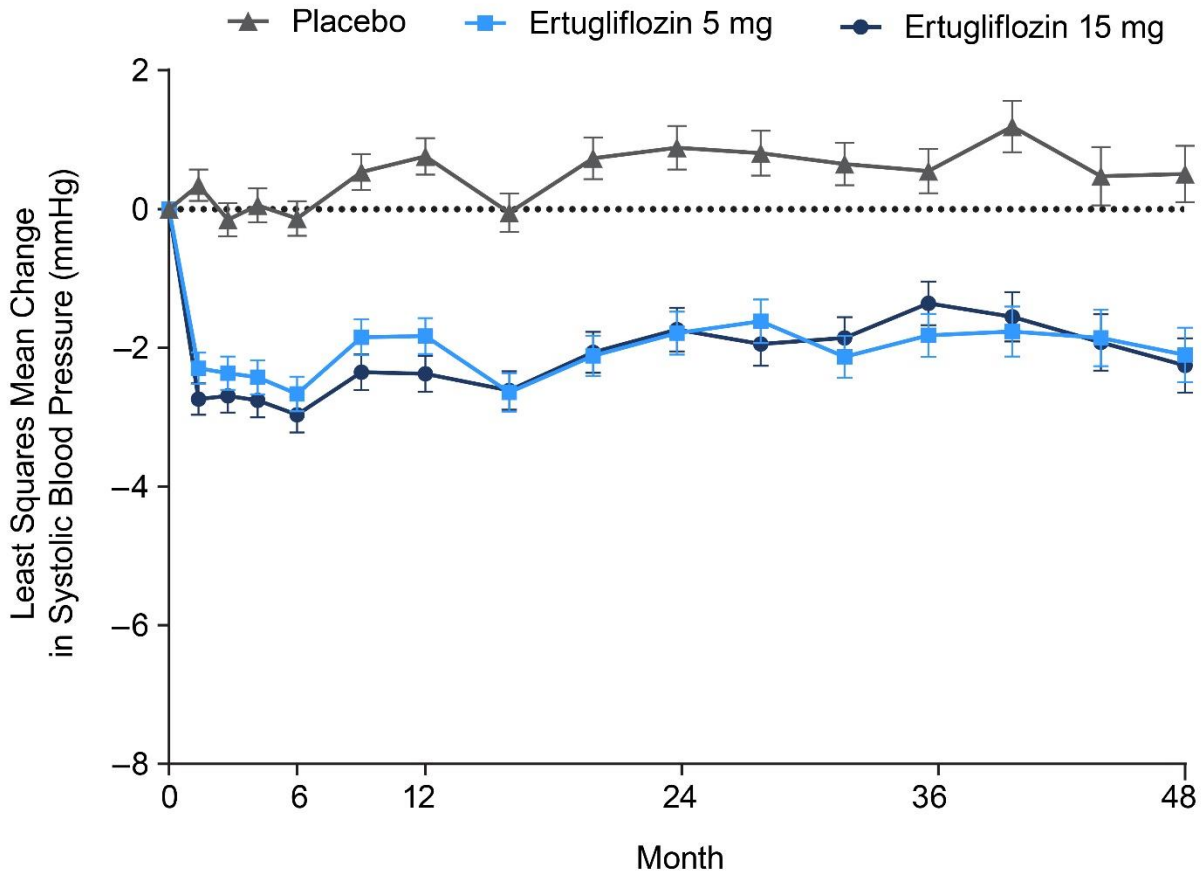


Figure S7. Systolic Blood Pressure

Shown are least squares mean (±SE) change in systolic blood pressure in the three treatment groups, analyzed using a constrained longitudinal data analysis model to estimate least squares mean changes for patients who received at least one dose of a study drug and had at least one measurement (baseline or post-baseline). The model used fixed effects for treatment, time, trial, baseline estimated glomerular filtration rate (eGFR), and the interaction of time by treatment.



