Design and baseline characteristics of the eValuation of ERTugliflozin efficacy and Safety CardioVascular outcomes trial (VERTIS-CV)

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Background Ertugliflozin is an inhibitor of sodium-glucose co-transporter-2 (SGLT2), approved in the United States and European Union to improve glycemic control in adults with type 2 diabetes mellitus (T2DM). The VERTIS cardiovascular (CV) outcomes trial (NCT01986881) has a primary objective to demonstrate non-inferiority of ertugliflozin versus placebo on major adverse CV events: time to the first event of CV death, nonfatal myocardial infarction, or nonfatal stroke. Secondary objectives are to demonstrate superiority of ertugliflozin versus placebo on time to: 1) the composite outcome of CV death or hospitalization for heart failure (HF); 2) CV death; and 3) the composite outcome of renal death, dialysis/transplant, or doubling of serum creatinine from baseline.

Methods Patients ≥40 years old with T2DM (HbA1c 7.0–10.5%) and established atherosclerotic cardiovascular disease (ASCVD) of the coronary, cerebral, and/or peripheral arterial systems, were randomized 1:1:1 to once daily double-blind placebo, ertugliflozin 5 mg or 15 mg added to existing therapy.

Results 8246 patients were randomized and 8238 received at least 1 dose of investigational product. Mean age was 64.4 years, 11.0% were ≥75 years old, and mean diabetes duration was 12.9 years with screening HbA1c of 8.3%. At entry, coronary artery disease, cerebrovascular disease, and peripheral arterial disease were present in 76.3%, 23.1%, and 18.8% of patients, respectively. HF was present in 23.1%, and Stage 3 kidney disease in 21.6% of patients.

Conclusion The results from the VERTIS-CV trial will define the CV and renal safety and efficacy of ertugliflozin in patients with T2DM and ASCVD. (Am Heart J 2018;206:11-23.)

Epidemiological studies consistently demonstrate that patients with type 2 diabetes mellitus (T2DM) have a 2- to 4-fold increased risk of cardiovascular (CV) disease relative to those without T2DM, and CV disease is the leading cause of morbidity and mortality in patients with T2DM.[1-2] In recent clinical trials, despite the use of background evidence-based secondary prevention therapies for CV disease, individuals with T2DM and atherosclerotic cardiovascular disease (ASCVD) remain at high residual CV risk. In the sitagliptin CV outcome trial (TECOS) of patients with T2DM and established ASCVD, the incidence rate for major adverse cardiovascular events (MACE) and CV death was 3.62 and 1.67 per 100-patient years, respectively, among patients in the placebo group.[3] The risk of MACE among individuals with diabetes in the placebo arm of the PEGASUS-TIMI 54 trial studying patients with chronic, stable coronary artery disease was 11.6% over a median follow-up of 33 months.[4] These high event rates highlight the unmet medical need that exists for additional treatments to reduce the burden of CV disease in patients with T2DM and established ASCVD.

Results from 2 completed placebo-controlled CV outcome trial programs with the sodium-glucose co-transporter-2 (SGLT2) inhibitors empagliflozin and canagliflozin have shown significant reductions in MACE, with nearly identical magnitude of benefit for MACE along with other outcomes including heart failure (HF) hospitalization.[5-6] However, a significant reduction in CV death was observed only with empagliflozin.[5] The patient populations enrolled in the completed and ongoing CV outcome trials of SGLT2 inhibitors differ with respect to the proportions with established CV disease and spectrum of baseline kidney function, which may be relevant to effects of the SGLT2 inhibitors on CV and/or renal outcomes.[5-7] Moreover, differences in certain safety end points, namely risk of amputation and fractures, were observed in the completed SGLT2 inhibitor trials.[5-6]

Ertugliflozin (MK-8835, PF-04971729) is an oral, highly selective SGLT2 inhibitor with greater than 2000-fold higher selectivity for SGLT2 compared with SGLT1. Ertugliflozin inhibits renal glucose reabsorption resulting in urinary glucose excretion and thereby reducing plasma glucose and glycated hemoglobin (HbA1c) in patients with T2DM. In a large Phase 3 development program, ertugliflozin demonstrated significant and clinically meaningful reductions in HbA1c, fasting plasma glucose, body weight, and blood pressure (BP).[8-12] Ertugliflozin is approved in the United States (US) and the European Union as an adjunct to diet and exercise to improve glycemic control in adults with T2DM.[13-14]

The long-term effects of ertugliflozin on CV and renal outcomes are being assessed in the eValuation of ERTugliflozin effIcacy and Safety CardioVascular Outcomes Trial (VERTIS-CV) (ClinicalTrials.gov identifier: NCT01986881). In this article, we present the trial design, baseline characteristics, and analysis plan from the VERTIS-CV trial.

Methods
Study design
The VERTIS-CV trial is a multicenter, prospective, randomized, event-driven trial in patients with T2DM and established ASCVD intended to address two overarching objectives, one focused on CV safety (non-inferiority) and the other on CV and renal efficacy (superiority). The trial was designed to satisfy the US FDA guidance on demonstration of CV safety for novel anti-hyperglycemic agents in the pre-approval and post-approval time periods. To demonstrate adequate CV safety to support the US regulatory approval for ertugliflozin (ie, to rule out an 80% increase in CV risk in the pre-marketing period), a CV meta-analysis across all Phase 2/3 studies, including CV outcome events captured in VERTIS-CV up to the time of the meta-analysis, was conducted and submitted to the US FDA. To preserve the integrity of the trial data, access to the unblinded CV meta-analysis results during the ongoing conduct of VERTIS-CV was restricted by a data access plan endorsed by the US FDA and governed by confidentiality agreements. The CV meta-analysis was prepared by a small firewalled team that included a very limited number of sponsor personnel with no direct or other involvement in the ertugliflozin program. None of the authors or individuals overseeing the VERTIS-CV trial or with any role in the operations of the trial were allowed any knowledge of the CV meta-analysis results while the study was ongoing (ie, prior to database release).

