NCT03496298

STATISTICAL ANALYSIS PLAN

A Randomized, Double-blind, Placebo-controlled, Parallel-group, Multicenter Study to Evaluate the Effect of Efpeglenatide on Cardiovascular Outcomes in Type 2 Diabetes Patients at High Cardiovascular Risk

EFC14828 (AMPLITUDE-O)

SAR439977 (efpeglenatide)

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

ADA:	anti-drug antibody
AE:	adverse event
BMI:	body mass index
BP:	blood pressure
CABG:	coronary artery bypass graft
CEC:	Clinical Endpoint Committee
CV:	cardiovascular
GI:	gastrointestinal
HbA1c:	hemoglobin A1c
hectic f:	estimated glomerular filtration
HHF:	hospitalization for heart failure
HLGT:	high-level group term
HLT:	high-level term
IMP:	investigational medicinal product
IRT:	interactive response technology
LLT:	lower-level term
MACE:	major adverse cardiac events
MDRD:	Modification of Diet in Renal Disease
MedDRA:	Medical Dictionary for Regulatory Activities
MI:	Myocardial infarction
NI:	non-inferiority
PCI:	percutaneous coronary intervention
PT:	preferred term
QW:	once per week
SGLT2:	sodium-glucose linked transporter-2
SOC:	system organ class
T2DM:	type 2 diabetes mellitus
TEAE:	treatment-emergent adverse event
UACR:	urinary albumin creatinine ratio
ULN:	upper limit of normal
WHO-DD:	World Health Organization-Drug Dictionary

[redacted]

1 OVERVIEW AND INVESTIGATIONAL PLAN

1.1 STUDY DESIGN AND RANDOMIZATION

This is a Phase 3, multicenter, randomized, double-blind, placebo-controlled, parallel-group study in approximately 4000 Type 2 Diabetes Mellitus (T2DM) patients at high cardiovascular (CV) risk. The study will consist of three periods:

- A 2- to 3-week screening period.
- A double-blind, placebo-controlled, multiple-dose treatment period, including up to 8 weeks for dose titration.
  - If, at any time during the study, a participant does not tolerate the study treatment, the investigational medicinal product (IMP) may be temporarily discontinued or if medically necessary, permanently discontinued.
  - If a maximum of two consecutive doses are missed, the IMP can be restarted with the latest dose given; if three or more consecutive doses are missed, the IMP will be restarted using a new titration kit.
  - All IMP discontinuation should initially be considered as temporary unless permanent discontinuation is mandated by the protocol.
- A follow-up period of 6 weeks after the last dose of IMP.

Patients who meet all eligibility criteria will be randomized centrally by an Interactive Response Technology (IRT) using a permuted-block randomization schedule with a fixed block size at a 1:1:1 ratio to efpeglenatide 4 mg, efpeglenatide 6 mg or placebo. Randomization will be stratified by the current or potential future use of a sodium-glucose linked transporter-2 (SGLT2) inhibitor (current use, potential future use, neither current nor potential future use).

All randomized participants, including those who prematurely and permanently discontinued from IMP, will be followed from Randomization until the Study close-out visit or death, whichever comes first. A post-treatment safety follow-up visit 6 weeks after the last dose of IMP will be implemented for patients still on study treatment at the Study close-out visit.

The study is event driven and will continue until 330 participants have at least one primary event (3-point major adverse cardiac events [MACE]) positively adjudicated by the Clinical Endpoint Committee (CEC). All randomized participants will be asked to return to the site for a study close-out visit once the projected date of the required number of positively adjudicated events has been determined. Approximately 4000 patients will be randomly assigned to study intervention to end up with an estimated total of 330 participants with at least one positively adjudicated 3-point MACE event.

[redacted]

1.2 OBJECTIVES

1.2.1 Primary objectives

The primary objective of this study is to demonstrate that efpeglenatide (pooled 4 mg and 6 mg) is noninferior to placebo on 3-point MACE in T2DM patients with high CV risk.

1.2.2 Secondary objectives

- To demonstrate that efpeglenatide (pooled 4 mg + 6 mg) is superior to placebo on 3-point MACE in T2DM patients with high CV risk.
- To demonstrate that efpeglenatide (pooled 4 mg + 6 mg) is superior to placebo on the expanded CV outcome in T2DM patients with high CV risk.
- To demonstrate that efpeglenatide (pooled 4 mg + 6 mg) is superior to placebo on the composite outcome of new or worsening nephropathy in T2DM patients with high CV risk.
- To assess the safety of efpeglenatide 4 and 6 mg once per week (QW), both added to standard of care in T2DM patients with high CV risk.

1.2.3 Tertiary/Exploratory objectives

- To compare efpeglenatide versus placebo on the occurrence of the following events in T2DM patients with high CV risk:
  - CV death;
  - Stroke (fatal and non-fatal);
  - Myocardial infarction (MI) (fatal and non-fatal);
  - All cause death;
  - Hospitalization for unstable angina;
  - Hospitalization for Heart Failure (HHF);
  - Coronary revascularization procedures (percutaneous coronary intervention [PCI] or coronary artery bypass graft [CABG]).
- To compare efpeglenatide versus placebo on the following endpoints:
  - Change in hemoglobin A1c (HbA1c);
  - Change in body weight;
  - Change in blood pressure (BP);
  - Change in Urinary Albumin-Creatinine Ratio (UACR).
- To compare efpeglenatide versus placebo on immunogenicity.

[redacted]

1.3 DETERMINATION OF SAMPLE SIZE

It is estimated that approximately 4000 participants are needed to obtain approximately 330 participants with a positively adjudicated event for the primary composite cardiovascular endpoint (3-point MACE), based on the following trial design characteristics assumptions:

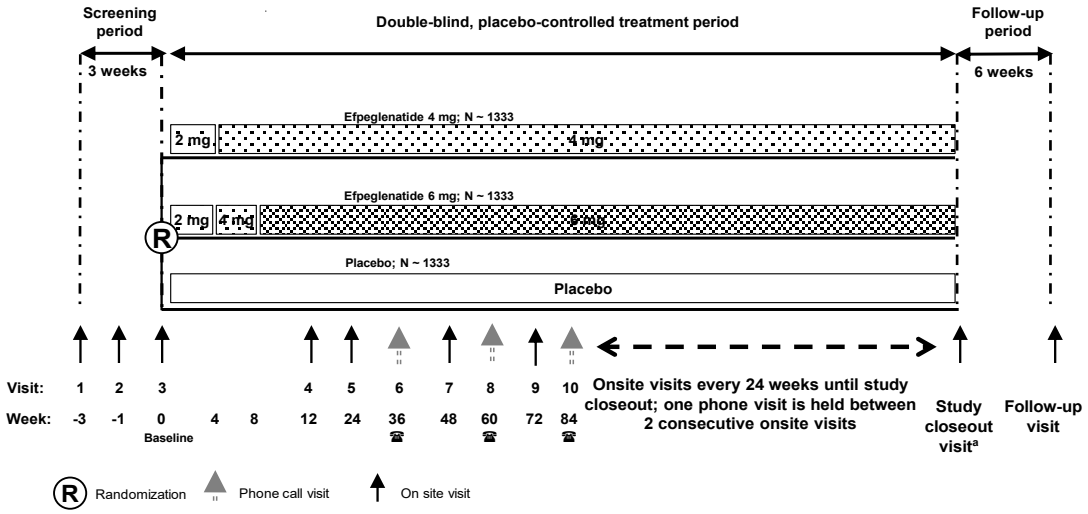
- A recruitment period of approximately 12 months
- Study duration is estimated to be approximately 24 months of follow-up after the last randomized patient, estimated follow-up ranging from 24 to 36 months
- 2% annual early study discontinuation
- Yearly event rate in placebo group: 4.4% for participants not using a SGLT2 inhibitor, and 3.7% for participants using a SGLT2 inhibitor
- Treatment effect of efpeglenatide compared to placebo: 15% risk reduction for participants not using a SGLT2 inhibitor, and a neutral effect for participants using a SGLT2 inhibitor
- 20% of participants using a SGLT2 inhibitor at baseline, and additional 10% participants in placebo group and 5% participants in efpeglenatide group adding a SGLT2 inhibitor during the study period

This will provide:

- 90% power to demonstrate non-inferiority (NI) of efpeglenatide vs placebo with a 1.3 NI margin {upper bound of the 95% CI of the estimated hazard ratio <1.3} for the 3-point MACE (CV death, non-fatal MI or non-fatal stroke)
- >99% power to demonstrate NI with a 1.8 margin

1.4 STUDY PLAN

The following figure presents graphically the study design:



1:1:1 randomization, stratified by the current or potential future use of SGLT2 inhibitor (Current use, Potential future use, Neither current nor potential future use).

[a] All randomized patients will be asked to return to the study site for a study close-out visit when approximately 330 participants have at least one primary event (3-point MACE) positively adjudicated by the CEC

R: randomization; CEC: Clinical Endpoint Committee; SGLT2: sodium-glucose linked transporter-2

The study flow chart is detailed in the protocol.

1.5 MODIFICATIONS TO THE STATISTICAL SECTION OF THE PROTOCOL

This section summarizes major changes to the protocol statistical section with emphasis on changes after study start (after the first patient was enrolled).

The protocol history table below gives the timing, rationale, and key details of major changes to the protocol statistical section.

The first patient was enrolled on 11 May 2018. There is no planned interim analysis.

Table 1 - Protocol amendment statistical changes

Amendment Number	Date Approved	Rationale	Description of statistical changes
1	28-May-2018	Type of AEs to be summarized during the on-study period, as well as the definition, were clarified	All AEs, SAEs, AEs leading to permanent treatment discontinuation, and AEs leading to death will be summarized for the on-study period
2	30-Jul-2018	To harmonize the anti-drug antibodies (ADA) endpoint with the other efpeglenatide Phase 3 clinical protocols	Change of ADA objective/endpoint from secondary objective/endpoint to tertiary/exploratory objective/endpoint
		Section 9.4.3 describes statistical analysis of secondary endpoints and the ADA endpoint has been moved to tertiary/exploratory endpoint	Removal of Table 9 describing the statistical analysis of ADA

1.6 STATISTICAL MODIFICATIONS MADE IN THE STATISTICAL ANALYSIS PLAN

Not applicable.

[redacted]

2 STATISTICAL AND ANALYTICAL PROCEDURES

2.1 ANALYSIS ENDPOINTS

Key definitions:

Completion of Study: as study approaches to the end, the team will make prediction of time window when the target 330 first occurrence of 3-point MACE (positively adjudicated) can be achieved. Once projected visit window is determined, the site will be notified of the time window. Following announcement of the project study close-out visit:

1) for subjects remaining on IMP at announcement of project study close-out visit, sites will schedule a study close-out visit and an off-drug follow-up visit as per the time and events scheduled in protocol;
2) for subjects that have prematurely and permanently discontinued IMP prior to announcement of the project study close-out visit but still in study at the announcement, sites will schedule a study close-out visit;
3) for subjects that have prematurely and permanently discontinued study prior to announcement, sites will be required to make a final contact for efficacy outcome collection (if patients allow further contact by family member and health provider) or vital status check (if allowed by local law) as soon as possible after the announcement.

Scheduled study-close out visit: a study visit window projected by the sponsor during which the sites are required to bring all patients back to site for study closeout. It is a fixed calendar time window. For patients who already discontinued study prematurely, they'll miss this visit and their efficacy events after this scheduled visit will not be included for efficacy analysis even positively adjudicate.

Scheduled last study visit: later of study closeout visit or follow-up visit. That is, for patients still on IMP at study close-out visit, their scheduled last study visit will be follow-up visit; while for patients not on IMP at study close-out visit, study close-out visit will be their scheduled last study visit.

End of study date: defined as date of last scheduled visit for those completed the study (follow-up visit or study closeout visit if premature discontinued IMP) and the date collected on eCRF form 'Completion of End of Study' for those who did not complete study. If death is reason collected on the 'Completion of End of Study', date of death will be used

2.1.1 Study completer: subjects completed study closeout visit (in person or by phone) or has died while in study Demographic and baseline characteristics

The baseline value (with the exception of serum creatinine and estimated glomerular filtration rate [eGFR]) is defined generally as the last available value prior to the first dose administration of double-blind IMP or the last available value on or before the date of randomization for patients

[redacted]

who were randomized but never exposed to IMP. For lab parameters, only central lab values should be used for baseline value derivation.

For serum creatinine and eGFR, baseline is defined as the average of all central lab values before the first dose of the double-blind IMP for those randomized and exposed or before randomization for those who were randomized but never exposed to double-blind IMP.