SECTION S9. Supplementary Tables

Table S1. Summary Of Non-Randomized Patients Who Did Not Meet Inclusion Criteria Or Did Meet Exclusion Criteria

	Total no. (%)
Non-randomized patients	6355
Non-randomized patients who did not meet inclusion criteria or did meet exclusion criteria	6350
Inclusion criteria not met	
HbA1c at the Screening visit (V1) of 7.0 10.5% (53 91 mmol/mol) on stable allowable AHA(s) or on no background AHA for at least 8 weeks prior to the Screening visit (V1)	3549
In the investigator's opinion patients are willing and likely able to comply with scheduled visits, treatment plan, laboratory tests, and other study procedures whether or not they receive investigational product for the duration of the trial.	358
Patients must have evidence or a history of atherosclerosis involving the coronary, cerebral or peripheral vascular systems	331
There is adequate documentation of the objective evidence that the patient has established vascular disease such as investigational site's medical records, copies of such records from other institutions, or a letter from a referring physician that specifically states the diagnosis and date of the most recent occurrence of the qualifying event(s) or procedure(s).	50
Body Mass Index ≥18.0 kg/m^2	50

Patients ≥40 years of age at the time of the initial Screening visit (V1) with a diagnosis of T2DM in accordance with American Diabetes Association (ADA) guidelines.	49
Patient meets one of the following criteria (a, b or c): a. Is a male; b. Is a female not of reproductive potential defined as one: 1. Is postmenopausal: defined as at least 12 months with no menses in women ≥45 years of age. Or 2. Has had a hysterectomy and/or bilateral oophorectomy, or had bilateral tubal ligation or occlusion at least 6 weeks prior to the Screening visit (V1). c. Is a female of reproductive potential and: 1. Agrees to remain abstinent from heterosexual activity (if this form of birth control is accepted by local regulatory agencies and ethics review committees as the sole method of birth control); or 2. Agrees to use (or have their partner use) acceptable contraception to prevent pregnancy while the patient is receiving investigational product and for 14 days after the last dose of investigational product. Two methods of contraception will be used to avoid pregnancy. Acceptable combinations of methods include: Use of one of the following double barrier methods: diaphragm with spermicide and a condom; cervical cap and a condom; or a contraceptive sponge and condom; Use of hormonal contraception (any registered and marketed contraceptive agent that contains an estrogen and/or a progestational agent [including oral, subcutaneous, intrauterine and intramuscular agents, and cutaneous patch]) with one of the following: diaphragm with spermicide; cervical cap; contraceptive sponge; condom; vasectomy; or intrauterine device (IUD); Use of an IUD with one of the following: condom; diaphragm with spermicide; contraceptive sponge; vasectomy; or hormonal contraception (see above); Vasectomy with one of the following: diaphragm with spermicide; cervical cap; contraceptive sponge; condom; IUD; or hormonal contraception (see above).	49
Insulin ≥20 units/day with or without metformin ≥1,500 mg/day, where doses of insulin with or without metformin have been stable for at least 8 weeks prior to the time of the Screening visit (V1) and during the period between the Screening visit (V1) and randomization. Variations in the total daily dose of insulin of up to 10% are permitted and still meet the definition of stable insulin dose.	45

Monotherapy with a SU at the doses specified in Inclusion Criteria in Protocol. The dose of the SU monotherapy must have been stable for at least 8 weeks prior to the time of the Screening visit (V1) and during the period between the Screening visit (V1) and randomization	40
Exclusion criteria met	
Patients currently being treated for hyperthyroidism, patients on thyroid replacement therapy that have not been on a stable dose for at least 6 weeks prior to the Screening visit (V1) and/or patients who have a thyroid stimulating hormone (TSH) outside of the laboratory reference range at the Screening visit (V1). Patients excluded due to TSH criterion may be re-tested after being on a stable thyroid replacement regimen for at least 6 weeks.	1134
Patients with a hemoglobin <10 g/dL (100 g/L). Confirmed via a single repeat if deemed necessary.	462
Screening fasting plasma or finger-stick glucose >270 mg/dL (15 mmol/L), confirmed by a single repeat following counseling on exercise and diet.	325
Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) >2 X the upper limit of normal (ULN) at the Screening visit (V1), or a total bilirubin >1.5 X the ULN unless the patient has a history of Gilbert's.	243
eGFR <30 mL/min/1.73 m^2 as determined by the 4-variable Modification of Diet in Renal Disease (MDRD) equation, confirmed via a single repeat if deemed necessary.	134
Fasting triglycerides >600 mg/dL (6.78 mmol/L) at Screening (V1), confirmed by a single repeat if deemed necessary. For patients with fasting triglycerides >600 mg/dL the investigator or treating physician is allowed to adjust background lipid altering medication(s) to lower fasting triglycerides in order for the patient to be re-assessed for enrollment eligibility.	117