Beyond the primary objective of demonstration of adequate CV safety, VERTIS-CV also includes pre-specified and alpha-protected hierarchical analyses to assess the CV and renal efficacy of ertugliflozin by testing for superiority for CV and renal outcomes as described below. The trial also includes 3 glycemic sub-studies to assess the efficacy of ertugliflozin on glycemic end points, body weight, and BP in patients receiving specific anti-hyperglycemic background therapies (insulin with or without metformin; sulfonylurea monotherapy; and metformin plus sulfonylurea). The analysis plan also includes an assessment of the efficacy of ertugliflozin on glycemic parameters in those patients with stage 3A (estimated glomerular filtration [eGFR] 45 to <60 mL/min per 1.73 m^2) chronic kidney disease.

The VERTIS-CV original protocol was finalized in August 2013 and had a planned sample size of approximately 4000 patients. The objective from the original protocol was to assess the non-inferiority of ertugliflozin versus placebo on MACE (defined as time to the first event of CV death, nonfatal myocardial infarction [MI], and nonfatal stroke) in order to meet US FDA regulatory guidance for type 2 diabetes medications. Following the publication of the EMPA-REG OUTCOME results,[5] the protocol for VERTIS-CV was amended in March 2016. The key changes were to double the sample size of the trial to approximately 8000 patients and to include efficacy objectives for superiority on CV outcomes along with an efficacy assessment of a renal composite outcome. The protocol amendment for VERTIS-CV occurred prior to the conduct of the CV meta-analysis described above.

Study population
The full details of trial eligibility criteria are listed in Appendix A. Patients were eligible if they were at least 40 years of age with T2DM (HbA1c 7.0–10.5%, inclusive), and had stable, established ASCVD involving the coronary, cerebrovascular, and/or peripheral arterial systems. Specific inclusion criteria satisfying the entry criteria of established ASCVD were patients having at least 1 of the following: (a) coronary artery disease as indicated by a history of presumed spontaneous MI OR (b) coronary artery disease as indicated by a history of coronary

revascularization through either a percutaneous coronary intervention or coronary artery bypass graft OR (c) ischemic (presumed atherothrombotic) cerebrovascular disease as indicated by a history of ischemic stroke OR (d) peripheral arterial disease. The most recent qualifying ASCVD event must have occurred at least 3 months prior to screening. The key exclusion criteria were type 1 diabetes mellitus or history of ketoacidosis; patients experiencing a CV event or undergoing percutaneous coronary or peripheral artery intervention between the time of screening and randomization; patients undergoing any CV surgery within 3 months of screening; eGFR <30 mL/min per 1.73 m^2 at the screening visit; New York Heart Association Class IV HF symptoms (following protocol amendment; exclusion had been Class III–IV prior to protocol amendment).

This trial was conducted in compliance with Institutional Review Boards/Ethics Committees, the principles laid down in the last revision of the Declaration of Helsinki, the International Conference on Harmonisation Good Clinical Practice guidelines, and local laws and regulations relevant to the use of new therapeutic agents. All patients provided written informed consent.

Treatment protocol, follow-up, and data collection procedures

The trial schema is shown in Figure 1. Eligible patients were centrally randomized using an interactive voice response system in a 1:1:1 ratio to placebo, ertugliflozin 5 mg, or ertugliflozin 15 mg once daily added-on to background standard of care treatment. Randomization was based on a computer-generated schedule with randomly permuted blocks. Investigational product was administered once daily in the morning without regard to food. The initial dose of investigational product was administered in the clinic at day 1. Clinic visits occur at weeks 6, 12, 18, 26, 39, and 52 during the first year of trial participation. Following the first year, participants had clinic visits every 4 months. At each visit, interval medical history, investigational product compliance, review of concomitant medications, adverse events (AEs), serious adverse events (SAEs), and potential outcomes were assessed, along with measurement of body weight and BP. Body weight was measured in duplicate using a standardized, digital scale provided by the sponsor. Triplicate measurement of sitting BP and pulse rate were performed using an automated oscillometric device. Cases of amputation were collected on a concomitant procedure page of the Case Report Form and also identified based on a search of AEs and procedures using a Customized MedDRA Query and a thorough search of the SAE comments field. Blood and urine samples were collected at selected time points throughout the trial and analyzed in a central laboratory. Patients were also counseled on appropriate dietary and lifestyle guidelines for T2DM, in accordance with local medical standards of care for patients with T2DM. Review of patients' self-monitoring glucose logs and hypoglycemia logs was performed at each visit. A centrally read 12-lead electrocardiogram was collected at baseline, week 18, week 52, and annually thereafter. For patients providing additional informed consent, whole blood (DNA), plasma, and serum were collected at baseline and at various time points following randomization and stored for future analysis of relevant biomarkers for diabetes, cardiovascular disease, and renal disease.

