AstraZeneca

Statistical Analysis Plan

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DECLARE

Dapagliflozin Effect on CardiovascuLAR Events

A Multicenter, Randomized, Double-Blind, Placebo-Controlled Trial to Evaluate the Effect of Dapagliflozin 10 mg Once Daily on the Incidence of Cardiovascular Death, Myocardial Infarction or Ischemic Stroke in Patients with Type 2 Diabetes

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Study Statistician [redacted]

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Statistics Team Leader [redacted]

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LIST OF ABBREVIATIONS

The following abbreviations and special terms are used in this Statistical Analysis Plan (SAP).

Abbreviation or special term	Explanation
AE	Adverse Event
ARB	Angiotensin Receptor Blocker
ACEi	Angiotensin-Converting-Enzyme inhibitor
BMI	Body Mass Index
BP	Blood pressure
CEC	Clinical Event Adjudication Committee
CI	Confidence interval
CrCl	Creatinine Clearance
CRF	Case Report Form (electronic/paper)
CV	Cardiovascular
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
DAE	AE leading to discontinuation of study drug
DMC	Data Monitoring Committee
DNA	Deoxyribonucleic acid
DPP4	Dipeptidyl peptidase 4
E-code	Enrolment code
eCRF	electronic Case Report Form
eCVD	Established CardioVascular Disease
eGFR	Estimated Glomerular Filtration Rate
Ethics Committee	Synonymous to Institutional Review Board and Independent Ethics Committee
EoT	End of Treatment
ESRD	End State Renal Disease
FAS	Full Analysis Set
FPG	Fasting plasma glucose
GFR	Glomerular Filtration Rate
GLP-1	Glucagon-like peptide-1
HbA1c	Glycated haemoglobin
HDL-C	High-density lipoprotein-cholesterol

Abbreviation or special term	Explanation
HR	Hazard ratio
ICF	Informed Consent Form
IP	Investigational Product
IVRS/IWRS	Interactive voice response system/interactive web response system
LDL-C	Low-density lipoprotein-cholesterol
LS	Least Squares
MA	Marked Abnormality
MACE	Major Adverse Cardiovascular Events (CV Death, MI, Ischemic Stroke)
MedDRA	Medical Dictionary for Regulatory Activities
MI	Myocardial infarction
MRF	Multiple Risk Factors
PT	Preferred Term
RR	Relative Risk
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
SCr	Serum Creatinine
SD	Standard Deviation
SE	Standard Error
SEER	Surveillance, Epidemiology and End Results
SOC	System Organ Class
SU	Sulphonylurea
T2DM	Type 2 diabetes mellitus
ULN	Upper Limit of Normal
WHO	World Health Organization

Notable Changes in SAP Edition 8, as compared to SAP Edition 7

Section	Description of Change	Rationale
Section 1.1.4 (Exploratory Objectives); Section 3.3 (Other efficacy variables)	Moved "Surgical Amputation and related events" from the list of exploratory efficacy objectives to the safety section.	To consolidate the analysis of amputations and related events as a safety variable in the safety section.
Section 2.1 (Definition of analysis sets)	Removed the following provision regarding site 5709 in SAP Edition 7, *"Sensitivity analyses on primary endpoints and for bladder cancer may be performed including these patients."*	To improve clarity.
Section 3 (PRIMARY AND SECONDARY VARIABLES)	Clarified how the deaths adjudicated as undetermined cause will be handled in the statistical analyses.	To improve clarity.
Section 3.3 (Other efficacy variables)	Added eGFR slopes as a new exploratory efficacy variable.	In consideration of the NKF/EMA/FDA workshop on albuminuria and GFR in March 2018.
Section 3.3 (Other efficacy variables)	Added a new renal composite endpoint under "Other efficacy variables". As compared to the secondary renal composite endpoint, this new exploratory endpoint excludes CV death as a component.	To further characterize the treatment effect on the components specifically for renal outcomes.
Section 4.1 (General principles)	Clarified imputation of partially missing dates.	To improve clarity.
Section 4.1.9 (Cox Proportional Hazards Model)	Specified that HR estimates will not be generated for subgroups with fewer than 15 total events across the two treatment groups.	In consideration of the large variability associated with few events.

Section	Description of Change	Rationale
Section 4.1.9 (Cox Proportional Hazards Model); Section 4.1.12 (Analysis of incidence rate ratios and differences); Section 4.5.1.4 (Adverse events of special interest)	Clarified how event rates will be calculated.	To improve clarity.
Section 4.3.2 (Measurements of Treatment Compliance)	Changed definition for study drug compliance from visit specific to study specific.	To adapt to the data where study drug returned was associated with not only the preceding dispense visit but also earlier dispense visits.
Section 4.4.1.2 (Analyses of the primary variables)	Added a sensitivity analysis of competing risks with respect to the primary endpoints.	As requested by the FDA.
Section 4.4.1.3 (Considerations of incomplete follow-up)	Added sensitivity analyses regarding LTFU patients, specifically, multiple imputations and tipping point analysis.	As requested by the FDA.
Section 4.4.1.2 (Analysis of the primary variables); Section 4.4.1.3 (Considerations of incomplete follow-up)	Re-organized the sensitivity analyses between the two sections.	To improve clarity and readability.
Various sections	Minor clarifications and editorial changes.	To improve clarity and readability.

Section	Description of Change	Rationale

INTRODUCTION

This statistical analysis plan (SAP) is a comprehensive and detailed description of the strategy, rationale and statistical techniques that will be used to assess the safety and efficacy of dapagliflozin compared to placebo in patients with Type 2 diabetes mellitus (T2DM) and with either known cardiovascular (CV) disease or at least two risk factors for CV disease in addition to T2DM.

1. STUDY DETAILS

1.1 Study objectives

1.1.1 Primary objectives

The primary objective is to determine the effect of dapagliflozin relative to placebo on cardiovascular outcome when added to current background therapy in patients with T2DM with either established cardiovascular disease or at least two cardiovascular risk factors.

This objective will be evaluated in two steps. The first step will determine if dapagliflozin is non-inferior to placebo for the incidence of the composite endpoint of CV death, MI or ischemic stroke, assessed with a non-inferiority margin of 1.3. If this is met the second step will determine if dapagliflozin reduces the incidence of the co-primary endpoints: the composite of cardiovascular death, myocardial infarction (MI), or ischemic stroke, and the composite of hospitalization for heart failure or CV death compared to placebo

1.1.2 Secondary objectives

Secondary objectives
The secondary objective is to determine whether treatment with dapagliflozin compared with placebo when added to current background therapy in patients with T2DM with either established CV disease or at least two CV risk factors in addition to T2DM will result in a reduction of:

- Renal composite endpoint: Confirmed sustained ≥40% decrease in eGFR to eGFR <60 mL/min/1.73m^2 and/or ESRD (dialysis ≥90 days or kidney transplantation, confirmed sustained eGFR <15 mL/min/1.73m^2) and/or renal or CV death
- All-cause mortality

1.1.3 Safety objectives

Safety and tolerability will be assessed from overall adverse events, serious adverse events, adverse events of special interest, and laboratory test results. The safety assessment will include an evaluation of the incidence of adjudicated bladder cancer and liver injury.

1.1.4 Exploratory objectives

Other efficacy objectives are to determine whether treatment with dapagliflozin compared with placebo when added to current background therapy in patients with T2DM and either established CV disease or at least two CV risk factors in addition to T2DM will result in a reduction of:

- The individual components of the co-primary efficacy endpoints (cardiovascular death, MI, ischemic stroke, hospitalization for heart failure)
- The composite endpoint of CV death, MI, ischemic stroke, hospitalization for heart failure, hospitalization for unstable angina pectoris, or hospitalization for coronary or non-coronary revascularization and the additional individual components of hospitalization for unstable angina pectoris and hospitalization for coronary or non-coronary revascularization
- Glycosylated hemoglobin A1c (HbA1c)
- Initiation of insulin therapy in patients not receiving insulin therapy at baseline
- Need for any of the following: an increase in dose for an oral anti-diabetes medication or ≥ 25% increase in insulin dose or the addition of new anti-diabetes medication, for ≥ 3 months
- Major hypoglycaemia and/or hospitalization for hypoglycaemia
- Confirmed sustained macroalbuminuria (UACR ≥300 mg/g) in subjects without macroalbuminuria at baseline
- Development of albuminuria
- Albuminuria
- Decrease in eGFR
- Albumin to creatinine ratio
- Body weight
- Retinal laser and/or intraocular treatment due to development of and/or deterioration in diabetic retinopathy
- Blood pressure
- Peripheral revascularization/Limb ischemic events
- Any stroke (ischemic, hemorrhagic, or undetermined)

[redacted]

An exploratory objective is to collect and store biomarkers for future exploratory research that may influence response, (e.g., distribution, safety, tolerability and efficacy) to treatment with dapagliflozin or other drugs that may influence susceptibility to T2DM and/or associated CV conditions and their risk factors.

1.2 Study design

This is a multicenter, randomized, double-blind, placebo-controlled Phase 3b study to determine the effect of dapagliflozin relative to placebo on the primary composite endpoints in patients with T2DM and with either known CV disease or at least two risk factors for CV disease in addition to T2DM. It is estimated that approximately 27000 patients will be enrolled to reach the target of 17150 randomized patients. The anticipated duration of the study is approximately 6 years, including an anticipated enrollment period of 3 years and a median follow-up period of 4.5 years. Closeout of the trial will commence when 1390 subjects with adjudicated MACE events required to test the primary objective has been reached.

All patients should be treated according to regional standards of care for diabetes (HbA1c goals) and other CV risk factors (e.g., hypertension, hyperlipidemia).

The study will recruit T2DM patients at increased risk for CV events according to the two categories below:

- Patients with established CV disease (eCVD)
- Patients with at least 2 CV risk factors (age and one additional), but without established CV disease (Multiple Risk Factors; MRF)

Approximately 17150 patients meeting all eligibility criteria at approximately 1200 study sites will be randomized (1:1) to receive either dapagliflozin or placebo.

Enrollment of patients based on disease state (MRF vs. eCVD), geographic region and sex will be monitored and may be capped to ensure adequate representation.

All potentially eligible patients will undergo a screening visit. Each patient will sign an Informed Consent Form (ICF) prior to having any screening evaluations performed. Patients who fulfill all eligibility requirements will enter into a 4 to 8 weeks placebo run-in period during which they will be given placebo in a single-blind fashion (blind to patient only) on top of previous treatment and assessed for compliance (80 to 120%, unless a reason for non-compliance is judged acceptable by the Investigator).

Approximately 4 to 8 weeks after entering the run-in period, based upon Investigator discretion, patients will be expected to undergo a randomization visit. Patients may withdraw prior to the randomization visit, or be withdrawn by study staff for any reason. At this visit patients will be re-evaluated by study staff to determine if after testing performed at screening, after assessment of compliance, and any clinical changes that may have occurred during the run-in period, the patient remains eligible and committed to participation in the study. If for any reason, prior to or during the randomization visit the patient is no longer eligible or interested in participating in the trial, he or she will be considered a run-in failure, will not be randomized and will not have additional follow up.

If a patient is committed to participation, completes placebo run-in period and continues to meet criteria at the randomization visit, he or she will be randomized and will receive either dapagliflozin 10 mg daily or matching placebo in a double-blind fashion.

During the randomized treatment period, diet and life-style modification will continue to be reinforced, in addition to adjustments of drug treatments for diabetes and or CV risk factors, as applicable.