Mean value for triplicate screening sitting systolic blood pressure >160 mm Hg and/or diastolic blood pressure >90 mm Hg after at least a 5-minute seated rest at the Screening visit (V1), confirmed via 1 repeat triplicate set at the Screening visit (V1) if deemed necessary. For patients with a mean triplicate value of sitting systolic blood pressure >160 mm Hg and/or diastolic blood pressure >90 mm Hg after at least a 5-minute seated rest at the Screening visit (V1) the investigator or the treating physician is allowed to adjust background blood pressure medication(s) to lower blood pressure values in order for the patient to be re-assessed for enrollment eligibility.	91
Other severe acute or chronic medical or psychiatric condition or laboratory abnormality at the Screening visit (V1) that may increase the risk associated with trial participation or investigational product administration or may interfere with the interpretation of trial results and, in the judgment of the investigator, would make the patient inappropriate for entry into this trial.	71
Patients experiencing a cardiovascular event (e.g., myocardial infarction or stroke) or undergoing coronary angioplasty or peripheral intervention procedure between the Screening visit (V1) and randomization.	58
Patient has a history of malignancy ≤5 years prior to signing informed consent, except for adequately treated basal cell or squamous cell skin cancer or in situ cervical cancer. Note (1) A patient with a history of malignancy >5 years prior to signing informed consent should have no evidence of residual or recurrent disease. Note (2) A patient with any history of melanoma, leukemia, lymphoma, or renal cell carcinoma is excluded.	57
At randomization, patient has developed a new medical condition, suffered a change in status of an established medical condition, developed a laboratory or ECG abnormality, or required a new treatment or medication during the pre-randomization period which meets any previously described trial exclusion criterion or which, in the opinion of the investigator, exposes the patient to risk by enrolling in the trial.	55
Patient has a clinically significant electrocardiogram (ECG) abnormality at Screening visit (V1) that requires further diagnostic evaluation or intervention (e.g., new, clinically significant arrhythmia or a conduction disturbance).	45

The following therapeutic agents are prohibited for the duration of the trial. These medications are not to be used from 8 weeks before the Screening visit (V1) until the completion of the trial. Treatment with another SGLT2 inhibitor; Treatment with rosiglitazone; Treatment with chlorpropamide.	35
Patient has active, obstructive uropathy or indwelling urinary catheter.	28
Patients currently taking blood pressure or lipid altering medications that have not been on a stable dose for at least 4 weeks prior to randomization. Patients who require a change in blood pressure and/or lipid altering medications to meet the entry criteria related to blood pressure and/or triglycerides must be on a stable dose of such therapy for at least 4 weeks prior to randomization.	28
Patient is on or likely to require treatment for ≥14 consecutive days or repeated courses of pharmacologic doses of corticosteroids. These medications are not to be used from the time of the start of the Day 1 Visit (Visit 2) to the completion of the trial. Note: Inhaled, nasal, and topical corticosteroids and physiological replacement doses of adrenal steroids are permitted.	25
Patients with any planned coronary revascularization or peripheral intervention procedure or other cardiovascular surgery.	23
History of type 1 diabetes mellitus or a history of ketoacidosis.	19
History of one or more severe hypoglycemic episodes within 6 months of Screening (V1) or a severe hypoglycemic episode occurring during the interval between the Screening visit (V1) and randomization.	18
Patients with: Known history of Human Immunodeficiency Virus (HIV);Blood dyscrasias or any disorders causing hemolysis or unstable red blood cells.	18
Patients who meet any of the following categories: Patient is on a weight-loss program and is not weight-stable; Patient is on a weight-loss medication (e.g., orlistat, phentermine/topiramate, lorcaserin) and is not weight-stable; Patient is on other medications associated with weight changes (e.g., anti-psychotic agents) and is not weight-stable; Patient has undergone bariatric surgery	17