All patients in the trial, including those patients taking part in the glycemic sub-studies, were required to keep their prior anti-hyperglycemic treatment stable during the first 18 weeks to enable the assessment of the glycemic effects of ertugliflozin. Adjustments in background anti-hyperglycemic therapy during the initial 18 weeks of the study were permitted in patients who exceeded progressively more stringent glycemic thresholds based on a repeated, confirmed fasting plasma glucose measurement. After the initial 18 weeks, the investigator and/or treating health care provider was able to make necessary adjustments in background anti-hyperglycemic therapy regimen to achieve an appropriate HbA1c level for the patient (with the exception of prohibited concomitant medications: another SGLT2 inhibitor, rosiglitazone, or chlorpropamide). A patient experiencing clinically significant hypoglycemia, according to the investigator, at any time during the trial was permitted to have the dose of appropriate background anti-hyperglycemic agent adjusted (eg, insulin, sulfonylurea, glinide). The investigator and/or treating health care provider was also able to make any changes in the background treatment regimen to achieve appropriate targets for secondary CV disease prevention, in accordance with local guidelines and standards of care.

Patients who prematurely discontinued investigational product remained in the study to continue to provide information on clinical outcomes, except in circumstances where patients withdrew consent from further participation. A follow-up phone call was conducted 14 days after the last dose of study medication to assess for AEs, SAEs, and to collect information on potential clinical events. Vital status was attempted to be collected for all patients in the trial, except where prohibited by local laws or regulations.

Study objectives and outcomes

The primary objective of the trial is to demonstrate non-inferiority of ertugliflozin versus placebo on time to first MACE, defined as CV death, nonfatal MI, or nonfatal stroke. The secondary objectives are to demonstrate superiority of ertugliflozin versus placebo on time to: (1) first event of CV death or hospitalization for HF; (2) CV death; and (3) first event of renal death, dialysis/transplant, or doubling of serum creatinine from baseline.

Figure 1
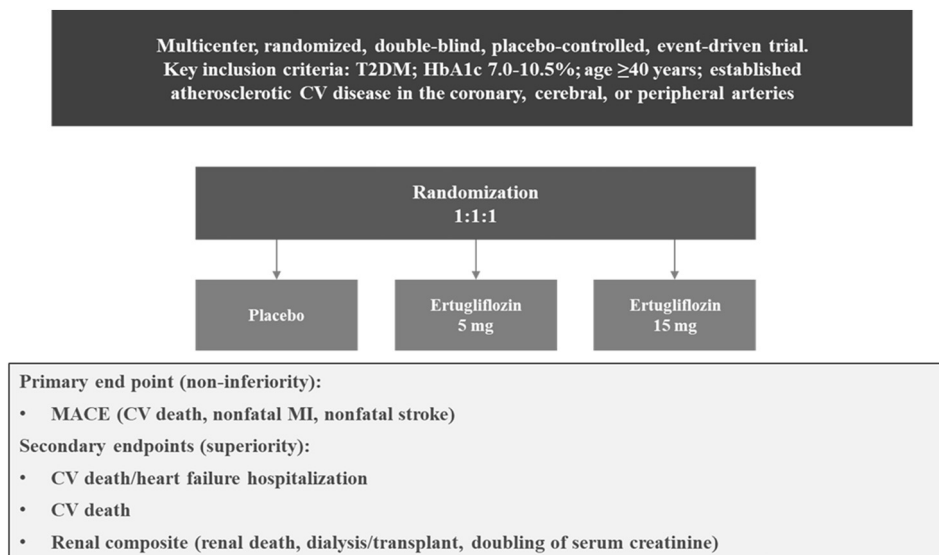
Study schematic. CV, cardiovascular; HbA1c, glycated hemoglobin; MI, myocardial infarction; T2DM, type 2 diabetes mellitus.

In accordance with US FDA guidelines, non-inferiority will be declared if the upper limit of the 95% confidence interval for the hazard ratio (HR) for MACE excludes 1.3. If non-inferiority at the 1.3 margin is established for the primary MACE outcome, then tests of superiority on the secondary outcomes will be performed in a fixed testing sequence.

Other CV outcomes pre-specified for analysis, but not part of the formal testing sequence, are the individual components of MACE, the composite of MACE-plus (CV death, nonfatal MI, nonfatal stroke, hospitalization for unstable angina), fatal or nonfatal MI, fatal or nonfatal stroke, hospitalization for HF, all-cause mortality, all MACE events (first + all recurrent), and all CV deaths or hospitalizations for HF (first + all recurrent). For all analyses of CV outcomes, only CV events confirmed by the CV Clinical Adjudication Committee will be included.

Statistical considerations

Primary and secondary time-to-first-event outcomes will be analyzed using a stratified Cox proportional hazards model including treatment group (pooled ertugliflozin dose groups vs placebo) as a term in the model and enrollment cohort as the stratification factor. A point estimate and 2-sided confidence interval (adjusted for multiplicity) for the HR will be calculated based on the Cox model. A non-inferiority margin of 1.3 on the HR for MACE will be utilized as per US FDA guidance. One planned interim analysis will be conducted when ~76% of the primary MACE outcome and CV deaths have been confirmed. In order to control the overall Type I error rate across multiple analyses and multiple outcomes, an O'Brien-Fleming alpha spending function will

be utilized, and a hierarchical testing sequence will be utilized across the primary and secondary end points in the following order: (1) MACE (non-inferiority); (2) the composite of CV death or hospitalization for HF (superiority); (3) CV death (superiority); and (4) the composite of renal death, dialysis/transplant, or doubling of serum creatinine from baseline (superiority). The primary analysis set for the non-inferiority analysis of the primary outcome of MACE will be the full analysis set, which will include all patients who were randomized and who received at least 1 dose of investigational product and will include confirmed events occurring up to 365 days after the last dose of investigational product for those with premature discontinuation. For the superiority analyses of CV and renal outcomes, an intent-to-treat analysis set will be utilized, which will include all randomized patients and all confirmed events with no upper limit on the event ascertainment window.