An independent Data Monitoring Committee (DMC), a blinded independent Clinical Event Adjudication Committee (CEC) (see Section 12.4 in protocol) and Executive and Steering Committees (see Section 12.5 in protocol) will be selected by the Sponsors and the academic leadership.

The study plan, including screening, randomization and follow-up visits, is outlined in the protocol. If the study would need to be prolonged to accrue the predetermined number of subjects with the MACE events (1390), visits and assessments will be added according to the same schedule as described in the study plan.

Patients will return every 6 months for assessment of events related to the objectives of the study, tolerability and safety. Assessment of treatment compliance and provision of study drug will be done at these 6-month visits. In addition, phone contacts will be performed at a 3-month interval in between regular visits. Patients have the option to visit the center at these 3-month time points if desired; however, this is not required. If a patient prematurely and permanently discontinues study drug, an End of Treatment (EoT) visit will be completed, with the patient continuing in the study for follow-up. If recommended by the Executive Committee, the Sponsor may make a decision to close the trial, and all Investigators will receive a communication to complete a Closing Visit for both patients still being treated with study drug and patients who have prematurely and permanently discontinued study drug. The latter patients should have completed the EoT visit in connection with the discontinuation of study drug and subsequently attended the scheduled visits to capture any adverse events (AEs), suspected CV events, body weight and diabetes medication. Refer to Section 5.8 in protocol for details on procedures for discontinuing patients from study drug.

The Investigator/qualified designee will arrange for the Closing Visit as soon as possible after the date estimated by the Executive Committee as the start of close out period. Patients who

have a regularly scheduled visit within approximately 8 weeks after start of close out period can use the scheduled visit as the closing visit.

All randomized patients, whether taking randomized study drug or not, should be followed up to the end of the study for vital status, CV events and occurrence of cancer. Survival based on publicly available sources, where possible, will be investigated at study end for patients who have withdrawn consent or are lost to follow-up. It is recommended that anyone being followed by regular telephone contacts or a contact at study closure attend the final visit in person. The approach taken should be registered in the eCRF, and medical records.

1.3 Randomization

Randomization will be stratified by CV risk category (2 levels: established CV disease; multiple risk factors without established CV disease) and hematuria status (2 levels: positive and negative).

Positive hematuria is defined as a positive microscopy (≥3 RBCs) at the screening visit and/or a urine dipstick result indicative of hematuria (positive or trace) at the randomization visit. Negative hematuria would include patients with negative results for hematuria at both the screening visit (by microscopy) and randomization visit (by dipstick).

Randomization will be performed using a fixed block size. Blocks will be divided into four stratification groups, 1, 2, 3 and 4. When a patient is to be randomized, randomization code will be selected according to the following scheme:

1. If patient has hematuria=positive and MRF use the next consecutive number from stratification group 1.

2. If patient has hematuria=positive and eCVD use the next consecutive number from stratification group 2.

3. If patient has hematuria=negative and MRF use the next consecutive number from stratification group 3.

4. If patient has hematuria=negative and eCVD use the next consecutive number from stratification group 4.

AstraZeneca will create the randomization via GRand. The list will be kept securely within AstraZeneca, with access only by GRand group and Patient Safety. The list will be shared with the IVRS which will assign patients to randomization numbers and allow emergency unblinding by investigators. It will also be shared with the independent statistics group supporting the DMC. Country, sex and CV risk category will also be tracked within the IVRS to be able to control patient recruitment.

1.4 Number of patients

1.4.1 Sample size calculations

This study is a group sequential design study with two interim analyses, using O-Brian Fleming boundaries, leaving a one-sided alpha of 2.31% for the final analysis.

Non-Inferiority for MACE
The non-inferiority hypothesis to be tested in this trial is H_0:HR[dapa:placebo] ≥ 1.3 vs H_1:HR < 1.3. Assuming 2.1% common annual event rate, a 3-year accrual period, a 6-year maximum follow-up period, 1.0% annual study withdrawal rate, randomizing 17150 patients is expected to yield 1390 MACE events, which would provide >99% power to test the stated hypothesis at the 2.31% 1-sided level.

The annual study withdrawal rate of 1.0% are considering patients that are lost to follow up and patients that withdraw their consent.

Superiority for MACE
1390 MACE events will be required to have 85% power to demonstrate superiority of dapagliflozin to placebo if the true HR is 0.85, i.e., a 15% relative risk reduction, with a one-sided alpha of 2.31%. To achieve this number of MACE events, we have designed the study with the following conditions: 17150 randomized patients will be required for the study, with assumed annual event rate of 2.1% on placebo, and an annual study withdrawal rate of 1.0% over a 3-year accrual period and 3-year minimum follow-up.

The final sample size will depend on multiple factors including the rate of accrual of MACE events. Therefore the sample size may be changed if planning assumptions are modified by blinded data review. The Executive Committee of the trial will monitor the aggregate event rate and rate of study drug discontinuation and may suggest to alter the sample size, number of primary endpoints or duration of the trial in accordance with the goals of the trial. Such changes will be made in consultation with the Sponsor.

The composite of CV death or hospitalization for heart failure:

We anticipate approximately 770 events for the composite of CV death or hospitalization for heart failure, which would provide 87% power to detect a hazard ratio of 0.80 with a 1-sided alpha of 2.31%. The alpha levels at the final analysis upon study completion will depend on the alpha spending function, the observed number of events for each endpoint at interim and final analyses and the hierarchical testing procedure.

Bladder and breast cancer
The SEER rate for the general US population of 0.044% per person-year for bladder cancer may be conservative; higher bladder cancer rates could be observed in this trial. If the SEER rate is adjusted to reflect an increased risk in a diabetes population, an estimated annual rate of 0.06% could occur. In the dapagliflozin Phase 2b and 3 program, the bladder cancer rate was 0.16% in dapagliflozin-treated patients. When patients with baseline hematuria were excluded,

the bladder cancer rate was 0.07% in dapagliflozin-treated patients and 0.046% amongst all treated patients (dapagliflozin and comparator combined).

In planning for this study, it is assumed that the detection of early bladder cancers may be higher than for the general population (i.e., SEER) since this study is in diabetics and will stipulate yearly assessments of hematuria, more than would be expected in standard medical practice. Table 1 illustrates the levels of risk that can be ruled out if the rate were the same as the SEER population or slightly higher. We assume that the overall bladder cancer rate will be 0.06% per person-year for this study. With this assumption, 46 bladder cancers may be expected during the study. With 46 events, a relative risk of 2.28 can be ruled out with one-sided 97.5% confidence and 80% power under the hypothesis that the true relative risk is 1. In parallel, an absolute difference in incidence rates of 0.049% could be ruled out using the same assumptions.

For breast cancer, assuming 40% of the patients in the study are female, and predicted background breast cancer rate of 292 cases per 100,000 person-years (also based on background rates of breast cancer in the general U.S. population using SEER data, for women aged between 45 to 79 years). With this assumption, 90 breast cancers may be expected during the study. With 90 events, a relative risk of 1.80 can be ruled out with one-sided 97.5% confidence and 80% power under the hypothesis that the true relative risk is 1. In parallel, an absolute risk difference of 0.171% (over the whole study) could be ruled out using the same assumptions. Corresponding calculations are also provided if the study population is 30% females.

These cancer rate estimates are intended to be realistic but also conservative. If the rates of cancers are actually observed at higher rates, even smaller relative risks and risk differences can be ruled out.

Table 1 Levels of bladder and breast cancer relative risks and incidence rate differences that can be ruled out under different assumptions

			One-sided 97.5% confidence level		
Event rate	**Expected number of events**	**Power**	**True RR that can be ruled out**	**True rate diff that can be ruled out**	**Max value that can be observed and rule out true RR, rate diff**
Bladder cancers					
0.044%	34	80%	2.62	0.042%	1.33, 0.013%
0.06%	46	80%	2.28	0.049%	1.28, 0.015%
Breast cancers					

			One-sided 97.5% confidence level		
Event rate	**Expected number of events**	**Power**	**True RR that can be ruled out**	**True rate diff that can be ruled out**	**Max value that can be observed and rule out true RR, rate diff**
Assuming 40% women in the study, 0.292%	90	80%	1.80	0.171%	1.19, 0.052%
Assuming 30% women in the study, 0.292%	68	80%	1.98	0.198%	1.23, 0.060%

RR = relative risk; risk diff = absolute incidence rate difference

[redacted]

2. ANALYSIS SETS

2.1 Definition of analysis sets

Patients could by error have been randomized more than once. These patients will be analyzed according to their first randomization assignment. SAEs, hematuria forms, medication and endpoint forms will be consolidated and re-entered under the patient identifier used in the first randomization. The redundant records associated with the same patients will be stored in a separate dataset for future references.

Patients that were randomized at site 5709 will not be included in primary statistical analysis. AstraZeneca has reported the investigator to regulatory authorities for potential scientific misconduct in another AstraZeneca study and made the decision to exclude the patients from this site from the analyses.

2.1.1 Full analysis set (FAS)

All patients who have been randomized to study treatment will be included irrespective of their protocol adherence and continued participation in the study. Patients will be analyzed according to their randomized study drug assignment (not to which treatment they actually received) irrespective of whether the event occurred before or following discontinuation of study drug. Patients who withdraw consent to participate in the study (or are lost to follow-up) will be included up to the date of their study termination except for vital status known through public records (for use in the analyses of deaths). All primary, secondary, and exploratory efficacy variables will be analyzed using the FAS. The FAS will be considered the primary analysis set for the primary and secondary variables and for the exploratory efficacy variables.

2.1.2 Safety analysis set

All patients who received at least 1 dose of randomized dapagliflozin or placebo and who have data observed at any time after first randomized dose until the end of the study, will be included in the safety population. Throughout the safety results sections, erroneously treated patients (patients randomized to one of the treatment groups but actually given the other treatment) will be accounted for in the actual treatment group. Patients with erroneous treatment would be analyzed according to that treatment only if they only received the erroneous treatment and none of the correct treatment. All safety variables will be analyzed using the safety analysis set. The Safety analysis set will be considered the primary analysis set for malignancies and fractures.

2.1.3 On-treatment analysis set

An on-treatment analysis set will also be created. The on-treatment population is defined as all randomized patients who have received at least one dose of investigational product and who have data observed at any time after first randomized dose till the end of the study. However, only those observations collected during treatment with study drug or within a certain number of days of the last dose of investigational product will be part of this analysis set, as noted below:

- Primary, secondary, and categorical exploratory variables: 30 days
- Continuous exploratory and safety variables (e.g. changes in lab values and vital signs): 7 days
- SAEs: 30 days
- AEs of special interest, that are not serious: 7days

For the primary and secondary efficacy variables, analyses will be repeated using the on-treatment set as sensitivity analyses.

All safety variables will be analyzed using the on-treatment analysis set. The on-treatment analysis will be considered as the main analysis for these safety variables (with exception for cancers and fractures).

Primary and secondary efficacy analyses based upon the On-treatment analysis set will evaluate patients strictly according to their randomized assignment. In contrast, safety analyses using the On-treatment analysis set will evaluate patients according to the treatment received. Patients who receive the wrong investigational product and never receive any correct investigational product will be evaluated for safety in the treatment group for which they received medication.