>12 months prior to Visit 1/Screening and is not weight-stable; Patient has undergone bariatric surgery within 12 months of Screening visit (Visit 1).Note: Weight-stable is defined as <5% change in body weight in the last 6 months.	
Patient routinely consumes >2 alcoholic drinks per day or >14 alcoholic drinks per week, or engages in binge drinking. Note (1): One alcoholic drink is defined as 5 oz (150 mL) of wine, or 12 oz (350 mL) of beer, or 1.5 oz (50 mL) of 80-proof liquor. Note (2): Binge drinking is defined as a pattern of 5 or more alcoholic drinks (male), or 4 or more alcoholic drinks (female) in about 2 hours.	16
Patient has a medical history of active liver disease (other than non-alcoholic hepatic steatosis), including chronic active hepatitis B or C (assessed by medical history), primary biliary cirrhosis, or symptomatic gallbladder disease.	16
Patients with New York Heart Association (NYHA) Class IV heart failure at the Screening visit (V1).	15
Patients who have undergone a surgical procedure within 4 weeks prior to signing informed consent or have planned major surgery during the trial. Note: A patient who has undergone minor surgery within the 4 weeks prior to Screening Visit (V1) and is fully recovered or a patient who has planned minor surgery may participate. Minor surgery is defined as a surgical procedure involving local anesthesia. For exclusion regarding cardiovascular surgery, see exclusion criterion #0.	15
Participation in other studies involving investigational drug (s) (Phases 1-4) within 30 days before the Screening visit (V1) and/or during trial participation	15
Patients undergoing any cardiovascular surgery (e.g., valvular surgery) within 3 months (90 days) of the Screening visit (V1).	12
Any clinically significant malabsorption condition.	11
Patients who had been previously randomized into this trial.	10
Patients with a known hypersensitivity or intolerance to any SGLT2 inhibitor.	9
History of other specific types of diabetes (e.g., genetic syndromes, secondary pancreatic diabetes, diabetes due to endocrinopathies, drug- or chemical-induced, and post-organ transplant).	7

Patients who have donated blood or blood products within six weeks of Screening (V1) or who plan to donate blood or blood products at any time during the trial.	7
Patients using prandial insulin alone without basal insulin	7
Patients who have previously been randomized in a trial with ertugliflozin.	6
Patients who are investigational site staff members directly involved in the conduct of the trial and their family members, site staff members otherwise supervised by the investigator, or patients who are Pfizer/Merck employees directly involved in the conduct of the trial.	5
Patient is expecting to undergo hormonal therapy in preparation to donate eggs during the period of the trial, including 14 days following the last dose of blinded investigational product.	3

A patient may appear for two or more trial entry criteria but was counted only once in the overall total.

Table S2. Anti-Hyperglycemic and Cardiovascular Medications at Baseline and at the End of Study

	Baseline		End of study	
Medication	Ertugliflozin (N=5499)	Placebo (N=2747)	Ertugliflozin (N=5499)	Placebo (N=2747)
Anti-hyperglycemic medications — no. (%)*				
None	77 (1.4)	29 (1.1)	103 (1.9)	30 (1.1)
Metformin	4168 (75.8)	2124 (77.3)	4069 (74.1)	2095 (76.3)
Insulin	2556 (46.5)	1344 (48.9)	2743 (49.9)	1514 (55.2)
Sulfonylurea	2268 (41.2)	1122 (40.8)	2194 (39.9)	1078 (39.3)
Dipeptidyl peptidase 4 inhibitor	619 (11.3)	292 (10.6)	756 (13.8)	392 (14.3)
Glucagon-like peptide-1 receptor agonist	192 (3.5)	86 (3.1)	268 (4.9)	153 (5.6)
Cardiovascular medications — no. (%)†				
Any antihypertensive	5221 (94.9)	2632 (95.8)	5186 (94.3)	2608 (94.9)
Renin-angiotensin-aldosterone system blocker	4447 (80.9)	2239 (81.5)	4349 (79.1)	2217 (80.7)
Beta-blocker	3789 (68.9)	1903 (69.3)	3814 (69.4)	1926 (70.1)
Calcium channel blocker	1847 (33.6)	950 (34.6)	1961 (35.7)	1027 (37.4)
Diuretic (any)	2346 (42.7)	1196 (43.5)	2414 (43.9)	1311 (47.7)
Diuretic (loop)	826 (15.0)	426 (15.5)	1007 (18.3)	551 (20.1)

Mineralocorticoids receptor antagonists	450 (8.2)	224 (8.2)	544 (9.9)	298 (10.8)
Any anticoagulant	4880 (88.7)	2446 (89.0)	4890 (88.9)	2459 (89.5)
Platelet aggregation inhibitor	4647 (84.5)	2331 (84.9)	4592 (83.5)	2312 (84.2)
Lipid-lowering drugs	4655 (84.7)	2313 (84.2)	4730 (86.0)	2342 (85.3)
Statin	4505 (81.9)	2242 (81.6)	4594 (83.5)	2264 (82.4)
Ezetimibe	178 (3.2)	115 (4.2)	225 (4.1)	147 (5.4)

Every patient was counted a single time for each applicable specific medication. A patient with multiple medications within a medication category is counted a single time for that category.