For the primary non-inferiority analysis, it is estimated that the study will have ~96% power to demonstrate non-inferiority, assuming accrual of at least 939 MACE events for the final analysis and a true HR of 1.00. For the secondary analyses, it is estimated that the study will have ~90% power to demonstrate superiority for the composite outcome of CV death or hospitalization for HF, assuming accrual of at least 582 composite events for the final analysis and a true HR of 0.75; and ~83% power to demonstrate superiority for CV death, assuming accrual of at least 377 CV deaths for the final analysis and a true HR of 0.725. For the renal composite end point, it is estimated that the study will have ~79% power to demonstrate superiority assuming accrual of at least 190 renal composite events and a true HR of 0.65. The study is event-driven and will continue until accrual of

approximately 939 MACE events and 377 adjudicated CV deaths, unless the trial is stopped for efficacy or futility at the interim analysis.

Study organization

VERTIS-CV was designed by staff at Pfizer Inc. and Merck Sharp and Dohme Corp., a subsidiary of Merck & Co. Inc. in collaboration with an external group of academic investigators who comprised the Scientific Advisory Committee (SAC) for the ertugliflozin program. The SAC members are listed in Appendix B. The authors are solely responsible for the drafting and editing of the manuscript and its final contents. The VERTIS-CV study is funded by Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc, Kenilworth, NJ, USA, in collaboration with Pfizer Inc., New York, NY, USA. No extramural funding was used to support this work.

External committees

The CV Clinical Adjudication Committee is an independent, external committee comprising cardiologists and vascular neurologists who reviewed pre-specified events in a blinded manner (Appendix B). The following events were adjudicated by the CV Clinical Adjudication Committee: all deaths, nonfatal MI or any hospitalization for chest pain where MI needs to be ruled out, nonfatal stroke (and all events that may be a stroke including all transient ischemic attack events), hospitalization for unstable angina, hospitalization for HF, and venous thromboembolism/pulmonary embolus. Any electrocardiogram that was noted via a central core-lab read to signify a potential new MI was sent for adjudication and, if positively adjudicated, was included in the end point of nonfatal MI. The trial included 4 other external adjudication committees to review safety events of interest including fractures, pancreatitis, hepatic events, and renal events (Appendix B). An internal review committee (independent of the study team) reviewed potential events of ketoacidosis.

A fully independent 5-member external Data Monitoring Committee consisting of 2 cardiologists, 2 endocrinologists, and 1 statistician (Appendix B) reviews data from the trial on an ongoing basis and will also assess the results of the pre-specified interim analysis against the stopping rules for the trial. A group of National Retention Experts were identified to work with sites to provide updates on study milestones and discuss the importance of minimizing missing data (Appendix B).

Results
Enrollment status and baseline characteristics

The initial cohort under the original protocol was randomized from December 2013 through July 2015; following a protocol amendment, the second cohort of patients was enrolled from June 2016 through April 2017. A total of 14,607 patients were screened for the trial and 6355 (43.5%) did not meet 1 or more eligibility criteria, leaving 8252 patients randomized into the trial. The most common reason for screen failure was not meeting the HbA1c entry criterion. Of the patients randomized, 6 individuals were found to have simultaneously enrolled in more than 1 ertugliflozin study and were excluded from the analysis sets because of this GCP violation. Thus, 8246 randomized patients enrolled in 34 countries comprise the intent-to-treat analysis population used for superiority testing. A total of 8238 patients received at least 1 dose of investigational product and constitute the full analysis set for the non-inferiority analysis for MACE.

Baseline demographics and characteristics of the full analysis set are shown in Table I. Patients were on average 64.4 years of age and 11% were ≥75 years old at baseline, 30% were female, and 87.8% were white. In all, 22% of patients were enrolled in North America and 56.2% enrolled from Europe. Mean baseline low-density lipoprotein cholesterol was 89 mg/dL and mean BP was 133/77 mm Hg. Mean screening HbA1c was 8.3% with an average duration of diabetes of 12.9 years. Mean eGFR was 76.0 mL/min per 1.73 m^2, and chronic kidney disease, defined as an eGFR <60 mL/min per 1.73 m^2, was present in 22%. Microalbuminuria (30–300 mg/g) was present in 30.2% of participants and macroalbuminuria (>300 mg/g) in 9.2%. A history of amputation existed in 3.6% of patients.

Baseline CV disease history in the full analysis set is summarized in Table II. Nearly all patients had established ASCVD at baseline with 76.3% having coronary artery disease, 23.1% having cerebrovascular disease, and 18.8% peripheral arterial disease (not mutually exclusive). At baseline, 47.9% of patients had a prior MI and 57.3% had undergone coronary revascularization. A history of stroke was present in 21.0%, and a history of HF was present in 23.1%. Information on ejection fraction (EF) at baseline was available for 1433/1900 (75.4%) of the patients with a history of HF. Among patients with a history of HF and with EF data available, the majority had HF with preserved EF defined as the most recent EF of >40% (Table II).

At baseline, 81.4% of patients were on a statin; 84.6% were on an anti-platelet agent; 81.4% were on a renin-angiotensin-aldosterone system blocker; 69.1% on a beta-blocker; and 40.6% were on a diuretic, including 15.4% who were receiving a loop diuretic (Figure 2A). Regarding anti-hyperglycemic medication at study entry, 76.3% of patients were taking metformin, 41.1% were taking a sulfonylurea, and 47.2% were taking insulin (not mutually exclusive; Figure 2B).