2.1.4 Summary of analysis sets and variables to be analyzed

Table 2 Clarification on what analysis sets will be considered as primarily and as sensitivity for efficacy and safety variables

Variable	Primarily analysis	Sensitivity analysis
Primary variables	FAS	On-Treatment set
Secondary variables	FAS	On-Treatment set
Exploratory Efficacy variables	FAS	On-Treatment set for selected variables
Cancer, Amputations and Fractures	Safety analysis set	On-Treatment set
Other Safety variables	On-Treatment set	Safety analysis set

2.2 Protocol deviations

The below listed important protocol deviations will be summarised by randomized treatment group and will include:

- Patients who received incorrect investigational product, completely or at any time during the study
- Patients previously randomized into the study
- Patients randomized but took no investigational product
- Patients assigned a randomization code according to incorrect entry of baseline stratification factors
- Patients without type 2 diabetes
- Patients with end stage renal disease at baseline
- Current or recent (within 24 months prior to randomization) treatment with pioglitazone and/or use of pioglitazone for a total of 2 years or more during lifetime
- Current or recent (within 12 months prior to randomization) treatment with rosiglitazone
- Previous treatment with any SGLT2 inhibitor
- Study drug non-compliance - Patients identified as >120% or <80 compliant with study drug during run-in will be termed non-compliant.
- Patients without established CV disease and less than 2 risk factors

- Patients with acute CV disease at randomization
- History of bladder cancer
- NYHA Class IV HF at randomization
- Screening or run-in HbA1c out of range (≥12% or <6.5%)
- CrCl < 60ml/min at enrolment
- Unexplained hematuria at randomization
- Abnormal LFTs (AST or ALT >3xULN or Total bilirubin >2.5xULN) at enrolment.

Patients meeting criteria for protocol deviations will be identified by statistical programming prior to unblinding.

3. PRIMARY AND SECONDARY VARIABLES

The primary and secondary CV efficacy variables will be adjudicated by the independent, blinded CEC.

Note that, MI will include both non-fatal and fatal MI, Ischemic stroke will include both non-fatal and fatal ischemic stroke. The causes of deaths, as adjudicated by the CEC, will include CV cause (death due to Sudden Cardiac Death, Acute MI, Stroke, Heart Failure, CV Procedure, CV Hemorrhage and Other CV death), non-CV cause, and undetermined cause. The primary analyses of the endpoints concerning CV deaths, either as a component of a composite or on its own, will include deaths adjudicated as CV cause. Deaths adjudicated as undetermined cause will not be counted as CV deaths in these analyses.

3.1 Primary variables

The primary outcome variables of the study are the composite endpoint of CV death, MI or ischemic stroke (time to first event) and the composite of hospitalization for heart failure and CV death (time to first event).

3.2 Secondary variables

The secondary variables comprise the following:

- Renal composite endpoint: Confirmed sustained ≥40% decrease in eGFR to eGFR <60 mL/min/1.73m^2 using CKD-EPI equation and/or ESRD (dialysis ≥90 days or kidney transplantation, confirmed sustained eGFR <15 mL/min/1.73m^2) and/or renal or CV death (time to first event)
- All-cause mortality (time to event)

3.3 Other efficacy variables

The other efficacy variables comprise the following:

- The individual components of the co-primary efficacy endpoints (cardiovascular death, MI, ischemic stroke, hospitalization for heart failure) (time to first event)
- The composite endpoint of CV death, MI, ischemic stroke, hospitalization for heart failure, hospitalization for unstable angina pectoris, or hospitalization for coronary or non-coronary revascularization and the additional individual components of hospitalization for unstable angina pectoris and hospitalization for coronary or non-coronary revascularization (time to first event)
- Exploratory renal composite endpoint: Confirmed sustained ≥40% decrease in eGFR to eGFR <60 mL/min/1.73m^2 using CKD-EPI equation and/or ESRD (dialysis ≥90 days or kidney transplantation, confirmed sustained eGFR <15 mL/min/1.73m^2) and/or renal death (time to first event)
- Change from baseline in HbA1c (mean change)
- Initiation of insulin therapy in patients not receiving insulin therapy at baseline (proportion)
- Need for any of the following: an increase in dose for an oral anti-diabetes medication or ≥ 25% increase in insulin dose or the addition of new anti-diabetes medication, for ≥ 3 months (proportion)
- Major hypoglycaemia and/or hospitalization for hypoglycaemia (proportion)
- Confirmed sustained macroalbuminuria (UACR ≥300 mg/g) in subjects without macroalbuminuria at baseline (time to first event)
- Development of sustained confirmed albuminuria in patients without albuminuria at baseline (UACR≥30 mg/g ; time to first event)
- Regression in sustained confirmed albuminuria (defined in three ways: 1. Baseline microalbuminuria to normoalbuminuria 2. Baseline macroalbuminuria to microalbuminuria or normoalbuminuria 3. The previous two combined) (proportions)
- eGFR total slope and chronic slope using CKD-EPI equation
- eGFR (sustained confirmed decrease ≥30% to sustained confirmed eGFR <60 mL/min/1.73m^2 using CKD-EPI equation; time to first event)
- eGFR (sustained confirmed decrease ≥40% to sustained confirmed eGFR <60 mL/min/1.73m^2 using CKD-EPI equation; time to first event)

- Change in Albumin to Creatinine Ratio (adjusted mean percent change after 2 years and 3 years)
- Change in body weight at 2 years and at 3 years
- Proportion of patients with 5% body weight loss and 10% body weight loss after 2 years and after 3 years
- Retinal laser and/or intraocular treatment due to development of and/or deterioration in diabetic retinopathy (proportion)
- Blood pressure change from baseline (mean change) (blood pressure values used in analyses will be the mean of two measurements for each applicable time point)
- Peripheral revascularization/Limb ischemic events (proportion)
- Any stroke (ischemic, hemorrhagic, or undetermined) (proportion)

3.4 Safety variables

Safety and tolerability will be assessed from serious adverse events, adverse events leading to discontinuation, adverse events of special interest, and laboratory test results. The assessment will include an evaluation of the incidence of bladder cancer, liver injury and diabetic ketoacidosis. All possible malignancies (excluding non-melanoma skin cancer), liver injury and all potential diabetic ketoacidosis will be independently adjudicated.

Only events that fall into the following categories are collected in this study: serious AEs, AEs leading to discontinuation of study drug, suspected CV events, elective coronary and non-coronary revascularisations, heart failure, potential diabetic ketoacidosis, amputation and related events and AEs of special interest. AEs of special interest in this study fall into the following categories: malignancies, hepatic events, hypoglycemic events that are major or lead to hospitalization, fractures, renal events, symptoms of volume depletion, hypersensitivity reactions (serious or lead to discontinuation of study drug), urinary tract infections (serious or lead to discontinuation of study drug) and genital infections (serious or lead to discontinuation of study drug). Therefore, AE summaries will be limited to these particular categories and general summaries of all AEs are not planned.

[redacted]

3.6 Analysis of biomarkers

Will be specified in a supplementary SAP.

4. ANALYSIS METHODS

All statistical analyses will be performed using Version 9.4 (or higher) of the SAS® statistical analysis system (SAS Institute Inc., Cary, NC) and, where appropriate, additional validated software.

4.1 General principles

All tables and figures will present results by treatment group, except for presentation of the disposition of patients prior to randomization which will be summarized for all patients who signed an informed consent. Select tables (e.g. demographics) may also have a column for the total population.

Incomplete dates

In statistical analysis, it is sometimes necessary to impute incomplete dates for the purpose of data derivations such as treatment period, time to event, etc. In such situations, the general rules for imputations are:

If only the year of a date is given (YY), then the date shall be set to 'YY0701'. If only the year and month of a date is given (YYMM), then the date shall be set to 'YYMM15'.

Appropriate rules will be applied to ensure that dates will not be imputed as prior to randomization, not as prior to date of first dose, not after date of death, not after date of closing visit, not after date of withdrawal of consent, and not as start date occurs after end date for an event.

If the onset date of an adverse event is completely missing then the maximum of date of randomisation and date of first dose will be imputed as onset date.

Special cases for date of death:

For a patient that died with the date of death imputed, the maximum of the imputed date and last date the patient was known to be alive will be used as date of death.

If adjudicated date of death is completely missing, the site-reported date of death will be used.

For a patient that died that have a completely missing date of death, the last date the patient was known to be alive will be imputed and used as date of death.

By-patient presentations

Treatment group, CV risk category, age, sex and E-code (patient identifier) will be present in all data listings. Study visit/month will be included in all data listings whenever an assessment date is presented.

Descriptive statistics

Numerical variables will be summarised using standard summary statistics including the number of patients, mean, standard deviation (SD), median, Q1, Q3 and range (i.e., minimum and maximum) as appropriate. For categorical data, proportions will be presented in a frequency table format.

Tabulation of events and censoring

For CV outcomes, events will be cross-tabulated by initial investigator assessment and final adjudicated result. Only CV events adjudicated and confirmed by the CEC will be included in the analyses of CV events.

A patient may have one or more events. For composite endpoints, the time to first event within the composite list will be used. For each component of a composite (e.g. MI), the time to first component event will be used, regardless of other events occurring earlier (e.g., if a stroke precedes an MI in a patient, then the stroke counts in the composite as the first event, but the MI counts in the time to first MI analysis).

The Executive Committee will monitor the accrual of the aggregate number of MACE events and when the required MACE events have occurred, upon confirmation from the Sponsor, will instruct all sites that to perform all Closing Visits by a certain defined date.

The end-of-study will be defined as the time of the last visit or study contact (where a clinical event assessment was performed) for each individual patient. If no event occurs for an endpoint, withdrawal of consent, last clinical event assessment, or death (whichever is earliest) will be treated as the censoring event. If none of these are available, date of last documented contact (i.e. last visit) will be used for censoring. For all-cause mortality and CV death, censoring will occur at Closing Visit for patients known to be alive, or otherwise at the date last known to be alive. If none of these are available, date of last documented contact (i.e. last visit) will be used for censoring. For analysis of CV death, a patient who dies of a non-CV cause (or undetermined cause) would be censored at the time of death. Deaths occurring after the date of withdrawal of consent (and for patients lost to follow-up) and documented in publicly available source data will be recorded in the eCRF, adjudicated if possible, and included in the analyses of deaths.

For the On-Treatment analyses, censoring will occur according to the same pattern that defines the on-treatment analysis set.

To test the robustness, censoring at the fixed calendar date (the date that the executive committee instructs the sites to commence Closing Visits) will be used in a sensitivity analysis. See section 4.4.1.2.

Clinical events will be handled in the following manner according to their timing with respect to study milestones

- Events that are recorded as beginning prior to the date of randomization will not be included in the event analyses

- Events that occur at any time after randomization and up to and including the last visit/contact and reported *before* database lock will be adjudicated, if possible, and included in all efficacy and safety analyses.

- Events that occur at any time after randomization and up to and including the last visit/contact and reported *after* database lock may be adjudicated but will not be included in the primary efficacy and safety analyses. They will be recorded in a tabular fashion as part of the final study report and may be included in sensitivity analyses.

- Events that occur after last visit/contact will not be included in the primary efficacy and safety analyses but may be included in sensitivity analyses for the study. Adverse events occurring after the study will be included in the Sponsor's Safety database if they fulfill safety reporting criteria.

4.1.1 Baseline value

For each patient, the baseline value of each laboratory parameter or physical examination endpoint is defined as the last assessment on or before randomization, and on the same day or before the first dose of double-blind study drug.

4.1.2 Baseline hematuria:

Positive hematuria is defined as a positive microscopy (≥3 RBCs) at the screening visit and/or a urine dipstick result indicative (positive or trace) of hematuria at the randomization visit. Negative hematuria would include patients with negative results for hematuria at both the screening visit (by microscopy) and randomization visit (by dipstick).