All baseline safety and efficacy parameters (apart from those listed below) are presented along with the summary statistics in the safety and efficacy sections (Section 2.3.4 and Section 2.3.5).

Demographic characteristics

Demographic variables to be summarized are:

- Age (years),
- Age groups (<50, ≥50 and <65, ≥65 and <75, ≥75 years),
- Sex (Male, Female),
- Race (White, Black or African American, Asian, American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, Multiple, Unknown),
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino, Unknown),
- Region (North America, Latin America, Europe, Other),
- Baseline body mass index (BMI) (kg/m^2),
- Baseline BMI categories (<30, ≥30 to <40, ≥40 kg/m^2),
- Baseline body weight (kg),
- Smoking status (never, current, former),
- Alcohol habit (never, occasional, at least daily, at least weekly, at least monthly).

Medical or surgical history

Medical (or surgical) history includes general medical or surgical history. This information will be coded using the version of Medical Dictionary for Regulatory Activities (MedDRA) currently in effect at Sanofi at the time of database lock.

Disease characteristics at screening or baseline

Specific disease history includes:

- Duration of diabetes (years) derived as: (Date of informed consent - Date of diagnosis of diabetes + 1)/365.25,
- Duration of diabetes categories (<10, ≥10 years),
- Age at diagnosis of type 2 diabetes (years) derived as: Year of diagnosis of diabetes - Year of birth,

[redacted]

- Baseline HbA1c (%),
- Baseline HbA1c categories (<8%, ≥8%),
- Retinopathy history (Yes/No),
- Baseline eGFR (mL/min/1.73m^2),
- Baseline eGFR categories (<15 mL/min/1.73m^2 [End stage renal disease], ≥15 to <30 mL/min/1.73m^2 [Severe decrease in GFR], ≥30 to <60 mL/min/1.73m^2 [Moderate decrease in GFR], ≥60 to <90 mL/min/1.73m^2 [Mild decrease in GFR], and ≥90 mL/min/1.73m^2 [Normal]),
- Randomization strata of SGLT2 use (Current use, Potential future use, Neither current nor potential future use),
- Use of SGLT2 at baseline (yes, no),
- History of heart failure.

The following summary will also be provided:

- Baseline Serum creatinine (µmol/L),
- Baseline Systolic blood pressure (mmHg),
- Baseline Diastolic blood pressure (mmHg),
- Baseline Heart rate (beats per min),
- Baseline UACR (mg/g),
- Baseline lipid profile (total cholesterol, HDL, LDL, triglycerides),
- Patients with at least 1 CV risk factor at screening or baseline,
- History of cardiovascular disease (CVD) (e.g. Coronary artery disease [CAD], cerebrovascular disease, and peripheral vascular disease),
- CV risk factors.

Any technical details related to computation, dates, and imputation for missing dates are described in Section 2.5.

2.1.2 Prior or concomitant medications

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) that the participant is receiving at the time of enrollment or during the study must be recorded in the corresponding case report form page.

All medications will be coded using the World Health Organization-Drug Dictionary (WHO-DD) using the version currently in effect at Sanofi at the time of database lock.

[redacted]

Medications will be classified into the following 3 groups:

- Prior medications are those the patient used prior to first IMP intake. Prior medications can be discontinued before first administration or can be ongoing during treatment phase.
- Concomitant medications are any treatments received by the patient concomitantly to the IMP(s), from first dose to the end of treatment + 30 days (+ 7 days for antidiabetic drugs). A given medication can be classified both as a prior medication and as a concomitant medication. Concomitant medications do not include medications started during the posttreatment period (as defined in the observation period in Section 2.1.4).
- Posttreatment medications are those the patient took in the period running from the 31st day (8 days for antidiabetic drugs) after the last injection of IMP up to the end of the study.

Any technical details related to computation, dates, imputation for missing dates are described in Section 2.5.

2.1.3 Efficacy endpoints

An independent Clinical Endpoint Committee (CEC) will review and adjudicate all events of death and selected CV events (MIs, strokes, unstable angina requiring hospitalization, hospitalization for heart failure (HHF), and coronary revascularization) in a blinded manner. Only events positively adjudicated by the CEC will be included for main efficacy analysis, unless otherwise specified.

All randomized patients (irrespective of whether they experienced efficacy event[s] or whether they permanently discontinued double-blind treatment) will be followed from randomization until the planned last study visit (follow-up visit or study closeout visit for patient premature discontinued IMP). All events occurring on or after randomization and up to patient's end of study date will be included, unless otherwise specified below.

For positively adjudicated efficacy endpoint events with onset date after the patient's end of study date:

1. For patients who prematurely discontinued study, these events will be included in efficacy analysis if the events occur on or before the scheduled study-close out visit. Otherwise, these events will be listed as applicable and not be included in primary efficacy analysis
2. For study completers, these events will be included in efficacy analysis if the proceeding/related event onset date is on or before the patient's scheduled last study visit. Otherwise, these events will be listed separately as applicable and not be included in primary efficacy analysis

   For example, for a CV death, if the onset date of its preceding fatal stroke is before the patient's follow-up visit and the CV death date is after follow-up visit (before data base lock (DBL) date), this CV death will be included in efficacy analysis if adjudicated as cardiovascular death.

[redacted]

Any endpoint events reported in the database, but not listed above, will not be included in the efficacy analysis.

2.1.3.1 Primary efficacy endpoint(s)

The primary efficacy endpoint is:

- Time to the first occurrence of any of the following 3-point MACE events:
  - CV death
  - Non-fatal MI
  - Non-fatal stroke

The death events adjudicated by CEC as 'undetermined death' will be considered as CV death and included in efficacy analysis.

2.1.3.2 Secondary efficacy endpoint(s)

- Time to first occurrence of non-fatal stroke and death
- Time to the first occurrence of any of the following expanded CV events:
  - CV death
  - Non-fatal MI
  - Non-fatal stroke
  - Coronary revascularization
  - Hospitalization for unstable angina
- Time to the first occurrence of any of the following new or worsening nephropathy:
  - New onset or progression to macro albuminuria (>300 mg/g) accompanied by an UACR value increase of ≥30% from Baseline
  - Sustained ≥40% decrease in eGFR from Baseline (for ≥30 days)
  - Chronic dialysis (for ≥90 days)
  - Renal transplant
  - Sustained eGFR <15 mL/min/1.73 m^2 (for ≥30 days)

Low eGFR value and 40% eGFR decrease from baseline will be captured from dedicated eGFR page "Renal event-eGFR Decrease". Participants with a suspected renal event (reduction of eGFR) should have a repeat assessment of renal function 30 to 45 days following the onset of the event to confirm it is sustained. For UACR increase, it will be captured and reported by lab. Chronic dialysis and renal transplant will be recorded in eCRF procedure pages: "Renal Event – Dialysis Procedure" and/or "Other Procedures".

[redacted]

2.1.3.3 Exploratory efficacy endpoint(s)

The exploratory efficacy endpoints are:

- Time to CV death
- Time to first occurrence of Stroke (fatal and non-fatal)
- Time to first occurrence of MI (fatal and non-fatal)
- Time to all cause death
- Time to first occurrence of hospitalization for unstable angina
- Time to first occurrence of HHF
- Time to first occurrence of coronary revascularization procedures (PCI or CABG)
- Changes from Baseline to scheduled visits per protocol in:
  - HbA1c
  - Body weight
  - BP
  - UACR
  - Heart rate

2.1.4 Safety endpoints

The safety endpoints include the reported adverse events (AE), hypoglycemia and other safety information, such as clinical laboratory data, vital signs, and electrocardiogram (ECG).

Observation period

The observation period will be divided into 3 periods:

- The pre-treatment period or screening period is defined as the time from signed informed consent up to the time of first injection of the double-blind IMP
- The treatment-emergent adverse event period (on-treatment period) is defined as the time from the first injection of the IMP to the last injection of the IMP + 30 days (or +7 days for hypoglycemia).
- The posttreatment period is defined as the period after the end of the treatment-emergent adverse event period.

The on-study observation period/on-study is defined as the time from first IMP until the end of (the) study date (defined as the last scheduled visit for those who completed the study and the study discontinuation date collected on eCRF form ‘Completion of End of Study’ for those who did not complete the study. If death is reason collected on the ‘Completion of End of Study’ form, date of death will be used).

The post-study observation is defined as anything after the on-study observation period.

[redacted]

2.1.4.1 Adverse events variables

Adverse event classification

The AE observations will be classified per the observation periods of safety data as defined above into:

- **Pre-treatment AEs** are adverse events that developed or worsened or became serious during the pre-treatment period
- **Treatment-emergent AEs (TEAEs)** are adverse events that developed or worsened or became serious during the on-treatment period
- **Post-treatment AEs** are adverse events that developed or worsened or became serious during the post-treatment period
- **On-study AEs** are adverse events that developed or worsened or became serious during the on-study period

All AEs (including SAEs), AEs of special interest (AESI) and AEs requiring specific monitoring (AERSM) will be coded to a lower-level term (LLT), preferred term (PT), high-level term (HLT), high-level group term (HLGT), and associated primary system organ class (SOC) using the version of MedDRA currently in effect at Sanofi at the time of database lock.

AESI include the following terms:

- Pregnancy of a female participant entered in a study as well as pregnancy occurring in a female partner of a male participant entered in a study with IMP
- Symptomatic overdose (serious or nonserious) with IMP
- alanine aminotransferase (ALT) ≥3 upper limit normal (ULN) (if baseline ALT <ULN) Or ALT ≥2 times the baseline value (if baseline ALT ≥ULN)

AERSM include the following terms:

- Severe gastrointestinal (GI) events
- Severe hypoglycemia
- Pancreatic events (including abnormal values of pancreatic enzymes, pancreatitis and pancreatic neoplasm)
- Calcitonin increase >5.9 pmol/L (20 pg/mL) and thyroid C-cell neoplasm
- Acute renal failure
- Diabetic retinopathy complications
- Severe injection site reaction
- Severe allergic reactions
- Severe immune complex disease

The CEC will review pancreatic events in a blinded manner.

[redacted]

The criteria of AESI and AERSM are defined in below Table 2.

Table 2 - Criteria for AESI and AERSM

AE Grouping	Criteria
AESI	
Pregnancy	"Pregnancy" checked
Symptomatic Overdose	"Overdose" checked and symptomatic (AEOVSYMP) = "Yes"
ALT ≥3 ULN (if baseline ALT <ULN) Or ALT ≥2 times the baseline value (if baseline ALT ≥ULN)	"ALT Increase" checked and Yes to the question "Is the event an AESI?" in eCRF form "Adverse Events"
AERSM	
Severe GI events	AE severity= "severe" using Gastrointestinal disorders CMQ
Severe hypoglycemia	Any hypoglycemia event which either required assistance (from hypoglycemia page) or missed answering 'Assistance Required' but with at least one of the 4 symptoms of ne of the 4 symptoms (ie, coma, seizure, loss of consciousness, and confusion)
Pancreatic events	cases reported in pancreatic specific eCRF page or AE with category = "Pancreatic neoplasm" selected
Calcitonin and thyroid C-cell neoplasm	Using Calcitonin increase CMQ Using Medullary thyroid cancer CMQ
Acute renal failure	Using Acute renal failure Narrow CMQ
Diabetic retinopathy complications	AE category = "Diabetic Retinopathy"
Severe injection site reaction	Intensity = "Severe" + Using Injection site reaction_ CMQ
Severe allergic reactions	Intensity = "Severe" + CMQs for anaphylactic reaction, angioedema, severe cutaneous adverse reaction, anaphylactic/anaphylactoid shock conditions (under SMQ "Shock"), and hypersensitivity
Severe immune complex disease	Intensity = "Severe" using Immune complex disease CMQ

2.1.4.2 Deaths

The deaths observation period is per the observation periods defined above.

- Death on-treatment: deaths occurring during the on-treatment period
- Death on-study: deaths occurring during the on-study observation period
- Death poststudy: deaths occurring after the on-study observation period

[redacted]

2.1.4.3 Laboratory safety variables

Clinical laboratory data consists of blood analysis (including hematology, clinical chemistry, and lipids) and urinalysis. Clinical laboratory values after conversion will be analyzed in standard international units and international units will be used in all listings and tables. Additional results using conventional units will be presented as necessary.