Discussion

The VERTIS-CV trial has completed enrollment of over 8200 patients with T2DM and established ASCVD, including a substantial proportion of elderly patients, those with HF, and those with moderate renal impairment. Studying this population will optimize the assessment of the effect of ertugliflozin on the CV and renal outcomes specified in the trial. The trial will also provide

Table I. Baseline demographics and characteristics in VERTIS-CV

	N = 8238
Age (years)	64.4 ± 8.1
≥75, n (%)	903 (11)
Male, n (%)	5764 (70)
Race, n (%)	
White	7232 (87.8)
Black	235 (2.9)
Asian	497 (6.0)
Other	274 (3.3)
Ethnicity, n (%)	
Hispanic or Latino	1042 (12.6)
Region of enrollment, n (%)	
North America	1812 (22.0)
Europe (including Russia)	4632 (56.2)
Asia	522 (6.3)
Australia/New Zealand	173 (2.1)
South and Central America	722 (8.8)
South Africa	377 (4.6)
Diabetes duration (years)	12.9 ± 8.3
Number of anti-hyperglycemic agents at screening, n (%)	
0	104 (1.3)
1	2657 (32.3)
2	4154 (50.4)
≥3	1323 (16.1)
BMI (kg/m^2)	32.0 ± 5.4
Retinopathy, n (%)	1384 (16.8)
Diabetic neuropathy, n (%)	2283 (27.7)
Nephropathy, n (%)	755 (9.2)
Amputation history, n (%)	300 (3.6)
Vital signs	
Systolic blood pressure (mm Hg)	133 ± 13.8
Diastolic blood pressure (mm Hg)	77 ± 8.5
Heart rate from ECG (bpm)	68 ± 11.3
Laboratory data	
HbA1c (%)[*]	8.3 ± 0.9
eGFR (mean), mL/min per 1.73 m^2	76.0 ± 20.9
≥90, n (%)	2044 (24.8)
60 to <90, n (%)	4387 (53.3)
30 to <60, n (%)	1776 (21.6)
<30, n (%)	31 (0.4)
Albuminuria category (mg/g), n (%)	
Normoalbuminuria (<30)	4763 (57.8)
Microalbuminuria (30-300)	2486 (30.2)
Macroalbuminuria (>300)	754 (9.2)
Total cholesterol (mg/dL)	169 ± 46.5
LDL-C (mg/dL)	89 ± 38.3
HDL-C (mg/dL)	44 ± 12.1
Triglycerides (mg/dL)	181 ± 114.6

+/− values are means ± SD.
BMI, Body mass index; *ECG,* electrocardiogram; *eGFR,* estimated glomerular filtration rate (calculated via Modification of Diet in Renal Disease equation); *HbA1c,* glycated hemoglobin; *HDL-C,* high-density lipoprotein cholesterol; *LDL-C,* low-density lipoprotein cholesterol; *SD,* standard deviation.
[*] HbA1c data from screening visit.

data on the glycemic efficacy of ertugliflozin in patients receiving specific anti-hyperglycemic treatments and in patients with stage 3A chronic kidney disease. Finally, the trial will provide additional data on the safety of ertugliflozin in a population at high CV risk with regard to events of special interest such as amputations, fractures, and diabetic ketoacidosis. These data will be

Table II. History of cardiovascular disease

	N = 8238
Established ASCVD, n (%)	8236 (99.9)
Coronary artery disease	6286 (76.3)
Cerebrovascular disease	1902 (23.1)
Peripheral arterial disease	1548 (18.8)
Myocardial infarction, n (%)	3942 (47.9)
Coronary revascularization, n (%)	4720 (57.3)
CABG	1809 (22.0)
PCI	3413 (41.4)
Peripheral revascularization, n (%)	676 (8.2)
Stroke, n (%)	1731 (21.0)
HF, n/N	1900/8238 (23.1)
HFrEF (≤40%)[*]	278/1433 (19.4)
HFpEF (>40%)[*]	1155/1433 (80.6)

ASCVD, atherosclerotic cardiovascular disease; *CABG,* coronary artery bypass graft; *HF,* heart failure; *HFrEF,* HF with reduced ejection fraction; *HFpEF,* HF with preserved ejection fraction; *PCI,* percutaneous coronary intervention.
[*] Percentage based on the 1433 patients with a history of heart failure and ejection fraction data available.

helpful in defining the clinical impact of ertugliflozin on CV and renal outcomes and will provide further safety data for ertugliflozin. The data presented herein are based on a May 2018 data extraction date; because VERTIS-CV is ongoing, the data presented should be considered preliminary and subject to change prior to database lock.

To put VERTIS-CV and the characteristics of the patients enrolled into appropriate clinical context, the baseline characteristics of 3 other SGLT2 inhibitor CV outcome trials/trial programs are presented in Table III.[5-7,15-18] As shown, the VERTIS-CV and EMPA-REG OUTCOME trials exclusively enrolled patients with ASCVD, whereas the CANVAS program included 34% primary prevention patients and DECLARE just under 60% primary prevention. The percentage of patients with prior HF at baseline is highest in VERTIS-CV. Outcome trials comprising a mix of primary and secondary CV risk patients can yield results suggesting heterogeneity of efficacy in these 2 populations,[18-20] perhaps related to differences in underlying risk of the population, differential efficacy of the intervention, or the play of chance.