4.1.3 Change from baseline

Change from baseline to any randomized treatment period Time t is defined as follows:

$C_{Time\ t} = M_{Time\ t} - M_{baseline}$, where:

- $C_{Time\ t}$ is the change from baseline at Time t
- $M_{Time\ t}$ is the measurement at Time t
- $M_{baseline}$ is the baseline measurement.

4.1.4 eGFR and Creatinine Clearance formulas

Estimated creatinine clearance using the method of (Cockcroft and Gault 1976):

$$\text{CrCl} = \frac{(140 - \text{age}) \times (\text{weight in kg})}{\text{serum creatinine (mg/dL)} \times 72} \quad (\times 0.85 \text{ for females})$$

Estimated GFR using MDRD equation:

eGFR (mL/min/1.73m^2) = 175 x (Scr)$^{-1.154}$ x (Age)$^{-0.203}$ x (0.742 if female) x (1.212 if black)

Estimated GFR using CKD-EPI equation (Levey et al 2009):

eGFR (mL/min/1.73m^2) = 141 x min (SCr/k,1)^a x max (SCr/k,1)$^{-1.209}$ x 0.993Age x [1.018 if female] x [1.159 if black]

k is 0.7 for females and 0.9 for males, a is -0.329 for females and -0.411 for males, min indicates the minimum of SCr/k or 1, and max indicates the maximum of SCr/k or 1.

4.1.5 Body Mass Index

BMI is calculated as the ratio of patient's weight (kg) to the square of the patient's height (m): BMI = kg/m^2.

4.1.6 Descriptive summaries of continuous variables

Summaries for continuous variables will present absolute values and changes from baseline, for each treatment group. They will include mean, SD, median, Q1, Q3, minimum and maximum, and will be presented by visit when applicable. Summaries for some continuous variables will include 95% CIs for means or mean treatment differences. Summaries for continuous variables known to have skewed distributions will also include the interquartile range.

4.1.7 Descriptive summaries of categorical variables

Summaries of categorical variables will provide frequencies and percentage, for each treatment group. Summaries for some categorical variables will include 95% CIs for the difference in percent from placebo.

4.1.8 Summaries of shifts from baseline in categorical variables

Changes from baseline in certain categorical variables might be summarized using shift tables. Frequencies and percentage of patients within each treatment group will be generated for levels of cross-classifications of baseline and the on-treatment value of the variable. The on-treatment value can be either the value at a certain time point, or, for e.g. laboratory tests, the minimum/maximum value in the direction of toxicity, which has been observed during a study period. Treatment group differences will not be assessed in summaries of shifts.

4.1.9 Cox Proportional Hazards Model

Cox proportional hazards model will be used to analyze the time-to-events variables. The model will be stratified by baseline hematuria and baseline CV risk category, with treatment as a model term.

The following model will be used:

$$Log[\, h_{ijk}(t)/\, h_{ij0}(t)] \;=\; \beta_1 x_{ijk}$$

Where

- $h_{ijk}(t)$ hazard function at time t for subject k in CV risk category stratum i and baseline hematuria stratum j given covariate value x_{ijk}

- β_1 is the regression coefficient associated with treatment group

With respect to randomized treatment, hazard ratio estimates and 2-sided confidence intervals (CIs) will be presented as defined in section 4.4. No hazard ratio estimates will be given for subgroups with less than 15 events in total, both arms combined. P-values will be presented from the Wald's test.

The co-primary efficacy endpoints are MACE (composite endpoint of CV death, MI or ischemic stroke) and the composite of hospitalization for heart failure or CV death. Each will be evaluated as the time to the first event included in the composite. The general intent is to analyze patients from the date of randomization up until the date of study closure visit. For the primary endpoints, the time of event will be determined by the date of first adjudicated event. Patients without an adjudicated event will be censored at the earliest date among the following: non-CV death (and undetermined death), withdrawal of consent and last clinical event assessment. If none of these would be available, the last documented contact (i.e. the last visit) will be used for censoring. The last documented contact may be by office visit, by telephone call directly with the patient or by contact with another person (family member, caregiver, primary or treating physician) where it is possible to gain knowledge of possible CV events or death. Indirect contact such as medical records, letter, e-mail or text message, if applicable, will be used to inquire for possible events and may lead to adjudicated events and a last documented contact. The person who made the contact (i.e. investigator or study nurse/coordinator) will also be documented.

The rules for censoring time to events for secondary and exploratory efficacy endpoints are the same, with the two exceptions: 1) that CV death will be included as a censoring point for the single components of the composite time to event endpoints and 2) non-CV deaths and undetermined deaths are events for the endpoint of all-cause mortality (and not censoring points).

A patient may have 1 or more events. However, only a patient's first applicable event will contribute to the analysis of each specified endpoints.

Event rates will have denominators which represent the total number of years in the study or time to first event (whichever occurs first). Patients without events will be censored using the rules above. The rates will be derived as total number of patients with an event divided by the corresponding number of patient-years. The rates will be expressed in units of "per 1000 patient-years". The number of patients with an event and the corresponding number of patient-years will be truncated as appropriate for analyses using the On-treatment analysis set.

4.1.10 Analysis of repeated measures

Repeated measure analysis (using MIXED model) will be used to analyze the response variable change from baseline in body weight, HbA1c, blood pressure variables (and other applicable continuous variables) to each relevant time point. The model contains terms for randomized treatment group, baseline measurement, CV risk category, baseline hematuria, time (each relevant visit) and time by randomized treatment group. The following model will be used:

$$C_{ijk} = intercept + \beta\,[M_{baseline,ij}] + \tau_i + \alpha_k + (\alpha\,\tau)_{ik} + x_a + Y_b + error_{ijk}$$

where

- C_{ijk} is the each relevant visit change from baseline of patient j in treatment group i
- β is the slope of C_{ij} regressing on the baseline measurement
- $M_{baseline,ij}$ is the baseline measurement of patient j in treatment group i
- τ_i, is the mean effect of treatment group i
- α_k, is the mean effect at time k and
- $(\alpha\,\tau)_{ik}$ is the interaction term between treatment group i and time k
- x_a, is the mean effect of CV risk category a
- Y_b, is the mean effect of baseline hematuria category b

The MIXED model will present least squares (LS) mean estimates for Time k by treatment group and 2-sided 95% confidence intervals (CIs) for mean changes from baseline within and between treatments.

To model the covariance structure, the within patients unstructured covariance structure will be used. The MIXED model is computationally intensive, if the algorithm does not converge, the Toeplitz first-order autoregressive or compound symmetric covariance structure will be used.

4.1.11 Analysis of proportions

The proportions of patients with at least a 5% (and 10%) body weight loss after 2 and 3 years compared to baseline will be analyzed using the methodology of Cochran-Mantel-Haenszel with stratification for CV risk category and baseline hematuria. Weighted proportions for treatment groups and differences between treatment groups will be obtained along with 95% confidence intervals using Mantel-Haenszel weights, with stratification for CV risk category and baseline hematuria.

Other proportions, such as the following, will be examined using summary statistics that will include 95% confidence intervals for treatment effects and for the difference between treatments as well as nominal 2-sided p-values. These variables will also be analyzed using the time to first event approach by Cox modeling, and corresponding Kaplan-Meier curves will be produced.

- Initiation of insulin therapy in patients not receiving insulin therapy at baseline
- Need for any of the following: an increase in dose for an oral anti-diabetes medication or ≥25% increase in insulin dose or the addition of new anti-diabetes medication, for ≥3 months
- Major hypoglycaemia and/or hospitalization for hypoglycaemia
- Regression in albuminuria
- Retinal laser and/or intraocular treatment due to development of and/or deterioration in diabetic retinopathy
- Peripheral revascularization/Limb ischemic events
- Surgical amputation and related events
- Any stroke (ischemic, hemorrhagic, or undetermined)

4.1.12 Analysis of incidence rate ratios and differences

Selected safety endpoints (e.g. malignancies) will be analyzed with incidence rates, incidence rate ratios and corresponding 95% confidence intervals using exact methods for the Mantel-Haenszel relative risk estimates. Exact methods will be used to determine the 95% confidence intervals for incidence rate differences also (Lu Tian et al 2008). Analyses will be stratified by CV risk category and baseline hematuria.

Incidence rates will have denominators which represent the total number of years in the study or time to first event (whichever occurs first). Patients without events will be censored using the same rules as for the Time to event analyses described in section 4.1.9. Incidence rates will be derived as total number of patients with an event divided by the corresponding number of patient-years. Incidence rates will be expressed in units of “per 1000 patient-years”.

4.1.13 Kaplan-Meier curve and estimates for time-to-event analyses

Kaplan-Meier plots (Kaplan EL and Meier P 1958) of time to event variables will be displayed by treatment group. A table will accompany the plot and will display the Kaplan-Meier estimates of the cumulative proportion (with 95% CI calculated based on Greenwood's method) of patients with event at specific time points by treatment group. The curves will be truncated as appropriate

4.1.14 Stratification of analyses

Stratification of analyses will be performed using the stratification values as entered in IVRS to determine the randomization assignment.

4.2 Study population

4.2.1 Patient disposition

The number and percent of patients who completed the study, discontinued from the study, and reasons for discontinuation from the study will be summarized by treatment group and overall, for all randomized patients. Listings of patients who prematurely discontinued from the study will be provided.

The number and percent of patients who discontinued randomized treatment and reasons for discontinuation of treatment will be summarized by treatment group and overall, for all randomized patients. Listings of patients who prematurely and permanently discontinued treatment and for whom post-discontinuation data are excluded from the on-treatment population will be provided.

Kaplan-Meier estimates of the cumulative probabilities to discontinue from the study and to discontinue from randomized treatment will be calculated and plotted, by treatment.

4.2.2 Protocol deviations

Patients having important protocol deviations (see section 2.2) will be summarized by treatment group and overall, using the FAS population. By-patient listings will also be presented.

4.2.3 Demographic and other baseline characteristics

Demographic and other baseline characteristics will be summarized by treatment group and overall using the FAS. Baseline demographics will also be summarized for the eCVD and MRF subgroups. Demographic and diabetes-related characteristics at baseline to be summarized are listed in Table 3. CV risk levels and risk factors at randomization to be summarized are listed in Table 4. Number of CV risk factors per patient will also be summarized. Summaries of concomitant medication drug class at randomization will be based on data collected on concomitant case report forms. No statistical test will be performed for comparison of any baseline measurement among treatment groups.

All summaries of continuous characteristics will be based on non-missing observations. For categorical characteristics, percentage will be calculated out of the total number of patients in the data set, overall and by treatment group (i.e., each denominator includes the number of patients with missing/unknown values for the variable).

Duration of type 2 diabetes is calculated from date of diagnosis to date of randomization.

Table 3 Summaries of Demographic, Diabetes-Related Characteristics and Cancer risk factors at Baseline.