Blood samples for clinical laboratories will be collected as described in the study flow chart in the protocol. The laboratory parameters will be classified as follows:

- Serum hematology
  - Red blood cells and platelets: platelet count, red blood cell count, hemoglobin, hematocrit
  - White blood cells: white blood cell count, differential count (neutrophils, lymphocytes, monocytes, eosinophils, basophils)
- Serum clinical chemistry
  - Pancreatic enzymes: Amylase, Lipase;
  - Electrolytes: potassium, sodium;
  - Renal function: creatinine, eGFR (calculated by the central laboratory using the Modification of Diet in Renal Disease (MDRD) formula), UACR;
  - Liver function: alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), total bilirubin (TB), Lactic acid dehydrogenase (LDH)
  - Calcitonin
- Lipid profile
  - Total cholesterol, high-density lipoprotein cholesterol (HDL-C), Low-density lipoprotein cholesterol (LDL-C) (calculated by Friedwald formula), Non-HDL-C (calculated as the difference between TC and HDL-C), Triglycerides (TG)

Technical formulas are described in Section 2.5.1.

2.1.4.1 Vital signs variables

Vital signs include: heart rate and blood pressure (systolic and diastolic), all in a seated position.

2.1.4.2 Electrocardiogram variables

12-lead ECGs performed locally at the Investigator site. ECG assessments will be described as normal or abnormal.

[redacted]

2.1.5 Immunogenicity endpoints

Serum samples are collected to assess the Anti-drug antibody (ADA) status (positive/negative) at baseline. The titer of confirmed positive samples will be reported. Cross-reactivity of confirmed positive samples to endogenous GLP-1 (positive/negative), endogenous glucagon (positive/negative), neutralizing capacity of ADAs, and presence of anti-polyethylene glycol (PEG) antibodies (positive/negative) will also be evaluated in serum. Below are some important definitions needed for ADA analysis.

Treatment induced ADAs: ADAs developed de novo (seroconversion) following administration of the biotherapeutic (i.e., formation of ADAs any time after the initial drug administration in a subject without pre-existing ADAs). If the baseline ADA sample is missing or non-reportable and at least one reportable ADA sample is available during the treatment (including follow-up period) the baseline sample will be considered as "negative" for data analysis. This is considered being a conservative approach for ADA assessment.

Treatment boosted ADA: Pre-existing ADAs that were boosted to a higher level following administration of efpeglenatide (i.e., any time after the initial drug administration) the ADA titer is significantly higher than the baseline titer.

2.2 DISPOSITION OF PATIENTS

This section describes patient disposition for both patient study status and the patient analysis populations.

Screened patients are defined as any patients who signed the informed consent.

Randomized patients consist of all patients with a signed informed consent form who have had a treatment kit number allocated and recorded in the IRT database, regardless of whether the treatment kit was used.

For patient study status, the total number of patients in each of the following categories will be presented in the clinical study report using a flowchart diagram or summary table:

- Screened patients
- Screen failure patients and reasons for screen failure
- Nonrandomized but treated patients, if any
- Randomized patients
- Randomized but not treated patients
- Randomized and treated patients
- Patients who did not complete the treatment as per protocol (i.e. those not completed treatment and their main reason for premature end of treatment is not death per 'treatment status' eCRF)

[redacted]

- Patients who discontinued the treatment by main reason for permanent treatment discontinuation (Note: patients who died while on treatment will be considered as completed treatment)
- Patients who completed the study per protocol (i.e. subject status is death or completed on the 'Completion of end of study' eCRF form)
- Patients who did not complete the study per protocol and the reasons for study discontinuation
- Patient vital status at last study contact (alive, dead)
- Patient vital status at planned study close out visit (alive, dead, unknown)

For all categories of patients (except for the screened, screen failure and nonrandomized but treated categories) percentages will be calculated using the number of randomized patients within each treatment group as the denominator. Reasons for treatment discontinuation will be supplied in tables giving numbers and percentages by treatment group. Patients who prematurely and permanently discontinue from treatment and/or study for other reasons will also be listed. A summary of screened, screen failed, randomized, discontinued treatment and study will also be provided by region, country and site.

Number (%) of patients who prematurely discontinued the study will further be summarized according to whether or not the patients had either primary efficacy endpoint confirmed by the CEC prior to study discontinuation.

Kaplan-Meier (KM) plots/estimates of the cumulative incidence of prematurely permanent treatment discontinuation due to any reason (note: deaths on treatment will be considered completers), or due to AE will be provided on the randomized population. Randomized not treated patients will be considered as a treatment discontinuation at Day 1 (day of randomization). All treatment completers, including patients who died while on-treatment, will be considered as right-censored at last IMP administration date (death date will be used for patients who died while on-treatment when the last IMP date is incomplete or missing).

The duration of study participation will be summarized using mean, SD, median, minimum and maximum. Study duration (days) is defined as date of study completion/ study discontinuation/death date – date of randomization + 1.

All critical or major deviations will be summarized in tables giving numbers and percentages of patients with deviations by treatment group in ITT population, including the critical or major protocol deviations due to COVID-19 impact. Listing of participants with at least one critical or major deviation (including deviation due to COVID-19) will be provided.

Additionally, the following analysis populations will be summarized by treatment group.

- Randomized population
- Efficacy population: intent-to-treat (ITT) population
- Safety population
- ADA population

[redacted]

2.2.1 Randomization and drug dispensing irregularities

Randomization and drug-dispensing irregularities occur whenever:

1. A randomization is not in accordance with the protocol-defined randomization method, such as a) an ineligible patient is randomized, b) a patient is randomized based on an incorrect stratum, or c) a patient is randomized twice.

   OR

2. A patient is dispensed an IMP kit not allocated by the protocol-defined randomization, such as a) a patient at any time in the study is dispensed a different treatment kit than as randomized (which may or may not contain the correct-as-randomized IMP), or b) a nonrandomized patient is treated with IMP reserved for randomized patients.

Randomization and drug-dispensing irregularities will be monitored throughout the study and reviewed on an ongoing basis.

All randomization and drug-dispensing irregularities will be documented in the clinical study report. If the number of irregularities is large enough to make a tabular summary useful, the irregularities will be categorized and summarized among randomized patients (number and percentages). Nonrandomized, treated patients will be described separately.

2.2.2 Analysis populations

The randomized population includes any patient who has been allocated to a randomized treatment regardless of whether the treatment kit was used.

For any patient randomized more than once, only the data associated with the first randomization will be used in any analysis population. The safety experience associated with any later randomization will be assessed separately.

Patients treated without being randomized will not be considered randomized and will not be included in any efficacy population. The safety experience of patients treated and not randomized will be reported separately, and these patients will not be in the safety population.

2.2.3 Efficacy populations

The efficacy analysis population will be the ITT population.

2.2.3.1 Intent–to-treat population

The ITT Population is defined as:

- All randomized participants irrespective of compliance with the study protocol and procedures. Participants will be analyzed according to the treatment group allocated by randomization.

[redacted]

2.2.4 Safety population

The Safety Population is defined as:

- All randomized participants who have received at least 1 dose of double-blind treatment, regardless of the amount of treatment administered. Participants will be analyzed according to the treatment actually received.

In addition:

- Nonrandomized but treated patients will not be part of the safety population; however, their safety data will be presented separately.
- For participants receiving 1 or more injections of efpeglenatide during the trial, regardless of being assigned to the efpeglenatide groups or not, the treatment group allocation for as-treated analysis will be included in the efpeglenatide dose group that they are exposed for longer duration (by counting the number of kits received). In case of tie, highest dose group will be used.
- Participants, who prematurely and permanently discontinued study treatment during the titration phase will be summarized in their planned treatment group for as-treated analysis.
- Randomized patients for whom it is unclear whether they took the IMP will be included in the safety population in their planned treatment group.
- Randomized patients will be excluded from the safety population only if there is documented evidence (i.e., all study dates recorded as no medication taken) that patients have not taken the study treatment. If a patient is dispensed double-blind IMP and is lost to follow-up without any documented evidence, the patient will be considered exposed.

2.2.5 ADA population

ADA population is defined as:

- All participants from the safety population with at least 1 post-baseline valid ADA sample after study treatment (efpeglenatide) administration.

2.3 STATISTICAL METHODS

Continuous data will be summarized using the number of available data, mean, standard deviation (SD), median, minimum, and maximum for each treatment group. Categorical and ordinal data will be summarized using the number and percentage of patients in each treatment group.

Unless otherwise specified, all descriptive summary will be by treatment groups (4 mg efpeglenatide, 6 mg efpeglenatide, pooled 4 mg+6 mg efpeglenatide, placebo, and all (if needed)). Only pooled efpeglenatide treatment group (4 mg + 6 mg efpeglenatide) will be compared with placebo for formal statistical hypothesis testing.

[redacted]

2.3.1 Demographics and baseline characteristics

Parameters will be summarized on the randomized population analyzed in the treatment group to which they were randomized.

Parameters described in Section 2.1.1 will be summarized by treatment group and overall treatment groups using descriptive statistics.

All reported medical and surgical history will be presented by primary SOC and HLT. The tables will be sorted by SOC internationally agreed order and decreasing frequency of HLT based on the overall incidence across treatment groups.

In addition, medical history of specific interest (cancer [any], fracture [any], hypo or hyper thyroidism, thyroidectomy, cholelithiasis, cholecystectomy, diabetic nephropathy, TIA [transient ischemic attack], atrial fibrillation, hypertension, heart failure, hyperlipidemia, cardiovascular disease history and CV risk factors, retinopathy history) will be presented by treatment group..

P-values on demographic and baseline characteristic data will not be calculated.

2.3.2 Prior or concomitant medications

The prior and concomitant medications as described in Section 2.1.1 will be presented for the randomized population.

Medications will be summarized by treatment group according to the WHO-DD dictionary, considering the first digit of the anatomic category (ATC) class (anatomic category) and the first 3 digits of the ATC class (therapeutic category). All ATC codes corresponding to a medication will be summarized, and participants will be counted once in each ATC category (anatomic or therapeutic) linked to the medication. Therefore, participants may be counted several times for the same medication.

The table for prior medications will be sorted by decreasing frequency of ATC followed by all other therapeutic classes based on the overall incidence across treatment groups. In case of equal frequency regarding ATCs (anatomic or therapeutic categories), alphabetical order will be used.

The tables for concomitant and posttreatment medications will be sorted by decreasing frequency of ATC followed by all other therapeutic classes based on the incidence in the efpeglenatide group (pooled 4 mg + 6 mg groups). In case of equal frequency regarding ATCs (anatomic or therapeutic categories), alphabetical order will be used.

These prior and concomitant medications will be summarized using ATC code by therapeutic subgroup (2nd ATC level), pharmacological subgroup (3rd ATC level) and chemical subgroup (4th ATC level). Patients will be counted once in each ATC level linked to the medication; therefore patients may be counted several times for the same medication. The numbers and percentages of patients in each level will be presented by treatment group.

[redacted]

Medications will also be summarized by special interest, i.e., glucose lowering medication, antihypertensive medication, anti-platelet, and statins by treatment group.

In addition, the following summaries will also be provided:

- Number (%) of patients taking SGLT2 at baseline (yes, no) by randomization strata of SGLT2 use.
- Number (%) of patients taking SGLT2 during the study (yes, no) by randomization strata of SGLT2 use.
- Number (%) of patients taking metformin + SGLT2 at both baseline and during the study
- Number (%) of patients taking metformin + sulfonylurea at both baseline and during the study

2.3.3 Extent of investigational medicinal product exposure

The extent of IMP exposure will be assessed and summarized by actual treatment within the safety population (See Section 2.3.2).

2.3.3.1 Extent of investigational medicinal product exposure

The extent of IMP exposure will be assessed in the safety population by duration of IMP exposure and by category.

Duration of IMP exposure is defined as last dose date – first dose date + 7 day, regardless of unplanned intermittent discontinuations (see Section 2.5.3 calculation in case of missing or incomplete data).

Duration of IMP exposure will be summarized descriptively as a quantitative variable (number, mean, SD, median, minimum, and maximum). In addition, duration of treatment exposure will also be summarized by numbers and percentages for each category and cumulatively. Following are the categories of exposure-range (in months): <3 months, >3 to 6 months, >6 to 12 months, >12 to 18 months, >18 to 24 months, > 24 to 36 months, > 36 months.

Additionally, the cumulative duration of treatment exposure will be provided, defined as the sum of the duration of treatment exposure for all patients, and will be expressed in patient years.

Percentage of injection taken will be summarized, calculated as (total number of planned injections – number of missed injections)/total number of planned injections*100 during treatment period.

2.3.4 Analyses of efficacy endpoints

Unless otherwise specified, all efficacy analyses will be performed on the ITT population and will include all efficacy endpoint events positively adjudicated by the CEC, and as reported by investigator for renal events, occurring on or after randomization up to the scheduled last study

[redacted]

visit, inclusive, even after the patient has prematurely and permanently discontinued the study treatment. For details of what efficacy events will be included, please refer to Section 2.1.3.