* All patients as treated population that included all randomized patients who received at least 1 dose of study treatment (N=5493 for ertugliflozin and N=2745 for placebo).

† Intention-to-treat analysis set that included all randomized patients.

Table S3. Treatment and Observation Times

	Ertugliflozin 5 mg N=2752	Ertugliflozin 15 mg N=2747	Pooled ertugliflozin N=5499	Placebo N=2747	Total N=8246
Overall population					
Treatment — years[*]					
Mean	3.0 ± 1.4	2.9 ± 1.4	2.9 ± 1.4	2.8 ± 1.4	2.9 ± 1.4
Median (range)	2.8 (<0.1–5.6)	2.8 (<0.1–5.8)	2.8 (<0.1–5.8)	2.7 (<0.1–5.7)	2.7 (<0.1–5.8)
Observation — years					
Mean	3.5 ± 1.2	3.5 ± 1.2	3.5 ± 1.2	3.5 ± 1.1	3.5 ± 1.2
Median (range)	3.0 (<0.1–5.9)	3.0 (<0.1–5.8)	3.0 (<0.1–5.9)	3.0 (<0.1–5.7)	3.0 (<0.1–5.9)
Cohort I	N=1342	N=1341	N=2683	N=1340	N=4023
Treatment — years[†]					
Mean	3.6 ± 1.7	3.5 ± 1.7	3.5 ± 1.7	3.3 ± 1.7	3.5 ± 1.7
Median (range)	4.4 (<0.1–5.6)	4.3 (<0.1–5.8)	4.3 (<0.1–5.8)	4.3 (<0.1–5.7)	4.3 (<0.1–5.8)
Observation — years					
Mean	4.4 ± 1.1	4.3 ± 1.1	4.3 ± 1.1	4.3 ± 1.0	4.3 ± 1.1
Median (range)	4.6 (<0.1–5.9)	4.6 (<0.1–5.8)	4.6 (<0.1–5.9)	4.6 (<0.1–5.7)	4.6 (<0.1–5.9)

Cohort II	N=1410	N=1406	N=2816	N=1407	N=4223
Treatment — years‡					
Mean	2.4 ± 0.8	2.4 ± 0.8	2.4 ± 0.8	2.3 ± 0.8	2.4 ± 0.8
Median (range)	2.6 (<0.1–3.4)	2.6 (<0.1–3.3)	2.6 (<0.1–3.4)	2.6 (<0.1–3.3)	2.6 (<0.1–3.4)
Observation — years					
Mean	2.7 ± 0.4	2.7 ± 0.4	2.7 ± 0.4	2.7 ± 0.5	2.7 ± 0.4
Median (range)	2.7 (<0.1–3.4)	2.7 (<0.1–3.3)	2.7 (<0.1–3.4)	2.7 (<0.1–3.4)	2.7 (<0.1–3.4)

Intention-to-treat analysis set that included all randomized patients.

Plus–minus values are means ± standard deviation.

* Data were available for 2745 patients in the placebo group, 2746 patients in the ertugliflozin 5 mg group, and 2747 patients in the ertugliflozin 15 mg group.

† Data were available for 1340 patients in the placebo group, 1339 patients in the ertugliflozin 5 mg group, and 1341 patients in the ertugliflozin 15 mg group.

‡ Data were available for 1405 patients in the placebo group, 1407 patients in the ertugliflozin 5 mg group, and 1406 patients in the ertugliflozin 15 mg group.