Characteristic	Summarized as	Categories
Age	Categorical and Continuous	<65, ≥65, <75 and ≥75 years
Sex	Categorical	Female Male
Race	Categorical	White Black or African American Asian American Indian or Alaska Native Native Hawaiian or Other Pacific Islander Other
Ethnicity	Categorical	Hispanic or Latino Not Hispanic or Latino
Waist/Hip ratio	Categorical and Continuous	High (>0.90 for males and >0.85 for females) Low (≤0.90 for males and ≤0.85 for females)
BMI	Categorical and Continuous	<30 kg/m^2 and ≥30 kg/m^2
Weight	Continuous	-
Duration of Type 2 Diabetes	Categorical and Continuous	≤5 years >5 years >10 years >20 years
HbA1C	Categorical and Continuous	<7% (<53 mmol/mol) ≥7 - <8% (≥53-<64 mmol/mol) ≥8 - <9% (≥64-<75 mmol/mol) ≥9% (75 mmol/mol)

Characteristic	Summarized as	Categories
FPG	Categorical and Continuous	<100 mg/dL [<5.6 mmol/L] ≥100 - <126 mg/dL [≥5.6 mmol/L - <7.0 mmol/L] ≥126 - <150 mg/dL [≥7.0 mmol/L - <8.3 mmol/L] ≥150 - <250 mg/dL [≥8.3 mmol/L - <14.0 mmol/L] ≥250 mg/dL [≥14.0 mmol/L]
Diastolic and Systolic Blood Pressure	Categorical and Continuous	Diastolic Blood Pressure: <80 mmHg ≥80 mmHg Systolic Blood Pressure: <130 mmHg ≥130 mmHg Diastolic Blood Pressure / Systolic Blood Pressure: <80 and <130 mmHg ≥80 and ≥130 mmHg Pulse Pressure: <60 mmHg ≥60 mmHg
eGFR (CKD-EPI)	Categorical and Continuous	<60 mL/min/1.73m^2 60 - <90 mL/min/1.73m^2 ≥90 mL/min/1.73m^2
eGFR (MDRD)	Categorical and Continuous	<60 mL/min/1.73m^2 60 - <90 mL/min/1.73m^2 ≥90 mL/min/1.73m^2
Urinary Albumin/creatinine ratio	Categorical and Continuous	<30 mg/g [≥1.7 mg/mmol - <3.4 mg/mmol] ≥30 - ≤300 mg/g [≥3.4 mg/mmol - ≤33.9 mg/mmol] >300 mg/g [>33.9 mg/mmol]
Creatinine Clearance	Categorical and Continuous	<60 mL/min 60 - <90 mL/min ≥90 mL/min
Region and Country	Categorical	North America Latin America Asia/Pacific Europe (Western, Eastern) Countries (see Appendix B)
Baseline Insulin use	Categorical	Yes/No

Characteristic	Summarized as	Categories
Baseline Diabetic Medication use in addition to Insulin	Categorical	Metformin Metformin + SU Metformin + DPP4 inhibitor Metformin + GLP-1 agonists Metformin + Other diabetic medication SU DPP4 inhibitor GLP-1 agonists Other drugs or drug combinations
Baseline Diabetic Medication use (for patients without Insulin)	Categorical	Metformin Metformin + SU Metformin + DPP4 inhibitor Metformin + GLP-1 agonists Metformin + Other diabetic medication SU DPP4 inhibitor GLP-1 agonists Other drugs or drug combinations
Baseline Diabetic Medication use (regardless of Insulin use)	Categorical	Metformin SU DPP4 inhibitor GLP-1 agonists Other drugs
Baseline CV Medication Use	Categorical	Acetylsalicylic Acid Statin/Ezetimibe ACE Inhibitor/ARB Dual Antiplatelets Any Antiplatelets Anticoagulants Beta blockers Calcium channel blockers Diuretics – Loops Diuretics –Thiazides MRA (Mineralcorticoid receptor antagonist)
Baseline Hematuria status	Categorical	Positive Negative

Table 4 Summary of Baseline CV Risk Level and Risk Factors

Characteristic	Summarized as	Categories
Baseline CV Disease	Categorical	MRF- Patients with multiple risk factors for CV events, but without established CV disease eCVD- Patients with established CV disease
MRF	Categorical	In addition to being ≥ 55 years male or ≥ 60 years female, at least one of the following: - Dyslipidemia - Hypertension - Current Tobacco use
Number of risk factors	Categorical	1 additional risk factor (dyslipidemia, hypertension, or smoking) 2 additional risk factors (dyslipidemia, hypertension, or smoking) 3 additional risk factors (dyslipidemia, hypertension, and smoking)
eCVD (Established CV Disease)	Categorical	Ischaemic heart disease Cerebrovascular disease Peripheral Arterial Disease
Number of documented CV Diseases	Categorical	1 CV disease 2 CV diseases 3 CV diseases
History of HF	Categorical	No Yes
LVEF at baseline	Categorical	HFrEF (Heart Failure reduced Ejection Fraction, <=45%) HFpEF (Heart Failure preserved Ejection Fraction, >45%)

4.2.4 Specific and General Disease Histories

The numbers and percentage of patients with specific disease history such as diabetes-related disease and vascular disease histories will be provided for the FAS population.

4.3 Extent of exposure

Extent of exposure is defined as the number of days between the start and the end dates of study therapy.

Extent of exposure (days) = Last dosing date - First dosing date + 1.

Extent of exposure to treatments will be summarized using the Safety population. Also the mean, SD, median, Q1, Q3 and range of extent of exposure will be presented.

Duration of follow-up (time from randomization to last contact) will also be summarized by treatment group, using FAS and Safety analysis set.

4.3.1 Medication at randomization and Concomitant Medications

Concomitant medications defined as medications taken on at least 1 day between the date of randomization and date of last contact, inclusive, will be summarized using the FAS population by Anatomical Therapeutic Chemical class (ATC class) and preferred name. Medications will be classified according to the AstraZeneca Drug Dictionary. A summary will be produced for concomitant medications during the treatment period.

Medication at randomization is defined as medication with at least one dose taken before date of randomization and with no stop date before date of randomization. This will also be summarized.

Changes in concomitant diabetes medications will be summarized, by identifying these categories from the medicines module in the eCRF (an increase for oral medications, addition/replacement of non-insulin medications, addition of insulin for ≥ 3 months, > 25% increase in insulin dose for ≥ 3 months).

The dose of insulin at randomization will also be summarized.

4.3.2 Measurements of Treatment Compliance

Patients are considered compliant if percent compliance is ≥80% and ≤120% for the treatment period. The number and percent of compliant patients will be displayed using the FAS population.

4.4 Analysis methods for primary, secondary and exploratory efficacy variables

4.4.1 Primary variables

4.4.1.1 Hypotheses

The Type I error rate for the analysis of the primary endpoints will be adjusted for the interim analyses performed by the DMC.

For the MACE the following hypothesis will be tested at the 2.31% 1-sided level:

H_{01}: HR [dapagliflozin:placebo] ≥1.30

vs

H_{11}: HR [dapagliflozin:placebo] <1.30.

If the null hypothesis is rejected, then an increased CV risk of 1.30 for dapagliflozin-treated patients is ruled out and superiority will then be tested in terms of:

H_{02}: HR [dapagliflozin:placebo] ≥1

vs

H_{12}: HR [dapagliflozin:placebo] <1

and

H_{03}: HR [dapagliflozin:placebo] ≥1

vs

H_{13}: HR [dapagliflozin:placebo] <1

in a closed test procedure. See Section 4.4.3 for a description of the full closed testing procedure including the secondary variables.

4.4.1.2 Analyses of the primary variables

The primary variables are the time to first event included in the composite endpoint of CV death, MI, or ischemic stroke and the time to first event included in the composite endpoint of hospitalization for heart failure or CV death. The primary analysis will be based on the FAS population, using events adjudicated and confirmed by the CEC.

Hazard Ratios (HR) and Confidence Intervals (CIs) will be derived from a Cox proportional hazards model with a factor for treatment group stratified by CV risk category (established CV disease, or multiple risk factors without established CV disease) and baseline hematuria. Event rates by 1000 patient years will be presented.

The assumption of proportional hazards for the factor for treatment groups will be assessed visually using log-cumulative hazard plots. The effect of any departures from proportional hazards will be discussed as part of the presentation of results of the analyses. Additionally, the assumption of proportional hazards for the factor for treatment group will be evaluated with a model which assess the treatment effect in categorized time intervals (< 1 year and ≥ 1 year).

The contribution of each component of the primary composite endpoints to the overall treatment effect will be examined. Methods similar to those described for the primary analysis will be used to separately analyze the time from randomization to the first occurrence of each component of the primary composite endpoints. This will be done for CV death, all MI, all ischemic stroke and all hospitalizations for heart failure. Nominal p-values will be presented. Non-fatal MI and Non-fatal stroke will be presented descriptively. Events of non-fatal MI are defined as events that are adjudicated to be MI and for which the patient did not die due to MI. The same goes for non-fatal Stroke.

HRs and CIs for overall analysis and subgroups will be presented with forest plots. Kaplan-Meier estimates of the cumulative incidence to the first occurrence of any event in the primary endpoints will be calculated and plotted, for the overall analysis and for the individual components.

Kaplan-Meier plots, overall and by CV risk category will be presented, by treatment, for the primary analyses as well as for the individual components.

Subgroup analyses to evaluate variation in treatment effect will be performed on the basis of tests for interaction using the Cox model.

The p-values for the subgroup analyses will not be adjusted for multiple comparisons as the tests are exploratory and will be interpreted descriptively. Event rates by treatment and HRs with 95% confidence intervals will be reported for each subgroup.

Subgroup analyses will be performed for the stratification factors as well as for all variables in Tables 3 and 4.

A sensitivity analysis of the primary objectives will be performed using the same methods as above on the on-treatment analysis set.

The primary analysis will use each patient's last contact as the censoring date for patients that complete the study without any primary events, see 4.1 for detailed definition. To test the robustness of the co-primary endpoints result, censoring at the fixed calendar date (the date that the Executive Committee instructs the sites to commence closing visits) will be used in a sensitivity analysis.

A sensitivity analysis of completers will be performed for the primary variables. Completers is defined as all patients except those that have incomplete follow-up of primary endpoints or withdraw consent (who did not have a primary endpoint event prior to withdrawal of consent).

A sensitivity analysis of CV death replaced with all-cause mortality, including vital status information from patients who have withdrawn consent (or have incomplete follow-up of primary endpoints), will be performed for the co-primary endpoints.

Non-CV death (and undetermined death) is considered a competing risk for the co-primary efficacy endpoints. A sensitivity analysis will be performed to estimate the cumulative incidence functions corrected for the competing risk based on Fine and Gray (1999). This analysis will take into account the same covariates as in the primary Cox model. Sub-distribution hazard ratios will be presented.

As a patient can have recurrent events, an exploratory analysis of the total number of co-primary composite events will be performed using the Andersen-Gill modified Cox regression approach, for Dapagliflozin versus Placebo.