2.3.4.1 Analysis of primary efficacy endpoint(s)

2.3.4.1.1 Statistical Hypotheses

The statistical hypothesis for the primary endpoint of 3-point MACE is to test that efpeglenatide is noninferior (1.8 and 1.3 margin) to placebo at the two-sided 5% alpha level:

- H0: Hazard ratio of efpeglenatide (pooled 4mg and 6mg groups) versus placebo ≥1.8 vs. Ha: Hazard ratio of efpeglenatide versus placebo <1.8

and

- H0: Hazard ratio of efpeglenatide (pooled 4mg and 6mg groups) versus placebo ≥1.3 vs. Ha: Hazard ratio of efpeglenatide versus placebo <1.3

The time to the first occurrence of the composite 3-point MACE endpoint (CV death, non-fatal MI, non-fatal stroke) will be analyzed using a Cox proportional hazards model with treatment (efpeglenatide 4 mg, efpeglenatide 6 mg, placebo), region (Norther America, Latin America, Europe, other), and randomization stratum of use of an SGLT2 inhibitor (current use, potential future use, neither current nor potential future use) as the factors. The analyses will be performed by including only events positively adjudicated by the CEC. Participants who receive either 4 mg or 6 mg of efpeglenatide will be combined as one efpeglenatide treatment group when making comparisons using appropriate contrast for the purposes of the primary analysis. The hazard ratio between pooled efpeglenatide and placebo will be estimated along with the associated 2-sided 95% CI. The NI with the 1.8 and 1.3 margin will be demonstrated on the primary endpoint if the upper bound of the 2-sided 95% CI is less than 1.8 and 1.3, respectively.

The time to event will be calculated as date of event as determined by the CEC (or date of censoring) – randomization date +1.

2.3.4.1.2 Censoring rule

Patients will be right-censored at the last date with information available on the CV outcomes if they have not experienced any positively-adjudicated component of the primary composite CV events on or before their end of study visit. Specifically, the censoring date is defined as follows:

- Patients who completed the study will be censored at their scheduled last study visit date (study close-out visit date or final follow-up visit date)
- Patients who died before completing or discontinuing the study (ie, death reported on the Completion of End of Study form) will be censored at their date of non-CV death

[redacted]

- Patients who discontinued the study will be censored at their later of study discontinuation date or latest date with cardiovascular efficacy endpoint information (MI/UA, heart failure, cerebrovascular event, admission to hospital/emergency room, coronary procedure, or cardiac biomarkers as collected in eCRF) collected. For more details of censoring rule, please refer to Appendix C.

Kaplan-Meier curves of the cumulative incidence rate will be provided by treatment groups over on-study efficacy period (from randomization to end of study date). The incidence rate per 100 patient-years (calculated by 100 * number of patients with events / sum of time at risk (days) over all patients/365.25) will be reported. For patients with an event, patient-year is time from randomization to first event; for patient without any event, patient-year is from randomization to censoring date.

Underlying assumptions of the Cox proportional hazards model will be checked by visual inspection of the Kaplan-Meier plots (log(-log(survival) vs log(survival time)).

Individual components of the primary endpoints will be analyzed using the same Cox proportional hazards model described above. Censoring rules described above will be used, and for components other than CV death, patients who died before completing or discontinuing the study will be censored at date of death (i.e. CV or non-CV death). See Appendix C for specific censoring rules.

2.3.4.1.3 Sensitivity analysis

- The primary analysis of the primary endpoint will be repeated by censoring the events at the time a participant starts treatment with a SGLT2 inhibitor (for participants who were not receiving a SGLT2 inhibitor at baseline) or stops treatment with a SGLT2 inhibitor (for participants who were already receiving an SGLT2 inhibitor at baseline).
- The primary analysis of the primary endpoint will be repeated using the ITT analysis set, by excluding deaths adjudicated as ‘undetermined cause of death’ by the CEC.
- The primary analysis of the primary endpoint will be repeated by including only events from randomization to last IMP administration date + 30 days or patient’s last study visit date, whichever is earlier. For patient not having a primary endpoint during this period, the patient will be right-censored at the earlier date of last IMP administration date + 30 days, and patient’s censoring date defined above.
- If discrepancy in stratum assignment between IRT and eCRF occurred in more than 5% of patients, the primary analysis will be repeated using the actual use of SGLT2 inhibitor at baseline (yes, no).

Assessment of missing data

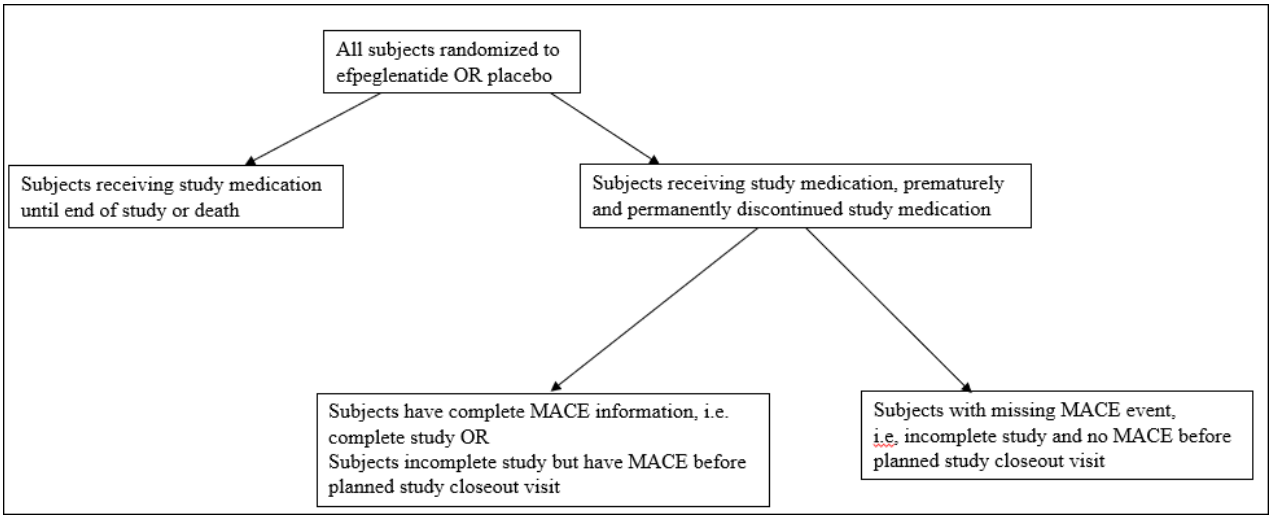
For patients who discontinued study but no MACE event was positively adjudicated by scheduled study closeout visit, the missing data are events that may occur after a patient is censored (the later of the patient’s study discontinuation date and the last date they have information on CV efficacy endpoint for patients who discontinued the study).

[redacted]

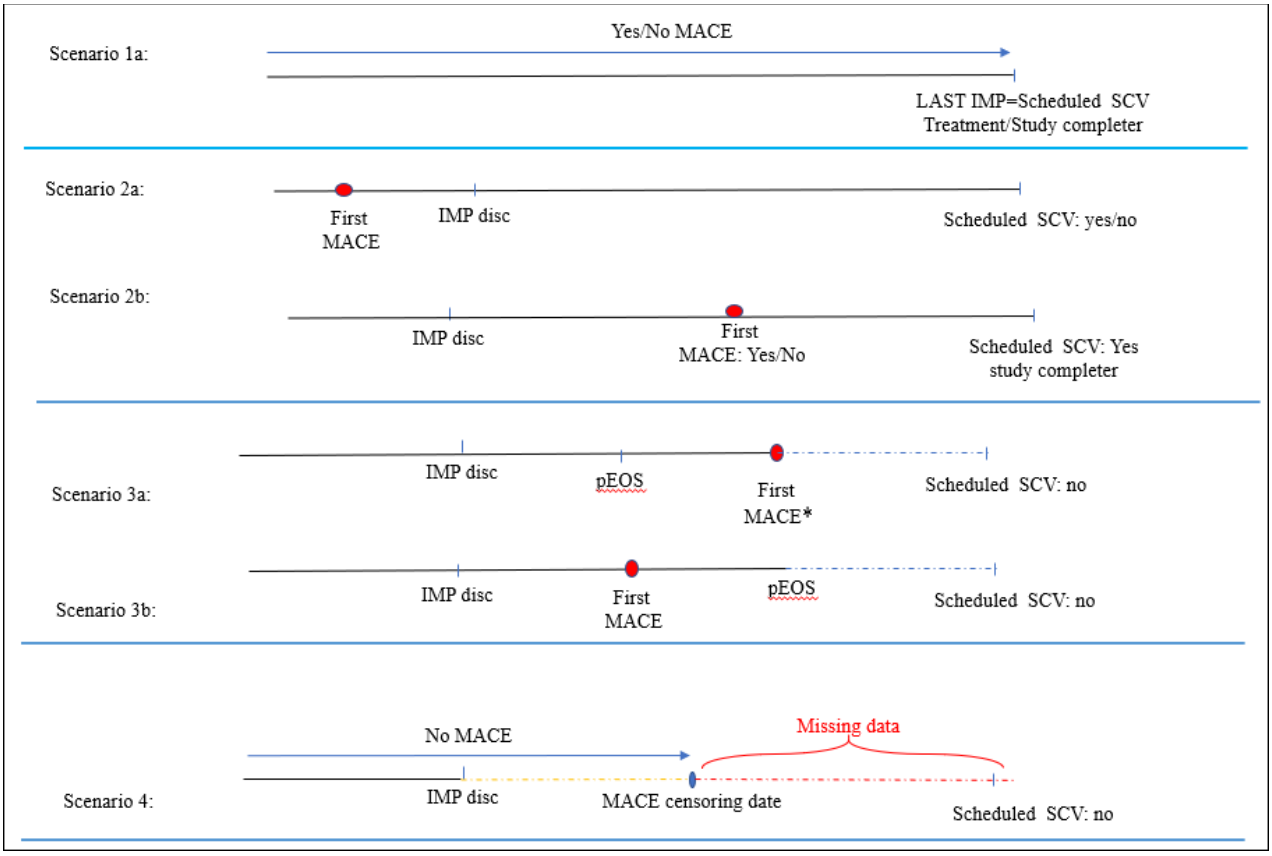
Reasons for censoring (including non-CV death, completed study, and study discontinuation reasons) will be summarized. For patients who discontinued the study, the time from censoring date to planned study close-out visit date will be summarized to show the magnitude of missing information.

Subjects prematurely and permanently discontinuing IMP, for other reason than death, prior to study end could have a different event and hazard rate from those who stay on IMP 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 primary MACE endpoints, see figure below.

Diagram showing subjects divided into subgroups related to missing information about MACE.



Subjects with information related to the MACE endpoint events (either discontinued study but have MACE prior to scheduled study closeout visit, or completed the study) will be used to impute data in subjects without MACE endpoints (discontinued study and no MACE event reported through third party data by scheduled study closeout visit). Subjects who developed MACE prior to the IMP discontinuation are included for imputation and their time to MACE data will be used for the imputation modeling. With these subjects included, the model estimate of hazard should fully reflect the potential hazard of the subjects with missing outcome. More specifically, subjects from below scenarios 2 and 3 will be used to impute the missing data of scenario 4 of the same treatment arm:



Note:

1. SCV: study close-out visit;

2. MACE censoring date of scenario 4 is the later of study discontinuation date or latest date with CV event information collected

The following supportive analyses will be performed to evaluate how the primary efficacy results could be influenced by different assumptions about the missing data. In particular, a 4-step approach will be used:

- Step 1: For each arm, the hazard rate after treatment discontinuation will be generated from the posterior distribution of the parameters in the exponential survival function in subjects who have discontinued treatment but either have MACE event prior to scheduled study closeout visit or have completed study.

  Note: the Kaplan-Meier curve based on observed pooled data is nearly a straight line, so constant hazard rate is assumed. So exponential survival function is used for hazard rate for each arm.

- Step 2: The missing event date of scenario 4 will be imputed multiple times by the samples of the hazard rate generated in Step 1. The imputed event date will be censored by the planned study close-out visit date if the imputed event date is after the study close out visit date.

[redacted]

- Step 3: In each imputation, the imputed dataset will be analyzed by the same Cox proportional hazards model as the primary analysis.
- Step 4: The results of the above analyses will be combined using Rubin's formula

- A tipping point analysis will be performed, where time to events will be imputed by using the same multiple imputation method as described above (step 1-4) and vary the hazard rates for subjects not complete study and have missing MACE event. The goal of the analysis is to find the scenarios where the result from the primary endpoints analyses will be "tipped", i.e., the conclusion of non-inferiority will change. More specifically, a grid-search with hazard rates for the efpeglenatide group increased by an increment (e.g. 1, 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, …) will be implemented to explore the plausibility of missing data assumptions. A proper range of the hazard rates will be searched to estimate the point where the upper bound of 95% CI for the hazard ratio exceeds 1.3, and 1.8 respectively, when the corresponding comparison fails to declare statistical significance for non-inferiority.