Table S4. Summary of Trial Disposition and Vital Status

	Ertugliflozin 5 mg	Ertugliflozin 15 mg	Placebo
	N=2752	N=2747	N=2747
	no. (%)	no. (%)	no. (%)
Completed the study alive	2422 (88.0)	2401 (87.4)	2389 (87.0)
Discontinued the study	329 (12.0)	344 (12.5)	356 (13.0)
Reasons for discontinuation of the study			
Death	228 (8.3)	233 (8.5)	247 (9.0)
Lost to follow-up	51 (1.9)	44 (1.6)	55 (2.0)
Physician decision	7 (0.3)	4 (0.2)	6 (0.2)
Study terminated by sponsor	2 (0.1)	2 (0.1)	3 (0.1)
Withdrawal by patient	41 (1.5)	60 (2.2)	45 (1.6)
Patient moved	0 (0.0)	1 (<0.1)	0 (0.0)
Unknown	1 (<0.1)	2 (0.1)	2 (0.1)
Completed the study medication alive	1980 (72.0)	1965 (71.5)	1850 (67.4)
Discontinued the study medication prior to completion (including patients for whom death was the reason)	772 (28.1)	782 (28.5)	897 (32.7)
Reasons for discontinuation of the study medication			
Adverse event	204 (7.4)	199 (7.2)	184 (6.7)
Death	137 (5.0)	126 (4.6)	130 (4.7)
Lost to follow up	50 (1.8)	42 (1.5)	40 (1.5)
Noncompliance with study drug	1 (<0.1)	2 (0.1)	0 (0.0)
Physician decision	34 (1.2)	32 (1.2)	54 (2.0)
Pregnancy	1 (<0.1)	0 (0.0)	0 (0.0)
Study terminated by sponsor	1 (<0.1)	2 (0.1)	3 (0.1)
Withdrawal by patient	318 (11.6)	355 (12.9)	422 (15.4)

Creatinine/estimated glomerular filtration rate	0 (0.0)	0 (0.0)	1 (<0.1)
Excluded medication	10 (0.4)	10 (0.4)	38 (1.4)
Patient moved	16 (0.6)	14 (0.5)	25 (0.9)
Final vital status available	2730 (99.2)	2727 (99.3)	2730 (99.4)
Alive	2495 (90.7)	2489 (90.6)	2476 (90.1)
Dead	235 (8.5)	238 (8.7)	254 (9.3)
Lost to follow-up for vital status	22 (0.8)	20 (0.7)	17 (0.6)
With non-fatal MACE*	0 (0.0)	0 (0.0)	0 (0.0)

Intention-to-treat analysis set that included all randomized patients. For the calculation of percentage, the denominator is the number of randomized patients.

* Patients who were lost to follow-up for vital status but had a known non-fatal MACE event contributed to the primary MACE analysis and relevant secondary analyses.

MACE denotes major adverse cardiovascular events.

Table S5. Key Outcomes Analyzed by On-treatment +14-day Approach (Sensitivity Analyses)

	Ertugliflozin (N=5493)		Placebo (N=2745)		Hazard Ratio (95% CI)
	no. (%)	Rate/100 patient-years	no. (%)	Rate/100 patient-years	
Cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke	525 (9.6)	3.3	262 (9.5)	3.5	0.96 (0.83, 1.11)
Cardiovascular death or hospitalization for heart failure	262 (4.8)	1.6	150 (5.5)	1.9	0.83 (0.68, 1.02)
Cardiovascular death	166 (3.0)	1.0	86 (3.1)	1.1	0.92 (0.71, 1.20)
Renal death, renal replacement therapy, or doubling of serum creatinine	139 (2.5)	0.9	83 (3.0)	1.1	0.80 (0.61, 1.05)
Hospitalization for heart failure	109 (2.0)	0.7	79 (2.9)	1.0	0.66 (0.49, 0.88)

Noninferiority set that included all randomized patients who received at least one dose of study medication. The on-treatment approach includes confirmed events that occurred between the date of the first dose of study medication and the on-treatment censor date (14 days).

CI denotes confidence interval.

Table S6. Primary and Secondary Outcomes by Cohort

	Ertugliflozin (N=5499)		Placebo (N=2747)		Hazard Ratio (95% CI)
	no. (%)	Rate/100 patient-years	no. (%)	Rate/100 patient-years	
Primary outcome (and individual endpoint):					
Cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke (FAS)*					
Cohort I	372 (13.9)	3.8	193 (14.4)	4.1	0.92 (0.78, 1.10)
Cohort II	281 (10.0)	4.0	134 (9.5)	3.9	1.04 (0.85, 1.28)
Cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke (ITT) †					
Cohort I	438 (16.3)	4.0	227 (16.9)	4.2	0.95 (0.81, 1.12)
Cohort II	297 (10.6)	4.1	141 (10.0)	3.9	1.05 (0.86, 1.29)
Key secondary superiority outcomes: †					
Cardiovascular death or hospitalization for heart failure					
Cohort I	271 (10.1)	2.4	152 (11.3)	2.7	0.88 (0.72, 1.08)
Cohort II	173 (6.1)	2.3	98 (7.0)	2.6	0.88 (0.69, 1.12)
Cardiovascular death					
Cohort I	209 (7.8)	1.8	115 (8.6)	2.0	0.91 (0.72, 1.14)
Cohort II	132 (4.7)	1.7	69 (4.9)	1.8	0.95 (0.71, 1.28)