In the completed CV outcome trials with 2 SGLT2 inhibitors, the effects on some CV outcomes (eg, MACE and HF hospitalization) were nearly identical between empagliflozin and canagliflozin. In contrast, for CV death, a significant reduction was observed with empagliflozin[5] but not with canagliflozin.[6] Even among the 66% of the population in the CANVAS trials program with established ASCVD at entry, the magnitude of the estimate of the effect of canagliflozin on CV death[18] was smaller than the effect observed with empagliflozin. This could reflect a real difference in the effect of individual members of the SGLT2 inhibitor class on CV death, the result of differences in trial design or populations studied, or simply the play of chance. The results from VERTIS-CV will provide important data on the effect of ertugliflozin

Figure 2
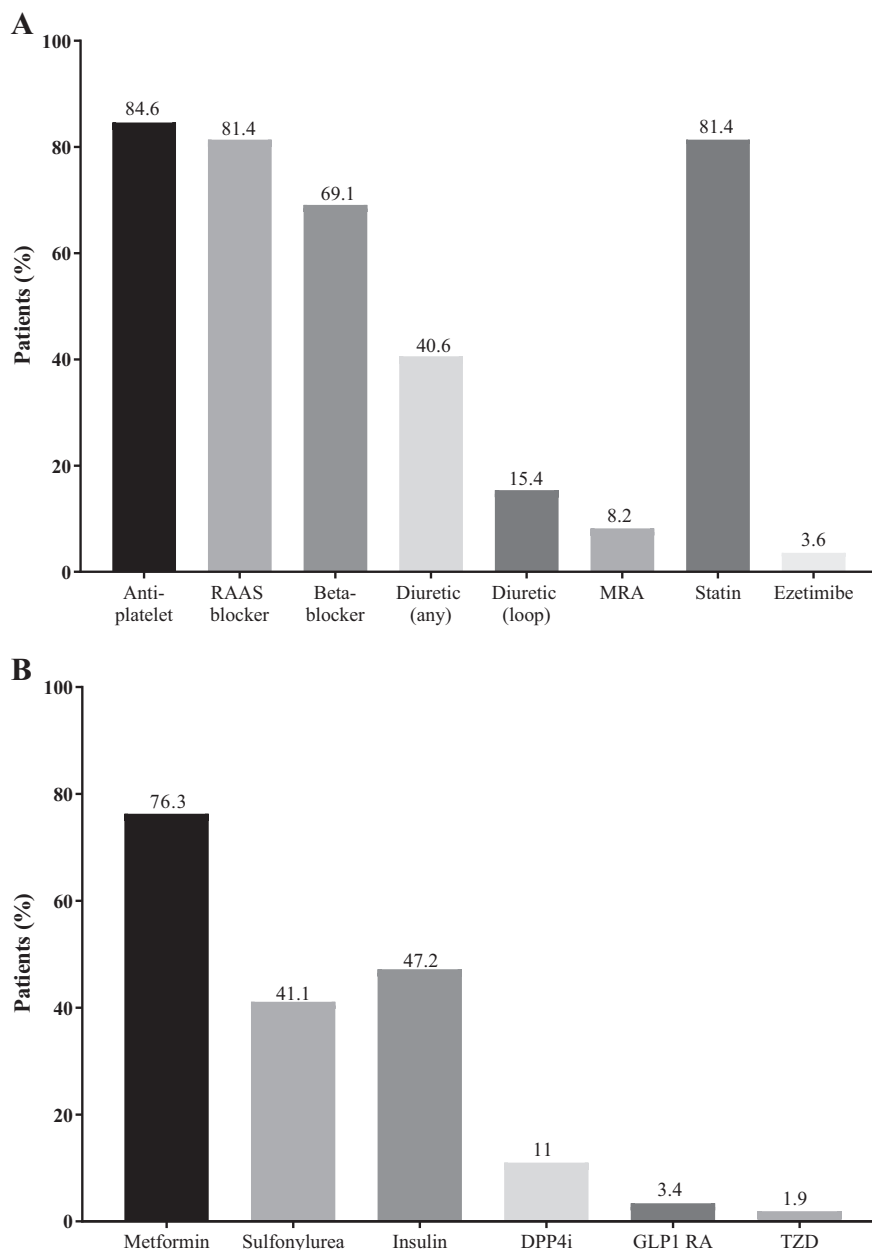
Background cardiovascular (A) and anti-hyperglycemic (B) medications. CVD, cardiovascular disease; DPP4i, dipeptidyl peptidase-4 inhibitor; GLP1 RA, glucagon-like peptide-1 receptor agonist; MRA, mineralocorticoid receptor antagonist; RAAS, renin-angiotensin-aldosterone system; TZD, thiazolidinedione.

on CV death in a large trial population to further enhance understanding of the effect of this class of medication on CV death and within-class heterogeneity of efficacy in patients with ASCVD.

Type 2 diabetes is a major risk factor for the development of HF and in many trials of patients with T2DM and ASCVD, the incidence of HF hospitalization is similar to the incidence for the outcomes of MI and stroke.[21] Thus, there is a clear unmet medical need for agents that can improve HF outcomes in patients with T2DM, especially given the increased risk of HF observed with thiazolidinediones, saxagliptin, and alogliptin.[22] As a result of the reduction in HF hospitalization risk with empagliflozin versus placebo seen in EMPA-REG

Table III. Comparison of the cardiovascular outcomes trials of 4 SGLT-2 inhibitors.