SAS pseudo-codes is provided in Appendix D.

2.3.4.1.4 Subgroup Analysis

Subgroup analyses will be conducted for the primary endpoint for the following factors:

Key subgroup analyses:

- Age (< median age value, ≥ median age value)
- Sex (male, female)
- Race (White, Black or African American, Asian, and Other (American Indian or Alaska native + Not reported + Unknown + multiple).
- Region (North America, Latin America, Europe, other)
- Use of SGLT2 at baseline (Yes, No)
- Baseline BMI categories (<median BMI value, ≥ median BMI value)
- Duration of diabetes (< 10, ≥10 years)
- Baseline HbA1c categories (<8%, ≥8%)
- Baseline eGFR categories (<median eGFR value, ≥ median eGFR value)
- Baseline metformin use (Yes, No)
- History of CV disease (CVD) (yes, no)

Other subgroup analyses:

- Age (<65, ≥65 and <75, ≥75 years)
- Randomization strata of SGLT2 use (Current use, Potential future use, Neither current nor potential future use)
- Baseline BMI categories (<30, ≥30 to <40, ≥40 kg/m^2)

[redacted]

- Ethnicity (Hispanic, not Hispanic)
- Baseline eGFR categories (< 30 mL/min/1.73m^2, 30 to <60 mL/min/1.73m^2, 60 to <90 mL/min/1.73m^2, ≥90 mL/min/1.73m^2)

Each of these factors will be analyzed statistically using a Cox proportional hazard model including the effects of the primary analysis model and effects for subgroup and subgroup-by-treatment interaction. The incidence rate, estimated hazard ratios between pooled efpeglenatide and placebo, and associated 95% confidence intervals will be calculated within each of the subgroups generated by these analyses. Subgroup by treatment interaction p-values will be reported, and results will be plotted using forest plot.

2.3.4.2 Analyses of secondary efficacy endpoints

If the NI with the 1.8 and 1.3 margin is demonstrated on the primary endpoint, the superiority of pooled efpeglenatide vs placebo for the primary endpoint will be tested in a hierarchical order. The superiority will be claimed if the UB of the 2-sided 95% CI of hazard ratio is less than 1. The nominal p-value using the log-rank test (stratified by randomization stratum of use of an SGLT2 inhibitor) will also be calculated.

The secondary time to event endpoints will be analyzed using the same Cox proportional hazards model as used for the analysis of primary endpoint described above. The analyses will be performed by including events positively adjudicated by the CEC for cardiac events, and events as reported by investigator for renal events. The hazard ratios between pooled efpeglenatide and placebo will be estimated along with the associated 2-sided 95% CIs. See Appendix C for the censoring rule.

Kaplan-Meier curves of the cumulative incidence rates will be provided by treatment groups. The incidence rate per 100 patient-years will be reported. The p-value using the log-rank test (stratified by randomization stratum of use of an SGLT2 inhibitor) will also be calculated.

Individual components of the secondary endpoints will be analyzed using the same Cox proportional hazards model described above.

In addition, the total number of events sent for adjudication and positively adjudicated will be summarized as well as the concordance rate between investigator opinion and adjudication by the CEC for each cardiac event type.

2.3.4.3 Exploratory efficacy analyses

Time to event endpoints will be analyzed using the same model described for the secondary primary endpoints.

For continuous efficacy endpoints, summary statistics at scheduled visits using observed data will be provided for each treatment group. The summary will include the number of observations, mean, SD, SE, minimum, median, and maximum. Graphical presentations will be used to examine trends over time using mean values (±SE) and mean changes from baseline (±SE) at each scheduled visit.

In addition, Kaplan-Meier plot of time to initiation of SGLT2 use will be provided. See Section 2.5.3 for handling missing medication dates. Patients on SGLT2 at baseline will be censored at randomization. Patients who never start SGLT2 will be censored at the patients of end of study date (refer to Section 2.1.4).

2.3.4.4 Multiplicity issues

A hierarchical testing procedure will be used to strongly control the overall Type-1 error rate at 2-sided 0.05 (0.025 for 1-sided).

The primary hypotheses will be tested first with below fixed sequence, each at alpha=0.05 (2-sided) level:

1. Non-inferiority of efpeglenatide (pooled 4 mg + 6 mg) versus placebo on 3-point MACE with NI=1.8
2. Non-inferiority of efpeglenatide (pooled 4 mg + 6 mg) versus placebo on 3-point MACE with NI=1.3

If the hypotheses above are statistical significant, the secondary hypotheses will be tested in below fixed sequence with each testing at significance level of 0.05 (2-sided) to continue to control the overall family-wise error rate at 0.05 (2-sided):

- Superiority for 3-point MACE
- Superiority for expanded MACE
- Superiority for the new or worsening nephropathy

Inferential conclusions about successive secondary hypotheses require statistical significance of the prior one. No further multiplicity adjustments will be made for other efficacy endpoints or subgroup analyses for which nominal p-values may be provided for descriptive purpose only.

2.3.5 Analyses of safety data

The summary of safety results will be presented by treatment group. All safety analyses will be performed on the safety population. The AE analysis will exclude the CV events reported and final diagnosed as CV events by investigator and also positively adjudicated as CV events by CEC.

In addition to the on-treatment period, all AEs, SAEs, AEs leading to permanent treatment discontinuation, and AEs leading to death will be summarized for the on-study period as defined in Section 2.1.4.

[redacted]

General common rules

All safety analyses will be performed on the safety population as defined in Section 2.2.4, unless otherwise specified, using the following common rules:

- Safety data in patients who do not belong to the safety population (e.g., exposed but not randomized) will be listed separately
- For WBC and differential counts, the baseline is defined as the last available value before the first injection of IMP where no differential component is missing.
- The potentially clinically significant abnormality (PCSA) values are defined as abnormal values considered medically important by the Sponsor according to predefined criteria/thresholds based on literature review and defined by the Sponsor for clinical laboratory tests, vital signs, and ECG (PCSA version dated May 2014 [Appendix A])
- PCSA criteria will determine which patients had at least 1 PCSA during the on-treatment period, taking into account all evaluations performed during the on-treatment period, including unscheduled or repeated evaluations. The number of all such patients will be the numerator for the on-treatment PCSA percentage
- The treatment-emergent PCSA denominator by group for a given parameter will be based on the number of patients assessed for that given parameter during the on-treatment period by treatment group in the safety population.
- For laboratory and vital sign parameters defined as efficacy endpoints, descriptive statistics and graphs will be provided in the efficacy section only, and PCSAs summaries will be provided in the safety section.
- For quantitative safety parameters based on central laboratory/reading measurements, descriptive statistics will be used to summarize results and change from baseline values by visit and treatment group. Summaries will include the last on-treatment value. The last on-treatment value is defined as the value collected on the same day/time of the last injection of IMP. If this value is missing, this last on-treatment value will be the closest value prior to the last injection of IMP.
- The analysis of the safety variables will be essentially descriptive, and no statistical hypothesis testing is planned.

2.3.5.1 Analyses of adverse events

Generalities

The primary focus of AE reporting will be on TEAEs. Pretreatment and posttreatment adverse events will be described separately.

If an adverse event date/time of onset (occurrence, worsening, or becoming serious) is incomplete, an imputation algorithm will be used to classify the adverse event as pretreatment, treatment-emergent, or posttreatment. The algorithm for imputing date/time of onset will be conservative and will classify an adverse event as treatment emergent unless there is definitive information to

[redacted]

determine it is pretreatment or posttreatment. Details on classification of adverse events with missing or partial onset dates are provided in Section 2.5.3.

Adverse event incidence tables will present by SOC and PT, sorted in alphabetical order for each treatment group, the number (n) and percentage (%) of patients experiencing an adverse event. Multiple occurrences of the same event in the same patient will be counted only once in the tables within a treatment phase. The denominator for computation of percentages is the safety population within each treatment group.

Sorting within tables ensures the same presentation for the set of all adverse events within the observation period (pretreatment, treatment-emergent, and posttreatment). For that purpose, the table of all TEAEs presented by SOC and PT sorted by the internationally agreed SOC order and decreasing frequency of PTs within SOCs will define the presentation order for all other tables unless otherwise specified. Sorting will be based on incidence in the pooled efpeglenatide group.

Analysis of all TEAEs

The following TEAE summaries will be generated for the safety population.

- Overview of TEAEs, summarizing number (%) of patients with any
  - TEAE
  - Serious TEAE
  - TEAE leading to permanent treatment discontinuation
  - TEAE leading to death
  - Serious TEAE leading to permanent treatment discontinuation
- All TEAEs by primary SOC and PT, sorted by the internationally agreed SOC order and by decreasing incidence of PTs within each SOC. This sorting order will be applied to all other tables by SOC and PT, unless otherwise specified.
- All TEAEs related to IMP by primary SOC, and PT
- All TEAEs by maximal severity, presented by primary SOC and PT
- Common TEAEs (e.g., PTs ≥2% in any treatment group) by primary SOC, and PT
- Common TEAEs (e.g., PTs ≥5% in any treatment group) by primary SOC and PT and by intrinsic factors: age group (<50, ≥50 to <65, ≥65 to <75, ≥75 years), sex (Male, Female), race (White, Black or African American, Asian, Other), and any pertinent subgroups as appropriate.
- All TEAEs by primary SOC and PT and by subgroup BMI (<30, ≥ 30 to <40, ≥40 kg/m^2)
- All TEAE by primary SOC and PT and by anti-efpeglenatide antibody status (positive, negative)
- Kaplan-Meier plot, for the time to first onset of the following PTs: nausea, vomiting and diarrhea

[redacted]

- The frequency of TEAEs over time will be provided for nausea, vomiting and diarrhea, using 3-month time intervals, i.e., [0-3] month, (3-6] month, (6-9] month, (9-12] month, etc. In each time interval, the numerator in the calculation of percentages will be the number of participants with at least 1 TEAE occurring in this time interval. Two types of analyses will be included:
  - (1) only the first event will be counted for each participant and all recurrent events will not be included, and the denominator for the calculation of percentages will be the number of participants at risk at the beginning of the time interval who did not experience a first event in the preceding intervals;
  - (2) the recurrent events in subsequent intervals will be counted once for each participant in the numerator of the corresponding interval, and the denominator for the calculation of percentages will be the number of participants at risk at the beginning of the time interval.

    A histogram of the frequency over time (by 3-month intervals) will also be presented as appropriate.

Analysis of all treatment emergent SAEs

- All serious TEAEs by primary SOC and PT
- All serious TEAEs related to IMP by primary SOC and PT

Analysis of all TEAEs leading to permanent treatment discontinuation

- All TEAEs leading to permanent treatment discontinuation by primary SOC, HLGT, HLT, and PT
- All TEAEs leading to permanent treatment discontinuation by primary SOC and PT

Analysis of on-study AEs

- All the analyses in above categories, including AEs, SAEs, AEs leading to permanent treatment discontinuation, and AEs leading to death will be summarized for the on-study period by SOC and PT.

Analyses of events of special interest and events requiring specific monitoring

Unless otherwise specified, AESI and AERSM will be summarized during the TEAE period by prespecified- grouping (AE category of interest) and PT, showing the number (%) of participants, sorted by decreasing frequency of PT.

Severe hypoglycemia

The severe hypoglycemia will be analyzed on TEAE period.

The following analysis will be provided for severe hypoglycemia:

- Number (%) of patients with at least one severe hypoglycemia
- Number of events per 100 patient-years of total IMP exposure.

[redacted]

Pancreatic events

The Pancreatic events will be reviewed, assessed and/or adjudicated by CEC.

The following analysis will be provided for positively adjudicated events during the TEAE period:

- The number (%) of patients with at least one positively adjudicated pancreatitis by type: 1) acute pancreatitis, 2) acute on chronic pancreatitis, 3) chronic pancreatitis, 4) unknown pancreatitis;
- The number (%) of patients with at least one positively adjudicated pancreatic neoplasm by type: 1) malignant - confirmed, 2) Malignant - probable, 3) Benign.

Analysis of pretreatment and posttreatment adverse events

- All pretreatment AEs by primary SOC and PT, showing the number (%) of patients with at least 1 pretreatment adverse event
- All posttreatment AEs by primary SOC and PT, showing the number (%) of patients with at least 1 posttreatment adverse event
- All posttreatment SAEs by primary SOC and PT, showing the number (%) of patients with at least 1 posttreatment serious adverse event

Listing

Supporting AE listings will be provided for SAEs, AESIs, deaths, severe hypoglycemia, pancreatic events and AEs leading to treatment discontinuation and/or death.