Renal death, renal replacement therapy, or doubling of serum creatinine					
Cohort I	100 (3.7)	0.9	62 (4.6)	1.1	0.80 (0.59, 1.11)
Cohort II	75 (2.7)	1.0	46 (3.3)	1.2	0.81 (0.56, 1.17)
Hospitalization for heart failure					
Cohort I	79 (2.9)	0.7	58 (4.3)	1.0	0.68 (0.48, 0.95)
Cohort II	60 (2.1)	0.8	41 (2.9)	1.1	0.73 (0.49, 1.08)

[*] Noninferiority set that included all randomized patients who received at least one dose of study medication (Cohort I: N=2680 for ertugliflozin and N=1340 for placebo; Cohort II: N=2813 for ertugliflozin and N=1405 for placebo). For patients who prematurely permanently discontinued study medication, only confirmed cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke (MACE) events occurring up to 365 days after the last dose of study medication were included in the primary analysis.

[†] Intention-to-treat analysis set that included all randomized patients with no limit on the ascertainment window for the superiority outcomes (Cohort I: N=2683 for ertugliflozin and N=1340 for placebo; Cohort II: N=2816 for ertugliflozin and N=1407 for placebo).

CI denotes confidence interval, MACE major adverse cardiovascular events

Table S7. Primary Outcomes for the Intention-to-treat Population (Sensitivity Analyses)

	Ertugliflozin (N=5499)		Placebo (N=2747)		Hazard Ratio (95% CI)
	no. (%)	Rate/100 patient-years	no. (%)	Rate/100 patient-years	
Cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke	735 (13.4)	4.0	368 (13.4)	4.0	0.99 (0.88, 1.12)

Intention-to-treat analysis set that included all randomized patients with no limit on the ascertainment window for the superiority outcomes.

CI denotes confidence interval.

Table S8. Primary and Secondary Outcomes by Dose

	Ertugliflozin 5mg (N=2746)		Ertugliflozin 15mg (N=2747)		Placebo (N=2745)	
	no. (%)	Rate/100 patient-years	no. (%)	Rate/100 patient-years	no. (%)	Rate/100 patient-years
Primary outcome:						
Cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke (FAS)*	307 (11.2)	3.6	346 (12.6)	4.2	327 (11.9)	4.0
Hazard Ratio (95.6% CI)	0.91 (0.77, 1.07)		1.04 (0.89, 1.21)			
Cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke (ITT) †	352 (12.8)	3.8	383 (13.9)	4.2	368 (13.4)	4.0
Hazard Ratio (95% CI)	0.94 (0.82, 1.09)		1.04 (0.90, 1.20)			
Secondary outcomes:†						
Cardiovascular death or hospitalization for heart failure	224 (8.1)	2.4	220 (8.0)	2.3	250 (9.1)	2.7
Hazard Ratio (95.8% CI)	0.89 (0.74, 1.07)		0.88 (0.73, 1.06)			

Cardiovascular death	172 (6.3)	1.8	169 (6.2)	1.7	184 (6.7)	1.9
Hazard Ratio (95.8% CI)	0.93 (0.75, 1.15)	0.92 (0.74, 1.14)				
Renal death, renal replacement therapy, or doubling of serum creatinine	83 (3.0)	0.9	92 (3.4)	1.0	108 (3.9)	1.2
Hazard Ratio (95.6% CI)	0.76 (0.57, 1.03)		0.85 (0.64, 1.14)			
Hospitalization for heart failure	71 (2.6)	0.8	68 (2.5)	0.7	99 (3.6)	1.1
Hazard Ratio (95% CI)	0.71 (0.52, 0.96)	0.68 (0.50, 0.93)				

[*] Noninferiority set that included all randomized patients who received at least one dose of study medication (N=5493 for ertugliflozin and N=2745 for placebo). For patients who prematurely discontinued study medication, only confirmed cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke (MACE) events occurring up to 365 days after the last dose of study medication were included in the primary analysis.