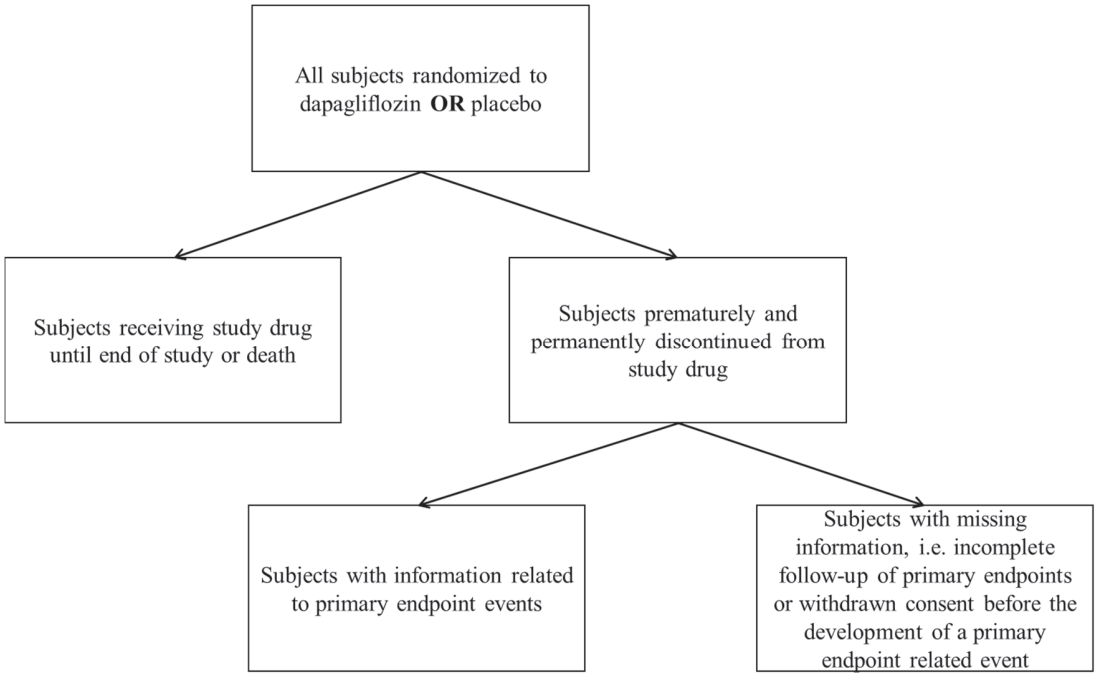
4.4.1.3 Considerations of incomplete follow-up

In the primary analysis of the primary endpoints, the patients who withdraw consent or have incomplete follow-up of primary endpoints will be censored at the date of last clinical contact on study according to Section 4.1, if they have not developed an event for the primary endpoints. For these patients, the data between the date of last clinical contact on study and planned study closure date are considered missing.

The time-to-event analysis (Cox regression) relies on the assumption of non-informative censoring. To examine this assumption, presence of informative censoring will be assessed by comparing the event rates between subjects receiving study drug until end of study or death and subjects prematurely and permanently discontinued from study drug with information related to co-primary endpoint events. The rates of subjects prematurely and permanently discontinued from study drug will also be compared between treatment arms to assess potential differential dropouts.

Subjects prematurely and permanently discontinuing study drug, for other reason than death, prior to study end could have a different event and hazard rate from those who stay on treatment throughout the study, and their corresponding dropout could be considered informative. This subgroup can be divided into subjects with information and subjects with missing information regarding events related to primary endpoints, see figure below.

Diagram showing subjects divided into subgroups related to missing information during follow up



In a sensitivity analysis, subjects with information related to the co-primary endpoint events will be used to impute data in subjects without information in the subgroup described above. For subjects with missing data, time to event will be imputed during the follow up time (i.e. time from censoring to study end). This will be done by using random values from exponential distributions based on the observed data in the subgroup. In the imputation models, CV history will be included as a covariate for both primary endpoints. For the composite endpoint of Hospitalization for heart failure or CV death, history of heart failure will also be added as a covariate in the imputation model. Imputations will be done separately in each treatment arm.

In addition, a tipping point analysis will be performed, where time to events will be imputed during the follow up time (i.e. time from censoring to study end) using the same covariates in the imputation models as described above and vary the hazard rates for subjects with missing information. This will be done separately in each treatment arm in the subgroup of subjects prematurely and permanently discontinuing study drug. The goal of the analyses is to find the scenarios where the result from the primary endpoints analyses will be “tipped”, i.e. the conclusion will change.

When the imputation models are used, if the simulated time is less than the elapsed time between the last contact and end of study, an event is imputed for the corresponding subject with the time to event set to be last contact plus the simulated time. Otherwise, the subjects will be censored at end of study. Imputed events and time to events will be integrated with the observed data and the Cox proportional hazard model described in section 4.1.9 will be used. For each scenario, this will be repeated 1000 times and the results will be combined into

overall estimates of HR and 95% CI using Rubin's rules (Rubin, D. B. 1987 ; Little R et al 2016).

4.4.2 Secondary and exploratory variables analysed as time to event

Time to event for secondary and exploratory efficacy variables will be analyzed in the same way as for the primary efficacy variables:

Renal composite endpoint: Confirmed sustained ≥40% decrease in eGFR to eGFR <60 mL/min/1.73m^2 using CKD-EPI equation and/or ESRD (dialysis ≥90 days or kidney transplantation, confirmed sustained eGFR <15 mL/min/1.73m^2) and/or renal or CV death

- All-cause mortality
- Exploratory renal composite endpoint: Confirmed sustained ≥40% decrease in eGFR to eGFR <60 mL/min/1.73m^2 using CKD-EPI equation and/or ESRD (dialysis ≥90 days or kidney transplantation, confirmed sustained eGFR <15 mL/min/1.73m^2) and/or renal death
- The individual components of the co-primary efficacy endpoints (cardiovascular death, MI, ischemic stroke, hospitalization for heart failure)
- The composite endpoint of CV death, MI, ischemic stroke, hospitalization for heart failure, hospitalization for unstable angina pectoris, or hospitalization for coronary or non-coronary revascularization and the additional individual components of hospitalization for unstable angina pectoris and hospitalization for coronary or non-coronary revascularization
- Confirmed sustained macroalbuminuria (UACR ≥300 mg/g) in subjects without macroalbuminuria at baseline
- Development of sustained confirmed albuminuria in patients without albuminuria at baseline (UACR≥30 mg/g)
- eGFR (sustained confirmed decrease ≥30% to sustained confirmed eGFR <60 mL/min/1.73m^2 using CKD-EPI equation)
- eGFR (sustained confirmed decrease ≥40% to sustained confirmed eGFR <60 mL/min/1.73m^2 using CKD-EPI equation)

The secondary variables will be analyzed by the same subgroups as for the primary variables. The 4 individual components included in the co-primary endpoints will also be analyzed for all subgroups.

The secondary variables will also be analyzed for the on-treatment population as sensitivity analyses.

Time to the Exploratory renal composite endpoint: Confirmed sustained ≥40% decrease in eGFR to eGFR <60 mL/min/1.73m^2 using CKD-EPI equation and/or ESRD (dialysis ≥90 days or kidney transplantation, confirmed sustained eGFR <15 mL/min/1.73m^2) and/or renal death will be analyzed separately per the subgroups of baseline urinary albumin to creatinine ratio (<30mg/g, >=30mg/g).

For time to albuminuria/macroalbuminuria, and for time to decrease in eGFR (using CKD-EPI equation), confirmation is required, meaning that the observation should be present at two consecutive visits separated with at least 4 weeks. Time to onset would be the first of the two subsequent laboratory assessments. If no confirmation can be obtained the observation will not be included in the main analyses. A sensitivity analysis for time to albuminuria/macroalbuminuria will be conducted including also all non-confirmed observations.

4.4.3 The closed testing procedure

Type I error will be controlled at a one-sided 0.025 level for multiplicity across primary and secondary objectives and in consideration of planned interim analyses. If the trial goes to completion, statistical significance will be assessed in the order of the endpoints given in Table 5. If statistical significance is met for non-inferiority for MACE, the alpha will split and testing will be performed in parallel for superiority for MACE and for superiority for hospitalization for heart failure/CV death. Recycling of alpha will be used, and if both superiority for MACE and superiority for hospitalization for heart failure/CV death are reached, then testing will proceed with full alpha further down the hierarchy. (Burman et al 2009). Alpha-levels for the interim analyses are described in Section 5.

Recycling:

STEP1: Test the non-inferiority hypothesis for MACE, H01 ($\alpha = 0.0231$, one-sided).

If H01 is rejected, then proceed to STEP2, otherwise testing will be stopped

STEP2: The two hypotheses H02 ($\alpha = 0.01155$, one-sided, weight = 50%), and H03 ($\alpha = 0.01155$, one-sided, weight = 50%) are tested at their initial α levels. If none of the two hypotheses can be rejected, testing stops at that point. If at least one of the hypotheses is rejected, then the α can be recycled to the non-rejected hypothesis.

Table 5 Confirmatory Testing Procedures Using One-sided Alphas

H01: Non-inferiority for MACE (alpha = 0.0231)[a]	
Now the alpha will split into independent testing of the co-primary composites in parallel:	
H02: Superiority for MACE (alpha = 50% of primary alpha)[c]	**H03: Superiority for hospitalization for heart failure/CV death (alpha = 50% of primary alpha)[c]**
• H04: Superiority for renal composite endpoint: Confirmed sustained ≥40% decrease in eGFR to eGFR <60 mL/min/1.73m^2 and/or ESRD (dialysis for at least 90 days or kidney transplant, confirmed sustained eGFR <15 mL/min/1.73m^2) and/or renal or CV death [b]	
• H05: Superiority for all-cause mortality[d]	

[a] The alpha of 0.0231 represents the final one-sided significance level to be used when the study has been completed in entirety. At an interim analysis, testing for superiority will occur, and the alpha for superiority will be replaced by 0.000095 at the first and 0.00614 at the second interims. Non-inferiority will be tested only at the completion of the study.

[b] With the exception of all-cause mortality, secondary endpoints will only be tested once, at the completion of the trial or if the decision is made to terminate the trial early. The alpha will be controlled for the overall Type I error across the primary and secondary endpoints and across the interims and final analysis.

[c] If this analysis occurs at completion of the trial, the alpha will be 0.01155 (50% of 0.0231) for superiority for MACE and 0.01155 (50% of 0.0231) for superiority for hospitalization for heart failure/CV death.

[d] All-cause mortality is assessed at interim analyses as part of the stopping guidelines. At the interim analyses, it will be tested second following MACE. If the study terminates at an interim analysis, all-cause mortality will remain as the 2nd endpoint following the test for superiority of MACE. If the final analysis occurs at the completion of the trial, all-cause mortality will be tested as presented in this table,.

4.4.4 Other efficacy variables

Body weight:

Change from baseline to each visit for body weight will be analyzed by a repeated measures method. All non-missing visit data will be used, including off-treatment measurements. The model will include terms for treatment group, CV risk category, baseline hematuria, visit, visit*treatment group and baseline measurement as a covariate. The model will be used to derive a least squares estimate of the treatment difference with 95% confidence interval and corresponding two-sided p-value. Further, two-sided 95% confidence intervals for the mean change within each treatment group will be calculated. Missing data will not be imputed. This model will be used to assess the timepoints of 1 year, 2 years, 3 years and 4 years although summaries at all visits will also be presented.

The proportions of patients with at least a 5% body weight loss after 1, 2, 3 and 4 years compared to baseline will be analyzed using the methodology of Cochran Mantel-Haenszel. Estimates for treatment effects and differences between treatment groups will be obtained

along with 95% confidence intervals and p-values using this methodology with stratification for CV risk category and baseline hematuria. The same method will be repeated for the additional body weight endpoints: proportions of patients with at least a 10% body weight loss after 1, 2, 3 and 4 years.

The body weight analyses will be performed for all patients and for the subgroups of patients with/without insulin at baseline. And for the subgroup of patients with baseline BMI >=30 and <30 separately.

Albumin to creatinine ratio:

Percent change from baseline to each visit measurement for urinary albumin to creatinine ratio will be analyzed by a repeated measures method. All non-missing visit data will be used, including off-treatment measurements. The model will include terms for treatment group, CV risk category, baseline hematuria, visit, visit*treatment group and baseline measurement as a covariate. The model will be used to derive a least squares estimate of the treatment difference with 95% confidence interval and corresponding two-sided p-value. Further, two-sided 95% confidence intervals for the mean percent change within each treatment group will be calculated. Missing data will not be imputed. This model will be used to assess the timepoints of 1 year, 2 years, 3 years and 4 years although summaries at all visits will also be presented. If data suggests, the analysis might be performed applying a logarithm scale instead. This analysis will also be performed separately per the subgroups of baseline urinary albumin to creatinine ratio (<30mg/g, >=30mg/g).

eGFR (using CKD-EPI equation):

Change in eGFR from baseline to each visit will be analyzed by a repeated measures model. The model will include fixed effect terms for treatment group, CV risk category, baseline hematuria, time, time*treatment group and baseline eGFR, with time coded as a categorical variable defined by the follow-up visit. The variance-covariance matrix structure is assumed to be unstructured.