These listing sorted by treatment, participant identification, onset date, will include the following information: treatment, participant identification, country, age, gender, race, BMI, primary SOC, PT, reported term, onset date, study day (relative day to the start date of IMP), AE duration, duration of exposure, intensity, corrective treatment, action taken with IMP, date of treatment discontinuation (if relevant), relationship to IMP/NIMP/study procedures, outcome, date of death if any, seriousness, seriousness criteria, and AE status.

Similar to AE listing, listing for all adjudicated AEs will be provided plus adjudication outcome.

2.3.5.2 Deaths

The following summaries of deaths will be generated for the safety population.

- Number (%) of patients who died by study period (on-study, on-treatment, post-study)
- Deaths in nonrandomized patients or randomized but not treated patients
- Primary cause of death as adjudicated by CEC (by 3 major categories of causes [i.e., cardiovascular, non-cardiovascular, and undetermined], and by additional subcategories per CEC charter).
- Primary cause of death as reported by the investigator.

[redacted]

- Treatment-emergent adverse events leading to death (death as an outcome on the adverse event case report form page as reported by the Investigator) by primary SOC and PT showing number (%) of patients sorted by internationally agreed SOC order, with PT presented in alphabetical order within each SOC.
- TEAEs leading to death (death as an outcome on the adverse event case report form page as reported by the Investigator) by primary SOC and PT
- Number (%) of patients with AEs leading to death by primary SOC and PT during the on-study period

2.3.5.3 Analyses of laboratory variables

This section will be organized by biological function as specified in Section 2.1.4.3.

The summary statistics (including number, mean, median, standard deviation, minimum and maximum) of all protocol-required laboratory variables (central laboratory values, changes from baseline and/or percent change from baseline [e.g., lipid parameters, albumin, total protein, hemoglobin, hematocrit]) will be calculated for each visit or study assessment (baseline, each post-baseline time point, last on-treatment value) by treatment group. For selected laboratory parameters (eg, ALT, AST, and ALP), descriptive statistics will also be summarized by upper limit of normal (ULN) values. Graphical presentations will be used to examine trends over time using mean (±SE) and/or mean change from baseline (±SE) at scheduled visits. Results will be presented in standard international unit.

The incidence of PCSAs (list provided in Appendix A) at any time during the treatment-emergent adverse event period will be summarized by biological function and treatment group whatever the baseline level and/or according to the following baseline status categories:

- Normal/missing
- Abnormal according to PCSA criterion or criteria

For parameters for which no PCSA criteria are defined, similar table(s) using the normal range will be provided as necessary. For calcitonin, no PCSA criterion is defined. Similar summaries will be provided using the pre-defined categories: ≤ULN, >ULN - 20 ng/L, ≥20 - <50 ng/L, and ≥50 ng/L (Note that ng/L is the standard international unit and is equivalent to pg/mL).

All measurements collected during the On-treatment period, including values from unscheduled visits, will be considered for the PCSA summaries. However, when several measurements are performed on the same date and at the same time for a given laboratory test, the central laboratory value will be selected over the local lab value. These summaries will include patients in the safety population who have at least 1 assessment performed during the On-treatment period. When a PCSA definition involves a change from baseline value, patients must also have a baseline value to be included in the summaries, and when required by the definition of the abnormality, patients must also have available laboratory normal ranges.

[redacted]

For some parameters, such as liver enzymes, the lower limit of normal (LLN) is not considered clinically relevant, and values below this limit are considered normal. When there are multiple PCSA criteria for a specific parameter (eg, ALT), the participant will be counted once during the On-treatment period for the specific parameter in question under the worst/maximum PCSA category.

Elevation of liver parameters will be summarized by treatment group in safety population.

For PCSA, both central and local lab data will be used, though centralized data will be used preferentially to the local measures in the analysis when several measurements are performed on the same date and at the same time for a given laboratory test.

A listing of patients with at least 1 on-treatment PCSA (or out of normal range when no PCSA criteria is defined) will be provided (except for mild and moderate eGFR decreases) and will display the entire patients' profile across time for all parameters belonging to the corresponding biological function. Individual data listings will include flags when applicable:

- Baseline values will be flagged "B".
- Normal laboratory ranges, available for most laboratory parameters, will be identified as ULN and LLN. Baseline, last on-treatment value, and individual data will be flagged "L" if the value is below the LLN and will be flagged "H" if it is above the ULN.
- Laboratory PCSA criteria will be used for the corresponding laboratory parameters. Values reaching a PCSA limit will be flagged (+, ++, -, or -- depending upon the direction and level of the abnormality). Flags for WBC and differential counts will be determined using data expressed in international units.

For parameters whose PCSA criteria are multiples of the ULN, the parameter's value will also be expressed as a multiple of the ULN in the individual data provided.

2.4.4.1 Analyses of vital sign variables

The summary statistics (including number, mean, median, standard deviation, minimum and maximum) of all vital sign variables (values and change from baseline) will be calculated for each scheduled visit (baseline, each post-baseline time point, last on-treatment value) by treatment group.

The incidence of PCSAs at any time during the On-treatment period will be summarized by treatment group irrespective of the baseline level and/or according to the following baseline status categories:

- Normal/missing
- Abnormal according to PCSA criterion or criteria

[redacted]

A listing of patients with at least 1 post-baseline PCSA will be provided and will display the patient's profile over time of all vital sign parameters. Individual data listings will include the following flags:

- Baseline values will be flagged "B",
- Parameter values reaching a PCSA limit will be flagged ('+' or '-' depending on the direction).

2.4.4.2 Analyses of electrocardiogram variables

The frequency and percentage of 12-lead ECG interpretation (normal, abnormal) will be provided at each scheduled visit by treatment group.

2.4.5 Analyses of immunogenicity variables

An anti-drug antibody positive participant is defined as a participant with at least one treatment-induced or treatment-boosted ADA-positive sample at any time.

Summaries of ADA data will be provided for participants treated with efpeglenatide only. All summaries related to kinetics of ADA response (ADA status and magnitude, ADA attributes, participant status, ADA incidence) will be descriptive; no statistical significance tests will be performed on ADA data. The incidence of ADA status (positive/negative/inconclusive) will be summarized by visit, treatment, and individual titer for the ADA population. Incidence of treatment induced and treatment-boosted (treatment emergent) ADA during on-study period will be summarized by treatment. Incidence of participants with ADA cross-reactivity to endogenous GLP-1 (positive/negative), and to endogenous glucagon (positive/negative) will be summarized by visit and treatment. Incidence of participants with ADA directed against PEG linker, HMC001 moiety and exendin-4 moiety (positive/negative), will be summarized by visit and treatment. Analysis will be conducted as appropriate to assess the relationship with hypersensitivity reactions.

Incidence of participants with neutralizing antibodies against efpeglenatide and against endogenous GLP-1 and Glucagon will be summarized by visit and treatment.

ADA data from unscheduled visits (due to SAE for example) will not be included in summary and will be presented only in ADA values listing.

2.4.6 Analyses of pharmacokinetic variables

Not applicable.

2.4.7 Analyses of quality of life/health economics variables

Not applicable.

[redacted]

2.5 DATA HANDLING CONVENTIONS

2.5.1 General conventions

The following formulas will be used for computation of parameters.

Demographic formulas

The participant's duration of diabetes (years) is calculated using the date of informed consent and the date of diabetes diagnosis.

If date of diabetes diagnosis is a complete date, then the duration of diabetes is (date of informed consent - date of diabetes diagnosis + 1) / 365.25. If date of diabetes diagnosis is a partial date:

a) year and month are not missing, but day is missing, then day = 01

b) year is not missing, but month and date are both missing, then month = January and day = 01.

Renal function formulas

The estimated GFR (mL/min/1.73 m^2) will be calculated using the 4 variable MDRD formula:

Standard unit: eGFR (mL/min/1.73 m^2) = 175 x [Serum Creatinine (µmol/L)/88.4]$^{-1.154}$ x Age (year)$^{-0.203}$ x 1.212 (if Black) x 0.742 (if female)

Conventional unit: eGFR (mL/min/1.73 m^2) = 175 x Serum Creatinine (mg/dL)$^{-1.154}$ x Age (year)$^{-0.203}$ x 1.212 (if Black) x 0.742 (if Female)

Laboratory safety variables

For data below the lower limit of quantification (LLOQ) / limit of linearity, half of the lower limit value (i.e., LLOQ/2) will be used for quantitative analyses. For data above the upper limit of quantification (ULOQ) / limit of linearity, the upper limit value plus a unit value based on the digit of the variable following the sponsor's standard convention (i.e., ULOQ+0.01 if the digit is 2 for the parameter) will be used for quantitative analyses. Note: this rule not applicable to UACR.

2.5.2 Data handling conventions for secondary efficacy variables

Rules defined for the primary efficacy variable will apply to time-to-event of secondary efficacy variables.

2.5.3 Missing data

For categorical variables, patients with missing data are not included in calculations of percentages unless otherwise specified. When relevant, the number of patients with missing data is presented.

[redacted]

Derived variables will be considered missing if any of the original variables required to calculate them are missing. For example, if either a baseline assessment or an endpoint assessment is missing for a particular patient, then change from baseline at endpoint will be missing. Depending upon the assessment, analyses may not include all patients in the analysis population, because certain patients in the intended population may have missing data.

Handling of computation of treatment duration if IMP end of treatment date is missing

For the calculation of the treatment duration, the date of the last dose of IMP is equal to the date of last administration reported on the end-of-treatment case report form page. If this date is missing or a partial date, the exposure duration should be left as missing.

Handling of medication missing/partial dates

In general, no imputation of medication start/end dates or times will be performed. If a medication date or time is missing or partially missing and it cannot be determined whether it was taken prior or concomitantly or at baseline, it will be considered a prior, concomitant, baseline, and post-treatment medication.

For partial start and stop dates for SGLT2 concomitant or post-treatment medications, the following imputation rules apply:

- If the day of the start date is missing the start date is set to 15th of the month
- If the day and month of the start date are missing, then the start date is set to 15th June of the year.

Handling of adverse events/hypoglycemia with missing or partial date/time of onset

Missing or partial AE/hypoglycemia onset dates and times will be imputed so that if the partial AE/hypoglycemia onset date/time information does not indicate that the AE/hypoglycemia started prior to treatment or after the TEAE period, the AE/hypoglycemia will be classified as treatment-emergent. No imputation of AE end dates/times will be performed. These data imputations are for categorization purpose only and will not be used in listings. No imputation is planned for date/time of AE resolution.

Handling of adverse events/hypoglycemia when date and time of first IMP administration is missing

When the date and time of the first IMP administration is missing, all AEs/hypoglycemia that occurred on or after the day of randomization should be considered as TEAEs. The exposure duration should be kept as missing.

Handling of adverse events/hypoglycemia when IMP end of treatment date is missing

For the purpose of defining TEAE period, the date of the last administration of double-blind IMP is equal to the date of the last administration reported on the e-CRF “Treatment Status” page.

[redacted]

If the date of last administration reported on the e-CRF "Treatment Status" page is

- Partially missing, it will be imputed with a date as late as possible before or on the date of death, if the end of treatment reason was death or study discontinuation date if available on the eCRF "Completion of End of Study" or study close-out visit date for patients who completed the study.
- Completely missing, it will be imputed with the date of death, if the end of treatment reason was death or study discontinuation date if available on the eCRF "Completion of End of Study" or study close-out visit date for patients who completed the study.

If the study discontinuation date on eCRF "Completion of End of Study" page is

- Partially missing, it will be imputed with a date as late as possible.
- Completely missing, all adverse events occurred on or after the first administration of double-blind IMP will be considered as treatment emergent adverse events.

Handling of missing assessment of relationship of adverse events to IMP

If the assessment of the relationship to IMP is missing, then the relationship to IMP has to be assumed and the adverse event considered as such in the frequency tables of possibly related adverse events, but no imputation should be done at the data level.

Handling of missing severity of adverse events

If the severity is missing for 1 of the treatment-emergent occurrences of an adverse event, the maximal severity on the remaining occurrences will be considered. If the severity is missing for all the occurrences, a "missing" category will be added in the summary table.

Handling of potentially clinically significant abnormalities

If a patient has a missing baseline he will be grouped in the category "normal/missing at baseline."

For PCSAs with 2 conditions, one based on a change from baseline value or a normal range and the other on a threshold value, with the first condition being missing, the PCSA will be based only on the second condition.

For a PCSA defined on a threshold and/or a normal range, this PCSA will be derived using this threshold if the normal range is missing; eg, for eosinophils the PCSA is > 0.5 GIGA/L or >ULN if ULN ≥0.5 GIGA/L. When ULN is missing, the value 0.5 should be used.