[†] Intention-to-treat analysis set that included all randomized patients with no limit on the ascertainment window for the superiority outcomes (N=5499 for ertugliflozin and N=2747 for placebo).

CI denotes confidence interval.

Table S9: Serious Adverse Events (Incidence >1% in One or More Treatment Groups)

	Ertugliflozin 5 mg (N=2746) n (%)	Ertugliflozin 15 mg (N=2747) n (%)	Placebo (N=2745) n (%)
Patients with at least one serious adverse event	958 (34.9)	937 (34.1)	990 (36.1)
Cardiac disorders	362 (13.2)	384 (14.0)	434 (15.8)
Acute myocardial infarction	52 (1.9)	76 (2.8)	73 (2.7)
Angina pectoris	38 (1.4)	42 (1.5)	49 (1.8)
Angina unstable	74 (2.7)	71 (2.6)	89 (3.2)
Atrial fibrillation	30 (1.1)	31 (1.1)	37 (1.3)
Cardiac failure	35 (1.3)	34 (1.2)	43 (1.6)
Cardiac failure congestive	19 (0.7)	28 (1.0)	35 (1.3)
Coronary artery disease	35 (1.3)	34 (1.2)	38 (1.4)
Myocardial infarction	39 (1.4)	49 (1.8)	37 (1.3)
Eye disorders	19 (0.7)	21 (0.8)	31 (1.1)
Gastrointestinal disorders	78 (2.8)	84 (3.1)	59 (2.1)
General disorders and administration site conditions	95 (3.5)	58 (2.1)	75 (2.7)
Death	35 (1.3)	22 (0.8)	25 (0.9)
Hepatobiliary disorders	30 (1.1)	24 (0.9)	35 (1.3)
Infections and infestations	197 (7.2)	179 (6.5)	176 (6.4)
Cellulitis	21 (0.8)	31 (1.1)	21 (0.8)
Pneumonia	51 (1.9)	46 (1.7)	45 (1.6)
Injury, poisoning, and procedural complications	78 (2.8)	69 (2.5)	80 (2.9)

Metabolism and nutrition disorders	54 (2.0)	40 (1.5)	62 (2.3)
Musculoskeletal and connective tissue disorders	65 (2.4)	54 (2.0)	58 (2.1)
Neoplasms benign, malignant, and unspecified (including cysts and polyps)	141 (5.1)	135 (4.9)	118 (4.3)
Nervous system disorders	150 (5.5)	155 (5.6)	145 (5.3)
Ischemic stroke	29 (1.1)	40 (1.5)	41 (1.5)
Renal and urinary disorders	49 (1.8)	39 (1.4)	55 (2.0)
Respiratory, thoracic, and mediastinal disorders	59 (2.1)	48 (1.7)	66 (2.4)
Vascular disorders	84 (3.1)	74 (2.7)	99 (3.6)

All patients as treated population that included all randomized patients who received at least 1 dose of study treatment (N=5493 for ertugliflozin and N=2745 for placebo). Every patient is counted a single time for each applicable row and column. A system organ class or specific adverse event is reported only if its incidence in 1 or more of the columns meets the incidence criterion, after rounding.

Table S10. Analysis of Patients with Amputation (Exposure-Adjusted Incidence Rate Per 100 Patient Years)

	Ertugliflozin 5mg (N=2746)		Ertugliflozin 15mg (N=2747)		Pooled ertugliflozin (N=5493)		Placebo (N=2745)	
	no. (%)	Rate/100 patient-years	no. (%)	Rate/100 patient-years	no. (%)	Rate/100 patient-years	no. (%)	Rate/100 patient-years
Amputation	54 (2.0)	0.6	57 (2.1)	0.6	111 (2.0)	0.6	45 (1.6)	0.5
Risk Difference (95% CI)*	0.1 (–0.1, 0.3)		0.1 (–0.1, 0.3)		0.1 (–0.1, 0.3)			

Data are for patients included in the all post-randomization follow-up period, which included all available data after randomization with no upper limit on the ascertainment window.

* Risk difference and 95% confidence interval for ertugliflozin vs placebo were calculated based on a pre-specified analysis.

CI denotes confidence interval.