The model will be used to derive least squares mean changes within each treatment group and the treatment difference in mean changes, along with 95% confidence intervals and corresponding nominal two-sided p-values. The estimates of the treatment effect will be provided for 6 months, 1 year, 2 years, 3 years, and 4 years after randomization. The total slopes (between randomization and 1 year, 2 years, 3 years, and 4 years, respectively) and the chronic slopes (between 6 months and 1 year, 2 years, 3 years, and 4 years, respectively) will be estimated via linear contrasts within the same model. The comparison of the mean total slopes will serve as the primary assessment of the effect of the treatment on eGFR slope; the comparison of the mean chronic slopes will serve as a secondary comparison.

The main analysis, based on the Full Analysis Set (FAS), will include all randomized subjects and available on- and off-treatment scheduled measurements. The unscheduled eGFR assessments will not be included. No imputation will be carried out for missing data. A secondary analysis will be conducted in a similar way by excluding off-treatment

measurements. These analyses will also be performed separately per the subgroups of baseline urinary albumin to creatinine ratio (<30mg/g, >=30mg/g).

Other continuous variables:

Change from baseline to each visit for HbA1c, DBP, SBP and BMI will be analyzed by a repeated measures method following the method in Section 4.1.10. All non-missing visit data will be used, including off-treatment measurements. The model will be used to derive a least squares estimate of the treatment difference with 95% confidence interval and corresponding two-sided nominal p-value. Further, two-sided 95% confidence intervals for the mean change within each treatment group will be calculated. Missing data will not be imputed. This model will be used to assess the timepoints at 1, 2, 3 and 4 years although summaries at all visits will also be presented.

The definition of the 1 year time point in these analyses is each patient's visit within +/- 3 months that is closest to 1 year. Corresponding logic applies also for the definition of the other time points. Patients without measurements within a time interval will be counted as failures, and will be included in the denominator.

All continuous endpoints will be plotted over time presenting LS means and SE.

Proportions:

Retinal laser and/or intraocular treatment due to development of and/or deterioration in diabetic retinopathy, all strokes, need for an increase in dose for an oral diabetes medication or ≥ 25% increase in insulin dose or the addition of new diabetes medication, for ≥ 3 months, initiation of insulin therapy in patients not receiving insulin therapy at baseline, major hypoglycaemia and/or hospitalization for hypoglycaemia, peripheral revascularization/limb ischemic events and regression in albuminuria will be examined using statistics according to analysis of proportions described in Section 4.1.11 that will include 95% confidence intervals for treatment effects and for the comparison between treatments as well as nominal 2-sided p-values. Time to event analyses will also be performed for these variables.

The Modified Rankin Scale values for strokes will be summarized by treatment.

4.5 Analysis methods for safety variables

Safety observations will be summarized in two ways. The first way will include patients in the on-treatment analysis set, and additionally, all safety data will be summarized for all patients from the safety analysis set regardless if study treatment was discontinued or not. The adjudicated outcome will be considered the main analysis, and applies to malignancies, hepatic events and DKA.

4.5.1 Adverse events, including hypoglycaemia

Only events that fall into the following categories are collected in this study: serious AEs, AEs leading to discontinuation of IP, suspected CV events, elective coronary and non-coronary revascularisations, heart failure, potential diabetic ketoacidosis, amputation and related events and AEs of special interest. AEs of special interest in this study fall into the following categories: suspect neoplasm (benign, malignant or unspecified), hepatic events, hypoglycemic events that are major, fractures, renal events, symptoms of volume depletion, hypersensitivity reactions (serious or lead to discontinuation of IP), urinary tract infections (serious or lead to discontinuation of IP) and genital infections (serious or lead to discontinuation of IP). Therefore, AE summaries will be limited to these particular categories and general summaries of all AEs are not planned.
AEs will be coded using the current version of MedDRA at the time of the database lock.

No statistical tests will be performed to compare AE rates between treatment groups.

For the on-treatment set, adverse events will be included if they occurred on or after the date of first randomized dose and within the windows listed below:

- AEs of special interest which are not serious AEs will be summarized if their onset dates were on or before the 7th day after the last blinded drug dose date, or at the Closing visit (whichever is earlier)

- Serious AEs will be summarized if their onset dates were on or before the 30th day after the last blinded drug dosing date, or at the closing visit (whichever is earlier).

- All AEs leading to discontinuation of investigational product will be summarized, and no upper day range applies

A summary table of the total numbers of patients with SAEs, discontinuations due to AEs, and any AE in each category of special interest will be provided. In summaries by system organ class (SOC) and preferred term (PT), or only PT where applicable, AEs will be sorted by decreasing frequency within each PT and SOC according to the “dapagliflozin” patient incidence. Summaries by PT will be sorted by decreasing frequency according to the “dapagliflozin” patient incidence.

4.5.1.1 Procedures for counting AEs

A patient will be counted once for a reported AE by PT even if the patient had multiple occurrences.

4.5.1.2 Serious Adverse Events

The patient incidence of all SAEs will be presented by SOC, PT and treatment group.

The patient incidence of the most common SAEs will be presented by PT and treatment group. A most common SAE is defined as a PT that has been reported by at least 0.2% of patients in any treatment group.

A listing of all SAEs will be provided.

4.5.1.3 Adverse Events leading to discontinuation

AEs reported with an action taken of "Investigational product permanently stopped" will be summarized by SOC, PT, and treatment group.

The patient incidence of the most common AEs leading to discontinuation (DAE) of investigational product will be presented by PT and treatment group. A most common DAE is defined as a PT that has been reported by at least 0.2% of patients in any treatment group.

In addition, a patient listing of discontinuations due to AEs will be produced.

4.5.1.4 Adverse events of special interest

Analyses will be performed separately for AEs of special interest. AEs of special interest in this study fall into the following categories: malignancies, hepatic events, hypoglycemic events that are major, fractures, renal events, symptoms of volume depletion hypersensitivity reactions that are serious or lead to discontinuation of investigational product, urinary tract infections that are serious or lead to discontinuation of investigational product and genital infections that are serious or lead to discontinuation of investigational product. At the end of the study, AEs of special interest will be identified as:

- AE of special interest category collected on the eCRF or
- AE MedDRA PT matching the current MedDRA version prespecified PT list for AEs of special interest or
- the laboratory criteria for a marked abnormality (liver and renal categories only) specified in Appendix A.

For each category of AE of special interest, frequency and proportion of patients with AEs will be summarized by PT, overall and by subgroups (see Table 3) based on:

Fractures: baseline eGFR using CKD-EPI equation, age, sex

Osteoporetic fractures (WHO definition by location): baseline eGFR using CKD-EPI equation, age, sex

Renal events: baseline eGFR using CKD-EPI equation, age, urinary albumin/creatinine ratio, baseline systolic and diastolic blood pressure, diabetes duration, ACEi/ARB, diuretic use

Volume depletion: baseline eGFR using CKD-EPI equation, age, diuretic use, loop diuretics, baseline systolic and diastolic blood pressure, ACEi/ARB

SAE/DAE of urinary tract infection: sex, age

SAE/DAE of genital infection: sex, age

Malignancies:

- Overall: sex, age
- Bladder: baseline hematuria
- Prostate: males only

Time to first onset of each AE of special interest will be summarized by treatment group using Kaplan-Meier estimates of the cumulative proportion (with 95% CI) within each treatment group (see Section 4.1.13).

SAE/DAE of urinary tract infections and SAE/DAE of genital infections will each be summarized by treatment group.

The number and percentage of patients with AE of special interest will be summarized by category and preferred term for each treatment group.

Specific patient data listings for selected AEs of special interest will be performed.

Event rates per 1000 patient years will be calculated per AE of special interest. The same rules for censoring (for patients both with and without events) will be used as described in section 4.1.9.

More information on hypoglycaemic events, cancer events and hepatic events is presented below.

Hypoglycaemic Adverse Events:

At each visit the Investigator will inquire about occurrence of major hypoglycemic events according to the below definition.

Major hypoglycemic event defined as symptomatic events requiring external assistance due to severe impairment in consciousness or behavior, and prompt recovery after glucose or glucagon administration. Plasma glucose measurements may not be available during such an event, but neurological recovery attributable to the restoration of plasma glucose to normal is considered sufficient evidence that the event was induced by a low blood glucose concentration.

Hypoglycemic episodes should be reported if the event fulfills the definition of a major hypoglycemic event, the protocol criteria for an SAE or leads to discontinuation of investigational product. For major hypoglycemic episodes additional details will be recorded in the eCRF. Other definitions for hypoglycemic events may also be applied and summarized, for example hypoglycemic events requiring external assistance.

Cancer Adverse Events:

All potential neoplasms, excluding non-melanoma skin cancers, will undergo blinded adjudication by the CEC, and only those that are adjudicated to be malignant will be included in the analysis of cancer events. Patients with any cancer will be summarized. Plus, the subcategories of cancers will be analyzed according to the adjudication outcome, incidence rate ratios and confidence intervals will be tabulated and depicted in a forest plot.

Incidence rate differences and corresponding confidence intervals will be provided according to the methodology in Section 4.1.12 for bladder cancer, breast cancer and prostate cancer. These cancers will also be examined using the time to event approach using the Cox model as described in Section 4.1.9.

Hepatic Adverse Events:

Summary statistics by treatment group will be presented by severity and causality.

Severity Scale:

1 ALT or AST > 3X ULN, usually transient and reversible by adaptation (mild)
2 Also TB > 2X ULN, after or concurrent, indicating early functional loss (Hy's Law Case)
3 Serious, meaning disabling, requiring or prolonging hospitalization because of liver dysfunction
4 Acute liver failure, with secondary failure of brain or kidney function due to liver injury
5 Fatal, or requiring liver transplantation due to liver failure

Causality	Likelihood	Description
Definite	> 95%	The evidence for the study drug causing the injury is beyond a reasonable doubt
Highly Likely	75 - 95%	The evidence for the study drug causing the injury is clear and convincing but not definite
Probable	50 - 74%	The preponderance of the evidence supports the link between the study drug and the liver injury
Possible	25 - 49%	The evidence for the study drug causing the injury is equivocal but present
Unlikely	< 25%	There is evidence that an etiological factor other than the study drug caused the injury is clear

4.5.2 Laboratory Evaluation

All scheduled laboratory evaluations are performed by central laboratories. Evaluations done by local laboratories will not be included in summaries of changes from baseline but will be included in Marked Laboratory Abnormalities.

Laboratory parameters will be presented in SI units and summarized by treatment group with descriptive statistics.

In the on-treatment safety analysis, safety laboratory results will be summarized only if measured on or before the 7th day after the last blinded drug dosing.

Changes from baseline to each scheduled time point for each clinical laboratory test, including estimated GFR and estimated creatinine clearance will be summarized by treatment group. In addition, the number and percent of patients with a marked abnormality in clinical laboratory tests will be summarized by treatment group.