Measurements flagged as invalid by the laboratory will not be summarized or taken into account in the computation of PCSA values.

[redacted]

Linked adverse events that worsened or became serious

An AE that worsened or became serious will have a separate record in the data from the original event record with a reference identification number that links the new record to the original record. An AE that worsened or became serious will be considered a new recurring AE in the summary of recurrent events or in the summary of events by time intervals.

2.5.4 Windows for time points

Time windows will not be applied to visits. Nominal visits will be used for descriptive statistics.

Display of safety data by visit (laboratory variables and vital signs)

Descriptive statistics (N, mean, SD, minimum, median, maximum) of quantitative laboratory variables and vital signs (observed data and change from baseline) during the TEAE period for all scheduled visits as per protocol will be provided (i.e., only including participants having non-missing assessments at a nominal visit). Summaries showing data by visit will be presented according to the visit number and labeled with the targeted approximate month.

As specified in the study protocol, laboratory data from scheduled visits are reported by central laboratories. When both central and local laboratories report values from the same blood sample (ie, sample collected at the same date and time), only measurements from the central laboratory will be included in the analyses. When only local laboratory results are reported and central laboratory results are unavailable, the local results will not be used in the efficacy analyses. In the safety analyses, local results will only be used in the PCSA summary if they are accompanied by a local laboratory normal range.

When a participant has more than 1 measurement from the central laboratory for the same laboratory parameter on the same date, the average of the measurements will be used. For the same laboratory parameter, if a participant has more than one measurement on different dates for the same scheduled visit, the value closest to the scheduled visit will be used for the scheduled visit. When the values for the same scheduled visit are equidistant, the last value should be used for the scheduled visit.

2.5.5 Unscheduled visits

Unscheduled visit measurements of laboratory data, vital signs, and ECG will not be included in the by-visit summaries, but will be used for computation of baseline, last on-treatment value, and PCSAs.

2.5.6 Pooling of centers for statistical analyses

Center will not be included in the statistical models for efficacy analyses. However, all centers within a region will be pooled, and region will be included as a fixed factor in a parametric statistical model (e.g., Cox proportional hazards model, etc.) for primary and secondary efficacy endpoints.

2.5.7 Statistical technical issues

None.

[redacted]

3 INTERIM ANALYSIS

No interim analysis is planned.

[redacted]

4 DATABASE LOCK

The database is planned to be locked approximately 4 to 6 weeks after the last patient last visit.

[redacted]

5 SOFTWARE DOCUMENTATION

All summaries and statistical analyses will be performed by using SAS® version 9.4 or higher.

6 REFERENCES

Not applicable.

[redacted]

7 LIST OF APPENDICES

Appendix A: Potentially clinically significant abnormalities (PCSA) criteria

Appendix B: Summary of statistical analyses

Appendix C: Calculation/Derivation details of time-to-event efficacy/safety endpoints

Appendix D: Sample SAS® code for supportive analyses for missing data of primary efficacy endpoint

[redacted]

Appendix A Potentially clinically significant abnormalities criteria

CRITERIA for POTENTIALLY CLINICALLY SIGNIFICANT ABNORMALITIES
for phase 2/3 studies (oncology excepted)
(From 30 May 21, 2014)

Parameter	PCSA	Comments
Clinical Chemistry		
ALT	By distribution analysis: >3 ULN >5 ULN >10 ULN >20 ULN	Enzymes activities must be expressed in ULN, not in IU/L. Concept paper on DILI – FDA draft Guidance Oct 2007. Internal DILI WG Oct 2008. Categories are cumulative. First row is mandatory. Rows following one mentioning zero can be deleted.
AST	By distribution analysis: >3 ULN >5 ULN >10 ULN >20 ULN	Enzymes activities must be expressed in ULN, not in IU/L. Concept paper on DILI – FDA draft Guidance Oct 2007. Internal DILI WG Oct 2008. Categories are cumulative. First row is mandatory. Rows following one mentioning zero can be deleted.
Alkaline Phosphatase	>1.5 ULN	Enzymes activities must be expressed in ULN, not in IU/L. Concept paper on DILI – FDA draft Guidance Oct 2007. Internal DILI WG Oct 2008.
Total Bilirubin	>1.5 ULN >2 ULN	Must be expressed in ULN, not in µmol/L or mg/L. Categories are cumulative. Concept paper on DILI – FDA draft Guidance Oct 2007. Internal DILI WG Oct 2008.
Conjugated Bilirubin	>35% Total Bilirubin and TBILI>1.5 ULN	Conjugated bilirubin dosed on a case-by-case basis.
ALT and Total Bilirubin	ALT>3 ULN and TBILI>2 ULN	Concept paper on DILI – FDA draft Guidance Oct 2007. Internal DILI WG Oct 2008. To be counted within a same treatment phase, whatever the interval between measurements.
CPK	>3 ULN >10 ULN	FDA Feb 2005. Am J Cardiol April 2006. Categories are cumulative. First row is mandatory. Rows following one mentioning zero can be deleted.

[redacted]

CRITERIA for POTENTIALLY CLINICALLY SIGNIFICANT ABNORMALITIES
for phase 2/3 studies (oncology excepted)
(From 30 May 21, 2014)

Parameter	PCSA	Comments
CLcr (mL/min) (Estimated creatinine clearance based on the Cockcroft-Gault equation)	<15 (end stage renal disease) ≥15 - <30 (severe decrease in GFR) ≥30 - <60 (moderate decrease in GFR) ≥60 - <90 (mild decrease in GFR) ≥90 (normal GFR)	FDA draft Guidance 2010 Pharmacokinetics in patients with impaired renal function-study design, data analysis, and impact on dosing and labeling
eGFR (mL/min/1.73 m²) (Estimate of GFR based on an MDRD equation)	<15 (end stage renal disease) ≥15 - <30 (severe decrease in GFR) ≥30 - <60 (moderate decrease in GFR) ≥60 - <90 (mild decrease in GFR) ≥90 (normal GFR)	FDA draft Guidance 2010 Pharmacokinetics in patients with impaired renal function-study design, data analysis, and impact on dosing and labeling
Creatinine	≥150 µmol/L (Adults) ≥30% change from baseline ≥100% change from baseline	Benichou C., 1994.
Uric Acid Hyperuricemia Hypouricemia	 >408 µmol/L <120 µmol/L	Harrison- Principles of internal Medicine 17th Ed., 2008.
Blood Urea Nitrogen	≥17 mmol/L	
Chloride	<80 mmol/L >115 mmol/L	
Sodium	≤129 mmol/L ≥160 mmol/L	
Potassium	<3 mmol/L ≥5.5 mmol/L	FDA Feb 2005.
Total Cholesterol	≥7.74 mmol/L	Threshold for therapeutic intervention.
Triglycerides	≥4.6 mmol/L	Threshold for therapeutic intervention.
Lipasemia	≥3 ULN	
Amylasemia	≥3 ULN	
Glucose Hypoglycaemia Hyperglycaemia	 ≤3.9 mmol/L and <LLN ≥11.1 mmol/L (unfasted); ≥7 mmol/L (fasted)	 ADA May 2005. ADA Jan 2008.
HbA1c	>8%	
Albumin	≤25 g/L	
CRP	>2 ULN or >10 mg/L (if ULN not provided)	FDA Sept 2005.
Hematology		
WBC	<3.0 Giga/L (Non-Black); <2.0 Giga/L (Black) ≥16.0 Giga/L	Increase in WBC: not relevant. To be interpreted only if no differential count available.
Lymphocytes	>4.0 Giga/L	

[redacted]

CRITERIA for POTENTIALLY CLINICALLY SIGNIFICANT ABNORMALITIES
for phase 2/3 studies (oncology excepted)
(From 30 May 21, 2014)

Parameter	PCSA	Comments
Neutrophils	<1.5 Giga/L (Non-Black); <1.0 Giga/L (Black)	International Consensus meeting on drug-induced blood cytopenias, 1991. FDA criteria.
Monocytes	>0.7 Giga/L	
Basophils	>0.1 Giga/L	
Eosinophils	>0.5 Giga/L or >ULN (if ULN≥0.5 Giga/L)	Harrison- Principles of internal Medicine 17th Ed., 2008.
Hemoglobin	≤115 g/L (Male); ≤95 g/L (Female) ≥185 g/L (Male); ≥165 g/L (Female) Decrease from Baseline ≥20 g/L	Criteria based upon decrease from baseline are more relevant than based on absolute value. Other categories for decrease from baseline can be used (≥30 g/L, ≥40 g/L, ≥50 g/L).
Hematocrit	≤0.37 v/v (Male) ; ≤0.32 v/v (Female) ≥0.55 v/v (Male) ; ≥0.5 v/v (Female)	
RBC	≥6 Tera/L	Unless specifically required for particular drug development, the analysis is redundant with that of Hb. Otherwise, consider FDA criteria.
Platelets	<100 Giga/L ≥700 Giga/L	International Consensus meeting on drug-induced blood cytopenias, 1991.
Urinalysis		
pH	≤4.6 ≥8	
Vital signs		
HR	≤50 bpm and decrease from baseline ≥20 bpm ≥120 bpm and increase from baseline≥20 bpm	To be applied for all positions (including missing) except STANDING.
SBP	≤95 mmHg and decrease from baseline ≥20mmHg ≥160 mmHg and increase from baseline ≥20 mmHg	To be applied for all positions (including missing) except STANDING.
DBP	≤45 mmHg and decrease from baseline ≥10 mmHg ≥110 mmHg and increase from baseline ≥10 mmHg	To be applied for all positions (including missing) except STANDING.
Orthostatic Hypotension Orthostatic SDB Orthostatic DBP	 ≤-20 mmHg ≤-10 mmHg	
Weight	≥5% increase from baseline ≥5% decrease from baseline	FDA Feb 2007.
ECG		Ref.: ICH E14 guidance (2005) and E14 Q&A (2012), and Cardiac Safety Research Consortium White Paper on PR and QRS (Nada et al. Am Heart J. 2013; 165(4) : 489-500)

[redacted]

CRITERIA for POTENTIALLY CLINICALLY SIGNIFICANT ABNORMALITIES
for phase 2/3 studies (oncology excepted)
(From 30 May 21, 2014)

Parameter	PCSA	Comments
HR	<50 bpm	Categories are cumulative
	<50 bpm and decrease from baseline ≥20 bpm	
	<40 bpm	
	<40 bpm and decrease from baseline ≥20 bpm	
	<30 bpm	
	<30 bpm and decrease from baseline ≥20 bpm	
	>90 bpm	Categories are cumulative
	>90 bpm and increase from baseline ≥20 bpm	
	>100 bpm	
	>100 bpm and increase from baseline ≥20 bpm	
	>120 bpm	
	>120 bpm and increase from baseline ≥20 bpm	
PR	>200 ms	Categories are cumulative
	>200 ms and increase from baseline ≥25%	
	>220 ms	
	>220 ms and increase from baseline ≥25%	
	>240 ms	
	>240 ms and increase from baseline ≥25%	
QRS	>110 ms	Categories are cumulative
	>110 msec and increase from baseline ≥25%	
	>120 ms	
	>120 ms and increase from baseline ≥25%	
QT	>500 ms	
QTc	Absolute values (ms)	To be applied to any kind of QT correction formula.
	>450 ms	Absolute values categories are cumulative
	>480 ms	
	>500 ms	QTc >480 ms and ΔQTc>60 ms are the 2 PCSA categories to be identified in individual subjects/patients listings.
	Increase from baseline	
	Increase from baseline]30-60] ms	
	Increase from baseline >60 ms	

[redacted]

Appendix B Summary of statistical analyses

EFFICACY ANALYSIS

Endpoint	Analysis population	Primary analysis	Supportive analysis	Subgroup analysis	Other analyses
Primary endpoints					
Time to first occurrence of CV death, non-fatal MI, non-fatal stroke (non-inferiority)	*ITT*	*Cox proportional hazards model with treatment, region, and stratification as fixed effect factors*	*Yes sensitivity analyses (see Section 2.3.4.1.3)*	*Yes Subgroups: age, sex, race etc. (see Section 2.3.4.1.3)*	*No*
Secondary endpoints					
Time to first occurrence of CV death, non-fatal MI, non-fatal stroke (superiority)	*ITT*	*Cox proportional hazards model with treatment, region, and stratification as fixed effect factors*	*Same as primary endpoint*	*Above*	*No*
Time to first occurrence of CV death, non-fatal MI, non-fatal stroke, coronary revascularization, hospitalization for unstable angina	*ITT*	*Cox proportional hazards model with treatment, region, and stratification as fixed effect factors*	*No*	*No*	*No*
Time to first occurrence of New onset or progression to macro albuminuria (>300 mg/g) accompanied by a UACR value increase of ≥30% from Baseline, *Sustained ≥40% decrease in eGFR from Baseline (for ≥30 days), Chronic dialysis (for ≥90 days), Renal transplant, Sustained eGFR <15 mL/min/1.73 m2 (for ≥30 days)*	*ITT*	*Cox proportional hazards model with treatment, region, and stratification as fixed effect factors*	*No*	*No*	*No*
Exploratory endpoints					
Time to stroke or death	*ITT*	*Cox proportional hazards model with treatment, region, and stratification as fixed effect factors*	*No*	*No*	*No*
Time to Death	*ITT*	*Cox proportional hazards model with treatment, region, and stratification as fixed effect factors*	*No*	*No*	*No*
Time to stroke	*ITT*	*Cox proportional hazards model with*	*No*	*No*	*No*