	VERTIS-CV	EMPA-REG OUTCOME[15-16]	CANVAS[6,17-18]	DECLARE[7]
	Ertugliflozin	Empagliflozin	Canagliflozin	Dapagliflozin
N	8238	7034	10,142	17,160
Age (years)	64.4 ± 8.1	63.1 ± 8.6	63.3 ± 8.3	63.8 ± 6.8
Male	5764 (70)	5026 (72)	6509 (64.2)	10,738 (62.6)
Race				
White	7232 (87.8)	5089 (72)	7944 (78.3)	79.6%
Black	235 (2.9)	357 (5)	336 (3.3)	3.5%
Asian	497 (6.0)	1518 (22)	1284 (12.7)	13.4%
Other	274 (3.3)	70 (1)	578 (5.7)	3.5%
Diabetes duration (years)	12.9 ± 8.3	NA	13.5 ± 7.8	NA
HbA1c (%)	8.3 ± 0.9	8.1 ± 0.8	8.2 ± 0.9	8.3 ± 1.2
BMI (kg/m^2)	32.0 ± 5.4	30.6 ± 5.3	32.0 ± 5.9	32.1 ± 6.0
eGFR (mL/min per 1.73 m^2)	76.0 ± 20.9	74 ± 21	76.5 ± 20.5	86.1 ± 21.8
≥90	2044 (24.8)	1534 (22)	2474 (24.4)	6855 (39.9)
60 to <90	4387 (53.3)	3671 (52)	5620 (55.5)	8739 (50.9)
30 to <60	1776 (21.6)	1796 (26)	2010 (19.8)	1565 (9.1)†
Established CVD (%)	99.9	>99	65.6	40.6
Myocardial infarction	3942 (47.9)	3275 (47)	2956 (29.2)	3580 (20.9)
Coronary revascularization				
CABG	1809 (22.0)	1738 (25)	1427 (14.1)	1678 (9.8)
PCI	3413 (41.4)	NA	2558 (25.3)	3655 (21.3)
Stroke	1731 (21.0)	1631 (23)	1291 (12.8)	1107 (6.5)‡
Peripheral arterial disease	1548 (18.8)	1449 (21)	2113 (20.8)	1025 (6.0)
History of HF	1900 (23.1)	706 (10.1)*	1461 (14.4)	1698 (9.9)

Data are n (%) or mean ± SD, unless otherwise shown.
BMI, body mass index; *CABG*, coronary artery bypass graft; *CVD*, cardiovascular disease; *eGFR*, estimated glomerular filtration rate (calculated via Modification of Diet in Renal Disease equation); *HbA1c*, glycated hemoglobin; *HF*, heart failure; *PCI*, percutaneous coronary intervention.
* Percentage based on 7020 patients.
† Less than 60 mL/min per 1.73 m^2.
‡ Ischemic stroke.

OUTCOME,[5,16] the VERTIS-CV protocol was amended to double the sample size of the trial and to include pre-specified superiority hypotheses that are linked to the putative mechanism of action of this class of agents; namely the risk reduction for the composite of CV death/hospitalization for HF and CV death. The inclusion of pre-specified hypothesis testing for the composite outcome of CV death/hospitalization for HF distinguishes VERTIS-CV from EMPA-REG OUTCOME and from the CANVAS trials program. The amended VERTIS-CV protocol included instructions to collect EF information to be able to characterize the type of HF of the patients enrolled.

Favorable effects of SGLT2 inhibitors on diabetic kidney disease progression have been consistently demonstrated by results of placebo-controlled trials with empagliflozin and canagliflozin.[6,23] Inclusion of the pre-specified renal composite outcome of renal death, renal replacement therapy, or doubling of serum creatinine in the VERTIS-CV hierarchical statistical testing scheme will provide further data to assess the potential for renal protection on top of standard of care treatment, including use of ACE inhibitors or angiotensin receptor blockers.

While the mechanistic underpinnings of the CV and renal efficacy observed with empagliflozin and canagliflozin and

the CV mortality benefit observed with empagliflozin remain uncertain, a number of intriguing hypotheses have been proposed.[24] The early benefits on these outcomes suggest that factors other than traditional atherothrombotic risk factors contribute to the reduction in events with empagliflozin and canagliflozin. One hypothesis hinges on the effects of SGLT2 inhibition on renal sodium handling, increasing delivery of sodium to the macula densa in the juxtaglomerular apparatus and restoring tubuloglomerular feedback, the effects of which reduce glomerular hypertension and favorably modulate the renin-angiotensin-aldosterone system and sympathetic nervous system activity.[25] A second proposed mechanism relates to the effects of the SGLT2 inhibitors to increase circulating ketones, especially beta-hydroxybutyrate, a particularly efficient myocardial metabolic substrate.[26-27] Third, based on their mechanism of action in the renal tubule, SGLT2 inhibitors are diuretics via osmotic effects due to urinary glucose excretion as well as natriuretic effects.[28] Finally, SGLT2 inhibitor treatment results in increased circulating hemoglobin concentration/hematocrit, and though initial interpretation was that this most likely reflected plasma volume contraction and hemoconcentration,[29] some evidence suggests red cell mass expansion mediated by increased erythropoietin.[30] Each of these mechanisms individually and in combination

could favorably affect myocardial oxygen supply/demand balance and by such mechanism(s), reduce both HF and CV death risk. Of course, all such explanations remain speculative at this point and further investigation into each is ongoing.

Conclusions

The VERTIS-CV trial is studying the safety and efficacy of ertugliflozin in T2DM patients with established ASCVD, including older patients, those with kidney disease, and those with HF. The results from this trial should define the clinical impact of ertugliflozin in patients with T2DM and ASCVD.