4.5.2.1 Marked Laboratory Abnormalities

Laboratory abnormalities will be evaluated based on marked abnormality (MA) criteria. The list of MAs is provided in Appendix A. If both the baseline and on-treatment values of a parameter are beyond the same MA limit for that parameter, then the on-treatment value will be considered a MA only if it is more extreme (farther from the limit) than was the baseline value. If the baseline value is beyond the low MA limit, and the on-treatment value is beyond the high MA limit (or vice-versa), then the on-treatment value will be considered a MA.

Laboratory MAs occurring during treatment period will be summarized by treatment group. The directions of changes (high or low) in MAs will be indicated in the tables. Additionally, for each patient with a MA for a parameter, all the patient's values of that parameter over the treatment period will be listed.

4.5.2.2 Changes from baseline values

Changes from baseline will be summarized over all scheduled visits, presenting n, mean, median, SD, Q1, Q3 and 95% CI.

This applies to all laboratory variables.

4.5.3 Physical findings and other observations related to safety

4.5.3.1 Vital signs

The values and changes from baseline for systolic and diastolic blood pressures and heart rate will be summarized by treatment group at each scheduled time of assessment.

4.5.3.2 Amputations and related events

Surgical or spontaneous/non-surgical amputations, AEs leading to amputation, contributing factors and conditions that triggered amputations will be summarized and analyzed, including an investigation of competing risks and baseline parameters and medications. Time to event analyses as well as KM plots will be performed. Hazard Ratios (HR) and Confidence Intervals (CIs) will be derived from a Cox proportional hazards model, see section 4.1.9. Differences in proportions will also be analyzed and presented, see section 4.1.11. The competing risks of peripheral revascularization and all-cause mortality will be looked upon using time to event analyses.

4.5.3.3 Potential diabetic ketoacidosis

Potential diabetic ketoacidosis will be adjudicated and reported as definite, probable, possible or not diabetic ketoacidosis.

5. INTERIM ANALYSES

A DMC will be appointed jointly by the Sponsors and the academic leadership of the study. The DMC will be responsible for safeguarding the interests of the patients in the outcome study by assessing the safety of the intervention during the trial, and for reviewing the overall conduct of the clinical trial. In addition, the DMC will have the responsibility to assess the efficacy data of the interim analysis and make recommendations based upon stopping guidelines.

A group sequential design with 2 interim analyses will be assessed for MACE and all-cause mortality. The analyses will take place at 1/3 and 2/3 of the MACE events using an O'Brien–Fleming alpha-spending rule. The interim analyses will assess superiority of dapagliflozin to placebo for MACE because the study will only be considered for early termination if superiority is met. All-cause mortality is included as an endpoint to the interim analyses for an additional assessment of benefit. The first interim analysis will have a one-sided alpha level of 0.000095. The second interim analysis will have a one-sided alpha level of 0.00614. According to the O'Brien-Fleming spending rule this will leave a 1-sided alpha level of 0.023095 for the final analysis. At each interim analysis, MACE will be tested first at the specified alpha level, and if found to be statistically significant, all-cause mortality will then be assessed for significance at the same alpha level. If superiority is achieved for both endpoints, an action is triggered whereby the DMC will evaluate the CV data and safety data, including bladder cancers and liver events, to determine if benefit is unequivocal and overwhelming such that the DMC recommends ending the study.

If an interim analysis leads to a decision to terminate the trial early based on pre-defined stopping guidelines, the interim analysis database will become the basis of statistical inference for the endpoints of MACE and All-cause mortality. Following such a decision, study closeout procedures will commence toward database lock. A follow-up analysis based on the locked database will be conducted to support the full reporting of the trial. The consistency between the interim analysis database and the subsequently locked database will be assessed.

In the follow-up analysis based on the locked database, the date when the Executive Committee instructs the sites to commence final visits will be used as a common study end date and as a date for censoring endpoint events for efficacy analyses. All endpoint events that occur on or prior to this date will be included in the analyses, regardless when they are identified relative to this date. All events occurring after the common study end date will be documented and adjudicated by the same procedures as events occurring up to this date, and will be summarized in the reporting.

In the follow-up analysis based on the locked database, nominal p-values will be presented for all efficacy endpoints. The alpha level for those endpoints that have not been formally tested at the interim analyses will be calculated by controlling the

overall Type I error across the primary and secondary endpoints and across the interim analyses and the follow-up analysis.

If, outside of the 2 pre-specified interim efficacy analyses, the DMC feels compelled for safety concerns to examine efficacy data formally with consideration of stopping the trial early for overwhelming efficacy, then the alpha applied to such efficacy analyses would be determined according to the O'Brien-Fleming spending function, and subsequent alpha-levels for any remaining planned efficacy interim and final analyses would also be adjusted according to the O'Brien-Fleming spending function to maintain the control of the Type I error. Any unscheduled interim analysis would evaluate both MACE and all-cause mortality in the same way as for a scheduled interim analysis. The SEER rate for the general US population of 0.044% per person-year for bladder cancer may be conservative; higher bladder cancer rates could be observed in this trial. If the SEER rate is adjusted to reflect an increased risk in a diabetes population, an estimated annual rate of 0.06% could occur.

We assume that the rate of bladder cancers observed in this study will be 0.06%, which would correspond to a total of 46 bladder cancers.

Interim monitoring for bladder cancers is planned for the purposes of communicating potential signals with regulatory authorities. The accumulation of patients with bladder cancer would suggest 4 interim analyses at 8, 16, 24 and 32 events, followed by the final analysis. The earliest difference where a result could possibly be significant is with 7 events, and with a minimum split of bladder cancers 7 versus 0. The interim analysis would take place at approximately 26, 37, 46 and 55 months. The bladder analyses would be assessed at an overall alpha-level of 0.10 with a Pocock spending rule. If an interim analysis is significant, the DMC would inform others according to a strict communication plan. Note that this rule is not a reason for stopping the study. An analysis of the primary CV variables may be performed additionally in order to allow the DMC to assess benefit and risk concurrently. The number of interim analyses for bladder cancers may be adjusted if the event rate is different than expected.

The overall type I error will be set to 0.10. Using a Pocock spending rule, the alpha levels for the five bladder analyses will be as follows:

First interim analysis:	alpha level of 0.026
Second interim analysis:	alpha level of 0.029
Third interim analysis:	alpha level of 0.031
Fourth interim analysis:	alpha level of 0.034
Final analysis:	alpha level of 0.043

Table 6 **Imbalance of bladder cancers. Significant difference (binomial) between bladder cancers at different alpha levels. Under the condition that there is no true difference in bladder cancer incidence between Dapagliflozin and Placebo.**

Total number of patients with bladder cancer	Analysis	Minimum split of cancers for statistical significance (binomial)
8	IA1	1 versus 7
16	IA2	3 versus 13
24	IA3	6 versus 18
32	IA4	9 versus 23

6. CHANGES OF ANALYSIS FROM PROTOCOL

eGFR total slope and chronic slope have been added as new exploratory efficacy variables.

Exploratory renal composite endpoint: Confirmed sustained ≥40% decrease in eGFR to eGFR <60 mL/min/1.73m^2 using CKD-EPI equation and/or ESRD (dialysis ≥90 days or kidney transplantation, confirmed sustained eGFR <15 mL/min/1.73m^2) and/or renal death (time to first event) has been added as new exploratory efficacy variable.

Amputations and related events was specified as an exploratory efficacy objective in the protocol. It has been moved to the safety section in the Statistical Analysis Plan.

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Appendix A Laboratory Abnormality Criteria

The set of labs requested in this study is summarized in Table 7, along with the laboratory abnormality criteria.

Fasting Designation for Labs: Fasting labs are evaluated under fasting criteria (if applicable) and unspecified (if applicable).

Table 7 provides the criteria for assessing marked abnormalities in safety laboratory parameters. If both the baseline and on-treatment values of a parameter are beyond the same MA limit for that parameter, then the on-treatment value will be considered a MA only if it is more extreme (farther from the limit) than was the baseline value. Also, if the on-treatment value of a parameter is beyond a MA limit and the baseline value is not beyond the same limit then the on-treatment value will be considered a MA.

The following three criteria will also be summarized by treatment group in examination of the elevated AT (ALT and/or AST) and total bilirubin:

- (AST or ALT > 3XULN) and (Total Bilirubin > 1.5XULN within 14 days on or after AT elevation)
- (AST or ALT > 3XULN) and (Total Bilirubin > 2XULN within 14 days on or after AT elevation)
- (AST or ALT > 3XULN) and {(Total Bilirubin > 2XULN and no ALP ≥ 2XULN) within 14 days on or after AT elevation}

The following criteria will be summarized by treatment group:

- Estimated Creatinine Clearance < 45 mL/min
- Estimated GFR < 45 mL/min/1.73m^2

Table 7 Marked Abnormality Criteria for Safety Laboratory Parameters Marked abnormality criteria for safety laboratory variables and elevated AT (ALT and/or AST) and total bilirubin

		Marked Abnormality Criteria	
Clinical laboratory variables	**Units**	**Low**	**High**
Hematology			
HCT males/females	vol	<0.20	>0.55

		Marked Abnormality Criteria	
Clinical laboratory variables	**Units**	**Low**	**High**
HCT males/females	vol		>0.60
Hemoglobin males/females	g/L	<60 g/L	>180 g/L
Hemoglobin males/females	g/L		>200 g/L
Blood Chemistry			
ALP	U/L		>1.5X ULN
ALP	U/L		>3X ULN
ALT	U/L		>3X ULN
AST	U/L		>3X ULN
AST or ALT	U/L		>3X ULN
ALT	U/L		>5X ULN
AST	U/L		>5X ULN
AST or ALT	U/L		>5X ULN
ALT	U/L		>10X ULN
AST	U/L		>10X ULN
AST or ALT	U/L		>10X ULN
ALT	U/L		>20X ULN
AST	U/L		>20X ULN
AST or ALT	U/L		>20X ULN
Total Bilirubin	µmol/L		>1.5X ULN >2X ULN
Na (Sodium)	mmol/L	<130 mmol/L	>150 mmol/L
Na (Sodium)	mmol/L	<120 mmol/L	
K (Potassium)	mmol/L	≤2.5 mmol/L	≥6.0 mmol/L
HCO3 (Bicarbonate)	mmol/L	≤13 mmol/L	
Creatinine	µmol/L		≥1.5X PreRx CREAT
Creatinine	µmol/L		≥2X PreRx CREAT
Creatinine	µmol/L		≥221 µmol/L

		Marked Abnormality Criteria	
Clinical laboratory variables	**Units**	**Low**	**High**
Calcium	mmol/L	<1.875 mmol/L	≥0.25 mmol/L from ULN **and** ≥0.125 mmol/L from PreRx CA
Magnesium	mmol/L	<0.5 mmol/L	>2.0 mmol/L
Phosphorus	mmol/L	Age 17-65: ≤0.58 mmol/L	Age 17-65: ≥1.81 mmol/L
		Age 66: ≤0.68 mmol/L	Age≥ 66: ≥1.65 mmol/L
Urine			
UACR (Urinary Albumin-to-Creatinine Ratio)	mg/mmol		>203.62 mg/mmol

Appendix B Definition of Regions

Region	**Countries**
North America	Canada
	United States
Latin America	Argentina
	Brazil
	Mexico
Asia/Pacific	Australia
	China
	Hong Kong
	India
	Taiwan
	Thailand
	Japan
	Philippines
	South Korea
	Vietnam

Region	Countries
Europe	Western: France Germany Italy Netherlands Spain Sweden United Kingdom Turkey Belgium Eastern: Hungary Bulgaria Czech Republic Poland Romania Russia Slovakia Ukraine Israel South Africa