Endpoint	Analysis population	Primary analysis	Supportive analysis	Subgroup analysis	Other analyses
		treatment, region, and stratification as fixed effect factors			
Time to CV Death	*ITT*	*Cox proportional hazards model with treatment, region, and stratification as fixed effect factors*	*No*	*No*	*No*
Time to MI	*ITT*	*Cox proportional hazards model with treatment, region, and stratification as fixed effect factors*	*No*	*No*	*No*

ITT= Intent-to-treat

SAFETY ANALYSES

Endpoint	Analysis population	Primary analysis	Supportive analysis	Subgroup analysis	Other analyses
Adverse events	*Safety*	*Follow safety guidelines*	*No*	*By intrinsic factors*	*See* AESI and AERSM *section*
Clinical laboratory data	*Safety*	*Follow safety guidelines*	*No*	*No*	*No*
Vital signs	*Safety*	*Follow safety guidelines*	*No*	*No*	*No*
Hypoglycemia	*Safety*	*Follow safety guidelines*	*No*	*By intrinsic factors*	*See* analysis of hypoglycemia *section*
Anti-drug Antibody	*Safety*	*Follow safety guidelines*	*No*	*No*	*See* analyses of immunogenicity variables *section*

[redacted]

Appendix C Calculation/Derivation details of time-to-event efficacy/safety endpoints

This section describes the calculation of the time to event and the time that patients without event and were in the study (under risk).

For patients with an event, the time to event is calculated as:

Date of event – start date + 1

For patients without an event, the time at risk is calculated as:

Date of censoring – start date + 1

For specific analysis, events that occur any time during the data period of the corresponding analysis will be considered as eligible events.

Start date

In general, the start date of an efficacy event will be the date of randomization unless otherwise specified. However, the date of first IMP taken will be used as the start date for the analysis (analyzed as occurrence of and time to first event) of following events:

- AE (including AE, AESI, AERSM)

Onset of event (date of event)

If the event is adjudicated, the date of event will always be the date determined by the CEC adjudication even it is different from the investigator reported date.

For composite outcomes, e.g. time to CV death, non-fatal MI and non-fatal stroke, the earliest onset date of each individual component will be used.

For the analysis of the endpoints 'time to CV death' and 'time to all-cause death', the time to death rather than time to the first onset of the fatal event will be used.

Handling of missing or incomplete event dates

If the onset dates (adjudicated by CEC) of time-to-event endpoints is completely missing, then use investigator reported onset date given this investigator date is complete and available. If the onset dates (adjudicated by CEC) is partial missing, then if the partial available dates be consistent with the investigator dates, use investigator date given it is more complete. And impute any remaining missing onset dates using following algorithm.

- If only month of the event is known, then the 15th day of this month will be imputed for a missing day and year of the start date will be imputed as the year, or

[redacted]

- If only the year of the event is known, then 15th of June will be imputed for the missing day and month, or

If the resulting imputed dates are prior to the randomization date, imputed date will be reset to the randomization date. For non-death event, no imputation will be made for completely missing date. For death, the impute date be the latest of all imputed event dates and patient's last trial contact date.

Censoring

The underlying rule for censoring is that the censoring date should be the last date the patient is known to be free of the event endpoint (free of each component for composite endpoint) on or before study close-out visit.

a. General censoring rule for primary MACE efficacy endpoint:

For patients who have no primary MACE endpoints, they will be censored using the following rules:

- Patients who completed the study and not died before the study completion will be censored at their study close-out visit date or follow-up visit date.

  Note: If there are CV events happening after the patient's study close-out visit date and the event's proceeding/related event's onset date is on or before the study close-out visit date, in this case, this CV events will be included in efficacy analysis if it positively adjudicated. The patient will still be censored at study close-out visit date if these events not adjudicated positively.

  For example, for a CV death, if the onset date of its proceeding fatal stoke is before the patient's study close-out visit date and the CV death date is after study close-out visit date (before DBL date), this CV death will be included in efficacy analysis if positively adjudicated as CV death.

  Another example, for a HHF, if the onset date of its proceeding HF is before study close-out visit date and its resulted hospitalization is after study close-out visit date, this HHF will be included in efficacy analysis if positively adjudicated. Otherwise, the patient will be censored at study close-out visit date if the HHF is not positively adjudicated.

- Patients who died before study close-out (i.e. Death reported on the 'Completion of End of Study') will be censored at their date of Non-CV death

- Patients who discontinued the study will be censored at their later of study discontinuation date or latest date with cardiovascular efficacy endpoint information (MI/UA, heart failure,

[redacted]

cerebrovascular event, coronary procedure, admission to hospital/emergency room, or cardiac biomarkers as collected in eCRF) collected.

More specific: If there are events happening after the patient's study discontinuation date and the events are not positively adjudicated, the latest date of these events will be the new censored date of the patient.

b. Specific censoring rule for all-cause mortality

Patients who did not die will be censored at the latest date of: study close-out visit date, date of vital status (if alive), or date last known to be alive (if LTFU). Usually, this is the date of 'Date of last available information' in 'Subject Status' form for patient alive at that date.

c. ***Specific censoring rule for composite renal endpoints***

Patients without the event will be considered censored at their latest of last laboratory sample date where eGFR/UACR results are available and patient's last visit date. If a patient doesn't have the eGFR/UACR measurements after a certain timepoint, but a dialysis procedure not meeting the definition of chronic occurs after the last eGFR/UACR measurement and last visit date, the patient will be censored at the last start date of dialysis.

Patients without laboratory measurement at either baseline or post-baseline will be censored at Day 1.

d. Specific censoring rule for eGFR (UACR) endpoint only

Patients without an event will be considered censored at the earlier of their last laboratory sample date where eGFR (UACR) results are available.

Patients without laboratory measurement at either baseline or post-baseline will be censored at Day 1.

e. Censoring for severe hypoglycemia or AE (as part of general AE analysis)

To keep the analysis of severe hypoglycemia consistent with the overall AE analysis, for AE, a patient without an adverse event will be considered censored at the date of last IMP taken + 30 days or date of death, if earlier. For severe hypoglycemia, a patient without a severe hypoglycemia will be considered censored at the date of last IMP taken + 7 day or date of death, whichever earlier.

[redacted]

Appendix D Sample SAS® code for supportive analyses for missing data of primary efficacy endpoint

```
* VARIABLES;
* cnsrn -  censoring indicator, cnsrn=1-cnsr with 1=event, 0=censor;
* adt -  event or censoring date;
* rfstdt – randomization date
* EOSSTT – whether patients completed or discontinued from study;
* EOTSTT – weather patients either completed or discontinued from treatment;
* TRTEDT– treatment end date;* armn – treatment arm, 0 for control;
* planned_closeout_date – planned closeout visit date for patients without closeout visit

data sce1 sce2 sce3 sce4;
      set &data;
      aval_trted= adt-trtedt+1 ;

     ** subjects are treatment completer**;
    if EOTSTT ^='DISCONTINUED' THEN output sce1;
     *** 2a: subjects with MACE before IMP discontinuation; 2b:
subjects with first MACE after IMP disct and study completer ***;
    if (EOTSTT='DISCONTINUED' and CNSRN=1 and ADT<=TRTEDT ) OR
(EOTSTT='DISCONTINUED' and CNSRN=1 AND ADT>=TRTEDT and
EOSSTT^="DISCONTINUED")   then output sce2;
     *** subjects discontinued IMP and study, 3a: first MACE after
pEOS, 3b: first MACE after pEOS ***/;
    if EOTSTT='DISCONTINUED' AND EOSSTT = 'DISCONTINUED' AND  CNSRN=1
AND ADT>=TRTEDT  then output sce3;
     **** 4: subjects of discontinued treatment and study without MACE
by study closeout visit ****;
    if EOTSTT='DISCONTINUED' AND EOSSTT='DISCONTINUED' and CNSRN=0
THEN OUTPUT SCE4;
  run;

   *** combine scenario 2 and 3 to estimate hazard rate **;
    data pattern1;
      set sce2 sce3;
    run;

    proc sort data=pattern1;
       by armn;

    run;
ods output  PosteriorSample = PostSamp;
    proc phreg data = pattern1;
         model aval_trted*cnsrn(0)=;
    ** Number of imputation times = nmc/thinning = 100 times;
         bayes seed=14828 piecewise=hazard (ninterval=1 prior=gamma)
nbi =2000 thinning=10 nmc=1000;
         by armn;
```

```
     run;

    /*proc print data=postsamp;
      run; */

    proc sort data=postsamp;
         by armn;
    run;

   data parout;
     retain _imput_ ;
         set PostSamp;
         by armn;

     if first.armn then
           _imput_=0;
            _imput_ =_imput_ +1;
    run;


   DATA PATTERN2;
       SET SCE4;
   RUN;

   proc sort data=PATTERN2;
     by armn;
   run;

  proc sql;
     create table pattern2_a as
           select *
                from pattern2 as r full join parout as l
                     on r.armn=l.armn;
    quit;
************************************************************;
   data tempdata;
       set  pattern2_a;
       by armn;
      *** Note: Simulate time to event. As a sensitivity analysis,
multiply hazard (lambda) for treated subjects by the delta1 ***;

        if armn=1 then
             _lbdcur=Lambda1*1;
         else    _lbdcur=Lambda1*&delta1;
            Scens=1*exp(-1*(adt-trtedt)*_lbdcur);  ** compute 1-
survival at censored time;
            Fcens=1-Scens;
            u=Fcens+ranuni(14828)*(1-Fcens);  ** simulate uniform r.v
from Fcens to 1;
            imp_censor_date =trtedt - (log(1-u))/_lbdcur;
            format imp_censor_date YYMMDD10.;
```


[redacted]

```
        if imp_censor_date > scv then
             do; imp_censor_date  = scv;
                  imp_censor=0;   /*imp-censor: 1 event, 0 further
censored*/
            end;
       else
            do;  imp_censor=1;    end;

         run;
/*observed data no missing data first: sce2 and sce3*/
   data complete;
       set sce1 sce2 sce3;
        imp_censor=cnsrn;
        imp_censor_date=adt;
        _imput_=0;
       do i = 1 to 100;
            _imput_=_imput_+1;
            output;
        end;
    run;

   /*combine observed data with imputed data (sce4 with missing data)
*/
   data imputed;
        set complete tempdata;
        imp_time=imp_censor_date- rfstdt;
        if armn=1 then armpool=1; else armpool=2; /*armpool combine
treatment group 4mg and 6mg in one group*/
        drop loglike logpost u iteration;
    run;

   /*proc print data=imputed (obs=1000);
   var armn armpool;
    run; */

   proc sort data=imputed;
        by _imput_ armpool;
   run;

  proc phreg data = imputed;
       by _imput_;
       class armpool (ref=first) region1 STRATUM;
       model imp_time*imp_censor(0)=armpool region1 STRATUM/risklimits
rl;
       ods output ParameterEstimates=_es;
   run;
/*********************************************************/
    proc sort data=_es;
         by parameter ClassVal0;
     run;
    proc mianalyze data=_es alpha=0.05;
```


[redacted]

```
          by Parameter ClassVal0;
           modeleffects Estimate;
           STDERR StdErr;
          ods output ParameterEstimates = _es_mianal;
    run;

   data mihr;
        set _es_mianal;
        where parameter='armpool';  /*only keep hazard ratio of
treatment*/
        LogHR_mi=Estimate;
        HR_mi=exp(Estimate);
        HR_LCL_mi=exp(LCLMean);
        HR_UCL_mi=exp(UCLMean);
        Delta=&delta1;
        keep Parameter ClassVal0 LogHR_mi HR_mi HR_LCL_mi HR_UCL_mi
Probt delta;
        rename Probt=Probt_mi;

       run;
```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