Sources of funding

Acknowledgements

Disclosures

BC has received fees from AstraZeneca, Boehringer Ingelheim, Lilly, Merck Sharpe & Dohme, Novo Nordisk, Sanofi, and Takeda. CPC has received fees from Alnylam, Amarin, Amgen, Arisaph, AstraZeneca, Boehringer Ingelheim, Bristol- Myers Squibb, Eisai, GlaxoSmithKline, Kowa, Lipimedix, Merck & Co., Inc., Pfizer, Regeneron, Sanofi, and Takeda, as well as research grants from Amgen, Arisaph, Boehringer Ingelheim, Bristol-Myers Squibb, Daiichi Sankyo, Janssen, Merck & Co. Inc., and Takeda. DKM has led clinical trials for AstraZeneca, Boehringer Ingelheim, Eisai, Esperion, GlaxoSmithKline, Janssen, Lexicon, Merck & Co., Inc., Novo Nordisk, Sanofi Aventis, and has received consultancy fees from AstraZeneca, Boehringer Ingelheim, Lilly, Merck & Co., Inc., Pfizer, Novo Nordisk, Metavant, and Sanofi Aventis. FC has received fees from Abbott, AstraZeneca, Bayer, Bristol-Myers Squibb, Merck Sharp & Dohme, Novo Nordisk, and Pfizer, as well as research grants from Swedish Research Council, Swedish Heart & Lung Foundation, and the European Foundation for the Study of Diabetes.

RP has received fees (directed to his institution) from AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, Hanmi Pharmaceutical Co., Ltd, Janssen, Ligand Pharmaceuticals, Inc., Lilly, Merck & Co., Inc., Novo Nordisk, Sanofi Aventis, and Takeda. SD-J has led clinical trials for AstraZeneca, Novo Nordisk, Inc., and Boehringer Ingelheim, and has received fees from AstraZeneca, Boehringer Ingelheim, Janssen, Merck & Co., Inc., Response Scientific, Inc., and Sanofi. WJS declares no conflict of interest. GG, and SH are employees of Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc, Kenilworth, NJ, USA, who may own stock in the company. BL was an employee of Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA, at the time of manuscript preparation who may own stock in the company. JM, SG, SGT, and UM are employees and shareholders of Pfizer Inc.

Appendix A. VERTIS-CV 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 [eg, 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 (eg, MI or stroke) or undergoing coronary angioplasty or peripheral intervention procedure between the Screening visit (V1) and randomization.

3. Patients undergoing any cardiovascular surgery (eg, 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 at the Screening visit (V1).

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 (eg, 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 (eg, 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 (eg, orlistat, phentermine/topiramate, lorcaserin) and is not weight-stable.
- Patient is on other medications associated with weight changes (eg, 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 per 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× the upper limit of normal (ULN) at the Screening visit (V1), or a total bilirubin >1.5× 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.

Appendix B. List of External Committee Members, National Retention Experts, Participating Countries, and Principal Investigators

Scientific Advisory Committee
Bernard Charbonnel, Christopher P. Cannon, Francesco Cosentino, Samuel Dagogo-Jack, Darren K. McGuire, Richard Pratley, Weichung J. Shih.

Data Monitoring Committee
William Herman (Chair), Gary Cutter, Peter McCullough, Mark Molitch, Gilles Montalescot.

Cardiovascular Endpoint Adjudication Committee
Blair O'Neill (Chair), Cecilia Bahit, Sherryn Roth, Joseph Schindler, Isaac Silverman, Philippe Gabriel Steg, Tanya Turan, James Udelson.

Fracture Adjudication Committee
Thomas Link (Chair), Andrew Haims, Joel Newman

Pancreatitis Adjudication Committee
Jorge Obando (Chair), Ziad Gellad, Keyur Patel, Martin Poleski

Renal Adjudication Committee
David Charytan (Chair), John Forman, Emily Robinson, Sushrut Waikar, Daniel Weiner

Hepatic Adjudication Committee
Mark Russo (Chair), Karin Andersson, Fredric Gordon, Amir Qamar, Andrew Stolz

Participating Countries (National Retention Experts [NREs] for the Country)
Argentina (Diego Aizenberg), Australia (Anthony Roberts), Bosnia (Azra Durak-Nalbantic), Bulgaria (Dimitar Raev), Canada (Thomas Ransom), Colombia (Jose Luis Accini-Mendoza), Croatia (Silvija Canecki-Varzic), Czech Republic, Georgia (Elene Giorgadze), Greece (Konstantinos Tsioufis), Hong Kong (Katheryn Tan Choon Beng), Hungary, Israel (Basil Lewis), Italy (Piermarco Piatti), Korea (Bong Soo Cha), Latvia (Valdis Pirags), Lithuania (Vaidotas Urbanavicius), Mexico (Pedro Alberto Garcia Hernandez), Netherlands, New Zealand (Scott Russell), Philippines (Florence Santos), Poland (Monika Lukaszewicz), Romania (Noemi Pletea), Russia (Svetlana Berns), Serbia (Teodora Beljic Zivkovic), Slovakia, South Africa (Larry Distiller), Sweden, Taiwan (Dee Pei), Thailand (Clara Chow), Turkey, Ukraine (Oleksandr Parkhomenko), United Kingdom (Manish Saxena), United States (William French). Countries without an NRE listed were overseen by the Baim Institute for Clinical Research (Christopher Cannon, Julie Sutherland, Jessica Lamp, Hoey Chyi Lim).

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